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# Prevention and Treatment of Common Postoperative Complications of Cataract Surgery

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# Original Publications

This dissertation is based on the following original publications, which will be referred to in the text by their Roman numerals:

I. Lindholm J-M, Taipale C, Ylinen P, Tuuminen R. Perioperative subconjunctival triamcinolone acetonide injection for prevention of inflammation and macular oedema after cataract surgery. *Acta Ophthalmol*. 2020;98(1):36-42.

II. Lindholm J-M, Laine I, Tuuminen R. Five-year cumulative incidence and risk factors of Nd:YAG capsulotomy in 10 044 hydrophobic acrylic 1-piece and 3-piece intraocular lenses. *Am J Ophthalmol*. 2019;200:218-223.

III. Lindholm J-M, Laine I, Tuuminen R. Intraocular lens power, myopia, and the risk of Nd:YAG capsulotomy after 15,375 cataract surgeries. *J Clin Med*. 2020;9(10).

IV. Lindholm J-M, Laine I, Hippala H, Ylinen P, Tuuminen R. Improving eye care services with a lean approach. *Acta Ophthalmol*. 2018;37:1003.

# Abbreviations

| | |
|---|---|
| ANOVA | Analysis of variance |
| BCVA | Best corrected visual acuity |
| CDVA | Corrected distance visual acuity |
| CI | Confidence interval |
| CME | Cystoid macular edema |
| COX | Cyclooxygenase |
| CRT | Central retinal thickness |
| CTGF | Connective tissue growth factor |
| ESCRS | European Society of Cataract and Refractive Surgery |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FA | Fluorescein angiography |
| FGF | Fibroblast growth factor |
| HGF | Hepatocyte growth factor |
| HR | Hazard ratio |
| IOL | Intraocular lens |
| IOP | Intraocular pressure |
| LEC | Lens epithelial cell |
| logMAR | Logarithm of the minimum angle of resolution |
| MMP | Matrix metalloproteinase |
| Nd:YAG | Neodymium-doped yttrium aluminum garnet |
| NSAID | Non-steroidal anti-inflammatory drug |
| OCT | Optical coherence tomography |
| PCME | Pseudophakic cystoid macular edema |
| PCO | Posterior capsular opacification |
| PMMA | Polymethyl methacrylate |
| PREMED | PREvention of Macular EDema after cataract surgery study |
| RCT | Randomized controlled trial |
| SD | Standard deviation |
| SHR | Subhazard ratio |
| SUSAR | Suspected unexpected serious adverse reaction |
| TGFβ | Transforming growth factor β |
| VEGF | Vascular endothelial growth factor |

# 1 Abstract

This study was undertaken to advance the treatment and prevention of common postoperative complications of cataract surgery. Study I aimed to compare the efficacy, safety, and tolerability of a subconjunctival injection of triamcinolone acetonide with topical dexamethasone eye drops for the prevention of inflammation and macular edema after cataract surgery. Study II was carried out to evaluate the real-world cumulative incidence and risk factors of Nd:YAG capsulotomy. Study III attempted to assess the risk of Nd:YAG capsulotomy in association with myopia and the diopter power of the implanted intraocular lens (IOL). Study IV focused on the potential for improving the Nd:YAG treatment process with the help of Lean methodology.

I. Treatment with perioperative 20 mg subconjunctival injection of triamcinolone acetonide was found to be effective for the prevention of inflammation and macular edema. It was shown non-inferior to topical dexamethasone and may prevent pseudophakic cystoid macular edema more successively. The mean change in central retinal thickness at 28 days was higher with topical dexamethasone compared to triamcinolone (difference +27.1 μm; 95% confidence interval (CI): +7.28 μm to +47.0 μm; $p = 0.008$). Corrected distance visual acuity and intraocular pressure (IOP) changes were similar, and ocular tolerance was good in both groups. No serious adverse events were observed.

II. The 5-year cumulative incidence of Nd:YAG capsulotomy after cataract surgery was estimated at 13.2% (95% CI: 12.5%–14.0%) with competing risks methodology for common hydrophobic acrylic IOLs. Real-world evidence of this retrospective cohort study of 10,044 eyes suggested that implantation of SN60WF and ZA9003 IOLs was associated with lower risk compared to ZCB00, after accounting for other predictors. Increased risk of Nd:YAG capsulotomy was associated with the eyes of patients aged younger than 60 years, female sex, and eyes implanted with an IOL of <22.5 diopters power.

III. The 5-year cumulative probability of Nd:YAG capsulotomy after cataract surgery was 27.4% (95% CI: 22.9–32.6%) for low-diopter (5–16.5 D) IOLs, 14.6% (95% CI: 13.8–15.5%) for mid-diopter (17–24.5 D) IOLs, and 13.6% (95% CI: 11.7–15.6%) for high-diopter (25–30 D) IOLs. Results showed that low-diopter IOLs are associated with a significantly higher risk of Nd:YAG capsulotomy within five years following implantation. Estimation should help in evaluating the risks of cataract surgery in myopic eyes.

IV. This study described a Lean-oriented process improvement project to develop a streamlined Nd:YAG capsulotomy treatment protocol. The improved treatment protocol was evaluated and compared with the conventional protocol, which showed substantial reductions in lead times without compromising patient satisfaction. Number of patients treated in hours more than tripled, and the patient reception time per patient was shortened by approximately 20%.

The main findings of the current series of studies should contribute to achieving better outcomes and preventing postoperative complications in cataract surgery. Rising burden of age-related diseases in ophthalmology adds to the challenge of providing high quality health services, and attention must be paid to the prevention and management of the most common complications.

# 2 Introduction

Cataract surgery is the most common form of ophthalmic surgery worldwide; therefore, it carries major public health implications. In developed countries, blindness caused by cataracts is very low, but in Finland, for example, one-third of people over the age of 65 are estimated to have some degree of vision-impairing cataract (Laitinen et al. 2010). Challenges facing the healthcare systems in developed countries, such as the soaring dependency ratio due to an aging population and cost escalation, require reform and new approaches to health care provision.

Modern surgical techniques have improved treatment results and decreased intraoperative and postoperative complications associated with cataract surgery. Nevertheless, achieving the best outcomes and preventing later complications requires effective control of the postoperative inflammatory response and means to reduce the effect of postoperative care non-adherence. Successful anti-inflammatory treatment prevents the development of pseudophakic cystoid macular edema (PCME), which is considered the most frequent early postoperative complication of cataract surgery. PCME typically affects early recovery from surgery and emerges in proportion to the degree of postoperative inflammation and other predisposing factors.

Posterior capsular opacification (PCO) remains the most common later complication of cataract surgery, despite advancements in surgical techniques and IOLs. The risk factors for PCO can be generally classified as being related to the systemic or eye diseases of the patient, the surgical techniques, or the properties of the implanted IOL. Myopic eyes are a particular case in this context, since the effect of myopia on the incidence of PCO is still not precisely known. Evaluating the long-term cumulative incidence and risk factors of PCO and subsequent Nd:YAG laser capsulotomy treatment provides possible methods for prevention of this complication. Reducing the incidence of PCO also decreases the need for an Nd:YAG laser capsulotomy procedure, which is generally very safe, but is, nevertheless, associated with certain risks and imposes an economic burden on health services and society.

Reducing the morbidity from PCO depends upon both the primary prevention of the condition and providing timely treatment. Developing and implementing more efficient working principles in healthcare organizations can enable timely access to treatment. Lean methodology offers a set of tools for improving the efficiency of a treatment protocol for Nd:YAG laser posterior capsulotomy. There are also many other potential settings for Lean implementation in high-volume eye health services.

The present study was undertaken to explore and develop the treatment and prevention of complications after cataract surgery. Respectively, I aimed to study the effects of subconjunctival triamcinolone acetonide for the prevention of inflammation and macular edema after cataract surgery, the incidence and risk factors of Nd:YAG capsulotomy, and the potential for improving the Nd:YAG capsulotomy treatment process.

# 3 Review of the Literature

## 3.1 Pseudophakic Cystoid Macular Edema

### 3.1.1 Pathophysiology

The pathogenesis of pseudophakic cystoid macular edema, also known as Irvine–Gass syndrome, is multifactorial and not yet completely elucidated. However, postoperative inflammation seems to be the major etiology of PCME. Other factors that have been implicated in the development of PCME and other forms of cystoid macular edema (CME) include vitreomacular traction, vascular instability, and light toxicity (Gass et al. 1966; Schepens et al. 1984; Ursell et al. 1999).

Postoperative intraocular inflammation occurs as a result of surgical tissue injury. Tissue trauma leads to an inflammatory cascade in which cell membrane phospholipids are converted to bioactive inflammatory mediators through either the lipoxygenase pathway or the cyclooxygenase pathway. Phospholipase A2 releases arachidonic acid from cell membrane phospholipids. In the cyclooxygenase pathway, arachidonic acid is then converted into short-lived endoperoxides, such as prostaglandin G2 and prostaglandin H2, by the cyclooxygenases COX-1 and COX-2 (Simmons et al. 2004). Endoperoxides are metabolized by prostaglandin-endoperoxide synthases into prostanoids, including thromboxane and prostaglandins such as prostacyclin. In the lipoxygenase pathway, arachidonic acid is metabolized by lipooxygenases into leukotrienes, which are a family of eicosanoid inflammatory mediators. Prostanoids and leukotrienes are pro-inflammatory mediators that promote inflammatory reaction by dilating blood vessels, increasing the permeability of blood vessels, and recruiting leukocytes and chemotactically attracting them to the area of inflammation (Miller 2006).

Subsequently, the proinflammatory mediators diffuse posteriorly into the vitreous and retina. Inflammatory reaction leads to an increase in the permeability of perifoveal retinal capillary vessels, which is due to the disruption of the blood-retina-barrier (Flach 1998). Blood-retina-barrier is a selective barrier formed at the retinal pigment epithelial cell layer and the retinal capillary endothelial cells. Increased vascular permeability leads to leakage and accumulation of fluid in cystoid spaces within the inner layers of the retina, primarily in the outer plexiform layer. Accumulation of fluid is the result of a failure in the homeostatic mechanisms regulating the intrinsic balance of retinal and choroidal circulation. The degree of CME can range from mild subclinical retinal thickening to a clinically significant form, which decreases visual acuity (Grzybowski et al. 2006). Visual loss occurs due to the disruption of the photoreceptor cell architecture. The severity of PCME is linked to the degree of postoperative inflammation. Chronic or uncontrolled edema can cause permanent damage to the photoreceptors, lamellar macular holes, fibrosis, and subretinal fluid may also form. In the eye, this inflammatory cascade promotes symptoms such as pain, photophobia, hyperemia, miosis, and diminished visual acuity.

### 3.1.2 Epidemiology

PCME is considered the most frequent early postoperative complication of cataract surgery. Typically, it affects the early recovery from the surgery, and most cases occur within 3 months of surgery (Yonekawa et al. 2012; Wielders et al. 2015). Inflammation, as measured by aqueous flare and cells, peaks within the first few days after surgery and then decreases over 2–3 weeks postoperatively (Shah et Spalton 1994). Postoperative inflammation predisposes patients to the development of PCME (Ursell et al. 1999; Ersoy et al. 2013). Previously, levels of aqueous flare have been associated with the incidence of PCME, even to the extent that patients with and without PCME could be distinguished in almost all cases only based on flare values (Ersoy et al. 2013). The incidence of PCME usually peaks approximately 4–6 weeks postoperatively, but it can vary between 3 and 12 weeks after surgery, and late onset may occur even after months or years (Severin 1980; Yonekawa 2012).

Classification of PCME has been described as follows: acute (occurring within 3 months of surgery); late-onset (occurring after more than 3 months); chronic (persisting more than six months); and recurrent (Henderson et al. 2007). PCME has been commonly described as a relatively self-limiting condition with spontaneous recovery in many cases within 6 months (Shelsta et al. 2011; Zur et Loewenstein 2017). However, in some patients, it may become chronic and result in long-term visual deterioration or permanent visual loss. In fact, visual acuity has been found reduced significantly up to the latest time point, assessed up to 24 weeks, in eyes with PCME after surgery compared with those without (Chu et al. 2016).

The reported incidence rates of PCME have varied considerably in the literature, depending on which definition of PCME is used, the utilized methods of diagnosis, and surgical techniques. Unfortunately, there is no validated and universally accepted definition for PCME. Clinically significant PCME is defined as macular edema associated with visual deterioration. Visual loss has been interpreted in various ways, including postoperative visual acuity 20/30–20/40 or worse, or 1.5–2 lines less than the expected best-corrected visual acuity (BCVA) with or without visually symptomatic distortion, such as central scotomas and metamorphopsia, or a decrease in contrast sensitivity. (Percival 1981; McCafferty 2017). Subclinical PCME determined only by optical coherence tomography (OCT) imaging or angiographic findings has little or a transient effect on visual acuity. It is much more common and may be unrecognized and self-limiting without treatment. Depending on the study design, mild cases of PCME may be missed especially in retrospective studies, as such patients may not have undergone OCT or angiography imaging. This could have led to further underestimation of the incidence of subclinical PCME.

Earlier studies diagnosing PCME using fluorescein angiography alone have reported relatively high incidence rates of up to 20%–54.7% with extracapsular or phacoemulsification techniques in uncomplicated cataract surgeries (Wright et al. 1988; Miyake et al. 2000). More recent studies have reported lower incidence numbers in the range of 9%–19% using fluorescein angiography (FA) after routine modern small-incision cataract surgery (Ursell et al. 1999; Mentes et al. 2003). However, the angiographic definition of PCME does not correlate well with visual acuity and relies on qualitative subjective grading of macular edema (Kraff et al. 1982; Asano et al. 2008).

More recently, determining PCME based on OCT has allowed for a more quantitative and noninvasive method of diagnosis. Incidence of PCME after small-incision phacoemulsification has been evaluated at 3%–11% but has also been reported to reach as high as 41% (Lobo et al. 2004; Ching et al. 2006; Perente et al. 2007). The definition of PCME on OCT also lacks a commonly accepted method of reporting. Wittpen et al. (2008) defined PCME on OCT by stratification into three categories (definite, probable, and possible CME) by the retina specialist's evaluation of changes in retinal thickness and contour, as well as cystoid changes. They reported definite or probable PCME in 2.4% of patients treated with prednisolone. Wang et al. (2013) reported a combined 4.2% incidence of PCME, defined as central retinal thickness of more than 250 μm and the presence of intraretinal cystoid spaces in the fovea. Kim et al. (2008) proposed a method of reporting PCME as an increase of 40% from the baseline center point thickness on OCT. They validated the ≥40% cutoff by observing cystoid changes, retinal thickness, and visual improvement after uncomplicated cataract surgery. Comparing retinal thickness to the presurgical baseline, that is, using the change in retinal thickness, adjusts for the normal variation in retinal thickness, which may be as much as 100 μm (Kim et al. 2008; Liu et al. 2011). Defining PCME as an increase in retinal thickness without requiring the observation of cystoid changes may be more objective because the latter relies on interpretation, and mild cystoid changes may not be clinically relevant (Kim et al. 2015).

Finally, the incidence of clinically significant PCME after modern phacoemulsification surgery has been estimated to be 0.1%–3.3% (Lobo et al. 2004; Henderson et al. 2007; Greenberg et al. 2011; Yonekawa et al. 2012; Grzybowski et al. 2016) in general studies including patients with and without diabetes. This is much lower than the angiographic or OCT-based incidence rates, suggesting that most patients will not have visual changes. However, beyond the method of diagnosis and definitions, there are many variables, such as risk factors in patient populations and therapeutic interventions in clinical trials, that must be interpreted when determining the overall incidence of PCME.

