

Triamcinolone acetonide versus bevacizumab in treatment of neovascular age related macular degeneration

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Abstract

Purpose: To evaluate the effects of intravitreal triamcinolone acetonide (IVTA) and bevacizumab injection on visual acuity, electrophysiologic response and foveal thickness of patients with neovascular age related macular degeneration (CNVs).

Methods: The study included three groups. **Group 1** included fifty eyes (50 patients) with progressive occult or predominately occult subfoveal choroidal neovascularization treated with intravitreal injection of triamcinolone acetonide. **Group 2** included another fifty eyes (50 patients) with progressive macular degeneration of occult or predominately occult subfoveal choroidal neovascularization treated with intravitreal bevacizumab. The patients are followed up every month by biomicroscopy, optical coherence tomography (OCT), photography, fluorescein angiography, Ganzfeld full field electroretinogram (F-ERG), multifocal electroretinogram (MF-ERG) and determination of best corrected visual acuity (BCVA). **Group 3** (control group) included 50 eyes (50 patients) with neovascular age related macular degeneration who did not receive treatment for macular degeneration.

Results: Apparent improvement of morphological and functional characteristics were observed in 40/50 eyes after one month after first injection in group 1, and in 45/50 in group 2. The mean \pm SD visual acuity improved significantly ($p=0.003$) from $(0.12 \pm 0.19$ to $0.35 \pm 0.25)$ in group 1 and from 0.13 ± 0.2 to 0.40 ± 0.28 in group 2. Visual acuity was highest 1–2 month after intravitreal injection. Central macular thickness decreased from $325 \pm 50 \mu\text{m}$ to $275 \pm 40 \mu\text{m}$ at one month after first injection in group 1 and decreased from $320 \pm 53 \mu\text{m}$ to $255 \pm 41 \mu\text{m}$ in group 2 while in control group, there is statistically insignificant increase of the central thickness. The average amplitude of central macular ring of MFERG was improved from $25.5 \pm 5.8 \text{ nv}$ to $31 \pm 8.9 \text{ nv}$ in group 1 and from $26.6 \pm 6.1 \text{ nv}$ to $33 \pm 9.9 \text{ nv}$ in group 2, while no changes in F-ERG response. Intraocular pressure increased significantly ($p=0.009$) from $14 \pm 2.5 \text{ mmHg}$ to maximal $23 \pm 7.6 \text{ mmHg}$ in group 1. Intraocular pressure decreased significantly ($p=0.006$) to $16 \pm 2 \text{ mmHg}$ at the end of follow up while in group 2, there was no increase in intraocular pressure. No other serious drug related adverse events (endophthalmitis, retinal detachment, cataract or proliferative vitreoretinopathy) observed during the course of the study in groups 1,2. In control group, visual acuity, central foveal thickness and function did not change significantly during follow up period ($p=0.6$, $p=0.4$, $p=0.1$ respectively).

Conclusion: Intravitreal injection of triamcinolone acetonide may transiently stabilize or improve visual acuity in some patients with progressive neovascular age related macular degeneration. Intravitreal injection of bevacizumab led to a more visual improvement than IVTA in treatment CNVs. MFERG had an important role in describing the effect of treatment on retinal function. Intravitreal injection improved MFERG macular function responses with little insignificant change in F-ERG.

Introduction

None of the current treatment resulted in decreasing the loss of vision on the central 35° of the retina. Neovascular age related macular degeneration is important cause of irreversible severe decrease of vision and of legal blindness in the world [1]. Triamcinolone acetonide is one of the first drugs used for the management of age related choroidal neovascularization [2].

The effects of triamcinolone acetonide were stabilization of blood retinal barrier through decreasing the permeability and inflammation. Also, triamcinolone acetonide improves the diffusion, inhibits vascular endothelial growth factor and has antiangiogenic and antifibrotic properties [3]. There is evidence that vascular endothelial growth factor (VEGF) has a potential role in ocular neovascularization and the pathogenesis of AMD [4]. Bevacizumab is a recombinant humanized monoclonal antibody to human vascular endothelium growth factor (VEGF) that binds to VEGF and blocks it from binding to its receptors [5].

Electrophysiological investigation of neovascular macular degeneration provides information of the safety of treatment. MF-ERG represents the photopic retinal response to a rapidly changing

stimulus on the central 35° of the retina [6]. Neovascular age related macular degeneration affects the central amplitude which is altered in the presence of subretinal fluid [7]. MF-ERG is used to assess localized effect after treatment.

Full field ERG response reflects general retinal electrical response. Because the macula is only a small part of the retinal surface, changes in macular function even in severe neovascular age related macular degeneration are not reflected as F-ERG changes. But, global worsening of F-ERG response indicates retinal toxicity, so, F-ERG technique gives important informations of retinal toxicity with treatment.

The aim of the study was to evaluate and compare the effects of

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triamcinolone acetonide and bevacizumab on vision and foveal thickness in neovascular age related macular degeneration patients and to study the effects of triamcinolone acetonide and bevacizumab on the electrophysiologic response.

Subjects and methods

This study was carried out on patients attending the Outpatient's Clinic of Mansoura Ophthalmic Center during the period from February 2013 to December 2015. This study included one hundred and fifty patients (150) with neovascular age related macular degeneration.

