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MYDRANE INTRACAMERAL INJECTION CAN BE AN ALTERNATIVE TO MYDRIATIC DROPS INSTILLATION IN CATARACT SURGERY

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The aim of this study is to compare Mydrane (combination of tropicamide 0.02%, phenylephrine 0.31% and lidocaine 1%) and mydriatic drops (tropicamide 1% and phenylephrine 10%) used for cataract surgery in terms of efficacy in pupil dilation and impact on corneal endothelial cell density (CD) and central corneal thickness (CCT). Prospective study including 64 eyes of 64 patients that underwent phacoemulsification with intraocular lens implantation. Patients were randomized into two groups: Mydrane group received: tropicamide and phenylephrine one day preoperatively and Mydrane during the surgery. Reference group received: tropicamide and phenylephrine preoperatively. Pupil size was measured only in Mydrane group, in the same eye of the same patient one day preoperatively after mydriatic drops were given and during the surgery, after intracameral Mydrane injection. CD and CCT were evaluated one day preoperatively and one month postoperatively in all patients and compared between Mydrane and reference groups. The results show CCT and CD significantly decreased after surgery in both groups. There is no difference in this decrease between groups. In Mydrane group there was no difference in dilated pupil diameter between Mydrane and mydriatic drops. Gender, diabetes mellitus, POAG, alpha-1 blocker treatment failed to affect pupil dilation obtained with Mydrane. Cataract surgery affects CCT and CD regardless of which mydriatic protocol had been used. Pupil diameter was similar after drops instillation and after Mydrane injection in all patients from the Mydrane group.

Key words: *corneal endothelial cell density, central corneal thickness, pupil dilation, Mydrane, mydriasis, intracameral injection, cataract, phacoemulsification*

INTRODUCTION

Nowadays, cataract surgery with artificial intraocular lens (IOL) implantation is one of the most common surgical procedures in industrialized countries. The most popular type of surgery is microincision phacoemulsification. One of the risk factors for intraoperative complications is insufficient pupil dilation (1, 2). In a standard patient preparation for cataract phacoemulsification and IOL implantation, mydriasis and anaesthesia are achieved by a specifically scheduled instillation of mydriatic drops performed by the nursing staff prior to surgery. Drops are administered several times preoperatively, at certain intervals, which entails a number of limitations and difficulties such as being time-consuming and inconvenient for patients; medicine preservatives can be toxic to corneal epithelium; drop application may contaminate the operating field and systemic complications (*e.g.* from the cardiovascular system).

While preparing for cataract surgery, the toxic effect on the corneal endothelium needs to be taken into consideration. The corneal endothelium is a single layer of tightly adhering polygonal cells that protect the hydrophilic corneal stroma from being penetrated by the fluid from the anterior chamber, which would cause corneal decompensation leading to loss of its transparency (3). Endothelial cells are not replaced during the lifetime. Known factors that reduce the density of endothelial cells are certain diseases such as corneal dystrophies, glaucoma, pseudoexfoliation syndrome, keratitis, uveitis, diabetes and surgical procedures (4-7). Additionally, various substances may have a toxic effect on endothelial cells, including silicon oil administered during vitrectomy and eye drops containing benzalkonium chloride (8, 9).

An alternative to the traditional preparation for cataract surgery is a complex drug containing mydriatics and analgesics: Mydrane (Laboratoires Thea, Clermont-Ferrand, France), mixture of 0.02% tropicamide and 0.31% phenylephrine, and 1% lidocaine - injected directly into the anterior chamber of the eye during the procedure. The research has demonstrated effectiveness and safety of its use (10-12).

The aim of our study was to compare the effectiveness and safety of both methods - preoperative drops administration and intraoperative intracameral injection of Mydrane. The measurement of the pupil size of the operated eye was regarded as the indicator of the effectiveness of mydriasis, while the safety of both methods was tested by measuring pre- and postoperative endothelial cell density (CD) and central corneal thickness (CCT).

