RESEARCH PAPER

COMPARATIVE EVALUATION OF INTRAOCULAR PRESSURE DYNAMICS FOLLOWING STEROID INDUCTION AND EPISCLERAL VEIN CAUTERIZATION FOR ESTABLISHING RABBIT MODELS OF GLAUCOMA: A PRE-EXPERIMENTAL STUDY

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ABSTRACT

Background: Experimental animal models are essential for understanding glaucoma pathophysiology and evaluating potential therapeutic interventions. Rabbits are commonly used in glaucoma research because of their anatomical similarities to the human eye and their relatively low maintenance cost. However, the comparative effectiveness of different glaucoma induction methods in rabbits remains insufficiently explored.

Objective: To compare the effectiveness of steroid administration and episcleral vein cauterization methods in inducing experimental glaucoma in rabbit models based on intraocular pressure (IOP) elevation.

Methods: This preliminary experimental study involved eight male New Zealand rabbits divided into four intervention groups: topical steroid eye drops, subconjunctival steroid injection, three-vein episcleral cauterization, and four-vein episcleral cauterization. IOP measurements were obtained daily for one month using iCare and TonoVet tonometers. Comparative analyses were performed to evaluate the magnitude and duration of IOP elevation among groups.

Results: Steroid-induced models demonstrated higher and more sustained IOP elevation compared with episcleral vein cauterization methods. The mean IOP values were 20.45 mmHg in the topical steroid group, 19.98 mmHg in the subconjunctival steroid group, 19.45 mmHg in the four-vein cauterization group, and 16.69 mmHg in the three-vein cauterization group. Episcleral vein cauterization produced only transient IOP elevation lasting approximately 24 hours.

Conclusion: Steroid-based methods, particularly topical steroid administration, were more effective in producing stable and sustained IOP elevation in rabbit glaucoma models than episcleral vein cauterization techniques.

Keywords: Glaucoma animal model, Rabbits, Intraocular Pressure.

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INTRODUCTION

Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells (RGCs), optic nerve damage, and irreversible visual field loss that may ultimately lead to blindness. It is considered one of the leading causes of permanent blindness worldwide and represents a major global public health burden due to its chronic and asymptomatic progression. Recent epidemiological studies have estimated that the number of individuals affected by glaucoma will continue to increase substantially over the coming decades because of population aging and increased life expectancy. (Tham et al., 2014).

Elevated intraocular pressure (IOP) remains the most important and only modifiable risk factor associated with glaucoma progression. Persistent IOP elevation contributes to mechanical

compression, impaired axoplasmic flow, retinal ischemia, and oxidative stress, resulting in progressive RGC apoptosis and optic nerve degeneration. Although several mechanisms have been implicated in glaucoma pathogenesis, reduction of IOP remains the primary therapeutic target in current glaucoma management (McMonnies, 2017).

Experimental animal models play a crucial role in understanding glaucoma pathophysiology and evaluating novel pharmacological and surgical interventions. Various animal species, including rodents, primates, dogs, pigs, and rabbits, have been utilized to reproduce glaucomatous changes under controlled laboratory conditions. These models are essential for investigating neurodegenerative mechanisms, testing neuroprotective agents, and assessing the efficacy of emerging glaucoma therapies before clinical application. (Ishikawa et al., 2015).

Several techniques have been developed to induce experimental glaucoma, including topical or subconjunctival corticosteroid administration, episcleral vein cauterization, laser photocoagulation, and microbead injection into the anterior chamber. Steroid-induced glaucoma models mimic trabecular meshwork dysfunction and aqueous humor outflow obstruction similar to secondary open-angle glaucoma in humans. In contrast, episcleral vein cauterization increases venous resistance and episcleral venous pressure, leading to transient or sustained IOP elevation depending on the extent of vascular occlusion. (Vecino et al., 2018; Tartara et al., 2018).

Among available laboratory animals, rabbits are widely used in ophthalmic research because of their relatively large ocular size, anatomical similarities to the human eye, ease of handling, and lower maintenance costs compared with larger mammals. Rabbit glaucoma models also facilitate repeated tonometric evaluation and surgical manipulation, making them suitable for translational ophthalmology studies. Despite the availability of multiple induction techniques, direct comparative evaluation of steroid-induced and episcleral vein cauterization methods in rabbit models remains limited. (Gloe et al., 2019).

