Efficiency of a Titanium-platelet Rich Fibrin Membrane in Primary Pterygium Surgery

Primer Pterijyum Cerrahisinde Titanyum-plateletten Zengin Fibrin Membranın Etkinliği

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ABSTRACT

Objective: This study aimed to evaluate the efficacy and safety of titanium-platelet rich fibrin (T-PRF) membranes in primary pterygium surgery.

Methods: Twenty-three patients diagnosed with primary pterygium were included in our retrospective study. Patients underwent pterygium excision between January 2017 and October 2017 after T-PRF membrane autograft to close the scleral bed. Blood samples from the patients were centrifuged in titanium tubes and mechanically compressed to prepare T-PRF membranes. In this study, preoperative patient characteristics, spread of pterygium, T-PRF resorption time in postoperative controls, and pterygium recurrence and complications were evaluated.

Results: The mean follow-up period was noted as 8.9±3.1 months (4-14 months). The mean extension of the pterygium was 2.5±1.0 mm. Eleven patients had pterygium recurrence (42.3%). The mean time to recurrence was 3.9±1.8 months. No complications were observed during surgery. The T-PRF resorption time was noted as <7 days in seven patients. Postoperative follow-up revealed suture reaction in 7 (26.9%) patients, loss of graft in 1 (3.8%), conjunctival granuloma formation in 1 (3.8%), and Tenon’s cyst formation in 1 (3.8%) patient.

Conclusion: The T-PRF membrane is easily available, cost-effective, can be prepared with the desired size and thickness, and thus can be an alternative method for patients who are not eligible to receive conjunctival autograft for pterygium surgery. The surgical technique could be improved to be accepted as a standard method.

Keywords: Autograft, titanium tubes, conjunctival granuloma, ptergium surgery, suture reaction

ÖZ

Amaç: Bu çalışma, primer pterygium cerrahisinde titanyum-trombositten zengin fibrin (T-PRF) membranların etkinliğini ve güvenliğini değerlendirmeyi amaçlamaktadır.


Bulgular: Ortalama takip süresi 8,9±3,1 ay (4-14 ay) olarak kaydedilmiştir. Pterygiumun ortalama uzantısı 2,5±1,0 mm olarak ölçülmuştur. Yedi hastada (42,3%) pterygium tekrarlaması görülmüştür. Nüklek kadar geçen ortalamada süre 3,9±1,8 aydır. Ameliyat sırasında herhangi bir komplikasyon görülmemiştir. Yedi hastada T-PRF rezorpsiyon süresi <7 gün olarak kaydedilmiştir. Postoperatif takibe (7 %26.9%) hastada sutür reaksiyonu, 1 (%3,8) hastada greft kaybı, 1 (%3,8) hastada konjunktival granülom oluşumu ve 1 (%3,8) hastada Tenon kisti oluşumu görülmüştür.

Sonuç: T-PRF membran kolay bulunabilir, uygun maliyetli, istenilen ebat ve kalınlıkta hazırlanabilir ve bu nedenle pterygium cerrahisi için konjunktival otogreft uygulan maymun hastalar için alternatif bir yöntem olabilir. Standart bir yöntem olarak kabul edilebilmeyi için cerrahi teknikler geliştirilebilir.

Anahtar kelimeler: Otogreft, titanyum tüpler, konjunktival granülom, pterijyum ameliyatı, sutür reaksiyonu

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INTRODUCTION

Pterygium is a degenerative and proliferative ocular surface disease characterized by fibrovascular extension of the conjunctiva over the cornea. The disease is treated surgically to relieve symptoms, including stinging, burning, redness, and blurred vision, and for a better cosmetic appearance (1). The major problem encountered after pterygium surgery is recurrence. Lower recurrence rates have been observed in methods where tissue grafts are applied to the scleral bed following pterygium excision. The conjunctival (CA) and CA-limbal, amniotic membrane, and platelet rich fibrin (PRF) membrane have been used as tissue grafts in pterygium surgery (2-4). At present, CA and limbal conjunctival autograft (LCA) techniques are the most commonly used techniques in pterygium surgery because of their lower recurrence rates. The CA technique has significant disadvantages, including a long surgical time, the creation of a second CA defect, and being technically challenging. In addition, the use of upper CA tissue is not considered eligible in patients who are candidates for glaucoma surgery. Although the recurrence rates are low, CA and LCA techniques are not applicable in every patient because of their disadvantages (3).

