

Assessment of Three Therapeutic Procedures in the Prevention of Diabetic Macular Oedema after Phacoemulsification through Intraocular Lens Implementation

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Abstract: A cataract is an ocular complication of diabetes mellitus, and the risk of developing diabetic macular oedema (DME) increases in cataract surgery. This randomized, single-blind clinical trial study was conducted on 45 eyes (39 patients) with stable diabetic retinopathy with cataract to compare the efficacy of three therapeutic procedures in the prevention of DME after phacoemulsification through intraocular lens implantation. After cataract surgery by phacoemulsification, the patients were randomly assigned into three groups. The group A received 1.25 mg of intravitreal bevacizumab, and group B received a sub-tenon injection of 40 mg triamcinolone at the end of the surgery. The group C received topical diclofenac drops every 8h for four weeks after the surgery. Results showed there was no significant difference in the demographics and clinical features, central macular thickness, and systemic condition of the three groups at the beginning of the study. There was a significant difference between the preoperative and postoperative periods (i.e., three months after surgery) in the three groups regarding mean macular thickness; however, the difference among the three groups was not significant in the post-operative periods. The DME after cataract surgery occurred in 4 eyes (26.67%) in the diclofenac group and three eyes (20.00%) in the intravitreal bevacizumab and three eyes (20.00%) in sub-tenon triamcinolone groups. According to results, the administration of these three therapeutic procedures can be beneficial in the prevention of DME in patients with cataract and diabetic retinopathy.

Keywords: Diabetic macular oedema, Diabetic retinopathy, Bevacizumab, Diclofenac, Triamcinolone.

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common ocular complications in patients with diabetes mellitus. Moreover, DR can lead to moderate and severe vision loss in a young and middle-aged population of the developed countries [1, 2]. Approximately half of the diabetic population around the world is affected by different degrees of diabetic retinopathy. Diabetic macular oedema (DME) is one of the causes of vision loss in diabetic patients [3, 4]. The incidence of DME in people with diabetes is about 10%; however, this incidence rate significantly increases in eyes with a higher degree of retinopathy [4]. With the development of diabetes mellitus, DME can occur at any time of the disease [3]. The progression of diabetic proliferative retinopathy is complicated by retinal haemorrhage or tractional retinal detachment and is responsible for the most cases of severe vision loss, DME is the most common cause of moderate vision loss [5]. Hyperglycemia can damage the retinal vascular endothelium, which leads to an increased level of vascular permeability, obstruction, fluid accumulation, extracellular proteins within the

macular, bleeding, microaneurysm, and capillary blockage. Hypoxia is associated with the neovascularization of the retina and DME [6].

The DME occurs with the accumulation of fluid inside and under the retina as a result of retinal vascular occlusion [7]. The pathogenesis of diabetic retinopathy is associated with the loss of integrity of the blood-retina barrier, which results from structural changes in the capillary endothelium [5, 8]. A cataract is another complication of diabetes, which accounts for 20% of cataract surgery on diabetic patients. Some studies have shown that the risk of diabetic retinopathy, especially macular oedema, increases in cataract surgery [9-11]. The probable progression of diabetic retinopathy after cataract surgery is due to the increase of pro-inflammatory mediators, such as vascular endothelial growth factor, interleukin-1, and hepatocyte growth factor [12].

The DME is a chronic disease with a clinical manifestation that responds to various treatments and affects the entire life of afflicted patients. Therefore, there are various therapeutic strategies for DME. Previously, focal or grid macular laser photocoagulation (MLP) was the primary treatment of DME [1, 13]. Corticosteroids are another group of well-known drugs used as intravitreal injections in DME patients [14].

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Triamcinolone is a kind of corticosteroid with anti-inflammatory and anti-angiogenic properties. Intravitreal triamcinolone injection is another method for treating patients with clinically significant macular oedema, especially in advanced cataract [13, 15, 16]. Recently, the intravitreal injection of vascular endothelial growth factor (VEGF) for DME treatment has become widespread with the most common and most widely used bevacizumab [6, 17]. Bevacizumab is a humanized monoclonal hormone used in most of the new vascular formation diseases in the eye, including DME [18].