### 3.1.3 Predisposing Factors

Predisposing factors of PCME can be classified into demographic factors, systemic diseases, surgery-related complications, and pre-existing ocular conditions. Identifying risk factors is important for the prevention and appropriate treatment of PCME.

Diabetes mellitus is the most common systemic condition that promotes the development of PCME. It has been shown to increase the risk of CME, even in the absence of diabetic retinopathy (Pollack et al. 1992). In a large retrospective database study (n = 81,984), Chu et al. (2016) observed that diabetes, even without associated retinopathy, increased the risk of new macular edema after cataract surgery (risk ratio (RR) 1.80; 95% CI: 1.36–2.36), and the authors reported a near linear increase in risk according to the severity of retinopathy. The incidence of postoperative macular edema was 4.04% in eyes of patients with diabetes compared to a baseline risk of 1.17% in eyes of patients without diabetes or any other of the studied risk factors.

Older age and male gender have been associated with an increased risk of PCME (Chu et al. 2016). Systemic hypertension and cardiovascular disease may also increase the incidence (Flach 1998; Jain et al. 2001).

Intraoperative complications raise the risk for PCME. Posterior capsule rupture with or without vitreous loss significantly increased the relative risk of PCME (RR 2.61; 95% CI: 1.57–4.34) (Chu et al. 2016). Other surgical complications associated with the development of PCME include vitreous prolapse to the wound (Flach 1998), iris incarceration, need for early secondary YAG capsulotomy, vitrectomy for retained lens fragments (Yonekawa et al. 2012), and IOL dislocation (Yonekawa et al.

2012). The use of iris-fixated or anterior chamber IOLs, sulcus fixation of the IOL, and leaving the eye aphakic may promote the risk of PCME (Flach 1998; Cohen et al. 2006).

Pre-existing ocular conditions may predispose the eye to the development of PCME. The common factor is thought to be the increased vascular permeability associated with the breakdown of blood-retinal barrier. In eyes with prior diagnosis of uveitis among non-diabetic patients, the incidence of PCME was 3.36% and the relative risk was increased to 2.88 (95% CI: 1.50–5.51) (Chu et al. 2016). Belair el al. (2009) observed that the incidence of CME at 3 months was 8% for eyes with uveitis and, in uveitic eyes, active inflammation within 3 months before surgery increased the risk of CME (RR 6.19; $p = 0.04$).

Henderson et al. (2007) reported that a history of retinal vein occlusion, epiretinal membrane, and preoperative prostaglandin analog use were predictive of PCME in a retrospective study of 1659 surgeries. Chu et al. (2016) showed that a previous diagnosis of retinal vein occlusion, epiretinal membrane, uveitis, or retinal detachment surgery were associated with an increased risk of PCME in a database study of 81,984 surgeries. In this study, however, prostaglandin analog use, high myopia, or age-related macular degeneration did not increase the risk of PCME. The use of prostaglandin analogs among glaucoma patients may increase the risk of PCME by contributing to the postsurgical inflammation which induces blood-retinal barrier breakdown and subsequent development of macular edema (Holló et al. 2020). Evidence on the relationship of prostaglandin analogs and increased risk of PCME is not conclusive, but some studies have reported the use of topical prostaglandin analogs to be associated with higher incidence of PCME (Henderson et al. 2007; Wendel et al. 2018). There was no significant difference in the prevalence of clinical cystoid macular edema after cataract surgery between patients with and without diagnosis of glaucoma (of any type) in a retrospective study of 1253 surgeries (Law et al. 2010). However, patients with certain type of glaucoma such as pseudoexfoliative glaucoma may be at increased risk (Ilveskoski et al. 2019).

Previous surgical procedures, for example, penetrating keratoplasty and vitreoretinal surgery, have been associated with postoperative CME, which could affect the severity of PCME after cataract surgery (Flach 1998). Retinal dystrophies, such as retinitis pigmentosa and Goldmann–Favre syndrome, are also associated with macular edema, which could worsen after cataract surgery (Flach 1998).

### 3.1.4 Diagnosis

The diagnosis of clinically significant PCME includes subjective or objective worsening of vision and evidence of cystoid macular edema on fundoscopy or imaging studies. Clinical symptoms may include blurry vision, metamorphopsia, central scotoma, ocular irritation, and low-grade eye redness. Postoperative visual acuity has to be interpreted in relation to the expected BCVA, taking into account ocular comorbidities. Reduced contrast sensitivity may be an early sign of macular edema.

Clinical findings in biomicroscopy include retinal thickening and loss of the foveal depression. Intraretinal cystoid spaces, small splinter hemorrhages, or optic disc swelling may also be present. Higher magnification fundus lens and red-free light filter may assist in the detection of macular abnormalities. PCME can also be missed in slit lamp microscopy in 5–10% of cases, making imaging studies important (Tolentino et Schepens 1965).

Fluorescein angiography (FA) findings include retinal telangiectasias, capillary dilation and leakage of perifoveal capillaries in early phase frames of FA, and pooling of fluorescein in the classic "petalloid" staining pattern in late phase frames. The staining has also been described as having a "honeycomb" appearance in severe CME (Tolentino et Schepens 1965). Optic nerve staining due to capillary leakage is also commonly observed. Fluorescein angiography has been described as the gold standard in diagnosing PCME because it can also rule out other causes of CME (Yonekawa et al. 2012).

OCT has become the standard practice in diagnosing PCME. Compared to FA, OCT imaging provides a non-invasive, fast tool for imaging and allows for easier monitoring of disease progression. Retinal structural changes can be quantitatively evaluated in high-resolution cross-sectional images of the macula. PCME diagnosed with OCT has been shown to correlate with visual acuity, contrary to angiographic CME. The potential advantages of OCT angiography have also been studied in PCME. Sacconi et al. (2018) observed that patients with PCME have disruption of the parafoveal capillary arcade and cystoid spaces in the deep capillary plexus, which was partially reversible after treatment.

The differential diagnosis of PCME is extensive and includes ocular and systemic diseases. These include diabetic macular edema, retinal vein occlusion, hypertensive retinopathy, retinal dystrophies such as retinitis pigmentosa, age-related macular degeneration, and radiation retinopathy. Some of these conditions are also risk factors for PCME per se, or may present as a pre-existing conditions, which sometimes makes PCME a diagnostic challenge and also has implications for treatment.

### 3.1.5 Prevention

The prevention of PCME has been a topic of discussion for a decade (Ylinen et al. 2018). A lot of the debate has concerned the optimum treatment strategy to prevent PCME. Medical treatment strategies target the postulated mechanism for PCME pathogenesis, that is, the postsurgical inflammation. Ocular inflammatory reaction is an important protective mechanism, but it is important to manage its effect postoperatively to achieve the best outcomes. Prolonged inflammation or disruption of its regulation processes may lead to the development of postoperative complications.

Inflammation is conventionally treated with steroids or nonsteroidal anti-inflammatory drugs (NSAID). Topical administration of eye drops has been established as the first-line modality in the prevention of PCME, but several modes of delivery have been investigated, including subconjunctival, intracameral, and intravitreal dosing. Preventive strategies can also be classified according to the timing of intervention—preoperative, intraoperative and postoperative. With each anti-inflammatory pharmacological agent, ocular penetration and efficacy depend on the chemical properties of the drug and the mode of delivery. Comparing the therapeutic benefits of the preventive strategies is not straightforward because of the differences in methodology between the studies, for example, diagnostic methods and criteria for PCME.

This review of the literature will emphasize preventive treatment strategies that are more relevant to my dissertation, such as intraoperative corticosteroids.

#### 3.1.5.1 Corticosteroids

Corticosteroids reduce the production of several pro-inflammatory factors and, at the same time, increase the synthesis of anti-inflammatory agents, both of which attenuate humoral and cell-mediated immune responses (Coutinho et Chapman 2011). The response of glucocorticoids is mediated by a receptor in the cytoplasm of the cell. The activated glucocorticoid-receptor complex affects the expression of many genes by either increasing or decreasing protein synthesis in cells. Glucocorticoids inhibit phospholipase A2 synthesis, reducing the release of arachidonic acid from cell membranes. This leads to a reduction in production of both prostaglandins via the cyclooxygenase pathway and leukotrienes via the lipoxygenase pathway. Glucocorticoids also widely inhibit the function of inflammatory cells. The amount of adhesion proteins in the vascular endothelium is reduced, which slows down the migration of inflammatory cells from the bloodstream to the tissues.

Topical corticosteroids are commonly used in the prevention of PCME. However, properly controlled randomized studies comparing topical steroids to placebo are surprisingly scarce (Flach 1998). The published evidence consists of comparisons between active treatments: topical steroids have been often studied in comparison or in combination with topical NSAIDs. Two recent Cochrane reviews which evaluated topical NSAIDs and corticosteroids concluded that there is low-certainty evidence of decreased risk of cystoid macular edema with topical NSAIDs or the combination treatment compared with topical corticosteroids alone (Juthani et al. 2017), but limited evidence to suggest any important benefit on visual acuity after surgery (Lim et al. 2016).

The anti-inflammatory efficacy of each topical steroid depends on the corneal penetration and the resultant aqueous humor concentration of the drug. Prednisolone acetate 1% and dexamethasone 0.1% are common corticosteroids in postoperative use, and although dexamethasone has a greater anti-inflammatory potency compared to prednisolone acetate due to a greater binding affinity for glucocorticoid receptors, there were no differences in the efficacy between the drugs by clinical assessment or fluorophotometric findings (Diestelhorst et al. 1992).

Subconjunctival and sub-Tenon injections of corticosteroids at the end of surgery have been shown to be effective in the prevention of PCME. Dieleman et al. (2011) compared the efficacy of subconjunctival betamethasone acetate and dexamethasone eye drops in the prevention of anterior segment inflammation and macular edema. The results showed no difference in foveal thickness or clinically significant macular edema.

Kim et al. (2008) assessed the effect of sub-Tenon injection of triamcinolone on the progression of diabetic retinopathy and the incidence of PCME. They concluded that triamcinolone lowered the incidence of PCME and improved visual recovery but did not alter diabetic retinopathy progression over the 6-month follow-up. The study enrolled 46 eyes of 23 patients, and one eye of each patient was treated with intraoperative injection of triamcinolone and postoperative prednisolone acetate 1% eye drops, whereas the control eye was treated with prednisolone acetate 1% eye drops only.

Negi et al. (2006) evaluated the safety and efficacy of a 20 mg and 30 mg sub-Tenon triamcinolone injection compared to betamethasone 0.1% eye drops and reported similar improvement in visual acuity and postoperative anterior chamber flare measurements. The incidence of angiographic CME was slightly lower in the 30 mg triamcinolone group compared to the eye drops group, but the number of patients was too small to draw conclusions.

Merkoudis et al. (2014) compared 20 mg subconjunctival methylprednisolone injection with dexamethasone 0.1% eye drops and concluded that both were equally safe and effective in prevention of anterior chamber inflammation postoperatively. However, the incidence of PCME was not investigated in this study.

A recent large European multicenter trial (ESCRS Premed) investigated the additional therapeutic benefit of a subconjunctival 40 mg triamcinolone injection in addition to postoperative topical treatment with a combination of dexamethasone and bromfenac in diabetic patients. The results showed that the central subfield mean macular thickness was lower at 6 and 12 weeks postoperatively in patients who received subconjunctival triamcinolone, and none of these patients developed PCME (Wielders et al. 2018b).

There are several potential benefits for subconjunctival and sub-Tenon modes of delivery in the prevention of PCME. A subconjunctival injection of corticosteroid induces a higher intraocular concentration (Weijtens et al. 1999; Weijtens et al. 2002), which is also more rapid and sustained than topical administration. Subconjunctival injection can be an alternative to eye drops when compliance is an issue. The adherence to eye drop administration multiple times a day for several weeks after surgery can be unpredictable in the elderly cataract surgery patient population (Ylinen et al. 2018). A subconjunctival injection of triamcinolone also seems to have a long-lasting anti-inflammatory effect, as pharmacologically active triamcinolone has been identified even up to 13 months following subconjunctival injection, ranging from 3 to 13 months (Kalina et al. 1995). This can be advantageous in late onset PCME.

The use of intravitreal corticosteroids has been studied in the treatment of various types of macular edema, such as diabetic macular edema and after retinal vein occlusion, but there is a paucity of studies demonstrating the effect on the prevention of PCME. Ahmadabadi el al. (2010) demonstrated that an additional intravitreal injection of 2 mg triamcinolone at the end of cataract surgery reduced the increase of macular central 1.0 mm subfield mean thickness and PCME compared to treating only with topical betamethasone postoperatively. Study patients were diabetics and at high risk for PCME, but none (0/20) of the eyes in the intravitreal triamcinolone group developed PCME, compared to 19% (4/21) in the control group. Intravitreal injection of corticosteroid is more invasive than the subconjunctival approach, and it has been associated with endophthalmitis (Moshfeghi et al. 2003), although the risk should not noticeably differ between routine cataract surgery with or without intravitreal injection.

Intracameral injection of corticosteroid has also been studied in the treatment of postoperative inflammation after cataract surgery, but evidence on the potential effect in prevention of PCME is lacking. Karalezli el al. (2008) observed that 1 mg intracameral triamcinolone intraoperatively was effective in controlling postoperative inflammation after cataract surgery. There was no difference in postoperative visual acuity and anterior chamber cells and flare compared with 1% topical prednisolone acetate. Another study by Gungor et al. (2014) compared the results of intracameral 0.4 mg of dexamethasone and intracameral 2 mg of triamcinolone in controlling postoperative inflammation after cataract surgery. The study found that both corticosteroids were equally effective.

The most important and common adverse effect of corticosteroid treatment is an increase in intraocular pressure. Risk factors for IOP increase during corticosteroid treatment include history of open-angle glaucoma or glaucoma suspect, higher age, high myopia, type 1 diabetes, and family history of glaucoma (Kersey et Broadway 2006). IOP elevation has been associated with all methods of corticosteroid administration, including systemic, topical, subconjunctival, sub-Tenon, and intravitreal dosing. Recently, anterior migration of triamcinolone acetonide particles after posterior sub-Tenon injection for treatment of macular edema has also been reported to predispose eyes to IOP elevation (Yang et al. 2021). Steroid response has been reported to be proportional to the relative potency of the corticosteroid (Cantrill et al. 1975; Pleyer et al. 2013).

Elevation of IOP can be treated with IOP lowering drugs or with cessation of corticosteroid therapy when deemed appropriate. A potential steroid-induced IOP rise following subconjunctival corticosteroid injection can be effectively managed by surgical excision of the triamcinolone depot (Kalina et al. 1995). Intravitreally administered corticosteroids cannot be easily removed. Triamcinolone-treated eyes had an increased risk of developing mild or moderate IOP elevation in a previous clinical trial, but topical glaucoma medication reduced intraocular pressure to acceptable levels in all patients (Gillies et al. 2004). However, also medically unresponsive IOP increase has been reported to occur as late as 6 months following subconjunctival triamcinolone injection (Kalina et al. 1995). Another well-known adverse effect of corticosteroids is the progression of cataract, but discussing this topic in relation to prevention of PCME is not relevant because the conditions should be mutually exclusive. Other potential adverse effects related to corticosteroids include delayed wound healing and increased susceptibility to infection (Becker 1964).

