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Evaluation of the optic nerve head and peripapillary retinal nerve fiber layer thickness in patients receiving Electro-Convulsive Therapy

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Abstract

Background: Electroconvulsive therapy (ECT) is a method commonly used in the treatment of psychiatric disorders. As ocular side effects from OCT are less studied and discussed, the aim of this study was to evaluate the profile of the peripapillary retinal nerve fiber layer thickness in patients receiving ECT. **Method:** This study was performed on 30 patients who had indication for ECT. After recording demographic data, retinal nerve fiber layer thickness was measured by using spectral domain optical coherence tomography (Heidelberg Engineering, Heidelberg, Germany) of optic nerve head and peripapillary retinal nerve fiber layer. **Results:** Our results showed that for most of the studied variables, the normal range was observed in less than 85% of patients receiving ECT. Variables which were outside the normal range were: cup disk (C/D) ratio (right and left eyes were 50% and 46.7%, respectively), vertical C/D ratio (right and left eyes were 53.3% and 46.7%, respectively), and cup volume (right and left eyes were 53.3% and 33.3%, respectively). **Conclusion:** This study showed that a high percentage of patients receiving ECT had changes in the optic nerve head while intra-ocular pressure in these patients was normal. It is warranted for examiners to pay attention to diagnosis of normal tension glaucoma in patients receiving ECT.

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Keywords

Electroconvulsive therapy, Optic nerve, Optical coherence tomography, Peripapillary, Retinal nerve fiber layer

Introduction

Electro-convulsive therapy (ECT) is an electrical current to the brain from the patient for one tenth of a second which produces a major seizure. In other words, the electroshock from two electrodes on the head releases an electrical current to the brain that can lead to a change in brain size (Pompili et al., 2014; Read and Bentall, 2010). ECT is one of the most effective treatments in psychiatry (Mowla et al., 2013). It is an effective short-term treatment for major depression and is probably more effective than drug therapy (Group, 2003; Khalid et al., 2008). ECT is also an effective psychiatric treatment for mania, catatonic states, and, to a lesser degree, some schizophrenias (O'CONNELL, 1982). It generates an epileptic seizure by means of a brief pulse of electrical current under general anesthesia. As noted, it has been used to treat psychiatric disorders (Dols and Stek, 2009).

Recently, reports suggest that patients with glaucoma have higher prevalence of depression in contrast to the control group (Mabuchi et al., 2008; Yochim et al., 2012). Taking this into consideration, it is expected that more and more patients with glaucoma require treatment for their depression and some of these patients with severe depression may require ECT (Aneja et al., 2013). For shock therapy, there is a general anesthetic to help prevent muscle contractions due to seizure and bone fractures, and to prevent other side effects such as increased intraocular pressure. Due to increased arterial blood pressure and reduced venous return during electrical shock therapy, it can be expected that intraocular pressure will also increase due to electrical shock therapy (Boroojeny et al., 2012).

At present, optical coherence tomography (OCT) is widely used in the diagnosis of optic nerve diseases, especially retinal nerve fiber layer (RNFL). OCT is useful for early diagnosis and evaluation of glaucoma. The OCT device has made clear progress; the most important advancement has been in the Spectoral domain OCT technology. The thickness of RNFL measured with the OCT device is interpreted naturally (or abnormally) using data of RNFL thickness. These data are calculated on a normal basis for each age, and each device has its own data (Asl et al., 2014; Lashkari et al., 2014; Shirzadi et al., 2015).

The aim of this study was to investigate the profile of the optic nerve head and the thickness of the nerve fibers of the peripapillary retina in patients receiving

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ECT. Additionally, the study aimed to evaluate the adverse effects of ECT on optic nerve head and RNFL pattern.

Materials-Methods

This study was approved by the Ethics Committee of Zahedan University of Medical Sciences in Zahedan, Iran. In this analytical-descriptive study, patients referred to the Baharan Psychiatric Hospital in 2016 and whom were undergoing electro-shock therapy were assessed; 30 patients were selected based on the criteria below.

Inclusion criteria

All patients with major depression, bipolar disorders, catatonia and other acute psychiatric disorders; patients must have undergone more than six courses of ECT for a minimum of three months.

Exclusion criteria

Patients were excluded if they had ocular surgical history, history of glaucoma (for the individual and for his/her family), and/or history or evidence of other eye diseases (e.g. diabetic retinopathy, retinal diseases, uveitis, visual acuity, etc.).

