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Effectiveness of calcific band keratopathy treatment with Ethylenediaminetetraacetic acid combined with cataract extraction in pediatric patients

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Purpose. *To demonstrate the effectiveness of combined surgery including calcific band keratopathy (CBK) treatment followed by cataract extraction with intraocular lens (IOL) implantation in pediatric patients, assessed through preoperative and postoperative best-corrected visual acuity (BCVA) and changes in corneal transparency.*

Material and Methods. *This retrospective study was conducted on the medical records of patients treated for CBK combined with cataract secondary to chronic uveitis between January 2018 and December 2020. The study included 15 eyes of 14 pediatric patients. Clinical parameters recorded included age, primary diagnosis, and preoperative and postoperative BCVA using a Tumbling E chart. Postoperative data were collected at 3 days, 6 months, and 12 months after surgery.*

Results. *Preoperative BCVA averaged 2.03 ± 0.69. On the 3rd postoperative day, BCVA improved to 0.82 ± 0.39, with further improvements to 0.78 ± 0.43 at 6 months and 0.69 ± 0.45 at 12 months. The mean BCVA increased by 2 lines, and BCVA improved by 6 lines within one year postoperatively. Recurrence of CBK was observed in 3 eyes (20%) at 6-month follow-up.*

Conclusion. *Simultaneous EDTA chelation of calcium plaques and phacoaspiration with IOL implantation is an effective and safe treatment for CBK combined with cataract in pediatric patients. This combined approach resulted in significant improvements in visual acuity and corneal transparency and symptomatic relief. However, the high recurrence rate indicates the need for further research.*

Key words:

Calcific band keratopathy, cataract, Ethylenediaminetetraacetic acid

Introduction. Calcific Band Keratopathy (CBK) is a corneal dystrophy characterized by the appearance of a gray or white band, depending on the progression of degeneration, formed by the deposition of calcium salts in the superficial layers of the cornea, leading to visual impairment and discomfort [1, 2]. These layers usually include the epithelial basement membrane, Bowman layer, and anterior stroma. CBK may develop simultaneously with another intraocular condition, such as cataracts [3]. Cataracts in children with chronic uveitis commonly develop not only due to chronic inflammation but also as a result of long-term use of steroids.

Among the various approaches for managing CBK, Ethylenediaminetetraacetic acid (EDTA) has proven to be a particularly effective method for chelating calcific deposits [4]. As a chelating agent, EDTA binds to calcium ions, thereby facilitating their removal from the corneal matrix and improving corneal clarity and visual acuity [5, 6]. This treatment has shown promise in improving corneal transparency and best-corrected visual acuity (BCVA) by effectively clearing the visual axis without invasive surgical procedures in adults.

A MEDLINE search revealed no reports on analogous treatment in pediatric patients; there are studies concerning adults only. For this reason, the main purpose of our study was to show the effectiveness of combined surgery in pediatric ophthalmology practice.

Material and Methods

This retrospective study was performed using the medical records of patients who had undergone treatment of CBK followed by cataract extraction with intraocular lens (IOL) implantation in the main tertiary referral center between January 2018 and December 2020.

Preoperatively, all patients were evaluated to ensure they were in a period of uveitis remission, as determined by the absence of active intraocular inflammation for at least three months. Systemic immunosuppressive therapy was managed by specialized pediatricians and/or rheumatologists. Throughout the perioperative period, the system-

ic treatment regimens were unchanged; patients continued to receive their prescribed medications according to their established schedules.

The clinical parameters recorded for each patient included age, primary diagnosis, and preoperative and postoperative BCVA using a Tumbling E chart. Postoperative data were collected at 3 days, 6 months, and 12 months after surgery.

The study was approved by the Local Ethics Committee and was conducted in accordance with the Declaration of Helsinki. All required informed consent was obtained from the parents.

Description of surgical technique

After general anesthesia was administered, an eye speculum was placed and an elevated calcium band was removed with a corneal spatula. EDTA 5% eye drops were applied for 5 minutes to completely remove calcific deposits from the areas of opacification, followed by rinsing with 50 mL of a balanced salt solution. This procedure was repeated several times until the calcific deposits were completely removed. After the complete removal of the calcific deposits, the standard technique of phacoaspiration with IOL implantation and posterior capsulotomy was performed.