MATERIAL AND METHODS

Of the 86 patients with cataract referred to the Outpatient Clinic of the Department of Ophthalmology and Ocular

Oncology in Cracow, Poland, between January and June 2018, 64 individuals were included in this randomized prospective study.

The cataract grade was assessed on slit-lamp examination and LOCS III grading system scale (13). For the purpose of this study only the nuclear density was taken into account, as it can influence the time and power of ultrasound use during the phacoemulsication procedure. To evaluate whether mydriatic agents used for cataract phacoemulsification have an impact on CCT and CD and if there is any difference between Mydrane compared to topical mydriatics we measured CCT and CD in all patients one day preoperatively and one month after the surgery. We assessed CCT with anterior segment optical coherence tomography (OCT) (Optovue, Fremont, California, USA) by placing the calliper in the centre of the cornea. We measured CD with specular microscopy (EM-3000 Tomey, Nagoya, Aichi, Japan).

One day preoperatively all participants underwent visual acuity examination using Snellen's chart, slit-lamp examination, dilated eye fundus examination and tonometry.

The inclusion criteria were: age ≥ 18 years, intraocular pressure (IOP) ≤ 21 mmHg and no history of previous ophthalmic surgeries in a study eye, scheduled to have unilateral, primary cataract surgery under topical anaesthesia with a phacoemulsification device and insertion of an acrylic intraocular lens.

The exclusion criteria included the presence of corneal degenerations and dystrophies and diabetic retinopathy.

One day prior to the cataract surgery the patients were assigned into two groups according to the Mydrane product characteristics indicating that it should only be used in patients who have demonstrated a minimum of 6 mm diameter of pupil dilation with topical mydriatic therapy. All participants received one drop of tropicamide 1% repeated three times every 10 minutes with phenylephrine 10% once and had dilated pupil diameter measurement done 10 min after instillation of the last mydriatic eye drop. Satisfactory pupil dilation was observed in 29 patients who were assigned into Group I - Mydrane group. All individuals in this group received mydriatic drops one day before surgery and Mydrane during a surgery. Group II - the reference group, included 35 patients that were not eligible for Mydrane and were only given mydriatic drops preoperatively. Patients from Mydrane group to obtain mydriasis received 200 µL of Mydrane during the surgery just after the first corneal incision was performed. Patients assigned to the reference group received only topical regimen of one drop of tropicamide 1% repeated three times every 10 minutes and phenylephrine 10% once on the day of the surgery (*Fig. 1*).

To compare the efficacy in pupil dilation between Mydrane and a standard topical regimen we measured - only in patients from Mydrane group - dilated pupil diameter by placing a medical ruler with millimetre divisions vertically in the centre of the cornea as close as possible to the plane of the iris. This measurement took place in the same eye of the same patient in two time points. First time - one day prior to surgery, 10 minutes after the last mydriatic drop was given, measurement was performed and read by two doctors during the slit-lamp examination. Second time - on the day of surgery, during the procedure and after Mydrane injection, immediately before capsulorrhexis and at the end of surgery, it was measured (the same way as one day preoperatively, by placing a medical ruler with millimetre divisions vertically in the centre of the cornea as close as possible to the plane of the iris) and read at the same time by the surgeon, the assisting doctor and the operating theatre attendant.

The research was conducted in accordance with the ethical standards of the institutional research committee and with the Declaration of Helsinki. The study was approved by Warsaw Medical University Bioethical Committee. All patients and control individuals provided written informed consent to participate in the study.

Surgical procedure

All phaco procedures were done using the phaco machine (Infiniti, Alcon, Fort Worth, Texas, USA). All patients received topical anaesthesia (proxymetacaine 0,5%). All procedures were performed by two experienced surgeons in cataract surgery. The standard technique for a clear corneal incision was used. The surgeon proceeded with the surgical procedure using the standard technique for 5 – 7 mm continuous circular capsulorhexis with the capsule forceps, hydrodissection in multiple directions, divide and conquer technique used to deal with central nucleus and remove the cataract, injection of an acrylic intraocular lens (IOL) (Adapt AO, Baush & Lomb, Rochester, New York, USA) after a complete cortex removal. Mean total time ultrasound energy applied was 32 seconds (range 10 – 57 s), the mean phaco energy applied was 36% (range 21 – 55 %). There were no intraoperative complications. The femtosecond laser was not used during any procedure.