#### 3.1.5.2 Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs reduce inflammation by inhibiting the cyclooxygenases, which are enzymes responsible for prostaglandin synthesis (Miyake et al. 2002). NSAIDs have many useful functions regarding the management of cataract surgery outcomes, as they reduce pain and photophobia, prevent intraoperative pupillary miosis, reduce inflammation, and prevent PCME (Hoffman et al. 2016).

Placebo-controlled randomized trials have shown that topical NSAIDs are effective in the prevention of PCME detected by angiography or OCT (Kim et al. 2015). However, there is there is limited evidence on long-term benefits such as NSAIDs preventing visual loss or impacting vision-related quality of life at 3 months or more after cataract surgery (Kim et al. 2015; Lim et al. 2016).

Systematic reviews and meta-analyses have compared topical NSAIDs to steroids and the combination of both with inconclusive results. A systematic review and meta-analysis by Kessel et al. (2014) found low to moderate quality of evidence that topical NSAIDs are more effective than topical steroids in controlling postoperative inflammation after cataract surgery and high-quality evidence that they are more effective in preventing PCME.

A Cochrane meta-analysis by Lim et al. (2016) concluded that topical NSAIDs may reduce the risk of developing macular edema after cataract surgery, but the benefit of NSAIDs in combination or as an alternative to topical steroids is uncertain regarding the impact on visual function or reducing poor visual outcome after cataract surgery.

A systematic review by Kim et al. (2015) stated that there is a lack of level I evidence which would support the long-term benefit of topical NSAID therapy to prevent vision loss from cystoid macular edemaCME at 3 months or morebeyond after cataract surgery.

A Cochrane meta-analysis by Juthani et al. (2017) could not conclude the equivalence or superiority of NSAIDs with or without corticosteroids compared to corticosteroids alone. The results showed low-certainty evidence that the risk of cystoid macular edema may be lower with topical NSAIDs or the combination treatment compared with topical steroids alone.

The ESCRS PREMED study 1 demonstrated that patients treated with a combination of topical bromfenac 0.09% and dexamethasone 0.1% had a lower risk for developing clinically significant macular edema within 12 weeks postoperatively than patients treated with a single drug (Wielders et al. 2018a). According to the results, the postoperative macular thickness was lower with topical bromfenac compared with topical dexamethasone, and a combination treatment could not further reduce macular thickness or improve corrected distance visual acuity compared with topical bromfenac alone.

#### 3.1.5.3 Anti-vascular Endothelial Growth Factor Therapy

The efficacy of intravitreal anti-vascular endothelial growth factor (VEGF) agents in the prevention of PCME has been studied because of the postulated role of VEGF in postoperative inflammation. In a study by Dong et al. (2015) in diabetic patients following cataract surgery, the aqueous concentration of VEGF and several other cytokines was associated with a higher incidence of macular edema, and the aqueous levels of VEGF were positively correlated with postoperative foveal center point thickness.

Chae et al. (2004) reported that 0.5 mg of intravitreal ranibizumab during cataract surgery may prevent the postoperative worsening of macular edema and may improve the final visual outcome compared to placebo in patients with stable diabetic retinopathy without significant macular edema. The results showed a lower incidence of postoperative diabetic macular edema at 1 month but not thereafter and better visual acuity improvement from baseline to 6 months after surgery. The authors did not mention any topical postoperative treatment used in addition to the bevacizumab or placebo injection.

However, the ESCRS Premed randomized controlled trial could not identify any significant effect of bevacizumab injection in addition to topical combination treatment in preventing macular thickening after cataract surgery (Wielders et al. 2018b). The study compared the efficacy of an intravitreal 1.25 mg bevacizumab injection, a subconjunctival 40 mg triamcinolone injection, or a combination of both, in addition to topical bromfenac 0.09% and dexamethasone 0.1%, to reduce the risk for developing cystoid macular edema after cataract surgery in diabetic patients.

### 3.1.6 Treatment

Treatment of PCME poses a therapeutic challenge if the prevention fails. Although many cases of macular edema can be subclinical and resolve spontaneously (Shelsta et al. 2011; Zur et Loewenstein 2017), there is a need to manage patients with PCME and visual loss effectively before the edema causes permanent damage to the macula. There are several forms of therapeutic interventions available, but no generally accepted standardized treatment. However, a stepwise treatment algorithm for PCME is often suggested.

Topical corticosteroids and NSAIDs, either as monotherapy or combined, are often suggested as a first-line treatment of PCME. Heier el al. (2000) found that in the treatment of acute, visually significant pseudophakic CME with ketorolac and prednisolone, combination therapy appears to offer benefits over monotherapy with either agent alone.

Recalcitrant PCME refractory to topical treatments can be managed with administration of corticosteroids through various other modes of delivery. Randazzo et Vinciguerra (2010) reported that five sub-Tenons' injections of 4 mg betamethasone performed at 1-week intervals reduced postsurgical macular edema, improving BCVA in a patient with chronic macular edema 18 months after cataract surgery.

Intravitreal triamcinolone has been shown to reduce chronic PCME. Behamou et al. (2003) observed a quick but transient regression of PCME after intravitreal injection of 8 mg triamcinolone acetonide. However, after 2–4 months, the edema recurred, and the effect appeared transient even after a second injection. Koutsandrea el al. (2007) reported that intravitreal triamcinolone injection in eyes with chronic PCME improved visual acuity and reduced central retinal thickness at 3 months after treatment. During 1-year follow-up, the visual acuity remained improved at 6 and 12 months compared to baseline, but at 6 and 12 months, the macular thickness did not differ from baseline.

To address the issue of the long-term efficacy of the treatment, a biodegradable intravitreal dexamethasone implant has been studied in the treatment of PCME resistant to topical medication. Belloq et al. (2015) conducted a retrospective analysis on 50 patients treated with 0.7 mg dexamethasone implant for treatment of post-surgical macular edema. They observed that the initial treatment response was good, and more than half of the patients did not present functional or anatomical recurrence during 1 year of follow-up. The patients who received a second intravitreal implant obtained a treatment response similar to that of the first injection.

Antiangiogenesis drugs are another class of therapy suggested for recalcitrant PCME. Falavarjani el al. (2012) reviewed the use of intravitreal bevacizumab for the treatment of PCME and suggested that intravireal bevacizumab injection may be considered for patients with refractory PCME unresponsive to intravitreal steroids. Bevacizumab seemed to be associated with a favorable response, but considering the low quality of evidence and usually self-limiting nature of PCME, the authors did not recommend anti-VEGF agents as routine treatment for PCME. Ranibizumab also seemed effective for the treatment of PCME in a small case series by Miropoulos et al. (2014), where seven eyes with CME were treated with intravitreal ranibizumab and followed-up monthly thereafter. BCVA and central retinal thickness were improved, and a recurrence was observed in one patient.

Carbonic anhydrase inhibitors such as acetazolamide have also been suggested in the treatment of PCME because they increase fluid resorption from the retina through the retinal pigment epithelium (Zur et Loewenstein 2017). Case reports of oral acetazolamide in the treatment of PCME have shown positive effect (Tripathi et al. 1991; Ismail et al. 2008)

Pars plana vitrectomy can be considered in eyes with chronic PCME and vitreomacular traction. Studies have shown vitrectomy is effective in chronic aphakic CME (Fung 1985) and chronic PCME with vitreous incarceration (Harbour et al. 1995). Pendergast et al. (1999) studied the benefit of vitrectomy in pseudophakic eyes with chronic CME unresponsive to medical treatment. Eyes with vitreous incarceration were excluded. Patient underwent pars plana vitrectomy on average 32 months (median 20 months) after cataract surgery. Preoperative visual acuity was 20/200, which improved to 20/60 by the final postoperative visit, and CME resolved in all eyes by biomicroscopic examination.

## 3.2 Posterior Capsule Opacification

### 3.2.1 Pathophysiology

Lens epithelial cells (LEC) that remain on the inner surface of the capsule after cataract surgery form the starting point for PCO pathogenesis. The development of posterior capsular opacification can be characterized by examining the proliferation, migration, and differentiation of these residual lens epithelial cells. This process has previously been studied by a range of experimental models, including cell cultures (Dawes et al. 2007), in vivo animal models (Behar-Cohen et al. 1995), capsular bag models (Liu et al. 1996), in vivo observations (Grewal et al. 2008), and analysis of post-mortem material (Marcantonio et al. 2000). The condition has also been described as a wound-healing response that exhibits features of fibrosis such as hyperproliferation, migration, matrix deposition, matrix contraction, and transdifferentiation into myofibroblasts (Marcantonio et Vrensen 1999; Wormstone 2002; Awasthi et al. 2009).

Proliferation of LECs begins with resilient cells remaining on the inner surface of the anterior lens capsule (Wormstone 2002). As the cells proliferate, they form a monolayer on the anterior and posterior capsular surfaces. LECs at the equator of the lens bag may form a Soemmerring's ring, which is an annular thickening of the periphery of the lens capsule (Apple et al. 1992). This structure is a closed system limited by the fusion of the anterior and posterior capsular leaflets peripheral to the IOL optic edge. Lens cells in this closed space retain their lens-like cellular structure and exhibit elongation like native lens cells (Marcantonio 2000). The LECs that migrate to the posterior capsule form a monolayer of cells that does not yet have detrimental visual consequences. However, the transition of epithelial cells to mesenchymal, myofibroblast-type cells results in cell aggregation, increased extracellular matrix deposition, cell structure swelling, and lens capsule wrinkling (Wormstone et al. 2009).

Several growth factors and inflammatory cytokines have been associated with survival, proliferation, and migration of the residual LECs. The most research data has been accumulated on the effects of transforming growth factor β (TGFβ) (Hales et al. 1994). TGFβ is believed to act as an immune regulator of the eye, and after cataract surgery, its induction causes transdifferentiation of LECs into myofibroblast cells with an alpha smooth muscle actin (αSMA) marker that gives retractile property to the cells (Saika et al. 2002; de Iongh et al. 2005; Dawes et al. 2007). These cells also secrete various types of extracellular matrix proteins such as fibronectin, collagen type I, and collagen type III, among others. Other significant known growth factors include connective tissue growth factor (CTGF) (Garrett et al. 2004), fibroblast growth factor (FGF) (McAvoy et Chamberlain 1989), epidermal growth factor (EGF) (Maidment et al. 2004), and hepatocyte growth factor (HGF) (Choi et al. 2004). Extracellular matrix components such as heparin sulphate proteoglycans (Yayon et al. 1991), proteoglycan lumican (Saika et al. 2003) and vitronectin (Linnola et al. 2003; Taliana et al. 2006) are known to be important in growth factor mediated events. Migration of LECs is enabled by integrins (Walker et Menko 2009), which are LEC transmembrane receptors that facilitate cell-extracellular matrix adhesion, and matrix metalloproteinases (MMP), which can degrade extracellular matrix proteins, remodel tissue, and process bioactive molecules (Vaughan-Thomas et al. 2000; Wong et al. 2004).

### 3.2.2 Epidemiology

Posterior capsule opacification is considered the most common later complication of cataract surgery. The development of PCO takes from months up to a few years, and historically reported incidences have varied widely between 1% and 50% (Spalton 1999; Apple et al. 2001). Studies comparing modern hydrophobic acrylic IOLs have reported a 5–35.6% incidence at 3 years and 12–24% at 5 years after cataract surgery measured by Nd:YAG rates (Buehl et al. 2005; Leydolt et al. 2013; Sundelin et al. 2014; Ursell et al. 2018). The reported incidence numbers vary according to different definitions and treatment indications for PCO, patient population characteristics, surgical techniques, IOL design and materials, and the length of follow-up. Follow-up period in most studies has been up to 3–5 years (Findl et al. 2010), and only few studies have reported longer times (Chang et al. 2013; Chang et Kugelberg 2017). Estimating the real-world long-term incidence of capsulotomy in elderly cataract surgery patients using standard survival analysis methods is also complicated by the competing risk of death, which precludes the occurrence of the event of interest (Fine et al. 1999; Andersen et al. 2012). Advancements in surgical technology appear to have decreased the incidence of PCME or at least led to a later onset of the condition.

Definitions and diagnostic methods of PCO affect the estimations of incidence. A large proportion of studies measure the incidence of PCO based on the occurrence of Nd:YAG capsulotomy. Nd:YAG capsulotomy is interpreted as a proxy variable for visually significant PCO. In a randomized study by Hayashi et al. (2001), the amount of PCO at 2 years between different IOL materials was estimated based on computer-aided scoring of Scheimpflug images, and the number of Nd:YAG capsulotomies was comparative with this score. Kobayashi et al. (2000) reported that posterior capsule opacification detected in retro-illumination imaging required capsulotomy in only about 50% of patients.

Comparing incidences between studies that measure the incidence of PCO similarly by reporting Nd:YAG rates may not be straightforward either, because the indications for Nd:YAG laser capsulotomy may differ between the studies. In prospective studies, a decrease of 2 or more lines in visual acuity and an observed posterior capsule opacity have often been defined as an indication for the Nd:YAG capsulotomy (Kobayashi et al. 2000; Hayashi et al. 2001). In retrospective studies, the indications for capsulotomy cannot be precisely defined. In a large retrospective multicenter study based on medical records, approximately 70% of patients who received PCO diagnosis required an Nd:YAG capsulotomy procedure (Ursell et al. 2018).

### 3.2.3 Predisposing and Preventive Factors

The risk factors for PCO can be generally classified as being related to the systemic or eye diseases of the patient, the surgical techniques during the cataract operation, or the properties of the implanted IOL. Recently, growing interest has emerged in studying and improving IOL biomaterials and haptic design to prevent PCO. Knowledge of the effects of IOL design on PCO is inconclusive, except for the evidence on reduced risk associated with sharp-edged versus round-edged IOLs.

#### 3.2.3.1 IOL Material

Over the decades, IOL materials have evolved from rigid polymethyl methacrylate (PMMA) to more flexible acrylic polymer and silicone materials, which are foldable and can be implanted through a smaller corneal incision. The effect of different materials on PCO formation has been studied in many experimental and clinical studies.

The suitability of the IOL material for surgical implants is evaluated in terms of biocompatibility. The term uveal biocompatibility is associated with measuring the inflammatory foreign body response of the eye against the IOL material. In general, PMMA, newer acrylic materials, and silicone are sufficiently biocompatible, but there are some differences. A study comparing biocompatibility between PMMA, silicone, and hydrophobic acrylic lenses found fewer giant cells on the surface of the hydrophobic acrylic lens (Hollick et al. 1998). Postoperatively, this giant cell macrophage foreign-body response is associated with chronic inflammation.

Capsular biocompatibility is related to the relationship between the LECs and the implanted IOL. IOL biomaterial influences the residual LECs' proliferation, migration, and transdifferentiation and thus the development of anterior capsule opacification and PCO development. A study comparing a silicone lens, two hydrophobic and one acrylic lens, found that there was the lowest presence of fibrosis of the anterior capsule and no membrane growth on the hydrophobic IOL (Tognetto et al. 2003).

IOL materials can also be described as bioactive if they have bioadhesive properties. Bioadhesive material allows the LECs to attach to both the IOL surface and the capsular bag. Effective adhesion would form a sealed sandwich structure, including the capsular bag and IOL, which can reduce LEC migration and prevent PCO (Linnola 1997). After IOL implantation, a biofilm containing proteins, such as albumin, collagen, fibronectin, and laminin, is rapidly formed on the lens surface. This IOL biomaterial-dependent protein adsorption affects its interaction and adhesion with LECs. Studies have shown that a hydrophobic acrylic lens adsorbs more fibronectin and laminin to its surface than other biomaterials (Linnola et al. 2000).

