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Main issues in penetrating keratoplasty

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Abstract:

This review explores contemporary challenges in penetrating keratoplasty (PK), focusing on technical intricacies, technological advancements, and strategies for preventing graft rejection. A systematic literature search from January 2018 to July 2023 was conducted across PubMed, Cochrane, Web of Science, Scopus, and EMBASE. The inclusion criteria comprised studies on PK and its comparison with other corneal pathologies, with emphasis on keratoconus (KC). Two independent reviewers screened studies, extracting relevant data. The review covers PK evolution, highlighting infra-red femtosecond lasers' impact on graft shapes, minimizing astigmatism, and enhancing wound healing. Graft rejection, a primary complication, is examined, detailing risk factors and preventive measures. Preoperative considerations, diagnostic techniques for rejection, and PK in KC are discussed. Postoperative care's significance, including intraocular pressure monitoring and steroid administration, is emphasized. The paper concludes with a comprehensive approach to prevent graft rejection, involving topical and systemic medications. An outlook on evolving monoclonal antibody research is presented. As the field progresses, personalized approaches and ongoing therapeutic exploration are expected to refine strategies, enhancing PK outcomes.

Keywords:

Corneal surgery, graft rejection, keratoplasty, laser, penetrating, trephining

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Introduction

Corneal transplantation encompasses various surgical approaches, with penetrating keratoplasty (PK) standing as one of the oldest and most widely employed techniques. Particularly effective in addressing long-term vision impairments associated with dysfunction of endothelial or extensive scarring of the cornea extending to the Descemet membrane (DM) level. In this article, our focus centers on the contemporary challenges faced in the realm of PK, delving into technical intricacies such as trephination, suturing techniques, and immunological considerations. These insights are gleaned from the findings derived from randomized controlled trials exploring diverse PK techniques.[1]

Although the United States' keratoplasty trends from 2015 to 2020 continued the previous decade's trend of declining PK and rising DM endothelial keratoplasty.[2] However, a noteworthy stride in enhancing clinical outcomes lies in the transition from traditional manual corneal incisions to advanced methodologies, including the utilization of lasers. The integration of infra-red femtosecond laser (FSL) technology has ushered in novel surgical graft shapes (e.g. "top-hat," "mushroom," "zig-zag," etc.). Beyond merely expanding the wound surface area, these shapes play a pivotal role in mitigating surgically induced astigmatism and other aberrations, thereby fostering superior wound healing and stability. The benefits encompass heightened precision, automation, and repeatability, rendering the learning curve more accessible while concurrently reducing complications. Noteworthy among the advantages are early suture removal and improved short- and long-term visual outcomes attributable to infra-red FSLs.[3,4] Additional laser modalities, including nonmechanical pulsed

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ultraviolet light from excimer lasers and excimer-assisted lasers, have indeed demonstrated enhanced outcomes not only in PK but also in various other surgical interventions.[5] Nevertheless, akin to any surgical procedure, PK entails potential complications, ranging from minor concerns such as astigmatism and protracted recovery to more severe issues like graft failure.

Methods

A thorough and systematic literature search was meticulously carried out to identify pertinent studies for this systematic review. Key electronic databases, such as PubMed, Cochrane, Web of Science, Scopus, and EMBASE, underwent extensive scrutiny to locate publications spanning January 2018 to July 2023. In addition, a supplementary search ensured the inclusion of all relevant studies. The search strategy was meticulously crafted to cover research related to PK, emphasizing its comparative analysis with deep anterior lamellar keratoplasty (DALK) in treating corneal pathologies, particularly focusing on keratoconus (KC). The search incorporated Medical Subject Headings terms and keywords. For a visual representation of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses is shown in Figure 1.

