• Clinical Research •

Comparison of topical nepafenac 0.1% with intravitreal dexamethasone implant for the treatment of Irvine-Gass syndrome

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Received: 2018-01-29 Accepted: 2018-04-25

Abstract

• AIM: To compare safety and efficacy of intravitreal dexamethasone (IVD) implant with topical nepafenac (TN) 0.1% in previously untreated Irvine-Gass syndrome (IGS) in clinical practice.

• METHODS: This was a retrospective study of 62 eyes with IGS after phacoemulsification with posterior chamber intraocular lens (IOL) implantation. None of the patients used treatment before IVD or TN. Best-corrected visual acuity (BCVA) with Early Treatment Diabetic Retinopathy Study chart (ETDRS), slit-lamp, intraocular pressure (IOP) measurement, fundus examination, spectral-domain optical coherence tomography (OCT) and fundus florescein angiography were performed to all subjects at baseline, 1, 3 and 6mo.

• RESULTS: The mean BCVA of the IVD group was 49.3±6.8, and the mean BCVA of the TN group was 32.9±7.3 ETDRS letters in post-treatment month 6. The mean central macular thickness (CRT) of IVD group was 266.6±53.5 μm and the mean CRT of TN group was 364.9±56.3 μm in post-treatment month 6. Baseline BCVA has correlation with final BCVA in TN group however there was no correlation between baseline BCVA and final BCVA in IVD group.

• CONCLUSION: IVD is found to be better than TN in controlling pseudophakic macular edema and improving visual acuity. IVD group also has significantly lower CRT however IOP is not significantly different between two groups in post-treatment month 6.

• KEYWORDS: intravitreal dexamethasone implant; nepafenac; Irvine-Gass syndrome; cystoid macular edema; inflammation

DOI:10.18240/ijo.2019.02.12

Citation: Guclu H, Pelitli Gurlu V. Comparison of topical nepafenac 0.1% with intravitreal dexamethasone implant for the treatment of Irvine-Gass syndrome. *Int J Ophthalmol* 2019;12(2):258-267

INTRODUCTION

Irvine-Gass syndrome (IGS) commonly known as pseudophakic cystoid macular edema (CME) which is one of the leading causes of low visual acuity after complicated or uncomplicated cataract surgery[1-4]. Although the etiology of IGS is multifactorial, it is suggested that the main cause is the increased inflammatory mediators in aqueous and vitreous which causes disruption of the blood-aqueous and blood-retinal barriers after surgery[5-7].

Incidence of CME is higher in complicated cases related to posterior capsule rupture, iris irritation, vitreous loss, vitreous traction through the wound, vitrectomy for residual lens materials, early postoperative capsulotomy, anterior chamber intraocular lens (IOL), iris fixated IOLs, IOL dislocations and traumatic cataract. The other risk factors for CME are diabetes, uveitis, glaucoma medications and intracamaral ophthalmic solutions[8-12]. CME may occur in weeks to years after surgery but commonly it occurs in 6 to 8wk after the surgery[3-7]. Increased vascular permeability and gathered eosinophilic transudates in the outer plexiform and inner nuclear layers of the retina induces cystic cavity which combines to create larger cavity of fluid[5-7]. Although spontenous resolution of the CME is seen in most of the patients, long standing macular edema is a risk for persistant poor visual acuity in 2% of the patients[3]. Rapid recognation and treatment of the syndrome is needed because of developement of subretinal fluid, lamellar hole and photoreseptor loss due to persistant macula edema[7].

Treatment of the CME was experienced with topical nonsteroidal anti-inflammatuar agents (NSAIDs), COX inhibitor (valdecoxib), oral carbonic anhydrase inhibitors (CAIs), systemic, topical, periocular, intravitreal corticosteroids as triamcinolone, anti-VEGF agents and intravitreal infliximab, subcutanous interferon α2a, hyperbaric theraphy, and vitrectomy[13-19]. NSAIDs inhibit the cyclooxygenase enzymes responsible for prostaglandin production[20]. Topical nepafenac (TN; Nevanac, Alcon, Puurs, Belgium) spread into the cornea and sclera and is converted to its active metabolite, amfenac,

in the retina, choroid and ciliary body[21-22]. Nepafenac and amfenac block the inflammation related breakdown of blood-retina barrier[23]. Ozurdex (Allergan, Irvine, CA) is a biodegradable intravitreal drug delivery system that maintains continous delivery of the preservative free dexamethasone[24]. It is demonstrated that the dexamethasone implant is effective in macular edema related with retinal vein occlusion, uveitis, diabetic macular edema, resistant macular edema and IGS[24-25]. The aim of this study was to compare the safety and efficacy of TN and IVD in previously untreated IGS patients in clinical practice.