A Cochrane review (Findl et al. 2010), which assessed the interventions for preventing posterior capsule opacification in clinical studies, showed no significant differences in PCO scores between the different IOL optic materials (PMMA, hydrophilic acrylic, hydrophobic acrylic, silicone). They concluded that the interpretation of these studies was often complicated by the fact that many of the included studies were also comparing round edge IOLs with sharp edge IOLs. However, in some studies, lens material appears to be relevant. The sharp-edge hydrophobic lens was associated with a lower PCO incidence at 6 and 12 months after surgery compared to the sharp-edge PMMA lens (Shah et al. 2008). The Cochrane group also estimated that the amount of PCO appeared lower with silicone lenses and higher with hydrophilic acrylic lenses compared to the other groups (Findl et al. 2010). In their meta-analysis, the results of studies comparing hydrophilic and hydrophobic acrylic lenses were contradictory: pooled results favored hydrophobic IOL regarding PCO scores, but for YAG rates, results favored hydrophilic IOLs.

#### 3.2.3.2 IOL Design

There have been many advancements in IOL design in reducing PCO incidence. The development of PCO is associated with the proliferation, migration, and transdifferentiation of LECs. IOL design can have a particular effect on the migration step. The purpose is to create a mechanical barrier effect that inhibits LECs migration. The IOL design also affects the adhesion of the IOL and lens capsule. IOL design which allows complete fusion of the lens capsule around the IOL, prevents LEC migration (Nishi et al. 2000; Sugita et al. 2004).

Most research evidence has been established on the benefits of sharp edge optic design. A number of experimental studies have shown the benefits of the sharp posterior optics edge compared with the round edge design. Nishi et al. (2000) demonstrated that silicone and hydrophobic acrylic IOLs with sharp rectangular optic edges prevented PCO by inducing contact inhibition of migrating LECs. Oshika et al. (1998) reported that the adhesion of the IOL and lens capsule plays a role in creating a sharp capsular bend and inhibitory effect preventing lens epithelial cells from migrating.

Clinical studies comparing different IOL designs have confirmed the effective role of the sharp optic edge. The pooled results of 66 prospective randomized controlled trials in Cochrane meta-analysis supported the benefits of sharp optic edge design when assessing either PCO scores, YAG rates, or the best corrected distance visual acuity (Findl et al. 2010). Hayashi et Hayashi (2005) demonstrated that the PCO value and Nd:YAG rates were significantly less in sharp posterior edge versus rounded-edge design with an acrylic IOL of the same optic material and loops during 2 years of follow-up.

Related both to the optic edge design and IOL haptic design, the optic-haptic junction appears to be an important region where the physical barrier inhibiting LEC migration may fail. IOLs with interrupted sharp edge designs may allow LEC migration onto the posterior capsule. Nixon et al. (2010) reported significantly less PCO with a continuous 360-degree sharp-edged IOL than with a similar sharp-edged IOL that had interrupted sharp edge at the optic-haptic junction. However, contrasting results with no differences or opposite results have been obtained between continuous and interrupted sharp optic edges (Leydolt et al. 2013; Leydolt et al. 2017).

The IOL haptic-optic junction is also postulated to explain some of the differences when single-piece or multi-piece IOLs were used. The thin haptics of 3-piece IOLs may enable a more uniform fusion between the anterior and posterior capsules. The bulky size of the 1-piece lens haptic may prevent this ‘‘shrink wrap’’ effect, especially at the haptic-optic junction. Study results comparing 1-piece and 3-piece IOLs have been equivocal. Zemaitiene et al. (2007) compared a 1-piece IOL and a 3-piece IOL with similar acrylic hydrophobic material and reported lower PCO values with the 1-piece IOL during the 1st postoperative year, but there were no significant differences in anterior capsule opacification and PCO development at 2 years postoperatively. A randomized trial by Nejima et al. (2004) reported no significant differences between 1-piece and 3-piece hydrophobic acrylic IOLs in the degree of posterior capsule opacification. A case series of acrylic 1-piece and 3-piece IOLs by Bender et al. (2004) showed no evidence of a difference between the IOLs, which were otherwise matched for material and lens geometry.

Despite the advances in IOL design in preventing LEC migration, there is evidence that the mechanical barrier effect of IOL edge and haptic design may be overrun with time (Schartmüller et al. 2019). The physical barrier of sharp optic edge may fail after Soemmering's ring formation at the capsule periphery (Fişuş et Findl 2020)

#### 3.2.3.3 Inflammation and Medical Prophylaxis

Surgical tissue trauma associated with cataract surgery and a foreign body response against the implanted IOL trigger an inflammatory process that eventually leads to posterior capsular opacification (Nibourg et al. 2015). Inflammatory mediators and pathways induce the activation of residual LECs, which includes proliferation, migration, and transdifferation of the cells from epithelial to mesenchymal cells (Wormstone et al. 2009). Because posterior capsule opacification is the result of an inflammatory process, the use of anti-inflammatory and immunomodulatory drugs has the potential to prevent or reduce posterior capsule opacification.

Various pharmacological agents, including anti-proliferative, anti-inflammatory, and apoptosis-inducing agents, have been studied in the prevention of posterior capsule opacification (Meacock et al. 2000; Rękas et al. 2012 Maedel et al. 2013; Joshi et Hussain 2017). Most of the agents have been studied using in vitro cell cultures, animal models, or ex vivo tissue cultures, such as human lens capsules (Wormstone et Eldred 2016). However, the use of many agents found to be promising in preclinical studies is limited by the potential toxic effects on other ocular tissues.

Agents that have progressed to clinical trials include immunotoxin MDX-RA, anticoagulant heparin, hypo-osmotic deionized water, and trypan blue. Patients receiving the immunotoxin MDX-RA intracamerally at the time of surgery had a lower PCO score at 1 year than those in the placebo group (Meacock et al. 2000). MDX-RA is an immunoconjugate in which the ricin A toxin is attached to a monoclonal antihuman LEC antibody. Heparin-coated IOLs have been studied due to promising results obtained in the eyes of rabbits, but in a randomized, small human study, there was no difference in the amount of postoperative inflammation and PCO between the groups (Maedel et al. 2013). Rinsing the capsular bag during surgery for three minutes with deionized water using the sealed-capsule irrigation technique reduced the amount of PCO at two-year follow-up in a randomized clinical trial (Rękas et al. 2012). Hypo-osmotic deionized water causes swelling of LEC cells and subsequent cell membrane damage. Capsular bag irrigation with trypan blue reduced PCO scores at 6 months in a randomized study, but there were no differences between study groups after 36 months (Joshi et Hussain 2017).

The effect of postoperative topical anti-inflammatory medication has also been studied in PCO prevention. Dexamethasone had no significant effect compared to placebo in two randomized studies based on the number of Nd:YAG capsulotomies and retroillumination imaging (Laurell et Zetterström 2002; Zaczek et al. 2004). Topical diclofenac also did not show a significant benefit over placebo in the above studies. No significant differences were observed between dexamethasone and diclofenac in two randomized studies (Barequet et al. 2002; Zaczek et al. 2004). The duration of topical postoperative anti-inflammatory medication in the above studies was 3–4 weeks, which can be considered as the standard duration for postoperative treatment. It is a relatively short treatment time in relation to the slow process of capsular opacification formation. However, in a randomized study comparing topical treatment with betamethasone and diclofenac used for 3 months postoperatively, the number of Nd:YAG capsulotomies at 3 years was 11.5% in the diclofenac group and 17.6% in the betamethasone group ($p = 0.8375$), with no difference between groups in terms of YAG rate or Scheimpflug imaging (Tsuchiya 2003). In a recent retrospective cohort study by Hecht et al. (2020), treatment with topical steroids resulted in significantly lower Nd:YAG capsulotomy rates compared to NSAIDs. Combination therapy with steroids and NSAIDs showed no additional benefit in their study.

Medical treatment has the potential to influence the inflammatory process, which leads to the development of PCO, but so far, the research results have been equivocal. There are too few evidence-based studies up to now, and not enough is understood about the effect of anti-inflammatory drugs on LECs to provide therapeutic benefits for cataract surgery patients.

#### 3.2.3.4 Surgical Technique

Some surgical methods have been studied in the prevention of PCO. PCO is a regenerative process of surviving LECs, so surgical techniques for removing as many LECs as possible are helpful to an extent to slow down the development of PCO. However, near 100% removal of the LECs may be necessary to prevent a resilient PCO response.

Continuous curvilinear capsulorhexis may reduce the amount of PCO (Birinci et al. 1999). However, there is no clear evidence on whether the capsulorhexis diameter or the overlap of the IOL and anterior capsule affects posterior capsule opacification. A large capsulorhexis with no overlap may delay PCO by the fusion of the anterior and posterior capsules (Raj et al. 2007). This creates a closed space at the equatorial capsule, which could prevent LECs migration. However, it has also been postulated that a capsulorhexis smaller than the IOL optic, which creates anterior capsule overlap on the optic, would allow adhesion between the two and decrease LECs migration (Aykan et al. 2003). Anterior capsule overlap is thought to be important in the formation of the ”shrink wrap” effect of the capsular bag and IOL, and in contributing to the physical barrier effect of an IOL optic edge (Apple 2000). Clinical studies have reported mixed results. Ravalico et al. (1996) reported that a smaller capsulorhexis with the free edge located on the IOL optic for 360 degrees reduced the incidence of PCO compared to a larger capsulorhexis with the free edge located partially or totally peripherally to the IOL optic. On the other hand, Hayashi et al. (2004) observed that there was no correlation between the size of the anterior capsule opening area 1 day after surgery and the degree of PCO 1 year after surgery.

Hydrodissection has been demonstrated to be an effective means to remove equatorial LECs (Peng et al. 2000). Vasavada et al. (2006) also investigated whether cortical hydrodissection performed in multiple quadrants would reduce the incidence of PCO, and although there was no difference at 4 years, the area of the central posterior capsule involved by PCO was significantly lower in eyes that had multiquadrant hydrodissection than in those that did not. Hydrodissection combined with rotation of the implanted IOL was observed to remove significantly more LECs and residual cortical fibers from the equatorial zone of the capsular bag (Vasavada et al. 2006). With the purpose of enhancing cortical cleanup, the efficacy and safety of a sealed capsule irrigation device was investigated by Rabsilber et al. (2007); however, using distilled water irrigation, it was not possible to reduce PCO development significantly. Bimanual irrigation and aspiration can also be helpful in the thorough removal of residual cortical fibers (Vasavada et al. 2009).

Polishing of the anterior capsule may prevent capsulorhexis aperture contraction, but study results on the effect of this on reducing PCO are mixed. Liu et al. (2010) observed in an experimental study of human cadaver eyes that although anterior capsular polishing removed many LECs, it did not decrease residual cell growth but actually enhanced cell proliferation. They concluded that this may explain why polishing does not reduce PCO in some clinical studies. Menapace et al. (2006) reported in their 3-year clinical trial that polishing the anterior capsule was effective in reducing fibrotic opacification but ineffective in reducing regenerative opacification.

In-the-bag placement of IOLs has been shown to reduce PCO compared to sulcus placement (Martin et al. 1992). In-the-bag fixation enhances the barrier effect of the capsular bend at the IOL optic edge (Peng et al. 2000). More advanced IOL fixation techniques, such as posterior optic buttonholing through a primary posterior capsulorhexis, may prevent PCO altogether, as this precludes the LECs from accessing the posterior surface of IOL optic (Menapace 2006). Another technique combined with a posterior capsulorhexis, the bag-in-the-lens principle, has been shown to prevent LEC proliferation (Tassignon et al. 2002). Devices such as a capsular bending ring with rectangular cross-section and sharp edges have been studied in PCO prevention. Menapace et al. (2008) reported that ring implantation, adjunct to a standard in-the-bag IOL implantation, was effective in reducing PCO scores 3 years postoperatively.

### 3.2.4 Diagnosis

The symptoms of PCO include decreased and blurred vision, glare, light sensitivity, and halos around lights. Studies have shown that PCO decreases visual acuity and contrast sensitivity and increases glare disability. These measures of visual function correlate with the degree of PCO, and after laser capsulotomy, all of them improve significantly (Claesson et al. 1994; Tan et al. 1999). Mango et al. (1997) showed improvement of visual acuity, contrast sensitivity, and glare disability measurements after Nd:YAG capsulotomy using the ETDRS chart, Pelli-Robson contrast sensitivity chart, and Brightness Acuity Tester as test methods. PCO, especially within the central 3 mm zone, affects visual function in terms of high- and low-contrast visual acuity, contrast sensitivity, and forward light scatter (Meacock et al. 2003). A study assessing the benefit of Nd:YAG laser capsulotomy in eyes with a healthy macula or dry age-related macular degeneration showed that macular sensitivity is also negatively affected by PCO and improves after laser treatment (Varga et al. 2008).

Visual acuity correlates most closely with PCO score and therefore reflects most accurately the degree of PCO. Hayashi et al. (2003) reported that before Nd:YAG capsulotomy, all the visual functions mentioned above correlated significantly with the degree of PCO, but visual acuity had the strongest correlation. However, it has been postulated that some patients with early stages of PCO may have impaired contrast sensitivity or glare disability despite having good visual acuity. Accordingly, Hayashi et al. (2003) studied a group of patients having visual acuity of 20/25 or better before Nd:YAG capsulotomy. However, the authors reported that contrast sensitivity and glare sensitivity did not correlate with the PCO value before or after capsulotomy. After Nd:YAG capsulotomy, visual acuity and PCO values improved significantly, but contrast sensitivity and glare sensitivity did not show significant improvement. They concluded that high-contrast visual acuity is therefore the most relevant outcome measure.

There are several methods for PCO diagnosis and quantification. In clinical practice, the diagnosis of PCO is usually made during slit lamp microscope examination. For research purposes, however, there are several ways to assess PCO. Comparing Nd:YAG capsulotomy rates in clinical studies is an indirect measure for PCO, but permits a larger sample size than prospective studies directly assessing PCO severity. It is also more cost-effective and provides a functional indicator of morbidity related to PCO. However, it may be affected by local healthcare treatment practices and the patient's subjective perception.

Direct assessment of PCO on imaging allows quantification of the area and severity of opacification. Subjectively graded slit lamp-acquired retro-illumination images were used to study PCO before the advent of digitally acquired retro-illumination photography (Harris et al. 1993). Digital images provided excellent image quality and enabled the development of automated quantification of PCO with new software systems. Software systems for the analysis of retro-illumination PCO images include, for example, Evaluation of Posterior Capsule Opacification (EPCO) computer-aided scoring system (Tetz et al. 1997), Automated Quantification of After-Cataract (AQUA) automated PCO analysis program (Findl et al. 2003), Open-access Systematic Capsule Assessment (OSCA) automatic image-analysis system (Aslam et al. 2006), and POCOman software for semiobjective assessment of percentage area and severity score of PCO (Barman et al. 2000).

The Scheimpflug video photography technique can also be used as an alternative to retro-illumination images. Scheimpflug camera measures reflected light, light scatter density from intraocular structures, instead of standard retro-illumination images (Lasa et al. 1995). However, IOL material affects the light density measurements, and IOLs with different materials cannot be directly compared (Tanaka et al. 2004).

Optical coherence tomography imaging can also facilitate PCO assessment. An early OCT system was reported to quantitate PCO and discriminate between different types of PCO (Moreno-Montañés et al. 2005). An ultrahigh-resolution OCT system was demonstrated to be a powerful tool in anterior segment imaging and evaluation of the capacity of IOL materials and designs to induce capsular bag adhesion (Linnola et al. 2005).