The patients were divided into three groups: **Group 1** included patients with progressive occult or predominately occult subfoveal choroidal neovascularization who received intravitreal injection of triamcinolone acetonide, **group 2** included patients with occult or predominately occult subfoveal choroidal neovascularization who received intravitreal injection of bevacizumab and **group 3 (control group)** included patients with neovascular age related macular degeneration but did not receive intravitreal injection for this disease. The reason for including these patients to control group was that they did not want an intravitreal injection and they refused injection after explanation the importance of injection.

Patients were thoroughly informed about the injection procedure, postoperative results and possible complications and written consents were taken from all patients. All patients were carried out in accordance with the tenets of the Declaration of Helsinki (1989) of the world medical association. The study was approved by Mansoura University Hospital trust ethics committee.

Exclusion criteria: included patients with classic type of neovascular age related macular degeneration, glaucoma, cataract surgery, retinal or vitreoretinal surgery. Sub-retinal hemorrhage should not have extended beyond the temporal vascular arcade. All patients were to be re-examined at the first postoperative day, in first postoperative week, then at monthly intervals for 6 months. A repeated injection was performed if there were signs of choroidal neovascularization (CNV) activity. Signs of CNVs activity included intra-retinal and sub-retinal fluid accumulation, new intra-retinal and sub-retinal hemorrhage and CNVs growth. The presence of signs of CNV activity and decreasing visual acuity were warranted to re-treatment.

At baseline of the study and at monthly intervals, all patients underwent a routine ophthalmological examination including visual acuity measurement using Snellen charts (Snellen acuities were converted to logarithm of the minimum angle of resolution (Log MAR), slit lamp biomicroscopy, Goldman applanation tonometry, ophthalmology (direct and indirect), optical coherence tomography (OCT), electroretinogram (ERG).

Fluorescein angiography was done using Topcon Corporation 2000, TRC, 50IX, Japan. Fluorescein angiography performed for all patients (at baseline, 3months, 6 months) showed neovascular age related macular degeneration. The membrane was occult.

Optical coherence tomography (OCT)

OCT was performed with Topcon, 3 dimensional OCT-1000 (Topcon Corporation, Tokyo, Japan). Internal fixation (subject fixated with the eye being tested) was chosen because of better reproducibility. It scanned a cube of 6×6 mm length at resolution of 512×128 with fixation at the macula. A Measurement of macular thickness was done using the fast scan. Central macular thickness of a circular 1-mm radius

area around the fovea was calculated. The print out included thickness map and the cross-sectional scan that shows morphological changes before and after intravitreal injection.

ERG

Full field ERG and MF-ERG were recorded using Roland Consult, Brandenburg, and Germany system Roland. ERG was done according to ISCEV standard [8]. After topical corneal anesthesia (Benoxinate hydrochloride 4%), Dawson, Trick and Iitzkow (DTL) electrode (positive electrode) was placed just contact with corneal limbus, ground electrode was installed on the forehead and negative electrode was placed near orbital rim temporary. The recording was monocular and contra-lateral eye was occluded with light pressure to suppress blinking.

Full field ERG

The test was started and recorded in 5 steps: scotopic rod response, scotopic combined response, oscillatory potential then light adaptation for 10 minute then photopic cone response and flicker response recording.

MF-ERG

Patients were positioned 30 cm from the stimulus monitor. Stimulus clarity was adjusted by over-refraction. White hexagons had a luminance of 185 to 200 cd/m² and dark frames were 1 to 2 cd/m² resulting in local contrasts of 98% to 99%. Each hexagon was temporally modulated between light and dark according to binary m-squence, [9,10] at any time, approximately 50% of the stimulus are white and 50% are black. Patients fixated a spot in the center of the stimulus. To improve fixation stability, the sessions were divided into 30 second periods with brief rest periods. The results of two 8-minute recordings were averaged to improve the signal to noise ratio.

Intravitreal injection of triamcinolone acetonide (IVTA)

All patients in group1 received Intravitreal injection of 25 mg of crystalline triamcinolone acetonide (Volona A; Bristol-Myers-Squibb, Munich, Germany, containing 40 mg of triamcinolone acetonide in 1 ml). The injection of 25 mg of crystalline triamcinolone acetonide was performed using sharp 27-gauge needle in inferio-temporal quadrant 3.5 mm from limbus (The crystals were concentrate before injection and the triamcinolone was washed and vehicle removed). Then antibiotic ointment was applied.

Intravitreal injection of bevacizumab

All patients in group2 received Intravitreal injection of 1.25 mg/0.05 of bevacizumab. A total of 0.05 ml Bevacizumab was injected into vitrous cavity 3.5 mm from limbus in inferotemporal quadrant using 30 gauge needle. Postoperative antibiotics were used and a light patch was placed. The eye patch is removed the next day.