SUBJECTS AND METHODS

Ethical Approval The study adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

This retrospective, single center study included consecutive IGS patients after phacoemulsification with posterior chamber IOL implantation between January 2013 and November 2015. A full ophthalmological examination, including a detailed medical history, best-corrected visual acuity (BCVA) with Early Treatment Diabetic Retinopathy Study (ETDRS) chart, slit-lamp, intraocular pressure (IOP) measurement, fundus examination and central macular thickness (CRT) measurement by spectral-domain optical coherence tomography (OCT; RS-3000 Lite, Nidek) and fundus florescein angiography (FFA) were performed in all subjects at baseline, 1, 3 and 6mo. The data comprising demographic characteristics, presence of diabetes, presence of complications associated with surgery, BCVA, IOP, CRT, fluorescein angiography findings during the follow up period were reported. The criteria used for IGS were any of the following after cataract surgery: CRT≥250 μm; prescence of cysts on OCT; ≥30% increase in CRT from the preoperative baseline measurement; the classic petalloid leakage in the late phase on FFA[20,26].

In addition to the above criteria, the re-injection criteria were persisted macular edema at the end of 4th month of the injection and recurrence of the macular edema. History of any ocular disease as diabetic maculopathy, diabetic retinopathy, glaucoma, age related macular degeneration, uveitis, epiretinal membrane, vitreomacular traction, retinal vein or artery occlusion, any ocular surgery before cataract surgery, any other previous treatment (systemic or intravitreal) for CME, any history of systemic disease out-of control, uveitis findings in FFA were the exclusion criteria. Any of the patients did not have topical NSAIDs medication before the surgery. No selection criterion was applied for IGS treatment. Consecutive cases were alternately selected for one of two treatments: either intravitreal dexamethasone (IVD) implant injection or TN 0.1%. TN was received four times daily. The duration of IGS before treatment was 2mo for all subjects. The topical treatment group receive their treatment for 3mo. We excluded five patients from IVD group who required re-treatment with Ozurdex.

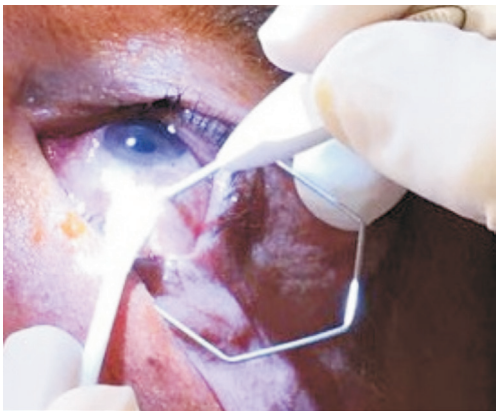

Figure 1 Dexamethasone intravitreal implant Ozurdex implantation.

Injection Technique Intravitreal injections were performed under sterile conditions in the surgery unit following standardized procedures. After instilling topical anesthetics, preoperative antisepsis was made with 5% povidone iodine. IVD was injected to the eye 3.5 mm posterior to the limbus with its 22 gauge applicator. After application the site of the injection was compressed with a cotton applicator in order to avoid vitreus reflux[25-26] (Figure 1).

Statistical Analysis Categorical variables were described using absolute and relative frequencies, and quantitive variables were described using mean and standard deviation. Linear mixed effects models were performed to evaluate BCVA, CMT, and IOP over the follow up period with a 95% confidence interval (CI). Mann-Whitney *U* test, Student's *t* test and Chi-square with continuity correction were used to compare the data between variables. Friedman test was used to determine the difference between the measurements. Wilcoxon signed rank test was performed for continuous variables with non-normal distribution. The Spearman test was used to assess the correlation between variables. Statistical analysis was performed using SPSS software (version 15, SPSS Inc, IL), *P* value <0.05 was assumed significant for all analysis.

RESULTS

Totally 62 eyes of 62 IGS patients enrolled to this study. The IVD group included 32 eyes, and the TN group 30 eyes. The mean±standard deviation (SD) age of patients was 68.9±10y and 66.4±9.4y in the IVD and TN groups, respectively. Demographic data, BCVA, CRT and IOP of the two groups can be seen in Tables 1 and 2. The relation between prescence of diabetes and BCVA, CRT and IOP are shown in Table 3. The relation between prescence of complication and BCVA, CRT and IOP are shown in Table 4. Total 10 patients in IVD group and 9 patients in TN group had complications related with surgery (posterior capsule rupture, iridodialysis, vitreous incarceration, zonular dialysis).