Statistical analysis

The statistical analysis was performed using STATISTICA 13.1 software (StatSoft, Tulsa, OK, USA). The values of descriptive statistics for continuous variables are presented as medians and interquartile ranges (IQR). Nominal variables are described as percentages and the number of patients in the corresponding group (in parentheses). The assumptions for

Table 1. The demographic and clinical characteristics of Mydrane and reference group.

		Mydrane group		**Reference group**		**P-value**
Gender (No/%)	Female	17	58.6%	26	74.3%	0.2768
	Male	12	41.4%	9	25.7%	
Age (years)		50 – 88 (mean 75.4)		59 – 88 (mean 73.6)		0.8992
Systemic diseases	Diabetes	6	20.7%	7	20.0%	0.8074
	Prostatic hyperplasia (α-blocker treatment)	5	17.2%	4	11.4%	0.7200
Ocular diseases	Primary open angle glaucoma	3	10.3%	3	8.6%	1.0000
Degree of nucleous opacification (LOCS scale) (No/%)	N2-N3	19	65.5%	28	80.0%	0.8408
	N4-N5	10	34.5%	7	20.0%	

parametric tests were verified by the Shapiro-Wilk and Levene's tests. The student's *t* test or Mann-Whitney's U test was used to compare continuous variables between the two groups in univariate analysis, respectively to their assumptions. Paired comparisons were evaluated by paired student's *t* test or Wilcoxon test depending on difference distribution. Depending on the sample size, analyses of proportions were performed using the Chi-square test, the Chi-square test with Yates correction, or the Fisher's exact test. Correlations between variables were assessed using the Spearman's rank test. ANOVA with repeated measurements was used for comparison of measurements from two time points with respect to group allocation. P value < 0.05 was considered as statistically significant.

RESULTS

The majority of patients' population were women (43/64; 67.2%). The mean age of the total population was 75.6 years ± 8.5 years. Accordingly to LOCS III grading scale we rated our patients' cataract grade (13).

Forty seven patients (73.4%) had cataract rated as LOCS N2-N3 (nuclear grades 2 or 3), and 17 patients (26.6%) had cataract rated as LOCS N4-N5 (nuclear grades 4 or 5). Among patients at least one systemic disease was present: 20.3% of them had diabetes, 14% suffered from prostate hyperplasia. No significant differences between two studied groups in terms of age, sex, cataract stage and associated systemic diseases were noted.

The demographic and clinical characteristics of patients in analysed groups are presented in *Table 1*.

In both groups of patients differences in CCT and CD at baseline examination and one month after surgery were observed. The baseline CCT in Mydrane group ranged from 463 to 604 µm (mean: 535.72 µm) and in the reference group it was from 458 to 590 µm (mean: 536.66 µm). One month after surgery the CCT decreased significantly as compared to the preoperative period in both groups of patients (P = 0.0114 in Mydrane group and P = 0.0295 in reference group). However there was no significant statistical difference in decreased CCT between analysed groups (P = 0.9706). The detailed CCT changes in Mydrane and reference group in a follow-up period are presented in *Table 2* and in *Fig. 2*.

