(02)

Central corneal thickness and intraocular pressure before the intravitreal administration of ranibizumab and in the early period following the injection

Centralna grubość rogówki i ciśnienie wewnątrzgałkowe przed podaniem doszklistkowej iniekcji ranibizumabu i we wczesnym okresie po jej podaniu

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Summary: The aim of the study was to determine the differences in the central corneal thickness and intraocular pressure measured before intravitreal administration of ranibizumab and at 30 to 60 minutes after the injection. The intraocular pressure was analysed as a stand-alone parametre and in correlation with the central corneal thickness. 72 patients (144 eyes) were enrolled. The treated eyes were compared to the fellow, non-treated eyes. The mean central corneal thickness in a treated eye was 558 μm and 596 μm at baseline (before the injection) and after the injection, respectively ($p < 0.05$). The mean intraocular pressure not correlated to the central corneal thickness in a treated eye 15.29 mmHg and 16.83 mmHg at baseline and post-injection, respectively ($p < 0.05$). When assessed in correlation with the central corneal thickness, the intraocular pressure did not increase post-injection in the treated eyes.

Key words: central corneal thickness (CCT), intraocular pressure (IOP), corneal edema, intravitreal injection, ranibizumab.

Streszczenie: Ocenie poddano centralną grubość rogówki i ciśnienie wewnątrzgałkowe przed podaniem iniekcji ranibizumabu oraz po 30–60 minutach od jej podania. Analizie poddano wartości ciśnienia wewnątrzgałkowego bez uwzględnienia grubości rogówki oraz w korelacji z grubością rogówki. Badanie wykonano w 72 przypadkach (144 oczu). Porównano dwie grupy oczu: grupę oczu poddanych iniekcji doszklistkowej ranibizumabu – 72 przypadki – z grupą oczu towarzyszących u każdego z pacjentów, oczu nieleczonych (oko kontrolne) – 72 przypadki. Średnia centralna grubość rogówki w oku leczonym przed iniekcją wynosiła 558 μm, po zabiegu – 596 μm ($p < 0,05$). Średnia wartość ciśnienia wewnątrzgałkowego, które nie było skorygowane z grubością rogówki, w oku leczonym wynosiło: przed zabiegiem – 15,29 mmHg, po zabiegu – 16,83 mmHg ($p < 0,05$). Natomiast wartości ciśnień wewnątrzgałkowych po uwzględnieniu grubości rogówki nie uległy zmianie.

Słowa kluczowe: centralna grubość rogówki (CCT), ciśnienie wewnątrzgałkowe (IOP), obrzęk rogówki, iniekcja doszklistkowa, ranibizumab.

Introduction

The intravitreal injections of anti-VEGF agents have been used for treatment of conditions associated with the growth of pathological vessels – mainly in age-related macular degeneration, central retinal vein occlusion, high myopia, neovascular glaucoma and central serous chorioretinopathy for a few years now.

The efficacy and safety of such treatment have been evaluated in many studies. In the early post-injection period, conjunctival irritation, subconjunctival hemorrhages, decreased corneal translucency and corneal epithelial edema can occur, which explains the importance of monitoring corneal health. In our study, we evaluated changes to the corneal thickness caused by corneal edema as well as the intraocular pressure (IOP) in correlation to the central corneal thickness (CCT). So far, the authors focused mainly on intraocular pressure fluctuations caused by an intravitreal drug administration, disregarding the role of central corneal thickness and the need to adjust the IOP reading accordingly.

Aim of the study

To determine the effect of the intravitreal ranibizumab injection on CCT and IOP during the early post-injection period (30–60 minutes).

Material and methods

72 patients (144 eyes) treated between October 2011 and October 2012 were enrolled in the study. The indications for intravitreal administration of ranibizumab included age-related macular degeneration (AMD) in 70 cases and central retinal

vein occlusion (CRVO) in 2 cases. 59 eyes were phakic and 13 were pseudophakic. 4 patients were treated for glaucoma. However, indication-based subgroup analysis was not possible due to the limited number of cases.

