• Review Article •

Limbal stem cell deficiency secondary to topical glaucoma medication: a scoping review

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Abstract

● This scoping review aims to focus on the association between topical anti-glaucoma medication and limbal stem cell deficiency through a comprehensive analysis from the available relevant case reports, research articles and experimental studies. By understanding the potential risks associated with long-term anti-glaucoma medication use and their impact on corneoscleral limbus, precautions can be taken to balance between the risk of glaucoma progression and limbal stem cell deficiency. All relevant publications from 2000 to 2023 were included and evidence of strong emerging potential link between topical glaucoma eyedrops and the disruption of limbal stem cell homeostasis were found. Prolong use of topical glaucoma medication with preservatives were found to have a negative effect on limbal stem cells. The frequent use of topical preservative-free prostaglandin analogues and beta-blockers, commonly prescribed for glaucoma, is associated with morphological alterations in the corneoscleral limbus. These changes appear to be mediated through an inflammatory process, leading to disruption of the corneoscleral limbal niche which eventually results in limbal stem cell deficiency. With the advancement of glaucoma surgical treatment, it is possible for glaucoma treatment to shift towards earlier surgical modality to reduce topical anti-glaucoma burden leading to limbal stem cell deficiency.

● **KEYWORDS:** limbal stem cell deficiency; anti-glaucoma medication; glaucoma

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INTRODUCTION

Limbal Stem Cells Pericorneal palisade was first coined by Vogt in 1921 with a detailed description of the clinical appearance[1]. It was later understood that the basal layer of corneoscleral limbus resides limbal stem cell not only for corneal epithelium healing, but also in prevention of neovascularization, conjunctivalisation of the cornea and maintaining the cornea surface integrity[2].

Orphanet reports a prevalence of 1 to 5 cases per 10 000 individuals has limbal stem cell deficiency (LSCD)[3]. LSCD is estimated to account for 15%–20% of corneal blindness cases and would benefit from limbal stem cell transplant therapy[4]. Furthermore, a review article indicates that in the United States alone, approximately 2.1% of the population (roughly 2.9 million individuals) with glaucoma are at an elevated risk of developing LSCD[5].

LSCD evolved through three main classifications of aetiologies: genetic, acquired, and immunological[6]. Genetics aetiologies include aniridia keratopathy, xeroderma pigmentosa, and dyskeratosis congenita. Acquired aetiologies are due to environmental insults like contact lens, radiation, ocular burn, and ocular surgery. Immunological aetiologies result from medication toxicity, Steven Johnson syndrome, pterygium, and ocular surface squamous neoplasia[6-7].

LSCD may present with a wide variety of symptoms. Poor corneal wound healing with persistent or recurrent corneal erosions, is the hallmark of the disease. Other symptoms include eye redness, foreign body sensation, pain, tearing, photophobia, blepharospasm, and blurring of vision[8]. Initial clinical findings may be subtle with stippled corneal staining pattern, alongside dull and irregular corneal reflex, commonly known as lackluster appearance. The limbal palisade of Vogt may become flattened. As the disease progresses, the features become more apparent with corneal conjunctivalisation, superficial vascularization, and persistent late fluorescein staining in a vortex pattern seen with cobalt blue light, signifying the advance stages of LSCD[8]. In sectorial LSCD,

Table 1 Staging system of LSCD established by the LSCD International Working Group

Staging	Corneal involvement	A	B	C
Stage I	Normal corneal epithelium within the central 5 mm zone of the cornea	<50% of limbal involvement	≥50% but <100% limbal involvement	100% of limbal involvement
Stage II	The central 5 mm zone of the cornea is affected	<50% of limbal involvement	≥50% but <100% limbal involvement	
Stage III	The entire corneal surface is affected			

Source adopted from Deng *et al*[10]. LSCD: Limbal stem cell deficiency.

there may be a sharp demarcation between healthy corneal epithelium and abnormal corneal epithelium. In advanced stages, stromal scarring and neovascularization may occur[9].

