Effect of Tamsulosin on Corneal Biomechanical Features

Tamsulosinin Korneanın Biyomekanik Özellikleri Üzerine Etkisi

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ABSTRACT Objective: Tamsulosin (Flomax®) usage was reported to increase central corneal thickness (CCT). As CCT and ocular biomechanical parameters are closely related, this study was conducted to investigate the possible effects of tamsulosin on biomechanical parameters of cornea as measured with Reichert Ocular Response Analyser (ORA) in patients with benign prostate hyperplasia. **Material and Methods:** Besides full eye examination (best corrected visual acuity, intraocular pressure (IOP) measured with Goldmann applanation tonometry, CCT) ORA (corneal hysteresis, corneal resistance factor, corneal compensated IOP, Goldmann correlated IOP) measurements of 30 eyes of 15 male patients before and one month after tamsulosin therapy were performed. For comparisons paired t-test was used. **Results:** Mean age in the study group was 61.50±6.10 (range 47-69) years. Pre-tamsulosin CCT was lower than post-tamsulosin values (pre-: 549.18±28.84 micrometers, post-: 556.77±24.86 micrometers; p=0.002). Although statistically insignificant corneal resistance factor after tamsulosin use was lower (pre-: 10.73±1.05 mmHg, post-: 9.45±1.51 mmHg; p=0.071). Measurements before and after tamsulosin treatment was not statistically different for any of the other parameters. **Conclusion:** Tamsulosin seems not only to cause an increment on CCT, but also effect corneal resistance factor. The long term effects of tamsulosin on corneal biomechanical properties should further be investigated with larger group of patients.

Key Words: Cornea; tamsulosin; eye

ÖZET Amaç: Tamsulosin (Flomax®) kullanımı sonrası merkezi kornea kalınlığında (MKK) artış olduğu bilinmektedir. Kornea kalınlığı ile korneanın biyomekanik özellikleri arasındaki yakın ilişki bulunduğundan, benign prostat hiperplazisi sebebiyle tamsulosin kullanan hastalarda korneada gelişebilecek muhtemel biyomekanik özellik değişikliklerinin Reicher Oküler Response Analiz cihaz (ORA) ile incelenmesi amacıyla bu çalışma planlanmıştır. **Gereç ve Yöntemler:** Tamsulosin kullanılmasından önce ve kullanımından 1 ay sonra 15 hastanın 30 gözünde tam oftalmolojik muayeneye (en iyi düzeltilmiş görme keskinliği, göz içi basınç ölçümü GİB) ilaveten MKK ölçümü ve ORA (korneal histerezis, korneal rezistans faktör, kornea kompanse GIB ve Goldmann korele GIB) ölçümleri yapılmış ve sonuçlar karşılaştırılmıştır. İstatistiksel analiz için eşleştirilmiş-t testi kullanılmıştır. **Bulgular:** Çalışma grubundaki hastaların ortalama yaşı 61,50±6,10 (range 47-69) yıl idi. Tamsulosin öncesi ve sonrasındaki MKK sırasıyla 549,18±28,84 ve 556,77±24,86 µm (p=0,002)idi. İncelenen parametreler içerisinde hiçbir parametre için tedavi sonrasında anlamlı değişiklik izlenmemekle beraber yalnızca korneal rezistan faktör için , bir miktar azalma eğilimi olduğu izlenmiştir (pre-: 10,73±1,05 mmHg, post-:9,45±1,51 mmHg; p=0,071). **Sonuç:** Sonuçlarımız tamsulosinin MKK'da artış yarattığını göstermek dışında, korneal rezistans faktörde de değişiklikler yapabildiğini açıpa çıkarmıştır. Ancak tamsulosinin kornea biyomekanik özellikleri üzerindeki etkilerinin daha net anlaşılabilmesi için daha büyük hasta gruplarının, uzun takipli sonuçlarının incelenmesinin faydalı olacağı kanaatindeyiz.