Inclusion criteria comprised original research articles, systematic reviews, and meta-analyses involving human subjects, with relevant data availability and adherence to the specified time period. Exclusion criteria involved conference abstracts, studies lacking pertinent outcome data or relevance, and those involving nonhuman subjects. To ensure the review's robustness, two independent reviewers performed the initial screening, followed by a thorough examination of the full text of potentially relevant studies.

Data extraction was executed with precision, capturing crucial study characteristics, patient demographics, surgical techniques, visual outcomes, graft survival rates, and complications. Any discrepancies in data extraction were resolved through discussion and evaluation to reach a consensus.

This systematic review was prospectively registered in the PROSPERO International Prospective Register of Systematic Reviews ([CRD42024497756]). A qualitative synthesis of the included studies was undertaken, specifically focusing on analyzing the fundamental aspects related to PK concerning DALK. This synthesis facilitated a comprehensive exploration of the advantages and limitations associated with PK, particularly within the context of KC and other corneal pathologies. The review aimed to provide insights into the intricate details of these surgical procedures, highlighting outcome variations and elucidating key factors influencing graft survival and postoperative complications.

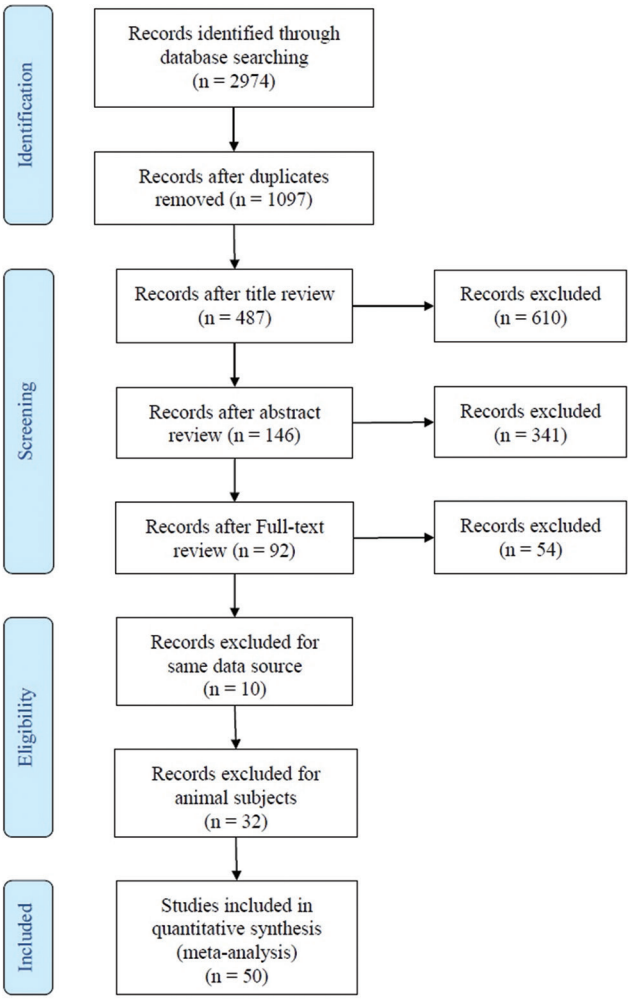

Figure 1: Preferred reporting items for systematic reviews and meta-analyses

Result

Graft rejection

Understanding the causes of both early and delayed graft rejection is pivotal in addressing postoperative challenges following PK. Immunological rejection of the allograft stands out as the primary contributor to graft failure after PK, emerging as the leading cause post-PK. Among the various forms of graft rejection, the predominant is endothelial rejection, while subepithelial and epithelial rejections are relatively rare. Molecular evidence underscores a consistent decline in endothelial cell density post-PK, serving as a predictive marker for graft failure attributed to decompensation by endothelium.[6,7] Recognized risk factors linked to corneal graft failure encompass glaucoma, nonviral infections, viral herpetic infections,[8] elevated intraocular pressure (IOP)/ glaucoma, ocular surface diseases (OSDs), recurrence

of the primary disease, trauma, and wound hypotonia or dehiscence.[9] While these factors operate as risk factors rather than direct causes, they underscore the multifaceted nature of graft complications. Primary donor failure, uncorrectable refractive error, and OSDs further contribute to allograft rejection in the cornea.[10]