### 3.2.5 Treatment

The treatment of PCO in adults is implemented by creating an opening in the posterior lens capsule with Nd:YAG laser capsulotomy, thus clearing the visual axis. Occasionally the treatment may be carried out by a surgical intervention such as posterior capsule scraping. Indications for treatment include decreased visual acuity and a decrease in other measures of visual function caused by PCO. Patient's functional impairment related to vision loss, referring to limitations due to the illness in certain functions in their daily lives, has to be taken into account (Sundelin et al. 2005). Accordingly, bilateral PCO has a significant adverse impact, but unilateral PCO can also reduce binocularity and stereopsis, which may increase the incidence of falling and traffic accidents. The subjective discomfort due to visual symptoms and the decrease in patient satisfaction related to losing vision again after recovering from cataract surgery need to be addressed. The risk to benefit ratio of Nd:YAG capsulotomy has to be evaluated in the presence of associated risk factors such as high myopia, high risk CME, or history of retinal detachment (Vasavada et al. 2014). In specific circumstances, such as in patients with multifocal IOLs, the timing and indications of treatment, such as positive or negative dysphotopsias, need to be carefully considered (Salerno et al. 2017). After opening the posterior capsule, a potential later IOL exchange procedure becomes more difficult to perform.

Determining the appropriate size and site of posterior capsule opening may be challenging (Raj et al. 2007). Optimal size for posterior capsulotomy depends on considering the optical and mechanical effects induced by the capsular opening (Holladay et al. 1985). Optical effects may include increased diffraction of light through the capsular opening, leading to reduced image quality on the retina and increased glare. Mechanical effects may include a shift in the IOL position after capsulotomy and a refractive hyperopic shift (Karahan et al. 2014). In a rare case, the IOL may also be significantly dislocated after the procedure (Petersen et al. 2000). Holladay et al. (1985) suggested that the optimal size for capsular opening should be equal to the scotopic pupil diameter to avoid glare and other optical aberrations. In their case series, the average scotopic pupillary diameter following cataract surgery was 3.9 mm.

The Nd:YAG capsulotomy procedure is generally very safe, but it is associated with a risk of complications such as IOL damage or dislocation, transient rise in intraocular pressure, cystic macular edema, iris hemorrhage, corneal edema, corneal endothelial cell loss, and retinal tears and detachment. Newland el al. (1999) demonstrated that the damage threshold of the Nd:YAG laser on IOLs depends on the IOL material, and that silicone IOLs are more susceptible to damage than acrylic and PMMA IOLs. IOL dislocation is a rare event, but case reports are available (Petersen 2000; Nghiem-Buffet et al. 2001). A late IOL dislocation after Nd:YAG capsulotomy may be aided by myofibroblast activation and capsular contraction after the procedure. Migliori et al. (1987) reported a statistically significant mean rise in IOP of +0.8 ± 5.15 mmHg in placebo-treated group in comparison with a -3.2 ± 4.83 mmHg decrease in the timolol-pretreated group one hour after laser capsulotomy. Pretreating with timolol did not prevent late pressure rises. The risk of retinal detachment has been previously estimated at 0.01–3.6% (Coonan et al. 1985; Durham et Gills 1986; Powell et al. 1995; Ranta et al. 2004), but recently lower estimations have been reported. Wesolosky et al. (2017) described an increased risk for retinal detachment in the first 5 months after Nd:YAG. The rate of retinal tear after Nd:YAG capsulotomy at 5 months was 0.29%, and the rate of retinal detachment was 0.87%. There-after, the risk for retinal detachment returned to the baseline plateau. However, some patient groups, especially high myopes, are probably at higher risk (Koch et al. 1989).

PCO and laser capsulotomy also place an economic burden on health services and society. In addition to the direct costs of the Nd:YAG procedure and associated additional consultation visit costs, indirect costs can incur from the lowered functional vision of the patient, which may increase the incidence of accidents, laser capsulotomy complications, and the time and effort required by the treatment for the patient and caregivers (Cullin et al. 2014; Aaronson et al. 2019).

# 4 Aims of the Study

The purpose of this study was to explore and develop the treatment and prevention of complications after cataract surgery. The specific aims of each study were as follows:

I to compare the efficacy, safety, and tolerability of subconjunctival injection of triamcinolone acetonide with topical dexamethasone eye drops for the prevention of inflammation and macular edema after cataract surgery

II to evaluate the real-world cumulative incidence and risk factors of Nd:YAG capsulotomy

III to assess the risk of Nd:YAG capsulotomy in association to the diopter power of the implanted IOL

IV to explore the potential for improving the Nd:YAG treatment process with help of the Lean methodology

# 5 Materials and Methods

## 5.1 Study Design and Subjects

### 5.1.1 Study I

Subconjunctival injection of triamcinolone acetonide was compared with topical dexamethasone drops for the prevention of macular edema and ocular inflammation after cataract surgery in a prospective non-randomized controlled clinical trial.

Eligible to this study were patients aged 60–90 years having a cataract that met the indications for surgery according to the Current Care Guidelines of Cataracts by the Finnish Medical Society Duodecim (2019). All patients were operated on at the Ophthalmology Unit of Kymenlaakso Central Hospital, Kotka, Finland.

Exclusion criteria included intraoperative complication during the cataract surgery, prior or active wet age-related macular degeneration, retinal vein/artery occlusion, retinal detachment, retinal necrosis, uveitis, endophthalmitis, vitreous hemorrhage, retinal phlebitis or optic neuritis, myopia above 6 diopters, previous intraocular procedures, diabetes mellitus, a history of elevated intracranial pressure, alcohol abuse, thyroid disease with abnormal thyroid stimulating hormone levels, continuous use of anti-inflammatory or immunomodulatory drugs, known or suspected sensitivity to any of the medications used in the operation or postoperatively, and inability to use topical steroid drops as prescribed.

The study period began in April 2017 and ended in October 2017. Within this period, 109 eyes of 103 patients were enrolled for the study according to the eligibility criteria. Eyes were assigned an equal allocation ratio in the dexamethasone group (52 eyes of 50 patients) receiving postoperative topical dexamethasone eye drops, and in the triamcinolone group (57 eyes of 53 patients) receiving a perioperative subconjunctival injection of triamcinolone acetonide suspension. Only one randomly selected eye from each simultaneous bilateral surgery was included in the analysis. Two eyes were lost during follow-up in the triamcinolone group, where one patient withdrew consent and discontinued follow-up visits, and another one was lost to the follow-up. Eventually, 50 eyes of 50 patients remained in the dexamethasone group, and 51 eyes of 51 patients remained in the triamcinolone group.

### 5.1.2 Study II

The cumulative incidence of Nd:YAG laser capsulotomy was evaluated in a retrospective cohort study. Patients who had phacoemulsification cataract surgery and in-the-bag implantation of a ZCB00 (Abbott Medical Optics Johnson & Johnson Vision, Inc., Abbott Park, Illinois, USA), a SN60WF (Alcon Laboratories, Inc., Fort Worth, Texas, USA), and a ZA9003 (Abbott Medical Optics Johnson & Johnson Vision, Inc., Abbott Park, Illinois, USA) IOL were eligible to participate in this study. All patients were operated on at the Ophthalmology Unit of Kymenlaakso Central Hospital, Kotka, Finland.

The study period began on September 3, 2007, and ended on September 15, 2016. Within this period, a total of 17,691 eyes underwent cataract surgery. Only one eye of each patient having cataract surgery was included in the study. In all, 10,044 eyes were included in the study according to the inclusion criteria.

### 5.1.3 Study III

The cumulative probability of Nd:YAG laser capsulotomy was estimated in a retrospective cohort study. Eyes of patients who had phacoemulsification cataract surgery and in-the-bag implantation of a ZCB00 or an equivalent preloaded version PCB00, an SN60WF, or a preloaded AU00T0 (Alcon Laboratories, Inc., Fort Worth, Texas, USA), and a ZA9003 IOL were eligible to participate in this study. All eyes were operated on at the Ophthalmology Unit of Kymenlaakso Central Hospital, Kotka, Finland.

The study period began on September 3, 2007, and ended on September 15, 2016. Within this period, a total of 17,691 eyes underwent cataract surgery. In all, 15,375 eyes were included in the study according to the inclusion criteria.

### 5.1.4 Study IV

The Nd:YAG laser capsulotomy treatment protocol was improved by a Lean-oriented quality improvement process and then compared with the previous conventional treatment protocol in a non-randomized controlled trial. The research setting was the Ophthalmology Unit of Kymenlaakso Central Hospital, Kotka, Finland.

The study period began in February 2015 and ended in August 2016. After implementing the improved treatment protocol, a total of 206 Nd:YAG laser capsulotomy procedures were evaluated, where the Lean-oriented treatment protocol was utilized in 158 of the procedures and the conventional treatment protocol was followed in 48 of the procedures.

## 5.2 Interventions and Exposures

### 5.2.1 Study I

Patients in the dexamethasone group received postoperative treatment with topical dexamethasone (1 mg/ml, Oftan Dexa; Santen Oy, Tampere, Finland) eye drops three times a day for a postoperative period of 3 weeks. Patients in the triamcinolone group received a single subconjunctival 0.5 ml injection of triamcinolone acetonide suspension (40 mg/ml, Triesence; Novartis, Basel, Switzerland) at the end of the surgery.

**Surgical Technique.** Phacoemulsification technique was used in all cataract surgeries. A 2.75 mm clear cornea incision was followed by capsulorhexis, phacoemulsification, and IOL implantation into the capsular bag. An Ozil phacoemulsification handpiece and a 0.9 mm 30-degree beveled Kelman tip were used in the phacoemulsification system (Infiniti; Alcon Laboratories, Inc., Fort Worth, Texas, USA). Anesthesia was topical in all surgeries. Hyaluronic acid 1.6%–chondroitin sulfate 4.0% (DisCoVisc; Alcon Laboratories, Inc., Fort Worth, Texas, USA)) was used as an ophthalmic viscosurgical device. Preloaded AU00T0 and PCB00 IOLs were used. Patients in the triamcinolone group received a 0.5 ml subconjunctival triamcinolone suspension injection with a 23G needle at the end of surgery in the inferior part of the bulbar conjunctiva. All patients received 1 mg of intracameral cefuroxime (Aprokam; Laboratoires Thea, Clermont-Ferrand, France) antibiotic prophylaxis at the end of surgery. None of the patients received postoperative topical antibiotic prophylaxis.

### 5.2.2 Study II

The patients enrolled in the study underwent phacoemulsification cataract surgery and implantation of an intraocular lens implant.

**IOL Implantation.** During the cataract surgery, patients were implanted with ZCB00, SN60WF, or ZA9003 IOLs (Table 1). All included IOLs had monofocal, hydrophobic, aspheric, 1- or 3-piece acrylic material and design.

**Table 1.** Intraocular lens characteristics

| IOL model | ZCB00/PCB00 | SN60WF/AU00T0 | ZA9003 |
|---|---|---|---|
| Optic material | Hydrophobic acrylic | Hydrophobic acrylic | Hydrophobic acrylic |
| Haptic material | Hydrophobic acrylic | Hydrophobic acrylic | Polymethylmethacrylate |
| Haptic design | 1-piece | 1-piece | 3-piece |
| Posterior edge design | 360 sharp | Non-360 sharp | 360 sharp |
| Optic diameter (mm) | 6.0 | 6.0 | 6.0 |
| Overall diameter (mm) | 13.0 | 13.0 | 13.0 |
| Haptic angulation | 0 | 0 | 5 |
| Refractive index | 1.47 | 1.55 | 1.47 |

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### 5.2.3 Study III

The patients enrolled in the study underwent phacoemulsification cataract surgery and implantation of an intraocular lens implant. Patients were implanted with similar types of monofocal, hydrophobic, aspheric, 1- or 3-piece acrylic IOLs as in Study I, but the preloaded counterparts of ZCB00 and SN60WF IOLs, respectively, PCB00, and AU00T0, were also included in the study (Table 1).

### 5.2.4 Study IV

The efficiency of the treatment protocol for Nd:YAG laser capsulotomy was improved by implementing the principles of the Lean methodology. Predetermined quality targets were a patient-oriented and patient-safe approach and the development of a clinical care process with purposeful use of competences. The improved protocol also aimed at standardizing the tasks of each employee to improve the quality and safety of the treatment and to reduce waiting times.

**Streamlined Treatment Protocol.** The improved treatment protocol includes standardized steps for the treatment process and specific tasks for the employees, which aim at making the process faster and safer (Table 2).

**Table 2.** Description of the lean-oriented treatment model

| |
|---|
| **Department secretary** |
| Sends a letter of invitation with informative description of the treatment protocol to the patient |
| Logs and bills the patient visit |
| **Nurse I** |
| Receives checked-in patient in the hallway and escorts him/her to the waiting lobby for preparation |
| Interviews the patient, including questions of drug allergies |
| Color codes the laterality of the procedure |
| **Nurse II** |
| Administers preoperative eye drops and attends to other necessary preparations |
| Instructs the patient about the procedure |
| Escorts the patient to the operating room and positions him/her to the operating device |
| **Nurse III** |
| Logs an entry to the patient's medical record using standard phrases |
| Checks that the patient's medication record is in accordance with the prescriptions |
| **Nurses II and IV** |
| After surgery, escorts the patient out of the operation room |
| Administers postoperative eye drops |
| Maintains the patient care equipment, for example, cleaning the lenses |
| Controls intraocular pressure by rebound tonometry |
| Ensures possible follow-up examinations upon discharge |
| Discharges the patient |
| **Operating physician** |
| Uses a checklist |
| -reads the referral |
| -confirms the patient's identity |
| -confirms the laterality of the eye from the patient |
| Evaluates the anterior segment and lens status with a YAG-laser biomicroscope |
| Discusses about the procedure with the patient when necessary |
| Performs the procedure |
| Ensures that the follow-up care instructions are clear and that there are no unanswered questions |

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## 5.3 Data Collection

### 5.3.1 Study I

**Baseline Evaluation.** The clinical parameters recorded at baseline were demographic and surgical characteristics, which included patient's age, sex, laterality of the eye, glaucoma history, smoking history, signs of pseudoexfoliation syndrome, duration of the surgery, cumulative dissipated energy during the phacoemulsification, and the use of a pupil expansion device.

**Follow-up Evaluation.** Patients were examined preoperatively and reviewed 7, 28, and 90 days after the surgery. Preoperative visual acuity was measured by the referring ophthalmologist on a Snellen chart and postoperatively by a trained research technician with an auto-refractometer (AR-1s; NIDEK Co. Ltd., Aichi, Japan). Intraocular pressure was measured with rebound tonometry (iCare tonometer, Revenio Group, Vantaa, Finland). Aqueous flare was measured with a laser flare meter (FM-600; Kowa Company, Ltd., Nagoya, Japan) to assess ocular inflammatory activity. The mean of five reliable measurements was used in the analysis. Central retinal thickness was evaluated with spectral-domain optical coherence tomography (HEIDELBERG EYE EXPLORER Version 1.9.10.0 and HRA/SPECTRALIS Viewing Module Version 6.0.9.0; Heidelberg Engineering GmbH, Heidelberg, Germany). Follow-up 30-frame spectral-domain OCT scans were performed with AUTORESCAN software (Heidelberg Engineering GmbH, Heidelberg, Germany). All patients received a structured home questionnaire on the day of surgery and were instructed how to fill it out by a research technician. Regularity of eye drop use (in the dexamethasone eye drops group), the date of eye redness cessation, the date of irritation symptom cessation, and the overall satisfaction of the patients were recorded. Ocular/systemic adverse events or suspected unexpected serious adverse reactions (SUSAR) were recorded.