Despite improved knowledge and clinical practice of LSCD, there are conflicts in making the diagnosis and treatments. This has led to establishment of the global consensus on definition, classification, diagnosis and staging of LSCD in 2019[10]. The consensus requires the following clinical signs and symptoms alongside other testing modalities in making the diagnosis of LSCD.

Impression cytology (gold standard test) Samples from either the superficial or deeper layers of corneal epithelium using filter paper phenotypic analysis containing globlet cells indicates cornea conjunctivalisation. It has high false negative result due to different material used for sampling which affects the outcome, pressure applied during sampling on cornea and the location and size of sampling[5,10].

***In vivo* scanning confocal microscopy** This test is less invasive and a great tool to monitor severity. This test detects globlet cells, epithelial thinning, reduction of subtarsal nerve plexus and basal cell density[5,10-11].

Anterior segment optical coherence tomography This is a non-invasive alternative imaging of ocular surface. However, it does not show cellular details seen with *in vivo* scanning confocal microscopy (IVCM)[10].

The severity of LSCD is classified clinically into 3 stages with subtypes A, B, and C depending on the degree of limbal stem cell involvement by the LSCD International Working Group (Table 1)[10]. Stage I of disease involves only the periphery of cornea, sparing the central 5 mm zone of the cornea. Stage II involves the central 5 mm zone of cornea, and Stage III involves the entire corneal surface. Subtype of A, B, and C shows the extent of limbal involvement as depicted in Figure 1[10-13].

Other clinical features pertinent to staging include abnormal limbal anatomy, neovascularisation or fibrovascular pannus, epithelial erosion and filaments, persistent epithelial defects leading to ulceration, cornea melting, and perforation. Based on the clinical features, Dua *et al*[14] classifications stage LSCD into mild, moderate and severe grades.

Mild has loss of limbal anatomy; and irregular, thin epithelium without notable vascularization. Moderate has irregular, thin epithelium, filaments and erosions, and fibrovascular pannus formation. Severe has superficial and deep vascularization, persistent epithelial defects, fibrovascular pannus, scarring, keratinization, and calcification[13].

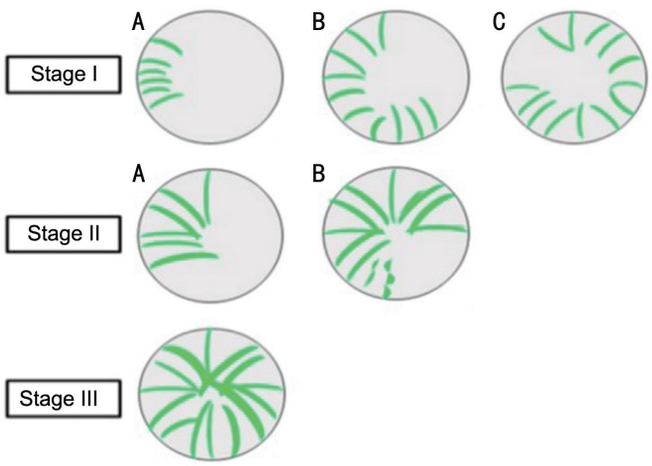

Figure 1 Staging system of LSCD established by the LSCD International Working Group showing the involvement of limbal stem cell deficiency Stage I involves only the periphery of the cornea, and the degree of limbal stem cell involvement represented by the green stroke is staged as A, B, and C. Stage II disease involves both the periphery and the central 5-mm of the cornea. Stage III disease involves the entire corneal surface. Source adopted from Deng *et al*[13]. LSCD: Limbal stem cell deficiency.

Staging of the disease established by the LSCD International Working Group is important in management of patients. Treatment of LSCD is based on the global consensus[14], which include step by step optimization of ocular comorbidity and ensuring healthy eyelids and conjunctiva, reducing inflammation and adequate lubrication. If central visual axis is not affected or if patient is asymptomatic with unaffected vision surgical intervention is not necessary in such case. However, for eyes with significantly compromised vision as shown in Stage IIB and III disease, surgical intervention treatment is often required to preserve vision and stabilized ocular surface. Surgical intervention will depend on the patients' severity, laterality, and stages of the disease (Figure 2). For patients with unilateral or bilateral Stage I and IIA LSCD who have severely impaired vision or are experiencing complications due to LSCD, surgical intervention may be considered to promote re-epithelialization of the central visual axis. Procedures such as sequential sectoral conjunctival epitheliectomy, pannus removal, or amniotic membrane transplantation can be performed[15].