Therefore, this preliminary experimental study aimed to compare the effectiveness of steroid administration and episcleral vein cauterization methods in inducing experimental glaucoma in rabbits by evaluating the magnitude and duration of intraocular pressure elevation.

MATERIALS AND METHODS

Study Design and Experimental Animals

This study was designed as a preliminary comparative experimental animal study conducted between June and July 2024 at the Animal Laboratory of the Veterinary Teaching Hospital, Hasanuddin University, Makassar, Indonesia. The study used male New Zealand white rabbits weighing 1.5–2.0 kg that were clinically healthy and demonstrated normal motor activity prior to experimentation. The rabbits were acclimatized to the laboratory environment for one week before the intervention period to minimize environmental stress and physiological variability. A total of eight rabbits were initially included in the study. One rabbit was excluded during the adaptation period because of poor clinical condition, resulting in seven rabbits completing the experimental protocol. All animals were housed individually under controlled environmental conditions with free access to food and water throughout the study period.

Experimental Groups and Glaucoma Induction Procedures

The rabbits were divided into four experimental groups according to the glaucoma induction method. In Group I, topical steroid-induced glaucoma was established using Cendo Xitrol® eye drops containing polymyxin B sulfate 10,000 IU, neomycin sulfate 3.5 mg, and dexamethasone 1 mg. One drop was administered to the left eye every 6 hours throughout the observation period. In Group II, steroid-induced glaucoma was produced through subconjunctival injection of triamcinolone acetonide (Trilac®, 40 mg/mL) into the left eye. In Group III, experimental glaucoma was induced by cauterization of three episcleral veins in the left eye. In Group IV, four episcleral veins were cauterized to induce intraocular pressure elevation. All procedures were performed under standardized laboratory conditions.

Intraocular Pressure Measurement

IOP measurements were performed daily for one month using iCare® (iCare Finland Oy, Vantaa, Finland) and TonoVet® (Tiolat Oy, Helsinki, Finland) rebound tonometers. Measurements were obtained at approximately 12:00 PM each day to minimize the influence of diurnal IOP variation. The left eye was evaluated in all experimental groups, and serial IOP values were recorded throughout the study period. Before each measurement session, the tonometers were checked according to the manufacturer's instructions to ensure proper device function. Measurements were performed by an operator who was blinded to the intervention group whenever possible. Multiple readings were obtained for each eye, and the

average value was used for analysis.

Outcome Assessment

The primary outcome of this study was the effectiveness of each glaucoma induction method based on the magnitude and duration of IOP elevation. Secondary observations included the stability of IOP elevation and the time required to achieve peak IOP following intervention.

Statistical Analysis

Data were organized using Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and analyzed using JMP software (JMP Statistical Discovery LLC, Cary, NC, USA). Longitudinal IOP data were analyzed using a linear mixed-effects model to account for repeated measurements obtained from the same animals over time. IOP was included as the dependent variable. Induction method and observation day were included as fixed effects, while rabbit identity was treated as a random intercept.

Pairwise comparisons among induction methods were performed using least-squares means from the linear mixed-effects model with Tukey adjustment for multiple comparisons. A p-value < 0.05 was considered statistically significant. Because of the limited and unequal sample size among groups, all inferential analyses were considered exploratory and interpreted cautiously.

RESULTS

Animal Characteristics and Study Completion

A total of eight male New Zealand white rabbits were initially included in this preliminary experimental study. All animals underwent a one-week acclimatization period prior to intervention in order to minimize environmental stress and physiological variability. During the adaptation period, one rabbit developed poor clinical condition and was subsequently excluded from the study. Therefore, seven rabbits successfully completed the experimental protocol and were included in the final analysis. The final distribution of experimental animals consisted of one rabbit in the topical steroid eye drop group, two rabbits in the subconjunctival steroid injection group, two rabbits in the three-vein episcleral cauterization group, and two rabbits in the four-vein episcleral cauterization group. Throughout the study period, all remaining rabbits maintained stable general condition and demonstrated normal motor activity without severe ocular complications requiring termination of the experiment (Table 1).

Table 1. Summary of intraocular pressure response across rabbit ocular hypertension induction methods.