At the end of the surgery, a soft bandage contact lens was placed over thea cornea for the next seven days to promote corneal epithelialization. Additionally, preservative-free Dexamethasone 0.1% and Levofloxacin 0.5% eye drops were prescribed four times daily, and Tropicamide eye drops were prescribed three times daily for five days to manage inflammation and prevent infection.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism 10 software (GraphPad Software Inc., Boston, Massachusetts, USA). All data were expressed as means±standard deviation and range. The Shapiro-Wilk test was performed to evaluate whether data sets were normally distributed. The nonparametric Friedman test was used as an alternative to one-way analysis of variance (ANOVA) for performing a one-way repeated measures analysis of variance by ranks. In all analyses, a p value of 0.05 was considered statistically significant.

Results

Patient characteristics

In this retrospective analysis, 15 eyes of 14 patients diagnosed with cataract and concomitant CBK secondary to chronic uveitis were included. Three of the patients had uveitis as a primary idiopathic condition (20.0%), and eleven had uveitis associated with juvenile idiopathic arthritis (JIA) (80.0%). The mean age of the patients at the time of surgery was 9.5±2.7 years: six patients were female (42.86%) and eight were male (57.14%). A summary of the clinical data is presented in Table 1, and the clinical case of patient №14 is presented in Figure 1 (see cover page 2).

Postoperative outcomes and recurrence

Throughout the 12-month follow-up period, all patients continued to receive their prescribed systemic medications related to their primary conditions. There were three cases (3 eyes – 20%) of uveitis recurrence, all occurring 3–4 months postoperatively, specifically in patients №3, №6, and №13 as documented in Table 1. All patients experiencing uveitis recurrence were prescribed Dexamethasone 0.1% and Nepafenac eye drops, administered four times daily, and Tropicamide, administered three times daily until remission was achieved. Patients were also referred to rheumatologists, who considered modifications or adjustments to their prescribed systemic medications to further manage their conditions. Within one month, remission was achieved in all uveitis cases.

Additionally, CBK recurrences were observed in three patients (3 eyes – 20%) at the six-month follow-up. Patients №3 and №6, who experienced uveitis recurrence, also reported a recurrence of CBK. Another case of CBK recurrence was noted in patient №11, occurring in an eye without inflammatory signs, although this patient's visual acuity remained high. Patients with CBK recurrence reported symptoms of blurred and decreased vision.

Mean preoperative BCVA was 2.03±0.69. Postoperatively, on the 3rd day, the value reached 0.82±0.39, with a subsequent increase to 0.78±0.43 and 0.69±0.45 at 6 and 12 months, respectively. Repeated measures ANOVA indicates highly significant differences between treatment conditions. This was evidenced by an F value of 34.67 and a p value of less than 0.0001. The statistical significance ($p<0.05$) confirms that the observed differences were not due to random chance. Additionally, the R-squared value of 0.7123 suggests that approximately 71.23% of the variability in the outcomes can be explained by the different treatment conditions. This indicates a strong effect of the treatments on the measured outcomes.

Discussion

This study describes the advantages of combined surgical treatment for coexisting CBK and cataract in the same eye caused by chronic uveitis. It is known that children undergo surgery under general anesthesia. Meanwhile, there is research suggesting that repeated use of anesthetics or sedative medications affects children, putting them at risk of developing depression, anxiety, and sleep disorders [7]. To minimize or avoid repetitive use of general anesthesia, we performed combined surgery, including CBK treatment by chelation of calcific deposits with EDTA 5% solution, followed by cataract removal through phacoaspiration with IOL implantation.