Patients included in the study, along with any caregivers of the patients, were advised by the specialist (physician) about the study and were provided explanations about the process; they were also informed that all clinical information relating to them would remain confidential. Three months after the end of electro-shock therapy, all of the patients were examined by an expert ophthalmologist and their demographic as well as clinical information were recorded. Following that, for all subjects, the optical fiber coherence of the retina was assessed in the peripapillary region using spectral domain OCT (Heidelberg Engineering, Heidelberg, Germany). Images were taken to examine the visual acuity features using the OCT machine. All information was recorded and the necessary analyses were performed.

Statistical analysis

All data were entered into the SPSS version 16.1 software and analyzed using descriptive statistical methods (e.g. statistical tables, determination of central indexes and dispersion) and inferential statistical methods (e.g. mean comparison test with a constant number). As per standard, $P<0.05$ was considered statistically significant with 95% confidence interval (95%CI).

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Results

A total of 30 patients including 13 males (43.3%) and 17 females (56.7%) were selected for the study. The mean age of patients was 39.33 years (range, 16-66 years) (**Table 1**). All patients had undergone ECT for a minimum three months and had received ECT for a total of six times; there was no significant change in the number nor frequency of changes in OCT. The cup/disk ratios of right and left eyes were 0.49±0.21 and 0.51±0.19, respectively; both were in the normal range.

Table 1. The mean and range of the studied variables in patients undergoing electro-convulsive therapy

Variable	Mean ± SD	Range
Age, year	39.33 ± 15.34	16-66
Right eye RNFL thickness (μm)	97.43 ± 15.23	77-161
Left eye RNFL thickness (μm)	97.86 ± 16.41	84-163
RNFL symmetry (%)	86.96 ±5.80	71-97
Rim area of right eye (mm2)	1.44 ± 0.38	0.89-2.47
Rim area of left eye (mm2)	1.43 ± 0.34	1-2.25
Disc area of right eye (mm2)	2.09 ± 0.50	1.42±3.38
Disc area of left eye (mm2)	2.07 ± 0.50	1.35-3.12
C/D ratio of right eye	0.49 ± 0.21	0.06-0.74
C/D ratio of left eye	0.51 ± 0.19	0.06-0.87
C/D vertical ratio of right eye	0.48 ± 0.21	0.05-0.76
C/D vertical ratio of left eye	0.48 ± 0.17	0.05-0.69
CUP volume of right eye (mm3)	0.23 ± 0.20	0-0.63
CUP volume of left eye (mm3)	0.21 ± 0.17	0-0.70
Number of ECT	12 ± 5.58	6-32

RNFL: retinal nerve fiber layer; C/D: cup disk ratio.

The confidence interval of the studied variables in the patients undergoing ECT is shown in **Table 2**. RNFL symmetry (%) between the eyes was 86.96 ± 5.80 (p = 0.020).

Table 3 shows the mean and range of retinal nerve fiber layer quadrants studied in the patients undergoing ECT. For the right eye, the retinal nerve fiber layer (RNFL) in the inferior zone (129.93 μm) was greater than that of the temporal (64.43 ± 8.92 μm) or superior zone (119.76 ± 26.15 μm). However, for the left eye, the RNFL in the superior zone (126.03 ± 19.50 μm) was greater compared to the other zones. The lowest values were seen in the temporal zone of the right eye (64.43 ± 8.92 μm) and nasal zone of the left eye (62.86 ± 10.64 μm).

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Table 2. The confidence interval of the studied variables in patients undergoing electro-convulsive therapy

Variable	P-value	95%CI
Right eye RNFL thickness (μm)	0.030	91.74-103.12
Left eye RNFL thickness (μm)	0.032	91.73-103.99
RNFL symmetry (%)	0.020	84.79-89.13
Rim area of right eye (mm2)	0.040	1.3-1.59
Rim area of left eye (mm2)	0.050	1.3-1.56
C/D ratio of right eye	0.016	0.41-0.57
C/D ratio of left eye	0.001	0.44-0.59
C/D vertical ratio of right eye	0.009	0.40-0.56
C/D vertical ratio of left eye	0.001	0.42-0.55
Cup volume of right eye (mm3)	0.025	0.16-0.30
Cup volume of left eye (mm3)	0.047	0.15-0.27