### 5.3.2 Study II

Data recorded within electronic medical records between September 3, 2007 and September 15, 2016 were extracted for all patients undergoing phacoemulsification cataract surgery and Nd:YAG laser posterior capsulotomy. Interventional codes for cataract surgery and Nd:YAG laser posterior capsulotomy enabled the identification of patients undergoing the procedures. The length of follow-up for each eye was until 5 years after cataract surgery or until the end of the study period. Clinical parameters recorded at baseline were demographic and surgical characteristics, which included the patient’s age, sex, type of IOL, dioptric power of IOL, narrative operative report, and the operating surgeon. Information on a record of death from the Finnish Digital and Population Data Services Agency was combined with the follow-up of the patient.

### 5.3.3 Study IIII

Patients undergoing phacoemulsification cataract surgery and Nd:YAG laser posterior capsulotomy between September 3, 2007 and September 15, 2016 were identified within the electronic medical records system using the interventional codes for cataract surgery and Nd:YAG laser posterior capsulotomy. The length of follow-up for each eye was until 5 years after cataract surgery or until the end of the study period. Clinical parameters recorded at baseline were demographic and surgical characteristics, which included the patient's age, sex, type of IOL, dioptric power of IOL, narrative operative report, and the operating surgeon.

### 5.3.4 Study IV

**Baseline Evaluation.** Data recorded within electronic medical records regarding clinical parameters recorded at baseline were demographic and surgical characteristics, including patient's age, sex, laterality of the eye, the preoperative BCVA, date of the cataract surgery, duration of the cataract surgery, and the axial length of the eye.

**Follow-up Evaluation.** Follow-up data was prospectively collected and included measurements of the time spent on each step of the Nd:YAG laser capsulotomy visit, that is, preoperative arrangements, laser treatment, postoperative arrangements, and during switching the patients. The time measurements were clocked by a research assistant or nurses working at the unit. Patient satisfaction was assessed with a 6-step survey that was filled out by the patient after the operation. Patients were assisted by their relatives/escorts or the nurses if necessary. The questionnaire included questions regarding satisfaction with the invitation letter, waiting time during the whole process, the laser posterior capsulotomy procedure itself, instructions given after treatment, the process of discharge from the unit, and personal clinical encounters with the healthcare professionals, which were semi-quantitatively graded by the patient from 1 to 3.

## 5.4 Outcomes and Definitions

### 5.4.1 Study I

Evaluation was based on the efficacy, safety and tolerability criteria. The primary efficacy variables were aqueous flare and CRT. The safety variables were IOP and CDVA, subjective recovery from surgery, and adverse events under clinical examination.

**Central Retinal Thickness.** CRT was defined as the mean macular thickness in the central 1.0 mm area in the OCT image.

**Pseudophakic Cystoid Macular Edema.** PCME was defined as central subfield macular thickening with cystoid changes on OCT in combination with a decrease in expected corrected distance visual acuity (CDVA; both CDVA gain below 0.4 decimals from baseline and postoperative CDVA below 0.8 decimals) at any postoperative visit.

**Current Care Guidelines of Cataracts by the Finnish Medical Society Duodecim (2019).** Indications for surgery: cataract dependent difficulties in everyday life, in addition with a BCVA ≤ 0.5 (6/12) measured on the Snellen scale in the better-seeing eye, or BCVA ≤ 0.3 (6/18) in the worse-seeing eye. Surgery is also indicated in the following circumstances regardless of the measured BCVA: if a posterior subcapsular cataract causes vision-dependent difficulties in everyday life; if there is symptomatic anisometropia after surgery of the first eye (>2D); if cataract complicates the follow-up of another eye disease, such as diabetic retinopathy or glaucoma.

### 5.4.2 Study II

The study outcomes included the estimate of the overall cumulative incidence of Nd:YAG capsulotomy, cumulative incidence according to the type of IOL, and the assessment of survival during the follow-up period. The study also included the analysis of other potential risk factors associated with Nd:YAG capsulotomy.

**Interventional Codes.** CJE20 for phacoemulsification cataract surgery with implantation of artificial lens in posterior chamber; CJB10 for Nd:YAG laser posterior capsulotomy.

### 5.4.3 Study III

The study outcome was an estimate of the cumulative probability of Nd:YAG capsulotomy according to the diopter power of implanted IOL. Study also included the analysis of potential confounding factors associated with this relationship.

**Low-diopter IOL.** Low-diopter IOL group cut-off at 16.5 diopters was defined according to an SRK II estimation of the IOL power required in eyes with an axial length ≥25.2 mm (threshold for applying Wang-Koch adjustment in myopic eyes) and average corneal curvature.

**Interventional Codes.** CJE20 for phacoemulsification cataract surgery with implantation of artificial lens in posterior chamber; CJB10 for Nd:YAG laser posterior capsulotomy.

### 5.4.4 Study IV

The study outcomes included the assessment of value-adding factors and inefficiencies in the conventional Nd:YAG capsulotomy treatment protocol, and the evaluation of the efficiency of the improved treatment protocol according to lead times, per hour rate of patients and eyes treated, purposeful use of physician's work time, and patient satisfaction.

**Patient Satisfaction.** Survey result overall grade was categorized as poor (6–12), satisfactory (13–15), good (16–17), and excellent (18).

## 5.5 Statistical Analysis

The data were analyzed with Stata statistical software (version 13.0, StataCorp, College Station, TX, USA) with the STCRPREP Stata module (Lambert 2015) and IBM SPSS 23 statistical software (SPSS Inc, Somers, NY, USA). Descriptive statistics are given as a mean with a standard deviation for continuous variables and frequencies with proportions for categorical variables.

Competing risk survival analysis was used to estimate the cumulative incidence of Nd:YAG laser capsulotomy in Study II. Competing risks methodology estimates time-to-event outcomes such as cumulative incidence more accurately than the Kaplan–Meier method in a setting with frequent competing risks such as death in the elderly cataract surgery population. Competing risks regression modeling, according to the method of Fine and Gray (1999), was used to identify the potential risk factors for Nd:YAG laser capsulotomy.

Kaplan–Meier survival analysis was used to estimate the cumulative probability of Nd:YAG laser capsulotomy in Study III, where studying the effect of competing risks was not as relevant for the aim of the study. Cox proportional hazards regression modeling was used to assess the effect of the dioptric power of implanted IOLs on the probability of an Nd:YAG laser capsulotomy event and account for the effect of possible confounding factors.

The sample size estimation in Study I was based on the study hypothesis that the subconjunctival triamcinolone injection is non-inferior to topical dexamethasone in preventing intraocular inflammation and macular edema 28 days after cataract surgery. The non-inferiority margin was 10 photons/ms aqueous flare difference or 20 μm CRT difference between the groups. The sample size needed to be at least 28 + 28 patients (aqueous flare) and 38 + 38 patients (CRT) to provide a test power of 80%. Significance level was set at 5%. Assuming a 10% dropout rate required us to enroll 35 + 35 patients (aqueous flare) and 48 + 48 patients (CRT).

For two-group comparisons, the unpaired Student's t-test (between groups) and the paired t-test (within groups) were used to compare continuous and normally distributed data, and the Wilcoxon rank-sum (Mann–Whitney U-test) test (between groups) and Wilcoxon signed-rank test (within groups) were used to compare non-parametric data. Clinical parameter distributions were tested for normality by the Shapiro-Wilk test. For multiple group comparisons, the one-way ANOVA F-test was used to compare continuous and normally distributed data. Post-hoc comparisons among diopter groups in Study III were performed with ANOVA pairwise comparisons for the age variable and by identifying statistically significant Pearson's chi-square adjusted residuals for the categorical variables. The Pearson's chi-square test and Fischer's exact test were used to analyze all categorical variables. Statistical significance was set at the 5% level.

## 5.6 Ethical Approval and Permissions

The studies were conducted according to the tenets of the Declaration of Helsinki and approved by the concerning authorities, such as the Research Director and the Chief Medical Officer of Kymenlaakso Central Hospital. Study I protocol was approved by the Institutional Review Board of Helsinki University Hospital (Operative ethics committee) and the Finnish Medicines Agency, Fimea, (EU Clinical Trials Register 2016-004515-12; registered as phase I study). All patients signed an informed consent form before enrollment and could withdraw from the study at any time.

# 6 Results

## 6.1 Study I

Baseline patient (age, gender, laterality of eye, glaucoma, pseudoexfoliation syndrome, smoking history) and surgical (operation time, phacoemulsification energy cumulative dissipated energy, aid of pupil expansion device) characteristics were similar between the study groups (Table 3).

**Table 3.** Patient and surgical characteristics

| Variables | Dexamethasone n = 50 | Triamcinolone n = 51 | P value |
|---|---|---|---|
| Age (years) | 74.5 ± 6.5 | 74.7 ± 6.7 | 0.884 |
| Sex (male : female) | 16 : 34 | 17 : 34 | 0.839 |
| Laterality (right : left) | 28 : 22 | 29 : 22 | 0.743 |
| Glaucoma | 7 (14) | 5 (10) | 0.772 |
| Pseudoexfoliation syndrome | 2 (4) | 4 (8) | 0.679 |
| Smoking history | 6 (12) | 3(6) | 0.318 |
| Operation time (min) | 18.5 ± 7.5 | 16.7 ± 5.3 | 0.942 |
| Phacoemulsification energy (seconds) | 20.3 ± 10.8 | 19.2 ± 11.9 | 0.301 |
| Pupil expansion device | 1 (2) | 2 (4) | 0.999 |

Data is given as mean ± SD for continuous variables and absolute numbers (with proportions of observed values) for categorical variables. For two-group comparisons, continuous and normally distributed data (age) was analyzed with the unpaired Student's t test, non-normally distributed data (operation time and phacoemulsification energy) with the Wilcoxon rank-sum (Mann-Whitney U) test, and categorical data with the Pearson's chi-square test (sex, laterality, glaucoma) or the Fisher's exact test when the expected values in any of the cells of a contingency table were below five (pseudoexfoliation syndrome, smoking history and use of pupil expansion device). Modified from Lindholm J-M et al. *Acta Ophthalmol*. 2020;98(1):36-42 with permission from John Wiley & Sons, Inc.

### 6.1.1 Efficacy Outcomes

Aqueous flare values were comparable at baseline. The difference in aqueous flare between the dexamethasone and triamcinolone groups (mean change from baseline) was not significant at 7 days (+9.9 ± 22.5 and +5.4 ± 12.2 photons/ms; p = 0.320) or at 28 days (+5.5 ± 12.5 and +3.9 ± 14.9 photons/ms; p = 0.090). At 90 days, aqueous flare remained increased in the dexamethasone group (+3.3 ± 9.9 photons/ms), whereas in the triamcinolone group, it had recovered to baseline level (0.2 ± 6.6 photons/ms; p = 0.021). The mean aqueous flare change at 28 days was similar for both groups (DEX–TA difference +1.62 photons/ms; 95% CI: -4.02 to +7.25; p = 0.570).

The central retinal thickness values were similar at baseline. CRT increased in the dexamethasone group but not in the triamcinolone group at 7 days (+1.2 ± 20.1 and -9.2 ± 24.8 μm; $p = 0.031$), at 28 days (+23.8 ± 62.6 and -3.3 ± 27.7 μm; $p = 0.008$), and at 90 days (+8.5 ± 24.4 and -5.5 ± 33.4 μm; $p = 0.026$). The mean CRT changes at 28 days were higher in the dexamethasone group than in the triamcinolone group (difference +27.1 μm; 95% CI: +7.28 to +47.0; $p = 0.008$). During the 90-day follow-up, CRT increased over 20% from baseline at any given time point of follow-up visits in 26% of eyes in the dexamethasone group and 4% of eyes in the triamcinolone group ($p = 0.003$). Over 30% CRT increase was observed in 11% of eyes in the dexamethasone group and in none of the eyes in the triamcinolone group ($p = 0.025$). During the 90-day follow-up, three cases of PCME were diagnosed at the 28-day visit in the dexamethasone group and none in the triamcinolone group ($p = 0.118$).

### 6.1.2 Safety Outcomes

Mean intraocular pressure was lower at baseline in the dexamethasone group compared to the triamcinolone group (14.0 ± 3.4 and 15.4 ± 2.9 mmHg; $p = 0.046$). IOP reduction after cataract surgery was comparable between the dexamethasone and triamcinolone groups at 7 days (-2.7 ± 3.8 and -3.5 ± 3.2; $p = 0.334$), at 28 (-3.0 ± 3.5 and -3.1 ± 3.5; $p = 0.883$), and at 90 days (-3.3 ± 3.5 and -2.6 ± 4.5 mmHg; $p = 0.444$). During the 90-day follow-up, IOP increase over 5 mmHg from the baseline at any given time point of follow-up visits was observed in one eye in the dexamethasone group and in none of the eyes in the triamcinolone group ($p = 0.999$). Postoperatively, none of the study eyes had IOP higher than 25 mmHg or an IOP increase of more than 10 mmHg from baseline. IOP was comparable between patients with and without glaucoma preoperatively and during all follow-up visits. There were no differences in IOP between patients with and without glaucoma in the triamcinolone group.

The corrected distance visual acuity (CDVA) in logMAR values was similar between the groups at baseline. CDVA improvement was comparable between the dexamethasone and triamcinolone groups at 7 days (-0.32 ± 0.27 and -0.33 ± 0.32; $p = 0.827$), at 28 (-0.37 ± 0.28 and -0.39 ±0.28; $p = 0.796$), and at 90 days (-0.42 ± 0.27 and -0.42 ± 0.28; $p = 0.634$).

**Complications.** There were no perioperative complications in any of the cataract surgeries. No serious ocular or systemic adverse events were observed during the follow-up. In the triamcinolone group, one patient recognized a mild cosmetic disadvantage from the steroid deposit visible beneath the subconjunctival space.

**Ocular Tolerance.** Response rate for the structured home questionnaire for recovery from surgery was 39 of 50 patients in the dexamethasone group and 36 of 51 patients in the triamcinolone group. The median duration of eye redness after surgery was 2 days (range 0–7) in the dexamethasone group and 1 day (range 0–10) in the triamcinolone group ($p = 0.031$). The median duration of irritation symptoms was 3 days (range 0–24) in the dexamethasone group and 2 days (range 0–15) in the triamcinolone group ($p = 0.208$). The overall median patient satisfaction 28 days after surgery at scale 0–10 was 10 (range 8–10) in the dexamethasone group and 10 (range 7–10) in the triamcinolone group ($p = 0.247$).

## 6.2 Study II

Study II enrolled 10044 eyes, of which 3787 were implanted with ZCB00 IOL, 4882 eyes with SN60WF IOL, and 1375 eyes with ZA9003 IOL. The mean age on the day of surgery for all patients was 75.0 (SD 9.1), 62.7 per 100 were women, and 93.4 per 100 were aged 60 years or older. The median duration of follow-up after surgery was 45 months. A total of 969 Nd:YAG laser posterior capsulotomies were performed on the enrolled eyes during the follow-up. Death as a competing event was recorded for 1753 eyes.