Anahtar Kelimeler: Kornea; tamsulosin; göz

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Benign prostatic hyperplasia (BPH) is a common urological disorder that is frequently treated with α1 adrenergic receptor antagonists due to their good clinical potency. Intraoperative Floppy Iris Syndrome (IFIS), is a cataract surgery complicating problem usually observed in patients receiving systemic α1 adrenergic receptor antagonists-most commonly with tamsulosin (Flomax®), the specific α1a adrenergic receptor antagonist.[1,2] In a typical IFIS case, a flaccid, poorly dilated iris undulates and billows in response to ordinary fluid currents, and the stroma of the iris tends to prolapse through the main and side-port incisions.[1] These effects on the iris, pupillae, anterior chamber, and corneal endothelium have been evaluated previously with various instruments and techniques.[2-5] A recent study by Palamar et al[5] revealed changes on central corneal thickness (CCT) after 1 month of tamsulosin use.

(Ocular Response Analyzer ORA; (Reichert, Inc, Depew, NY), has been developed to measure the intraocular pressure (IOP) and Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF). The ORA utilizes a rapid air impulse to apply force to the cornea, and an advanced electro-optical system to monitor its deformation.[6,7] A precisely-metered collimated-air-pulse causes the cornea to move inwards, past applanation, and into a slight concavity. Milliseconds after applanation, the air pump shuts off and the pressure declines in a smooth fashion. As the pressure decreases, the cornea begins to return to its normal configuration.[6]

In the process, it once again passes through an applanated state. The applanation detection system monitors the cornea throughout the entire process, and two independent pressure values are derived from the inward and outward applanation events. One might expect these two pressure values to be the same. However, due to the dynamic nature of the air pulse, the viscous damping in the cornea causes delays in the inward and outward applanation events, resulting in two different pressure values.[6,7]

The average of these two pressure values provides a repeatable, Goldmann-correlated IOP value (IOPg).[6,7] The difference between these two pressure values is CH. The CH measurement has been shown to be significant and useful in its own right, but in addition, the dynamic bi-directional applanation process can be used to derive other valuable information; namely corneal-compensated IOP (IOPcc) and CRF. Both of these parameters are the result of large-scale clinical data analysis and are derived from specific combinations of the inward and outward applanation values using proprietary algorithms.

CH is a phenomenon that results from the dynamic nature of the air pulse and the viscous damping inherent in the cornea.[6,7] CRF, is also derived from this response. CRF is a measurement of the cumulative effects of both the viscous and elastic resistance encountered by the air jet while deforming the corneal surface. CRF exhibits the expected property of increasing at significantly elevated pressures. Though CH and CRF are, on average, the same for a normal population, they differ from person to person, providing us with distinct corneal information.

IOPcc is a pressure measurement that utilizes the new information provided by the CH measurement to provide an IOP value that is less affected by corneal properties. While we cannot yet claim to be measuring "true pressure", early investigations have demonstrated that IOPcc is a better indicator of the real IOP than IOP with Goldmann applanation tonometry.

As a known fact, the ocular biomechanical parameters -CH and CRF- are dependent on and correlated to CCT.[7] As changes on CCT are demonstrated to occur after tamsulosin use[5], we wondered if corneal biomechanics could also be affected by this medication. To our knowledge, no study to date has evaluated the effects of tamsulosin on the corneal biomechanics. For this purpose, corneal biomechanics were evaluated with ORA in this prospective study in patients with clinical symptoms of BPH treated with tamsulosin.

MATERIAL AND METHODS

A total of 15 male patients with BPH to whom tamsulosin was prescribed were enrolled in the study.

Patients with corneal pathology, glaucoma, uveitis, previous eye surgery or eye trauma, posterior segment pathology, and those using topical/systemic medications or with systemic diseases which might influence corneal biomechanics were excluded.

Between November 2010 and March 2011, 30 eyes of these 15 patients underwent full ocular examination prior to tamsulosin therapy initiation and one month following tamsulosin use. Besides full ocular examination [best corrected visual acuity (BCVA), IOP with Goldmann applanation tonometry, CCT with Pentacam (Oculus Optik geräte GmbH, Wetzlar, Germany) etc.] measurements with ORA were performed. IOP was measured with Goldmann applanation tonometry, and as IOPcc and as Goldmann IOPg on the computer screen attached to the ORA.

