Effects of Hyperuricemia Treatment with Allopurinol on Intraocular Pressure, Central Corneal Thickness, Nerve Fiber Layer and Visual Field

Allopurinol ile Hiperürisemi Tedavisinin Göz İçi Basınç, Merkezi Kornea Kalınlığı, Sinir Lifi Tabakası ve Görme Alanı Üzerine Etkileri

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Original Article

ABSTRACT

Purpose: To investigate the effects of lowering serum uric acid levels of hyperuricemia patients with allopurinol on ocular parameters associated with glaucoma.

Materials and Methods: 33 patients with hyperuricemia were assigned to oral allopurinol treatment for 3 months. Before the treatment with allopurinol and at the end of 3rd month of the treatment, all the patients underwent blood uric acid determination and intraocular pressure measurement with Goldman applanation tonometry, visual field examination, mean retinal nerve fiber layer thickness and central corneal thickness measurements.

Results: Mean uric acid level decreased to 5.27±1.58 mg/dl from pretreatment value of 7.60±0.53 mg/dl with allopurinol therapy at the end of 3rd month (p<0.001). There were no statistically significant changes in mean deviation, nerve fiber layer thickness, manifest refraction, central corneal thickness and intraocular pressure values after hyperuricemia treatment (p>0.05). Only pattern standard deviation value significantly decreased (p=0.02). However, with Pearson’s correlation test, there was no correlation between change of uric acid levels and other measured parameters.

Conclusion: Decreasing plasma uric acid concentrations with allopurinol therapy in hyperuricemic patients did not have significant effects on IOP, visual field, nerve fiber layer and central corneal thickness in a short term basis. Role of hyperuricemia in glaucoma pathogenesis seems to be controversial.

Key Words: Uric acid, intraocular pressure, glaucoma, allopurinol, corneal thickness.

ÖZ

Amaç: Hiperürisemili hastalarda serum ürik asit seviyesinin düşürülmesinin glokomla ilişkili parametrelerle olan etkisini incelemek.


Bulgular: Ortalama serum ürik asit seviyesi 7.60±0.53 mg/dl değeri allopurinol tedavisi sonrası 5.27±1.58 mg/dl değerine düştü (p<0.001). Görme alanını ortalamada sapma değeriinde, sinir lifi kalınlığında, manifest refraksiyonunda, merkezi kornea kalınlığında, göz içi basınıncında hiperürisemi tedavi sonrası istatistiksel olarak anlamalı fark izlenmedi (p>0.05). Yalnızca pattern standart sapma değeri anlamalı olarak düşüşü (p=0.02). Ancak Pearson korelasyon analizi ile ürik asit seviyesi değişimi ile diğer ölçülen parametreler arasındaki korelasyon tespit edilemedi.


Anahtar Kelimeler: Ürik asit, göz içi basınıc, glokom, allopurinol, kornea kalınlığı.

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INTRODUCTION

Uric acid is a significant constituent of aqueous humor and vitreous. Reviews by Ames and Becker have held up the concept that uric acid might have important function in certain mammalian species as an antioxidant. Elisaf et al. showed that abnormalities of urate metabolism such as hyperuricemia and defective renal tubular transport of the urate were more common in glaucoma patients compared to the healthy control population. Uric acid metabolism was suspected to play a role in glaucoma damage and pathogenesis. In addition, an increased risk of cataract and age related macular degeneration was found to be associated with increased serum levels of uric acid. However, there is no data about the effect of treatment of hyperuricemia on intraocular pressure (IOP), central corneal thickness (CCT), visual field, refraction and nerve fiber layer. We therefore designed this study to investigate the effects of lowering serum uric acid levels of hyperuricemia patients with allopurinol on ocular parameters associated with glaucoma.