The baseline CD in Mydrane group ranged from 1466 to 3154 cells/mm^2 (mean: 2424.76), while in the reference group was almost comparable and endothelial CD was from 1416 to 2900 cells/mm^2 (mean: 2409.60). One month postoperatively the CD significantly decreased as compared to the baseline

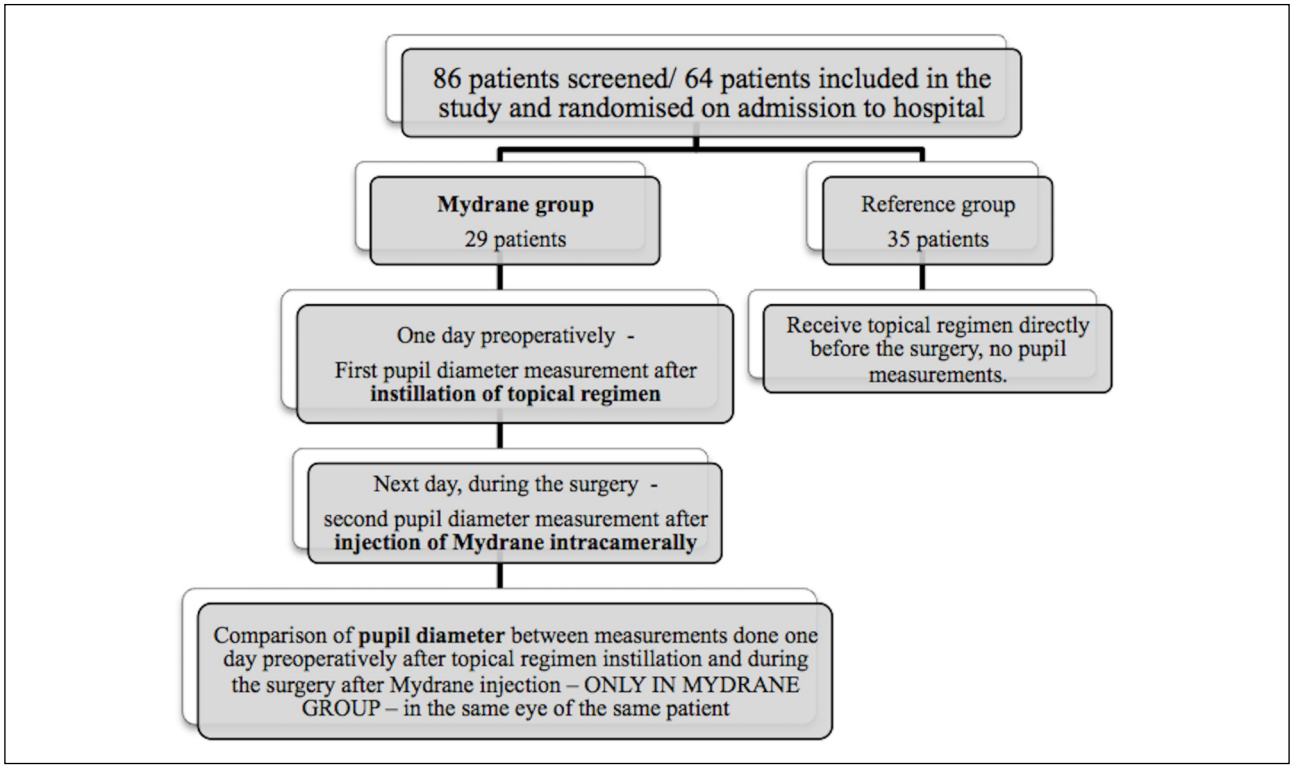

Fig. 1. Randomisation procedure and comparison of pupil size after topical regimen and after Mydrane injection in the Mydrane group patients.

Table 2. The detailed central corneal thickness (CCT) and corneal endothelial cell density (CD) change in analysed groups of patients in a follow-up period.

