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ORIGINAL RESEARCH

Intrascleral Knotless Zigzag Suture Fixation of Four-Haptic Hydrophilic Acrylic Foldable IOL: Clinical Outcomes

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Background: The main options for intraocular lens (IOL) placement without capsular bag support and/or zonular weakness are iris-fixated IOL and scleral-fixated IOL (SFIOL).

Purpose: To describe the surgical technique and the outcomes of intrascleral knotless zigzag suture fixation of Akreos AO60 foldable IOL.

Methods: Retrospective cohort study of consecutive cases.

Results: Ninety-nine eyes of 92 patients were retrospectively studied. The mean age was 72.1±15.2 years (range 18–94), and the median follow-up duration was 19.5 months (range 3–81). The best-corrected visual acuity improved from a mean±SD of 1.34±0.70 logarithm of the minimum angle of resolution (logMAR) units at baseline to 0.49±0.56 logMAR at the end of follow-up ($p<0.001$). The mean±SD final SE was −1.24±1.82 diopters. The mean±SD prediction error was −0.51±1.16 diopters. The overall perioperative complications rate was 44.4% (n=44). The rate of complications requiring invasive treatment was 19.2% (n=19). The most common perioperative complications were ocular hypertension (OHT, 20.2%, n=20), and cystoid macular edema (CME, 15.2%, n=15). The rate of IOL dislocation was 7% (n=7).

Conclusion: This knotless technique avoids the risks of haptics fixation but is more prone to IOL dislocation in cases of suture deterioration. Past ophthalmic history needs to be carefully considered in candidates who underwent SFIOL implantation.

Keywords: intraocular lens, scleral fixation, knotless, cataract, lens luxation

Introduction

Phacoemulsification with intraocular lens (IOL) placement in the capsular bag is the gold standard for cataract surgery with adequate capsular support. When an adequate capsule support is absent and/or zonules are weak or absence, the main options are iris-fixated IOL (IFIOL) and scleral-fixated IOL (SFIOL), with the expectancy of similar outcomes.[1–3] Some surgeons would rather to implant a SFIOL to ensure a more physiologic position and to avoid the risk of corneal decompensation.[4,5] However, the scleral fixation is technically challenging and not devoid of risks.

Over the last years, many surgical techniques have been described, and novel IOL designs have increased the armamentarium of SFIOLs. The method of fixating an IOL in the sclera may use sutures or not. The sutured techniques have been modified to incorporate scleral flaps or pockets to prevent the conjunctival erosion provoked by exposed knots.[4] Alternatively, the knot can be avoided by running the

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suture through the partial thickness of the sclera in a zigzag pattern.[6] Using thicker or other types of threads has been further suggested to reduce suture breakage and lens dislocation or tilt.[7] The sutureless techniques using fibrin glue[8] or scleral tunnels[5,9–12] have gained popularity recently. While novel techniques have been introduced, IOL designs have also evolved. CZ70BD IOL[13] (Alcon, Fort Worth, Texas), for example, includes eyelets to prevent the suture slippage and subsequent lens dislocation. Akreos AO60[14] (Bausch & Lomb, Rochester, New York) is a foldable IOL with eyelets, and its off-label use as a SFIOL has been reported. FIL SSF Carlevale IOL[15] (Soleko, Italy) was specifically engineered for scleral fixation without sutures.

In our center, intrascleral knotless zigzag suture fixation of Akreos AO60 foldable IOL has been adopted as the standard surgery for eyes with poor capsular support. The present study aims to describe the surgical technique, functional outcomes and perioperative complications of intrascleral knotless zigzag suture fixation of Akreos AO60 foldable IOL.

Methods

This is a retrospective, observational, single-center study of consecutive eyes submitted to scleral fixation of AkreosAO60 foldable IOL using the knotless zigzag technique at Centro Hospitalar Universitário do Porto (CHUPorto), a tertiary center, from December 2013 to February 2021. All consecutive cases with a follow-up of at least 3 months were included. The enrolled eyes were divided into groups according to the etiology: spontaneous IOL dislocation, intraoperatively complicated cataract surgery, traumatic natural lens or IOL dislocation, or, rarely, other causes. The research adhered to the principles of the Declaration of Helsinki and its latest amendment (Brazil, 2013). All patients provided informed consent for treatment, and the study protocol complies with the requirements of the institute's committee ("Departamento de Ensino, Formação e Investigação") on human research.