Experimental Group	Glaucoma Induction Method	Number of Rabbits (n)	Mean IOP (mmHg)	Estimated Minimum IOP (mmHg)	Estimated Maximum IOP (mmHg)	Time to Peak IOP	Duration of Elevated IOP	Pattern of IOP Elevation	Relative Procedural Cost
Group I	Topical steroid eye drops	1	20.45	12	28	Day 11	8 days	Gradual and sustained	Moderate
Group II	Subconjunctival steroid injection	2	19.98	11	27	Day 16	11 days	Stable and prolonged	High
Group III	Three-vein episcleral cauterization	2	16.69	8	22	1-hour post-intervention	24 hours	Rapid and transient	Low
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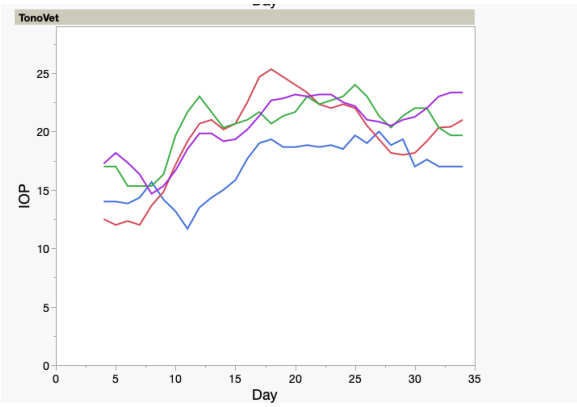
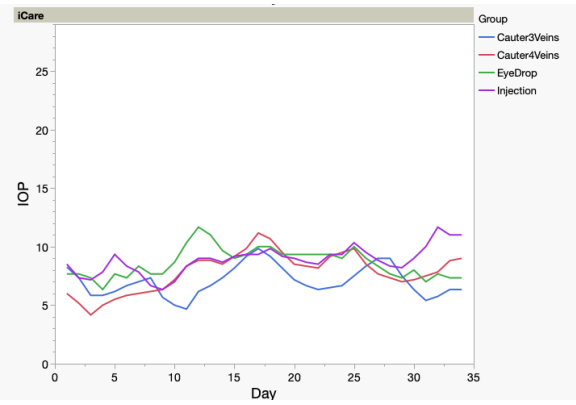
Intraocular Pressure Measurements

Daily IOP measurements were obtained using iCare® and TonoVet® rebound tonometers over a one-month observation period. Measurements were performed at approximately the same time each day to reduce the influence of diurnal IOP fluctuations. Both instruments successfully recorded serial IOP measurements throughout the experimental period. The TonoVet® rebound tonometer consistently produced higher IOP readings compared with the iCare® device in all experimental groups. Measurements obtained using iCare® ranged from 2 to 15 mmHg, whereas TonoVet® measurements ranged from 8 to 28 mmHg. The observed differences between devices may be associated with variations in calibration systems and measurement sensitivity in rabbit eyes. Nevertheless, both instruments demonstrated the ability to detect changes in IOP trends following glaucoma induction procedures. The pattern of IOP elevation varied substantially among intervention groups. Steroid-based induction methods demonstrated more gradual and sustained increases in IOP, whereas episcleral vein cauterization produced rapid but short-lasting elevation shortly after intervention.

Values are descriptive summaries of longitudinal observations; IOP = intraocular pressure.



(A)



(B)

Figure 1. Longitudinal intraocular pressure (IOP) trajectories in rabbit ocular hypertension models induced by steroid administration and episcleral vein cauterization, measured using iCare® (A) and TonoVet® (B) rebound tonometry.

Comparison of Intraocular Pressure Elevation Among Experimental Groups

Among all intervention groups, topical steroid administration demonstrated the highest mean IOP value, reaching 20.45 mmHg. The subconjunctival steroid injection group demonstrated a comparable mean IOP value of 19.98 mmHg. Meanwhile, the four-vein episcleral cauterization group achieved a mean IOP value of 19.45 mmHg, and the three-vein cauterization group produced the lowest mean IOP value at 16.69 mmHg.