CBK may be idiopathic or associated with a variety of systemic pathologies, such as nephropathic cystinosis and sarcoidosis, and intraocular diseases like uveitis, which is usually associated with JIA, glaucoma, and interstitial keratitis [3, 8-10]. It may also occur as a reaction to chemicals that may become hazardous to the eyes: for example,

Table 1. Patient-Specific Clinical Data and Outcomes of combined CBK and Cataract Surgery

№	Age (years)	Etiology	Gender	Pre-operative BCVA	Post-operative 3rd day BCVA	6th month BCVA	12th month BCVA	Uveitis recurrence	CBK recurrence	Received systemic medications
1	9	JIA	F	2.7	0.5	0.3	0.2	No	No	Methotrexate 10 mg per week; Adalimumab 40 mg every 2 weeks
2	9	JIA	F	2.7	0.5	0.4	0.4	No	No	-
3	13	Idiopathic uveitis	M	2.7	0.7	0.8	1.0	Yes	Yes	-
4	8	JIA	M	2.7	1.2	1.0	0.5	No	No	-
5	8	JIA	F	1.7	1.1	1.0	1.0	No	No	-
6	6	JIA	M	1.3	1.0	1.1	1.1	Yes	Yes	-
7	10	JIA	F	1.3	0.5	0.4	0.4	No	No	-
8	12	JIA	F	2.0	1.2	1.2	1.2	No	No	Methotrexate 15 mg per week
9	6	Idiopathic uveitis	F	1.0	0.3	0.2	0.2	No	No	-
10	14	JIA	F	2.7	0.3	0.3	0.3	No	No	-
11	7	JIA	M	1.3	0.8	1.1	0.2	No	Yes	Adalimumab 40 mg every 2 weeks
12	8	JIA	M	1.2	1.1	1.0	1.0	No	No	Methotrexate 15 mg per week; Adalimumab 40 mg every 2 weeks
13	8	JIA	M	2.7	1.7	1.7	1.7	Yes	No	-
14	13	Idiopathic uveitis	M	2.7	0.7	0.5	0.4	No	No	-
15	11	JIA	M	1.7	0.7	0.7	0.7	No	No	Methotrexate 15 mg per two weeks; Adalimumab 20 mg per week

Abbreviations: BCVA – best corrected visual acuity; CBK – caldific band keratopathy; IOL – intraocular lens; JIA – juvenile idiopathic arthritis; F – female; M – male.

intraocular silicone, phosphate-containing eye drops (e.g., steroid medicines, pilocarpine, viscoelastic agents) [3, 8, 9, 11, 12]. The reason why calcium salts precipitate in the interpalpebral zone at 3:00 and 9:00 o'clock is that this portion of the cornea has the highest exposure to the atmosphere and the tear film is insufficient or absent there. Evaporation of tears leads to an increase in osmolarity, causing the pH to become more alkaline. Alkalosis leads to the precipitation of calcium, resulting in its deposition [6, 13].

As mentioned earlier, the development of cataracts is associated with the use of steroids. It was discovered that clouding of the eye lens is associated with not only the duration of corticosteroid therapy but also a dose-dependent condition [14]. According to a previous study, the topical use of corticosteroids with ≤ 3 drops daily was associated with a lower risk of cataract formation compared with eyes treated with >3 drops daily [15].

In the early stages, calcium salts do not cause discomfort to patients. Once deposits break the corneal surface and involve the epithelium, pain, foreign body sensation, and irritation may appear [1, 4]. When the visual axis is involved, BCVA begins to decrease, which is also worsened by cataracts.

There are currently multiple treatment options for CBK. One of them is phototherapeutic keratectomy, which uses an excimer laser to treat corneal tissue via ablation; however, this method can induce refractive errors, such as hyperopia, myopia, and irregular astigmatism [16]. Manual debridement of CBK by scraping only with a surgical blade or spatula is effective, but it can also lead to an irregular corneal shape [4, 17].

CBK treatment using EDTA drops is preferred as the first step to improve visualization for cataract surgery. According to previous reports, researchers appear to use EDTA in the form of 0.37% disodium edetate eye drops and 2% or 3% solutions [4, 17, 18]. Although there is still no consistent standard for the EDTA concentration used for CBK treatment, these concentrations often require subsequent mechanical debridement or repetitive use. In our

cases, we used 5% EDTA eye drops because it allows for a single application sufficient to remove the calcific plaque without additional mechanical scraping or reapplication. Although EDTA is known to potentially cause corneal toxicity and ocular tissue damage, we mitigate this risk by limiting its use to a single intraoperative session [17, 19]. Therefore, we can say that the proposed method is safer than previous methods.

