ORIGINAL ARTICLE

The Effect of Mirtogenol Towards the Changes in Retinal Nerve Fiber Layer Thickness and Visual Field in Primary Open Angle Glaucoma

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ABSTRACT

Objective: To evaluate the effect of Mirtogenol towards the changes in retinal nerve fiber layer (RNFL) thickness and visual field in patients with primary open angle glaucoma (POAG) with controlled IOP.
Methods: This is a prospective, double blind, randomized study. Forty one POAG patients with IOP ≤ 18 mmHg were randomly assigned to receive either Mirtogenol or placebo. Changes in RNFL thickness and mean deviation of visual fields were evaluated before the treatment, as well as 4 weeks and 8 weeks after the treatment. Patients were asked for any side effects during the treatment period.
Result: The average RNFL thickness in the Mirtogenol group decreased -0.70±1.63 μm from 87.29±19.39 μm before the treatment to 86.58±19.43 μm after 8 weeks of treatment, however the change was not significant (p=0.121). The average RNFL thickness in the placebo group decreased -1.74±1.79 μm from 97.14±17.19 μm before the treatment to 95.40±18.56 μm after 8 weeks of treatment, the change was statistically significant (p< 0.001). The average MD of visual field in the Mirtogenol group increased 0.542±1.93 dB after 8 weeks of treatment while the MD of visual field in the placebo group decreased -0.083±1.36 dB after 8 weeks of treatment. Hoewever the changes in MD of visual field was not significant (p>0.05). No side effect was found throughout the study.
Conclusion: Mirtogenol seemed to maintain retinal nerve fiber layer thickness and increased mean deviation of visual fields.

Keyword: Mirtogenol, retinal nerve fiber layer thickness, visual field, primary open angle glaucoma

Primary open angle glaucoma (POAG) is a chronic and progressive anterior optic neuropathy and is the second cause of blindness worldwide.[1,2] In Cipto Mangunkusumo Hospital, blindness due to POAG reached 25.57% and the incidence is increasing yearly.[3] Intraocular pressure (IOP) plays an important part in the progressivity of POAG. However recent studies suggest that despite controlled IOP, optic nerve damage still progressed. Some studies proposed vascular damage and oxidative stress as one of the factors contributing to the progressivity of POAG.[1,4]

Current studies are aimed towards these non-IOP dependent factors. Some of the substances that have been investigated are citicholine and gingko biloba.[5,6] In Cipto Mangunkusumo Hospital, citicholine was proven to shorten the latency of visual evoke potential, reduce mean deviation of visual field and increase contrast sensitivity in Primary Angle Closure Glaucoma (PACG)[7], while gingko biloba showed improvement of visual field and increased retinal ganglion cell sensitivity in POAG.[8]

Mirtogenol is a combination of 40 mg bilberry extract (Mirtoselect) and 80 mg maritime pine bark (Pycnogenol). Several studies indicate that Mirtogenol has the ability to improved ocular blood flow[9], prevent overproduction of nitrit oxide and thus prevent further cell death process, and Mirtogenol also has a potent antioxidant effect.[10,11] With these effects, Mirtogenol is hoped to help slow down POAG progression in patients with controlled IOP. This study is aimed to evaluate the effect of Mirtogenol towards the changes in retinal nerve fiber layer (RNFL) thickness and mean deviation of visual field.

METHODS

This is a randomized, double blind study conducted in Glaucoma Division in Cipto Mangunkusumo Hospital between October 2014 and February 2015. POAG patients with IOP ≤ 18 mmHg, visual acuity of LogMAR 1 or better, and is cooperative during the visual field examination and RNFL measurement were included. Patients who are willing to participate in this study signed the informed consent.

Patients were excluded if they consumed any antioxidant or neuroprotective supplements within 2 weeks, patients with hypertension or diabetic retinopathy, patients with optic neuritis or other abnormalities of the eye that affect the visual pathway, active inflammation in either or both eye, any other ocular abnormalities at the cornea, macula or retina that might affect the visual field examination and/or RNFL measurement, and patients planned to undergo trabeculectomy or cataract surgery during the study.

