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The impact of common classes of topical antiglaucoma medications on central corneal thickness – own observations

Wpływ aktualnie stosowanych miejscowych leków przeciwjaskrowych na grubość centralnej rogówki – obserwacje własne

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Summary: Purpose: To investigate the influence of common classes of topical antiglaucoma medications used either in monotherapy or combined therapy on CCT.
Material and methods: In a retrospective study 487 eyes from consecutive 260 patients (148 F/ 112 M) with open angle glaucoma were examined. Depending on the topical treatment they were classified into 7 groups: A/ PGA (n = 212), B/ BB (n = 54), C/ CAI (n = 36), D/ PGA + CAI (n = 25) E/ PGA + BB (n = 23) F/ BB + CAI (n = 54), G/ non-treated (n = 83). The CCT was measured using ultrasound pachymetry Tomey AL-2000. The central corneal power was measured with the Topcon keratometer. ANOVA analyses were used for statistical analysis. Results: There were no statistically significant differences between CCT of all groups (F = 1.06, p = 0.3931); the lowest values were in the eyes treated with PGA + BB (535.9 μm SD 31.4) and the highest in the eyes treated with PGA + CAI (571.3 μm SD 46.3). The Mean CCT in group A was 550.4 μm (SD 40.8), group B 552.5 μm (SD 34.7), group C 562.6 μm (SD 40.2), group D 571.3 μm (SD 46.3), group E 535.9 μm (SD 31.4), group F 559.5 μm (SD 32.5), group F 557.5 μm (SD 42.2). There were no statistically significant differences between CCT of eyes treated with different PGA. The highest CCT was found in the eyes treated with bimatoprost (554.4 μm SD 46.0) and the lowest in the eyes treated with latanoprost (546.4 μm SD 37.7).
Conclusions: In this study CCT appears not to differ in eyes treated with different classes of antiglaucoma medications either in monotherapy or combined therapy. CCT appears not to differ in eyes treated with different prostaglandin and prostamide analogs. CCT of treated glaucoma eyes does not differ from CCT of untreated glaucoma eyes.

Słowa kluczowe: jaskra, grubość centralnej rogówki, analogi prostaglandyn, metaloproteinazy macierzy zewnątrzkomórkowej, beta-blokery, miejscowe inhibitory anhydrazy węglanowej.

Key words: glaucoma, central corneal thickness, prostaglandin analogs, matrix metalloproteinases, beta-blockers, topical carbonic anhydrase inhibitors.

Lowering of IOP remains the only current therapeutical approach for preserving visual function in patients suffering from glaucoma and is the goal of currently available glaucoma treatment. Topical application of antiglaucoma eyedrops has been the primary mode of glaucoma treatment. Prostaglandin $F_{2\alpha}$ analogs (PGA) and prostamides as the most potent IOP lowering agents, have revolutionized the treatment of glaucoma and they are poised to become the first line of drug therapy for this prevalent disorder. $PGF_{2\alpha}$ analogs exerts its biological effects by binding to and activating FP prostanoid receptors, which is concerned with activation and/ or production of four matrix metalloproteinases (MMPs): MMP-1, MMP-2, MMP-3 and MMP-9. Their action cause enzymatic degradation of components of ciliary muscle extracellular matrix (ECM) which finally leads to facilitate uveoscleral flow (1). It has been shown that $PGF_{2\alpha}$ receptors and MMPs are also expressed in the epithelium and stroma of the cornea (2) and PGA may induce biochemical and/or morphological changes in corneal stroma thus affecting central corneal thickness (CCT) (3). Beta-blockers (BB) and topical carbonic anhydrase inhibitors (CAI) were found to have rather no effect on CCT (3-6).

The purpose of the study was to investigate the influence of common classes of topical antiglaucoma medications used either in monotherapy or combined therapy on CCT in patients treated for open angle glaucoma.

Material and methods

In a retrospective study 487 eyes from consecutive 260 patients (148 F/ 112 M, aged 26-90, mean 58.7) with open angle glaucoma were examined. Depending on the topical treatment they were classified into 7 groups: A/ PGA (n = 212), B/ BB (n = 54), C/ CAI (n = 36), D/ PGA + CAI (n = 25) E/ PGA + BB (n = 23) F/ BB + CAI (n = 54), G/ non-treated (n = 83). The CCT was measured using ultrasound pachymetry Tomey AL-2000 (sequence of 5 measurements with an SD < 3 μm) between 9 AM and noon. The central corneal power was measured with the Topcon keratometer. ANOVA methods were used for statistical analysis. P -values <0.05 were considered statistically significant.

