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RESEARCH ARTICLE

Changes in the Density of Corneal Endothelial Cells in Elderly Diabetic Patients After Combined Phacovitrectomy and Ex-PRESS Glaucoma Implants

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Abstract: ***Background & Objective***: Corneal endothelial cells (ECD) are characterized by limited regenerative potential, which is additionally impaired in patients with diabetes. This retrospective study included 27 patients aged 58.1±13.6, 16 female and 11 males, who underwent 23-gauge vitrectomy in combination with cataract surgery (phacovitrectomy) and further Ex-PRESS shunt implantation throughout 2013-2017 at St. Barbara Hospital in Sosnowiec, Poland.

Methods: In our study, we distinguished 4 periods: initial period; post phacovitrectomy and removal of oil tamponade; and 3 and 12 months post implantation of the Ex-PRESS shunt. Statistical analysis was performed at the level of statistical significance of $p<0.05$. It included an analysis of variance (ANOVA) and Tukey's post-hoc test in order to determine the differences in the density of ECD cells/mm^2 between the periods of observation. The paired-samples t-Student test was also performed to determine whether the differences in visual acuity values before and after PPV and before and after Ex-PRESS shunt were statistically significant.

Results: The initial count of ECD cells was 2381.1±249, which decreased to 1872.8±350.7 cell/mm^2 and finally to 1677.9±327 at the endpoint. Differences in the density of ECD cells/mm^2 were observed to be statistically significant between the periods: after PPV *vs.* initial number of ECD ($p = 0.000138$); before 3 months after Ex-PRESS shunt *vs.* initial number of ECD ($p = 0.000138$); 12 months after Ex-PRESS shunt *vs*. initial number of ECD ($p = 0000138$). Analyzing the changes in visual acuity, we observed a deterioration both before and 3 months after Ex-PRESS shunt ($p = 0.007944$) and before and after PPV ($p = 0.060334$). In turn, correlation analysis indicated that there is a statistically significant, moderate, positive relationship. The relationship between visual acuity after Ex-PRESS shunt and ECD cells/mm^2 density turned out to be statistically significant ($r = +0.521381$; $p < 0.05$).

Conclusion: Regardless of the period of observation and the choice of ophthalmic treatment of diabetic complications, we observed a decrease in the number of ECD cells and a deterioration in visual acuity. It is, therefore, reasonable to provide the patient with complete information about the proposed procedures and to consider the risk-benefit balance.

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1. INTRODUCTION

Corneal endothelial cells (ECD) are a monolayer of polygonal cells with a thickness of 4-6 μm. This layer plays a fundamental role in maintaining optical transparency and is integral to visual function [1]. The endothelium has limited regenerative power. Loss of these cells is compensated only by the migration and enlargement of cells and an increase in their heterogeneity [2].

After the formation of a single layer of endothelium, the regeneration of the endothelial cells forming it occurs at an insufficient rate to replace dead or damaged cells. The con-

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sequence of this is that the number of cells decreases over the course of a person's life [3].

ECD density provides a direct measure of corneal endothelial health. A decrease in the number of ECD is a physiological phenomenon due to aging. Cell density ranges from almost 4000/mm^2 at birth to just over 1000/mm^2 in patients over 80 years of age [4]. ECD levels below 800/mm^2 can result in corneal edema. Several risk factors are known to accelerate this loss, including intraocular surgery, trauma and glaucoma [5-12].

A complication of diabetes is an increase in glucose concentration in an aqueous liquid, which results in the loss of normal corneal endothelial function [13]. Moreover, a reduced rate of replacement of abnormal endothelial cells with normal cells is observed in patients with diabetes compared to people without diabetes [14-16]. Patients with diabetes have been found to have a morphologically abnormal endothelium and a higher loss of corneal endothelial density after intraocular surgery [17-21]

Diabetic patients have frequent qualifications for intraocular surgery. Combined phacovitrectomy is very effective in the treatment of proliferative diabetic retinopathy. Unfortunately, in advanced stages of the disease and with increased patient age, it is not possible to eliminate the risk of secondary glaucoma, which in diabetic patients often proves resistant to treatment [22-24].

The aim of this study was to evaluate short-term changes in corneal endothelial cell density in diabetic patients after combined phacovitrectomy with silicon oil endotamponade and further an Ex-PRESS glaucoma implant-as a fourth surgical procedure in a single eye.