Table 1 Demographic data of IGS patients *n* (%)

Items	IVD Group	TN Group	*P*
Gender (M/F)	21 (65.6)/11 (34.3)	17 (56.6)/13 (43.4)	0.732
Diabetes (+/-)	16 (50.0)/16 (50.0)	7 (23.3)/23 (76.7)	0.165
Complication (+/-)	10 (31.2)/22 (68.7)	9 (30.0)/21 (70.0)	1.000

Continuity correction. IVD: Intravitreal dexamethasone; TN: Topical nepafenac.

Table 2 Age, BCVA, CRT and IOP results of the IVD and TN groups

Parameters	IVD Group		TN Group		[b]*P*
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age	68.9±10.0	70 (56-88)	66.4±9.4	65 (55-83)	0.445
BL BCVA	25±11.8	20.5 (12-46)	20.9±9.3	18 (12-42)	0.272
BCVA Mo 1	41.8±7.2	43 (25-55)	28.7±9.3	28 (18-48)	0.000[a]
BCVA Mo 3	47.6±6.6	48 (32-57)	29.3±9.7	30 (18-48)	0.000[a]
BCVA Mo 6	49.3±6.8	48 (35-62)	32.9±7.3	33 (22-43)	0.000[a]
BL CRT	522.7±120.7	490 (377-740)	501.2±104.2	472 (388-732)	0.558
CRT Mo 1	362.3±79.9	364 (244-550)	386.3±65.9	375.5 (255-556)	0.319
CRT Mo 3	304.1±67.1	277 (232-509)	373.0±62.1	368.5 (234-554)	0.001[a]
CRT Mo 6	266.1±53.4	247 (228-450)	364.9±56.3	364 (235-514)	0.000[a]
BL IOP	13.1±2.9	13 (9-18)	13.6±2.0	13.5 (10-17)	0.566
IOP Mo 1	15.1±3.0	16 (11-20)	13.4±1.8	13 (11-17)	0.09[a]
IOP Mo 3	15.7±3.6	15.5 (8-22)	13.4±1.8	14 (10-17)	0.02[a]
IOP Mo 6	14.9±3.5	14.5 (10-25)	13.6±1.7	13 (11-17)	0.184

IVD: Intravitreal dexamethasone; TN: Topical nepafenac; BL: Baseline; BCVA: Best corrected visual acuity; CRT: Central retinal thickness; IOP: Intraocular pressure; Mo: Month. [a]Statistically significant. [b]Mann-Whitney *U* test or Student's *t* test.

Table 3 The relation between prescence of diabetes and BCVA, CRT and IOP

Parameters	IVD Group		TN Group		[b]*P*
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Diabetes (+)					
BL BCVA	27.2±9.8	24 (16-46)	18.5±8.1	16 (12-30)	0.12
BCVA Mo 1	41.9±6.0	42 (34-51)	27.0±7.8	25 (20-38)	0.85
BCVA Mo 3	47.3±6.2	48 (37-57)	30.0±9.9	27 (22-44)	0.39
BCVA Mo 6	49.2±6.3	47 (40-60)	30.5±4.2	31 (25-35)	0.94
BL CRT	555.9±124.7	612 (400-704)	500.8±82.4	479.5 (432-612)	0.48
CRT Mo 1	408±72.0	391 (314-550)	451.8±74.2	434 (383-556)	0.26
CRT Mo 3	350.5±68.4	345 (258-509)	437.5±79.1	408 (380-554)	0.02[a]
CRT Mo 6	295.4±64.3	272 (244-450)	423.0±61.9	401.5 (375-514)	0.02[a]
BL IOP	13.6±2.6	13 (10-18)	13.0±2.5	13.5 (10-15)	0.56
IOP Mo 1	15.7±3.0	16 (12-20)	13.8±2.8	13.5 (11-17)	0.45
IOP Mo 3	16.0±4.3	15 (8-22)	13.3±3.0	13 (10-17)	0.62
IOP Mo 6	15.9±4.3	15 (10-25)	13.0±2.2	12.5 (11-16)	0.35
Diabetes (-)					
BL BCVA	22.8±13.8	15 (12-44)	21.6±9.7	18 (12-42)	0.66
BCVA Mo 1	41.7±8.6	44 (25-55)	29.1±9.9	30 (18-48)	0.83
BCVA Mo 3	47.8±7.3	49 (32-57)	29.1±9.9	30 (18-48)	0.82
BCVA Mo 6	49.4±7.6	48 (35-62)	33.6±7.9	34.5 (22-49)	0.46
BL CRT	489.4±113.7	435 (377-740)	501.3±112.4	472 (388-732)	1.00
CRT Mo 1	316.1±59.9	296 (244-428)	367.6±52.1	358 (255-489)	0.04[a]
CRT Mo 3	259.6±15.7	254 (232-280)	354.6±44.1	356.5 (234-430)	0.001[a]
CRT Mo 6	240.6±8.5	243 (228-254)	348.4±43.9	352.5 (235-425)	0.001[a]
BL IOP	12.7±3.3	11 (9-17)	13.8±1.9	13.5 (11-17)	0.51
IOP Mo 1	14.7±3.2	16 (11-20)	13.4±1.6	13 (11-16)	0.71
IOP Mo 3	15.4±3.0	16 (12-21)	13.5±1.5	14 (11-16)	0.74
IOP Mo 6	14.0±2.3	14 (10-17)	13.8±1.6	13.5 (11-17)	0.32