The rejection of corneal allografts is linked to several risk factors, including traces of stromal blood vessels in cornea of the recipient, which is considered a high-risk condition. Other contributing factors encompass a history of anterior segment surgery, preoperative glaucoma, large and eccentric grafts, active ocular inflammation or OSD, neurotrophic keratopathy, and herpes simplex keratitis, leading to iris anterior surface adhering to the corneal endothelium. The primary risk factors for immunologic rejection include corneal opacity caused by infection, neovascularization in more than two quadrants of the recipient cornea, congenital glaucoma, posttraumatic corneal opacity, and grafts exceeding 8 mm in diameter.[10] These factors collectively highlight the intricate interplay of variables influencing graft outcomes in PK procedures.

The management objective for addressing dry eye or OSD is to regulate the tear film hyperosmolarity state, thereby diminishing the response of the immune system to foreign object and inflammatory antigens.[11] Following transplantation, cost-effective measures include gene therapy and minor histocompatibility complex tissue matching. However, it's worthnoting that ABO antigen testing is less specific compared to more significant histocompatibility tests. The unique immune privilege of the cornea allows for the evaluation of major histocompatibility complex tissue matching.[8] When situation risk is estimated high, as in prolonged use of antiglaucoma medication, vascularization in the cornea or dry eye disease (DED), may adversely impact the survival rate of the corneal graft.[12] Emerging strategies, such as anti-vascular endothelial growth factor therapy injection,[13] use of Lifitegrast[14] in managing DED, and the application of subconjunctival nonpreservative topical lubricant as an adjunct in glaucoma treatment[15] are expected to contribute to future enhancement of the graft survival rate. To enhance the success of corneal graft in individuals with prior operation, especially when immunological factors may have contributed to the initial outcome, consider the following measures:

- Promptly perform the second operation after the initial one, ensuring an absence of inflammation during the procedure
- Opt for a sufficiently large second graft that encompasses all previously transplanted tissue, unless the initial transplantation was notably extensive and eccentric
- Initiate systemic immunosuppressive medication and steroids 2–7 days prior to the surgery, maintaining their use for an extended postoperative period
- Implement continuous supplementary therapy using immunosuppressive drops, including tacrolimus, in conjunction with topical steroids after the surgery. Surgeons must prevent elevated IOP and the accelerated development of interface corneal keratitis at all time
- Promptly remove any sutures that are loose or vascularized postsurgery and ensure unimpeded patient access to follow-up care provided by the treating physician.

Achieving anatomical success is commonly observed in PK, yet functional failure remains significant. Typically, PK wound requires a minimum of 1 year for the to fully recover. However, approximately one-third of eyes still exhibit uncorrectable astigmatism after this period, contributing significantly to suboptimal visual outcomes in keratoplasty.[16,17] Enhanced trephination, separating corneal button from the donor and recipient cornea using excimer or FSL-based, motor and handheld trephine methods, can mitigate the incidence of astigmatism. FSL technology uses optical coherence tomography assisted limbal-oriented centration to precisely address the centration issue during recipient's trephination. FSL employs side-cut profiles to improve the fit between recipient bed and the donor disc, providing optical advantages in PK and enhancing visual rehabilitation.[4,18] Mushroom-shaped side-cut profile incisions can also be manually made using a microkeratome, but zig-zag incision is exclusive to FSL.