The central corneal thickness (CCT) was measured in both eyes using Scheimpflug imaging technology (Pentacam, Oculus) before the injection and at 30–60 minutes following the injection. Each measurement was repeated three times and the results were averaged. Similarly, the intraocular pressure (IOP) was measured both at baseline and at 30-60 minutes following the injection using the Goldmann applanation tonometer. The measurements were performed in eyes with dilated pupils. 0.5 mg (0.05 ml) of ranibizumab was administered to 72 eyes. The fellow, non-treated eyes of our subjects were enrolled as controls and a comparison between the treated eyes and non-treated, healthy eyes (fellow eye the some patient) was made. Next, the values of intraocular pressure were analysed in correlation with CCT adjusted using the three formulas: Ehlers, Sah and Dresden's – all in-built in Pentacam software. The student T-test was used for the statistical analysis of obtained results.

Results

The mean CCT in a treated eye was 558 μm and 596 μm, at baseline and post-injection, respectively. The difference was statistically significant ($p< 0.05$) (Tab. Ia). The mean central corneal thickness in a fellow eye was 560 μm and 559 μm at baseline and post-injection, respectively. The difference was not statistically significant (Tab. Ib). The CCT gain of 10.0 μm or more was observed post-injection in 68 treated eyes (94%) and only in 8 fellow eyes (11%). The most prevalent range of fluctuation – 52 cases (59.7%) – was 20 to 50 microns, whereas it remained within the range of $\pm$10 microns in most fellow eyes 55 cases (76.4%) (Tab. II).

The baseline IOP above 21 mmHg was noted in 2 treated eyes (2.8%; each eye 23 mmHg), and in 3 control eyes (4.2%; 22, 22 and 23 mmHg, respectively). The post-injection IOP above 21 mmHg was observed in 9 treated eyes (12.5%, the mean reading of 23.8 mmHg) an in 3 control eyes (4.2%; the mean reading of 22 mmHg). 11 treated eyes had a difference between the pre- and post-injection IOP of 5 mmHg or more (one of these patients was a known glaucoma patient on topical medication), as compared to 3 control eyes (Tab. III). The mean intraocular pressure in a treated eye was 15.29 mmHg and 16.83 mmHg at baseline and post-injection, respectively. The difference was statistically significant ($p<0.05$) (Tab. IVa, IVb). The IOP increase by 1–4 mmHg was the most prevalent (31 eyes; 43%) (Tab. III).

The mean IOP in a fellow eye was 15.10 mmHg and 15.14 mmHg at baseline and post-injection, respectively. The difference was not statistically significant (Tab. IVa, IVb). The mean IOP values adjusted for the CCT in a treated eye were 14.43, 14.9, 14.97 mmHg and 13.22, 14.43, 14.96 mmHg at baseline and post-injection, respectively. The adjusted IOP values after ranibizumab injection did not increase significantly in treated or fellow eyes. The IOP values presented in Tables V–VIII were adjusted for the CCT using the Ehlers, Sah and Dresden's formulas and calculated using the Pentacam in-built software (Tab. V, VI, VII, VIII) (1–3).

Parameter/ Parametr	Treated eye at baseline/ Oko leczone przed iniekcją	Treated eye post-injection/ Oko leczone po iniekcji	Difference/ Różnica
Minimum	475	518	-9
Maximum	648	678	75
Median	551	594,5	43
Standard deviation/ Odchylenie standardowe (SD)	31.76	35.84	17.41
Mean/ Średnia	557.57	596.06	38.49 ($p<0.05$)

Tab. Ia. Central corneal thickness (CCT) in the treated eye (μm).
Tab. Ia. Centralna grubość rogówki w oku leczonym (μm).

