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Original Article

Comparison of therapeutic effects of two CCBs on glaucoma and analysis of their possible mechanisms

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Abstract: Objective: To respectively compare the therapeutic effects of nimodipine and nifedipine on glaucoma, and then analyze the possible protective effects of these two calcium channel blockers (CCBs) on glaucomatous retinal ganglion cells (RGCs). Methods: Fifty-four patients with glaucoma were divided into control group (n=15), treatment group 1 (n=20) and treatment group 2 (n=19) in accordance with a random number table. General clinical treatment of glaucoma was performed in all three groups, while nimodipine was applied in treatment group 1 and nifedipine was applied in treatment group 2. The therapeutic effects and incidence of adverse reactions (intraocular pressure (IOP), eyesight, retinal light sensitivity, progressive visual field damage and adverse drug reaction) were compared among the three groups. Results: There were no significant differences in IOP and eyesight before and after treatment among the three groups (P>0.05). The retinal light sensitivity in control group began to decline from the sixth month after treatment, which was significantly different from treatment group 1 and treatment group 2 (P=0.03; P=0.04). The survival curve of visual field damage indicated that the visual field damage in control group was obviously more serious than that in the two treatment groups with the increase of sick time (P=0.03). And the incidence of adverse reactions in treatment group 1 was lower than that in treatment group 2 (P=0.02). Conclusion: The therapeutic effects of nimodipine and nifedipine on glaucoma are evident, and nimodipine has a better safety. Therefore, we recommend clinicians to apply it as combined medicine in clinical treatment of glaucoma.

Keywords: Nimodipine, nifedipine, glaucoma, calcium channel blockers (CCBs), retinal ganglion cells (RGCs)

Introduction

Glaucoma, as a rather complex and common ophthalmic disease, has become the major cause of blindness [1]. Patients with glaucoma are always accompanied by pathological ocular hypertension or normal IOP but with damages of optic disk and retinal nerve fiber layer and visual field change [2-4]. Many studies claim that the ocular hypertension and the retinal ischemia caused by glaucoma can lead to continuous apoptosis of RGCs [5-8]. Therefore, the main goal of the approved treatment for glaucoma at present is to reduce the IOP. The clinical data on treatment, however, indicate that although IOP is under the control, many patients with glaucoma still have the symptom of progressive visual field defect, and that is why adjunctive therapeutic drug which can protect the function of retinal nerve is becoming the research hotspot [9, 10]. The apoptosis of RGC is the final common pathway in retinal nerve injury of glaucoma, and the treatment about blocking or delaying the primary and secondary RGC injury is known as the protective treatment for glaucomatous retinal nerves [11]. Previous studies have shown that the application of CCBsin improving the blood supply of retinal nerves and optic diskcan delay or block the injury of RCGs [12, 13]. Nimodipine and nifedipine are currently commercially available vasodilator medicines which can be used to protect the retinal nerves. However, nimodipine is commonly applied in the treatment of glaucoma while the researches about nifedipine application in glaucoma treatment are limited. This study aims to compare the therapeutic effects of nimodipine and nifedipine on glaucoma, and explore and analyze their possible mechanisms, thereby providing more detailed guidance for clinical medication.

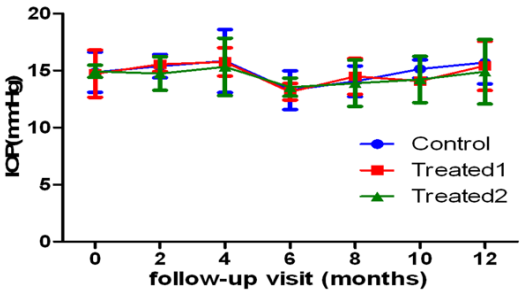

Figure 1. The comparison of IOP before and after treatment among the three groups (mean ± sd).

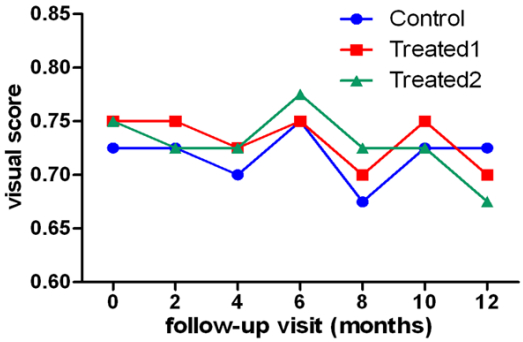

Figure 2. The comparison of visual score before and after treatment among three groups.

Materials and methods

General information

Fifty-four patients (29 males and 25 females with an average age of 45.6±4.2 years old) who were diagnosed with glaucoma in our hospital from August 2014 to September 2015 were included in this study. Approved by the Hospital Ethics Committee, all the patients in this study had signed informed consents before the experiment. Inclusive criteria: patients whose IOP was controlled under 18 mmHg with medication or post-operative combined medication; patients with clear refractive media, ametropia <3.0 D and corrected visual acuity >0.5. Exclusive criteria: patients who might affect the detection results of visual field, for example, the patients who had ocular fundus lesions or patients who applied medicines such as pilocarpine.