IVD: Intravitreal dexamethasone; TN: Topical nepafenac; BL: Baseline; BCVA: Best corrected visual acuity; Mo: Month; CRT: Central retinal thickness; IOP: Intraocular pressure. [a]Statistically significant. [b]Student's *t* test or Mann-Whitney *U* test.

Table 4 The relation between prescence of complication during surgery and BCVA, CRT and IOP

Complications	IVD Group		TN Group		[b]*P*
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Complication (+)					
BL BCVA	23.67±3.6	22 (15-38)	22.0±13.4	14 (12-42)	1.00
BCVA Mo 1	38.50± 3.4	39 (25-49)	29.6±12.9	24 (18-48)	0.17
BCVA Mo 3	43.67±3.4	44 (32-56)	31.2±13.7	24 (18-48)	0.07
BCVA Mo 6	44.83±2.8	45 (35-56)	32.8±10.3	32 (23-49)	0.04[a]
BL CRT	562±52.3	577 (412-704)	512.8±103.6	514 (388-618)	0.36
CRT Mo 1	355.1±59.5	363 (285-438)	440±73.7	425 (352-556)	0.06
CRT Mo 3	347.5±85.4	333 (275-509)	430.4±73.7	417 (352-554)	0.06
CRT Mo 6	300.3±80.3	279 (235-450)	416.66±62.7	402 (341-514)	0.04[a]
BL IOP	12.7±2.4	11 (10-15)	14±2.3	15 (10-16)	0.34
IOP Mo 1	14.0±2.2	14 (11-16)	14.8±2.2	15 (11-17)	0.29
IOP Mo 3	15.3±4.6	15 (8-22)	14.0±2.5	14 (10-17)	0.96
IOP Mo 6	14.8±3.4	14 (10-20)	13.8±1.9	14 (11-16)	0.92
Complication (-)					
BL BCVA	25.67±3.8	20.5 (12-46)	20.4±7.7	18 (12-36)	0.80
BCVA Mo 1	43.42±1.7	44.5 (34-55)	28.3±8.1	30 (18-42)	0.80
BCVA Mo 3	49.50±1.3	49.0 (43-57)	28.6±8.1	30 (18-42)	0.62
BCVA Mo 6	51.58±1.6	50.5 (44-62)	33.0±6.2	34 (22-45)	0.96
BL CRT	502±33.8	457 (377-740)	496.6±108.2	456 (398-732)	0.87
CRT Mo 1	365.9±90.7	296 (244-550)	365.5±51.5	358 (255-489)	0.41
CRT Mo 3	283.9±46.6	265 (232-377)	350.9±40.8	358 (234-386)	0.001[a]
CRT Mo 6	251.9±22.5	246 (228-312)	345.0±40.5	355 (235-379)	0.001[a]
BL IOP	13.5±3.0	13.5 (9-18)	13.4±1.9	13 (11-17)	0.62
IOP Mo 1	15.6±3.2	16 (11-20)	12.9±1.3	13 (11-15)	0.06
IOP Mo 3	15.9±3.2	15 (12-22)	13.2±1.5	13 (11-16)	0.39
IOP Mo 6	15.0±3.6	14 (10-25)	13.5±1.6	13 (11-17)	0.65

IVD: Intravitreal dexamethasone; TN: Topical nepafenac; BL: Baseline; BCVA: Best corrected visual acuity; CRT: Central retinal thickness; IOP: Intraocular pressure; Mo: Month. [a]Statistically significant. [b]Student's *t* test or Mann-Whitney *U* test.