Clinical Data

The clinical records were reviewed for demographic data, history of ocular and systemic diseases, indication for surgery, preoperative and postoperative best corrected visual acuity (BCVA), postoperative astigmatism and spherical equivalent (SE), and intraoperative and postoperative surgical complications. A comprehensive ophthalmic evaluation including BCVA and refraction, slit-lamp examination, measurement of intraocular pressure, and fundus examination was carried out at baseline and over the course of the follow-up. For statistical purposes, "counting fingers" was classified as 0.01, "hand movement" as 0.005 and "light perception" as 0.0005.[16] Visual acuity registered in decimals was converted to the logarithm of the minimum angle of resolution (LogMAR) equivalent.[17] Refractive prediction error was calculated as the difference between postoperative objective refraction expressed as SE, and the predicted SE of the refraction was obtained from preoperative biometry (IOLMaster 500, Carl Zeiss Meditec AG) using SRK-T formula and assuming in-the-bag IOL positioning. Absolute prediction error was calculated as the absolute value of the difference between the postoperative subjective SE and the formula prediction error.

Surgical Treatment

All surgeries were performed by three senior vitreoretinal surgeons (A.M., N.F., and B.P.) of the Department of Ophthalmology of CHUPorto, all of them with more than 10-years' experience.

The Akreos AO60 (Bausch & Lomb, Rochester, New York) is a single-piece four-haptic hydrophilic acrylic foldable intraocular lens (IOL) which is implanted inside the eye through a corneal incision as small as 1.8 mm. This IOL contains an eyelet in each haptic to provide a four-fixation point, thereby guaranteeing good centration and stability. The overall diameter varies from 10.5 to 11 mm according to the diopter power (between +0 and +30 diopters). The IOL power was calculated using an A-constant of 118.5, as recommended by the manufacturer.[18]

The intrascleral knotless zigzag suture fixation of Akreos AO60 foldable intraocular lens (IOL) technique is illustrated in Figure 1 and a postoperative slit-lamp photography is depicted in Figure 2. All cases underwent a standard 23-gauge pars plana vitrectomy (PPV) (Constellation 23-Gauge System; Alcon, Inc., Hunenberg, Switzerland), under peribulbar or subtenon anesthesia. After standard PPV, conjunctival peritomy was performed at 3 o'clock and 9 o'clock along the limbus to expose the sclera. A limbus corneal incision of 2.4 mm was created at 12 o'clock position to insert the IOL into the anterior chamber using the injector. Care should be taken to ensure that the optic vaults posteriorly. One foldable haptic was then externalized through the corneal incision using forceps, and a double thread 10-0 or 9-0 polypropylene suture was passed through the eyelet of the haptic outside the eye. Afterwards, the needle was carefully inserted through the corneal incision, passed behind the

