

PROVENS® IN THE TREATMENT OF GLAUCOMA AND OCULAR HYPERTENSION

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SUMMARY

PROVENS® IN THE THERAPY OF GLAUCOMA AND OCULAR HYPERTENSION

Objective: To assess the effect of the ProVens® dietary supplement administration on intraocular pressure in patients with glaucoma and ocular hypertension.

Material and Methods: The patients included in the trial were given the ProVens® dietary supplement once daily. One ProVens® tablet contains: 50 mg of maritime pine bark extract, 100 mg of green tea extract, and 3 mg of blueberry extract. The main ProVens® components are proanthocyanins from the bark of the maritime pine tree *Pinus pinaster*, polyphenols from green tea, and anthocyanins from blueberries. The total number of patients included in the trial was 46. Out of these, 35 patients were monitored for asymptomatic ocular hypertension and 11 patients for open-angle glaucoma treated with prostaglandin analogs. Intraocular pressure was measured by applanation tonometry in the beginning of the trial, after one month, and after three months of their inclusion in the trial, always at the same time of the day.

Results: In the group of patients with ocular hypertension, there was a statistically significant reduction in the intraocular pressure from the baseline values of 24.2 ± 2.1 mm Hg to 20.9 ± 2.5 mm Hg within the period of three months ($p < 0.0001$). In the group of patients with open-angle glaucoma, there was a statistically significant reduction of the intraocular pressure from the baseline values of 18.4 ± 3.2 mm Hg to 17.0 ± 3.1 mm Hg within the period of three months since the beginning of administration of the product ($p = 0.022$). When comparing both groups, we observed a significantly higher reduction in intraocular pressure ($p = 0.0001$) in the group of patients with ocular hypertension. In the whole group, no adverse effects were reported during the intake of this dietary supplement.

Conclusion: Intake of the ProVens® dietary supplement containing proanthocyanins from the bark of the maritime pine tree *Pinus pinaster* together with a mixture of herbal antioxidants appears to be one of the methods of how to improve the control of intraocular pressure, particularly in patients with ocular hypertension.

Key words: glaucoma, ocular hypertension, ProVens®, proanthocyanins, antioxidants, maritime pine bark extract

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INTRODUCTION

Glaucoma is a multifactorial pathology which is defined by the progressive loss of retinal ganglion cells, leading to atrophy of the optic nerve and defects in the visual field. The only risk factor which we are unequivocally able to influence medically at present is increased intraocular pressure (IOP) [16]. Both conservative and surgical procedures are used to reduce IOP. However, some patients also seek alternative possibilities for influencing this pathology [33]. Recently attention has been focused on the potential influence of dietary factors and the use of food supplements to influence the course of the disease and on the actual risk of its occurrence. For example, studies have been published assessing the influence of caffeine on IOP [15,23] or a possible linkage between increased iron and calcium intake and glaucoma [34]. Antioxidants and their protective influence on ganglion cells have been discussed in a number of international studies [9, 31, 35]. Kang et al. [14] in a prospective study did not demonstrate that a higher intake of antioxidants in food could act as prevention against the occurrence of glaucoma. On the other hand, epidemiological studies

published later demonstrated a potential correlation between a higher intake of a certain type of fruit and vegetables rich in vitamins A, C and carotenoids (in particular carrots, green leaf vegetables, conserved or dried peaches) and a lower risk of the incidence of glaucoma, mainly in older women [3,7]. Steigerwalt et al. [28] demonstrated a positive effect of the dietary supplement Mirtogenol® (extract from the bark of French maritime pine and blueberries) on reducing intraocular pressure and improving ocular perfusion in patients with asymptomatic ocular hypertension. They also demonstrated its additive effect to latanoprost [30].

The aim of our study was to determine the effect of administration of the dietary supplement ProVens® (extract from maritime pine bark, green tea and blueberries) on intraocular pressure in patients with ocular hypertension or open-angle glaucoma on monotherapy with prostaglandin analogues.