There was a statistically significant difference in the post treatment BCVA values both in the IVD group and in the TN group depending on the time (*P*=0.000, *P*=0.000 respectively; Friedman test). In IVD group there was a statistically significant difference between baseline BCVA and BCVA post treatment month 1, BCVA post treatment 1-3mo, BCVA post treatment 1-6mo and, BCVA post treatment 3-6mo (*P*=0.000, 0.000, 0.000, 0.005, respectively; Wilcoxon signed ranks test). In TN group there was a statistically significant difference between baseline BCVA and BCVA post treatment 1mo, BCVA post treatment 1-6mo and BCVA post treatment 3-6mo (*P*=0.000, 0.004, 0.008, respectively; Wilcoxon signed ranks test).

In IVD group there was not a statistically significant difference between baseline CRT and CRT post treatment 1mo (*P*=1.00, Wilcoxon signed ranks test), however in TN group there was a statistically significant difference between baseline CRT and CRT post treatment 1mo (*P*=0.0001; Wilcoxon signed ranks test). We found a statistically significant difference between post treatment CRT 1-3mo (in IVD group *P*=0.0001, in TN group *P*=0.002; Wilcoxon signed ranks test), and post treatment CRT 3-6mo in both groups (in IVD group *P*=0.002, in TN group *P*=0.0001, Wilcoxon signed ranks test; Figures 2 and 3).

In IVD group there was a statistically significant difference between the baseline IOP and IOP post treatment month 1 (*P*=0,001, Wilcoxon signed ranks test). We found no difference between the IOP post treatment 1-3mo (in IVD group *P*=0.312, in TN group *P*=1.0; Wilcoxon signed ranks test) and post treatment 3-6mo (in IVD group *P*=0.376, in TN group *P*=0.544, Wilcoxon signed ranks test) in both groups. There was a statistically significant difference in the post treatment CRT values both in the IVD group and in the TN group depending on the time (*P*=0.000, *P*=0.000 respectively, Friedman test). There was a statistically significant difference in the post treatment IOP values in IVD group depending on time however there was no significant difference in the post treatment IOP values in TN group (*P*=0.000, 0.701 respectively; Friedman test; Figures 4-6).

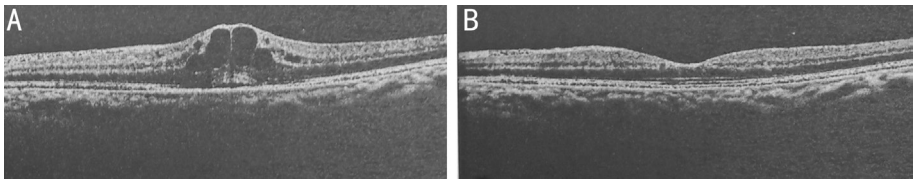

Figure 2 Dexamethasone implant treatment A: Baseline macular OCT image of a patient in IVD group; B: After 1 dexamethasone implant in 6mo.

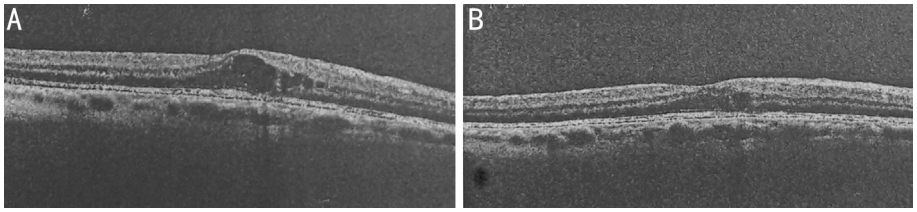

Figure 3 Topical Nepafenac treatment A: Baseline macular OCT image of a patient in TN group; B: OCT image of the patient after 6mo with nepafenac treatment**.**

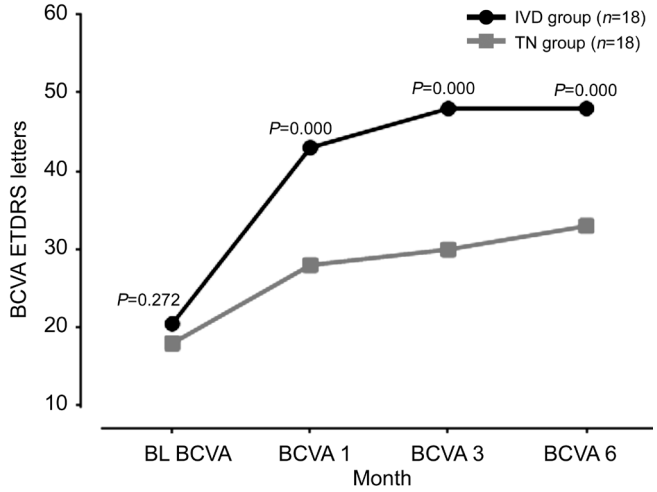

Figure 4 Changes in mean BCVA and *P* value of IVD and TN groups during each visit.