Results

253 right eyes and 234 left eyes were examined. There were no statistically significant differences between mean CCT of all groups (F = 1.06, p = 0.3931); the lowest values were in the eyes treated with PGA + BB (535.9 μm SD 31.4) and the highest were in the eyes treated with PGA + CAI (571.3 μm SD 46.3). The mean CCT in group A was 550.4 μm (SD 40.8), in group B 552.5 μm (SD 34.7), in group C 562.6 μm (SD 40.2), in group D 571.3 μm (SD 46.3), in group E 535.9 μm (SD 31.4), in group F 559.5 μm (SD 32.5) and in group F 557.5 μm (SD 42.2). There were no statistically significant differences between mean CCT of the group of eyes treated with different PGA.

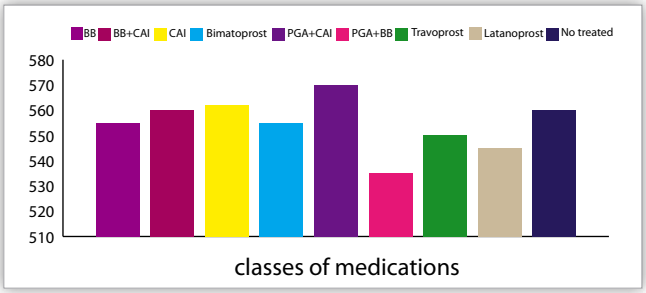

Fig. 1. Mean Central Corneal Thickness (CCT) (μm) in groups of eyes treated with different classes of antiglaucoma medications (BB-beta-blockers, CAI- topical carbonic anhydrase inhibitors, PGA – prostaglandin analogs).

Ryc. 1. Średnia grubość centralnej rogówki (CCT) (μm) w oczach pacjentów w grupach leczonych różnymi klasami leków przeciwjaskrowych (BB – beta-blokery, CAI – miejscowe inhibitory anhydrazy węglanowej, PGA – analogi prostaglandyn).

The highest mean CCT was found in the eyes treated with bimatoprost (554.4 μm SD 46.0) and the lowest in the eyes treated with latanoprost (546.4 μm SD 37.7). The mean CCT of treated and untreated glaucoma eyes did not differ significantly. No correlation was found between CCT and central corneal power. The results are presented in Tab. I and Fig. 1.

Discussion

In our study we did not observe any significant differences in CCT between eyes treated with different classes of antiglaucoma medications. We did not find lower CCT values in the eyes treated with PGA as compared to the eyes treated with other classes of hypotensive drugs. PGA are thought to lower IOP by stimulating remodeling of the ECM of the ciliary body in the mechanism of MMPs' activation. MMPs are secreted as inactive proenzymes and their activities are precisely regulated by some activators and inhibitors, including the tissue inhibitors of metalloproteinases (TIMPs). Human keratocytes produce two gelatinolytic enzymes of the MMPs family (MMP-2 and MMP-9) and two TIMPs proteins (TIMP-1 and TIMP-2), which inhibit the MMPs' activities (2). These observations suggest that PGA may also produce a similar ECM turnover in the corneal stroma via upregulation and downregulation of MMPs and TIMPs, respectively.

In some studies, PGA appear to cause thinning of the cornea. Pathak-Ray (7) found that CCT was significantly reduced after two months of PGA use (mean 533.9 μm, SD 39.7 vs. 542.0 μm, SD 41.6). These observations were also confirmed by Ferreira (8). The findings of Viestenz (4) study also suggest that topical application of PGA onto the cornea reduces the CCT significantly. The mean CCT in eyes treated with PGA was decreased significantly as compared to the untreated glaucomatous eyes, eyes treated with CAI and eyes with topical application of both PGA and CAI (529 μm SD 34 vs. 563 μm SD 37, 561 μm SD 32 and 555 μm SD 48, respectively). Other authors did not find any effect on CCT under two months (9) or one-year of topical PGA treatment (6). In Lass (6) study, the mean percent change in CCT after one year of latanoprost therapy was -1.1 μm SD 2,5%.

It has been shown in vitro study, that latanoprost may induce morphological and biochemical changes in cultured corneal stromal cells by altering type 1 collagen distribution (10). Liu (3) has found that latanoprost stimulates collagen type I

	PGA			BB	CAI	PGA CAI	PGA +BB	CAI +BB	No treated
	T	L	B						
Number of eyes	104	48	60	54	36	25	23	54	83
CCT mean (μm)	550.3	546.4	554.4	552.5	562.6	571.3	535.9	559.5	557.5
CCT range (μm)	475-685	474-626	481-657	492-615	496-630	483-640	593-600	465-625	470-660
CCT SD (μm)	38.8	37.7	46.0	34.7	40.2	46.3	31.4	32.5	42.4
ANOVA	F = 1.06 p = 0.3931								

Tab. I. Central corneal thickness (CCT) values in groups of eyes treated with different classes of antiglaucoma medications (PGAs – prostaglandin analogs, T-travoprost, L-latanoprost, B-bimatoprost, BB-beta-blockers, CAI- topical carbonic anhydrase inhibitors).