MATERIALS AND METHODS

33 adult patients (18 men, 15 women) with hyperuricemia participated in the study. For convenience, only the left eyes of the patients were recruited in the study when appropriate. The study was approved by the institutional review board, and patients gave informed consent for their participation. Included subjects had to fulfill the following inclusion criteria: normal renal function, defined as serum creatinine level less than 1.4 mg/dl, in stable general condition, patients not using any agents directly effect serum uric acid level such as thiazide. Patients with a history of renal stones, uncontrolled hypertension, diabetes mellitus, heart failure, clinical evidence of atherosclerosis (stroke, coronary, and peripheral artery disease), alcohol abuse, proteinuria (>500 mg/day), retinal vascular, hereditary or metabolic diseases, advanced cataract, history of ocular trauma or surgery, corneal pathologies, a known history of allopurinol hypersensitivity, already taking allopurinol therapy were not included in the study.

Hyperuricemia was defined as serum uric acid levels >7 mg/dl. For treatment, daily 300 mg oral allopurinol was prescribed for 3 months. Any adverse event considered to be related to the use of allopurinol was recorded. If adverse event, including Stevens-Johnson syndrome and hepatitis occurred, allopurinol therapy would be discontinued.

Systolic and diastolic blood pressure was measured before starting allopurinol and at 3 months after starting allopurinol. During the follow-up the antihypertensive therapy, as well as the concurrent medications, were kept constant. Patients with uncontrolled hypertension during the study were dropped out from the study.

Before the treatment with allopurinol and at the end of 3rd month of the treatment, all the patients underwent blood uric acid determination and a complete ophthalmologic examination including uncorrected and best corrected visual acuities, manifest refraction, slit lamp examination, dilated fundus examination, IOP measurement with Goldman applanation tonometry, visual field examination, mean retinal nerve fiber layer (RNFL) thickness with Heidelberg Retinal Tomography II, CCT measurement with pachymetry. CCT was determined by an ultrasonic pachymeter (Echo Scan US-80, Nidek, Japan). The pachymeter probe was placed on the center of the cornea over an undilated pupil and the mean of three readings within a standard deviation of ±5 μm was calculated for each eye.

Visual field testing was performed by Humphrey visual field analyser (Humphrey Instruments, San Leandro, CA, USA) using full threshold strategy and the central 30–2 program. Visual field tests were performed by the same technician in a standard fashion with appropriate refractive correction. Before the actual visual field testing was obtained, two initial visual field testings were done in order to minimize learning effect. The pupil size during perimetric tests was at least 4.5 mm. Regarding interpretation of visual fields, mean deviation (MD) indicating difference between mean sensitivity obtained and that expected, pattern standard deviation (PSD) indicating the

Table: Uric acid concentration, MD, PSD, RNFL thickness, refraction, CCT and IOP values before and after allopurinol treatment.

<table>
<thead>
<tr>
<th></th>
<th>Pretreatment</th>
<th>At the end of 3rd month</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid (mg/dl)</td>
<td>7.60±0.53</td>
<td>5.27±1.58</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>MD</td>
<td>-2.80±2.43</td>
<td>-2.71±2.58</td>
<td>p=0.804</td>
</tr>
<tr>
<td>PSD</td>
<td>2.64±0.69</td>
<td>1.81±0.48</td>
<td>p=0.02</td>
</tr>
<tr>
<td>RNFL thickness (μm)</td>
<td>234.28±70.44</td>
<td>238.07±84.48</td>
<td>p=0.636</td>
</tr>
<tr>
<td>SE of refraction (D)</td>
<td>0.66±1.50</td>
<td>0.57±1.55</td>
<td>p=0.063</td>
</tr>
<tr>
<td>CCT (μm)</td>
<td>546.93±23.97</td>
<td>547.71±26.00</td>
<td>p=0.644</td>
</tr>
<tr>
<td>IOP (in mmHg)</td>
<td>15.00±2.49</td>
<td>15.29±2.67</td>
<td>p=0.451</td>
</tr>
</tbody>
</table>

Statistically significant differences were given in bold.

Abbreviations: MD: mean deviation, PSD: pattern standard deviation, RNFL: retinal nerve fiber layer, CCT: central corneal thickness, IOP: intraocular pressure
regional non-uniformity of a visual field after adjusting for the mean defect of the entire field were evaluated.