In cases of Stage IIB and III LSCD, the primary goal shifts to ocular surface rehabilitation through limbal stem cell

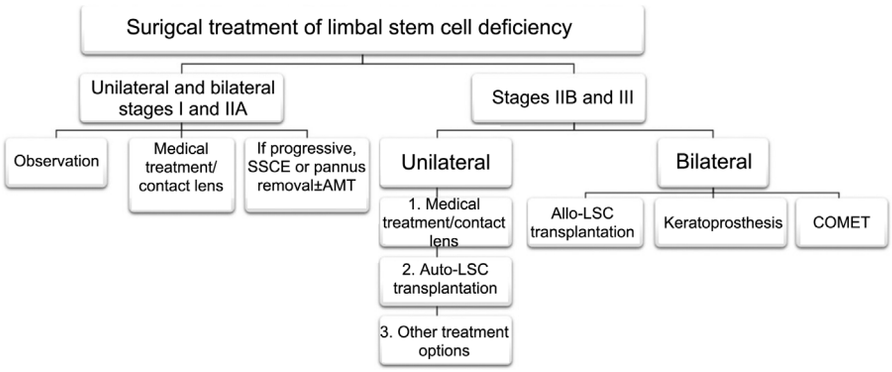

Figure 2 Summary on management of LSCD according to stages and laterality of LSCD Source adopted from Deng *et al*[13]. LSCD: Limbal stem cell deficiency; SSCE: Sectorial sequential conjunctival epitheliectomy; AMT: Amniotic membrane transplantation; COMET: Cultivated oral mucosal epithelial transplantation.

transplantation. For unilateral cases, autologous limbal stem cell transplantation is the preferred approach, as it reduces the risk of graft rejection and improves long-term graft survival. However, in bilateral cases, allogeneic limbal stem cell transplantation is often required. To minimize the risk of immunological rejection, systemic immunosuppression is typically necessary following allogeneic transplantation. In severe or total bilateral LSCD, alternative treatments such as cultivated oral mucosal epithelium transplantation or the use of keratoprostheses may be considered instead of allogeneic limbal stem cell transplantation.

Glaucoma Glaucoma is a prevalent ocular condition which causes optic nerve damage and visual field loss affecting more than 70 million people worldwide with approximately 10% being bilaterally blind[16]. It is the leading cause of global irreversible blindness, estimated to affect approximately 111.8 million people worldwide in 2040[17].

Glaucoma is clinically characterized by intraocular pressure (IOP)-associated optic neuropathy and retinal ganglion cell loss leading to visual loss[18]. IOP is the only modifiable factor, which causes mechanical stress on the posterior ocular structure, especially on the lamina cribrosa where retinal ganglion cells axons perforate the sclera and exits the eye[18-19]. Target IOP should be achieved with the least medications possible to prevent adverse effect. This is necessary to halt or slow down the disease progression as well as preserving vision[20].

Management of glaucoma over the years has evolved in both medical and surgical treatment. Medical management in the form of eye drops remains the first line treatment. The current choices of medications used in managing IOP are prostaglandin analogs (PGAs), β-adrenergic blocker, carbonic anhydrase inhibitor, α2-adrenergic agonist, cholinergic, rho-kinase inhibitor, and fixed-dose combinations. They may come in formulations with preservatives or preservative free forms.

Newer forms of medication delivery show promising results. In recent years, nanotechnology route of delivering medications has shown promising results in clinical trials[21]. The sustain release and long-acting ocular hypertensive with preservative free bimatoprost ring inserted in the fornix shows a 4-6 mm Hg IOP lowering effect. The intracanicular travoprost releasing device (known as OTX-TP) shows modest IOP-lowering effect but with 7% increase incident of canaliculitis. Intracameral formulation of sustained release bimatoprost[22] has also been studied.