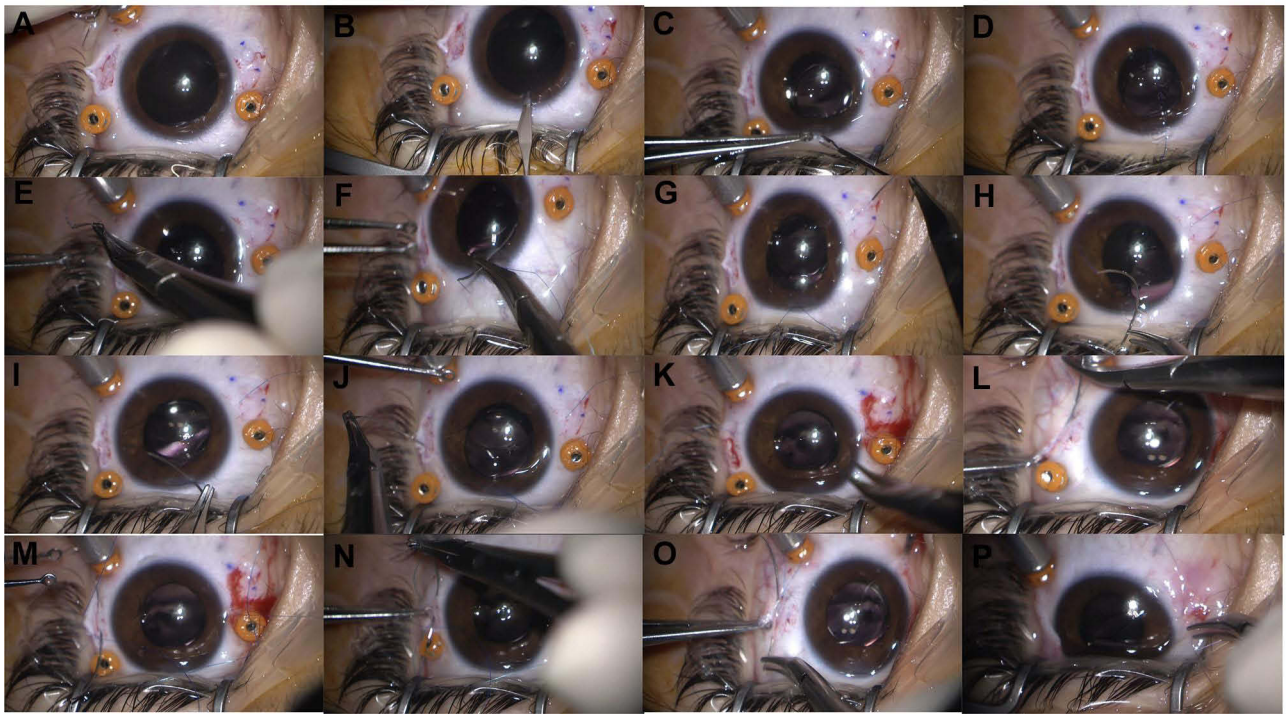

Figure 1 Intrascleral knotless zigzag suture fixation of Akreos AO60 foldable intraocular lens (IOL) technique. (**A**) Conjunctival peritomy at 3 and 9 o'clock to expose the sclera. (**B**) Limbus corneal incision at 12 o'clock. (**C**) One haptic is externalized through the corneal incision. (**D**) A double thread 10-0 or 9-0 polypropylene suture is passed through the eyelet. (**E**) The needle is passed between the arms of the thread. (**F** and **G**) The needle is inserted through the corneal incision, passed behind the iris, and came out through the sclera at about 2 mm from the limbus. (**H** and **J**) The steps are repeated using the 180° away haptic and orienting the needle to the opposite side. (**K**) Centration of the IOL. (**L**–**O**) The suture is run through the partial thickness of the sclera in a zigzag pattern (4 intrascleral passages), and the thread is cut flush to the sclera without knotting (this procedure is performed in the nasal and temporal sides). (**P**) Conjunctival suture.

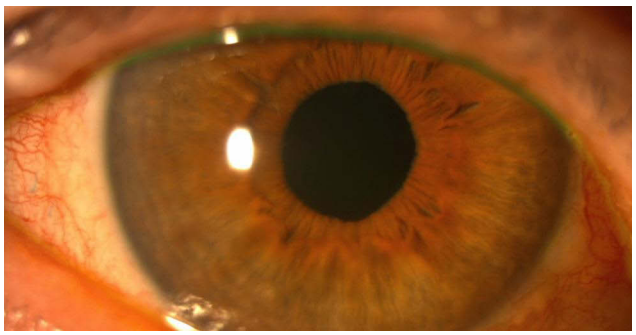

Figure 2 Postoperative slit-lamp photography of a patient that underwent intrascleral knotless zigzag suture fixation of Akreos AO60.

iris, and came out through the sclera at a distance of approximately 2 mm from the limbus in the nasal or temporal side. This ab interno maneuver was repeated using the 180º away haptic and orienting the needle to the opposite side. The exit sites of the needle in the nasal and temporal sclera should be 180º apart, and, ideally, in the 0- to 180-degree axis. By simultaneous pulling of the threads in both sides, the correct position and centration of the IOL was confirmed. Then, each suture was run through the partial thickness of the sclera in a zigzag pattern as described elsewhere.[6] After four parallel intrascleral passages, the IOL was fixated and the thread was cut flush to the sclera without knotting. The conjunctival peritomy was closed with polyglactin (Vicryl) 8-0, and the corneal incision was sealed with stromal hydration. Finally, the trocars were removed, and subconjunctival injection of antibiotic and steroids was given.