Table 1. Baseline characteristics

	Groups		p value
	Mirtogenol (n=21)	Placebo (n=20)	
Gender			
Male	15	12	0.520
Female	6	8	
Age (years)*	68 (47-79)	65.5 (47-81)	0.715
Anti-glaucoma medication			
Yes	19	19	1.000
No	2	1	
History of glaucoma surgery			
Yes	2	1	1.000
No	19	19	
History of other eye surgery			
Cataract extraction	15	12	0.520
None	6	8	
History of systemic disease			
Yes	8	9	0.756
None	13	11	
BCVA (LogMAR)*	0.1 (0-0.4)	0.1 (0-0.7)	0.589
Intial IOP (mmHg)**	12.62 ± 2.46	12.35 ± 2.23	0.814
CDR Horizontal**	0.71 ± 0.79	0.69 ± 0.11	0.477
CDR Vertical**	0.67 ± 0.90	0.66 ± 0.11	0.619

*Median (minimal-maximal)
** Mean ± SD

Patients were randomized to receive either Mirtogenol or placebo. History taking, best-corrected visual acuity (BCVA), slit lamp biomicroscopy examination, gonioscopy examination, IOP measurement, visual field examination and RNFL thickness measurement were performed before the study. Patients were asked to take the treatment given once daily in the morning. Patients were then requested to return after 4 and 8 weeks to evaluate their IOP, visual field examination and RNFL thickness measurement as well as asked for any side effects throughout the study.

Patients continued to receive their glaucoma medications during the entire study to keep their IOP ≤ 18 mmHg. Patients and the examiners were blinded throughout the study.

Data analysis was performed with IBM SPSS version 22 for MacIntosh. RNFL thickness, RNFL thickness changes, and MD changes were analyzed using unpaired t-test while MD of visual field was analyzed using Mann Whitney. RNFL thickness and MD of visual field at the beginning, after 4 weeks and 8 weeks of treatment for each group were analyzed using ANOVA.

RESULTS

During the study, 41 patients met the study criteria and were then randomized into each group. All patients completed the study, thus all patients were analyzed. The baseline characteristics are shown in table 1. Throughout the study, the IOP remained below 18 mmHg in all patients, so none needed additional treatment. The RNFL thickness between both groups was not significantly different (table 2).

The RNFL thickness in the Mirtogenol group were relatively stable, while the RNFL thickness in the nasal and inferior quadrants as well as the average RNFL thickness in the placebo group showed significant decrease. However, the changes in RNFL thickness between both groups were not stastistically significant (table 3).

Table 2. RNFL thickness

	Mirtogenol (n = 21) (*Mean* ± SD)	**Placebo (n = 20) (*Mean* ± SD)**	**p value***
Superior			
Intial	105.76 ± 25.42	118.80 ± 21.17	0.082
Week 4	105.86 ± 25.27	116.45 ± 21.51	0.156
Week 8	104.86 ± 25.97	116.85 ± 21.77	0.117
p value**	0.148	0.148	
Nasal			
Intial	67.05 ± 18.70	80.30 ± 21.14	0.04
Week 4	66.29 ± 18.01	79.15 ± 20.81	0.041
Week 8	65.95 ± 18.16	78.00 ± 21.96	0.064
p value**	0.254	0.005	
Inferior			
Intial	106.19 ± 37.00	115.05 ± 34.34	0.431
Week 4	103.90 ± 35.65	111.65 ± 34.72	0.485
Week 8	105.76 ± 36.43	112.80 ± 35.66	0.527
p value**	0.069	0.007	
Temporal			
Intial	70.14 ± 16.62	74.40 ± 17.98	0.437
Week 4	70.38 ± 16.58	73.65 ± 18.80	0.559
Week 8	69.76 ± 17.65	73.80 ± 18.68	0.482
p value**	0.546	0.294	
Average			
Intial	87.29 ± 19.39	97.14 ± 17.19	0.093
Week 4	86.61 ± 18.92	95.22 ± 17.90	0.142
Week 8	86.58 ± 19.43	95.40 ± 18.56	0.145
p value**	0.121	< 0.001	

Units in μm

* Unpaired t-test

** ANOVA

The MD of visual field from the Mirtogenol group increased from -4.23 dB to -2.98 dB though the difference is not significant.