Advances in surgical approach over the years has also improved with less adverse effects and better tolerability. The evolution of better surgical technique of trabeculectomy and the devices used in minimally-invasive glaucoma surgeries has shown exciting ways of enhancing effectiveness and safety of glaucoma surgeries[23].

METHODS

Design We performed a literature search using the Arksey and O'Malley's[24] framework to guide the scope of the review. The scoping review methodology was chosen to explore extensive literature on topical glaucoma eyedrops leading to LSCD.

Search Method We performed, a data-driven literature search in September 2023, following the PRIS-MA guidelines in selecting credible publications (Figure 3). The inclusion criteria were set to empirical articles published between 2000 and 2023 with specific focus on the relationship between topical glaucoma medication on LSCD. The database search engines used were Scopus, PubMed, and Ovid MEDLINE®. This was accomplished by combining the terms "Glaucoma Treatment" or "Glaucoma Management" and "Limbal Stem Cell Deficiency" with Boolean search methods like "AND", "OR", and "NOT" to discover relevant study that matches the review's objectives.

Exclusion criteria excluded article which were not written in English and publication unrelated to glaucoma treatment leading to LSCD.

Search Outcome The articles that met the inclusion

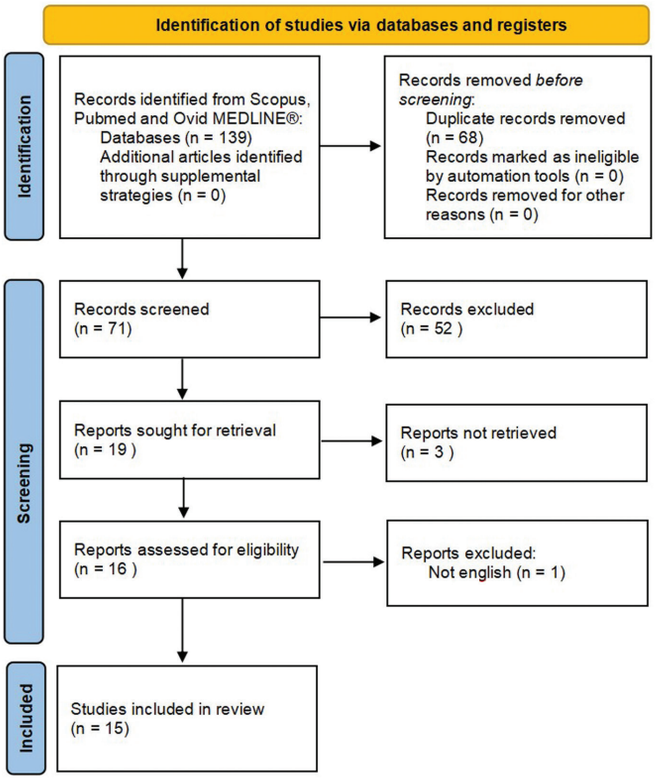

Figure 3 PRIS-MA flow diagram.

criteria (*n*=139) were imported into EndNote 20, a reference management software, and further screened for eligibility. Figure 3 shows the selection results in a flowchart using the PRIS-MA method. Sixty-eight articles with identical material were deleted after a duplication check, leaving 71 records. Further, title and abstract screening excluded 52 records leaving only 16 papers. One paper was excluded for language reason.

Our study methodology employs a careful, systematic approach to minimize bias at every stage. An initial literature search was conducted following the PRIS-MA flow diagram, with non-relevant studies excluded to ensure focus and relevance. Each included research article was critically evaluated based on study design and data analysis to ensure methodological soundness. Furthermore, all selected studies were sourced from high-impact, peer-reviewed journals, which inherently undergo stringent scrutiny to uphold scientific validity and reduce bias.

Most studies included in this scoping review are prospective in design, comprising case-control and experimental animal studies, enhancing the reliability of the evidence. One retrospective case series was included due to its contribution in providing real-world clinical outcomes on the treatment of LSCD.

RESULTS

Topical glaucoma medications have been well known to cause ocular surface disease ranging from disruption of tear film distribution, allergies, punctuate keratitis, and corneal ulceration[25-26]. Prolonged use of topical glaucoma medications is also associated with LSCD[27]. Management of complications from glaucoma treatment can be quite challenging as there is a need to balance between haulting the disease progression of glaucoma and preventing the devastating side effects of topical medications.