The patients were asked to fixate at the target in the ORA instrument (red-blinking light), and ORA was activated by pressing a button attached to the computer as described previously.[8] A non-contact probe scanned the central area of the eye and released an air puff and then sent a signal to the ORA. ORA calculated and then displayed the CH, CRF, and IOP both as IOPg on the computer screen attached to the ORA. IOPg is a value of IOP correlated to Goldmann tonometry that is estimated by the ORA system.[7] IOPcc value -that is calculated by the ORA system using a special formula- compensates for the viscoelastic properties of the cornea.[7] For this reason, IOPcc takes better account of the corneal biomechanic state, enabling IOP measurements that are less affected by corneal properties. All subjects underwent testing with the ORA by an experienced ophthalmologist. Four to five measurements were obtained for each eye, and the most reliable of these measurements per eye was considered for analysis.

Statistical analysis was performed with SPSS for Windows Version 16.0 (SPPS Inc., Chicago, IL, USA). All data were reported as averages ± standard deviations. A paired t-test was used to compare variables between the pre- and post-tamsulosin conditions. A value of $p < 0.05$ was considered statistically significant.

This study adheres with the tenets of the Declaration of Helsinki and all patients were included after their informed consent was received.

RESULTS

The mean age of the patients was 61.50±6.10 (range 47-69) years. Mean pre-tamsulosin BCVA was 0.02±0.07 (range 0-0.3) logMAR. Mean post-tamsulosin BCVA was 0.033±0.07 logMAR (range 0-0.3) (p=0.163, paired t-test). Mean pre-tamsulosin CCT of the patients was 549.18±28.84 micrometers, whereas mean post-tamsulosin CCT was 556.77± 24.86 micrometers (p=0.002; paired t-test).

Mean CH was 9.23 ± 1.78 (range 6.1 and 11.5) mmHg in pre-treatment period and 8.79±2.26 (range 4.2 and 11.4) mmHg in the post-treatment period (p=0.404; paired t-test) (Table 1). Although there was a trend towards mean CRF differences between the pre- and post-treatment periods, this did not reach statistical significance [pre-: 10.73±1.05 (range 7.3 and 12.6) mmHg, post-: 9.45±1.51 (range 7.4 and 12.3) mmHg; p=0.071; paired t-test].

Mean IOP measured by Goldmann applanation tonometry was 15.43±2.84 mmHg (range 12-21) before the treatment and 15.63±3.50 mmHg (range, 12-21) after the treatment (p=0.604; paired t-test) (Table 2).

Mean IOPcc was 18.09±3.68 (range 13 and 21) mmHg and 18.08±4.39 (range 12 and 21) mmHg pre-, post-tamsulosin, respectively (p=0.987; paired t-test). Mean IOPg was 16.56±3.13 (range 12 and 21) mmHg and 16.19±3.65 (range 11 and 21) mmHg pre-, post-tamsulosin, respectively (p=0.512; paired t-test).

DISCUSSION

Tamsulosin, the α1a/α1d subtype selective α1-adrenoreceptor antagonist is the most commonly prescribed medication for the treatment of lower urinary tract symptoms suggestive of BPH.[2,9,10] Tamsulosin was reported to lead IFIS, by causing diffuse atrophy and flaccidity of the iris by selectively blocking α1a-adrenergic receptors of the dilatator iris muscle.[1] Several studies suggest that discontinuing tamsulosin preoperatively does not

TABLE 1: The pre- and post-tamsulosin measured values of CH and CRF.

	Study Group (n=30)				
	Pre-tamsulosin (Range)	Post- tamsulosin (Range)	Mean Difference	SD of the difference	P value
CH	9.23 (6.1-11.5)	8.79 (4.2-11.4)	-0.44	1.76	0.404
CRF	10.73 (7.3-12.6)	9.45 (7.4-12.3)	-1.28	1.37	0.071

CH: Corneal Histeresis (mmHg); CRF: Corneal Resistance Factor (mmHg).