The duration of sustained IOP elevation differed considerably between steroid-induced and cauterization-induced glaucoma models. The subconjunctival steroid injection group maintained elevated IOP for approximately 11 days and reached peak IOP on day 16 of observation. Similarly, the topical steroid group demonstrated sustained IOP elevation for approximately 8 days, with the highest IOP recorded on day 11.

In contrast, episcleral vein cauterization methods produced only transient IOP elevation. Both the three-vein and four-vein cauterization groups demonstrated peak IOP elevation within the first hour following the procedure. However, the elevated IOP rapidly declined and returned toward baseline values within approximately 24 hours after intervention. Despite the transient nature of the response, the cauterization methods produced an immediate increase in IOP exceeding 100% compared with pre-intervention values. The four-vein episcleral cauterization group demonstrated slightly higher and more stable IOP elevation than the three-vein cauterization group, suggesting that

a greater degree of venous occlusion may contribute to increased resistance to aqueous humor outflow and temporary elevation of episcleral venous pressure.

An exploratory linear mixed-effects model was performed to compare longitudinal IOP trajectories among induction methods. The model demonstrated a significant overall group effect ($p = 0.0401$), indicating that IOP trajectories differed among the four induction methods. Tukey-adjusted pairwise comparisons showed that the three-vein episcleral cauterization group had significantly lower IOP than the subconjunctival steroid injection group (mean difference: −1.64 mmHg; 95% CI: −3.14 to −0.15; $p = 0.04$). No significant differences were observed between the topical steroid eye drop and subconjunctival steroid injection groups or between the four-vein episcleral cauterization group and the other induction methods (Table 1).

Table 2. Tukey-adjusted pairwise comparisons of longitudinal intraocular pressure trajectories based on exploratory linear mixed-effects analysis using iCare® tonometry.

Intervention Method	Comparison Group	Mean Difference (95% CI)	P-value
Topical steroid eye drops	Subconjunctival steroid injection	-0.12 (-1.89 to 1.65)	0.98
Three-vein episcleral cauterization	Topical steroid eye drops	-1.52 (-3.27 to 0.22)	0.07
	Subconjunctival steroid injection	-1.64 (-3.14 to -0.15)	0.04*
	Four-vein episcleral cauterization	-0.74 (-2.19 to 0.71)	0.21
Four-vein episcleral cauterization	Topical steroid eye drops	-0.78 (-2.51 to 0.94)	0.26
	Subconjunctival steroid injection	-0.90 (-1.89 to 1.65)	0.98

Pairwise comparisons were performed using least-squares means from the linear mixed-effects model with Tukey adjustment for multiple comparisons. Observation day was included as a longitudinal covariate, and rabbit identity was treated as a random intercept. $p < 0.05$ was considered statistically significant and is indicated by an asterisk (*).

Procedural Characteristics of Glaucoma Induction Methods

Each glaucoma induction technique demonstrated distinct procedural advantages and limitations. Episcleral vein cauterization methods required lower procedural costs and shorter intervention times because the procedure was performed only once to induce IOP elevation. In contrast, topical steroid administration required repeated application four times daily throughout the observation period, increasing labor intensity and handling frequency.

Subconjunctival steroid injection required less frequent intervention than topical steroid administration because injections were performed periodically rather than daily. However, steroid-based methods generally required higher material costs compared with cauterization techniques.

From an experimental perspective, steroid-induced glaucoma models demonstrated greater ability to maintain prolonged and relatively stable IOP elevation, making them more suitable for studies investigating chronic glaucomatous neurodegeneration and long-term therapeutic interventions. Conversely, episcleral vein cauterization produced rapid but transient IOP elevation, potentially limiting its applicability for chronic glaucoma studies while remaining useful for acute ocular hypertension models.

Potential complications associated with episcleral vein cauterization included thermal injury to episcleral tissues, ocular surface damage, intraocular inflammation, and retinal ganglion cell injury secondary to thermal stress. These mechanisms may differ from glaucomatous neurodegeneration caused primarily by chronic IOP elevation or oxidative stress, potentially influencing the biological relevance of the experimental model.