Benzalkonium chloride (BAK) is used in approximately 70% of preserved ophthalmic solution including topical glaucoma medications with concentrations typically ranging from 0.005% to 0.02%[28]. Studies on mouse model[29] show that high dose of BAK (0.5%) four times a day for 28d leads to a typical manifestation of LSCD. It is believed that BAK causes induction of Langerhan cell formation responsible for the progression of ocular surface disease (OSD)[30].

Pathogenesis of iatrogenic LSCD is believed to be secondary to inflammation and chronic limbitis disturbing the stem cell function[31-32]. Chronic inflammation and allergy reaction from prolonged use of topical glaucoma causes alteration of the limbal morphology. The microenvironment of the limbus is important to maintain the equilibrium and renewal of stem cells. Patients exposed to at least one topical glaucoma medications with or without preservatives are more susceptible to limbal alteration[33], including reduction in limbal epithelial thickness, as seen in anterior segment optical coherence tomography (AS-OCT). Similar results were also observed in another study[34] where limbal epithelial thickness was thought to be the direct presentation of limbal cells status correlating to the stem cell density[35].

It is uncertain whether all the medications used are related to LSCD. There is still very limited evidence to pinpoint certain glaucoma medication leading to LSCD. Latanoprost has been seen to cause infiltration of inflammatory cells and anisocytosis with increase in $CD45^+$ cells[36]. More toxicity with marked increase in inflammatory cells is observed in Latanoprost with preservatives. Levobunolol, a beta-blocker eye drop has been found to delay wound healing by inhibiting β2 adrenoreceptors on limbal stem cells, which leads to a reduction in corneal epithelial regeneration-related signaling. β2 adrenoceptor is predominantly found on cornea and limbal region, and therefore selective β1-adrenoceptor antagonist may be an alternative for glaucoma treatment[37]. Examples of nonselective β-blocker affecting both β1 and β2 adrenoceptor commercially available include timolol, levobunolol, metipranolol, and carteolol; and betaxolol is a selective β1 adrenoceptors (cardioselective).

Although topical medications remain the mainstay of glaucoma treatment, many patients may require surgical intervention in addition to topical glaucoma eyedrops. Anti-metabolite used in filtering surgeries can also cause LSCD[38]. Multiple surgeries also come with a risk of worsening LSCD. While surgical intervention might be able to better control

the IOP, topical glaucoma eyedrops are still needed for the optimisation in a fraction of patients. Topical glaucoma eyedrops has an additional pro-inflammatory influence on the conjunctiva, causing increase in subepithelial macrophages, lymphocytes, mast cells, and fibroblasts[39-40]. Topical use of glaucoma medications and preservatives add to the insult from anti metabolites and may further damage the limbal niche.

LSCD is almost irreversible in most patients. However, in very early stages of LSCD, complete recovery is possible. The medical therapy suggested by Nakakura *et al*[41] mostly consisted of adequate topical artificial tear eye drops and 3% diquafosol sodium to stabilize the tear film, low-concentrate corticosteroids to decrease inflammation and promote differentiation of healthy epithelium, rabamipide 2% in modifying epithelial cell function, improving tear stability as well as suppressing inflammation and antibiotic ointment used for tear lipid layer treatment, contributing to tear stability.

Surgical interventions were considered in cases where medical therapy fails. It was concluded that LSCD secondary to topical glaucoma medication is very challenging to treat due to the dependence on topical glaucoma medications to preserve eyesight[41].

DISCUSSION

Slit lamp biomicroscopy remains the primary diagnostic modality for LSCD. A systematic review revealed that 62.9% of published cases were diagnosed based solely on clinical findings, without the need for adjuvant testing. The remaining cases was confirmed with impression cytology (24.2%), IVCM (0.7%) or both impression cytology and IVCM (0.9%)[42]. Given this reliance on clinical examination, it is crucial to recognize glaucoma treatment as a potential risk factor for LSCD to ensure accurate and timely diagnosis.