METHOD

Study design

The multicentric prospective study, which took place in four

centres, included patients with ocular hypertension without local antiglaucomatous therapy or with open-angle glaucoma on monotherapy with prostaglandin analogues. The basic inclusion criterion for patients with ocular hypertension was intraocular pressure (IOP) (NOT) ≥ 22 mm Hg. At the time of inclusion in the study (and for at minimum six months previously) these patients did not apply any local antiglaucomatous treatment. In patients with open-angle glaucoma, the fundamental condition for inclusion in the study was local monotherapy using prostaglandin analogues for at least six months. Patients who had undergone an antiglaucomatous or other ocular surgical procedure were excluded from the study. All the patients were provided with detailed information and expressed consent to their inclusion in the study.

At the baseline examination we recorded the patients' demographic data, conducted a complete ophthalmological examination and measured the applanation value of IOP. The patients included in the study began to use the dietary supplement ProVens[®] in a dose of one tablet daily, taken in the morning. One ProVens[®] tablet contains: 50 mg of maritime pine bark extract, 100 mg of green tea extract and 3 mg of blueberry extract. The main components of ProVens[®] are proanthocyanins from the bark of the maritime pine tree *Pinus pinaster*, polyphenols from green tea, and anthocyanins from blueberries. A control examination was conducted on all patients after one month, with the final follow-up examination after 3 months. In all cases we measured IOP by applanation tonometry, always at the same time of day ± 1 h. At the final follow-up examination the patients completed a questionnaire focusing on their subjective feelings after three months of use of the dietary supplement ProVens[®].

Characteristics of study cohort

A total of 46 patients (92 eyes) were included in the study within the observed period. Of these, 35 patients (70 eyes) were observed for asymptomatic ocular hypertension – 11 men and 24 years within the age range of 19 to 85 years (average 50.9 years). 11 patients (22 eyes) were observed for open-angle glaucoma receiving treatment with prostaglandin analogues – 5 men and 6 women aged between 37 and 74 years (average 66.9 years).

Data analysis and statistical evaluation:

The data of each included patient was recorded in the forms which each centre received before the commencement of the study. The data was converted into electronic form, subjected to a descriptive analysis and statistically processed (average, standard deviation, median, quartiles, recorded extreme values). The normality of the data was verified using a Shapiro-Wilk test. A Wilcoxon paired test with Bonferroni correction of significance to multiple comparison was used for the comparison of IOP in the group with hypertension, and in the group with open-angle glaucoma a Student paired t-test with Bonferroni correction of significance to multiple comparison was used. For comparison of the size of the change of IOP between both groups after 1 and 3 months of therapy we used a Mann-Whitney U test. The tests were conducted on a level of significance of 0.05. For statistical analysis of data the software SPSS version 15 was used (SPSS Inc., Chicago, USA).

RESULTS

In the group of patients with ocular hypertension, a reduction of the average IOP value (\pm SD) was achieved from 24.2 ± 2.1 mm Hg to 21.4 ± 2.2 mm Hg after 1 month ($p < 0.0001$) and to 20.9 ± 2.5 mm Hg after 3 months ($p < 0.0001$). After both one and three months there was a significant reduction of IOP in comparison with its baseline values (graph 1). No significant difference was demonstrated between the IOP values after one and three months ($p = 0.153$).

In the group of patients with open-angle glaucoma, a reduction of the average IOP value (\pm SD) was achieved from 18.4 ± 3.2 mm Hg to 17.0 ± 3.6 mm Hg after 1 month ($p < 0.052$) and to 17.0 ± 3.1 mm Hg after three months from the beginning of administration of the supplement ($p = 0.022$). After three months there was a significant reduction of IOP in comparison with its baseline values (graph 2). No significant difference was demonstrated between the IOP values after one and three months ($p = 1.000$).

