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Inflammation score on the anterior chamber in open-angle primary glaucoma patients accompanied by cataracts post phacotrabeculectomy with the administration of intracameral dexamethasone injection is lower than subconjunctival dexamethasone injection



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ABSTRACT

Background: Glaucoma with cataract is common in older patients and tends to increase worldwide as people age. Combination of glaucoma and cataract surgery will lead to a postoperative inflammatory response. Steroids are a major therapy in the management of postoperative inflammation. Intracameral steroid injection is selected because of the advantage of working directly in the anterior chamber.

Aims: This study aims to determine differences of an inflammatory score of the anterior chamber post phacotrabeculectomy in the administration of intracameral dexamethasone injection and subconjunctival dexamethasone injection.

Methods: This study is a randomized clinical trial with prospective repeated measurements. taking samples at Sanglah Denpasar Hospital and Bali Mandara Eye Hospital. A total of 28 eyes with

primary open angle glaucoma with cataract were divided into groups receiving intracameral dexamethasone injection and subconjunctival dexamethasone injection. Data were analyzed with t-test, Friedman, Mann-Whitney, and repeated measurement. **Results:** The median value of inflammatory cells between the two groups was different in day 1 ($p=0.037$) and 1 week ($p=0.014$) postoperative. The median flare values between the two groups were different in the 1 week postoperative ($p=0.034$).

Conclusion: This study found the intracameral dexamethasone suppressed inflammation in anterior chamber larger than subconjunctival dexamethasone in primary open angle glaucoma patients with cataract during the first day to 1-month post phacotrabeculectomy. Injection of intracameral dexamethasone can be the therapy of choice to reduce postoperative inflammation.

Keyword: primary open-angle glaucoma, inflammation, cell flare, intracameral dexamethasone

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INTRODUCTION

Glaucoma is an abnormality of the eyes characterized by specific optical neuropathy on optic nerve papilla and visual field abnormality. Intraocular pressure is the major risk factor for glaucoma. High intraocular pressure (>20 mmHg) will disrupt the optic nerve and result in visual field disturbances. Open-angle primary glaucoma is a chronic optic nerve neuropathy and slowly progressive with specific pattern of optic nerve disruption and visual field loss.^{1,2,3}

Glaucoma patients usually accompanied by with cataract disease, particularly in elderly patients. There are some choices to manage this case, which are isolated cataract and glaucoma surgery or by combination of both surgeries in one procedure. Phacotrabeculectomy was preferably chosen because of its cost-effectiveness and time saving.^{4,5,6}

Some studies reported that there is an increase in inflammatory reaction on anterior chamber of the eye post phacotrabeculectomy surgery. Anti-inflammatory medication used after glaucoma surgery are oral and topical steroids. The application of subconjunctival steroid injection at the end of cataract surgery has also been widely used throughout the world but had more complications than intracameral steroid injection.^{6,7} Administration of intracameral steroid injection begins to be a choice as a modality in controlling inflammation of cataract surgery postoperatively.^{8,9} Intraoperative subconjunctival dexamethasone injection still being a standard in controlling inflammation postoperatively in Bali. Meanwhile, the use of intracameral dexamethasone injection in combination of phacoemulsification with trabeculectomy was never studied.

METHOD AND MATERIALS

This study is a randomized clinical trial with repeated measures prospectively to observe the difference of inflammatory response on anterior chamber of the eye, IOP, and visual acuity on day-0, 1, 7, and 30 after phacotrabeculectomy with intracameral dexamethasone injection and subconjunctival dexamethasone injection as a control. This study was conducted at Rumah Sakit Umum Pusat (RSUP) Sanglah from October 2016 to March 2017. Data were collected through questionnaire and eyes examination. Study target population are primary glaucoma patients and accompanied by with cataract. Study achievable population are primary glaucoma patients and accompanied by with cataract who came to Eyes Polyclinic of RSUP Sanglah and RS Mata Bali Mandara in the period from October 2016 to March 2017. Study subjects are chosen consecutively from all patients that meet inclusion and exclusion criteria.