The duration of glaucoma medication use required to induce LSCD remains uncertain. However, Nakakura *et al*[41] (2023) demonstrated that glaucoma medications may contribute to LSCD after as few as 6y of use (mean: 8y). Notably, even monotherapy has been shown to induce limbal niche injury. Güçlü *et al*[34] (2021) reported no significant difference in limbal epithelial thickness reduction between single- and multiple-therapy regimens, suggesting that even isolated treatments may pose a risk.

Among available glaucoma medications, preservative-free (PF) PGAs and β-blockers have been the most extensively studied, with evidence supporting their role in iatrogenic limbal injury (Table 2)[33,36-37]. Comparative analyses indicate that PGAs exhibit a stronger association with limbal damage than β-blockers. However, data on other classes of glaucoma medications remain scarce, leaving their potential effects on limbal stem cells largely unexplored. Further research is warranted to elucidate these risks. Given the variability in drug composition and concentration across formulations, the precise mechanisms underlying LSCD pathogenesis remain incompletely understood.

Topical glaucoma eye drops are recognized as the primary treatment for glaucoma. This paradigm is being challenged, due to the potential side effects associated with long-term use of these eye drops. In addition, adherence issues, inconvenience and costs should also be taken into consideration. With newer technologies in surgical implants and drug delivery system with appealing safety, efficacy, and cost effectiveness, it is possible for a paradigm shift towards earlier surgical interventions in the treatment of selected glaucoma patients.

The decision to pursue earlier surgery should be individualized, considering factors such as age, poor medication adherence (particularly with multi-drug regimens), signs of ocular surface disease, or disease progression despite maximal medical therapy. In some regions, limited access to affordable glaucoma medications may impose a financial burden on patients, while those in remote areas often present with advanced disease due to logistical barriers to follow-up. In such cases, early surgical intervention may be critical to preserving remaining vision.

The Treatment of Advanced Glaucoma Study (TAGS) compared outcomes in patients with advanced glaucoma managed either with early trabeculectomy or conventional medical therapy (glaucoma eye drops). At 24mo, the trabeculectomy group demonstrated significantly greater reductions in IOP from baseline at all measured time points compared to the medication-only arm. Additionally, surgically treated patients required far fewer topical medications to maintain IOP control. The trial reported no instances of severe vision loss attributable to trabeculectomy, supporting its safety profile in advanced disease. These findings suggest that early surgical intervention may offer superior IOP control while reducing treatment burden[43].

Evidence suggests that prolonged use of topical glaucoma medications, particularly multiple agents may reduce the success rates of glaucoma surgeries, including *ab interno* microhook trabeculotomy and trabeculectomy[44-45]. Proposed mechanisms include subconjunctival fibrosis secondary to chronic exposure to BAK and other preservatives, as well as diffuse atrophy of the conventional outflow pathways due to sustained reduction in aqueous humour flow through Schlemm's canal[44,46]. Notably, most glaucoma medications either enhance uveoscleral outflow or suppress aqueous production, potentially leading to functional disuse atrophy of the trabecular meshwork pathway over time.

The Collaborative Initial Glaucoma Treatment Study (CIGTS)[47], a randomized controlled trial evaluated whether patients newly diagnosed with open-angle glaucoma are better managed initially with medications or with trabeculectomy. It was found

Table 2 Summary of studies on topical anti-glaucoma induced limbal stem cell deficiency: class of glaucoma medications, risk factors, mechanisms, clinical outcomes, and therapeutic implications