The PRF membrane is a second-generation thrombocyte concentrate. This membrane is widely used for treating various diseases. The PRF membrane can be used as a graft to accelerate tissue regeneration. Platelets and leukocytes found in the structure of PRF play an essential role in wound healing. The PRF membrane has several advantages, including being a completely autogenous material, easy accessibility, short preparation time, low cost, and preparation in any desired size and thickness (5,6). Glass and titanium tubes can be used in the centrifuge stage in the preparation of the PRF membrane. According to several studies conducted, the PRF membrane obtained using a titanium tube [titanium-platelet rich fibrin (T-PRF)] resorbs relatively late, and fibrin consistency was found to be tighter and better organized (7,8).

Our study aimed to investigate the efficacy and safety of the T-PRF membrane in primary pterygium treatment. For this purpose, data from patients who underwent surgery for primary pterygium using T-PRF membrane between January 2017 and October 2017 and had sufficient follow-up time were retrospectively evaluated.

METHODS

Ethical Approval

The data from patients who used the T-PRF membrane in the surgical treatment of primary pterygium were retrospectively evaluated under the approval of the Bezmialem Vakıf University Non-invasive Clinical Research Ethics Committee dated 16th May 2017, decision number 10/86. The study was conducted at the department of ophthalmology in accordance with the Helsinki Declaration and Good Clinical Practices Guide. The patients included in the study signed the pre-operative informed consent and the written consent for the data evaluation.

Patients

Twenty-six eyes from patients (n=23) with a minimum follow-up period of 6 months were included in the study. Male patients included in the study (n=12) were higher than female patients (n=11). The inclusion criteria involved patients who were older than 20 years and underwent surgery by a surgeon using T-PRF fibrin membrane for primary pterygium diagnosis. Patients who had recurrent pterygium diagnosis and systemic diseases affecting wound healing, coagulopathy, corneal or conjunctival surgery in the same eye, or received permanent topical therapy for ocular diseases such as glaucoma or allergic conjunctivitis were excluded from the study.

Preoperative examination findings, including pterygium characteristics, best-corrected visual acuity, intraocular pressure, detailed anterior segment and fundus examination findings, age, gender, and systemic disease history, were enlisted. The pterygium extension size was defined as the distance in millimeters from the limbus to the apex of the lesion measured using a slit lamp. In this study, recurrent situation was defined as fibrovascular growth up to the surgical limbus and over the cornea. The presence of recurrence, the condition of the graft applied, and the presence of complications were evaluated at the postoperative 1st day, 1st week, 1st month, 3rd month, and 6th month control visits.

Preparation of the T-PRF

Right before surgery, 20 mL of venous blood was taken from the antecubital vein using a 20-22 G catheter. The blood samples were drained into two sterilized grade IV titanium tubes (being in 10 mL in each tube), without any anticoagulant contents. Immediately after, the titanium tubes were placed in a centrifuge device (IntraspinTM, USA) and centrifuged at 2700 rpm for 12 min. After centrifugation, the fibrin clot (Figure 1) formed in the middle layer of the tube was moved to the PRF kit (XpressionTM, USA). The erythrocyte-containing layer at the bottom of the fibrin clot was removed. On the PRF kit, the serum in the fibrin clot was discharged by mechanical compression, and thus, the fibrin membrane was obtained (Figure 1).