Methods

All the patients were divided into control group (n=15), treatment group 1 (n=20) and treatment group 2 (n=19) according to a random number table. In control group, there were 8 males and 7 females with an average age of 46.7±4.6 years old. And their average disease duration was 6.4±3.1 years and average treatment time was 4.8±1.7 years. In treatment group 1, there were 11 males and 9 females with an average age of 44.7±1.6 years old. And their average disease duration was 6.8±3.5 years and average treatment time was 5.2±1.5 years. In treatment group 2, there were 10 males and 9 females with an average age of 45.3±2.2 years old, and their average disease duration was 7.0±3.6 years and average treatment time was 5.5±2.1 years. The comparison of gender, age, disease duration, treatment time and other factors among the three groups showed that the differences were not statistically significant (P>0.05), which suggested that these factors were comparable. General clinical treatment of glaucoma was performed in all three groups. Briefly, nimodipine (30 mg per tablet, one tablet twice daily) was applied in treatment group 1 while nifedipine (15 mg per tablet, one tablet twice daily) was applied in treatment group 2. During one year of follow-up visit, the IOP and eyesight were measured at the second, fourth, sixth, eighth, tenth, and twelfth month before and after treatment. And at the same time period, the visual field was detected by the same automatic perimeter and the retinal light sensitivity and the retinal scotoma change in three groups before and after treatment were compared. The scotoma enlargement or deepening could be regarded as progressive visual field damage and adverse reactions.

Statistical methods

The SPSS17.0 statistical software was applied for statistical analysis. The enumeration data were presented as n (%), and the comparison between groups was performed by using the chi-square test. The measurement data was expressed as mean ± standard deviation, and comparison between groups was done by the one-way ANOVA. P<0.05 was considered to indicate statistical significance.

Results

Comparison of IOP before and after treatment amongthe three groups

From the second to twelfth month before and after treatment, the IOP in the two treatment

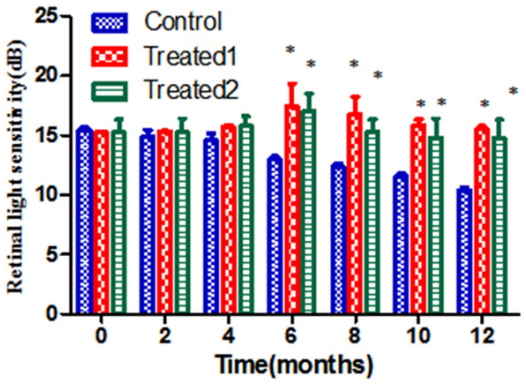

Figure 3. The comparison of retinal light sensitivity before and after treatment among three groups. Note: Compared with control group, *P<0.05. And there were no significant differences between treatment group 1 and treatment group 2, P>0.05.

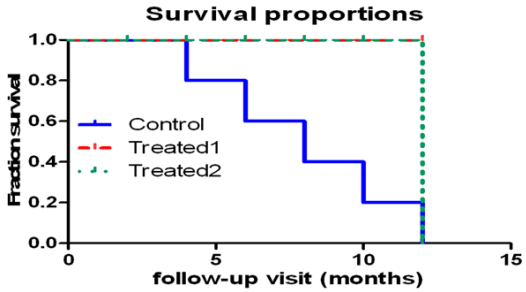

Figure 4. The comparison of progressive visual field damage before and after treatment among three groups.

groups were compared and the IOP in these two treatment groups were also compared with that in the control group. But the comparison results showed that there were no apparent differences (all P>0.05), as shown in **Figure 1**.

Comparison of visual score before and after treatment among the three groups

At each stage before and after treatment, the visual scores in the two treatment groups were compared and the visual scores in these two treatment groups were also compared with that in the control group. The comparison results showed that there were no obvious differences (P>0.05), as shown in **Figure 2**.

Comparison of retinal light sensitivity before and after treatment among the three groups

In the second and fourth month before and after treatment, there were no significant differences in retinal light sensitivity among three groups. After treating for six and twelve months, however, the retinal light sensitivity in control group started to decline from the sixth month after treatment. And the differences of retinal light sensitivity between the two treatment groups and control group were statistically significant (P=0.03; P=0.04), while there was no apparent differences between the two treatment groups (P=0.12), as shown in **Figure 3**.

Comparison of progressive visual field damage before and after treatment among the three groups

The survival curve of visual field damage showed that with the increasing of follow-up time, the visual field damage in control group was more serious than that in the two treatment groups (P=0.03). The visual field damage was milder in treatment group 1 and treatment group 2 and there was no significant difference between these two groups (P>0.05), as shown in **Figure 4**.