The standard procedure, as described above, was adapted according to the indication for surgery. In cases of subluxated IOL or complications related to anterior chamber IOL, the IOL was usually explanted. When the subluxated IOL was an Akreos AO60, the IOL was repositioned following the standard steps described. In cases of subluxated crystalline lens or cataract, either spontaneous or after trauma or complicated cataract surgery, a lensectomy was performed with the use of a vitrectomy cutter or phacoemulsification handpiece.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 26. Categorical variables are summarized as absolute and relative frequency and continuous variables as mean

and standard deviation. Shapiro–Wilk, Kolmogorov–Smirnov test and normal probability plots were used to confirm the normal distribution of the data. Parametric and nonparametric tests were used for comparison of continuous variables between groups, according to the normality of data. Comparisons of two categorical variables were made by using X^2, and continuous variables using Student's or paired *t*-test (Mann–Whitney or Wilcoxon tests). Comparison among groups were performed using ANOVA test with homogeneity variance analysis, or non-parametric Kruskal–Wallis test. A p-value less than 0.05 was considered statistically significant.

Results

This study included 99 eyes of 92 patients: 53 with spontaneous IOL dislocation, 23 with intraoperatively complicated cataract surgery, 17 with traumatic natural lens or IOL dislocation, and 6 with other causes. In the last group, four had spontaneous natural lens dislocation, of which two had Marfan syndrome and two had corneal decompensation due to anterior chamber IOL in eyes without an adequate capsular support.

Baseline and surgical characteristics of study population are presented in Table 1. The mean age was 72.1±15.2 years (range 18–94) and the median follow-up duration was 19.5 months (range 3–81). Almost half of the cases (46.5%, n=46) had a follow-up longer than 12 months. The pseudoexfoliative syndrome was present in 43% (n=23) of eyes with spontaneous IOL dislocation. Overall, 51.5% (n=51) had prior ocular history, and 15.2% (n=15) had prior ocular surgery (excluding cataract surgery).

Among 56 cases with spontaneous or traumatic IOL dislocation, IOL was repositioned in 4 cases, and exchanged in the remaining. The mean surgical time was 47.8±17.0 min. There were no differences in surgical time between study groups (44.8±17.3 min in spontaneous IOL

Table 1 Baseline Characteristics of Study Population

	All (n=99)	Spontaneous IOL Dislocation (n=53)	Complicated Cataract Surgery (n=23)	Traumatic Natural Lens or IOL Dislocation (n=17)	Other Causes* (n=6)	p-value†
Age, mean±SD	72.1±15.2	74.9± (14.5)	73.8±16.3	65.5±11.7	60.0±16.7	0.003
Male, n (%)	58 (58.6)	30 (56.6)	9 (39.1)	15 (88.2)	4 (67)	0.19
Follow-up (months), median (range)	19.5 (3–81)	21.3 (3–81)	17.1 (3–59)	13.0 (3–48)	30.0 (5–69)	0.322
Baseline BCVA (logmar), mean±SD	1.34±0.70	1.28±0.73	1.51±0.68	1.32±0.68	1.35±0.60	0.721
Pseudoexfoliative syndrome	29 (29.3%)	23 (43.4%)	6 (11.3%)	0 (0.0%)	0 (0.0%)	NA
Glaucoma	13 (13.1%)	10 (18.9%)	2 (8.7%)	1 (5.9%)	0 (0.0%)	NA
Diabetic retinopathy	6 (6.1%)	5 (9.4%)	1 (4.3%)	0 (0.0%)	0 (0.0%)	NA
Retinal detachment	4 (4.0%)	1 (1.9%)	0 (0.0%)	1 (5.9%)	2 (33.3%)	NA
Uveitis‡	3 (3.0%)	3 (5.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	NA
Others diseases**	17 (17.0%)	12 (22.6%)	4 (17.4%)	1 (5.9%)	0 (0.0%)	NA
Prior ocular surgery***	15 (15.2%)	9 (17.0%)	2 (8.7%)	1 (5.9%)	3 (50.0%)	NA

Notes: *Including spontaneous natural lens dislocation (n=4, 2 of them with Marfan syndrome), and corneal decompensation due to anterior chamber IOL in eyes without capsular support (n=2). **Including pigmentary retinitis, epiretinal membrane, age-related macular degeneration, high myopia, Fuchs dystrophy, and strabismus. ***Including pars plana vitrectomy, refractive surgery, corneal transplant and glaucoma surgery. ‡Including 2 cases of uveitis–glaucoma–hyphaema syndrome after scleral fixation of AcrySof SN60WF IOL. †Comparison between intraoperatively complicated cataract surgery, complicated cataract surgery, traumatic natural lens or IOL dislocation, and other causes.