Parameter/ Parametr	Fellow eye before at baseline*/ Oko towarzyszące przed iniekcją*	Fellow eye post-injection*/ Oko towarzyszące po iniekcji*	Difference/ Różnica
Minimum	489	482	-29
Maximum	643	650	18
Median	556.5	555.5	0
Standard deviation/ Odchylenie standardowe (SD)	32.93	34.03	9.24
Mean/ Średnia	559.61	559.1	-0.51

*injection was administered to the treated eye only/ iniekcja dotyczy oka leczonego

Tab. Ib. Central corneal thickness (CCT) in the fellow eye (μm).
Tab. Ib. Centralna grubość rogówki w oku towarzyszącym (μm).

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CCT change/ Zmiana CCT (μm)	Treated eye/ Oko leczone (n*)	Fellow eye/ Oko towarzyszące (n*)
↓ 21 – 30	0	1
↓ 11 – 20	0	8
↓ 1 – 10	2	22
0	0	7
↑ 1 – 10	3	26
↑ 11 – 20	8	8
↑ 21 – 30	9	0
↑ 31 – 40	12	0
↑ 41 – 50	22	0
↑ 51 – 60	11	0
> 60	5	0

*number of eyes/ liczba oczu

Tab. II. Change in the central corneal thickness (CCT) in the treated and the fellow eye as measured before and after the injection.
Tab. II. Różnica w centralnej grubości rogówki (CCT) w oku leczonym i oku towarzyszącym – pomiar przed iniekcją i po iniekcji.

Change in the intraocular pressure (IOP)/ Zmiana ciśnienia wewnątrzgałkowego (mmHg)	Treated eye/ Oko leczone (n*)	Fellow eye/ Oko towarzyszące (n*)
↓ 6 – 10	2	3
↓ 5	1	0
↓ 3 – 4	4	6
↓ 1 – 2	14	11
0	9	26
↑ 1 – 2	14	17
↑ 3 – 4	17	6
↑ 5	2	1
↑ 6 – 10	9	2

*number of eyes/ liczba oczu

Tab. III. Change in the intraocular pressure as measured before and after the injection.
Tab. III. Różnica ciśnienia wewnątrzgałkowego – pomiar przed iniekcją i po iniekcji.

Parameter/Parametr	Treated eye at baseline/ Oko leczone przed iniekcją	Treated eye post-injection/ Oko leczone po iniekcji	Difference/ Różnica
Minimum	8	7	-6
Maximum	23	26	10
Median	15	16	1.5
Standard deviation/ Odchylenie standardowe (SD)	3.19	3.93	3.35
Mean/ Średnia	15.29	16.83	1.46 ($p<0.05$)

Tab. IVa. Intraocular pressure (IOP) in the treated eye (mmHg).
Tab. IVa. Ciśnienie wewnątrzgałkowe w oku leczonym (mmHg).

Parameter/ Parametr	Fellow eye at baseline*/ Oko towarzyszące przed iniekcją*	Fellow eye post-injection*/ Oko towarzyszące po iniekcji*	Difference/ różnica
Minimum	10	9	-7
Maximum	25	23	7
Mediana	14	15	0
Standard deviation/ Odchylenie standardowe (SD)	3.24	3.05	2.54
Mean/ Średnia	15.1	15.14	0.1

*injection was administered to the treated eye only/ iniekcja dotyczy oka leczonego

Tab. IVb. Intraocular pressure (IOP) in the fellow eye (mmHg).
Tab. IVb. Ciśnienie wewnątrzgałkowe w oku towarzyszącym (mmHg).

	Mean intraocular pressure/ Średnie ciśnienie wewnątrzgałkowe	Adjusted intraocular pressure (Ehlers formula)/ Ciśnienie skorygowane wg Ehlersa	Adjusted intraocular pressure (Sah formula)/ Ciśnienie skorygowane wg Saha	Adjusted intraocular pressure (Dresden formula)/ Ciśnienie skorygowane wg Dresden
At baseline/ Przed iniekcją	15.29	14.43	14.9	14.97
Post-injection/ Po iniekcji	16.83	13.22	14.43	14.96
Change/ Zmiana	1.54	-1.21	-0.47	-0.01

Tab. V. Intraocular pressure in the treated eye at baseline and post-injection (mmHg) adjusted using the Ehlers, Sah and Dresden formulas.
Tab. V. Ciśnienie skorygowane w oku leczonym przed iniekcją i po iniekcji (mmHg).