RNFL: retinal nerve fiber layer; C/D: cup disk ratio

Table 3. The mean and range of retinal nerve fiber layer quadrants studied in patients undergoing electro-convulsive therapy

Variable	Mean ± SD (μm)	Range
Temporal zone of the right eye	64.43 ± 8.92	49-89
Temporal zone of the left eye	75 ± 18.88	50-158
Superior zone of the right eye	119.76 ± 26.15	91-239
Superior zone of the left eye	126.03 ± 19.50	97-177
Nasal zone of the right eye	75.60 ± 13.15	58-129
Nasal zone of the left eye	62.86 ± 10.64	48-88
Inferior zone of the right eye	129.93 ± 24.39	98-217
Inferior zone of the left eye	124.56 ± 30.57	38-238

The mean and range of zones of retinal nerve fiber layer o'clock in patients undergoing ECT is shown in **Table 4**. The maximum range of zones of retinal nerve fiber layer o'clock was six o'clock in both eyes (right and left eyes were 149.10 ± 35.03 and 146.23 ± 33.23, respectively).

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Table 4. The mean and range of zones of retinal nerve fiber layer o'clock in the patients undergoing electro-convulsive therapy

Variable	Mean ± SD (μm)	Range
Zone of one o'clock of the right eye	106.53 ± 27.86	71-194
Zone of one o'clock of the left eye	126.33 ± 23.53	84-171
Zone of two o'clock of the right eye	93.33 ± 20.48	63-143
Zone of two o'clock of the left eye	74.20 ± 12.58	56-115
Zone of three o'clock of the right eye	61.80 ± 14.91	43-124
Zone of three o'clock of the left eye	47.86 ± 7.44	30-60
Zone of four o'clock of the right eye	72.66 ± 12.88	52-121
Zone of four o'clock of the left eye	62.83 ± 10.80	47-83
Zone of five o'clock of the right eye	110.26 ± 39.09	70-267
Zone of five o'clock of the left eye	129.56 ± 16.22	95-158
Zone of six o'clock of the right eye	149.10 ± 35.03	105-241
Zone of six o'clock of the left eye	146.23 ± 33.23	106-275
Zone of seven o'clock of the right eye	130.33 ± 21.12	92-178
Zone of seven o'clock of the left eye	108.40 ± 39.15	64-287
Zone of eight o'clock of the right eye	63.53 ± 11.21	45-88
Zone of eight o'clock of the left eye	69.53 ± 21.65	51-173
Zone of nine o'clock of the right eye	50.93 ± 7.61	38-65
Zone of nine o'clock of the left eye	62.96 ± 15.99	38-126
Zone of ten o'clock of the right eye	78.73 ± 15.43	51-119
Zone of ten o'clock of the left eye	94.73 ± 30.25	60-174
Zone of eleven o'clock of the right eye	131.73 ± 26.98	90-229
Zone of eleven o'clock of the right eye	121.53 ± 28.03	87-215
Zone of twelve o'clock of the right eye	120.23 41.87	63-293
Zone of twelve o'clock of the left eye	132.16 ± 29.34	92-195

Normal range and percent of patients undergoing ECT for the studied variables are shown in **Table 5**. The data show that the frequency of right eye RNFL thickness, left eye RNFL thickness, RNFL symmetry, rim area of right eye, rim area of left eye, cup disk (C/D) ratio of right eye, C/D ratio of left eye, C/D vertical ratio of right eye, C/D vertical ratio of left eye, cup volume of right eye, and cup volume of left eye were 90%, 90%, 93.4%, 13.3%, 20%, 50%, 53.3%, 46.6%, 53.3%, and 46.6%, respectively. About 66.6% patients were in the normal range.

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Table 5. Frequency of studied variables in the patients undergoing electro-convulsive therapy