Statistical analysis

Statistical analysis was performed using software (SPSS WIN Version11.5; SPSS Inc, Chicago). Non parametric Wilcoxon test was applied for comparison. Spearman rank test and linear correlation analysis were used in order to evaluate the correlation with changes of MFERG, changes of OCT and best correct visual acuity. Significance was set at p=0.05 (2-tailed) for all statistical tests

Results

The study included one hundred and fifty (150) patients (one hundred and fifty eyes). The patients were divided into three groups: **Group 1** included fifty eyes (50) of fifty patients (50) with progressive occult or predominately occult subfoveal choroidal neovascularization who received one or more than one of intravitreal injection of 25 mg of triamcinolone acetonide, Mean age was 60 ± 8.6 years, ranged (55-75 years old). **Group 2** included another fifty eyes (50) of fifty patients with progressive occult or predominately occult subfoveal choroidal neovascularization) who received one or more than one of intravitreal injection of **1.25 mg/0.05 ml** of bevacizumab. The Mean age was 62 ± 6.9 years, ranged (58-74 years).

Group 3 (Control group) included fifty eyes (50) of fifty patients (50) (with neovascular age related macular but did not receive intravitreal injection of triamcinolone acetonide for this disease after explanation the importance of treatment for visual acuity and progression of CNVs. The Mean age was 61 ± 7.9 years, ranged (58-74 years). There was no significant difference between groups. In group 1, Ten (10) patients received a second intravitreal injection of 25mg of triamcinolone acetonide.

According to fluorescein angiography, group 1 were further divided into subgroups with occult or mostly (>50%) occult without hemorrhage (n=40, 80%), subgroup with sub-retinal hemorrhage (n=7,14%) and subgroups with retinal pigment detachment (n=4, 8%). While in group 2, occult CNV without haemorrhage was presented in 35 eyes (70%), with haemorrhage was present in 10 eyes (20%) and retinal pigment detachment was found in 5 eyes (10%) (Table 1).

All three subgroups did not vary significantly ($p=0.2$) at baseline. In control group, all subjects were had occult CNV without subretinal hemorrhage.

Visual acuity (VA)

All patients complained of decreased vision which were diagnosed by ophthalmologic examination within three months before IVTA. The mean VA at baseline in group 1, group 2 and control group (0.12 ± 0.19 , 0.13 ± 0.05 and 0.14 ± 0.22) respectively. Range from finger counting to 0.3 in group 1, from finger count to 0.32 in group 2 and from finger counting to 0.5 in control group.

For the **group 1 and 2**, mean VA increased significantly ($p=0.003$)

after first injection to maximum 0.35 ± 0.25 during the follow up period (Table 2). The maximum postoperative VA was detected 1-2 months after the injection. The increase in VA was statistically significant in 1st month ($p=0.003$) and 2nd month ($p=0.004$) after the injection. The preoperative visual acuity and postoperative visual acuity achieved at the end of the follow up period did not differ significantly ($p=0.2$) in group 1 while in group 2, there is statistically significant difference between VA at the baseline and VA at the end. In group 1, Visual acuity significantly decreased towards the end of the follow up period, parallel to a disappearance of triamcinolone acetate crystals out of vitreous cavity. In group 1, after 1 month, 40 eyes (80%) gained in visual acuity and 4 eyes (8%) lost visual acuity. Visual acuity was unchanged for 6 eyes (12%). While, in group 2, 45 eyes (90%) gained in visual acuity. There was no significant correlation between postoperative visual acuity and postoperative change in visual acuity ($p=0.6$). For three subgroups, there were significant difference in gain in visual acuity ($p=0.04$). Ten eyes received second injection three months after first injection, visual acuity increased in eight eyes about one month after the re-injection and declined again after about 3 month in group 1 while in group 2, fifteen eyes received second injection after 2 months, and fourteen eyes of fifteen improved after reinjection.

OCT

For group 1, Central subfield OCT thickness was $325 \pm 50 \mu\text{m}$ at baseline. The central subfield OCT thickness decreased to $280 \pm 55 \mu\text{m}$ at one week and $275 \pm 40 \mu\text{m}$ at one month (Table 3, Figure 1). In group 2, central subfield OCT thickness was $320 \pm 53 \mu\text{m}$ at baseline. The Central subfield OCT thickness decreased to $270 \pm 40 \mu\text{m}$ at one week and $255 \pm 41 \mu\text{m}$ at one month

ERG

F-ERG data is presented in (Table 4). No significant worsening of F-ERG response was observed during follow up period in the three groups. Most of the values were within the limits normal variation which did not exceed 20% of baseline value. Grover et al said that up to 50% change in amplitude for voltage is considered normal variation [11].

For most subjects retested one month with F-ERG, the amplitude returned to baseline after a slight decrease in scotopic and photopic amplitudes at one week. For all subjects who was received either

Table 1. Evaluation of lesion element.