	Mean intraocular pressure/ Średnie ciśnienie wewnątrzgałkowe	Adjusted intraocular pressure (Ehlers formula)/ Ciśnienie skorygowane wg Ehlersa	Adjusted intraocular pressure (Sah formula)/ Ciśnienie skorygowane wg Saha	Adjusted intraocular pressure (Dresden formula)/ Ciśnienie skorygowane wg Dresden
At baseline/ Przed iniekcją*	15.1	14.04	14.57	14.74
Post-injection/ Po iniekcji*	15.14	14.1	14.67	14.81
Change/ zmiana	0.04	0.06	0.1	0.07

*injection in treated eye/ iniekcja dotyczy oka leczonego

Tab. VI. Intraocular pressure in the fellow eye at baseline and post-injection (mmHg) adjusted using the Ehlers, Sah and Dresden formulas.
Tab. VI. Ciśnienie wewnątrzgałkowe skorygowane w oku towarzyszącym przed iniekcją i po iniekcji (mmHg).

Discussion

Intravitreal injections of anti-VEGF agents offer potential benefits and potential side effects such as subconjunctival hemorrhages, local pain, vitreal floaters, vitreal reflux, elevated IOP and endophtalmitis (4–10). In our study, we evaluated changes to the corneal thickness caused by corneal edema as well as the intraocular pressure (IOP) in correlation to the central corneal thickness (CCT). So far, the authors focused mainly on intraocular pressure fluctuations caused by an intravitreal drug administration, disregarding the role of central corneal thickness and the need to adjust the IOP reading accordingly. The IOP can fluctuate significantly within the first minutes after an intravitreal injection. Cases of transient short-lasting IOP elevation have been reported (7–12). It appears challenging to determine factors predisposing to such IOP elevation and to plan the appropriate pre- and post-injection management of such patient. According to different authors, the IOP elevation above 21 mmHg can be observed in 5% to 7% of patients receiving intravitreal injections (5, 6). In our study its incidence was 12.5%. The difference in IOP values adjusted for CCT before and after an intravitreal injection of ranibizumab was not statistically significant in our cohort. What attracted our attention, though, was a statistically significant increase in the central corneal thickness directly after an injection.

In the literature, there are only few reports on corneal alterations induced by an intravitreal injection of ranibizumab. Benitez-Herreroz et al. (13) evaluated the corneal endothelial morphology in patients treated with intravitreal injections of ranibizumab, and assessed the CCT at baseline as well as after 7 days and 6 months following an injection. No statistically significant differences in the CCT or the corneal endothelial cell count were found, which confirms the lack of ranibizumab toxicity on the cornea. The increase of central corneal thickness in our study cohort was observed shortly after an injection,

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Central Corneal Thickness (Microns)/ Centralna grubość rogówki (mikrony)	Adjustment in IOP (mmHg)/ Wartość skorygowania IOP (mmHg)
445	+7
455	+6
465	+6
475	+5
485	+4
495	+4
505	+3
515	+2
525	+1
535	+1
545	0
555	-1
565	-1
575	-2
585	-3
595	-4
605	-4
615	-5
625	-6
635	-6
645	-7

Tab. VII. Correction table used for adjusting IOP based on central corneal thickness (provided with Pachmate™ pachymeter and based on Ehlers et al.) (1, 2).

Tab. VII. Tabela do korygowania wartości ciśnienia wewnątrzgałkowego o wartość CCT dołączana do pachymetru Pachmate™, wg Ehlersa i wsp. (1, 2).