There are few studies on the effect of bevacizumab as a complementary treatment to DME [19]. The DME is caused by various pathophysiological pathways, including angiogenesis and inflammation, due to prostaglandin [20, 21]. Bevacizumab and triamcinolone as anti-angiogenic agents are used to inhibit VEGF and suppress prostaglandin-induced inflammation, respectively. Nonsteroidal anti-inflammatory drugs (NSAIDs) also inhibit prostaglandin biosynthesis and are introduced as new drugs for the possible treatment of DME [14, 22]. In order to prevent postoperative macular oedema, most researchers have recently focused on the combination of phacoemulsification and complementary therapies, such as intravitreal injection of bevacizumab and triamcinolone, for the prevention of DME with photocoagulation [23-25].

Despite the importance of DME, there are few comparative studies which address the effects of various therapeutic procedures in the prevention of DME. Moreover, the obtained results of these studies are mostly contradictory. Therefore, the present study aimed to compare the efficacy of three preventive methods including intravitreal injection of bevacizumab, sub-tenon injection of triamcinolone, and topical application of NSAID drops (Diclofenac) in the prevention of DME after phacoemulsification and intraocular lens implantation in patients with various diabetic retinopathy intensities.

METHOD

Participants

This study was a single-blind randomized clinical trial study (IRCT2017050833875N1) conducted during 2016-17 on diabetic patients with cataract and without DME in Imam Khomeini Hospital, and private specialized clinics of Ahvaz, Iran. The randomly selected eyes were divided into three groups of 15 (a total of 45 eyes of 39 patients).

The inclusion criteria in this study were the willingness to participate in the study, non-preoperative DME, and non-proliferative diabetic retinopathy (NPDR).

On the other hand, the exclusion criteria entailed 1) any diseases associated with the macula, 2) history of trauma, glaucoma, uveitis or other eye diseases related to retinal thickness, 3) history of any intraocular surgery or any other intraocular injection from 6 months ago, 4) macular ischemia (through assessment of previous fluorescein angiogram), 5) vitreomacular traction, and 6) macular hole. Furthermore, patients who went through laser therapy 12 months prior to cataract surgery, as well as those with the follow-up of fewer than three months were excluded from the study.

Research Procedure

This study was conducted at Imam Khomeini Hospital or private specialized clinics of Ahvaz after obtaining ethical code IORC 9602 from Ethical Committee of Ahvaz Jundishapur University of Medical Sciences. Subsequently, 45 eyes (39 patients) were selected on the basis of the inclusion and exclusion criteria by the project executives. The study was conducted according to the Declaration of Helsinki. Written informed consent forms were received from all patients before starting the treatment.

To begin the treatment, the demographic information of each patient (i.e., age and gender) and clinical information, including the duration of diabetes mellitus, types of medications used to control blood sugar (insulin/edible hypoglycemic/combotherapy), diabetic retinopathy severity, history of hypertension, hypercholesterolemia, and smoking were recorded in a form. The severity of NPDR was determined on the basis of the Early Treatment Diabetic Retinopathy Study (ETDRS) classification, and the slit-lamp examination was mild and severe. At the beginning of the study, the diagnostic criteria for DME were based on macular thickness greater than 268 μm at the centre of the fovea [26-27].

First of all, blood tests were performed to determine metabolic control status. The tests included glycated haemoglobin (HbA1c), fasting blood sugar (FBS), lipid profiles, including low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), and total cholesterol. Prior to the surgery, patients were evaluated in terms of macular thickness and best-corrected visual acuity (BCVA).

Performing Intervention

In this study, Phacoemulsification surgery was performed on all diabetic patients with cataract intraocular lens. Cataract surgery was conducted by phacoemulsification, which included local or general anaesthesia, clear corneal incision, capsulorrhexis, phacoemulsification, intraocular lens placement in the capsular bag, and eventually the injection of intravitreal bevacizumab or triamcinolone. Surgery was performed by two surgeons uneventful. Patients were randomly divided into three groups, namely A, B, and C, to prevent DME, three types of treatments were performed for patients as follows:

- The group A received 1.25 mg (0.55 mL) of intravitreal bevacizumab (manufactured by Roche Diagnostics GmbH, Mannheim, Germany) from a 3.5 mm of limbus with 27 gauge needle at the end of the surgery.
- The group B received a sub-tenon injection of 40 mg triamcinolone (manufactured by Iran Hormones, Iran) from the 3 mm sub-tenon at the end of the surgery.
- The group C received topical diclofenac drops (manufactured by Sina Darou Corporation, Iran) every 8h for four weeks after the surgery.