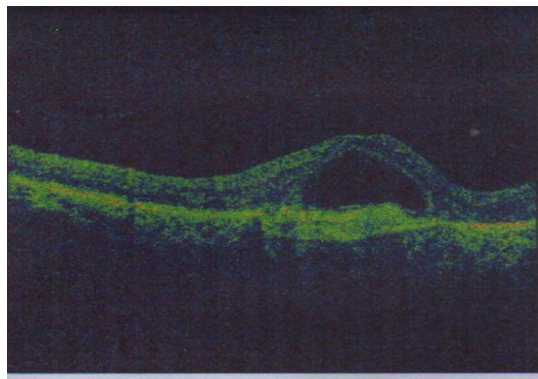
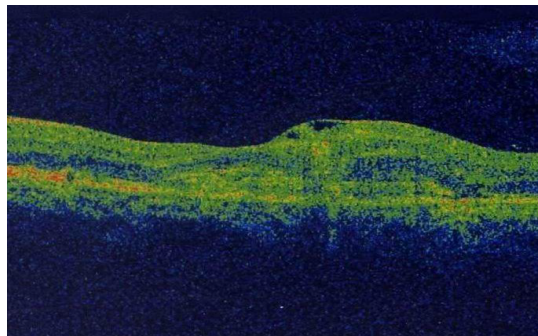
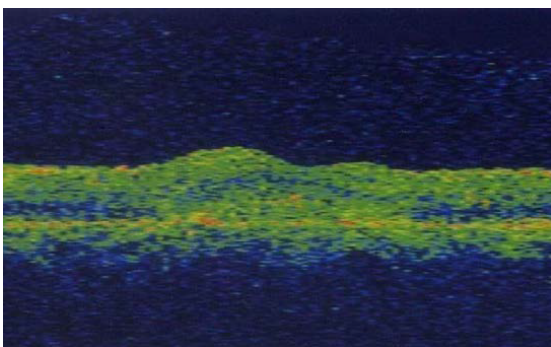
CNV lesion element	Group 1			Unchanged	Baseline	Group 2		
	Baseline	Decreased	Increased			Decreased	Increased	Unchanged
CNV	50	40(80%)	5(10%)	5(10%)	50	44(88%)	1(2%)	5 (10 %)
FA leakage	50	40	1	9	50	50	-	-
RPED	4	3	-	1	5	3	--	2
Subretinal Hge	7	-	-	3	10	8	-	2
Subretinal Fluid	30	20	2	8	25	23	1	1

Table 2. Visual acuity among groups.

Time	Group 1	Group 2	Group 3	P
At baseline	0.12 ± 0.19	0.13 ± 0.05	0.15 ± 0.22	0.2
1 week after first IVTA	0.17 ± 0.16	0.18 ± 0.22	0.15 ± 0.10	0.01
1 month	0.35 ± 0.25	0.40 ± 0.28	0.15 ± 0.19	0.01
2 month	0.33 ± 0.19	0.38 ± 0.21	0.15 ± 0.18	0.01
3 month	0.25 ± 0.15	0.32 ± 0.19	0.14 ± 0.17	0.01
4 month	0.20 ± 0.15	0.26 ± 0.1	0.14 ± 0.15	0.03
5 month	0.17 ± 0.19	0.22 ± 0.09	0.13 ± 0.12	0.05
6 month	0.16 ± 0.12	0.20 ± 0.1	0.12 ± 0.11	0.04

Table 3. OCT Findings of central macular thickness in μm .

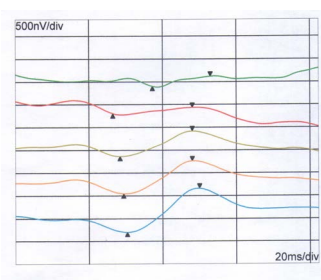
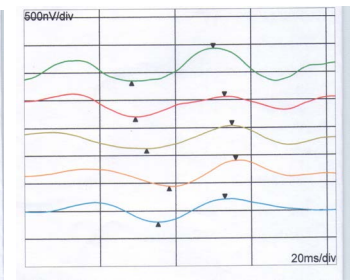
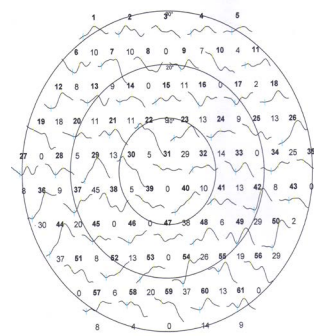
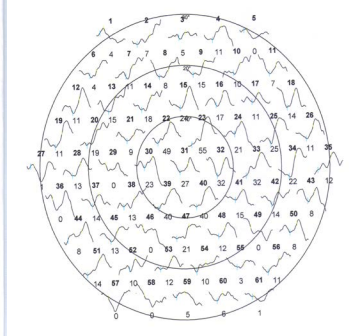
OCT (central 1mm thickness)	Group 1 After First injection	Group 2	Control group	P
Pre- injection	325 \pm 50	320 \pm 53	315 \pm 25	0.8
1 week	280 \pm 55	270 \pm 40	317 \pm 27	0.01
1 month	275 \pm 40	255 \pm 41	316 \pm 29	0.001
2 month	274 \pm 45	240 \pm 39	317 \pm 26	0.01
3 month	274 \pm 40	240 \pm 40	319 \pm 26	0.01
4 month	290 \pm 50	250 \pm 30	320 \pm 30	0.01
5 month	310 \pm 55	260 \pm 50	325 \pm 29	0.06
6 month	315 \pm 49	266 \pm 55	325 \pm 25	0.02

a**b.****c****Figure 1.** CNVs before and after IV injection in group 1. a. CNVs with PED before injection. b. CNVs after 1month of injection. c. CNVs after 2month of injection.

trimacinolone acetate or bevacizumab had an essentially stable F-ERG.

MFERG

In most cases, there was improvement at one week, one month and two months of IVTA, then return to baseline value at 3 months (Table 5, Figures

a**b****c****d**

2 and 3). In group 2, there is increase in amplitude and decrease in latency reach maximum after 2 months.