Adverse reactions

The blood pressure in the two treatment groups was decreased at different degrees after treatment as compared with that before treatment, ranging from 5 mmHg to 11 mmHg, while that in control group ranged from 3 mmHg to 5 mmHg. No patients felt uncomfortable. In treatment group 1, adverse reactions (facial flushing and transient dizzy) appeared in two patients respectively; in treatment group 2, adverse reactions such as facial flushing, dizziness, headache and tachycardia were experienced by six patients; and in control group, dizziness and headache appeared in one patient. The incidence of adverse reactions in treatment group 1 were significantly lower than that in treatment group 2 (P=0.02), See **Table 1**.

Discussion

Nowadays, glaucoma is the leading cause of blindness and the current treatment is mainly aimed at reducing the IOP. But clinical treatment has shown that the progressive visual field damage still occurs in patients even the IOP is well under control [10]. The pathogenesis of glaucoma is the continuous damage and apoptosis of RGCs: the high IOP and retinal ischemia in glaucoma patients can trigger lots

Table 1. The comparison of adverse reactions among three groups (n (%))

Group	Decrease of blood pressure	Facial flushing	Increase of heart rate	Dizziness and headache	Incidence
Treatment group 1 (n=20)	7.8±2.6	1	1	0	10%
Treatment group 2 (n=19)	8.3±3.1	3	2	1	31.5%*
Control group	4.3±1.1	0	0	0	6.7%

Note: Compared with Treatment group 1, *P<0.05.

of chain reactions: gradually lead to the decrease of neurotrophic factors within the RGCs layer, the increase of glutamic acid concentration in retina and vitrectomy, the calcium ion overload within the RGCs, and continuous increase of NO and free radical, all of which can result in the apoptosis of RGCs [11-13]. Previous studies have found that the visual functions in some glaucoma patients can improve effectively after the treatment with CCB [14-17]. In this study, we applied two common CCBs (nimodipine and nifedipine) and tried to investigate their therapeutic effects on glaucoma. The results of this study indicated that in the second, fourth, sixth, eighth, tenth and twelfth month before and after treatment, there were no obvious differences in the IOP and eyesight between the two treatment groups and control group (P>0.05). We speculated that on the one hand, it was because the general clinical treatment of glaucoma could well control the IOP, and CCB had no impact on the IOP in glaucoma patients. And on the other hand, it might also because the follow-up visit time was relatively short and the visual deterioration had not yet appeared in patients.

This study showed that the retinal light sensitivity and visual field in the two treatment groups after treatment had no significant differences with that before treatment, while which in control group were significantly decreased (P=0.03). It is known to all that the pathological basis which can lead to the glaucomatous visual function damage is the progressive apoptosis and loss of RGCs, which suggests that the improvement of glaucomatous visual function after applying nimodipine and nifedipine may be achieved by the effective protection to RGCs, and its possible mechanism is to correct the optic nerve ischemia [18]. Some studies have shown that the leading cause of nerve damage in glaucoma is the optic nerve ischemia, and the study of Schmidt et al. has indicated that there appears homeostasis function disorder in optic nerve vessels in glaucoma patients: the optic nerve vessel cannot automatically adjust to increase the blood flow when the IOP is increased [19]. The study of Ming Xiao et al. has found that the shrink of vessels is the main reason for the obvious decline of blood flow velocities in retrobulbar vessels in primary open-angle glaucoma patients and the application of nimodipine can significantly improve the blood flow of optic papillary laminar in glaucoma [20]. Besides, the abnormal blood rheology such as the increase of the whole blood viscosity may also occur in glaucoma patients, which can reduce the blood supply of the optic nerves. The application of CCBs can dilate the optic nerve vessels, prevent the vasospasm and increase the blood supply of optic nerves by preventing the calcium ion influx of vascular smooth muscle cells, thereby improving the visual field of patients. In addition, CCB can release and correct the calcium ionoverload of RGCs. Calcium ion, as the second intracellular messenger, plays a role of signals transmission during the apoptosis of RGCs. Therefore, the application of CCB can reduce the damage of RGCs in the high IOP state.

The studies mentioned above demonstrate that nimodipine and nifedipine (CCBs) can improve the ocular blood flow, correct optic nerve ischemia, reduce the damage and apoptosis of RGCs, and have significant therapeutic effects on the glaucoma treatment and visual function improvement. However, due to the limitation of our experimental conditions, the number of cases included in this study was limited, and there might have differences between the criteria for implementation of treatment program and the time or criteria for judging the results of treatment. Therefore, we need to further increase the number of sample cases to verify the results of this study.

In conclusion, nimodipine and nifedipine have similar therapeutic effects in protecting the visual field of glaucoma patients, and there have no adverse reactions on the IOP and eyesight among patients. The adverse reactions caused by nimodipine and nifedipine are similar, which mainly include transient hypotension, facial flushing, dizziness and headache, etc. However, the incidence of adverse reactions in the glaucoma treatment with nimodipine is significantly lower than that with nifedipine. Therefore, nimodipine is a safer and more ideal oral anti-glaucoma medication, which is worthy of clinical recommendation and application. And it can be applied as one of the combined medicines in the treatment of glaucoma.

Disclosure of conflict of interest

None.

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