Abbreviations: SD, standard deviation; IOL, intraocular lens; VEGF, vascular endothelial growth factor; NA, non-applicable.

dislocation, 52.3±18.6 min in complicated cataract surgery, 50.0±15.1 min in traumatic natural lens or IOL dislocation, 50.4±10.5 min in other causes, p=0.317).

The visual and refractive surgical outcomes are shown in Table 2. The BCVA improved from a mean±SD of 1.34 ±0.70 logMAR at baseline to 0.49±0.56 logMAR at the end of follow-up (p<0.001). The mean±SD final SE was −1.24±1.82 diopters. The mean±SD prediction error was −0.51±1.16 diopters and the median (range) absolute error was 0.62 diopters (0.02–4.06).

The overall perioperative complications rate was 44.4% (n=44), as shown in Figure 3. This rate was 41.5% (n=22) in cases of spontaneous IOL dislocation, 56.5% (n=13) in cases of complicated cataract surgery, 35.3% (n=6) in cases of traumatic natural lens or IOL dislocation, and 50.0% (n=3) in other causes (p=0.533, no differences between groups). The rate of complications requiring invasive treatment (intravitreal injection or surgery) was 19.2% (n=19) in total sample. The type of perioperative complications is detailed in Table 3.

The most common perioperative complications were ocular hypertension (OHT, 20.2%, n=20), and cystoid macular edema (CME, 15.2%, n=15). Eighty-five percent (n=17) of eyes with OHT after surgery had no previous history of glaucoma or OHT, and all of them were controlled with topical medication. Among 13 patients with previous history of glaucoma, 38.5% (n=5) underwent glaucoma surgery after implantation of SFIOL, after a median period of 14 months (range 3–51). None of 15 cases of CME had prior ocular surgery or diabetic retinopathy, and 13.3% (n=2) of them required steroid intravitreal injection.

The rate of IOL dislocation was 7% (n=7). Of these, two were submitted to a second surgery which consisted of re-fixation of IOL with zigzag technique. Goretex® suture was used in one of the two cases. Three cases had IOL haptic dislocation into the anterior chamber, and all of them were also surgically approached. One case of IOL dislocation occurred in a patient with Marfan syndrome.

Other complications were less common, such as pseudophakic bullous keratopathy (3%, n=3), endophthalmitis (1%, n=1), uveitis–glaucoma–hyphaema syndrome (1%, n=1), iridodialysis (1%, n=1), corneal leakage (1%, n=1), iris herniation (1%, n=1), and retained cortex fragments (1%, n=1).

There were no differences in perioperative complications rate between eyes with or without previous ocular diseases (45.1% vs 43.8%, p=0.893).

Discussion

Over the years, many alternatives for IOL implantation without capsular support have been developed,[19] including

Table 2 Visual and Refractive Surgical Outcomes

	All (n=99)	Spontaneous IOL Dislocation (n=53)	Intraoperatively Complicated Cataract Surgery (n=23)	Traumatic Natural Lens or IOL Dislocation (n=17)	Other Causes (n=6)	p-value†
BCVA (logmar), mean±SD	0.49±0.56	0.48±0.51	0.51±0.63	0.54±0.71	0.37±0.29	0.928
BCVA variation (logmar), mean±SD	−0.87±0.79	−0.79±0.78	−1.04±0.83	−0.85±0.82	−0.98±0.76	0.741
Cylinder error (D), mean±SD	1.43±1.35	1.62±1.45	1.14±1.15	1.17±1.41	1.43±0.84	0.290
Spherical equivalent (D), mean±SD	−1.24±1.82	−1.50±1.58	−0.70±2.25	−1.09±2.08	−1.33±1.39	0.424
Prediction error (D), mean±SD	−0.51±1.16	−0.65±1.08	−0.40±1.52	−0.14±0.88	−1.05±1.15	0.545
Absolute prediction error (D), mean±SD	0.92±0.87	0.95±0.81	1.09±1.00	0.58±0.64	1.22±1.04	0.468

Notes: †Comparison between intraoperatively complicated cataract surgery, complicated cataract surgery, traumatic natural lens or IOL dislocation, and other causes.
Abbreviations: BCVA, best corrected visual acuity; IOL, intraocular lens; D, diopters.