		Mean	SD	Min	Max	P-value
Mydrane group	Delta CCT (µm)	–4.59	–34.00	32.00	13.23	0.0114
	Delta CD (cell/mm^2)	–486.10	–1597.00	–4.00	441.48	0.0001
Reference group	Delta CCT (µm)	–4.46	–57.00	30.00	14.44	0.0294
	Delta CD (cell/mm^2)	–561.77	–2111.00	110.00	483.73	0.0001

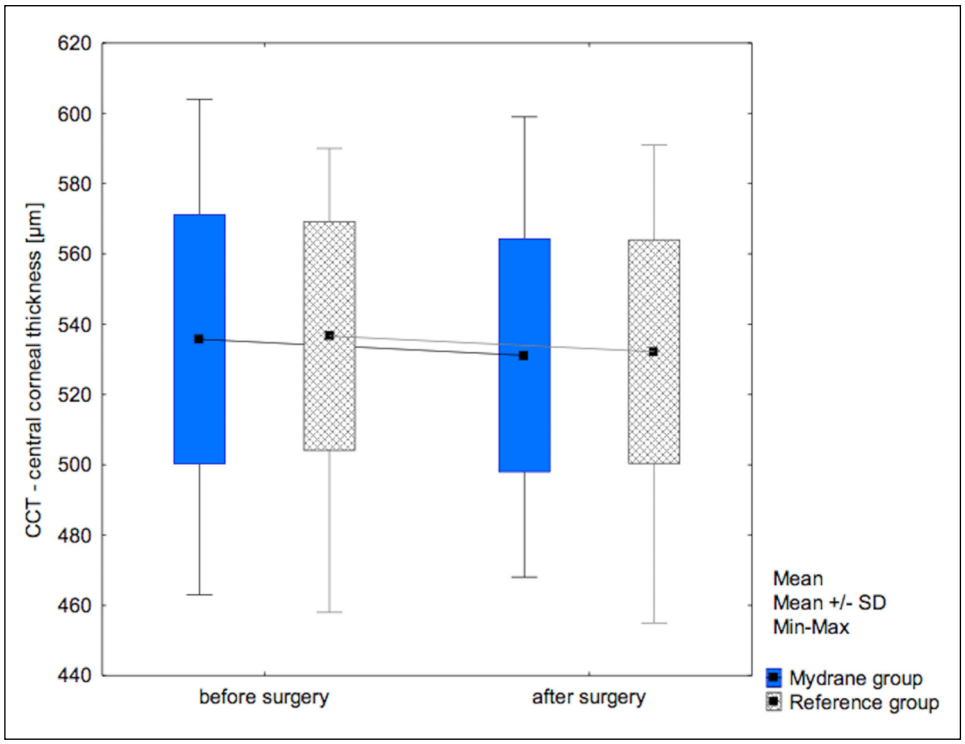

Fig. 2. Central corneal thickness (CCT) changes in Mydrane and reference groups before and one month after cataract surgery.