Assessment of the Effect of Treatment

The follow-up sessions of patients were performed after surgery on the first day, first month, and the third month after the surgery and all patients were evaluated for macular thickness and BCVA. The assessment of macular thickness was performed based on the ETDRS guideline using the spectral-domain optical coherence tomography (SD-OCT). The optical coherence tomography (OCT) evaluation was carried out using a high-resolution program on the retina. A total number of 6 scans were performed with a length of 6 mm of foveal centre and the displacement of 30° from each other. The thickness of the central macular was measured in every six scans. The average of these six sizes was intended as the central macular thickness. All images were examined to avoid any misalignment. Macular oedema was defined as significant when the increase of central macular thickness is more than 60 µm, compared to the central macular thickness at the beginning of the study [25]. Visual acuity was assessed with the help of E chart.

Data Collection Tools

The data in this study consisted of the demographic and clinical characteristics of the patients. Moreover, the macular thickness and visual acuity of the patients were assessed using SD-OCT and E-Chart, respectively. Therefore, the assessment values for macular thickness and visual acuity of the patients before the surgery, as well as follow-up sessions of the first and third months of the postoperative period were also recorded in a checklist for data collection.

Statistical Analysis

The statistical analysis of data was performed using SPSS (version 22). Normality of data and homogeneity of variances were evaluated by Kolmogorov-Smirnov test and Leven test, respectively. The Chi-square test, ANOVA, and t-test were used to compare quantitative and qualitative variables and also measure the significance of differences. A variance analysis test with repeated measurements was used to compare the average macular oedema thickness in each drug at different times. A p-value of less than 0.05 was considered statistically significant. Microsoft Excel was used to design the plot graphs and charts.

RESULTS

This clinical trial study was conducted on 45 eyes (39 patients) with stable diabetic retinopathy with cataract. The cataract surgery in this study was conducted on 19 eyes of male patients and 26 eyes of female patients. There was no significant difference among the people in the three groups in terms of gender ($P= 0.177$). The demographic characteristics and medical history of the studied patients in the three treatment groups showed that the mean age of the patients was 66.27 ± 6.58 years (ranged 52 to 80 years). Moreover, the duration of diabetes mellitus was within the range of 2-20 years with the mean of 7.84 ± 3.80 years. The results of the statistical analysis indicated no significant difference among people in the three groups regarding age, duration of diabetes, history of hypertension, hypercholesterolemia, history of smoking, type of glycemic control, the severity of diabetic retinopathy, and eye surgery ($P > 0.05$). The results of preoperative examinations of the patients in the three treatment groups also indicated that there was no significant difference among the three groups in terms of FBS, HbA1C, LDL, HDL, TG, and Cholesterol ($P > 0.05$). Table 1 shows the analysis of preoperative examinations.

Table 1: Demographic Characteristics and Medical History of the Patients

Variable		Diclofenac	Bevacizumab	Triamcinolone	P-Value
Gender	Male	(60.00) 9	(40.00) 6	(26.67) 4	0.177
	Female	(40.00) 6	(60.00) 9	(80.00) 11	
Age (year)		66.66±7.27	66.40±7.10	65.73±5.67	0.926
Duration of diabetes		7.20±2.75	8.66±4.56	7.66±3.99	0.570
Medicine use	Metformin	(60.00) 9	(46.67)7	(40.00) 6	0.709
	Combination	(20.00) 3	(20.00)	(40.00)	
	Insulin	(20.00) 3	(33.33) 5	(20.00)	
Blood pressure		(46.67) 7	(53.33) 8	(33.33) 5	0.533
Hypercholesterolemia		(53.33) 8	(46.67) 7	(40.00) 6	0.765
Cigarette		(46.67) 7	(33.33) 5	(13.33) 2	0.139
NPDR grade	Mild	(53.33) 8	(33.33) 5	(46.67) 7	0.533
	Moderate	(46.67) 7	(66.67) 10	(53.33) 8	
Surgical eye	OD	(46.67) 7	(53.33) 8	(40.00) 6	0.765
	OS	(53.33) 8	(46.67) 7	(60.00) 9	
FBS		180.33±31.49	207.06±48.24	184.40±38.58	0.156
HbA1C		6.82±0.36	6.88±0.36	6.78±0.32	0.770
LDL		111.73±33.52	117.46±28.25	96.26±32.02	0.172
HDL		47.40±9.58	50.13±6.66	46.66±7.79	0.473
TG		167.13±34.74	168.00±36.03	189.53±35.84	0.161
Total Cholesterol		190.40±20.40	202.73±37.82	184.80±42.67	0.406