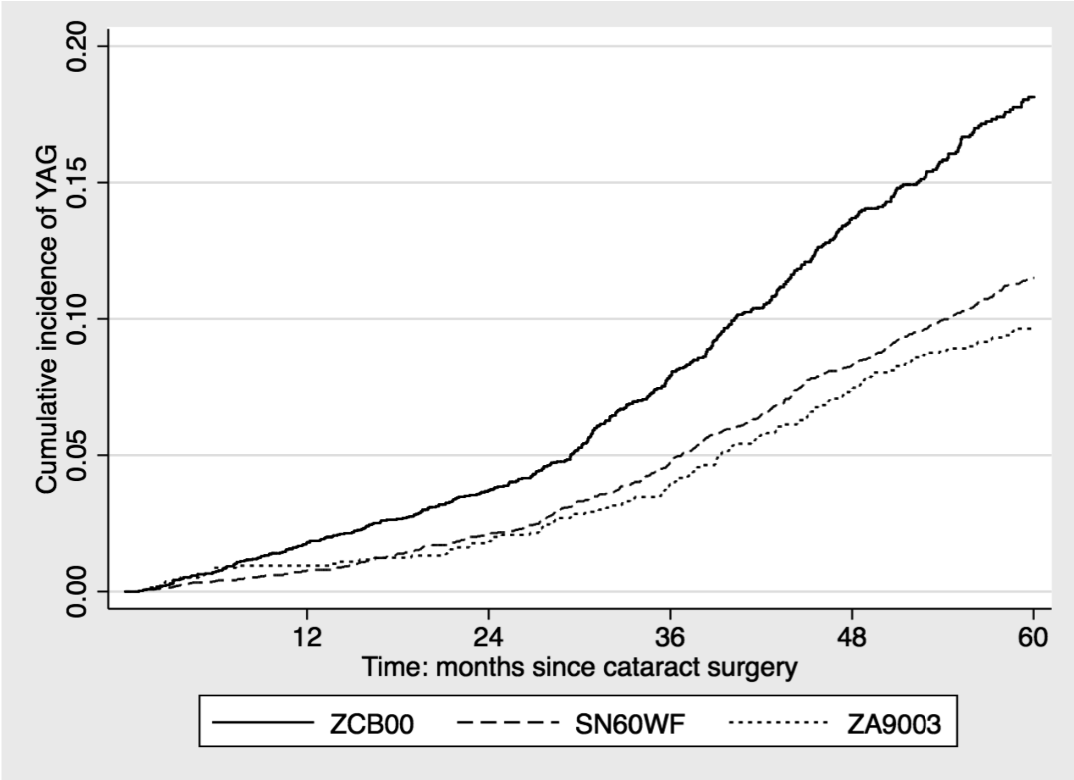


**Figure 1.** Cumulative incidence functions of Nd:YAG capsulotomy according to the type of implanted intraocular lens. Reprinted from Lindholm J-M et al. *Am J Ophthalmol. 2019;200:218-223* with permission from Elsevier, Inc.

The overall cumulative incidence of Nd:YAG capsulotomy after cataract surgery was 1.2% (95% CI: 1.0%–1.4%) at 1 year, 5.7% (5.3%–6.3%) at 3 years, and 13.2% (12.5%–14.0%) at 5 years. The 5-year cumulative incidences of Nd:YAG capsulotomy according to IOL models were 18.1% (16.5%–20.0%), 11.5% (10.5%–12.6%), and 9.6% (8.2%–11.4%) for ZCB00, SN60WF, and ZA9003, respectively (Figure 1).

**Table 4.** Univariate and multivariate competing risks regression analysis of potential risk factors associated with Nd:YAG capsulotomy

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Risk factor | SHR | 95% CI | P value | SHR | 95% CI | P value |
| Age (years) | | | | | | |
| < 60 | 1.73 | 1.41–2.12 | **< 0.001** | 1.69 | 1.37–2.07 | **< 0.001** |
| ≥ 60 | Ref | | | Ref | | |
| Sex | | | | | | |
| Female | 1.18 | 1.03–1.35 | **0.016** | 1.32 | 1.15–1.52 | **< 0.001** |
| Male | Ref | | | Ref | | |
| IOL model | | | | | | |
| SN60WF | 0.62 | 0.54–0.71 | **< 0.001** | 0.62 | 0.54–0.71 | **< 0.001** |
| ZA9003 | 0.53 | 0.43–0.65 | **< 0.001** | 0.53 | 0.43–0.64 | **< 0.001** |
| ZCB00 | Ref | | | Ref | | |
| IOL power (diopters) | | | | | | |
| < 22.5 | 1.16 | 1.02–1.31 | **0.023** | 1.19 | 1.05–1.35 | **0.007** |
| ≥ 22.5 | Ref | | | Ref | | |
| Surgeon | | | | | | |
| Specialist | 1.22 | 0.87–1.70 | 0.245 | | | |
| Resident | Ref | | | | | |

Significant variables on univariate analysis were included in the final multivariate model. P values ≤ 0.05 were considered significant (in bold). SHR = subhazard ratio; Ref = reference category. Modified from Lindholm J-M et al. *Am J Ophthalmol*. 2019;200:218-223 with permission from Elsevier, Inc.

Competing risks regression multivariate analysis of potential risk factors associated with Nd:YAG capsulotomy showed that implantation of SN60WF and ZA9003 IOLs was associated with a 38% and 47% subhazard reduction, respectively, compared to ZCB00, after accounting for other predictors (SHR = 0.62; 95% CI: 0.54–0.71; P < 0.001 and SHR = 0.53; 95% CI: 0.43–0.64; P < 0.001) (Table 4). Increased risk of Nd:YAG capsulotomy was associated with patients younger than 60 years of age (SHR = 1.69; 95% CI: 1.37–2.07; P < 0.001), female sex (SHR = 1.32; 95% CI 1.15–1.52; P < 0.001), and eyes implanted with an IOL of <22.5 diopters power (SHR = 1.19; 95% CI 1.05–1.35; P = 0.007).

## 6.3 Study III

15375 eyes were enrolled in the study according to the inclusion criteria, and a total of 1312 Nd:YAG capsulotomies were performed on these eyes during the follow-up. The median duration of follow-up after surgery was 40 months. The mean age at the day of surgery for all patients was 75.2 years (SD 9.0); 63.7 per 100 were women, and 93.7 per 100 were aged 60 years or older. Study patients were categorized into low-diopter (5–16.5D; n = 644), mid-diopter (17–24.5D; n = 12313), and high-diopter (25–30D; n = 2418) groups.

The 5-year cumulative probability of Nd:YAG capsulotomy after cataract surgery was 27.4% (95% CI: 22.9–32.6%) for low-diopter IOLs, 14.6% (13.8–15.5%) for mid-diopter IOLs, and 13.6% (11.7–15.6%) for high-diopter IOLs (Figure 2). A multivariate Cox regression analysis showed that low-diopter IOLs (HR 1.76; 95% CI: 1.38–2.25; p < 0.001) were associated with an increased risk of Nd:YAG capsulotomy compared to mid-diopter IOLs over the follow-up period after accounting for other predictors (Table 5).

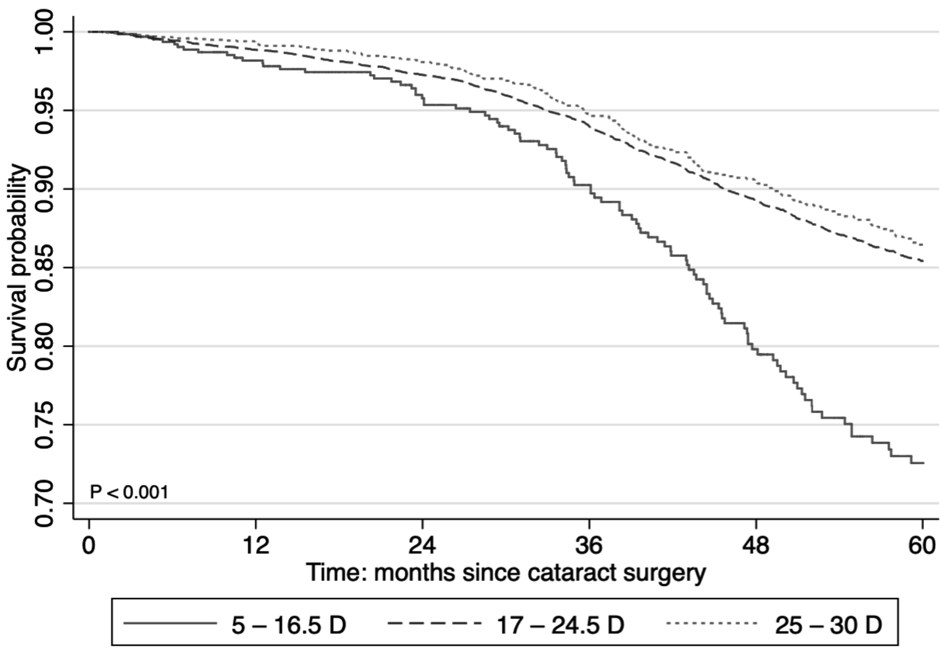


**Figure 2.** Kaplan–Meier estimates of the Nd:YAG capsulotomy free survival probability according to the diopter power of implanted IOL. Reprinted from Lindholm et al. *J Clin Med*. 2020;9(10), which was published under an open access Creative Common Attribution license.

**Table 5.** Crude and adjusted Cox regression analysis of potential risk factors associated with Nd:YAG capsulotomy

| Risk factor | Crude HR (95% CI) | P value | Adjusted* HR (95% CI) | P value |
|---|---|---|---|---|
| Age (years) | | | | |
| < 60 | 1.55 (1.27–1.89) | **< 0.001** | 1.41 (1.14–1.73) | **0.001** |
| ≥ 60 | 1.00 | | 1.00 | |
| Sex | | | | |
| Female | 1.12 (0.99–1.28) | 0.077 | 1.21 (1.06–1.38) | **0.006** |
| Male | 1.00 | | 1.00 | |
| IOL model | | | | |
| SN60WF/AU00T0 | 0.63 (0.55–0.72) | **< 0.001** | 0.63 (0.56–0.72) | **< 0.001** |
| ZA9003 | 0.53 (0.44–0.65) | **< 0.001** | 0.53 (0.44–0.65) | **< 0.001** |
| ZCB00/PCB00 | 1.00 | | 1.00 | |
| IOL power (diopters) | | | | |
| 5–16.5 | 1.92 (1.52–2.44) | **< 0.001** | 1.76 (1.38–2.25) | **< 0.001** |
| 17–24.5 | 1.00 | | 1.00 | |
| 25–30 | 0.89 (0.75–1.06) | 0.192 | 0.85 (0.71–1.01) | 0.062 |
| Surgeon | | | | |
| Specialist | 1.22 (0.90–1.66) | 0.193 | | |
| Resident | 1.00 | | | |

*Final multivariate Cox regression model with stepwise approach included 15280 observations. P values ≤ 0.05 were considered significant (in bold). HR = hazard ratio. Modified from Lindholm et al. *J Clin Med*. 2020;9(10) which was published under an open access Creative Common Attribution license

## 6.4 Study IV

The baseline characteristics (age, gender, laterality of the eye, preoperative BCVA, duration of the cataract surgery, the time elapsed between cataract surgery and Nd:YAG laser posterior capsulotomy, and axial length) between the two groups were similar (Table 6).

**Table 6.** Baseline demographics

| Variables | Conventional | Lean | P |
|---|---|---|---|
| Age (years) | 74.4 ± 14.1 (26 - 96) | 76.7 ± 8.4 (48 - 94) | 0.134 |
| Gender (Male:Female; n/%) | 21:34 (38:62 %) | 92:185 (33:67 %) | 0.477 |
| Laterality (Uni:Bilateral; n/%) | 39:16 (71:29 %) | 218:59 (79:21 %) | 0.207 |
| BCVA (decimal) | 0.45 ± 0.24 (0.05 - 1.0) | 0.45 ± 0.19 (0.05 - 1.0) | 0.989 |
| Time from cataract surgery (mo) | 54.8 ± 45.4 (6 - 187) | 65.9 ± 40.1 (3 - 205) | 0.121 |
| Operation time (min) | 14.9 ± 8.1 (5 - 40) | 12.8 ± 7.4 (4 - 49) | 0.143 |
| Axial length (mm) | 23.3 ± 1.1 (21.77 - 26.60) | 23.7± 1.4 (20.81 - 28.26) | 0.052 |

Data are given as mean ± SD and range (min-max) or absolute number and proportion. For two-group comparisons, two-factor $X^2$ test was used for qualitative data, and Student's t-test for continuous variables. BCVA; best corrected visual acuity on a standard Snellen chart. $P \leq 0.05$ was considered statistically significant. Reprinted from Lindholm J-M et al. *Acta Ophthalmol*. 2018;37:1003 with permission from John Wiley & Sons, Inc.

**Lead Time.** The total reception time per patient was shortened from 55:36 ± 30:23 to 44:40 ± 4:49 min when comparing the improved and conventional treatment protocols (p = 0.040). The number of patients and eyes that were treated in the operation room in 1 hour also increased from 4.7 ± 1.6 patients to 16.3 ± 2.3 patients, and from 5.5 ± 2.0 eyes to 18.0 ± 1.6 eyes (p < 0.001 for both).

**Work Flow and Cycle Time.** Purposeful use of physician's work time was measured by timing work flow in the operation room. The total work time in the operation room with patients who were treated unilaterally reduced from 8:19 ± 3:06 to 3:01 ± 1:00 min, when comparing the improved and conventional treatment protocols (p < 0.001). Similarly, the time spent in the operation room with patients who were treated bilaterally was shortened from 8:45 ± 3:55 to 4:40 ± 2:03 min (p < 0.006). Work time was shortened in every step of the process, that is preoperative arrangements, duration of operation, the postoperative phase, and time of switching the patients.

**Patient Satisfaction.** Patient satisfaction was measured with a survey. Response rate was 47 of 48 patients with the conventional protocol and 154 of 158 patients with the improved protocol. In the conventional treatment protocol group, 10.6% of the patients considered the treatment satisfactory (five of 47 patients), 21.3% good (10 of 47), and 68.1% excellent (32 of 47). In the improved treatment protocol, the respective values were 2.6% (four of 154), 10.4% (16 of 154), and 87.0% (134 of 154; p = 0.002). None of the patients considered the treatment unsatisfactory. The overall patient satisfaction rate was good with the conventional protocol (17.3 ± 1.04) and excellent (17.8 ± 0.61) with the improved protocol.

# 7 Discussion

## 7.1 Study I

Achieving the best outcomes in cataract surgery requires efficient control of the postoperative inflammatory cascade and identifying patients at risk for later complications. Addressing medication compliance with a perioperative long-acting triamcinolone depot appears to be a noteworthy option for dropless postoperative care.

Aqueous flare measurements, which provide a quantitative evaluation of aqueous protein concentration, correlate to blood–aqueous barrier breakdown and anterior chamber inflammatory activity (Shah et al. 1992). Flare values peak on the first postoperative day, then decline rapidly during the first week, and return to preoperative levels by 3 months after cataract surgery (Shah et Spalton 1994). Clinical follow-up in our study showed that flare values were highest at 7 days in both groups and then declined gradually. However, aqueous flare was increased in the dexamethasone group compared to the triamcinolone group at 90 days postoperatively. The mean aqueous flare also appeared consistently lower in the triamcinolone group during follow-up. Elevated flare values were previously observed at 3 months postoperatively, even with a longer course of steroid eye drop administration (q.i.d.) with or without tapering down dosing (Chang et Wong 1999; Negi et al. 2006; Wielders et al. 2018a). The results of our study suggest that the anti-inflammatory effect is longer lasting with subconjunctival triamcinolone.