The MD of visual field from the placebo group was relatively stable. When compared between the 2 groups, the difference is not significant (table 4). The changes in MD of visual field for both groups showed no significant difference. No side effect was observed during the entire study for both groups.

Table 3. Changes in RNFL thickness

	Mirtogenol (n = 21) (*Mean* ± SD)	Placebo (n = 20) (*Mean* ± SD)	p value*
Superior			
4 Weeks	0.10 ± 4.35	-2.35 ± 4.33	0.079
8 Weeks	-0.90 ± 3.28	-1.95 ± 3.62	0.34
Nasal			
4 Weeks	-0.76 ± 2.77	-1.15 ± 2.16	0.619
8 Weeks	-1.10 ± 1.87	-2.30 ± 2.39	0.081
Inferior			
4 Weeks	-2.29 ± 4.72	-3.40 ± 3.76	0.408
8 Weeks	-0.43 ± 2.60	-2.10 ± 2.97	0.063
Temporal			
4 Weeks	0.24 ± 2.26	-0.75 ± 2.47	0.189
8 Weeks	-0.38 ± 3.43	-0.60 ± 3.20	0.834
Average			
4 Weeks	-0.68 ± 1.87	-1.91 ± 1.72	0.034
8 Weeks	-0.70 ± 1.63	-1.74 ± 1.79	0.061

Units in μm

* Unpaired t-test

Table 4. Mean deviation of visual field

	Mirtogenol (n = 21) (*Median* (min-max))	Placebo (n = 20) (*Median* (min-max))	P value*
Intial	-4.23 (-11.00 - -0.50)	-4.21 (-15.00 - -0.32)	0.814
Week 4	-3.90 (-13.69 - -1.14)	-3.75 (-16.02 - -0.15)	0.865
Week 8	-2.98 (-13.19 - -0.47)	-4.50 (-13.90 - -0.47)	0.134
p value**	0.103	0.086	

Units in dB

* Mann Whitney

** ANOVA

Table 5. Changes in mean deviation of visual field.

	Mirtogenol (n = 21) (*Mean* ± SD)	Placebo (n = 20) (*Mean* ± SD)	p value*
4 Weeks	-0.002 ± 1.32	-0.186 ± 1.56	0.688
8 Weeks	0.542 ± 1.93	-0.083 ± 1.36	0.237

Units in dB

* Unpaired t-test

DISCUSSION

Glaucoma is a progressive multifactorial disease characterized by retinal ganglion cell loss. This leads to clinically detectable structural and functional changes such as glaucomatous optic disc change, RNFL thinning and visual field defect. The retinal ganglion cell deaths are affected by both IOP dependent and non IOP dependent factors such as vascular damage and free radicals.[12-14] Current POAG treatments, such as medications, laser or surgery, are aimed to control IOP.

Recent studies are developing adjuvant treatment to control the non IOP dependent factors. Some of the substances that are currently being developed are neurotropine receptor agonists, vasodilators such as vitamin E and gingko biloba that are hoped to improve ocular bloodflow, as well as antioxidants to prevent damage caused by oxidative stress.[15-17]

Mirtogenol is among the substances being studied. It is a combination of 40 mg bilberry extract (Mirtoselect) and 80 mg maritime pine bark (Pycnogenol).[9]

A study by Steigerwalt et al[10] using Color Doppler imaging showed that Mirtogenol improved ocular bloodflow through the centralis retinal artery, ophthalmica artery and posterior ciliary artery after being given for 2 months. Pycnogenol is known to play a part in the metabolism of nitric oxide and thus prevent overproduction of the substance and prevent further apoptosis of the retinal ganglion.[10] Mirtoselect is known to be a potent antioxidant and free radical scavenger.[11] The combination of these effects are hoped to help prevent POAG progressivity. However there have been no studies evaluating the effect of Mirtogenol towards the RNFL thickness changes and MD of visual field in POAG patients.