Variable	N (%)	Variable	N (%)
Right eye RNFL thickness (µm)		**C/D ratio of left eye**	
NL range : 75-107.2	27 (90)	<0.169	2 (6.7)
>107.2	3 (10)	NL range : 0.169-0.618	16 (53.3)
Left eye RNFL thickness (µm)		>0.618	12 (40)
NL range : 75-107.2	27 (90)	**C/D vertical ratio of right eye**	
>107.2	3 (10)	<0.165	5 (16.7)
RNFL symmetry (%)		NL range : 0.165-0.594	14 (46.6)
76	1 (3.3)	>0.594	11 (36.7)
NL range : 76-95	28 (93.4)	**C/D vertical ratio of left eye**	
>95	1 (3.3)	<0.165	2 (6.7)
Rim area of right eye (mm2)		NL range : 0.165-0.594	16 (53.3)
<1.015	4 (13.3)	>0.594	12 (40)
NL range : 1.015-1.615	4 (13.3)	**Cup volume of right eye (mm3)**	
>1.615	22 (73.3)	<0.004	5 (16.7)
Rim area of left eye (mm2)		NL range : 0.004-0.288	14 (46.6)
<1.015	2 (6.7)	>0.288	11 (36.7)
NL range : 1.015-1.615	6 (20)	**Cup volume of left eye (mm3)**	
>1.615	22 (73.3)	<0.004	2 (6.7)
C/D ratio of right eye		NL range : 0.004-0.288	20 (66.6)
<0.169	5 (16.7)	>0.288	8 (26.7)
NL range : 0.169-0.618	15 (50)		
>0.618	10 (33.3)		

RNFL: retinal nerve fiber layer; C/D: cup disk ratio; NL: normal

The normal range and percentage of the patients undergoing ECT for retinal nerve fiber layer quadrants are shown in **Table 6**. The temporal zone of the right eye, temporal zone of the left eye, superior zone of the right eye, superior zone of the left eye, nasal zone of the right eye, nasal zone of the left eye, inferior zone of the right eye, and inferior zone of the left eye were 93.3%, 83.3%, 83.3%, 80%, 90%, 83.3%, and 83.3%, respectively; about 86.7% patients were normal.

The normal range and percentage of patients undergoing ECT for zones of retinal nerve fiber layer o'clock are shown in **Table 7**. As noted, the following were recorded: zone of one o'clock of the right eye, zone of one o'clock of the left eye, zone of two o'clock of the right eye, zone of two o'clock of the left eye, zone of three o'clock of the right eye, zone of four o'clock of the right eye, zone of four o'clock of the left eye, zone of five o'clock of the right eye, zone of five o'clock of the left eye, zone of six o'clock of the right eye, zone of six o'clock of the left eye, zone of seven o'clock of the right eye, zone of seven o'clock of the

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left eye, zone of eight o'clock of the right eye, zone of eight o'clock of the left eye, zone of nine o'clock of the right eye, zone of nine o'clock of the left eye, zone of ten o'clock of the right eye, zone of ten o'clock of the left eye, zone of eleven o'clock of the right eye, zone of eleven o'clock of the left eye, zone of twelve o'clock of the right eye, zone of twelve o'clock of the left eye were 80%, 70%, 83.3%, 96.7%, 83.3%, 16.7%, 93.3%, 100%, 80%, 43.3%, 73.3%, 90%, 93.3%, 80%, 100%, 96.7%, 100%, 70%, 90%, 73.3%, 83.3%, 86.7%, 90%, and 80% respectively. About 80% of the patients were in normal range.

Table 6. Frequency of retinal nerve fiber layer quadrants studied in patients undergoing electro-convulsive therapy

Variables	N (%)
Temporal zone of right eye	
NL range : 45.1-82.2	28 (93.3)
>82.2	2 (6.7)
Temporal zone of left eye	
NL range : 45.1-82.2	25 (83.3)
>82.2	5 (16.7)
Superior zone of right eye	
NL range : 88.9-136.7	25 (83.3)
>136.7	5 (16.7)
Superior zone of left eye	
NL range : 88.9-136.7	24 (80)
>136.7	6 (20)
Nasal zone of right eye	
NL range : 50-86.2	27 (90)
>86.2	3 (10)
Nasal zone of left eye	
<50	3 (10)
NL range : 50-86.2	25 (83.3)
>86.2	2 (6.7)
Inferior zone of right eye	
NL range : 89.4-138.3	25 (83.3)
>138.3	5 (16.7)
Inferior zone of left eye	
<89.4	1 (3.3)
NL range : 89.4-138.3	26 (86.7)
>138.3	3 (10)

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Table 7. Frequency of zones of retinal nerve fiber layer o'clock in patients undergoing electro-convulsive therapy