Surgical Technique

The operations were performed under local anesthesia using a surgical microscope. Topical 5% proparacaine HCl and subconjunctival 10 mg/mL lidocaine with 0.0125 mg/mL epinephrine were used for local anesthesia. During the pre-operative preparation stage, the periorbital region and eyelids were disinfected with 10% povidone-iodine solution. The eyes of the patients were covered with an ophthalmic drape, and lid retractors were placed. The 5% povidone-iodine solution was dropped onto the ocular surface and was waited for 3 min. Pterygium tissue borders are marked under a surgical microscope. Pterygium tissue was excised using Wescott scissors and a crescent blade. Fibrotic tissue on the cornea was polished using a motorized diamond ball burr (Bien-Air OsseodocTM, Switzerland). Tenon’s tissue following pterygium excision was removed from the scleral surface, and hemostasis was performed using a thin-
tip single-use cautery pen (Accu-Temp®). The prepared T-PRF membrane was cut fittingly to the open edges of the wound bed and sutured to the wound edges of the conjunctiva with 5-7 8/0 polyglactin absorbable sutures (Polysorb™). After the surgical operation, the eye was closed with an eye bandage following the application of antibiotic pomade (tobramycin 0.3% pomade). Topical antibiotic drops 4 times a day (0.3% tobramycin), oral analgesic 3 times a day (500 mg paracetamol), topical lubricant drop 4 times a day (0.150 g hyaluronic acid sodium salt in 100 mL), and topical lubricant gel once a day (2 mg/g polyacrylic acid) were prescribed for 2 weeks postoperatively. Topical steroid drops 4 times a day (10 mg/mL prednisolone sodium phosphate) were prescribed for 2 months.

Statistical Analysis

To evaluate the distribution of categorical variables, chi-square or Fisher test results, as well as descriptive statistics of variables including frequency, percentage, median, and other parameters, were presented. All statistical analyses were performed using the computer software IBM SPSS Statistics package program. The $p<0.05$ was considered statistically significant.

RESULTS

Our study evaluated 26 eyes of patients (n=23) retrospectively. The T-PRF membrane was applied to all patients following pterygium excision under local anesthesia. In our study, 13 right (50%) and 13 left (50%) eyes of male and female patients were examined. The age of the patients ranged from 26 to 74 years, with a mean age of 50.7±13.5 years (Table 1).

Bilateral primary pterygium was detected in 10 patients (43.5%). Three of these patients had surgery for both eyes, and the remaining seven patients had one eye operation. In the pre-operative examinations of the patients, the extension of the pterygium varied between 1.2 and 5 mm, and the mean was noted to be 2.5±1.0 mm.

The extension of the pterygium was noted ≤2 mm in 11 eyes, between 2 and 4 mm in 11 eyes, and ≥4 mm in four eyes. On the postoperative 7th day examination, the T-PRF membrane was completely resorbed in six eyes (23.1%). The follow-up period of the patients ranged from 6 to 14 months, and the mean follow-up period was calculated as 8.9±3.1 months (Table 1).

Recurrence was observed in 11 (42.3%) of 26 eyes. Recurrent situations were detected in 41.7% of patients under 50 years of age and in 42.9% of patients over 50 years of age. The recurrence rate was 38.5% in male patients and 46.2% in female patients. No statistically significant difference was found between recurrence rates in terms of age and gender $p>0.05$ (Figure 2).

The recurrence prevalence was 27.3% in eyes with pterygium ≤2 mm, 54.5% in eyes with 2-4 mm, and 50.0% in eyes with ≥4 mm. The recurrence rate was 66.7% in eyes where T-PRF membrane resorption was <7 days and 35% in eyes ≥7 days. Less recurrence was detected in eyes with pterygium size ≤2 mm and autograft resorption time ≥7 days. No statistically significant difference was found between pterygium size and T-PRF membrane resorption time and recurrence rates $p>0.05$ (Table 2).
No pre-operative complications were encountered. In postoperative follow-up, one patient (3.8%) had graft loss on the 1st day, one patient (3.8%) had conjunctival granuloma in the 1st month, one patient (3.8%) had Tenon’s cyst in the 1st month, and seven patients (26.9%) had suture reaction in the 1st week (Figure 3).

Sutures are removed in patients who develop suture reactions. Recurrence was detected in five (71.4%) of the seven patients who developed a suture reaction. No statistically significant difference noted in a comparison of eyes with and without suture reaction in terms of recurrence p>0.05 (Figure 2). According to the evaluation of recurrence times, one patient had in the 1st month, six patients had in the 3rd month, and four patients had in the 6th month. The mean recurrence time was found to be 3.9±1.8 months in patients with recurrence (Table 3).