Study	Title	Methods	Study subjects	Class of glaucoma medication (preservative/non preservative)	Risk factors for limbal stem cell deficiency	Conclusion
Nakakura *et al*[41] 2023	Case report: Medical treatment for limbal epithelial stem cell deficiency in patients treated for glaucoma	Retrospective study	7 subjects	Unsure class of medication and preservative used, only mentioned patient on glaucoma medication	Mean duration of 8y on glaucoma medications; elderly age group	This study evaluated the outcomes of medical treatment for LSCD, revealing 37% of patients showed improvement, 2% experienced worsening, and 63% remained unchanged. It was concluded that treating LSCD is challenging due to the reliance on topical glaucoma eye drops for glaucoma management. Prolonged use of these eye drops can lead to irreversible structural changes, further complicating the condition.
Yuan *et al*[37] 2021	β-blocker eye drops affect ocular surface through β2 adrenoceptor of corneal limbal stem cells	Experimental study (animal study)	Mouse	β-blocker (non preservative); β1-adrenoceptor (β1AR)-specific antagonist–levobunolol; β2-adrenoceptor (β2AR)-specific antagonist-atenolol	β2-blocker/nonselective β blockers eye drops (inhibits β2AR of limbal stem cells causing decrease in corneal epithelial regeneration-related signaling)	The cornea contains predominantly β2 adrenoceptors compared to β1 adrenoceptors. β-blockers have been shown to inhibit the migration and proliferation of corneal epithelial progenitor cells, impair corneal wound healing, and reduce signaling pathways associated with corneal epithelial regeneration through β2 adrenoceptors. β1 adrenoceptor antagonists did not significantly affect corneal wound healing. Based on these findings, it was concluded that non-selective β-blocker eye drops may not be the optimal first choice treatment for glaucoma.
Güçlü *et al*[34] 2021	Corneal epithelium and limbal region alterations due to glaucoma medications evaluated by anterior segment optic coherence tomography: a case-control study	Case-control study	95 subjects	Glaucoma eyedrops with preservatives. Group 1: One drug regimen-latanoprost 0.005% including 0.02% benzalkonium chloride (BAK); Group 2: Two drug regimen-dorzolamide 2%, timolol maleate 0.5% including 0.01% BAK; Group 3: Three drug regimen-dorzolamide 2%, timolol maleate 0.5% including 0.01% BAK; Brimonidine including PuriteVR 0.005%; Group 4: Four drug regime-latanoprost 0.005% including 0.02% BAK, dorzolamide 2%, timolol maleate 0.5% including 0.01% BAK as a preservative component brimonidine including PuriteVR 0.005%	Preservatives present in glaucoma eyedrop; even single drug regime is a risk for LSCD; Elderly age group	The use of at least one glaucoma medication was associated with limbal area injury, alterations in ocular surface measurements, and a significant reduction in limbal epithelial thickness, where stem cells reside. No significant differences were observed between patients on a single-drug regimen and those on a four-drug regimen, as assessed by AS-OCT measurements and clinical ocular surface evaluations. Glaucoma patients have higher OSDI scores compared to the control group. However, there was no significant difference in OSDI scores between patients on multiple medications and those on a single-drug treatment.
Mastropasqua *et al*[33] 2015	Corneoscleral limbus in glaucoma patients: *in vivo* confocal microscopy and immunocytological study	Case control observational study	80 subjects	Comparison between preservative glaucoma eyedrops, PF glaucoma eyedrops and control groups	PF prostaglandin analogs (PGAs) more risk compared to PF β-blockers; preservative (BAK)	The study revealed a significantly higher dendritic cell density and immunoinflammatory marker positivity in patients receiving PF medications compared to controls. These findings suggest that even PF formulations may contribute to ocular surface inflammation, potentially leading to iatrogenic limbal stem cell alterations. Comparative analysis demonstrated that prostaglandin analogs (PGAs) induced greater inflammatory activity at the limbus compared to β-blockers, as evidenced by both laser scanning confocal microscopy and impression cytology. This aligns with the known pro-inflammatory properties of PGAs. Furthermore, PF PGA-treated eyes exhibited a significantly higher dendritic cell density than PF β-blocker-treated eyes (P<0.05). Notably, patients treated with benzalkonium chloride (BAK)-preserved medications exhibited more pronounced limbal inflammation than those on PF formulations. Based on these findings, we advocate for the preferential use of PF monotherapy or PF fixed-combination therapies to minimize iatrogenic ocular surface damage.
Lin *et al*[29] 2013	A mouse model of limbal stem cell deficiency induced by topical medication with the preservative benzalkonium chloride	Experimental study (animal study)	Mouse	Phosphate buffer solution (control) *vs* BAK solution (0.1%, 0.25%, 0.5%)	Preservative (BAK)	Topical application of 0.5% BAK resulted in persistent corneal neovascularization, chronic stromal inflammation, epithelial defects, and corneal conjunctivalization, consistent with LSCD in humans. Histological examination of tissue sections in groups treated with 0.5% BAK showed significant infiltration of inflammatory cells (CD4-positive cells) in the cornea and limbus by day 28. Additionally, corneal conjunctivalization was observed, characterized by increased invasion of K19- and K13-positive epithelial cells onto the corneal surface following BAK treatment on day 28.
Pauly *et al*[36] 2012	*In vitro* and *in vivo* comparative toxicological study of a new preservative-free latanoprost formulation	*In vitro* and *in vivo* experimental studies	3D-human corneal epithelial (HCE) model; albino rabbits	Comparison was done between 4 types of eyedrops: phosphate buffer solution; BAK 0.02%; BAK latanoprost; PF-latanoprost	PF Latanoprost; preservative (BAK)	Cytological evaluation of conjunctival imprints demonstrated that PF latanoprost was the most well-tolerated treatment compared to 0.02% BAK, and BAK-latanoprost. However, PF latanoprost also exhibited mild anisocytosis, a moderate rise in CD45+ cells, and minimal inflammatory cell infiltration. Both 0.02% BAK and BAK-latanoprost displayed significant inflammatory cell infiltration, damage to conjunctival epithelial cells and goblet cells, and elevated levels of CD45+ cells.