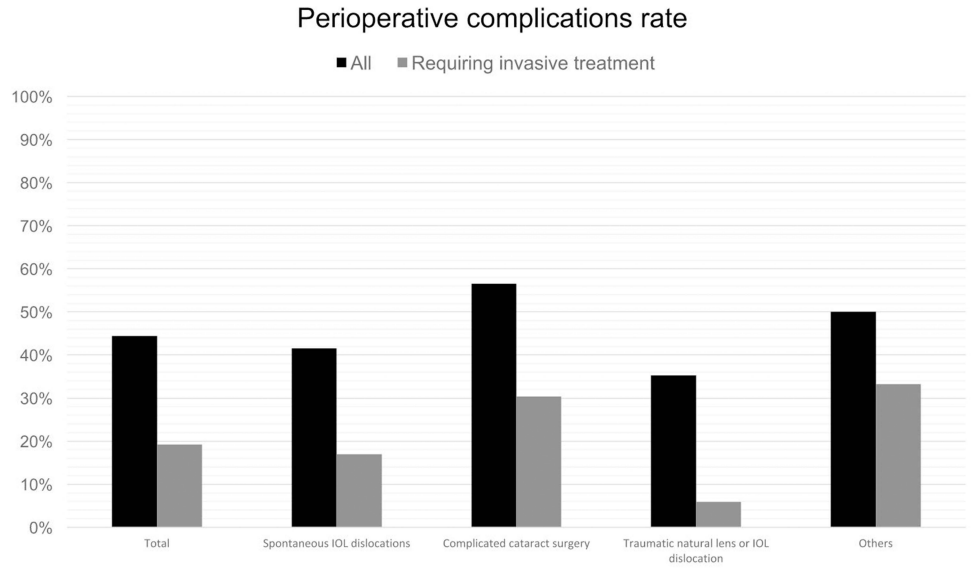

Figure 3 Perioperative complications rate.

anterior chamber IOL, IFIOL and SFIOL. So far, there is insufficient evidence to recommend any strategy over any other for patients suitable for all three options.[15] Scleral fixation of an IOL allows for a more physiological retro-iris positioning and avoids damage to the endothelial cells and angle structures.[19–21] In this study, we report our experience with a new technique of scleral fixation of an IOL, consisting of a zigzag suture fixation of the four-haptic hydrophilic acrylic foldable Akreos AO60. This IOL is intended for placement in the capsular bag, but "off-label" use of Akreos AO60 as a SFIOL has been previously reported.[14,22–24] In our series, all surgeries were performed by posterior segment surgeons.

Yamane et al[9] and Barca et al[25] presented the mean refractive difference from the predicted value by the Sanders–Retzlaff–Kraff trial formula for in-the-bag fixation

Table 3 Perioperative Complications

	All (n=99)	Spontaneous IOL Dislocation (n=53)	Intraoperatively Complicated Cataract Surgery (n=23)	Traumatic Natural Lens or IOL Dislocation (n=17)	Other Causes (n=6)
Ocular hypertension	20 (20.2%)	11 (20.8%)	5 (21.7%)	3 (17.6%)	1 (16.7%)
Cystoid macular edema	15 (15.2%)	6 (11.3%)	5 (21.7%)	3 (17.6%)	1 (16.7%)
IOL dislocation	7 (7.0%)	3 (5.7%)	2 (8.7%)	1 (5.6%)	1 (16.7%)
Pseudophakic bullous keratopathy	3 (3.0%)	2 (3.8%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Endophthalmitis	1 (1.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Uveitis–glaucoma–hyphaema syndrome	1 (1.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Iridodialysis	1 (1.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Iris herniation	1 (1.0%)	0 (0.0%)	1 (4.3%)	0 (0.0%)	0 (0.0%)
Corneal leakage	1 (1.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retained lens fragments	1 (1.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Abbreviation: IOL, intraocular lens.

and that was −0.21±0.99 D and −0.24 ± 0.81 D, respectively. Those authors used sutured[9] and plugs-fixated IOL.[25] Those values were slightly lower than the mean prediction error obtained in our series. However, the difference between studies is less than 0.5 diopters. Brunin et al[26] reported that 35% of the patients with transscleral-sutured intraocular lens fell within ±0.5D of refractive prediction error, whereas 65% were within ±1.0D. Overall, our refractive results are in agreement with those reported in the literature.