TABLE 2: The pre- and post-tamsulosin measured IOP-G, IOPcc and IOPg values.

	Study Group (n=30)				
	Pre-tamsulosin (Range)	Post-tamsulosin (Range)	Mean Difference	SD of the difference	P value
Mean IOP-G	15.43 (12-21)	15.63 (12-21)	0.2	2.09	0.604
Mean IOPcc	18.09 (13-21)	18.08 (12-21)	-0.01	3.82	0.987
Mean IOPg	16.56 (12-21)	16.19 (11-21)	-0.37	2.72	0.512

IOP-G: Intraocular Pressure measured by Goldmann applanation tonometry (mmHg); IOPcc: Corneal Compensated Intraocular Pressure (mmHg); IOPg: Goldmann Correlated Intraocular Pressure (mmHg)

return the IFIS condition, which supports the hypothesis that the effects of tamsulosin are not temporary.[11,12] The effects of other α1-adrenoreceptor antagonists regarding their effects on the iris are still being investigated.[4,13] There are various reports on the effects of tamsulosin on pupil diameter, iris morphology, anterior segment, and corneal endothelium. Palamar et al. recently reported the increment on CCT after 1 month of tamsulosin use.[5]

ORA is a new non-contact tonometer developed by Reichert, that measures IOP and new metrics, CH and CRF. It uses a metered collimated air pulse to applanate the cornea and an infrared electro-optical system to record inward and outward applanation events. The air pulse deforms the cornea through an initial applanation event, then beyond into concavity, and gradually subsides, allowing the cornea to rebound through a second applanation. This dynamic assessment of corneal biomechanical properties provides metrics of both the cornea's viscous and viscoelastic qualities as CH and CRF, respectively.[14]

The presence of α1 receptors in freshly fixed human corneal epithelium and endothelium was demonstrated earlier.[15] Additionally, direct radioligand binding studies indicate that intact corneal epithelial and endothelial cells both exhibit α1 adrenergic receptors.[16] Alpha-1 adrenergic receptors seem to play a role in regulation of inositol-1,4,5-tris-phospate formation.[17] Although the physiological role of α1 adrenergic receptors and their second messengers phosphatidyl inositol and cyclic AMP in corneal epithelium and endothelium is not clear, they may be involved in the regulation of corneal homeostasis and fluid transportation. A recent study by Storr-Paulsen et al. showed that endothelial cell loss after cataract surgery in patients with IFIS are more pronounced.[3] CCT increment in these patients group after tamsulosin therapy with no history of any surgical procedure was also demonstrated by Palamar et al.[5] These data support that not only iris and pupillae but also corneal tissue might also be involved by tamsulosin use.

The Goldmann-IOP, IOPcc and IOPg values did not display any differences one month after the tamsulosin treatment. Although there was no statistically significant changes in CH and CRF following one month of tamsulosin therapy, the increment in CRF was close to statistical significance (p=0.071). One may concern that if the follow-up period was longer, this increase would have been more distinct.

One of the limitations of our study is the small number of patients, but one should consider that, at the age of BPH it is hard to find patients to use no medications and have no systemic diseases. The second limitation of this study is the short follow-up time after the initiation of tamsulosin therapy.

However, the steady-state plasm concentration of tamsulosin is reached at the fifth day of tamsulosin therapy, and maximum effect is reported to take place in the second week.[18,19] Additonally, tamsulosin related IFIS was observed even after 2 weeks of use as reported earlier.[20] For this reason, we believe that period of one month is sufficent to observe any possible changes of tamsulosin use on corneal biomechanics.

In conclusion, there were no differences in terms of BCVA, IOP, and CH compared with pre- and post-tamsulosin use. However, one month therapy of tamsulosin seems to effect not only CCT but also the CRF of the cornea. In the long term this might influence the ocular dynamics of the eye. For this reason, long term effects of tamsulosin on corneal biomechanics require further investigation with larger patient groups.

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