Tab. I. Grubość centralnej rogówki (CCT) w oczach pacjentów w grupach leczonych różnymi klasami leków przeciwjaskrowych (PGA – analogi prostaglandyn, T – trawoprost, L – latanoprost, B – bimatoprost, BB – beta-blokery, CAI – miejscowe inhibitory anhydrazy węglanowej).

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gel contraction mediated by human corneal fibroblasts, thus affecting corneal shape and central corneal thickness. Induced $PGF_{2\alpha}$ receptor activates two pathways: a protein Gq pathway, resulting in the protein kinase C activation and in an increase in the intracellular free calcium concentration and a Rho signaling pathway, that results in formation of actin stress fibers and cell rounding. These events might lead to changes in cell morphology and in the cytoskeleton and thus might contribute to the increase in the contractility of corneal fibroblasts induced by latanoprost. Simultaneously, it has been noted that latanoprost does not affect collagen degradation by inducing the secretion of MMPs by corneal fibroblasts and is not cytotoxic for them.

Both isopropyl esters (latanoprost, travoprost) and C-1 N-ethyl amide (bimatoprost) are lipophilic prodrugs with enhance penetration through the cornea. They are next hydrolyzed in the cornea (by esterases and amidase, respectively) to the corresponding free acides. As Sjoquist (11) showed, approximately 7.7% of the applied dose was found in the cornea 15 minutes after topical latanoprost administration in the rabbit and cornea functioned as a depot for the slow release of the active substance into anterior segment of the eye. The peak concentration in corneal epithelium is detected half an hour after topical administration and a corneal elimination half-time is about 4 hours. The maximum concentration of latanoprost acid is detected in the aqueous humor 1-2 hours after topical administration (with a half-time of 2-3 hours) and is approximately 1000 times higher than in plasma. In the systemic circulation the peak concentration of active acid appears 5 minutes after topical administration with an elimination half-time of 17 minutes. In 50% patients that have been on drug continuously for more than one year, the plasma concentrations are below the detection limit. Repeated administration of this drug is neither related with induction or inhibition of the metabolism nor accumulation of the drug or drug metabolites. It was found that the pharmacokinetics of latanoprost was similar after a single and repeated topical administration (12). Ultrastructural studies by Tamm (13) and Richter (14) also showed that both after 5 days and one year of treatment with PGA there were signs of lysis of ECM components between ciliary muscle bundles and widening of the intermuscular spaces.

We did not find any significant changes between CCT of eyes treated with different prostaglandin and prostamide analogs. Analysis of pachymetry data of glaucomatous patients made by other authors (8,15) also did not find differences between group treated with different PGA. However, in Arcieri (16) study latanoprost and travoprost did not reduce CCT, whereas bimatoprost use was associated with a reduction in CCT. Our results, presenting the highest mean CCT value in bimatoprost-treated eyes among all PGA-treated eyes, does not agree with Arcieri's findings.

In our study, timolol has been found to have no effect on CCT, what is in agreement with other studies (5,6). In Lass (6) study, the mean percent change in CCT after one-year of treatment with timolol or latanoprost plus timolol was 0.2 SD 3.1% and -1.0 SD 2.0%, respectively. It has been shown in vitro studies by Liu (3), that timolol does not stimulate collagen gel contraction, mediated by corneal fibroblasts and thus does not affect corneal shape. It was also postulated by Ito (17), that BB administration may cause the reverse effects, that are observed with PGA, that is downregulation and upregulation of MMPs and TIMPs, respectively.

We did not also find any significant impact of CAI on CCT. However we noticed in our study that both the group of eyes treated with CAI and the group of eyes treated with the combination of CAI and PGA presented the highest value of the mean CCT. Observed by us tendency is in agreement with other studies (18-20). Topical CAI are inhibitors of carbonic anhydrase II and IV and may interfere with the pump function of the corneal endothelium (21), which could lead to corneal edema in patients with compromised corneal endothelium (cornea guttata) (22). In healthy corneas, the long-term studies have shown that dorzolamide did not affect both CCT (4,5) and corneal endothelial morphology (5).

In our study we also found that CCT of treated glaucoma eyes does not differ significantly from CCT of untreated glaucoma eyes. The study by Chan-Kai (15) showed that lowering IOP with the following topical agents: travoprost, latanoprost, levobunolol, brimonidine or dorzolamide results in a statistically, but not clinically significant increase in CCT. In treated eyes, the CCT increased from 530.75 μm to 533.13 μm ($p = 0.032$) after one-month medical therapy, whereas in the fellow, untreated eyes no change in CCT was detected.

In summary, in the current study we found that CCT appeared not to differ in eyes treated with different classes of antiglaucoma medications either in monotherapy or combined therapy. We found also that CCT of treated glaucoma eyes does not differ significantly from CCT of untreated glaucoma eyes. However further studies, both histochemical and epidemiological are required to determine the impact of long-term use of antiglaucoma medications on the biology of cornea.

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