Inclusion criteria include glaucoma patients aged ≥ 40 years old, primary glaucoma patients that accompanied by with cataract and already treated by medication for one month but IOP remains uncontrolled (>21 mmHg), and patients agreed to participate in the study and signed the informed consent. The exclusion criteria were patients with history of glaucoma surgery <3 months ago; patients with corneal and conjunctival abnormalities; patients with history of inflammation and infection of the eyes <1 month ago; patients with history of anti-inflammatory treatments within 2 weeks; patients with history of systemic disease such as diabetes mellitus; and patients with complication during surgery.

SPSS version 16.0 program did data analysis. Data obtained were analyzed descriptively in order to get the samples characteristic and presented in the table, graph, and narrative forms. Numeric data tested for normality data by Saphiro Wilk test. Normally distributed data obtained p -value >0.05 . Normally distributed numeric data tested by independent T-test. Abnormally distributed numeric data tested by Mann-Whitney and Friedman tests. Repeated measurement tested differences in inflammation score reduction between the two groups. Significance level determined at $p < 0.05$.

RESULTS

These samples are 28 eyes in total. Characteristics of the sample in this study are presented in [Table 1](#). The male is 24 people (85.7%) and female are 4 (14.3%). The mean age of all study samples are 65.96 ± 10.14 years. Most of the samples come from

Denpasar (25%) and Buleleng (25%).

The median value of inflammatory scores on the anterior chamber of the eyes is presented in [Table 2](#). The median value of inflammatory cells between the two groups was different on 1 day ($p = 0.037$) and 1 week ($p = 0.014$) postoperatively. The median flare values between the two groups differed on 1 week postoperatively (0.034). The median value of the inflammatory cell decreased and differed between the two groups ($p = 0.011$). Meanwhile, the median flare decreased in both groups but not significant ($p = 0.090$). Decreased inflammatory cells and flares were greater in the subconjunctival dexamethasone injection group. The table also shows the difference between median inflammatory cells and flares of both treatment groups at different period of examinations.

[Figures 1](#) and [2](#) shows a graph of inflammatory cell and flare reduction by treatment group. Decreased inflammatory cells and flares were greater in the subconjunctival dexamethasone injection group than intracameral dexamethasone injection group. The mean values of intraocular pressure are shown in [Table 3](#). The mean values of intraocular pressure between the two groups were significantly different at 1 week postoperatively ($p = 0.026$). The median value of visual acuity was presented in [Table 4](#). The median value of visual acuity shows no significant difference at all time of examinations. The average number of corneal endothelial cells before and after phacotrabeculectomy surgery were shown in [Table 5](#). The mean number of corneal endothelial cells before and after surgery and the decreased of endothelial cell counts in both groups did not differ significantly.

DISCUSSION

Glaucoma is an abnormality of the eyes characterized by specific optical neuropathy on optic nerve papilla and visual field abnormality, with intraocular pressure as a major risk factor for glaucoma.¹ Open-angle primary glaucoma is a chronic and slowly progressive optical neuropathy with a particular pattern of damage to the optic nerve and loss of the visual field.^{1,2,3} Glaucoma that is also accompanied by cataracts is common in elderly patients and this trend is increasing throughout the world as population aged.¹⁰

The incidence of primary open-angle glaucoma affects 2.4 million people annually. Prevalence of blindness caused by glaucoma is more than 8 million people, and 4 million people within it are the result of primary open-angle glaucoma.¹ Prevalence of glaucoma in Indonesia according to Riskesdas 2007 Database is 0.5% nationally.¹¹ Cataracts were

Table 1. Characteristics of the samples

Variable	Intracameral dexamethasone injection group (n=14)	Subconjunctival dexamethasone injection group (n=14)
Age[year(mean±SD)]	65.36±10.46	66.57±10.17
Sex (n)		
Male (%)	11 (78.6%)	13 (92.9%)
Female (%)	3 (21.4%)	1 (7.1%)
Domicile (n)		
Buleleng (%)	5 (35.7%)	2 (14.3%)
Denpasar (%)	3 (21.4%)	4 (28.6%)
Tabanan (%)	2 (14.3%)	2 (14.3%)
Gianyar (%)	1 (7.1%)	1 (7.1%)
Badung (%)	1 (7.1%)	2 (14.3%)
Karangsasem (%)	1 (7.1%)	1 (7.1%)
Bangli (%)	1 (7.1%)	0 (0.0%)
Klungkung (%)	0 (0.0%)	2 (14.3%)
Sample with hypertension (n)		
Yes (%)	4 (28.6%)	2 (14.3%)
No (%)	10 (71.4%)	12 (85.7%)