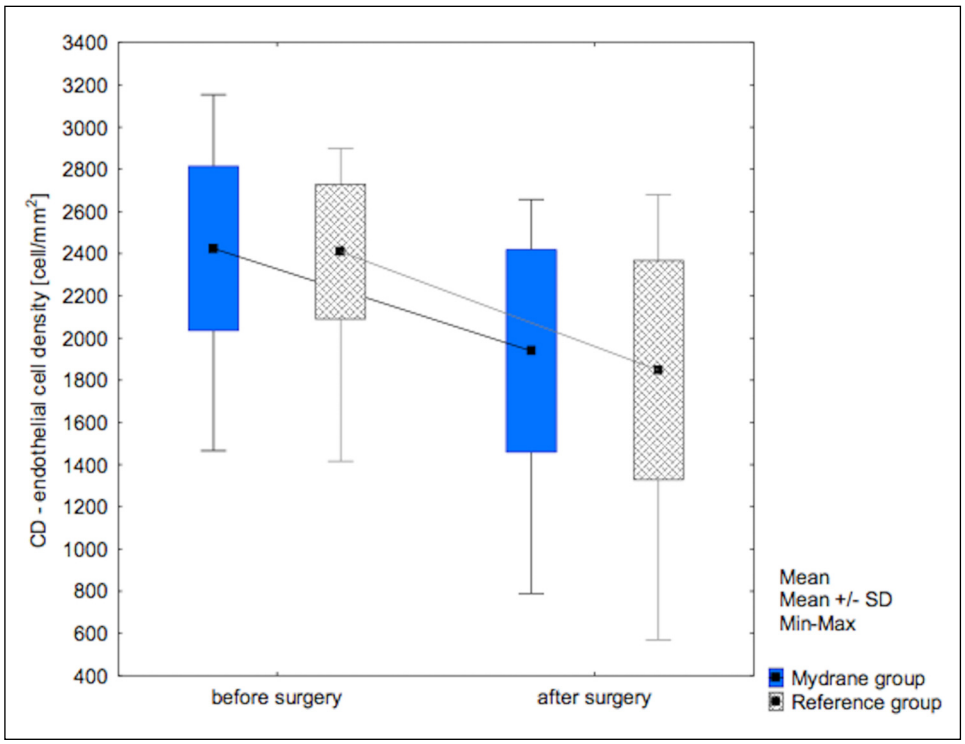

Fig. 3. Corneal endothelium cell density (CD) changes in Mydrane and reference groups before and one month after cataract surgery.

Table 3. Pupil diameter according to mydriasis regimen in Mydrane group before and after cataract surgery.

Pupil diameter (mm)	**Mean**	**SD**	**Min**	**Max**	**P-value**
After instillation of topical mydriatics one day prior to surgery	7.05	0.84	5.50	8.00	0.3937
After intracameral injection of Mydrane	6.90	1.06	4.50	9.00	

examination in Mydrane (P = 0.0001) and reference (P = 0.0001) group. However the difference in CD changes in pre- and postoperative period between these two groups was not statistically significant (P = 0.5195). The detailed CD changes in two analysed groups in a follow-up period are presented in *Table 2* and in *Fig. 3*.

The study demonstrated that age, sex, systemic comorbidities: diabetes and prostate hyperplasia treated with alpha-1 blocker agents as well as POAG did not affect pupil diameter as measured one day preoperatively after mydriatic eye drops instillation or during the surgery after intracameral Mydrane injection.

In Mydrane group there was no difference in dilated pupil diameter between intracameral injection of Mydrane solution and topical mydriatics (P = 0.3937) (*Table 3*).

The study had a power of 80% for detecting a difference of 0.7 SD (10 for SD 14) for the sample size of 29 patients in the Mydrane group and 35 patients in Reference group and with probability of type I error on the level of 0.05.

DISCUSSION

Obtaining adequate, quick and stable mydriasis is one of the key points of every cataract surgery procedure. Mydriatic eye drops are the standard method for pupil dilation in cataract surgery, but their limitations have provoked a search for different techniques (14).

In previous studies it had been proven that intracameral administration of mydriatics and analgesics induces rapid and safe mydriasis and can be an alternative to topical drugs in cataract surgery (10, 15, 16). Among various intracameral medications Mydrane proves to be safe and effective (10, 15). It is a mydriatic and analgesic solution that recently came into use; studies prove its non-inferiority in terms of dilated pupil size compared to standard pupil dilation with topical mydriatics (15). Multiple trials conclude, that Mydrane is safe, approved by surgeons (stable mydriasis, less challenging IOL insertion), comfortable for patients and medical staff (no need for multiple mydriatic drop administration preoperatively, patients reported to be more comfortable especially before IOL insertion) and cost-effective for hospitals - it shortens presurgical and surgical procedures (10, 15, 17).

In all clinical trials that assessed Mydrane efficacy for cataract surgery, patients were divided into two groups - one group received mydriatic eye drops and another - intracameral injection of Mydrane (10, 15). In our study we decided to evaluate effectiveness of mydriasis in the same eye of the same patient by comparing pupil dilation after mydriatic drops administration and then after Mydrane injection in one group of patients but on different days. It was possible because of the organisation of cataract surgery in our hospital - all patients are admitted one day prior to the surgery. We found no difference in dilated pupil diameter between Mydrane and mydriatic drops. We believe that by examining the mydriasis of the same eye we managed to show that Mydrane and mydriatic drops are not only equally effective while comparing their action between different patients but also there is no significant difference in their dilating potential for the same eye of the same individual.