**DISCUSSION**

Pterygium is an ocular surface disease characterized by fibrovascular proliferation. Although the underlying etiology and pathogenesis are not completely understood, UV-B radiation exposure remains a predisposing factor. Today, surgery is still the main treatment modality for pterygium. Among surgical approaches, techniques including the bare sclera technique and primary conjunctival closure are known (9). The major problem encountered in the surgical treatment of pterygium is high recurrence rates. In terms of recurrence of pterygium, the characteristics of pterygium (type, grade, and dimension), age of patient, environmental factors, and applied method of surgical intervention were stated to be risk factors (9). At the same time, surgical trauma, postoperative inflammation, fibroblast proliferation, and accumulation of extracellular matrix proteins have been associated with recurrence (10). Various surgical techniques and adjuvant treatment methods have been applied to reduce recurrence rates. Recurrence rates of 38-88% have been reported in patients who are operated with the bare sclera technique alone. In patients who are operated with the primary conjunctival closure technique, recurrence rates ranging between 45-70% have been reported. Both of these techniques have been discontinued because of unacceptably high recurrence rates, and tissue graft applications have become widespread after pterygium excision (11).
Kenyon et al. (12) revealed that the CA technique suturing the autograft (which is taken from the superior temporal bulbar conjunctiva) over the bare sclera following pterygium excision had a recurrence rate of 5.3% in complicated and recurrent pterygium cases. Coroneo (13) and Dushku and Reid (14) reported that deterioration in the limbal corneal-conjunctival epithelial barrier is the main cause of fibrovascular tissue invasion over the cornea and progressive corneal conjunctivalization. Based on the significance of the limbal barrier, limbal conjunctival tissue was used as a graft in later conducted studies. As per the mentioned studies, LCA showed better anatomical and functional results than CA. 0-15% recurrence has been reported in cases where LCA was applied in primary pterygium treatment (15). Al Fayez (16) compared CA and LCA techniques in primary and recurrent pterygium cases and reported a recurrence rate of 8.3% in primary pterygium and 33.3% in recurrent pterygium with CA. In the study, no recurrence was observed in the LCA group (16).

The CA and LCA techniques are not suitable for all patients due to the disadvantage of being candidates for upcoming glaucoma surgery. In addition, they have disadvantages including prolonged operative duration and complexity, low postoperative patient comfort, and secondary injury at the donor site (3).

The basal lamina and stromal structure of the amniotic membrane are similar to those of the conjunctiva. The amniotic membrane contains pro-inflammatory cytokines, including IL-6 and IL-8, and anti-inflammatory cytokines, including IL-10 and IL-1 receptor antagonist. The amniotic membrane contributes to the proliferation of conjunctival and corneal epithelial cells and to the structural restructuring of limbal tissue in pterygium. In addition, the amniotic membrane reduces postoperative pain by covering the free nerve endings (17). Recurrence rates of 6-40% have been reported when amniotics are used in patients with pterygium.

In a previous study, Liang et al. (18) reported a recurrence rate of 7.4% in 81 eyes using the CA technique and 19.2% recurrence rate in 52 eyes using the amniotic membrane transplant (AMT) technique. Tananuvat et al. (19) reported a recurrence rate of 4.76% with the CA technique in 42 eyes and a recurrence rate of 40.9% with the AMT technique in 44 eyes. Although higher recurrence rates have been reported with the AMT technique compared with the CA technique, studies have shown that this technique can be used in patients, especially those with large tissue defects where CA cannot be used (15). The application of amniotic membrane has several disadvantages, including being an allogenic material, risk of contamination, complex preparation procedure, and low availability. Several reasons for different recurrence rates in pterygium cases using the AMT technique have been reported, including different donor characteristics, different amniotic membrane contents, and postoperative sunlight exposure (20).

The PRF membrane consists of fibrin matrix, which contains a large amount of platelets, leukocytes, stem cells, growth factors, and cytokines released from them. The PRF contains pro-inflammatory and anti-inflammatory cytokines from platelets and leukocytes. Growth factors and cytokines inside the PRF support cell proliferation and migration by controlled release and have a chemotactic effect on extracellular matrix synthesis. They also serve as structural support for the migration of conjunctival and endothelial cells. Compression of PRF into membrane form provides suturing of PRF. Despite similar characteristics of both amniotic and PRF membranes, the PRF membrane has an advantage owing to its autogenous origin over the allogenic origin of the amniotic membrane, thus reducing the risk of contamination (5).