During PK, all corneal layers are replaced with donor tissue, and depending on the follow-up duration, rejection rates are reported to be ranging from 5.8% to 41%. Rejection can happen within a few weeks after the operation, but more often they occur after several months.[19,20] Some studies indicate favorable short-term outcomes (91% survival after a year)[21] and long-term results are impressive, with 85.4% graft survival rates of 25 years.[22] There has also been reports of 98.8%, 97.0%, and 93.2% graft survival rates at 10 years, 20 years, and 25 years after surgery, respectively.[23] The review about PK showed average graft survival rates of 88.6%, 81.2%, 78.9%, 72.8%, and 61.2%, at 1, 2, 3, 5, and 10 years, respectively.[24]

The adoption of new transplantation method, using microkeratome to prepare two-piece mushroom-shaped graft, demonstrated <5% graft immunologic rejection rate and graft survival exceeding 95% for 5 years. Notably, independent postoperative risk factors such as disease recurrence, infection, eyelid or glaucoma surgery, rejection or a repeat graft, decreased the 10-year graft

survival to 34%.[21,25-27] Figure 2 outlines the post-PK risk factors for graft rejection.[28]

Preoperative measures

Implementing preoperative precautions is paramount in minimizing the rejection risk, and several measures can be undertaken to enhance the overall success of corneal transplantation. Tacrolimus, whether applied topically or administered systemically, proves beneficial in treating vernal keratoconjunctivitis, contributing to a favorable preoperative environment. Conditions such as Mooren's ulcer, pemphigoid, and Stevens–Johnson syndrome, should be put off for a minimum of 1 year after inflammation is effectively controlled to minimize the risk of complications. Prior to corneal transplant surgery, it is imperative to adequately address infections, blepharitis, and eyelid inflammation or other disorders such as ectropion and entropion. In instances of significant corneal stem cell defects resulting from factors such as atopic keratoconjunctivitis or chemical burns, a stem cell is ideally transplanted at least 3 months before surgery.[29]

The diagnosis of corneal transplant rejection requires meticulous consideration of various factors, utilizing both traditional and advanced techniques:

- Patient complaints and slit lamp findings: Traditional approaches involve evaluating patient complaints, such as photosensitivity or eye pain, and slit lamp findings, including traces of keratic precipitates (KPs) or cells in the anterior chamber. However, these methods may lack early detection capabilities
- KP monitoring: Tracking the number of KPs can indicate increased corneal layer thickness but may not detect inflammatory cells, limiting its diagnostic capabilities
- *In vivo* confocal microscopy: Utilizing advanced techniques like *in vivo* confocal microscopy allows for the detection of microstructural changes in corneal cells, revealing early increases in immune cells (ICs) during transplant rejection. The density of ICs correlates with clinical symptoms, and severe pain may be associated with higher corneal IC density in the sub-basal level
- Subepithelial infiltrates and low-graft inflammation: Rejection may occur with low graft inflammation without the presence of KPs. Stromal edema or subepithelial infiltrates is treated similarly to full-thickness graft rejections
- Immune reactions in layered transplantation: A 3-year study reported immune reactions in 10% of layered transplantation and 23% of complete transplantation cases, emphasizing the importance of vigilance in monitoring immune responses.[30-33]

Various factors, including limbus stem cell defects, hypoxia, corneal edema, and inflammation, contribute to the initiation of blood vessel growth in the cornea. The process of angiogenesis seems to play a crucial role