LSCD: Limbal stem cell deficiency; AS-OCT: Anterior segment optical coherence tomography; OSDI: Ocular Surface Disease Index; PF: Preservative-free; BAK: Benzalkonium chloride.

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that patients in the medication arm had slightly lower impact on quality of life compared to the surgical arm. There were slightly more significant local side effects in patients who underwent trabeculectomy. However, this study was carried out in 1999, where minimally invasive glaucoma surgery (MIGS) and selective laser therapy (SLT) were still not available as a treatment option. There were also limited choices of topical glaucoma medications at the time.

SLT has been shown to be beneficial in the treatment of open angle glaucoma and ocular hypertension as shown in an randomised control trial, the LiGHT trial[35]. This recent trial published in 2022 compared a group of patients receiving SLT and a group receiving topical glaucoma eyedrops medication alone. Comparison on efficacy of treatment, safety and cost effectiveness were done. This study provides strong evidence for 360-degree treatment with SLT as a first line therapy for open angle glaucoma and ocular hypertension[22,35].

It is important to recognize the risk factors, signs, and symptoms of iatrogenic LSCD to prevent the occurrence and identifying condition at early stages when it is still reversible. Medical therapies used in improving ocular surface disease for example, preservative free artificial tears, treatment of ocular inflammation, minimizing toxicity from preservative may be helpful in the prevention of LSCD.

While it can be challenging to diagnose LSCD, the diagnosis of LSCD is typically established through a combination of patient history and clinical evaluation. Gold standard test currently in use is the impression cytology. However, there are some limitations of the test. The sensitivity of this test is affected by many factors including the filter pore size, the pressure applied during collection and also the location of collection[8]. Due to its high false negative result and minimally invasive technique, a trained professionals is required for its collections of sample[48-49]. Hence it is possible that the diagnosis of LSCD may go unnoticed for years. High suspicion is needed for the diagnosis of iatrogenic LSCD.

CONCLUSION

There is a strong link seen between topical glaucoma medications and LSCD. The treatment paradigm of glaucoma may shift towards earlier surgical intervention to reduce the drop burden from topical glaucoma eyedrops and preservatives.

Most cases of established LSCD diagnosis are irreversible due to prolonged insults from daily topical glaucoma medications leading to structural limbal damage. For patient diagnosed at early stage, trial of medical therapy aiming at reducing inflammation and stabilizing tear films.

Fixed-combination preparation of topical glaucoma medication may reduce topical glaucoma drop burden. Early surgical intervention in mild to moderate stages of open angle glaucoma proven with safe efficacy like MIGS is proven to be beneficial in reducing topical glaucoma eyedrops frequency. In cases where medical approach is unfavourable, surgical interventions like keratoplasty should be considered for visual improvement in LSCD patients.

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