Treatment strategies targeting the prevention of PCME also depend on blocking the postsurgical inflammatory response. Inflammatory reaction leads to an increase in the permeability of perifoveal retinal capillary vessels, leakage, and accumulation of fluid in cystoid spaces within the inner layers of retina. During the clinical follow-up in our study, the mean central retinal thickness increased and peaked at 28 days in the dexamethasone group, whereas in the triamcinolone group, macular thickness appeared to be consistently even lower than the baseline level. There were no cases of clinical PCME in the triamcinolone group during the follow-up versus three cases of PCME in the dexamethasone group, although the difference was not statistically significant. Although PCME has been commonly described as a relatively self-limiting condition with spontaneous recovery, chronic, or uncontrolled edema can cause permanent damage and result in long-term visual deterioration or permanent visual loss.

Supported by earlier studies, the essential finding of this study was that a subconjunctival 20 mg injection of triamcinolone was effective in preventing macular edema after cataract surgery. A recent large European multicenter trial, the ESCRS Premed study, investigated the additional therapeutic benefit of a subconjunctival 40 mg triamcinolone injection in addition to postoperative topical treatment with a combination of dexamethasone and bromfenac in diabetic patients and reported that the central subfield mean macular thickness was lower in patients who received subconjunctival triamcinolone, and none of these patients developed PCME (Wielders et al. 2018b). Our study suggests that subconjunctival triamcinolone is sufficient in itself to prevent macular edema without the use of postoperative topical medications in non-diabetic patients. Similarly, no cases of postoperative macular edema were observed with a subconjunctival 5mg injection of triamcinolone in combination with postoperative topical ketorolac among 200 non-diabetic patients (Reddy et al. 2019).

The safety evaluation of the treatment regimens was based on IOP, visual acuity improvement, subjective recovery from surgery, and adverse events under clinical examination. We did not observe any significant IOP increases; none of the operated eyes showed an IOP higher than 25 mmHg or an IOP increase from the baseline of more than 10 mmHg. Twelve eyes with glaucoma included in the study had comparable IOP changes, and we did not observe any steroid-response IOP rises. However, because steroid-induced increase in IOP has been reported to occur as late as 6 months following subconjunctival triamcinolone injection (Kalina et al. 1995), this study may have missed IOP rises after the follow-up period of 3 months. We did not observe any significant differences in visual acuity improvement between the groups during clinical follow-up. There were no perioperative complications, and no serious ocular or systemic adverse events were observed during the follow-up period. Ocular tolerance was good in both groups, but the median duration of eye redness after surgery was shorter in the triamcinolone group.

## 7.2 Study II

The results of the current study showed an overall 5.7% 3-year and 13.2% 5-year cumulative incidence of Nd:YAG capsulotomy after cataract surgery, whereas earlier studies comparing hydrophobic acrylic IOLs reported a 5–35.6% incidence at 3 years and 12–24% at 5 years after cataract surgery (Buehl 2005; Leydolt et al. 2013; Sundelin et al. 2014; Ursell et al. 2018). The reported incidences vary widely due to various reasons. Such reasons may include different treatment indications for Nd:YAG laser capsulotomy, patient population characteristics, surgical techniques, IOL design and materials, and the length of follow-up. Estimating the real-world long-term incidence of capsulotomy in elderly cataract surgery patients using standard survival analysis methods is also complicated by the competing risk of death, which precludes the occurrence of the event of interest.

The study results also demonstrated a significantly lower risk of Nd:YAG capsulotomy associated with the implantation of SN60WF and ZA9003 IOLs compared to ZCB00. The differences can be attributed to the effects of IOL design or biomaterial composition. Although all the included IOLs had hydrophobic acrylic optic material, the differences between the surface properties of each IOL biomaterial may have affected the IOL-capsule adhesion, the lens epithelial cells' migration, and thus PCO formation. Previous studies comparing IOL haptic design have been equivocal. The thin haptics of 3-piece design have been proposed to enable a more uniform fusion between the anterior and posterior capsules, a ”shrink wrap” effect. The current results showed a lower risk associated with the 3-piece ZA9003 compared to the 1-piece ZCB00, but inconsistently, both the 1-piece IOLs SN60WF and ZCB00 also had differing risk profiles. The Cochrane meta-analysis on interventions for preventing posterior capsule opacification supported the benefits of sharp optic edge design but found no difference between 1-piece and 3-piece IOLs (Findl et al. 2010).

The current study showed that the eyes of patients younger than 60 years old, women, and those eyes implanted with an IOL of <22.5 diopters power were at increased risk of Nd:YAG capsulotomy. Younger age has also been reported as a risk factor in previous studies (Baratz et al. 2001; Elgohary et Dowler 2006). Retained lens epithelial cells appear to be more proliferative in the eyes of younger patients (Sundelin et al. 2014). Younger patients may also have higher visual requirements for daily tasks. Female gender has also been previously associated with a higher risk of Nd:YAG capsulotomy (Ando et al. 2003), which could be explained by a more active attitude toward seeking medical care and concerning health problems. The lower risk associated with <22.5 diopters power IOLs could be explained by the reported weaker postoperative IOL-capsule adhesion in axially myopic eyes compared to emmetropic eyes (Zhao et al. 2013).

## 7.3 Study III

The development of PCO requires the migration of lens epithelial cells into the posterior capsule. Complete fusion of the lens capsule around the IOL can reduce LEC migration and prevent PCO. Myopic eyes often have larger capsular bags and are implanted with thinner IOLs, which can lead to weak capsular apposition (Vass et al. 1999). A previous study investigating the capsule–IOL interaction in emmetropic and highly myopic eyes revealed weak capsular adhesion and incomplete adhesive types of capsular bend formation in highly myopic eyes (Zhao et al. 2013).

The results of the current study showed that the need for Nd:YAG capsulotomy to treat PCO was approximately two times higher in patients implanted with low-diopter IOLs compared to higher diopter IOLs. The results of earlier studies have been inconclusive. In a previous prospective trial evaluating posterior capsule opacification in myopic eyes 4 years after implantation of a single-piece acrylic IOL, axial myopia was not found to significantly increase the area or incidence of PCO, although the percentage of eyes with PCO behind the central 3.0 mm zone of the posterior capsule was higher in the myopia group (Vasavada et al. 2009). The current results showed that implantation of low-diopter IOLs was associated with a 76% increase in the hazard of Nd:YAG capsulotomy compared to mid-diopter IOLs after accounting for other predictors. A similar large retrospective cohort study also reported that eyes implanted with lower-power IOLs were marginally but significantly associated with an increased risk of Nd:YAG capsulotomies, but did not specify this further (Ursell et al. 2018). A recent retrospective study by Hecht et al. (2020) reported an overall 10.2% Nd:YAG capsulotomy rate at 4 years after cataract surgery and an increased risk (odds ratio 1.343; $P < 0.001$) associated with implantation of lower diopter power IOLs (≤20.0D). Eyes of younger patients, females, and eyes implanted with ZCB00/PCB00 IOL were at increased risk of Nd:YAG capsulotomy in our study. These results are consistent with the findings of previous studies (Baratz et al. 2001; Ando et al. 2003; Elgohary et Dowler 2006) and are discussed in Section 7.2.

The results of this real-world study should help in evaluating the risk of PCO in myopic eyes. This is relevant because of the risks associated with Nd:YAG capsulotomy. Myopic eyes are at increased risk for retinal tear or detachment after cataract surgery, and with Nd:YAG capsulotomy, this rate will probably increase (Wesolosky et al. 2017). Other complications of laser capsulotomy, such as IOL damage and cystoid macular edema, and the economic burden of PCO on health services and society, also highlight the importance of assessing the risk involved and providing a basis for measures to reduce the incidence of PCO.

## 7.4 Study IV

The imbalance between the available healthcare resources and the increasing demand for care for age-related diseases requires the development of cost-effective operational principles to provide quality eye healthcare services. The Lean process improvement methodology is a set of concepts, principles, and tools that can also be utilized in improving health care provision. There are numerous reports of applying Lean principles in health care, but only a handful focus on ophthalmology (Sommer et Blumenthal 2019).

The results of the current study showed that the Lean principles were successively implemented in improving the treatment protocol for Nd:YAG laser capsulotomy, with substantial reductions in lead times without compromising patient satisfaction. With the improved protocol, the number of patients treated in 1 hour more than tripled, and the patient reception time per patient was shortened approximately 20%. Furthermore, the overall patient satisfaction grade improved. Similar positive results were attained in a Lean project by Ciulla et al. (2018) at the retina clinic of Midwest Eye Institute, USA, where patient flow was re-constructed and highly demanding tasks were prioritized. Improvements lead to a statistically significant shortening of the mean patient visit by 18% and a decrease in the intravitreal injection times by 50%. Improved productivity results have also been achieved in Finland with the implementation of revised operational concepts and new facilities, which together with a 15% increase in work contribution led to a 46% increase in overall productivity at Tampere University Hospital Eye Centre (Tuulonen et al. 2016).

The Lean process also aimed to improve the purposeful use of time and competences of the employees. The conventional treatment practice of PCO was evaluated with a value stream analysis-oriented approach by assessing the steps of the work process from the patient's and employee's points of view. Inefficiencies as well as the steps that added value in the process were assessed. Waiting times and non-essential tasks were identified as waste. The improved treatment protocol was developed with the purpose of reaching a seamless and safe workflow, which led to standardizing the tasks of each employee to improve the quality and safety of the treatment and to reduce waiting times. The results indicate that work time was shortened in every step of the process and that more purposeful use of physician's work time was accomplished. In a similar manner, a Lean implementation at the ophthalmology emergency clinic of Royal Alezandra Hospital, Canada, which targeted a "disorganized" workplace setting and identified inefficiencies (or waste) in the processes, reported that the implementation led to improved safety and working environment (Nazarali et al. 2017). Standardization as an operational concept has also been deemed an effective way to promote safety and productivity in the provision of high-volume eye health services (Tuulonen et al. 2016; Weingessel et al. 2017).

## 7.5 Strengths and Limitations

These studies have some strengths and limitations that must be considered as prospects for future research. Each study was conducted at a single center, which may limit the external validity of results but should avoid bias associated with the heterogeneity of center characteristics in multi-center studies, such as differences in follow-up and indications for treatment.

Studies II and III were carried out with an essentially population-based dataset of consecutive patients managed in a district hospital setting, which should allow for good generalizability of the findings. The retrospective cohort design allows for the assessment of the natural history of the disease, as well as the temporal relationships of exposures and outcomes. In relation to the retrospective design, however, the results may be affected by some unknown confounding factors, and there may be gaps in the study data. Some common systemic and ocular comorbidities were not accounted for in the analysis. The completeness of patient follow-up cannot be fully ascertained because, for example, a patient may have moved out of the region during follow-up. Study II also utilized competing risk methodology to factor out the competing risk of death, which provides more realistic estimates of incidences for clinicians. The studies used a large dataset, and the results included some of the largest cohorts of patients published. The length of follow-up was adequate in both studies. The studies included some of the most commonly used IOLs, several surgeons with varying degrees of experience, and the demographic characteristics of the study population corresponding to the source population of cataract surgery patients in the hospital district. Thus, the results offer real-world clinical practice evidence. Nd:YAG capsulotomy rate is not a direct measure for PCO and is also affected by the patient's tolerance to PCO-induced symptoms and clinical treatment practices; nevertheless, it provides a functional indicator of morbidity related to PCO.

Studies I and IV were conducted as prospective trials with the advantage of more control over potential sources of bias, but a marked limitation of these studies was the non-randomized allocation, which allows potential for allocation bias and confounding factors. In Study IV, the allocation was the result of patient appointment scheduling by hospital secretaries, which may be considered equivalent for most practical purposes to an almost random sample. In Study IV, some patients may have needed assistance of the hospital staff to fill out the patient satisfaction questionnaire, and this could have led to courtesy bias. In Study I, the treatment used was not masked by the patient or the investigator for practical reasons, and this could have affected the measured outcomes. However, the main outcomes were measured with quantitative methods. A relatively small study sample size in

Study I partially limits conclusions on safety aspects because SUSAR or other rare adverse events were not likely to occur in such a small sample.

## 7.6 Future Directions

Cataract surgery is a constantly developing field, with innovations in surgical technology and IOLs that improve surgical outcomes and patient experience. Achieving optimal outcomes and preventing later complications also requires attention to identifying risk factors for complications and choosing postoperative care accordingly.

Efficient prevention of postoperative inflammation improves the short- and long-term outcomes of cataract surgery. Poor adherence to topical medication can lead to increased postoperative pain, delayed visual recovery, or more serious complications, such as PCME. The results of this study showed that subconjunctival triamcinolone, as a part of dropless postoperative care, is efficient in the prevention of PCME. Currently, there is insufficient knowledge about the effects of long-term postoperative inflammatory reaction. In certain high-risk patient populations, a combination of NSAID drops and subconjunctival triamcinolone may be reasonable, and this should be addressed in future research. Reported incidences of PCME vary in the literature, and a more consistent definition of PCME across different studies would facilitate a comparison of the results of interventions.

Recognizing risk factors and patients at increased risk for PCO and subsequent Nd:YAG capsulotomy help reduce the morbidity and costs related to PCO. The results of this study indicated significant differences in capsulotomy rates between common hydrophobic IOLs, which can be attributed to the effects of IOL design and biomaterial composition. Health economic impacts of PCO and subsequent Nd:YAG capsulotomy are not insignificant and warrant further economic analysis. The rising popularity of multifocal and other presbyopia-correcting IOLs, as well as lens-based refractive surgery, raises concern about the possible pronounced visual disturbances associated with PCO in patients with these IOLs. The results of this study highlight that myopic eyes are at increased risk for Nd:YAG capsulotomy. Future research should address ways to prevent PCO in this patient group and assess the risk–benefit ratio of Nd:YAG capsulotomy in highly myopic eyes. Further epidemiologic evidence of a causal relationship between axial myopia and PCO formation should be demonstrated, preferably a dose–response relationship, by using methods of direct assessment of PCO severity.

The rising burden of age-related diseases in ophthalmology requires attention to efficient operational concepts in eye care provision. The results of this study demonstrated the benefit of a Lean-oriented Nd:YAG capsulotomy treatment protocol with reductions in lead times without compromising patient satisfaction. Future research should determine the external validity of these results in different hospital settings. There is also a need for quality improvement interventions in other fields of high-volume eye health services. With many methodologies available for improving organizational performance in addition to Lean, future research should identify which methods work best in eye health services.

# 8 Conclusions

I Subconjunctival injection of triamcinolone acetonide was effective in preventing macular edema and ocular inflammation after cataract surgery. It was non-inferior to dexamethasone eye drops in preventing ocular inflammation and may prevent PCME more successively. No significant adverse events were observed with the injection of triamcinolone acetonide and the ocular tolerance was good.

II The 5-year cumulative incidence of Nd:YAG capsulotomy after cataract surgery was estimated at 13.2% (95% CI: 12.5%–14.0%). There were significant differences in capsulotomy rates between common hydrophobic IOLs, which can be attributed to the effects of IOL design and biomaterial composition. Increased risk of Nd:YAG capsulotomy was associated with the eyes of patients aged younger than 60 years, female sex, and eyes implanted with an IOL of <22.5 diopters power.

III Implantation of low-diopter (5–16.5 D) IOLs were associated with a significantly higher risk of Nd:YAG capsulotomy within five years following surgery. Estimation should help in evaluating the risks of cataract surgery in myopic eyes.

IV The Lean methodology was successively implemented in improving the treatment protocol for Nd:YAG laser capsulotomy with substantial reductions in lead times without compromising patient satisfaction.

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