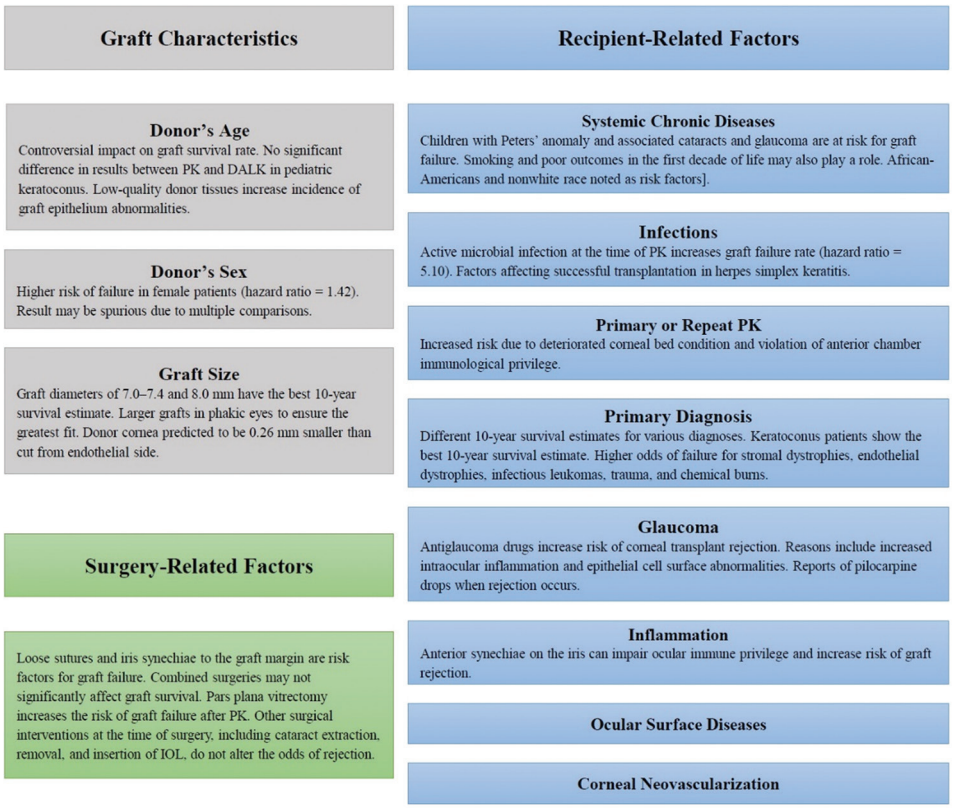

Figure 2: Postpenetrating keratoplasty graft failure risk factors. PK = Penetrating keratoplasty, DALK: Deep anterior lamellar keratoplasty

in corneal growth. In a study by Inatomi *et al*., a clinical classification for vascular growth in the cornea was proposed, comprising four levels: (1) start of vascular growth in the corneal environment, (2) progression of vascular growth in the mid-periphery, (3) development of moderate vascular growth throughout the cornea, and (4) manifestation of severe vascular growth across the entire cornea. When assessing corneal arteries, factors to consider include the depth, length, location, and diameter of vessels, their branching pattern, and the state of arterial blood flow.[34] A summary of the current angiogenesis treatment methods is presented in Table 1.

Penetrating keratoplasty in keratoconus

Currently, elective PK is specifically reserved for severe cases in which DM and endothelium show signs of previous corneal hydrops, highlighting a shift in the approach to surgery. While the general PK strategy for KC aligns with that used for other conditions, certain nuances apply. KC patients may find advantages in employing same-diameter trephines for both host and donor tissues. This method results in a reduction in the size of the donor button, contributing to a postoperative decrease in myopia. After securing the four 10-0 cardinal nylon sutures, the surgeon encounters several suture techniques for consideration, including the interrupted suture (IS), single continuous suture (SCS) or double continuous suture (DCS), and a combination of continuous and IS.

In scenarios where partial or complete suture removal may be anticipated, the IS is recommended as the preferred closure method. This is particularly applicable in pediatric keratoplasty (where sutures may loosen quickly), instances of multiple prior rejections, vascularization in the host cornea, or concurrent inflammatory conditions.[46] A comparative study investigating astigmatism in KC patients treated with a DCS versus a SCS demonstrated comparable astigmatism levels (DCS 4.6 D, SCS 5.2 D) after suture removal.[47] This underscores the critical consideration of the specific patient context and surgical requirements when selecting the suturing technique in PK for KC. Although report of graft rejection in KC was higher with PK,[48] it was associated with better visual acuity and refraction, and less complications