NPDR: non-proliferative diabetic retinopathy.

FBS: fasting blood sugar.

HbA1C: glycated haemoglobin.

LDL: low-density lipoprotein.

HDL: high-density lipoprotein.

TG: triglyceride.

Visual Acuity

The results of visual acuity in the three treatment groups at different times showed that the mean of visual acuity of patients before surgery was 0.10 ± 0.04 . Before surgery, visual acuity was significantly different among the three groups ($P=0.004$). However, the visual acuity of patients in the three groups did not differ significantly in the postoperative periods (i.e., first day, first month, and the third month after treatment [$P>0.05$]). On the other hand, the comparison of preoperative and postoperative periods (i.e., first day, first month, and third month after treatment) revealed a significant improvement of visual acuity in the three groups ($P<0.0001$).

Patients in group A and those in group B showed the most considerable improvement in visual acuity during the first and third month after the surgery.

However, patients in group C had the least improvement in visual acuity at different times, compared to the other two groups. As can be seen, different time intervals had no significant effect on the improvement of visual acuity among the patients in the three groups ($P>0.05$).

Macular Thickness

The values of macular thickness were 252.80 ± 15.08 μm , 284.91 ± 43.81 μm , and 299.69 ± 68.97 μm before the surgery, the first month after surgery, and the third month after surgery, respectively. Time intervals (i.e., before surgery, the first, and third month after surgery) had no significant effect on the magnitude of macular thickness of the three groups. The mean thickness of the macula increased significantly in all groups in the first and third month of surgery ($P<0.05$).

Development of Diabetic Macular Oedema

In the present study, 4, 3, 3 eyes in the groups C, B, and A were afflicted to DME after the cataract surgery, respectively (diagnosed through the change in the macular thickness more than 60 µm compared to the thickness at the beginning of the study). The analysis of the effectiveness of treatment results presented in Table 2 and Figure 1.

Relationship between Macular Thicknesses with Different Variables

The mean values of macular thickness in group C before the surgery (236.66±19.05 vs. 256.00±13.53, P=0.038), one month after the surgery (312.88±41.78 vs 251.16±24.73 (P=0.007), and three months after the cataract surgery (306.77±41.98 vs. 258.50±25.19, P=0.026) were higher in male patients than female ones (P<0.05). However, in groups, B and A, the thickness of the macula before and after the surgery had no significant relationship with the patients' gender (P>0.05).

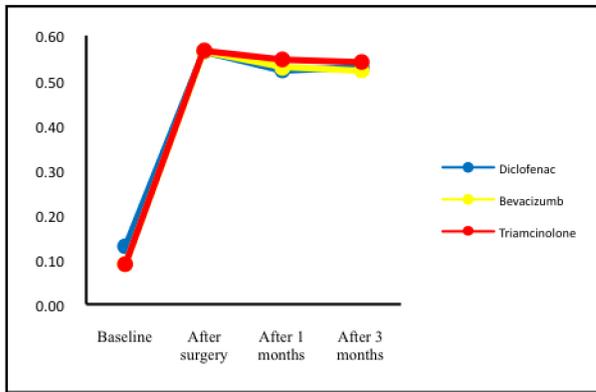
In the current study, there was no significant difference in the magnitude of macular thickness and severity of diabetic retinopathy among the three groups before the surgery and the first month after surgery (P>0.05). However, in all investigated groups, the mean macular thickness in patients with moderate retinopathy was significantly more than the macular thickness in patients with mild retinopathy in the third month after cataract surgery (P<0.05). Furthermore, no significant difference was observed between the macular thickness and the history of hypertension before the surgery (P>0.05). In the first and third months after cataract surgery, the mean macular thickness in patients with a history of hypertension was higher than those without a history of hypertension in all the three groups. However, this difference was only significant in group C (P<0.05).