This technique offers several advantages. Fixing the external suture to the sclera is quick and easy to perform with minimal opening of the conjunctiva. The use of a suture instead of haptics fixation as performed in other techniques[8,9,27] maintains the integrity of the IOL and enables a less destructive fixation for the sclera and conjunctiva. The knotless approach is another positive feature as knots may lead to scleral atrophy and conjunctival erosion, increasing the risk of endophthalmitis as the suture provides a direct route for exogenous bacteria to enter the eye.[28–30] This technique also avoids the use of scleral grooves and flaps, which delay but not prevent suture erosion.[31] Another important advantage is the safety and reliability of the suture fixation within the sclera. In this series, both 10-0 and 9-0 polypropylene sutures were used and seven cases of IOL dislocation (3 were IOL haptic dislocation into the anterior chamber) are described, with 1 of them being re-fixated with a Goretex suture. Several studies pointed out that IOL dislocation can occur years after implantation when 10-0 polypropylene is used.[32,33] Thus, there is a trend towards a more frequent resource of 9-0 sutures as the risk of degradation and secondary IOL shift is minor.[34]

One limitation of this technique is the discard of two of the four haptics of Akreos AO60, increasing the risk of lens tilt and decentration. It has been shown that lens tilt of just 5º can induce additional refractive error[35] and if >15º can lead to high-order aberrations that cannot be corrected with glasses.[36] Another limitation related to the lens material as the Akreos AO60 is hydrophilic and thus more prone to optic opacification via calcium salt deposition following intraocular gas or air fill.[37] In this series, almost half of the patients had at least one complication and 20% had a complication requiring invasive treatment. The most common complications were cystoid macular edema and ocular hypertension. These rates are substantially higher than some series[9,25] but similar to others.[38] No cases of ocular hypotony are hereby reported. Of note, this complication was more frequent than hypertension with haptic-fixation techniques.[9,39] Kam et al[38] reported early ocular hypertension and vitreous hemorrhage to be more frequent following SFIOL implantation without concurrent PPV. In our series, all patients were vitrectomized, which explains the lower rate of vitreous hemorrhage. Ocular hypertension may be explained by iris rubbing and consequent pigment dispersion. Among patients with glaucoma, 38.5% needed glaucoma surgery after Akreos AO60 scleral fixation. Thus, the overall risk–benefit must be well balanced as other techniques may be safer for these patients.

In 2003, an American Academy of Ophthalmology report showed that 80.5% of the eyes with SFIOL after complicated cataract surgery achieved BCVA of 20/40 or better, while 4.9% had BCVA of 20/200 or worse.[40] In our series, the results were 54.5% and 19.2% for final BCVA ≥20/40 and ≤20/200, respectively. However, we present a consecutive case series without exclusion of patients based on etiology or ocular pathology. Moreover, in this study, half of the patients had prior ocular history.

This study has some limitations. This is a single-center study that assessed the results of several surgeons with variable lengths of follow-up. Its retrospective nature with all the drawbacks associated does not allow to assess all variables intended, including the tilt. Due to inclusion of all consecutive patients, our sample is heterogenous – this gives us a real-world idea of this technique performance but limits the comparison with other studies that select patients based on cause or previous ophthalmic history.

Conclusion

In patients without adequate capsular support to allow in-the-bag or sulcus placement of an IOL, scleral fixation is an effective approach. This knotless technique avoids the risks of haptics fixation but is more prone to IOL dislocation in cases of suture deterioration. The most common postoperative complications were macular edema and ocular hypertension. Almost 40% of the patients with previous glaucoma ended up needing glaucoma surgery due to uncontrolled ocular hypertension. Therefore, past ophthalmic history needs to be carefully considered in candidates who underwent SFIOL implantation.

Ethics

The study was conducted according to the tenets of the Declaration of Helsinki in its latest amendment (Brazil, 2013) and was approved by the local IRB ("Departamento de Ensino, Formação e Investigação").

Informed Consent

All patients signed an informed consent form.

Acknowledgment

The abstract of this paper was presented at the 2019 EVRS Congress – Lisbon as a poster presentation with interim findings.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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