2. MATERIALS AND METHODS

This retrospective study included 27 patients (28 eyes) aged from 31 to 76 years (mean 58.1±13.6), 16 female and 11 males, who underwent 23-gauge vitrectomy in combination with cataract surgery (phacovitrectomy) and further Ex-PRESS shunt (Alcon, Novartis AG, Basel, Switzerland) implantation throughout 2013-2017 at St. Barbara Hospital in Sosnowiec, Poland.

The study group included 27 patients with poorly controlled type II diabetes and neovascular glaucoma. The patients had earlier undergone 23G PPV for diabetic complications, such as vitreoretinal proliferation with hemorrhage into the vitreous body chamber (17 eyes) and traction retinal detachment (7 eyes) or both (4 eyes). Patient's consent to review their medical records was not required by the bioethical committee due to the retrospective nature of this study and because patients' information was sufficiently anonymized.

Exclusion criteria consisted of any history of corneal dystrophy, pseudoexfoliation syndrome (PEX), complicated cataract surgery (lens subluxation, posterior synechiae), previous ocular surgery, history of ocular trauma or anterior capsule rupture and vitreous prolapse due to trauma which could affect the corneal endothelium, and additional procedures during the follow-up period. All the patients with at least 3 months of follow-up were included.

Each patient underwent a complete ophthalmologic examination, including best-corrected visual acuity (BCVA) on Snellen charts, slit-lamp examination, fundus examination, intraocular pressure (IOP) measurement with a Goldmann tonometer, and central endothelial cell count by non-contact specular microscopy (Conan, SP-3000, Japan) at the corneal center. At least five central measurements were obtained, from these, 5 results with good quality were averaged and presented in the study. Specular microscopy was performed both before and 3 months after surgeries-phacovitrectomy and Ex-PRESS implantation-and the last measurements were performed a year after the last procedure. All the patients signed an informed consent form before undergoing any surgical procedure. 23-gauge, 3-port pars plana vitrectomy was performed on all the eyes by the same vitreoretinal surgeon (AL-B) with the same technique and the same device (Constellation, Alcon, Forth Worth, USA). All the patients underwent vitrectomy with phacoemulsification and intraocular lens implantation. Surgery was combined with dyed ERM and ILM, removed in all cases with forceps and peeled (2-disk diameter around the macula) in a circular manner. Peripheral tractions in cases of retinal detachment were carefully removed, any tears in the retina were treated with a laser. Each eye was tamponaded with silicon oil. Thereafter, a silicon oil - fluid exchange was performed within a 60-day post-op period. Corticosteroid and antibiotic drops were applied after each surgery for 3 weeks.

An Ex-PRESS shunt (3 mm long and 400 μm wide providing filtration through a 50 μm channel) was implanted in a further follow-up period. Surgery was offered to the patient from 4 months to 4 years after the vitrectomy (mean 13.5±13.0 months from vitrectomy, only 28% of Ex-PRESS implantations were performed later than 12 months after vitrectomy).

Criteria for additional glaucoma treatment were: elevated IOP over 21 mm of Mercury, in need of 3rd anti-glaucoma eye drops despite a course of oral acetazolamide at a dose of 250 mg BID. A valve was placed under the scleral flap in the upper conjunctival quadrant. Following the surgery, all the patients received local antibiotic and steroid drops for 3 weeks. Measurements were performed 3 and 12 months after treatment.

Statistical analysis was carried out with the use of the Statistica 12 program (Cracow, Poland). Research hypotheses were verified at the level of statistical significance of $p < 0.05$. The distribution of the presented data in this paper fulfilled the assumptions of the normal distribution, which was verified by the Shapiro-Wilk test. Therefore, all the subsequent analyses were carried out using parametric methods ($p < 0.05$). First, ANOVA was performed. Then, the post-hoc Tukey's test was performed to indicate the statistically significant differences in the density of ECD cells/mm^2 between the periods of observation. The paired-samples t-Student test was also performed to determine whether the differences in visual acuity values before and after PPV and before and after Ex-PRESS shunt were statistically significant. In this study, an attempt was made to determine the relationship between visual acuity and ECD density after Ex-PRESS shunt (Pearson correlation coefficient-r).

Table 1. Characteristics of IOP and density of ECD cells depending on the kind of surgery.