Intraocular complications

In group 1, IOP increased significantly ($p=0.005$) from 14.5 ± 2.5 mmHg at baseline of the study to a mean maximal value of 20 ± 5.6 mmHg again decreased significantly to 16.5 mmHg at 6 months after IVTA at $p=0.001$. IOP measurements at the end were slightly and significantly ($P=0.05$) higher than pressure measurements at baseline of the study. During the study, IOP was higher than 22 mmHg in 30 eyes (60%).

In those patients, IOP normalized by topical anti-glaucomatous drugs. Optic nerve damage was not detected. While in group 2, there was no case with increase in intraocular pressure. With respect to other complication of IVTA, none of the patients had cortisone crystals settled on the macular region. The crystals were pre-retinally at 6 o'clock position and did not interfere with visual acuity.

Three cases of cataract were detected in group 1, while no case of cataract was observed in case 2. No postoperative infectious endophthalmitis, rhegmatogenous retinal detachment or proliferative vitreo-retinopathy were detected in groups 1 and 2.

Discussion

While, classic type of subfoveal neovascularization, photodynamic therapy with verteporfin stabilizes or increases visual acuity. Photodynamic therapy for occult subfoveal neovascularization is unsuccessful [12]. Steroids have anti-inflammatory, antiangiogenic, antifibrotic and antipermeability properties, which contribute to stabilization of the blood–retina barrier [13].

Penfold *et al.* [14,15], Challa *et al.* [16] injected triamcinolone intravitreal to treat exudative age related macular degeneration. Additionally, Danis *et al.* [17] detected a beneficial effect of triamcinolone in the study group compared with control group. Also, Ranson *et al.* [18] treated recurring subfoveal choroidal neovascularization after

Table 4. Ganzfeld ERG in group 1 and group 2.

ERG in group1	baseline	1 week	1 month	2 month	3 month	4 month	5 month	6 month
Scotopic								
Amplitude b-wave(μ v)	40 \pm 9.9	37 \pm 8.8	40 \pm 9.9	40.9 \pm 9.9	40.3 \pm 9.9	40.5 \pm 9.9	40 \pm 9.5	41 \pm 9.7
Latency b-wave(ms)	67 \pm 3.4	69 \pm 4.5	67 \pm 3.4	67 \pm 3.4	67 \pm 3.4	67 \pm 3.4	67 \pm 3.4	67 \pm 3.4
Combined								
b -amplitude(μ v)	105 \pm 37.9	100 \pm 38	105 \pm 37.9	105 \pm 37.9	105 \pm 37.9	105 \pm 37.9	105 \pm 37.9	105 \pm 37.9
b-latency(ms)	75 \pm 4.9	77 \pm 5	75 \pm 4.92	75 \pm 4.93	75 \pm 4.99	75 \pm 4.94	75 \pm 4.95	75 \pm 4.9
Oscillatory potential								
amplitude(μ v)	12 \pm 5.5	10 \pm 5.6	12.8 \pm 5.5	12.89 \pm 5.5	12 \pm 5.95	12 \pm 5.75	12 \pm 5.5	12 \pm 5.5
latency(ms)	35 \pm 4.5	37 \pm 5.5	35.9 \pm 4.5	35.77 \pm 4.57	36.5 \pm 4.5	37.75 \pm 4.5	36.95 \pm 4.5	35 \pm 4.5
Flicker								
Amplitude(μ v)	35 \pm 8.1	33 \pm 6.1	35.9 \pm 8.1	35.9 \pm 8.91	35 \pm 8.71	36.5 \pm 8.1	36.85 \pm 8.1	35 \pm 8.1
Latency(ms)	72 \pm 2.5	75 \pm 2.5	72 \pm 2.51	72 \pm 2	72.6 \pm 2.5	72.9 \pm 2.5	72 \pm 2.95	72 \pm 2.5
Photopic								
Amplitude(μ v)	25 \pm 6.5	23 \pm 3.9	25.9 \pm 6.5	25.8 \pm 6.5	25 \pm 5	25.1 \pm 6	25 \pm 6	25 \pm 6.5
Latency(ms)	37 \pm 4.5	38 \pm 4.9	35 \pm 4.3	37.1 \pm 4.5	37.7 \pm 4.5	36.7 \pm 4.5	36.87 \pm 4.5	37 \pm 4.5