Cakmak et al. (4) first reported the application of a PRF membrane prepared in glass tubes in the surgical treatment of pterygium. In this study, 20 patients who underwent CA technique and 15 patients who underwent PRF membrane technique were compared in terms of recurrence rates, operation time, and complications, with follow-up periods ranging from 6 to 24 months. No recurrence was observed in the CA group, but a recurrence was detected in one patient (6.6%) in the PRF membrane group. The average operation time was found to be approximately 10 min shorter in the PRF membrane group. In the CA group, graft loss was detected in two patients (10%) and suture reaction in 3 patients (15%). In one patient (6.6%) in the PRF membrane group, graft loss was observed, but no suture reaction was detected. Postoperative inflammation was significantly lower in the PRF membrane group. This study stated that PRF membrane can be used in ocular surface reconstruction after pterygium excision due to its several advantages, including easy preparation and shorter operation time, and providing similar results as CA in terms of recurrence and complications (4).

Titanium shows better biocompatibility with living tissues, owing to its resistance to corrosion, compared with other corrosion-resistant metals. Therefore, titanium can be safely used in the structure of dental implants, joint prosthetics, and artificial heart valves. The new product, T-PRF, has a tighter and better organized fibrin matrix structure than conventional PRF. The release of growth factors and cytokines is slower; therefore, the resorption time of the T-PRF membrane is longer (8).

In our study, we aimed to delay fibrin membrane resorption using T-PRF. Due to the delay in the resorption time, it reduces the risk of a bare scleral surface and prolongs the release of growth factors and cytokines. In addition, recurrence was observed in 11 (42.3%) of 26 eyes with a follow-up period of at least 6 months and a mean of 8.9±3.1 in our study. In an evaluation of the clinical features and follow-up examinations of the patients, a higher rate of recurrence was observed in cases with a pterygium size of >2 mm, suture.

### Table 3. Postoperative complications and their prevalence

<table>
<thead>
<tr>
<th>Complication</th>
<th>Number (%)</th>
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</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>11 (42.3%)</td>
</tr>
<tr>
<td>Suture reaction</td>
<td>7 (26.9%)</td>
</tr>
<tr>
<td>Graft loss</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Conjunctival granuloma</td>
<td>1 (3.8%)</td>
</tr>
<tr>
<td>Tenon’s cyst</td>
<td>1 (3.8%)</td>
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reaction, and resorption time of <7 days. In our data, recurrence was detected in eight (53.3%) of 15 patients with a pterygium size of >2 mm. As the size of the pterygium increases, the possibility of residual tissue remaining after surgery increases. We assume that with the effect of growth factors such as platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor in the structure of PRF, the proliferation of the residual pterygium tissue and stimulation of angiogenesis causes the fibrovascular tissue to extend over the cornea and thus result in recurrence. In our study, recurrence was detected in five (71.4%) of seven patients who developed a suture reaction. An end-to-end suturing technique with polyglactin suture material to the conjunctiva was used for stabilization of the T-PRF membrane.

In a similar study in the literature, Kim et al. (21) compared the use of 8-0 polyglactin and 10-0 nylon suture material in primary pterygium cases where they applied a conjunctival rotation flap. Absorbable polyglactin sutures were removed at the end of 1 month postoperatively if they were still present, and non-absorbable nylon sutures were removed 1 week postoperatively. A 7.31% recurrence rate was observed in 8-0 polyglactin group but a 0% recurrence rate was observed in the 10-0 nylon group (21). This study stated that polyglactin suture material could increase the recurrence rate by increasing conjunctival inflammation and irritation in the early postoperative period.