The obtained results of the study revealed that there was no significant difference in macular thickness with hypercholesterolemia history in any of the three groups before the surgery (P>0.05). The mean macular thickness in the first and third months after cataract surgery was higher in patients with a history of

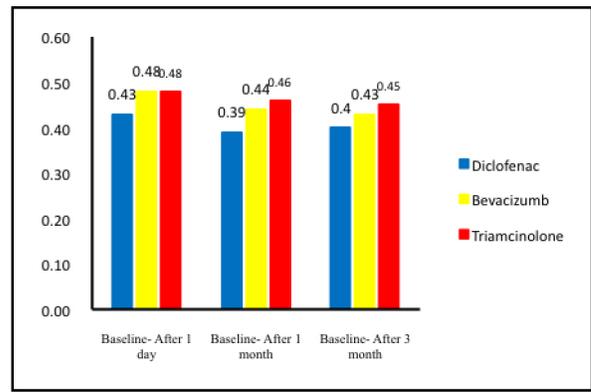
Table 2: Mean Values of Best-Corrected Visual Acuity and Optical Coherence Tomography as well as their Changes

Variable	Time	Diclofenac (Mean±SD)	Bevacizumab (Mean±SD)	Triamcinolone (Mean±SD)	P-value
BCVA	Baseline	0.13±0.05	0.09±0.02	0.09±0.04	0.004
	After 1 day	0.56±0.07	0.56±0.13	0.57±0.13	0.998
	After 1 month	0.52±0.12	0.53±0.14	0.55±0.12	0.859
	After 3 months	0.53±0.11	0.52±0.15	0.54±0.14	0.931
	**p-value (intra-group)	0.0001	0.0001	0.0001	
Changes in BCVA	Baseline- After 1 day	0.43±0.05	0.48±0.13	0.48±0.12	0.434
	Baseline- After 1 month	0.39±0.09	0.44±0.13	0.46±0.12	0.247
	Baseline- After 3 months	0.40±0.08	0.43±0.14	0.45±0.13	0.467
OCT	Baseline	248.27±18.20	251.80±15.77	258.33±8.89	0.181
	After 1 month	288.20±46.86	291.07±52.12	275.47±31.18	0.594
	After 3 months	287.47±42.82	303.33±71.16	308.27±88.32	0.699
	**P-value (intra-group)	0.008	0.024	0.048	
Changes in OCT	Baseline- After 1 month	39.93±39.84	39.27±62.19	17.13±32.67	0.323
	Baseline- After 3 months	39.20±36.81	51.53±80.97	49.93±90.54	0.882
	After 1 month- after 3 months	0.73±0.86	12.26±36.72	32.80±93.72	0.304

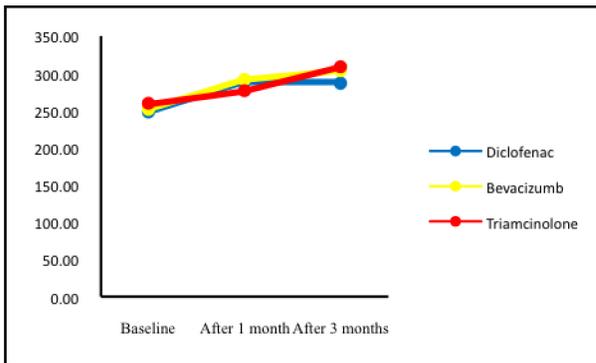
* ANOVA test.
 SD= standard deviation.
 BCVA: best-corrected visual acuity.
 OCT: optical coherence tomography.