Table 1: Current methods of treating angiogenesis

Drug/method	Considerations
Topical corticosteroids[34]	First line of defense for corneal angiogenesis
0.05% cyclosporine A[34]	Anti-inflammatory, inhibits endothelial cell migration and angiogenesis
Tacrolimus[34]	Anti-inflammatory, inhibits production of cytokines by T lymphocytes and reduces production of immunoglobulins
Bevacizumab and ranibizumab (anti-VEGF monoclonal antibodies)[35]	Slows growth of young, active vessels, no effect on mature or older vessels
Pegaptanib and aflibercept (subconjunctival injections)[36,37]	Have antiangiogenic effects
FD006 (new monoclonal antibody)[38]	Potent antiangiogenic properties
Topical monoclonal antibodies[34,39]	Safety questioned due to reports of delays in epithelial defect repair and increased expression of matrix metalloproteinases
Minocycline and doxycycline (tetracycline family)[34,40]	Antiangiogenic and anti-collagenase properties
Fasudil (Rho kinase inhibitor)[41]	Anti-angiogenic properties
FND[34,42]	Effective in treatment of corneal arteries in 80% of cases, best combined with topical application of anti-VEGF monoclonal antibodies
Verteporfin photodynamic therapy[43]	Selectively blocks corneal arteries, costly, risk of laser-related side effects and generation of oxygen-free radicals
AMT[44]	Repairs corneal epithelial defects, reduces inflammation and angiogenesis
SSCE[44]	Used in cases of damage to part of the corneal stem cells
CLAU[34]	Removed from one eye when only one eye is affected, most effective treatment of corneal stem cells associated with damage to >2-thirds of limbus stem cells
Cultured limbal epithelial transplants[34]	Used for complete defects in the stem cells of one or both eyes
Ir-CLAL and KLAL[34]	Recommended in cases where there is a significant corneal stem cell defect
SLET and COMET[45]	Recommended for stem cell defects, no risk of allogeneic transplant rejection, no need for suppressive drugs in the postoperative treatment regimen
Topical injection of 2.5 mg bevacizumab 0.1%[34]	Employed as an additional therapy if blood vessels remain active despite immunological treatment
Anti-herpes medication[34]	Required in addition to transplant rejection treatment

COMET=Cultivated oral mucosal epithelial transplantation, SLET=Simple limbal epithelial transplant, KLAL=Keratolimbal allograft, Ir-CLAL=Living-related conjunctival limbal allograft, CLAU=Conjunctival and limbus autograft, SSCE=Sequential sector conjunctival epitheliectomy, AMT=Amniotic membrane transplantation, FND=Fine needle diathermy, Anti-VEGF=Anti-vascular endothelial growth factor therapy

with suturing, compared to DALK, and in terms of graft survival both techniques were comparable.[49]

Postoperative care

After PK, meticulous postoperative care is crucial to ensure optimal outcomes and minimize the risk of complications. Regular monitoring of IOP is essential post-PK, as elevated IOP can signal complications such as graft failure or glaucoma. Several measures are essential for effective management in mitigating the rejection risk of the corneal transplant. First, patients should be informed about the symptoms associated with the operation and the potential loosening of sutures to facilitate early diagnosis. In addition, after suturing, it is recommended to prescribe topical steroids and antibiotics, serving the dual purpose of preventing both transplant rejection and infection [Figure 3]. Regular follow-up appointments play a crucial role in timely detecting corneal transplant rejection. Corticosteroids maintain their prominence as the primary drugs prescribed for the prevention and treatment of corneal transplants. Table 2 offers a comprehensive comparison of various topical corticosteroids.[29,45,50]

Discussion

Comprehensive comprehension of the stages of corneal transplant rejection is vital for prompt and effective intervention:

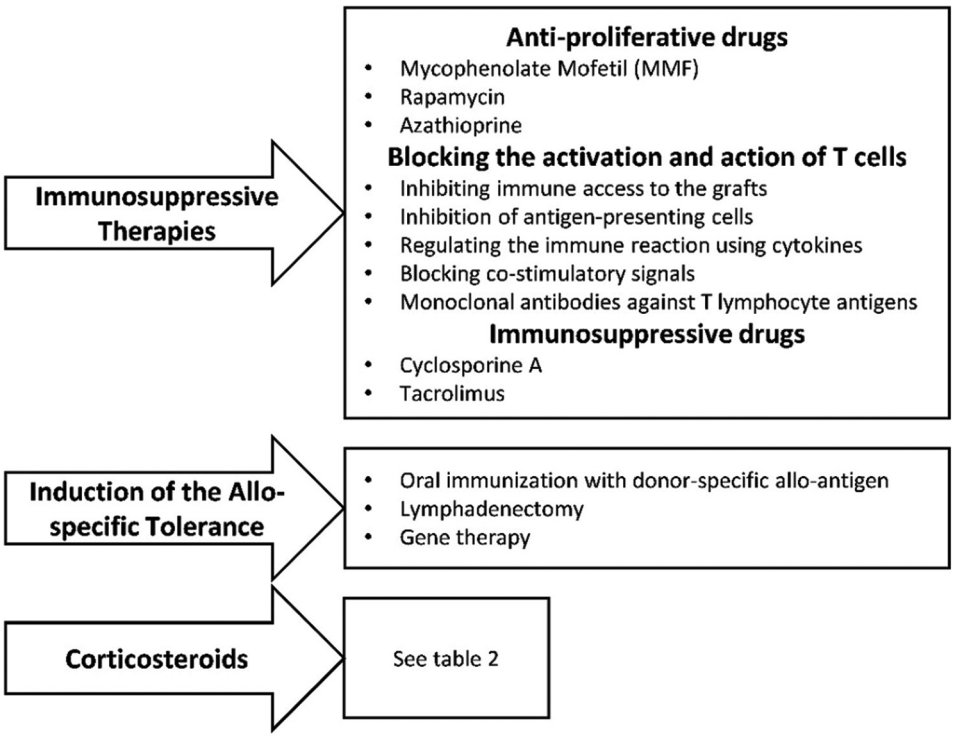

Figure 3: Postoperative management methods

Table 2: Available topical corticosteroids with their pharmakocinetic profiles

Topical corticosteroid	Available types	Available doses (%)	IOP increase	Penetration power	Anti-inflammatory effect
Fluorometholone (acetate)	Drops	0.10	Low	Low	Medium
	Ointment	0.10			
Loteprednol (etabonate)	Drops	0.2–0.5	Low	Low	High
Dexamethasone (sodium phosphate)	Drops	0.10	High	Medium	High
	Ointment	Complex			
Prednisolone (acetate, phosphate)	Drops	0.125–1	High	High	High
Difluprednate	Drops	0.05	Very high	High	Very high
Betamethasone (acetate and sodium phosphate)	Drops	0.10	High	High	Very high
	Ointment	0.10			
Hydrocortisone	Drops	0.5–1	Low	Low	High
	Ointment	1–3			
Medrysone	Drops	1	Low	Low	Medium
Rimexolone	Drops	1	Low	Low	High