SD: standard deviation

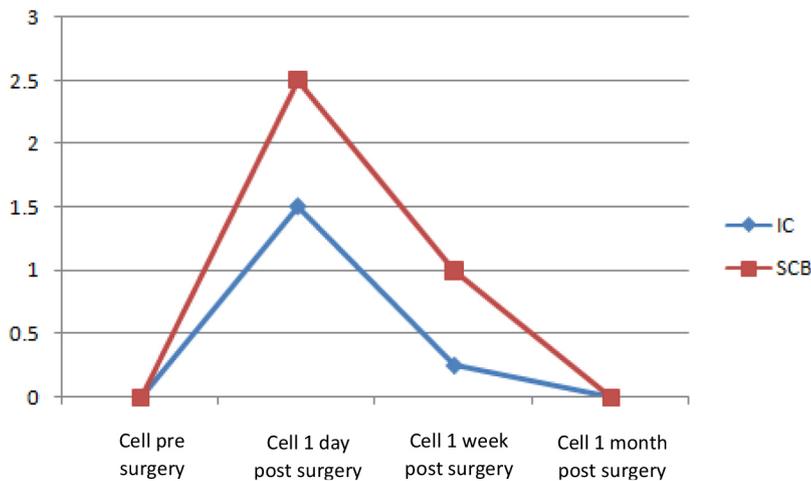


Figure 1. Graph of inflammatory cell reduction by treatment group

most commonly associated with increasing age. According to the World Health Organization (WHO), cataracts are the leading cause of blindness worldwide, 1 of 6 people over 40 years old will suffer from cataracts.¹²

The combination of phacoemulsification and trabeculectomy (phacotrabeculectomy) surgery has become an option for glaucoma patients with cataracts with very diminished visual acuity, which does not respond to any medication and laser therapy.¹³ Several studies have reported that phacotrabeculectomy is better at improving visual function and controlling intraocular pressure.^{4,5,6} This combination procedure will cause a postoperative inflammatory response, resulting in scar tissue formation in the bleb and a

desirable IOP decline could not be achieved.¹⁴

The samples in this study were 28 eyes, with male gender as many as 24 people (85.7%) and women as many as 4 (14.3%). Wang et al. found the number of men in his study was 61 people (48.4%) and women were 65 (51.6%). Gitte et al. in his study regarding combinations of trabeculectomy and small incision cataract surgery (SICS) reported that the male and female distributions are almost the same in males of 53% and females 47%.¹⁵ Another study by Naila Ali et al. reported that males are more susceptible to glaucomatous optic neuropathy.¹⁶ Sex differences regarding the prevalence of primary open-angle glaucoma remain controversial. Several studies have reported the prevalence of primary open-angle glaucoma is higher in males, while other studies reported higher in women.¹⁷

The mean age of the sample was 65.36±10.46 years in the intracameral dexamethasone injection group and 66.57±10.17 years in the subconjunctival dexamethasone injection group. Mittal et al. found that mean age in his study was 66.11 (49-83) years in the phacotrabeculectomy group and 64.13 (41-80) years in the SICS-trabeculectomy group.¹⁸ Murthy et al. found that the mean age in his study was 66.1±16.7 years trabeculectomy group and 73.1±12.4 years in the phacotrabeculectomy group.¹³ Most glaucoma patients also suffer from cataracts because both diseases were affecting the same age group in the elderly.¹⁵ Age is one of the major risk factors for open-angle glaucoma. Axonal loss occurs with increasing age in healthy people, but it remains unclear how it relates to optic nerve damage in glaucoma.¹⁹ A study suggests that age may be associated with an increase of tissue or ganglion cell damage, increased duration of exposure to other risk factors, and lower compliance to the therapies.²⁰