Baseline characteristics of this study showed the median age for the Mirtogenol group and placebo group are 68 years and 65.5 years respectively. This is in line with the study conducted by Beidoe et al[4] which showed that one of the risk factors for glaucoma is age above 60 years old. The BCVA for both groups are LogMAR 0.1 with a cup-to-disc ratio of < 0.8, indicating that all patients are eligible to undergo Humphrey perimetry examination as well as RNFL thickness measurement. The IOP for both groups are maintained below 18 mmHg throughout the study as suggested by *The Advanced Glaucoma Intervention Study* (AGIS)[18] study. Most patients only needed 1 medication and had never underwent laser treatment nor glaucoma surgery.

One of the outcome measured in this study is the RNFL thickness which is used to monitor glaucoma progression.[19] A study by Lalezary et al[20] indicate that a 10 μm RNFL thinning is related to a 1.5 fold glaucomatous change. In this study, the RNFL thickness of the Mirtgoneol group is relatively stable throughout the entire study as compared to the RNFL thickness of the placebo group in the nasal quadrant, inferior quadrant and the average thickness which showed significant thinning. However when compared between the 2 groups, the difference is no significant except for the nasal quadrants that showed a difference since the beginning of the study despite randomisation. The change in RNFL thickness for both groups in all quadrants showed no significant difference. Other factors that might affect the measurement is the use of Stratus OCT that has an axial resolution of 8-10 μm, and thus a difference of up to 10 μm might be considered as a variation in measurement. Besides that, measurement bias might still occur if the RNFL thickness measured during the follow-ups are measured at a different spot from the first evaluation thus giving a different axial cut resulting in different measurement of the RNFL thickness. This can be prevented by obtaining a signal strength of above 6, having the same examiner for the whole RNFL thickness measurement, and ensuring the centralization of the optic nerve during the examination.[21,22]

The result of this study is not comparable to other studies as no other studies evaluate RNFL thickness in Mirtogenol treatment. Studies by Wicaksono[8] and Zaini[7] showed tendency of increased retinal sensitivity during electroretinogram examination in patients receiving ginkgo biloba and citicholine. A study by Dzhumova et al[23] showed an improvement of structural parameters when given combination therapy with neuroprotective agents.

The other outcome measured in this study is the MD of visual field. Retinal or visual sensitivity measured by the Humphrey perimetry suggest the functional density of ganglion cells.[24] A study by Lee at al[25] showed that an MD change of -0.68 dB yearly (or -0.06 dB monthly) indicates glaucoma progression. In this study the MD of visual field from the Mirtogenol group increased from -4.23 to -2.98 though the difference is not significant. The MD of visual field from the placebo group was relatively stable. When compared between the 2 groups, the difference is not significant (table 4). The changes in MD of visual field for both groups showed no significant difference. This result is comparable with other studies such as by Wicaksono[8] and Zaini[7] in which gingko biloba and citicholine supplementation increased the MD of visual field significantly. Supplementation of citicholine for 2 consecutive years might slow down the progression of visual field damage.[26]

Other factor that might affect the MD of visual field in this study is the learning effect of the patient, which might cause a better result in the subsequent examination. The examination is also very patient-dependent, in which the patient condition has to be very optimal to undergo this examination. Thus a threshold of fixation loss < 20%, false negative < 20-30 % and false positive <15% is needed to achieve a reliable result.[27,28]

The safety of Mirtogenol was measured by asking the patients whether any side effect occurred throughout the study. No patients complained of any side effects, which is in line with other studies that stated that Mirtogenol is safe.[9-11]

The exact mechanism as to how Mirtogenol affect RNFL thickness and MD of visual field remained unknown. A few studies indicate that the potent antioxidant effect of Mirtogenol[11], the ability to prevent overproduction of nitrit oxide[10] as well as the ability to improved ocular blood flow[9] might help to prevent further retinal ganglion cell deaths, and thus prevent further RNFL thinning, and consequently prevent visual field loss. However, larger studies with longer follow up period are still needed as the follow-up time of this study is relatively short and the number of patients evaluated is small. Further studies are required to determine the duration needed for Mirtogenol to help slow down glaucoma progression.

CONCLUSION

Mirtogenol seemed to maintain retinal nerve fiber layer thickness and increased mean deviation of visual fields but further studies are still needed.

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