A trained operator obtained optic nerve head measurements three times through undilated pupils with a Heidelberg Retina Tomograph II (HRT version 2.11; Heidelberg Engineering, Heidelberg, Germany), the details of which have been reported elsewhere. A contour line was drawn as coincident with the inner border of the scleral ring (the Elschnig ring), or with the outer border rim edge when the Elschnig ring was unclear. Stereometric disc and retinal nerve fiber layer (RNFL) parameters were calculated automatically. Data from deformed discs (e.g., markedly tilted) or poor-quality images were excluded from the study. Mean retinal nerve fiber layer (RNFL) thickness was used for statistical evaluation.

Parameters were analyzed on computer (SPSS for Windows, ver. 12.0, Statistical Package for Social Sciences; SPSS, Inc., Chicago, IL). Unless otherwise stated, values are expressed as mean±standard deviation (SD). Pre and post-treatment changes in parameters were compared with paired t test. Pearson’s test was performed for analysis of correlation between changes in serum uric acid and changes in other parameters. Mann-Whitney U testing was used to compare results of hypertensive patients with that of the patients without hypertension. Statistical significance is defined as P value less than 0.05.

RESULTS

A total of 31 patients (17 males, 14 female) completed the 3-month follow-up period of observation. Two patients were dropped out of the study because of poor compliance. Mean age of the patients in study was 66.00±7.08 (range; 54 to 79). Hypertension was present in 12 patients. We could not detect glaucoma or increased IOP in any of the examined eyes before the therapy and at the 3rd month of hyperuricemia therapy with allopurinol.

Mean uric acid level at the end of 3rd month significantly decreased to 5.27±1.58 mg/dl from pretreatment value of 7.60±0.53 mg/dl with allopurinol therapy (table). When the pre and the post-treatment ocular parameters were compared, only pattern standard deviation value significantly decreased after decreasing uric acid concentration. There were no statistically significant changes in MD, RNFL thickness, spheric equivalent (SE) of manifest refraction, CCT, and IOP values after hyperuricemia treatment (table). Nerve fiber layer thickness, visual field examination and IOP were within normal range in all of the patients in the study. With Pearson’s correlation test, there was no correlation between change of uric acid levels and changes in MD, PSD, RNFL thickness, manifest refraction, CCT, and IOP values. There were no statistically significant differences between hypertensive and non-hypertensive patients in terms of pre and post-treatment values of serum uric acid concentration, MD, PSD, RNFL thickness, manifest refraction, CCT, and IOP.

At slit-lamp biomicroscopy, slight cortical and nuclear lens opacity was present in two eyes at pretreatment examination. In none of the eyes the progression or new development of the cataract was observed.

DISCUSSIONS

In this study, we examined possible associations between treatment of hyperuricemia with allopurinol and IOP; visual field examination, CCT, nerve fiber layer thickness. The analysis showed that decreasing plasma uric acid concentrations with allopurinol therapy did not have any effects on IOP, visual field examination, CCT, nerve fiber layer thickness of the patients with hyperuricemia.

Uric acid is the end product of purine metabolism in humans. Urate serves as a primary antioxidant in human blood because it can remove singlet oxygen and radicals as effectively as vitamin C. However, hyperuricemia can be detrimental in humans, as demonstrated by its proven pathogenetic roles in gout and nephrolithiasis and by its putative roles in hypertension and other cardiovascular disorders. Similar to plasma uric acid, aqueous humor uric acid which could normally have a protective role for ocular tissues may become detrimental on ocular tissues in case of increased concentration. Recently, Elisaf et al. showed that disturbances of urate metabolism such as hyperuricemia and defective renal tubular transport of the urate were more common in glaucoma patients compared to the control population. In addition to uric acid abnormalities, Elisaf et al. showed that disturbances of carbohydrate metabolism were fairly common in patients with POAG. They showed that urate metabolism abnormalities observed in POAG patients cannot be ascribed to the coexistent carbohydrate metabolism disturbances. Authors concluded that uric acid metabolism could play a role in glaucoma damage and pathogenesis. Jampel et al. have found that uric acid levels were higher at the time of surgery in eyes that had unsuccessful outcomes than in those with successful outcomes. A higher uric acid level in the aqueous humor has been proposed as a risk factor for trabeculectomy failure. Elevated uric acid might have deleterious effects on trabecular tissues, retinal cells and/or wound healing. These may enhance the progression of glaucomatous optic nerve damage.