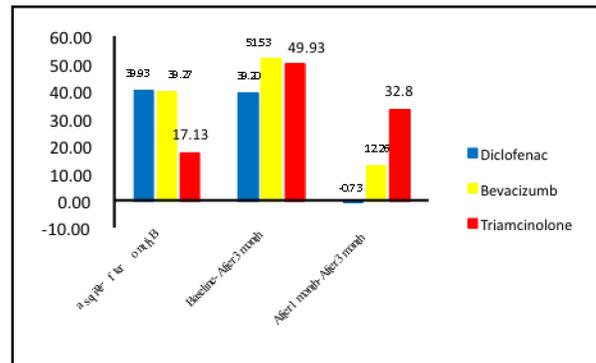
A. Visual acuity process at different points of time in the three treatment groups



B. Comparison of visual acuity at different points of time in the three treatment groups



C. Optical coherence tomograph process at different points of time in the three treatment groups



D. Comparison of optical coherence tomography at different points of time in the three treatment groups

Figure 1: Part A: Visual acuity process at different points of time in the three treatment groups, Part B: Comparison of visual acuity at different points of time in the three treatment groups, Part C: Optical coherence tomography process at different points of time in the three treatment groups, Part D: Comparison of optical coherence tomography at different points of time in the three treatment groups.

hypercholesterolemia than in patients without hypercholesterolemia history in all the three groups. However, this difference was only significant in the groups A and B three months after the surgery ($P < 0.05$). In the current study, there was no significant relationship between the macular thickness and cigarette smoking in any of the three groups before surgery ($P > 0.05$). The mean values of the macular thickness in the first and third months after cataract surgery in all three groups (except group B in the first month after surgery) were significantly higher in patients with a history of smoking, compared to those without a history of cigarette smoking ($P < 0.05$).

Moreover, macular thickness had no significant relationship with the duration of the disease before surgery in the three groups ($P > 0.05$). The analysis of the first and third month after surgery revealed that the mean macular thickness was higher in patients with diabetes more than ten years than those with a history of disease for a minimum of 10 years. However, this

difference was significant in all three groups only after the third-month follow-up. ($P < 0.05$). Table 3 presents the details about the relationship between macular thicknesses with different variables.

DISCUSSION

The eyes of diabetic patients are at high risk of the increased thickness of the central macular after cataract surgery, which is associated with the vision loss in month one and limited visual acuity improvement in month three after the surgery [28]. However, the surgery does not seem to have any significant long-term effects on the increased risk of macular oedema [29]. Therefore, due to the risk of developing DME after cataract surgery, the current comparative study investigated the effectiveness of three therapeutic interventions, including intravitreal bevacizumab, sub-tenon triamcinolone, and diclofenac eye drops for the prevention of DME after cataract surgery.

Table 3: Relationship of the Changes in Macular Thickness with a History of Hypertension, History of Hypercholesterolemia, History of Smoking, and Diabetes Duration of More than Ten Years

Variable	Group	Time	Yes	No	P-value
Hypertension	Diclofenac	Baseline	246.14±17.39	250.12±19.86	0.688
		After 1 month	317.85±47.55	262.25±28.36	0.015
		After 3 months	316.85±41.43	261.75±23.98	0.007
	Bevacizumab	Baseline	256.50±11.75	246.42±18.85	0.230
		After 1 month	296.37±52.92	285.00±54.68	0.689
		After 3 months	310.75±71.88	294.85±75.02	0.682
	Triamcinolone	Baseline	258.20±11.41	258.40±8.07	0.960
		After 1 month	294.60±45.12	265.90±17.38	0.093
		After 3 months	301.80±35.54	311.50±107.40	0.850
Hypercholesterolemia	Diclofenac	Baseline	244.62±21.23	252.42±14.45	0.428
		After 1 month	293.50±55.74	282.14±37.66	0.657
		After 3 months	239.00±57.52	281.14±18.16	0.611
	Bevacizumab	Baseline	257.85±17.23	255.25±14.60	0.358
		After 1 month	319.42±65.85	266.20±14.39	0.044
		After 3 months	341.71±91.43	269.75±14.09	0.046
	Triamcinolone	Baseline	255.33±9.11	260.33±8.67	0.303
		After 1 month	283.16±47.94	270.33±13.80	0.455
		After 3 months	347.50±135.97	282.11±13.02	0.048
Cigarette	Diclofenac	Baseline	254.42±15.19	242.87±19.83	0.233
		After 1 month	320.85±44.66	259.62±26.12	0.006
		After 3 months	318.00±40.11	260.75±23.22	0.004
	Bevacizumab	Baseline	245.80±18.80	254.80±14.12	0.315
		After 1 month	334.60±73.87	269.30±14.87	0.015
		After 3 months	375.20±84.94	267.40±19.11	0.002
	Triamcinolone	Baseline	257.00±7.07	258.53±9.36	0.829
		After 1 month	307.00±84.85	270.61±18.51	0.128
		After 3 months	468.50±180.31	280.84±16.76	0.0001
Diabetes duration of more than 10 years	Diclofenac	Baseline	246.18±16.95	254.00±22.97	0.482
		After 1 month	276.00±40.63	321.75±51.95	0.095
		After 3 months	273.00±28.67	327.25±54.19	0.023
	Bevacizumab	Baseline	257.00±15.25	245.85±15.20	0.181
		After 1 month	269.25±13.72	316.00±68.98	0.082
		After 3 months	266.37±19.70	345.57±86.36	0.025
	Triamcinolone	Baseline	259.54±9.78	255.63±5.47	0.401
		After 1 month	281.63±33.31	258.50±18.51	0.215
		After 3 months	287.63±29.50	365.00±166.26	0.039