Variable	N (%)	Variable	N (%)
Zone of one o'clock of right eye		**Zone of eight o'clock of right eye**	
<72.6	1 (3.3)	NL range : 42.2-90.2	30 (100)
NL range : 72.6-133.9	24 (80)	>90.2	0
>133.9	5 (16.7)	**Zone of eight o'clock of left eye**	
Zone of one o'clock of left eye		NL range : 42.2-90.2	29 (96.7)
<72.6	0	>90.2	1 (3.3)
NL range : 72.6-133.9	21 (70)	**Zone of nine o'clock of right eye**	
>133.9	9 (30)	NL range : 36.4-67.4	30 (100)
Zone of two o'clock of right eye		>67.4	0
NL range : 52.4-109.7	25 (83.3)	**Zone of nine o'clock of left eye**	
>109.7	5 (16.7)	NL range : 36.4-67.4	21 (70)
Zone of two o'clock of left eye		>67.4	9 (30)
NL range : 52.4-109.7	29 (96.7)	**Zone of ten o'clock of right eye**	
>109.7	1 (3.3)	<52.7	1 (3.3)
Zone of three o'clock of right eye		NL range : 52.7-100.5	27 (90)
NL range : 41.7-70.4	25 (83.3)	>100.5	2 (6.7)
>70.4	5 (16.7)	**Zone of ten o'clock of left eye**	
Zone of three o'clock of left eye		<52.7	0
NL range : 41.7-70.4	5 (16.7)	NL range : 52.7-100.5	22 (73.3)
>70.4	25 (83.3)	>100.5	8 (26.7)
Zone of four o'clock of right eye		**Zone of eleven o'clock of right eye**	
NL range : 44.8-89	28 (93.3)	<87.2	0
>89	2 (6.7)	NL range : 87.2-154.6	25 (83.3)
Zone of four o'clock of left eye		>154.6	5 (16.7)
NL range : 44.8-89	30 (100)	**Zone of eleven o'clock of left eye**	
>89	0	<87.2	1 (3.3)
Zone of five o'clock of right eye		NL range : 87.2-154.6	26 (86.7)
NL range : 61.9-125	24 (80)	>154.6	3 (10
>125	6 (20)	**Zone of twelve o'clock of right eye**	
Zone of five o'clock of left eye		<70.7	1 (3.3)
NL range : 61.9-125	13 (43.3)	NL range : 70.7-155.7	27 (90)
>125	17 (56.7)	>155.7	2 (6.7)
Zone of six o'clock of right eye		**Zone of twelve o'clock of left eye**	
NL range : 85.7-163.2	22 (73.3)	<70.7	0
>163.2	8 (26.7)	NL range : 70.7-155.7	24 (80)
Zone of six o'clock of left eye		>155.7	6 (20)
NL range : 85.7-163.2	27 (90)		
>163.2	3 (10)		
Zone of seven o'clock of right eye			
<84.8	0		
NL range : 84.8-159.4	28 (93.3)		
>159.4	2 (6.7)		
Zone of seven o'clock of left eye			
<84.8	5 (16.7)		
NL range : 84.8-159.4	24 (80)		
>159.4	1 (3.3)		

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Discussion

This study evaluated the characteristics of the optic nerve head and peripapillary thickness of the nerve fibers of the retina in patients undergoing ECT. It was found that for most of the variables studied (e.g. retinal nerve fiber layer quadrants, RNFL thickness and RNFL symmetry), the normal range was observed in less than 85% of the subjects. The variables most outside the normal range included the ratio of C/D (50% in the right eye and 53.3% in the left eye), vertical C/D ratio (46.6% in the right eye and 53.3% in the left eye), and cup volume (46.6% in the right eye and 66.6% in the left eye).

Yıldız *et al*. (2016) checked the efficacy of ECT on the thickness of the optic nerve in Turkey (19 patients had bipolar disorders and 18 were controls) (Yıldız et al., 2016). The average RNFL thickness, superior RNFL thickness, and nasal RNFL thickness had significant differences 'before ECT' compared with 'after ECT'. The ECT increased the mean of three variables (RNFL thickness, superior RNFL thickness, and nasal RNFL thickness) but did not have a significant effect on central macular thickness, inferior RNFL thickness, and temporal RNFL thickness. The average RNFL thickness, superior RNFL thickness, and nasal RNFL thickness before ECT compared with the control group showed significant differences; however, we did not have a comparison for 'after ECT' and the control group. At the end, the authors concluded that in the patients who underwent ECT, RNFL thickness was similar to the healthy controls. In this study, after intervention, patients undergoing ECT showed greater RNFL thickness than healthy controls.