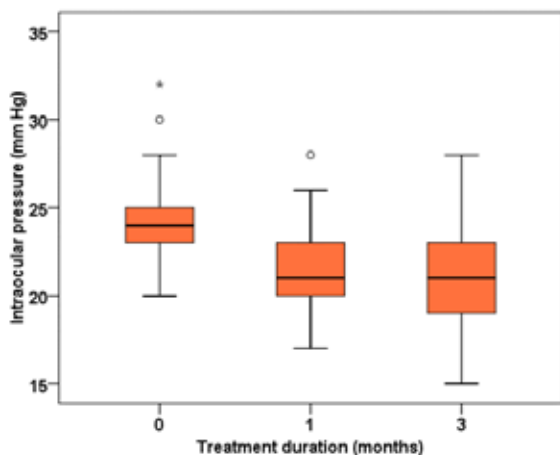
Upon a comparison of both groups, there was a significantly larger reduction of IOP after one month ($p = 0.003$) and after three months ($p = 0.0001$) in the group of patients with ocular hypertension (graph 3).

No adverse effects upon the use of this supplement were recorded throughout the entire study cohort. Subjectively the patients stated the following changes: 5 patients had a feeling of improved complexion, one patient less dryness of the skin on her hands, one patient an improvement of the condition of her nails, 10 patients had a feeling of improved vision and one patient better vision in twilight, 3 patients stated an improvement of dry eye syndrome, one patient less lachrymation, 10 patients a lesser feeling of cold hands and feet, 15 patients stated that they "felt better in general" and 2 patients felt an improvement in the sexual realm.

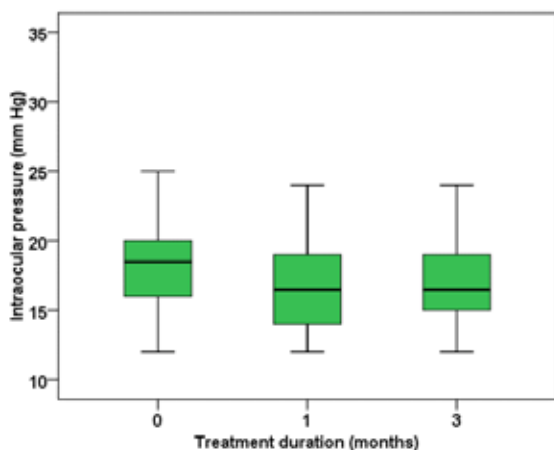
DISCUSSION

The positive effect of extract from the bark of the maritime pine *Pinus pinaster* on a whole range of degenerative diseases has been known for a long time in medicine, and highly diverse pharmacological properties are attributed to this extract [24]. It is commercially available as an over-the-counter dietary supplement under the protected name of Pycnogenol[®]. The potential for the use of the properties of Pycnogenol[®] in medicine is very broad. In studies its positive effect has been demonstrated especially on improving blood circulation, blood pressure and venous insufficiency [2, 10, 12].

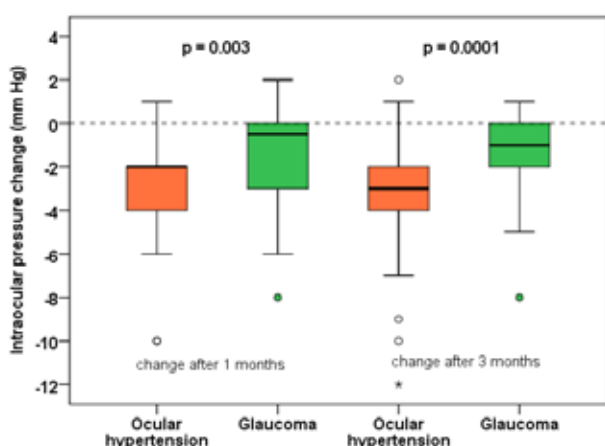
Use of maritime pine bark extract in ophthalmology appears to be promising especially for patients with diabetic retinopathy [26, 27, 29]. Pycnogenol[®] acts as an antioxidant, and in synergy with lutein prevents the oxidation of lipids [20]. It is also presumed to have an anti-inflammatory effect [13]. Furthermore it has been demonstrated that it stimulates the release of nitrous oxide. It thereby facilitates vasodilation and acts preventively against ischemia, which is a triggering factor for angiogenesis in diabetic retinopathy [21]. In clinical trials its positive effect on improving ocular perfusion has been demonstrated [28, 29, 30]. In addition to this, it inhibits alpha-glucosidase, which leads to a reduction in the level of glucose in the blood in diabetics [8].