The obtained results of the present study confirmed the results of previous studies, including a study conducted by Soheilian *et al.*, which showed the improvement of visual acuity and macular oedema in DME patients using 1.0 mL/mcg 500 of intravitreal diclofenac [30]. In another study conducted by Chae *et al.* [25], it was found that ranibizumab injection during cataract surgery in patients with NPDR without macular oedema could prevent the occurrence of macular oedema after surgery, and improve the results of visual acuity, compared to the patients in the control group. These findings lend support to the obtained results of the present study.

The results of a study by Faghihi *et al.* [14] on the effectiveness of bevacizumab and diclofenac in patients with DME after cataract surgery showed that intravitreal injection of anti-VEGF and NSAIDs improved visual acuity and significantly reduced the macular thickness and macular volume. These results were consistent with the findings of the present study. In another study, Soheilian *et al.* [31] indicated that visual acuity in patients who received intravitreal diclofenac injection was better than patients who received bevacizumab intravitreal injection until week 12. The results of visual improvement in both groups were in line with the findings of the present study, although intravitreal bevacizumab had a better effect on visual acuity than diclofenac in the present study.

Fard *et al.* [29] also pointed out no significant difference in BCVA, central macular thickness, and systemic conditions between the intravitreal bevacizumab and control groups before the surgery. One month after the surgery, the control group showed a significant increase in the central macular thickness, while the bevacizumab group did not show a significant increase. After six months, there was no significant difference in macular thickness and visual acuity between the two groups. Consequently, the injection of 1.25 mg of bevacizumab during cataract surgery was only effective for a short time and the results of the two groups were similar (control and experimental groups) in the 6-month follow-up session. These findings were consistent with the obtained results of the present study on the effectiveness of bevacizumab.

In a study conducted by Lanzagorta-Aresti *et al.* [32], the administration of intravitreal bevacizumab improved visual acuity and decreased macular thickness in diabetic patients with NPDR and macular oedema during cataract surgery in 3 and 6 months after surgery. These results showed that the

administration of intravitreal bevacizumab after phacoemulsification surgery prevented the exacerbation of macular oedema, which has been observed in many diabetic patients undergoing cataract surgery. In the present study, patients who received bevacizumab showed the most considerable increase in macular thickness, compared to the other two groups in the third month after surgery. However, the difference between the three groups was not significant. Increased macular thickness in the bevacizumab injection group during surgery was consistent with the results of a study conducted by Rauen *et al.* [33], which did not show a positive anatomical response to ranibizumab injection.

Gallego-Pinazo *et al.* [1] reported a significant increase in the central macular thickness during follow-up in the comparison of the patients in the control group (without treatment) and the two groups treated with bevacizumab and triamcinolone. However, the status of the triamcinolone group was better than the other two groups, which was in congruence with the findings of the current study. The investigation of triamcinolone in patients with cataract and DME, in a study conducted by Lam *et al.*, a significant improvement in BCVA lines (more than two lines) and a substantial decrease in macular thickness during all follow-up times [13].