Boroojeni *et al*. (2012) evaluated the efficacy of ECT combined to Propofol and Succinylcholine on intraocular pressure (Boroojeny et al., 2012). Intracranial base pressure had a significant decrease in patients undergoing ECT plus Propofol, and a significant increase in patients undergoing ECT plus Succinylcholine. In all patients at the one and five minutes compared with before intervention (base pressure), the pressure significantly increased (18.32±3.49 mmHg versus 15.41±3.46 mmHg). However, in 10 minutes the pressure was close to the base pressure (14.68±3.57 mmHg). ECT can increase the intraocular pressure that is not in risk range and, therefore, ECT can be prescribed to patients regardless of their ocular complications.

However, in the present study, intraocular pressure was not measured in patients, but it was found that some indices affected by intraocular pressure increased in patients and it seems that ECT procedure increases the intraocular pressure. Aneja *et al*. (2013) examined a patient who was suffering from major depression accompanied by psychiatric symptoms, which did not improve with normal symptoms of depression thus requiring an ECT (Aneja et al., 2013). On the other hand, it was found that the patient had open angle glaucoma. The

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patient was subjected to ECT and eventually, the symptoms of the patient improved and did not result in increased eye pressure or eye diseases.

Another study (Edwards et al., 1990) showed that intraocular pressure increased significantly after ECT but returned to basic pressure in 90 seconds after ECT was ended. Therefore, the results showed that an increase in intraocular pressure, although not dangerous in the non-glaucomatous eye, can affect eye function and cause recurrent complications in patients with severe glaucoma. However, any increase in intraocular pressure was of a transient nature. Mabuchi et al. (2008) investigated the relationship between anxiety and depression with increasing intraocular pressure (Mabuchi et al., 2008); the authors showed that the intraocular pressure in patients with depression and those with anxiety was significantly higher than that of the control group (13% and 1.5%, versus 5.2%, respectively). It was found that intraocular pressure was significantly higher in patients with depression and anxiety who underwent ECT.

One study reported that ECT is associated with a brief rise in intraocular pressure and probably does not cause a significant rise in intraocular pressure in patients with glaucoma (Good et al., 2004). Another study described a case of 49-year-old woman treated with ECT for depression, 13 days after phacoemulsification and intraocular lens implantation (Sienaert and Vanholst, 2013). That patient had 9 treatments until remission, without any complication. Saad *et al*. (2000) described two cases; one patient received ECT at 12 days post cataract surgery while the other patient received ECT one week post vitrectomy on one eye (a few years after that she received ECT 2.5 weeks post cataract surgery on the other eye) (Saad et al., 2000). There were no complications or adverse events for either patient.

There are four recommendations including: 1) regular monitoring of ophthalmic sign and symptoms, clinical examination and para-clinical tests for rapid and timely identification of ocular side effects in patients before and after treatment with ECT; 2) conduct sessions and provide information to psychiatric practitioners to introduce undesirable effects of ECT on the patients' eyes, and refer patients to ophthalmologists before and after treatment with ECT for diagnosis and supplementary therapies if needed; 3) considering a small number of studies, similar studies are suggested with larger sample sizes; and 4) perform a similar prospective study with regard to the variables studied, before and after ECT intervention and compared with the control group.

Conclusion

The results of this study showed that for most of the variables studied, the normal range was observed in less than 85% of patients undergoing ECT. The variables outside the normal range included C/D ratio, vertical C/D ratio, cup

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volume in the right eye, cup volume in the left eye, and at 5 o'clock. It was also found that these changes were at the head of the optic nerve and that the intraocular pressure in the patients was normal. It is suggested that examiners should be careful to distinguish these patients from normal torsion glaucoma cases.

Abbreviations

C/D: cup disk
ECT: Electroconvulsive therapy
NL:Normal
OCT: Optical coherence tomography (OCT)
RNFL: Retinal nerve fiber layer

Author Contribution

Kourosh Shahraki & Alireza Khosravi designed the study and contributed to analysis, interpretation of data, and drafting of manuscript. Shiva Kaffashipour collected data. Kianoush Shahraki reviewed and edited the manuscript for intellectual content. Masoud Sadeghi contributed to analysis and interpretation of data and revised the manuscript. All authors gave final approval of the version to be published.

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