ERG in group 2	baseline	1 week	1 month	2 month	3 month	4 month	5 month	6 month
Scotopic								
Amplitude b-wave(μ v)	41 \pm 8.9	36 \pm 8.8	44 \pm 9.1	44.9 \pm 9.9	40.3 \pm 9.9	40.5 \pm 9.9	40 \pm 9.5	41 \pm 9.7
Latency b-wave(ms)	66 \pm 3.4	68 \pm 4.2	65 \pm 3.1	65 \pm 3.4	67 \pm 3.4	67 \pm 3.4	67 \pm 3.4	67 \pm 3.4
Combined								
b -amplitude(μ v)	106 \pm 36.9	96 \pm 30	115 \pm 34.9	115 \pm 37.9	110 \pm 37.9	109 \pm 37.9	108 \pm 37.9	109 \pm 37.9
b-latency(ms)	74 \pm 4.5	74 \pm 3.5	72 \pm 4.5	72.7 \pm 4.93	72.5 \pm 4.99	73.5 \pm 4.94	73 \pm 4.95	73 \pm 4.9
Oscillatory potential								
amplitude(μ v)	11 \pm 5.2	12 \pm 5.6	13.8 \pm 5.9	13.89 \pm 5.5	13.2 \pm 5.95	12.9 \pm 5.75	13.2 \pm 5.5	12.8 \pm 5.5
latency(ms)	33 \pm 4.55	33 \pm 5.5	32.9 \pm 4.5	32.77 \pm 4.57	33.5 \pm 4.5	33.75 \pm 4.5	34.95 \pm 4.5	34.5 \pm 4.5
Flicker								
Amplitude(μ v)	32 \pm 7.1	36 \pm 6.8	35.9 \pm 8.1	35.9 \pm 8.91	35 \pm 8.71	36.5 \pm 8.1	36.85 \pm 8.1	35 \pm 8.1
Latency(ms)	70 \pm 2.5	69 \pm 2.3	65 \pm 2.3	65.8 \pm 2	70.6 \pm 2.5	70.9 \pm 2.5	71 \pm 2.95	70 \pm 2.5
Photopic								
Amplitude(μ v)	23 \pm 6.5	27 \pm 3.9	29.9 \pm 6.5	25.8 \pm 6.5	26 \pm 5	25.61 \pm 6	26.5 \pm 6	26.5 \pm 6.5
Latency(ms)	38 \pm 4.5	33 \pm 4.9	32 \pm 4.3	33.1 \pm 4.5	33.7 \pm 4.5	34.67 \pm 4.5	34.78 \pm 4.5	34.7 \pm 4.5

Table 5: MFERG among groups over central region.

Duration	Group1		Group2		Group3		P
	Amplitude	latency	Amplitude	Latency	Amplitude	latency	
Baseline	25.5 \pm 5.8	66 \pm 6.7	26.6 \pm 6.1	66.5 \pm 4.9	26 \pm 5.9	66.5 \pm 5.9	0.1
1 week	26 \pm 6.8	63 \pm 4.9	30 \pm 6.5	62.8 \pm 5.9	26.1 \pm 6.2	66.3 \pm 6.1	0.1
1 month	31 \pm 8.9	59 \pm 5.6	33 \pm 9.9	55.1 \pm 4.5	26.5 \pm 6.1	65.9 \pm 6.5	0.001
2 month	35 \pm 7.3	55 \pm 4.8	35 \pm 8.7	53 \pm 4.1	25 \pm 5.8	66 \pm 6.1	0.001
3 month	32 \pm 3.1	56.5 \pm 4.1	31 \pm 5.5	51 \pm 4.2	25.3 \pm 6.6	67 \pm 6.8	0.01
4 month	27 \pm 4.6	59 \pm 4.6	30.5 \pm 4.5	52.5 \pm 5	26.4 \pm 6.4	67 \pm 6.1	0.2
5 month	26 \pm 5.6	65 \pm 5.1	30 \pm 3.9	54 \pm 4.5	24.5 \pm 6.5	67 \pm 6.5	0.05
6 month	26 \pm 5.6	65 \pm 5.2	30 \pm 4.7	55 \pm 5.2	24 \pm 5.5	67 \pm 6.5	0.04

laser treatment by IVTA.

Challa *et al.* [16] evaluated the safety and efficacy of intravitreal of triamcinolone after one and half year of follow up in exudative age related macular degeneration considered unsuitable for laser photocoagulation. They reported that a single intravitreal injection of 4 mg of triamcinolone acetate was well tolerated and helpful in treatment of exudative age related macular degeneration.

In this study (in group 1), there was increase in visual acuity, reduction of fluorescein angiography leakage, reduction central macular thickness and increase in amplitude of MFERG with reduction of implicit time in 40 eyes of 50 eyes (80%) within 2 months. Ten eyes of 40 eyes (25%) receive another intravitreal injection after 3 months (after beginning of reduction of visual acuity with increase macular

thickness, reduction of amplitude of MFERG and increase implicit time). There was improvement of six of ten eyes (60%).

There was correlation between visual acuity and central macular thickness ($p=0.008$, $R=0.5$) and visual acuity and MFERG amplitude ($P=0.006$, $R=0.55$). Also, there was significant correlation between central macular thickness and MFERG amplitude ($P=0.001$, $R=0.65$) in group 1.

In this study, we injected high dose of triamcinolone acetate intravitreal in group 1, because the results of previous studies were not clear; Jonas *et al.* [19,20] found significant increase in visual acuity after intravitreal injection of 25 mg of triamcinolone acetate. While Gillies *et al.* [21] reported no effect of 4 mg of intravitreal injection of triamcinolone acetate on the development of severe visual loss over a