In the CA technique, several studies have been conducted on the use of fibrin glue instead of sutures to shorten the duration of the surgery and increase patient comfort. In these studies, the use of fibrin glue appeared to be more advantageous in terms of surgical time and patient comfort, although different results were reported in terms of recurrence rates. Koranyi et al. (22) reported a recurrence rate of 5.3% with fibrin glue application and 13.5% with suture application. Bahar et al. (23) reported a recurrence rate of 11.9% with the fibrin glue application technique and 7.7% with suture application. Some researchers used autologous blood for fixation of CA because of the high cost of fibrin glue and the presence of contamination risk. Kurian et al. (24) compared the autologous blood technique with the fibrin glue technique, reporting similar recurrence rates of 6.25% and 8.16% with graft loss of 3.13% and 2.04%, respectively. In the CA technique, de Wit et al. (25) let the small hemorrhage on the bare sclera coagulate spontaneously after pterygium removal, and when hemostasis occurred, they used the clot for autograft fixation. In this study of 15 cases, which were followed up for 6-14 months, no recurrence or complication was observed. de Wit et al. (25) targeted to avoid the foreign body reactions that may occur due to sutures and fibrin glue in this study. In the literature, Yang et al. (26) compared the use of PRF graft and LCA after pterygium excision and found 3.6% recurrence in the PRF graft group, but no recurrence in the LCA group. No suture reaction was observed because of the 10-0 nylon suture used for PRF graft stabilization. In addition, statistically significant postoperative inflammation (12.5%) was observed in the PRF graft group (26). In a similar study, Időpe et al. (27) compared the use of CA, PRF membrane, and AMT after pterygium excision and found that the recurrence rates were 0%, 7.7%, and 20%, respectively. In this study, fibrin glue was used for graft stabilization. In addition, significant improvement in ocular surface symptoms was observed in patients using PRF membranes. The mean resorption time of the PRF membrane was 12.67 days (27).

We assume that the beneficial effect of the PRF membrane on wound healing decreased because of the inflammation that developed in response to the suture material in the early postoperative period. Nylon sutures or fibrin glue can be preferred instead of polyglactin sutures in pterygium cases with a high risk of recurrence and significant inflammation. In our study, recurrence was detected in 4 (66.7%) of 6 patients whose T-PRF membrane resorption time was less than 7 days. Because the conjunctival epithelization is not fully finished, the scleral surface remains bare due to early resorption of the PRF membrane. We assume that methods that increase the PRF membrane resorption time will decrease the recurrence rates. We suppose that by modifying this technique, using a double-layer T-PRF membrane instead of a single-layer PRF membrane, we can extend the resorption time and thus avoid the early exposure of the scleral surface. We presume that early resorption increases the recurrence rate.

Mitomycin C (MMC) is applied intraoperatively on the wound bed, and MMC suppresses subconjunctival tissue proliferation and fibroblast activity. These adjuvant procedures are intended to suppress the fibroblastic activation of the remaining adjacent tissue after surgery. Ha et al. (28) compared the CA and AMT methods and simultaneously applied intraoperative MMC as an adjuvant in some patients. This study stated that the most important parameter in the development of recurrent pterygium is inflammation that arises in the early postoperative period (28). Koranyi et al. (29) emphasized that the CA method together with intraoperative use of 0.02% MMC is more effective than the CA method alone in primary pterygium. These studies have shown that recurrence rates decrease with the application of adjuvant MMC in pterygium treatment. We estimate that better results can be achieved with the use of intraoperative MMC with the T-PRF membrane method in terms of low recurrence rates.

**Study Limitations**

Our study has significant limitations. Because T-PRF membrane application is a new approach in primary pterygium cases, a limited number of patients were included in the study. Therefore, it was not possible to perform significant statistical analyses. Studies with longer follow-up periods are required for comparison with alternative treatment methods. This new approach should be used as an experimental group in randomized controlled studies with other surgical approaches as control groups in primary pterygium treatment.

**CONCLUSION**

In conclusion, our study revealed that the T-PRF membrane can be used as an alternative approach for patients who are not eligible...
to receive conjunctival autografts for pterygium surgery. Because the T-PRF membrane is easily available, cost-effective, and can be prepared in the desired size and thickness, the use of T-PRF membranes can be integrated into the treatment of pterygium. To be approved as a standard procedure, the surgical technique could be improved.

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Ethics Committee Approval: The data from patients who used the T-PRF membrane in the surgical treatment of primary pterygium were retrospectively evaluated under the approval of the Bezmialem Vakif University Non-invasive Clinical Research Ethics Committee dated 16th May 2017, decision number 10/86.

Informed Consent: The patients included in the study signed the pre-operative informed consent and the written consent for the data evaluation.

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