IOP=Intraocular pressure

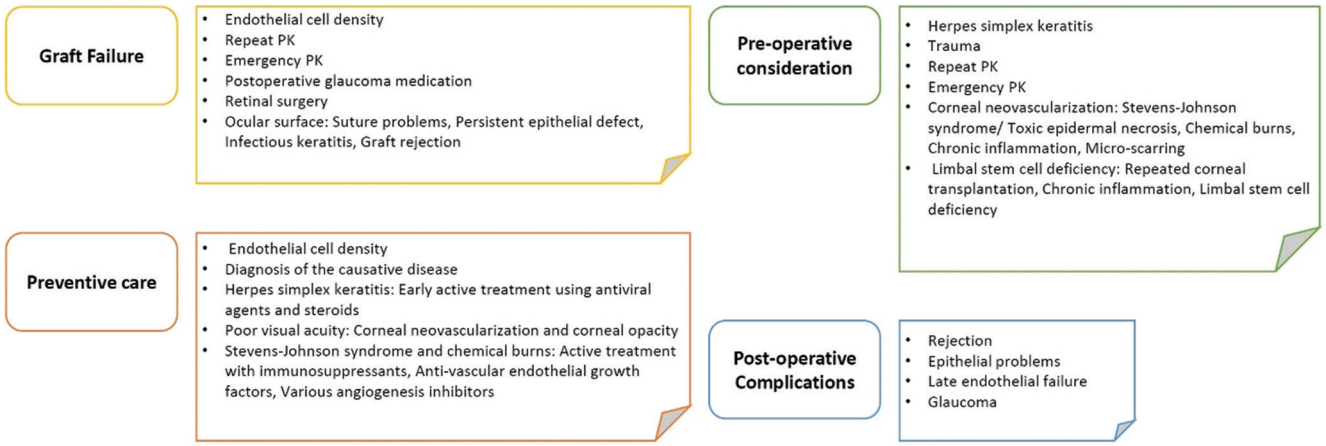

Figure 4: Summary of preventive, preoperative, and postoperative measures of penetrating keratoplasty. PK = Penetrating keratoplasty

- Possible rejection: clear transplant exhibits edema without clinical or inflammatory signs
- Probable rejection: corneal edema and inflammation, but no endothelial rejection line
- Definite rejection: corneal edema coupled with an endothelial rejection line.

It is noteworthy that hyperacute rejection, specific to organ transplantation, is not common in rejection of the corneal transplant. For severe rejection cases, the administration of a subconjunctival injection of betamethasone (2–4 mg) can be beneficial. Additional consideration may be given to the use of intravenous injections and oral steroids. Steroid drops should be administered at 1-h intervals, with betamethasone ointment used at night. KPs may initially be nonpigmented and can disappear with proper treatment. However, severe reactions may lead to large and pigmented KPs, which may persist even after inflammation subsides. Treatment continuation is advised until KPs completely vanish. In cases of iris adhesions, isolation is suggested as a supplement to overall management. The management of corneal transplant rejections should be continued until complete resolution of KPs is achieved. Figure 4 offers a summary of preventive, preoperative, and postoperative measures.

Conclusion

The prevailing guidelines for averting transplant rejection advocate for a comprehensive therapeutic strategy, emphasizing an approach that commences with the administration of high-dose topical corticosteroids. Subsequently, these doses are methodically tapered down, maintaining a low dosage for an extended duration. Furthermore, a recommended combined tactic suggests the utilization of topical cyclosporine 2% or tacrolimus, alongside prolonged use of topical corticosteroids.

The preventative role of systemic medications is significant, involving considerations for preoperative oral corticosteroids and systemic prescriptions such as rapamycin, mycophenolate mofetil, and azithromycin as potential substitutes. For a more holistic approach, a combination of oral cyclosporine or tacrolimus, coupled with oral mycophenolate mofetil, is proposed. The ongoing exploration of monoclonal antibodies in research indicates their potential to assume a more prominent role in future transplant rejection prevention regimens.

It is imperative to acknowledge that, despite the emergence of diverse options, the most efficacious treatment for acute rejection of the corneal transplant remains corticosteroid drops. The widespread adoption of 1% prednisolone acetate is attributed to its remarkable penetration of the healthy corneal epithelium and robust immunosuppressive effects. However, regional preferences, exemplified by the use of betamethasone 0.1% drops in Iran, underscore the nuanced nature of treatment choices. As research progresses, ongoing exploration of therapeutic possibilities and personalized approaches is poised to enhance and refine the landscape of transplant rejection prevention.

Data availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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