The results of the studies on the comparison of intravitreal injection of triamcinolone and intravitreal bevacizumab in DME treatment have been very inconsistent. Some studies have shown that the intravitreal injection of triamcinolone is more effective than compared intravitreal bevacizumab, some have reported similar effectiveness of intravitreal injection of triamcinolone and intravitreal bevacizumab, and some have also indicated intravitreal injection of triamcinolone is less effective, compared to intravitreal bevacizumab. In a study conducted by Elbendary *et al.* the benefits of using intravitreal diclofenac were compared to corticosteroids (triamcinolone acetonide) in the prevention of macular oedema (improving visual acuity and changes in macular thickness) in diabetic patients. They also reported that NSAIDs reduced intraocular pressure in patients treated with intravitreal injection of diclofenac [34]. These results are not consistent with the findings of this study since there was no significant difference in the effectiveness of treatments in the present study. The reason for this difference is that Elbendary *et al.* applied the intravitreal method to inject diclofenac in their study.

Direct injection into the retina could improve the therapeutic effects of the medicine due to the longer shelf-life of the medication in the retina, resulting in a longer half-life of the drug.

In another study, Hegazy *et al.* [4] examined the effectiveness of intravitreal diclofenac and intravitreal triamcinolone in the treatment of DME. The results showed that there was a significant decrease in the macular thickness of the two groups at various points of time after surgery; however, no significant difference was observed between the two groups of diclofenac and triamcinolone. Triamcinolone in the first month and diclofenac in the third and sixth months after surgery showed higher efficacy in reducing the central macular thickness. In both groups, significant improvement in BCVA was observed in one month after surgery. These results corresponded to the findings of this study.

The reason for some differences and contradictions in the results of various studies is due to the differences in the sample size, the treatment method and the basic characteristics of the patient before the surgery. The results of the current study revealed that patients with lower DR severity and no history of hypertension and hypercholesterolemia achieved better visual outcomes. This conclusion was consistent with the findings of previous studies, including Kim *et al.* [28]. The results of a study by Gallego-Pinazo *et al.* was also in line with these data because there was a significant relationship among all of these characteristics (more than ten years of diabetes, the severity of diabetic retinopathy, DME before surgery), BCVA, and ultimate central macular thickness [1].

In the present study, 4, 3, 3 eyes in the group C, B, and A were afflicted to DME after the cataract surgery, respectively (diagnosed through the change in the macular thickness more than 60 μm , compared to the thickness at the beginning of the study). However, the administration of diclofenac, intravitreal bevacizumab, and triamcinolone is equally useful in changing macular thickness and preventing DME. In confirming these results, Cheema *et al.* showed that the combination of cataract surgery with intravitreal bevacizumab caused the development of DME macular oedema only in 71.5% of patients, while this state was observed in 45.45% of the patients in the control group [35]. Accordingly, administration of intravitreal bevacizumab during cataract surgery is a safe and effective method for preventing DME in patients with cataract and DR.

In a study conducted by Salehi *et al.* [36], the progression of diabetic maculopathy was observed in

50% of the control group (surgery alone) and 7.4% of the eyes of the intravitreal bevacizumab group. As a result, it is safe and effective to use 1.25 mg intravitreal bevacizumab during cataract surgery as a therapeutic procedure in the treatment of DME in patients with diabetic retinopathy and cataract.

In general, the results of the present study were consistent with the findings of previous studies and indicated that the severity of diabetic retinopathy before cataract surgery could increase the incidence of DME after surgery. It is also worth mentioning that BCVA improvement was relatively moderate, although all three treatments created a positive response to visual improvement. Furthermore, the present study showed that the prescription of examined treatments does not have a dangerous side effect and can be used as a safe and effective medication to prevent DME, as well as anti-VEGF drugs, currently common choice for the treatment of DME patients. Additionally, NSAIDs and triamcinolone can also improve BCVA, and their effect on changing the macular thickness, which is approximately the same as that of bevacizumab. In the future, long-term follow-up clinical trials and larger sample size will help to decide, whether to select anti-VEGF, triamcinolone, NSAIDs or combine them with other types of medications.

CONCLUSION

The results of this study support the use of sub-tenon triamcinolone or intravitreal bevacizumab in cataract surgery, as well as the effectiveness of topical diclofenac in the prevention of DME in patients with cataract and DR. The present study is probably the first clinical experience in comparing these three treatments for the prevention of DME; therefore, there is a need to do further studies with longer follow-up duration with more participants in study groups along with the use of other recent diagnostic methods such as OCT angiography in order to derive conclusions and decisive decisions in selecting the best treatment.

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