The samples of this study are mostly originated from Denpasar (25%) and Buleleng (25%). The location of this study. Sanglah Hospital is a referral center hospital located in the city of Denpasar, so the subject mostly comes from Denpasar. A survey by Francis et al. found that 54% of the sample in his study were originated from urban areas.²¹ Patients in urban areas were hypothesized to have access to health care facilities that are easier. Glaucoma was more rapidly detected in patients who routinely came to the healthcare service to do the examination.^{21, 22} Samples suffering from hypertension in this study were 6 people (21.4%). There were only a few kinds of literature on the role of hypertension related to the occurrence of inflammation of the eyes. Several studies also reported there were increasing levels of inflammation in hypertensive patients.²³ The number of hypertensive patients in this study was

Table 2 Difference of inflammation score on anterior chamber by treatment groups

	Intracameral dexamethasone injection group (n=14)	Subconjunctival dexamethasone injection group (n=14)	<i>p</i> -value
Inflammatory cell before surgery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	
Inflammatory cell 1 day post surgery [median (IQR)]	1.5 (1.2)	2.5 (1.0)	<i>p</i> =0.037
Inflammatory cell 1 week post surgery [median (IQR)]	0.25 (1.0)	1.0 (0.0)	<i>p</i> =0.014
Inflammatory cell 1 month post surgery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	<i>p</i> =0.150
	<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.011
Flare before surgery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	
Flare 1 day post surgery [median (IQR)]	1.0 (1.0)	2.0 (1.2)	<i>p</i> =0.451
Flare 1 week post surgery [median (IQR)]	0.0 (0.6)	1.0 (1.0)	<i>p</i> =0.034
Flare 1 month post surgery [median (IQR)]	0.0 (0.0)	0.0 (0.0)	<i>p</i> =0.317
	<i>p</i> =0.000	<i>p</i> =0.000	<i>p</i> =0.090

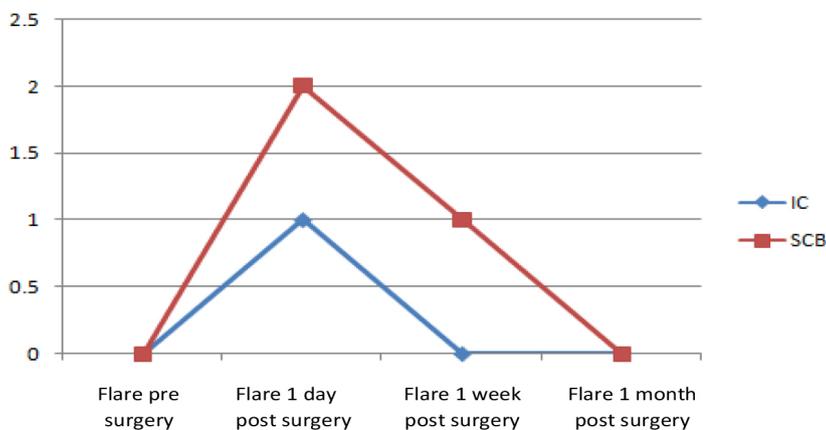
IQR: interquartile range

Difference between median value of inflammation score in each group tested with *Mann-Whitney test*

The difference in decrease median value of inflammation score between two groups tested with *General Linear Model*

Difference between median at different period of examinations tested with *Friedman test*

Significant if *p*<0.05

**Figure 2.** Graph of flare reduction by treatment group

small and similarly distributed in both treatment groups.

Wound healing modulation is crucial in determining the success of glaucoma surgery. Failure of glaucoma surgery is associated with the proliferation of fibroblasts and other inflammatory cells.²⁴ Recent developments in cataract surgery find ways to reduce physical trauma from surgery but cannot eliminate the formation and release of trauma-induced inflammatory mediators.²⁵ Surgical trauma will trigger a cascade of ocular inflammatory reactions. Trauma or surgical manipulation induces the synthesis and release of inflammatory mediators. Inflammatory responses after intraocular surgery such as cataract surgery, glaucoma, or a combination of both should be controlled in order to prevent complications. This inflammatory response is necessary in wound healing, but uncontrolled or sustained inflammation can lead to complications such as cystoid macular edema (CME), elevated IOP, posterior capsules opacification, excessive scarring tissues, and prolonged discomfort feelings.^{25,26}

The fibrinous uveitis incidence on early uveitis periods after phacotrabeculectomy surgery is reported from 24% to more than 50%, whereas fibrinous uveitis incidence after trabeculectomy is less common. The formation of fibrin will lead to an improvement in visual acuity in time. Synechia, loss of pupil function, membrane formation in the intraocular lenses, and secondary glaucoma.⁶