Right after CBK treatment, cataract surgery is performed via phacoaspiration with IOL implantation and posterior capsulotomy. There are studies describing the treatment of CBK in adults without cataract removal, whereas our study showed good results in all cases by solving both problems: treatment of CBK and cataract. The fact that our research involved children also makes it unique, as there are no previous investigations on the concurrent treatment of these two pathologies in pediatric patients.

According to the collected data, corneal opacifications tend to recur in approximately 28% of cases [4]. In this study, the recurrence rate was 20% within 6-12 months after treatment. It should be noted that the recurrence of calcium opacification is a common problem. Although EDTA removes the calcium precipitated on the cornea, it does not treat the underlying cause. Our hypothesis is that these recurrences may be attributed to intrastromal calcifications that are not adequately reached by surface-level EDTA chelation. These deeper calcific deposits likely remain after the initial treatment and can serve as a substrate for further opacification. This suggests a limitation in the efficacy of chelation therapy that is confined to superficial layers, pointing to the need for strategies that target calcifications that are more deeply embedded within the corneal stroma.

The recurrence of uveitis and CBK in this cohort highlights the complex interaction between inflammatory processes and the recurrence of CBK postoperatively. Notably, the simultaneous occurrence of uveitis and CBK recurrences in patients №3 and №6 suggests a potential exacerbation of underlying inflammatory mechanisms, thereby impacting both intraocular inflammation and calcific deposition.

In contrast, the recurrence of CBK in patient №11, in the absence of apparent inflammation, suggests that factors other than active uveitis might contribute to the recurrence of calcifications, such as inadequate initial removal and other subtle underlying causes. This case also highlights that high visual acuity can be maintained despite recurrent CBK, suggesting that the impact on visual function may vary significantly based on the location and extent of the recurrence.

The findings from our study suggest that EDTA 5% chelation in conjunction with cataract removal is effective and safe for children. They also showed symptomatic relief and an increase in BCVA in 100% of the patients; however, the total improvement in BCVA was limited due to amblyopia secondary to cataracts and corneal opacifications.

The findings of our research must be seen in light of some limitations. The main limitation of this study is that it was retrospective rather than prospective, leading to other limiting factors. The first limitation is the incomplete data on the causes of uveitis, which led to the appearance of CBK and cataracts in our patients. The second limitation is the short follow-up period of 12 months, while a longer period is needed for more accurate postoperative results. The final limitation is the lack of a single standard of EDTA concentration for chelation.

The repeated measures ANOVA results confirmed that the treatments had a significant effect on the outcomes, and the matching of subjects was effective in controlling for individual differences. These findings support the conclusion that combined surgery for calcific band keratopathy and cataract in pediatric patients is effective, as demonstrated by the significant improvements in visual acuity and the low rate of complications and recurrence.

In conclusion, treatment of CBK using EDTA in combination with phacoaspiration with IOL implantation is a safe and effective method for treating calcific band keratopathy and cataracts in one eye simultaneously. This approach allows for the restoration of the transparency of the visual axis, improving BCVA in pediatric patients, and providing symptomatic relief faster than performing each procedure separately. Nevertheless, the high recurrence rate highlights the need for further research.

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Information about authors and disclosure of information