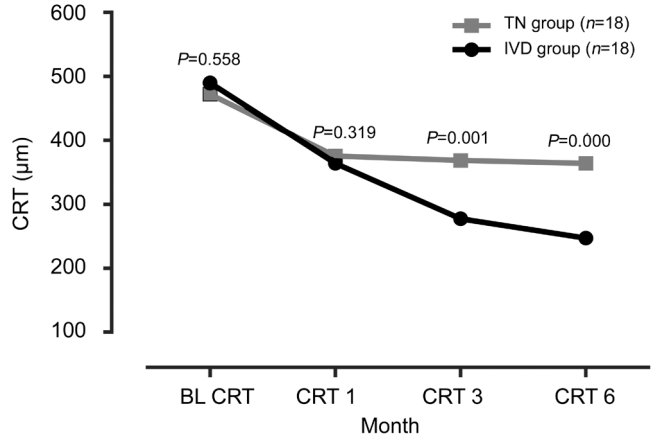

Figure 5 Changes in mean CRT and *P* value of IVD and TN groups during the follow-up period.

There was no correlation between age and the post-treatment BCVA month 6 and post-treatment CRT month 6 in IVD (r=0296, P=0.23, r=-0.171, P=0.49 respectively) and TN group (r=-0.02, P=0.93, r=0.27, P=0.27 respectively; Spearman's test). Baseline BCVA has a positive correlation with the post

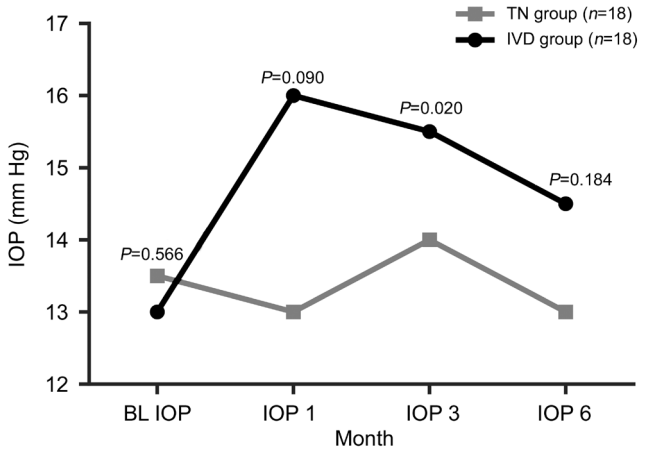

Figure 6 Changes in mean IOP and *P* value of IVD and TN groups during the follow-up period.

treatment BCVA month 6 in TN group (r=0.75, P=0.001; Spearman's test). There was no correlation between baseline BCVA and post treatment BCVA month 6 in IVD group (r=0.33, P=0.17; Spearman's test). There was no correlation between baseline CRT and post treatment CRT month 6 in both IVD and TN group (Tables 5 and 6).

Three patients with increased IOP (≥7 mm Hg increase from average baseline IOP) were managed successfully with standard topical medications; none required surgery. Five of the patients required ≤3 injection. Three of the patients had persistant CME and required re-injection, two of the patients had recurrent CME. Six patients had mild to moderate superficial punctate keratitis in TN group. No other systemic or local complication occured in IVD and TN group after the treatments.

DISCUSSION

In the present study, nepafenac ophthalmic solution 0.1% and dexamethasone intravitreal implant was used in treating pseudophakic cystoid macula edema. The dexamethasone group had higher visual acuity in all post treatment visits.

Table 5 Correlation analysis of age, baseline BCVA, final BCVA at month 6 and IOP in IVD group

Parameters (*r*, *P*)	Gender	BL BCVA	BCVA Mo 6	BL CRT	CRT Mo 6	BL IOP	IOP Mo 6
Age	0.435, 0.071	0.296, 0.233	0.171, 0.498	-0.148, 0.572	-0.171, 0.497	-0.334, 0.176	-0.232, 0.354
Gender		-0.011, 0.964	-0.376, 0.124	-0.102, 0.686	-0.341, 0.166	-0.438, 0.069	-0.092, 0.718
BL BCVA			0.338, 0.170	0.043, 0.867	0.0161, 0.522	-0.055, 0.828	-0.016, 0.949
BCVA Mo 6				-0.073, 0.775	-0.179, 0.477	0.025, 0.921	-0.159, 0.528
BL CRT					0.444, 0.065	-0.315, 0.203	0.036, 0.886
CRT Mo 6						0.045, 0.859	0.168, 0.504
BL IOP							0.664, 0.003[a]

BL: Baseline; BCVA: Best corrected visual acuity; Mo: Month; CRT: Central retinal thickness; IOP: Intraocular pressure. Spearman's correlation. [a]Statistically significant.