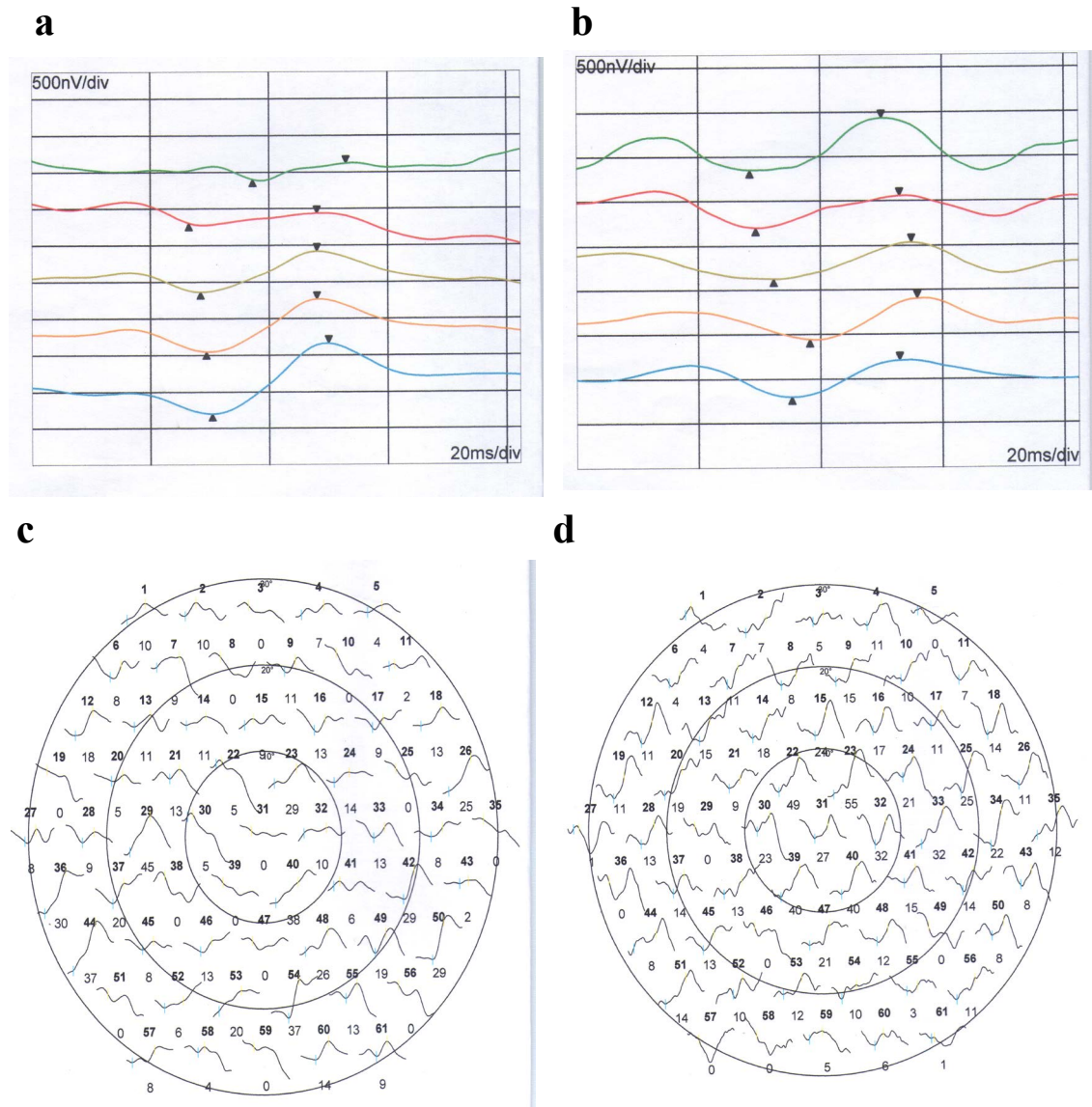


Figure 2. MFERG before and after injection in group 1. **a.** 5-rings of MFERG before injection. **b.** 5-rings of MFERG after injection. **c.** trace array of MFERG before injection. **d.** trace array of MFERG after injection.

follow up period of 1 year. The causes for the difference between studies may be the amount of injected triamcinolone acetate.

Another cause for difference between studies may be related to the effect of development of cataract on vision. An additional reason for discrepancy between this study and investigation of Gillies *et al.* [21] may be that their study included classic subfoveal choroidal neovascularization which is associated with a worse prognosis compared with occult choroidal neovascularization.

There was significant elevation in intraocular pressure in group1 compared with other groups. There were 30 eyes (60%) had increased intraocular pressure. All cases were controlled with medical anti-glaucomatous treatment.

Various studies have reported increase of IOP ranging from 11-30% of subjects following IVTA [17,19,22].

None of patients had been shown infectious endophthalmitis, rhgmatogenous retinal detachment, or proliferative vitreoretinopathy

in this study. Regards the duration of the therapeutic effect of 25 mg of intravitreal injection of triamcinolone acetate, Jonas *et al.* [18] found the reduction of visual acuity started 4-5 months after initial increase in visual acuity two months after injection.

Similarly, in the present study after initial increase of vision two month after injection, visual performance started to decrease again. This may be result from resolving of triamcinolone acetate crystals. Vascular endothelial growth factor (VEGF) plays an important role in the pathogenesis of AMD [22]. Intravitreal bevacizumab injection was reported to be effective for treatment exudative AMD. Bevacizumab inhibit VEGF, decrease angiogenesis and decrease vascular permeability [23-25].