Corticosteroids have been used since the early 1950's to suppress intraocular inflammation by decreasing inflammatory exudation as well as inhibiting fibroblast proliferation and granulation tissue formation.⁹ Topical steroids are most commonly used and have significant success in trabeculectomy.²⁷ Topical medications have arising problems with patient compliance due to some eye drops should regularly be administered postoperatively, inconvenience issues, and more expensive costs for patients. The disadvantages of topical drugs are also limited by corneal absorption, had varying intraocular concentrations during treatment, and disrupting the tear film resulting in irritation.^{9,26,28}

Subconjunctival steroid injection had been routinely used and considered as an option in post ocular surgery to reduce the postoperative inflammation, but had disadvantages such as pain during injection, resulting in subconjunctival bleeding, and chemosis.^{25,29} Intracameral steroid administration initially used primarily in post cataract surgery and had an advantage to act directly in the anterior chamber of the eyes in suppressing inflammation.²⁹

Table 3 Difference of intraocular pressure by treatment group

	Intracameral dexamethasone injection group (n=14)	Subconjunctival dexamethasone injection group (n=14)	p-value
IOP pre surgery (mean±SD)	28.3±5.8	27.8±9.4	0.867
IOP 1 day post surgery (mean±SD)	11.4±4.9	12.4±4.5	0.578
IOP 1 week post surgery (mean±SD)	9.5±2.0	12.2±3.8	0.026
IOP 1 month post surgery (mean±SD)	9.9±2.2	11.7±2.9	0.074

SD: standard deviation; the difference between the mean of IOP in each group tested with *independent sample t-test*; significant if $p < 0.05$

Table 4 Difference of visual acuity by treatment group

	Intracameral dexamethasone injection group (n=14)	Subconjunctival dexamethasone injection group (n=14)	p-value
Visual acuity before surgery [median (IQR)]	1.63 (1.42)	0.85 (1.06)	0.090
Visual acuity 1 day post surgery [median (IQR)]	0.80 (1.29)	0.85 (1.28)	0.710
Visual acuity 1 week post surgery [median (IQR)]	0.52 (1.14)	0.60 (1.10)	0.461
Visual acuity 1 month post surgery [median (IQR)]	0.52 (1.58)	0.61 (0.55)	0.908

IQR: interquartile range

Difference between median value of visual acuity in each group tested with *Mann-Whitney test*

Significant if $p < 0.05$

Table 5 Corneal endothelial cell count before and after surgery

	Intracameral dexamethasone injection group (n=14)	Subconjunctival dexamethasone injection group (n=14)	p-value
Before surgery [median (IQR)]	2517.00 (448.00)	2440.50 (336.00)	0.945
After Surgery (rerata±SD)	1983.86±470.94	2016.64±555.83	0.868
Decreased of endothelial cell counts (rerata±SD)	402.79±215.41	348.71±285.58	0.566

IQR: interquartile range; SD: standard deviation

Difference between median value of endothelial cell count before surgery in each group tested with *Mann-Whitney test*

Difference between the mean value of endothelial cell count after surgery and difference between the mean of endothelial cell count reduction in each group tested with *independent t-test*

Significant if $p < 0.05$

In this study we found the median values of inflammatory cells between the two groups differed significantly in 1 day and 1 week postoperatively. The median flare values between the two groups differed significantly in 1 week postoperatively. The median values of the inflammatory cells decreased and differed significantly between the two groups. Meanwhile, the median flare values decreased in both groups but did not differ significantly. Significant differences were also obtained from the median values of inflammatory cells and flares of both treatment groups at different period of examinations. This suggests that intracameral dexamethasone decreases inflammatory cells greater than subconjunctival dexamethasone at 1 day and 1 week postoperatively. Intracameral dexamethasone also decreases flares greater than subconjunctival dexamethasone at 1 week postoperatively. Decreased inflammatory scores occurred in both treatment groups. but decreased inflammatory cells in the subconjunctival dexamethasone injection group were better than the intracameral dexamethasone injection group.