Graph 1 In the group of patients with ocular hypertension, a reduction of the average value of intraocular pressure (\pm SD) was achieved from 24.2 ± 2.1 mm Hg to 21.4 ± 2.2 mm Hg after 1 month ($p < 0.0001$) and to 20.9 ± 2.5 mm Hg after 3 months ($p < 0.0001$).



Graph 2 In the group of patients with open-angle glaucoma, a reduction of the average value of intraocular pressure (\pm SD) was achieved from 18.4 ± 3.2 mm Hg to 17.0 ± 3.6 mm Hg after 1 month ($p < 0.052$) and to 17.0 ± 3.1 mm Hg after 3 months ($p < 0.022$).



Graph 3 Upon a comparison of the group of patients with ocular hypertension and the group of patients with open-angle glaucoma, a significantly larger reduction of intraocular pressure was achieved after one month ($p = 0.003$) and after three months ($p = 0.0001$) in the group of patients with ocular hypertension.

The potential influence of a combination of natural flavonoids on the level of intraocular pressure was evaluated by Steigerwalt et al. [28, 30]. The patients included in the published studies were administered the dietary supplement Mirtogenol®. This is a preparation containing extract from the bark of French maritime pine (Pycnogenol®) and blueberry extract (Mirtoselect®). One tablet contains 80 mg of Mirtoselect® and 40 mg of Pycnogenol®. In their first prospective trial [28] they administered Mirtogenol® to 20 patients with asymptomatic ocular hypertension in a dose of one tablet every morning and one tablet every evening for a total period of 6 months. After three months they demonstrated a significant reduction of IOP in comparison with the control group, from 25.2 mm Hg to 22.0 mm Hg. After 6 months they did not record any further reduction of IOP. This result also corresponded with an improvement of ocular perfusion. In their second trial [30] they randomised 79 patients with asymptomatic ocular hypertension into three groups. The first group took one Mirtogenol® tablet each morning, the second group applied latanoprost eye drops locally and the third group took one Mirtogenol® tablet each morning and also applied latanoprost locally. In the first group a reduction of IOP was achieved from baseline values of 38.1 mm Hg to 29.0 mm Hg after 16 weeks. After a further 8 weeks a further small reduction of IOP was recorded. In the second group a reduction of IOP was achieved from 37.7 mm Hg to 27.2 mm Hg after only 4 weeks, at subsequent follow-up examinations no further reduction of IOP was recorded. Mirtogenol® administered separately therefore had an effect on reducing IOP comparable to that of locally applied latanoprost, nevertheless the effect was manifested later (in the group with latanoprost after only 4 weeks, in the group with Mirtogenolem® after as long as 24 weeks). In the third group a reduction of IOP was achieved after 4 weeks from 38.0 to 27.3 mm Hg. After another 6 weeks IOP was reduced to 24.2 mm Hg, after 24 weeks to 23.0 mm Hg. After 24 weeks IOP in the third group was therefore significantly lower (23.0 mm Hg) than in the group applying only latanoprost (27.2 mm Hg). Combined administration of Mirtogenol® and latanoprost also had a more pronounced effect on improving ocular perfusion than separate application of latanoprost or only administration of Mirtogenol®.