Parameter	Minimum	Maximum	Average	Standard Deviation
BCVA before PPV	0.002	0.200	0.046	0.0534
BCVA after PPV	0.005	0.500	0.081	0.0922
BCVA before Ex-PRESS shunt	0.002	0.400	0.100	0.0904
BCVA after Ex-PRESS shunt	0.005	0.400	0.148	0.1278
Initial number of ECD cells [cell/mm^2]	1783	2833	2381.1	249
Density of ECD cells after PPV+ phacovitrectomy and removal of oil tamponade	972	2445	1872.8	350.7
Density of ECD cells 3 months after Ex-PRESS shunt [cell/mm^2]	758	2256	1765.923	329.5
Density of ECD cells 12 months after Ex-PRESS shunt [cell/mm^2]	785	2178	1677.9	327.2

3. RESULTS

The main loss of endothelial cells in the study group is caused by the first extensive surgery. Treatment of the anterior and posterior chambers of the eye and injection of silicone oil into the vitreous cavity causes a significant reduction in the number of cells. In our group, this was up to 23.3% cell loss until the silicone oil was removed. The initial count of 2381.1±249 decreased to 1872.8±350.7 cell/mm^2 and finally to 1677.9±327 at the endpoint. The characteristics of the level of IOP and density of ECD cells dependent on the kind of surgery are presented in Table **1**.

In 2 eyes, we were unable to count the density of endothelium; corneal thickness decreased to 600 μm of thickness, making the cells difficult to recognize in a specular microscope. Although the majority of patients achieved an improvement, the cumulative loss of endothelial cells after 12 months of surgery was nearly 30% compared to the initial density of ECD cells. ANOVA analysis demonstrated that differences in the density of ECD cells/mm^2 are statistically significant ($p = 0.0004$) between: after PPV *vs.* initial number of ECD ($p = 0.000138$); before 3 months after Ex-PRESS shunt *vs.* initial number of ECD ($p = 0.000138$); and 12 months after Ex-PRESS shunt *vs.* initial number of ECD ($p = 0.000138$). It can be concluded that the decrease in cell density between 3 and 12 months after surgery is not statistically significant ($p = 0.799301$) (Fig. **1**). In turn, in relation to the comparison of BCVA values before Ex-PRESS shunt and 3 months post Ex-PRESS shunt, the differences turned out to be statistically significant ($p = 0.007944$) (Fig. **2**). We did not find this regularity for the comparison of BCVA before and after PPV ($p = 0.060334$). In turn, correlation analysis indicated that there is a statistically significant moderate positive relationship ($r = +0.521381$; $p < 0.05$) between BCVA after Ex-PRESS shunt and ECD cell /mm^2 density.

In 60.7% of eyes, no additional medicine was needed to control IOP: 28.5% required one topical drug (timolol 0.5% or dorzolamid), while in 3 eyes (10.7%), 2 or 3 topical agents were applied to lower the pressure. In majority of cases, the quality of vision was improved; however, the improvement was limited to diabetic changes in the macula, including edema, exudates and hemorrhages. Another factor was glaucomatous atrophy of the optic nerves in the course of neovascular glaucoma.

4. DISCUSSION

From the point of view of safety, it is extremely important to determine the short and long-term effects of ophthalmic surgeries by determining the rate of corneal endothelial cell loss. It seems that in this way it should be possible to determine the highest percentage of ECD cell loss that would not result in complications.

This is more relevant given the relatively low regenerative capacity of ECD cells and their role in maintaining optical transparency [1,2].

Ex-PRESS shunt implantation, where the advantage is a lower risk of intraoperative hypotonia bleeding and postoperative induction of inflammatory development, is a less traumatic procedure compared to traditional trabeculectomy [25-27]. Yu *et al.* analyzed the efficacy and safety of primary Ex-PRESS shunt implantation on a group of 4 patients with neovascular glaucoma. On the basis of their analyses, they concluded that the procedure is safe and the effect in restoring normal IOP is comparable to traditional trabeculectomy [28]. Similar observations have been made by Hanna *et al.* and Kopinska *et al.* who also attributed IOP-reducing effects to Ex-PRESS [29,30]. Despite the control of glycemia and lipid profiles, and injections of steroids and anti-VEGF drugs into the vitreous body [31-33], about 5% of patients with diabetes require surgical treatment to control progressive diabetic retinopathy [34]. Therefore, it is important to search for effective solutions.