We assumed that factors that can additionally affect pupil dilation are diabetes and alpha-1 blocker treatment. There are observations indicating that mydriasis is poorer in diabetic patients when compared to non-diabetic individuals (18). The same risk concerns patients treated with alpha-1 blockers, which can cause floppy-iris syndrome and pupil contraction during cataract surgery (19, 20). For diabetic patients the idea of poorer mydriasis remains uncertain - there is a study showing no difference in pupil diameter between healthy people and patients with type 2 diabetes dilated with topical phenylephrine 10% and tropicamide 1% (21).

In our study 20.3% of patients had diabetes, 14% suffered from prostate hyperplasia treated with alpha-1 blockers. No significant differences were found between Mydrane and reference group in terms of frequency of diabetes and alpha-1 antagonist treatment. In our study diabetes and alpha-1 antagonist treatment did not affect significantly pupil diameter after mydriatic drop instillation and after Mydrane injection.

The second aspect that we evaluated in this study was the impact of cataract phacoemulsification on CCT and CD with pupil dilation using either Mydrane or topical medications. It was already proven, that cataract surgery itself, without use of intracameral drugs, causes CD reduction (6, 22, 23). Age, small pupil diameter, large nucleus and advanced nucleus opacification, greater infusion volume, type of IOL implanted, and a higher amount of total emitted ultrasound energy were associated with endothelial cell loss (22). It is also known that nuclear cataract density determines the amount of ultrasound use during the phacoemulsification procedure. Our patients' nuclear cataract density varied between N2-N5. We obtained no significant differences between Mydrane and reference group in terms of LOCS scale, as well as age and pupil diameter. All patients received the same type of IOL. Therefore we conclude that the influence of different factors on CD is negligible and our result is more accurate in terms of showing influence of mydriatic solutions on CD.

In previous studies Mydrane or diluted adrenaline were proven to be non-toxic to corneal endothelium and cause no more cell loss after cataract phacoemulsification compared to surgery accompanied with topical mydriasis (10, 24, 25). Some authors proved that although CD decreases after cataract surgery, CCT remains unchanged after procedure as compared to the preoperative examination (23).

Surprisingly our study revealed a significant reduction not only in CD but also in CCT in both groups of patients scheduled for Mydrane or topical regimen. To our knowledge there are no previous published data describing the same observation. Thus it may serve as a basis for further investigation to explain this phenomenon.

Apart from the influence of cataract surgery and intracameral solutions on CD, age is, as mentioned above, one of the factors associated with endothelial cell loss. Aging endothelial cells have less antioxidant activity and weaker ability of wound healing (26). Their antioxidant capacity is strictly bound to endogenous carbon monoxide (CO) production in the eye, released, among others, by corneal endothelium (27). It has by far the highest capacity to oxidize arachidonic acid, which takes part in the inflammatory cascade (27).

Experimental studies have shown, that CO produced by the eye apart from having an influence on local tissues, can have an impact on the whole organism. CO released by the eye can be transported from the retinal vessels, in ophthalmic venous blood, affecting the expression of clock genes and their transcriptional factors in the hypothalamus (28). Moreover, changes in CO concentration in ophthalmic venous blood can have an acute impact on the systemic melatonin level, which carries information about light intensity (29). It was also proven, that CO released to the ophthalmic venous blood may modulate reproductive activity, determined by CO level dependent changes in serum lutenizing hormone (LH) levels, as well as gonadotropin releasing hormone (GnRH) and GnRH receptor gene expression (30).

Limitations of this study relate mainly to a small number of patients in both analysed groups. However the results of this study showed that both mydriatic protocols, topical and

intracameral, are safe for the corneal endothelium and equally efficacious for pupil dilation. Mydrane as a ready-to-use combination of mydriatics and anaesthetics can be a good alternative to standard topical regimen providing more comfort for the patient and medical staff as well as shortening time of pre-surgical preparation of the patient and in consequence make the functioning of the operating room more efficient.

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