Increased susceptibility to glaucoma may results from long term exposure to hyperuricemia involving mechanism other than increased IOP. There is increasing evidence that uric acid has pro-inflammatory and proliferative effects on smooth muscle cells, and causes dysfunction of endothelial cells via stimulation of COX-2, PDGF A and C chain, blockage of nitric oxide and various inflammatory mediators, including C-reactive protein and monocyte chemoattractant protein-1. Similar interaction of elevated intraocular uric acid with cytokines may result in increased vulnerability to glaucoma. In ad-
dition, urate induced endothelial dysfunction may also affect corneal endothelium, hence cause increased corneal thickness.

In a short follow-up we could not find any significant changes in visual field, central corneal pachymetry, nerve fiber layer thickness and IOP between hyperuricemic and normouricemic status of the same patients. The decrease in PSD following allopurinol treatment may be ascribed to long term variations in visual field or learning effect despite preventive efforts by initial two visual field examinations before actual visual field. Visual field examination reveals the functional status of the retina and optic nerve as well as structural changes such as nerve fiber layer loss.19 Metabolic changes such as hypoglycemia can cause reversible visual field changes due to functional stress on retinal cells.20 In a similar manner, hyperuricemia might have affected visual field. However, we did not find significant visual field changes with decreased uric acid levels.

In vitro studies have indicated that uric acid can inhibit oxidative degradation of some glycosaminoglycans (GAG) antagonizing ascorbate.21 In the patients with primary open angle glaucoma, abnormal GAG accumulation was detected in the juxtaocular tissue of trabecular meshwork.22 In another, experimental studies have shown that increased concentration of hyaluronic acid and chondroitin sulfate could increase the outflow resistance at trabeculum.23 It is possible that increased intraocular uric acid may lead IOP increase through abnormal GAG accumulation in trabecular meshwork. In our study, we have not detected either IOP above normal range in patients with hyperuricemia or significant IOP change as blood uric concentration decreased with uricolyis, showing that blood uric acid levels do not have significant effect on IOP.

Human aqueous humor uric acid is only a fraction of human plasma concentration, signifying that uric acid does not easily enter the anterior-chamber.24 In an experimental rabbit study looking for sources for the high levels of uric acid in the aqueous humor from human glaucoma, Bonney et al. showed that the blood-aqueous barrier could effectively prevent equilibration between the systemic and ocular compartments.25 Accordingly, internal milieu of the human eye may not be influenced by changes in plasma uric acid concentration explaining absence of any significant changes in measured ocular parameters in our study.

CCT measurements were influenced by a number of factors such as time of the day, eye drops, dryness, hypothyroidism and plasma glucose levels.26-31 In contrast, nerve fiber layer thickness measurements was usually stable and only affected by age, progression of glaucoma.31,32 Proposed mechanisms for corneal thickness changes include disturbed ATPase and carbonic anhydrase activities, decreased oxygen availability, dehydration and upregulation of matrix metalloproteinases.28,31,32 In our study, changes in plasma uric acid concentrations had no influence on central corneal thickness and nerve fiber layer thickness. Possibly the plasma uric acid concentration might not have any significant effects on metabolism of corneal endothelium and/or epithelium.

Among the limitations of this study are that a 3-month duration is a short time in studying a slowly progressive disease such as glaucoma. In addition, the effect of allopurinol on intraocular uric acid levels was unknown, limiting the interpretation of the results.

In conclusion, decreasing plasma uric acid concentrations with allopurinol therapy in hyperuricemic patients did not have significant effects on IOP, visual field, nerve fiber layer and central corneal thickness in a short term basis. Role of hyperuricemia in glaucoma pathogenesis seems to be controversial and should be examined with randomized prospective studies.

KAYNAKLAR/REFERENCES