Central Corneal Thickness (Microns)/ Centralna grubość rogówki (mikrony)	Adjustment in IOP (mmHg)/ Wartość skorygowania IOP (mmHg)
475	(+)3.19
500	(+)2.13
525	(+)1.07
550	0.02
575	(-)1.04
600	(-) 2.10
625	(-) 3.16
650	(-) 4.21
675	(-) 5.27
700	(-) 6.33

Tab. VIII. The Dresdner correction table shows the dependence of the of the applanation intraocular pressure reading on corneal thickness in aplanation tonometry. See: Glaucoma. Editors F. Grehn, R. Stamper 2006 (3).

Tab. VIII. Dresdeńska tabela do korygowania wartości ciśnienia wewnątrzgałkowego ukazuje zależność wartości IOP od centralnej grubości rogówki w tonometrii aplanacyjnej, wg Glaucoma. Editors F. Grehn, R. Stamper 2006 (3).

i.e. 60 or fewer minutes. This parameter was not evaluated at a later time, as it is probably just a transient injection-induced effect. It is likely that the IOP fluctuations observed within the first minutes post-injection, as reported by other authors are caused by the corneal epithelial edema along with the effect of antiseptic preparations and anesthetics on the conjunctiva rather than by the presence of ranibizumab in the vitreous chamber (7–12).

Gismoni et al. (10) monitored the IOP in 54 patients after intravitreal injections. The mean IOP at baseline was 16.3 mmHg and it differed slightly between phakic and pseudophakic eyes (16.6 mmHg vs. 15.9 mmHg, respectively). The IOP values tended to reach the peak within the first 10 minutes following the injection. The mean IOP values were 44.1 mmHg, 29 mmHg, and 25.8 mmHg at 5 seconds, 5 minutes and 10 minutes following the injection, respectively. Then, the mean value at 10 minutes post-injection was 23.7, dropping to 21.9 mmHg at 30 minutes and decreasing further to 18.8 mmHg at 1 hour. On the next day, the IOP stabilized at the mean baseline level of 16.1 mmHg. There was no statistically significant difference between the phakic an pseudophakic eyes. We cannot address this observation, as in our research the group of patients with pseudophakic eyes was not numerous enough so as to allow a direct comparison between the phakic and pseudophakic eyes. Furthermore, a statistically significant difference was noted when comparing the axial length with the IOP measured 5 seconds post-injection. Short eyeballs tended to present with higher IOP.

Many studies have focused on IOP fluctuations over the late period following an intravitreal injection (14–21) with the patients being monitored over a period of several months. Wehrli et al. (15) monitored 302 eyes treated with intravitreal injections of ranibizumab or bevacizumab and 226 control eyes. The patients were divided into 2 groups: those with known and treated glaucoma and those with no medical history of glaucoma. The results showed no statistically significant difference between the treated and control eyes or between the glaucomatous and non-glaucomatous eyes. However, other authors appear to have come to contradictory conclusions. Adelman et al. (16) noted the IOP elevation above 21 mmHg after the mean number of 13 intravitreal injections in 3.5% of treated eyes. One case of hypotony was reported associated with cilliary body atrophy at the injection site. It was a 65 year old male whose IOP dropped from 60 mmHg to hypotony on day 5. post-injection. The physiological aqueous humour secretion was restored after 48 hours (17). Frenkel et al. (22) evaluated the IOP in patients treated with intravitreal injections dividing them into three groups: 1 – no preventive antiglaucoma treatment was used, 2 – one antiglaucoma medication was used as a part of prevention, 3 – two antiglaucoma medications were used as a part of prevention. Another division was into two subgroups according to the known diagnosis of glaucoma. The results showed no statistically significant difference between these groups.

Conclusions

The difference in the central corneal thickness pre- and post--injection supports the necessity to adjust the IOP reading for this parameter. In the first 30-60 minutes after iniection, a statistically significant increase in the central corneal thickness of the treated eye was observed. The intraocular pressure adjusted for the CCT did not change significantly in our study cohort. Due to the possible injection-induced corneal edema, it seems advisable to evaluate intraocular pressure with the adjustment for the central corneal thickness.

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