Table 6 Correlation analysis of age, baseline BCVA, final BCVA at month 6 and IOP in TN group

Parameters (*r*, *P*)	Gender	BL BCVA	BCVA Mo 6	BL CRT	CRT Mo 6	BL IOP	IOP Mo 6
Age	0.259, 0.299	-0.223, 0.375	-0.020, 0.936	0.247, 0.324	0.275, 0.270	0.038, 0.882	-0.220, 0.381
Gender		0.109, 0.665	-0.282, 0257	-0.226, 0.366	-0.151, 0.550	-0.044, 0.863	0.011, 0.965
BL BCVA			0.757, 0.0001[a]	-0.522, 0.026[a]	-0.386, 0.114	0.286, 0.250	0.104, 0.681
BCVA Mo 6				-0.363, 0.139	-0.263, 0.292	-0.031, 0.902	-0.140, 0.579
BL CRT					0.119, 0.639	0.126, 0.619	0.052, 0.838
CRT Mo 6						-0.113, 0.654	-0.051, 0.842
BL IOP							0.754, 0.0001[a]

Spearman's correlation. BL: Baseline; BCVA: Best corrected visual acuity; Mo: Month, CRT: Central retinal thickness; IOP: Intraocular pressure. [a]Statistically significant.

IVD group also had significantly lower CRT in post treatment month 3 and month 6. However, IVD group had no significant different IOP rates than TN group in post treatment month 3 and month 6.

IGS was first reported in 1953 as CME after cataract extraction[1,10]. Description of the disease supported with angiographic findings by Gass and Norton. Clinical findings of IGS (poor visual acuity and metamorphopsia) is seen in 0.1%-2% patients and it is detectable *via* OCT in 4%-11% patients after modern cataract surgery[27-32]. Although spontenous healing of the CME seen in IGS, it could be resistant and lead to irreversible injury to the macula and cause poor visual acuity in some of the patients[3,7,10].

Although IGS usually described as postsurgical CME, Bellocq *et al*[18] considered that IGS (macular edema after phacoemulsification surgery) and other postsurgical macular edema (vitrectomy for retinal detachment or epiretinal membrane peeling) could be two different entities. Because they reported a significant functional and anatomical improvement in IGS poor prognosis in other postsurgical macular edema have been associated with underlying macular disease[18]. Therefore in the present study we included the patients who have only phacoemulsification surgery to eliminate the macular and vitreomacular interface diseases.

The pathogenesis of IGS was reported to be multifactorial but inlammation is suggested as the major cause of IGS[4,10]. The releasing of multiple factors (histamin, prostaglandins and seratonin, bradykinin, acetylcholine, small peptides) induce inflammation and cause breakdown of the blood-retinal barrier and lead to macular edema[10,13,33]. Altough the major underlying cause is well known, there is no consensus on standart treatment protocol in IGS. The most common treatment is oral acetazolamide and topical NSAIDs combination[10]. Systemic acetazolamide had multiple adverse effects such as cramps, renal colic, asthenia and tingling. Multiple studies reported that topical NSAIDs speed the recovery of blood-aqueous barrier and decrease inflammation after cataract surgery[13,34-37].

Nepafenac is acyclooxygenase inhibitor. It has been shown to have 6 times faster corneal permeability than diclofenac[38]. Animal studies and clinical studies emphasized that topical NSAIDs such as nepafenac and bromfenac had increased penetration to the posterior segment[39-42]. Kapin *et al*[22] demonstrated that TN passes through the posterior segment and it decreases vitreous protein and PGE2 concentrations. In a recent article[23], none of the other topical NSAIDs have inhibited inflammation to the same degree. Such higher penetration to the posterior segment provides utilization of TN in IGS. Warren *et al*[43] and Ghanbari *et al*[44] suggested that TN and bromfenac could be more effective in combination with intravitreal corticosteroids and anti-VEGFs for chronic pseudophakic CME. A recently published prospective study showing the superiority of nepafenac comparison with

subtenon steroids in controlling pseudophakic CME[28]. In contrast, the present study showed that IVD was more effective than TN in previously untreated IGS.

A number of studies have reported conflicting outcomes of using bevacizumab in IGS. Barone *et al*[3] reported functional and anatomical improvement in a limited patient group. Spitzer *et al*[45] reported that postoperative pseudophakic CME will not benefit from intravitreal bevacizumab.

Ranibizumab is the other anti-VEGF treatment option for IGS. Case series have suggested its safety and efficacy for the treatment of pseudophakic CME[46-47]. Aflibercept was found to be effective traetment in a case report but the patient required multiple injections for cure[48].