A study by Chang et al. had found that administration of intracameral dexamethasone significantly decreased inflammatory cells in the anterior chamber of the eyes in glaucoma patients and without glaucoma who underwent cataract surgery.²⁸ Wang et al. in his study found that triamcinolone acetonide injection after phacotrabeculectomy decreased the inflammation and increased the results of visual acuity.⁶ In contrast to this, a study by Koval et al. reported that intracameral triamcinolone acetonide did not affect the success rate of glaucoma surgery.²⁴

The mean intraocular pressure in both groups decreased after surgery and between the two groups was significantly different at 1 week postoperative ($p = 0.026$). The study by Chang et al. demonstrated that intracameral dexamethasone is safely administered after surgery because it only slightly increases intraocular pressure. even the mean TIO decreases by 1.9 ± 1.2 mmHg.²⁸ The study by Gungor et al. compared the administration of dexamethasone with triamcinolone acetonide (TA) intracamera and reported that the mean IOP on both groups did not differ significantly.²⁵ Paganelli et al. in his study found that the IOP score was lower up until 28 days postoperatively in the group receiving subtenon posterior TA injection compared to the group receiving prednisolone drops.³⁰

Intraocular hypertension is a common side effect of intraocular corticosteroids.⁹ Intraocular dexamethasone has a rapid turnover and short half-life of aqueous volume. thereby reducing the risk of ocular hypertension due to steroids as well as

corneal and systemic side effects as a result of the long-term utility of topical corticosteroids.^{25,28} Wang et al. in his study found that triamcinolone acetonide injections that were effective in controlling IOP and steroid-induced glaucoma did not occur because filtration channels were already formed during the phacotrabeculectomy.⁶ Study by Gungor showed that IOP during the first postoperative day was higher in patients receiving triamcinolone acetonide injections than dexamethasone. This is probably due to the particle structure of triamcinolone acetonide.²⁵

The median values of visual acuity in this study did not differ significantly in all examination times. The study by Gungor et al. found that the mean visual acuity of his samples did not differ significantly between the intracameral dexamethasone injection group and the triamcinolone acetonide group.²⁵ Karalezli also reported that the mean visual acuity between the groups receiving triamcinolone acetonide injections compared to the controls in his study was not significantly different for up to 6 months postoperatively.⁹ Chang et al. reported that a decrease in visual acuity between the groups receiving an injection of intracameral dexamethasone and control did not differ significantly. The samples in his study were primary open-angle glaucoma patients with varying degrees of visual field disruption. so it was difficult to assess the visual acuity changes accurately.²⁸ A study by Wang et al. suggested that visual acuity improvements may be delayed due to fibrin formation in fibrinous uveitis after phacotrabeculectomy surgery.⁶

The decline or loss of corneal endothelial cells may be affected by several factors including surgical trauma. Inflammation, infection, genetic abnormalities, age, glaucoma, drug toxicity, and systemic diseases such as diabetes. Decreased endothelial cells count were also accelerated by surgical trauma such as cataract extraction, intraocular lens implantation, corneal transplantation, and in patients with Fuchs' endothelial dystrophy.^{31,32} Decreased endothelial cells count can lead to decreased corneal endothelial function. Dysfunction of endothelial cells will result in endothelial decompensation, corneal edema, and visual acuity impairment.³²

The mean of corneal endothelial cells count before and after surgery as well as the decreased of endothelial cells count between the two groups in this study did not differ significantly. A study by Wang et al. reported no significant difference between the number of corneal endothelial cells before surgery and after surgery.⁶ A study by Jamil et al. on the effect of intracameral dexamethasone on corneal endothelial cells found no significant

difference between the intracameral dexamethasone injection group with control.²⁹ Dexamethasone was found to be able to increase Na-K-ATPase activity and pump function of corneal endothelial cells of mouse cultures.³³

Several factors that play a role in reducing corneal endothelial cells damage includes experienced operator skills. good surgical preparation, choice of materials such as irrigating solution and ophthalmic viscoelastic device, proper surgical technique, and instrument hygiene.^{34,35}

CONCLUSION

Intracameral dexamethasone suppresses inflammation in the anterior chamber of the eyes greater than subconjunctival dexamethasone in open-angle primary glaucoma patients accompanied by cataracts during the first day to 1 month post-phacotrabeculectomy surgery.

CONFLICT OF INTEREST

The researcher does not have a conflict of interest on everything beyond the research objectives.

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