The main reason for endothelial damage is other procedures performed on the eye. Konopińska *et al.* described glaucoma-cataract combined procedures with trabeculectomy and Ex-PRESS shunt. In their paper, a one-year follow-up noted a decrease in endothelial cells to 37.4±19.2% in the Ex-PRESS group ($p = 0.006$) and to 23.2 ± 14.1% in the trabeculectomy group ($p = 0.008$). Combined phaco-Ex-PRESS and phacotrabeculectomy procedures did not significantly change central corneal thickness. However, the average density of the endothelium was lower compared with our group [28].

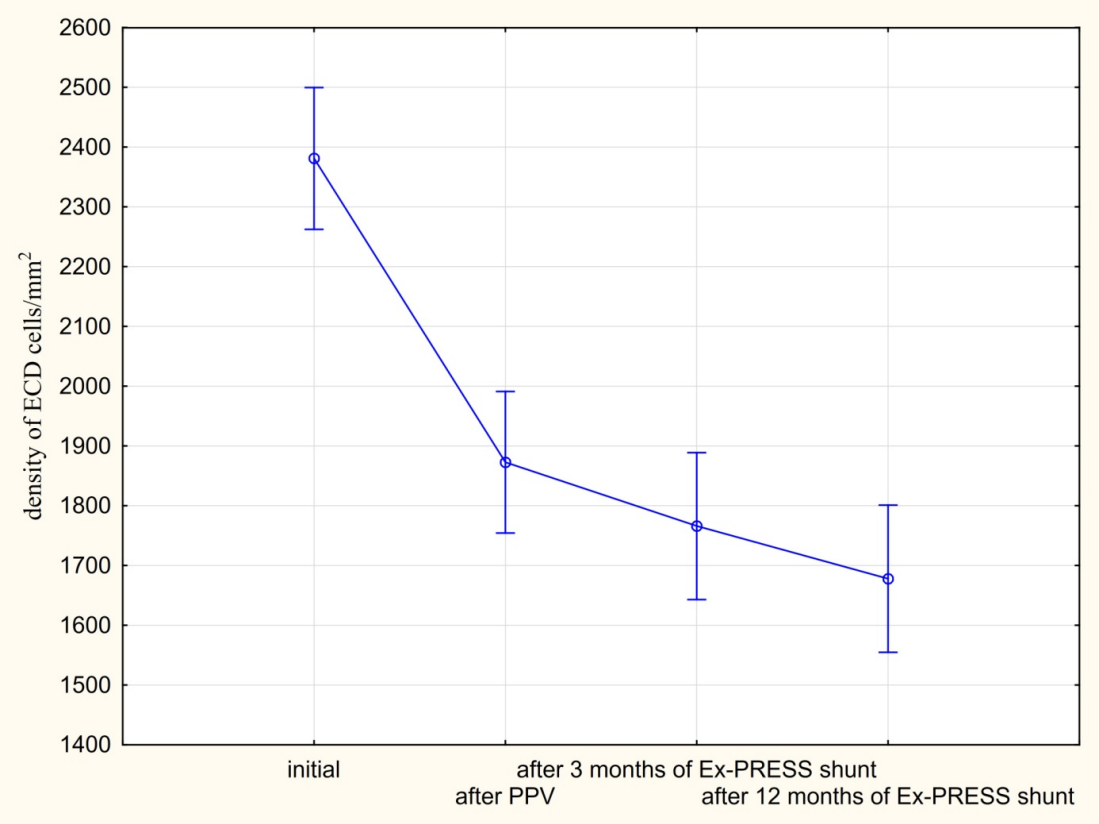

Fig. (1). Changes in the density of ECD cells/mm^2 during the whole observation period.