Steigerwalt et al. believe that the positive effect of the dietary supplement Mirtogenol® on reducing IOP in patients with ocular hypertension is very probably due to normalisation of the capillary filtration of the ciliary body [30]. Both of the agents contained in this preparation share actively in this process – extract from French maritime pine bark (Pycnogenol®) and extract of blueberry (Mirtoselect®). As stated above, Pycnogenol® stimulates the release of endothelial nitrous oxide [21]. It also improves pathological vascular permeability [25] and reduces blood pressure [10]. Liu et al. [17] demonstrated in their study that Pycnogenol® also reduces the level of endothelin-1 in plasma in type 2 diabetics. It is precisely endothelin-1 that has been identified in an increased quantity in the chamber fluid in patients with open-angle glaucoma [4]. The second agent in the preparation, blueberry extract, then acts against hyperpermeability of the ciliary capillaries [19, 32]. The effect of this extract on ocular microcirculation has also been studied in patients with glaucoma and myopia [1]. A positive

influence has also been demonstrated on patients with diabetic retinopathy, in which its use led to a significant reduction of retinal haemorrhages and a regression of focal retinal edema [22]. In addition to this, anthocyanins contained in blueberry extract are the only flavonoids that have been distributed in unaltered form in the ocular tissues on an animal model (following peroral administration and absorption) [6]. However, despite all these observations, it is still not unequivocally clear as to whether Mirtogenol® influences primary drainage of chamber fluid, its production, or both.

For our study we chose the dietary supplement ProVens®, which is freely available on our market. This preparation contains maritime pine bark extract (50 mg/tbl) and blueberry extract (3 mg/tbl), and additionally contains green tea extract (100 mg/tbl). This composition appeared ideal to us for the content of all three agents. The effects of proanthocyanins from the bark of maritime pine and anthocyanins from blueberries are discussed above. The main agent of green tea extract is epigallocatechin gallate (EGCG). This is a strong antioxidant with presumed neuroprotective, antiapoptotic and anti-inflammatory effects [11, 36]. Falsini et al. [5] in their double-blind trial determined a positive influence of three-monthly use of EGCG on the function of the internal layer of the retina in patients with open-angle glaucoma.

The dietary supplement ProVens® can be taken 2x daily. Nevertheless, in our study we administered it 1x daily, in the morning. We recommended that patients take the preparation in the morning hours precisely due to the green tea content. In the literature dosing of Pycnogelu® is recommended (for patients with diabetic retinopathy) within the range of 20 - 160 mg/day, depending on the severity of the disease. The length of use is recommended for at minimum 2 - 3 months [13]. For patients with asymptomatic ocular hypertension, Steigerwalt et al. demonstrated a positive effect on reduction of IOP upon the use of 40 mg of Pycnogenol® [30]. In our case we administered 50 mg of maritime pine bark extract daily. At this dose we demonstrated a positive effect of the preparation ProVens® on reducing IOP. At present the second part of the study is under

way, the objective of which is to determine whether the use of two tablets of ProVens® (thus 100 mg of maritime pine extract) will have a more pronounced effect on reducing IOP.

Adverse effects upon the use of Pycnogel® are described only very rarely in the literature. They include gastrointestinal discomfort, dizziness, nausea and headache. At present the long-term use of Pycnogel® in a dose of 20 – 100 mg daily, and short-term use in a dose of 100 – 300 mg daily is considered safe [18]. In our study we did not record any adverse effects of the use of ProVens® in a dose of 1 tablet daily (50 mg of maritime pine extract). On the contrary, a number of patients felt subjectively better after three months of use of one ProVens® tablet. Some patients recorded an improvement of the condition of their skin or nails, or of a feeling of cold hands and feet. Two male patients also spontaneously stated an improvement in the sexual realm (the questions in the subjective satisfaction questionnaire did not relate to this area).

CONCLUSION

The results of our study confirmed a positive effect of the use of the dietary supplement ProVens® on reducing IOP in patients with asymptomatic ocular hypertension. We also demonstrated its additive effect in combination with locally administered prostaglandin analogues on patients with open-angle glaucoma. These results are very promising. Use of the dietary supplement ProVens® with a content of proanthocyanins from the bark of the maritime pine *Pinus pinaster*, together with a compound of vegetable antioxidants may represent one of the paths to improving control of intraocular pressure in our patients.

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