In group 2, there were increase in visual acuity, reduction in retinal thickness and improvement of electrophysiological amplitudes and latencies. The improvement was slightly more significant in group 2 than in group1 (As seen in table 2ssss). The cause for this improvement in group 2 more than group 2 is that triamcinolone

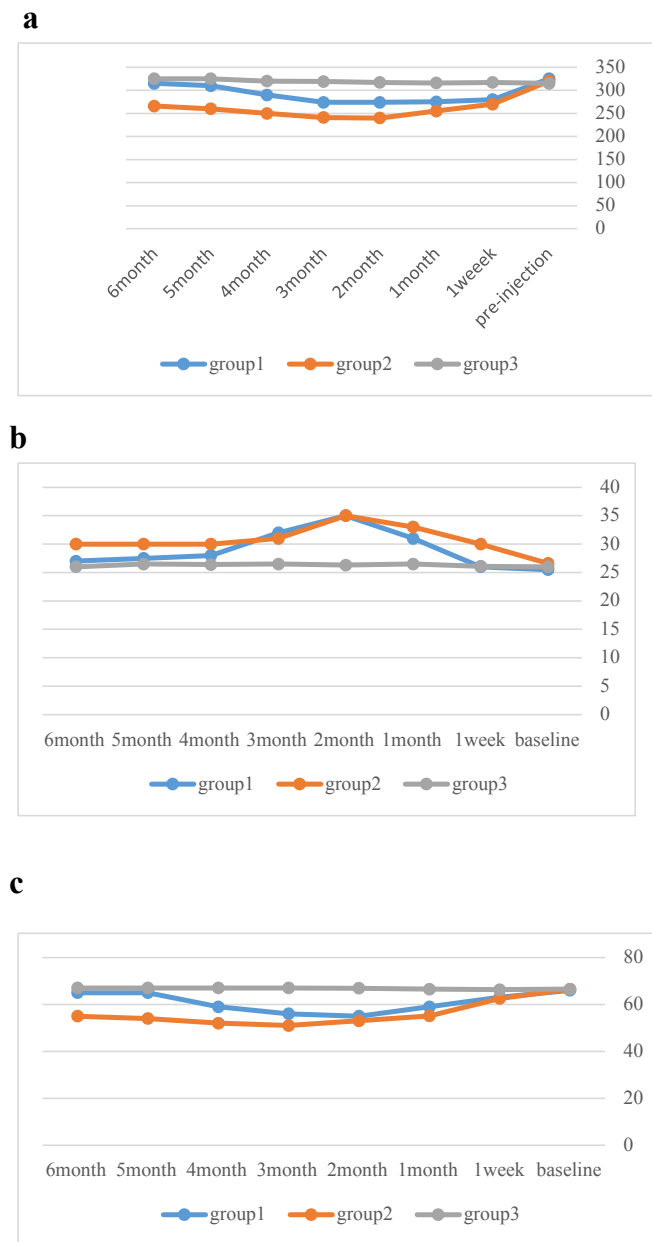


Figure 3. OCT and MFERG changes among groups. **a.** OCT changes among groups. **b.** MFERG changes of amplitudes among groups. **c.** MFERG changes of latencies among groups.

exerted its antiangiogenic effect by enhancing endostatin expression rather than suppressing VEGF expression [26]; While bevacizumab decrease angiogenesis by decreasing VEGF expression and enhancing endostatin [27].

There was correlation between visual acuity and central macular thickness ($p=0.006$, $R=0.55$) and visual acuity and MFERG amplitude ($P=0.005$, $R=0.65$). Also, there was significant correlation between central macular thickness and MFERG amplitude ($P=0.003$, $R=0.6$) in group 2. Similarly, Rosenfeld et al reported that intravitreal injection of bevacizumab cause marked decrease in retinal thickness without toxicity [28]. Ahmadi *et al.* [29] observed improvement of vision and reduction of thickness after bevacizumab.

Also, Falkenstein *et al.* [30] showed that primary bevacizumab therapy resulted in significantly visual improvement [30]. The bevacizumab preparation is unpreserved and contains no ingredients that are toxic to the eye [28]. Intravitreal bevacizumab is well tolerated in the majority of patients. In this study, there were no complication in group 2. Only subconjunctival heamorrhage in two cases which resolved within a week.

While, Ahmadi *et al.* [29] observed one case with pigment epithelial detachment without any cases of endophthalmitis or subconjunctival haemorrhage. Also, Cleary *et al.* [30] Found endophthalmitis in 1 of 112 eyes, submacular hemorrhage in 3 of 112 eyes and retinal pigment epithelial tears in 3 of 112 eyes. Ronan *et al.* [31] and Avery said that the presence of pigment epithelial detachment was risk factor for retinal pigment epithelial tear after IVB injection.

The limitations of this study, were the method of measuring visual acuity. Instead of the charts used for the Early Treatment Diabetic Retinopathy [33] visual acuity was determined using Snellen charts in a standardized fashion. But, the same method for detection visual acuity was applied to three groups. Other limitation of this study was limited follow up and limited number of the patients, the relatively high dose of triamcinolone acetate injected into eye.

In summary, intravitreal injection of triamcinolone acetate and bevacizumab improve visual acuity transiently in patients with neovascular age related macular degeneration. Furthermore, intravitreal injection caused anatomical changes and functional improvement of MFERG. Bevacizumab gave more favorable visual outcome and anatomical and functional improvement than triamcinolone acetate. To stabilize visual acuity, repeated intravitreal injection is recommended with 2-3 months apart with take care of complication especially intraocular pressure in cases of IVTA.

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Conflict of interest

All authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

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