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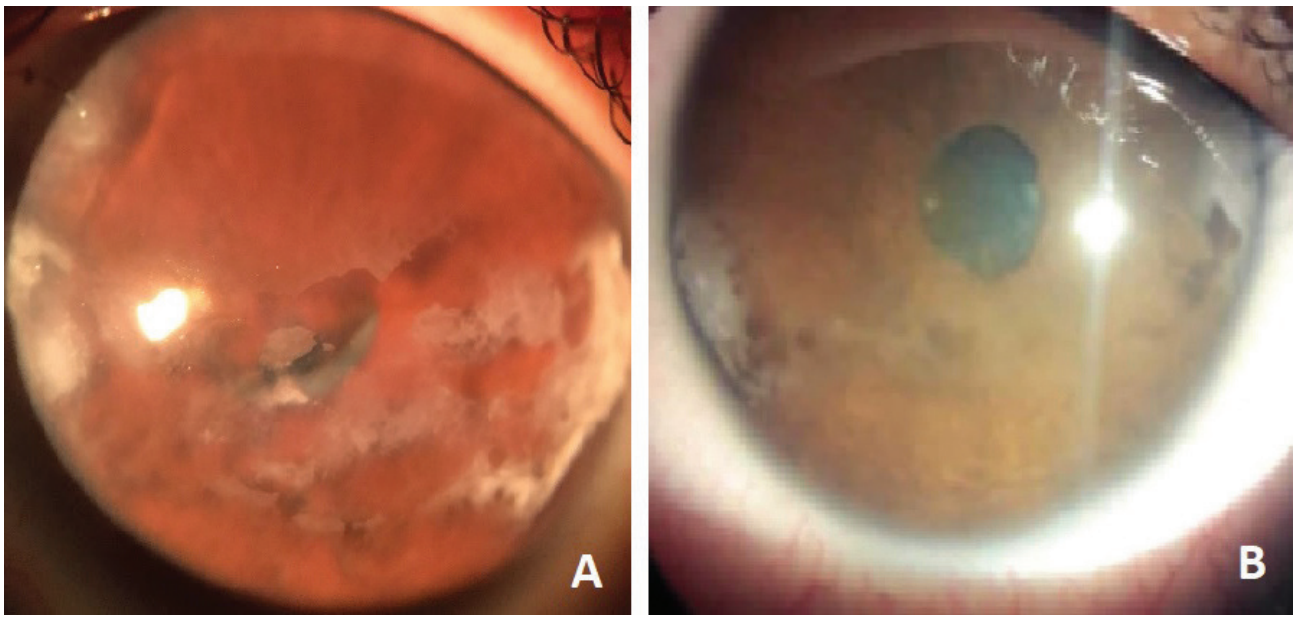

Figure 1. Clinical case №14: Patient S., 13 y.o. with a history of cataract and calcific band keratopathy secondary to juvenile idiopathic arthritis. Appearance before (A) and the next day after (B) treatment of calcific band keratopathy with Ethylenediaminetetraacetic acid and cataract extraction by phacoaspiration with intraocular lens implantation and posterior capsulotomy.

Рисунок до статті Могілевського С.Ю. з співав. «Прогностичні біомаркери прогресії непроліферативної діабетичної ретинопатії при цукровому діабеті 2 типу»

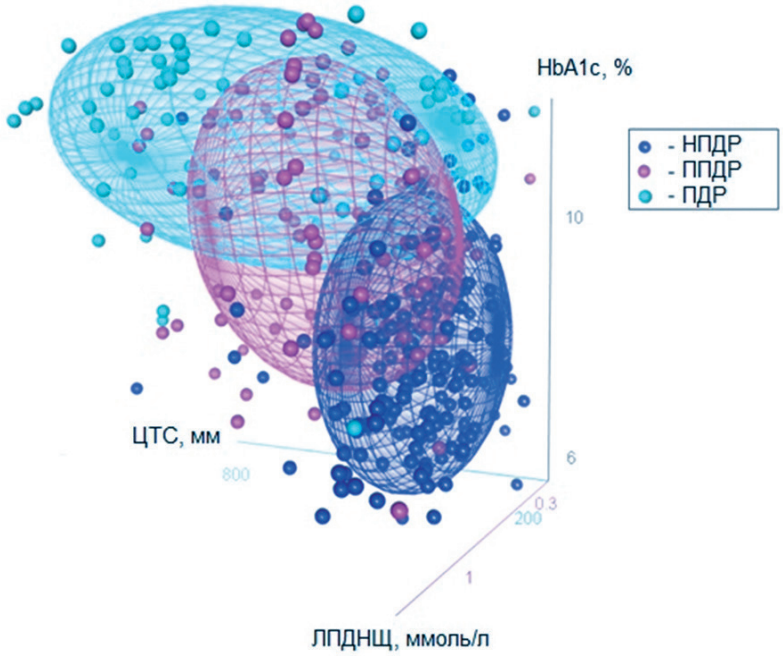

Рис. 2. Розподіл пацієнтів з ДР різних стаді в координатах HbA1c (%), ЛПДНЩ (ммоль/л) та ЦТС (мкм). HbA1c – глікований гемоглобін; ЛПДНЩ – ліпопротеїди дуже низької щільності; ЦТС – центральна товщина сітківки.