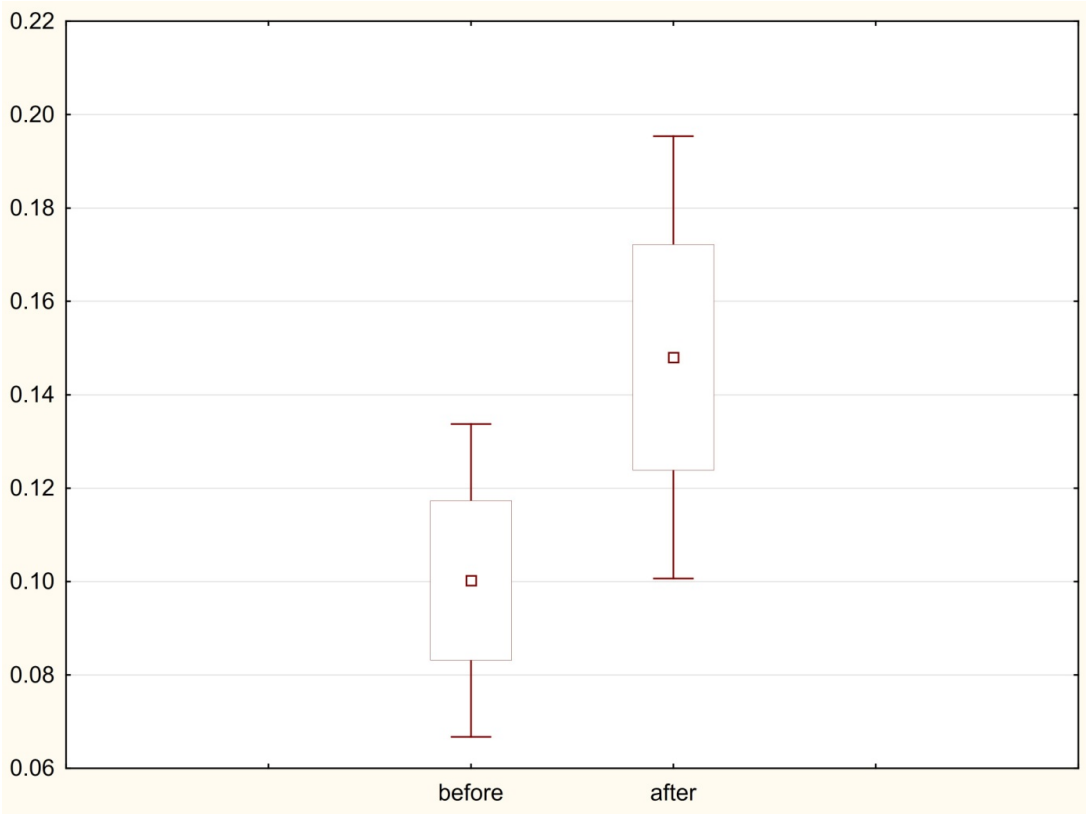

Fig. (2). BCVA values before and 3 months after Ex-PRESS shunt surgery ($p < 0.05$).

Therefore, in this study, we attempted to evaluate the loss of ECD cells after phacovitrectomy and removal of oil tamponade and also 3 and 12 months after Ex-PRESS shunt compared to the initial number of ECD cells. We observed a steady decrease in the density of ECD cells after each treatment compared to the initial number of ECD cells. In addition, our analysis showed that, with subsequent eye surgery, the density of ECD cells continues to decrease, eventually reaching 70% of cells 12 months after Ex-PRESS shunt compared to PPV. All of these differences were found to be statistically significant ($p < 0.05$).

Only between the observation periods of 3 and 12 months after Ex-PRESS shunt does the difference in the density of ECD cells seem to be relatively small, which was confirmed by statistical analysis ($p > 0.05$). Our observations seem to contradict the findings made by Konopińska *et al.*, who found a loss of about 15% of ECD between 6 and 12 months in the Ex-PRESS group, while our observations show only a 5% decrease in the number of ECD cells between 3 and 12 months after Ex-PRESS shunt. These discrepancies may result from the different sizes of the groups (27 patients in our study, 46 in the study by Kopinska *et al.*). Also in our study, the effects of ophthalmology were analyzed in a younger population (58.1±13.6 years), while Konopińska *et al.* [30] conducted observations in the age group 71.8 ± 9.46 years. Thus, taking into account the above and our studies, it seems that the number of ECD cells decreases with age [1, 2].

Usually, each invasive glaucoma surgery has a more significant impact on the endothelium. Arnaviele *et al.* compared endothelial cell loss after trabeculectomy and deep sclerectomy. They emphasized that endothelial cell loss is observed 12 months after glaucoma removal, although the number of ECD cells is subject to a decrease after only 3 months. The observation by Arnaviele *et al.* of the number of endothelial cells 3 and 12 months after surgery is the same as that observed in our study. The difference in cell loss was statistically higher in the invasive method: 9.6% and 4.5%, respectively. Concurrently, they suggest that although the difference was statistically significant, it was relatively small, which, according to the authors, is a motivation for further analysis in this area [35].