The positive effects of intravitreal triamcinolone were demonstrated, however repeated intravitreal injections were required[49-50]. Chin *et al*[51] reported that triamcinolone acetonide reduces faster in vitrectomized eyes after injection. However, it is suggested in multiple studies that dexamethasone implant is effective in vitrectomized eyes[5,52]. It is suggested that the patients with pre-existing glaucoma and steroid response are more likely to have severe increased IOP after intravitreal triamcinolone acetonide[53]. On the other hand recent study demonstrated that IVD implant has an admissible safety profile even in eyes with glaucoma and the eyes which are receiving treatment for ocular hypertension[54]. Even if increased IOP occured, it could be well controlled by a strict monitorization and topical treatment[55-56]. In the present study only three patient received topical treatment for IOP≤25 mm Hg and none of the patients required filtering surgery. As mentioned in multiple studies this result may be related with the sustained release mechanism of the implant which provides more controlled drug delivery to cause lower side effects[52,57]. Infliximab which is an anti tumor necrosis factor (TNF) α agent had positive effect in IGS but side effects such as retinal toxicity is reported[15,56].

In a recent study, TN has a significant narrowing effect on retinal arteriolar diameter in eyes with nonproliferative diabetic retinopathy[58]. Studies using retinal vessel caliber showed narrowing after a single-intravitreal triamcinolone acetonide application[59-60]. The injection of ranibizumab and bevacizumab also had constrictive effects on retinal blood vessel diameter[61]. The effect of nepafenac and its product, amfenac, involves retinal angiogenesis, inhibiting the effects of VEGF by reducing vasodilatation[62]. TN might have constrictor effects on the retinal artery trunk and may decrease CRT in eyes with diabetic macula edema[58].

In the current study, topical treatment group receive their treatment for 3mo. All the patients were compliant in using the TN treatment. Pollack *et al*[63] reported a 90d nepafenac treatment prevented macular edema after cataract surgery in patients with diabetic retinopathy and they demonstrated no safety issues within the study group.

Dexamethasone implant is the second step treatment for IGS. EPISODIC-2 study reported anatomical and functional positive effects in IGS. Bellocq *et al*[16] reported the predictive factors of functional effectiveness and they reported the patients who had at least one post surgical macular edema risk factor as capsular rupture, uveitis, retinal vein occlusion, diabetes, epiretinal membrane are more tend to develop IGS. Age, history of systemic or topical treatments, time to the initial injection were not predictive factors. Initial visual acuity was demonstrated as a predictive factor in EPISODIC-2 study[16]. In this study baseline visual acuity was correlated with final visual acuity in TN group, however there was no significant correlation between baseline visual acuity and final visual acuity at 6mo in IVD group. This outcome shows that the dexamethasone implant is superior to the long term nepafenac treatment in any case. Age was not correlated with final BCVA and CRT results in both group.

Mayer *et al*[10] reported in their prospective nonrandomized study that BCVA increased from 30.2±4.3 letters to 50.4±4.9 letters at 12mo with IVD in IGS. In EPISODIC-2 study naive status was demonstrated as a predictive factor related with lower risk of recurrence[16]. We included the patients who had naive status which means the patients had no treatment (systemic or topical) before for IGS. In our study the patients baseline BCVA was not different in IVD and TN groups. Visual acuity was improved at the end of the 6mo in both groups. CRT is determining the anatomical effectiveness[16]. Mayer *et al*[10] showed decreased foveal thickness from 520.8 μm to 232.8 μm at month 12 and in their study, 9 patients had recurrence after 3mo and needed re-treatment with IVD. Multiple previous studies have reported no adverse events related to IVD except the increased IOP which was controlled with only medical treatment[63-65]. In the present study we also found similar results with the literature in IVD group at post-treatment month 6 in terms of BCVA, CRT and adverse events.

Limitations of the present study are lack of control group and relatively short follow-up period. However to the best of our knowledge this study is the first study that comparing IVD injection with TN for treatment of IGS.

In conclusion, both TN and IVD found to be safe and effective in reducing macula edema and increasing visual acuity in previously untreated IGS patients. However according to the 6-month study results, IVD has been shown to be more effective method than TN in terms of clinical outcomes with very low complication rates. Currently, there is no standart treatment modality for IGS. We believe that our study will help to indicate a standart treatment protocol for IGS. However,

further prospective large sample size clinical studies are needed to reveal the best treatment algorithm in IGS.

ACKNOWLEDGEMENTS

Conflicts of Interest: Guclu H, None; **Pelitli Gurlu V,** None.

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