Kim *et al.* analyzed a group of 30 eyes with an implanted Ahmed glaucoma valve (AGV). They observed a progressive decrease in the loss of corneal endothelial cell density, reaching 10.5% at the 12th month. The Ahmed valve is also widely used in neovascular glaucoma despite it being a more invasive approach. Ex-PRESS shunts deliver a higher success rate, reaching 70.5% and 92.9% in neovascular glaucoma and non-neovascular glaucoma [36]. The results obtained by this research team point out the need for special care in the group of patients with AGV implantation in order to reduce damage as much as possible. Furthermore, the conclusions of this study confirm our study premise. The choice of an appropriate therapeutic strategy is a key element in maximizing the benefits of treatment while minimizing the potential risk. It should also be noted that the analysis of changes in the number of endothelial cells due to the type of surgical procedure was carried out at several time points, which are also the same as those selected for our study.

In the examined group, an additional factor is diabetes causing complications in each segment of the eye. Patients with diabetes or complications of diabetes have lower densities of endothelial cells [37]; therefore, we investigated safer methods of surgery to safeguard the endothelium during surgical treatment [38]. This was confirmed by a population study conducted by Sudhir *et al.* where they compared the density of ECD cells in diabetic patients compared to healthy volunteers (2550 ± 326 *vs.* 2634 ± 256; $p = 0.001$) [39]. A concurrent conclusion can also be drawn from the study carried out by Ahuja *et al.*, where the authors emphasized that the nature of changes in diabetic patients is similar to changes associated with the aging process. Thus, it seems that endothelial corneal cells in diabetic patients are characterized by accelerated aging [31]. In our study, we also determined the range of the difference in visual acuity before and after each of the two treatments. Statistically significant differences were only found between the period immediately after Ex-PRESS shunt treatment and 3 months after the treatment (an increase of 0.4 $p = 0.007944$). Although the difference turned out not to be statistically significant ($p = 0.060334$) for the comparison of visual acuity before and after PPV, it should be noted that the threshold for establishing statistical significance seems to be relatively small in this case. This may indicate that, in the case of an increase in the size of the compared groups, the differences could be statistically significant ($p < 0.05$). This is also confirmed by Pearson's analysis of the correlation between visual acuity and the number of ECD cells after Ex-PRESS shunt surgery. Correlation analysis indicated such a relationship ($r = +0.521381$; $p < 0.05$). The positive correlation observed between the compared features indicates that an increase in one value is accompanied by an increase in another and vice versa. Therefore, it should be borne in mind that the above necessary and performed procedures negatively affect the density of corneal endothelial cells. Abu Samra *et al.* pointed to the possibility of decompensatory retinopathy after implantation of the Ex-PRESS shunt in those patients with an increase in IOP within a short period of time [40]. On the other hand, Puerto *et al.* in their retrospective evaluation did not observe statistically significant differences in visual acuity before and after the Ex-PRESS shunt implantation procedure [41]. It seems that the probable cause of the difference in results between our analysis and the one by Puerto *et al.* is the criteria of inclusion to the study group. Therefore, an important element of the study is its proper planning and the precise definition of inclusion and exclusion criteria.

CONCLUSION

Given our observations and those carried out by other research teams, it should be borne in mind that, although the procedures discussed in this paper are necessary, they are associated with a decrease in the number of endothelial cells in the cornea and a decrease in visual acuity. Therefore, the choice of the best and safest treatment option should be

made individually for each patient, and the patient should be informed about the benefits and potential negative effects of the procedures.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The committee ruled that approval was not required for this study. This is a retrospective study based on medical records. According to the Polish statute, this is a non-interventional study (Article 37a (1) of the Pharmaceutical Law) and therefore, in the understanding of the Act of 5 December 1996 on the professions of doctor and dentist, does not require the Opinion of the Bioethical Committee and does not constitute clinical trials.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

Patient's consent to review their medical records was not required by the bioethical committee due to the retrospective nature of this study and because patients' information was sufficiently anonymized.

AVAILABILITY OF DATA AND MATERIALS

The data used to support the findings of this study are included in the article.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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