DISCUSSION

The present preliminary experimental study demonstrated that steroid-induced glaucoma models produced more stable and sustained intraocular pressure (IOP) elevation compared with

episcleral vein cauterization techniques in rabbits. Among the evaluated methods, topical steroid administration generated the highest mean IOP value, while subconjunctival steroid injection demonstrated the longest duration of sustained IOP elevation. In contrast, episcleral vein cauterization methods induced rapid but transient increases in IOP that returned toward baseline values within approximately 24 hours after intervention. These findings suggest that steroid-based induction methods may provide better suitability for chronic experimental glaucoma models in rabbits. (Tartara et al., 2018).

The sustained IOP elevation observed in steroid-induced models may be associated with corticosteroid-mediated alterations in aqueous humor dynamics. Corticosteroids are known to induce structural and biochemical changes within the trabecular meshwork, including extracellular matrix accumulation, suppression of phagocytic activity, and increased outflow resistance. These mechanisms reduce aqueous humor drainage through the conventional outflow pathway, thereby producing prolonged elevation of IOP similar to steroid-induced glaucoma in humans. (McMonnies, 2017).

The topical steroid group demonstrated slightly higher mean IOP values than the subconjunctival steroid injection group. Continuous topical administration every six hours may have contributed to persistent corticosteroid exposure at the ocular surface and anterior chamber, thereby maintaining sustained trabecular meshwork dysfunction throughout the observation period. However, subconjunctival steroid injection demonstrated longer duration of elevated IOP, possibly because of prolonged local depot effects and slower corticosteroid absorption within periocular tissues. These findings indicate that both methods may be effective for reproducing chronic ocular hypertension under experimental conditions. (Tartara et al., 2018).

In contrast, episcleral vein cauterization methods produced only temporary elevation of IOP despite showing rapid increases shortly after intervention. This phenomenon may be explained by the development of collateral venous drainage and vascular adaptation following episcleral venous obstruction. Increased episcleral venous pressure immediately after cauterization reduces aqueous humor outflow and elevates IOP; however, compensatory vascular mechanisms may subsequently restore venous circulation and reduce pressure elevation over time. Similar transient IOP responses have been reported in previous experimental glaucoma studies using episcleral vein occlusion techniques. (Vecino et al., 2018).

The four-vein episcleral cauterization group demonstrated higher mean IOP values compared with the three-vein cauterization group, suggesting that greater venous occlusion may produce more substantial impairment of aqueous humor drainage. Nevertheless, both cauterization methods failed to maintain prolonged ocular hypertension comparable with steroid-induced models. This limitation may reduce their suitability for studies investigating chronic glaucomatous neurodegeneration or long-term neuroprotective therapies. (Danias et al., 2006).

Differences in IOP measurements between iCare® and TonoVet® tonometers were also observed in this study, with TonoVet® consistently producing higher readings. Previous validation studies have demonstrated that TonoVet® rebound tonometry has strong correlation with manometric IOP measurements in rabbits and may provide more accurate estimates within clinically relevant pressure ranges. Variations between instruments may result from differences in calibration systems, corneal biomechanics, and sensitivity to ocular surface conditions. (Gloe et al., 2019).

In addition to differences in IOP elevation, each induction technique demonstrated distinct procedural advantages and limitations. Episcleral vein cauterization required lower procedural costs and shorter intervention time because the procedure was performed only once. Conversely, steroid-based methods required repeated administration and greater material costs, particularly in the topical steroid group. However, steroid administration produced more stable and prolonged IOP elevation, making these models potentially more appropriate for chronic glaucoma experiments and therapeutic investigations. (Ishikawa et al., 2015).

Potential complications associated with episcleral vein cauterization should also be considered when selecting experimental glaucoma models. Thermal injury during cauterization may induce ocular surface damage, intraocular inflammation, and retinal ganglion cell injury unrelated to chronic glaucomatous mechanisms. Retinal ganglion cell death caused by thermal injury may involve acute necrosis and inflammatory responses that differ biologically from progressive glaucomatous neurodegeneration induced by elevated IOP or oxidative stress. Consequently, the pathological relevance of cauterization-based models may differ from that of steroid-induced glaucoma models. (Blanch et al., 2012).

The present study has several limitations. First, the

sample size was limited and unequal among intervention groups, which may reduce statistical power and limit the generalizability of the findings. Second, evaluation of glaucomatous damage was based primarily on IOP measurements without additional histopathological assessment, retinal imaging, or retinal ganglion cell quantification. Third, the observation period was relatively short and may not fully represent long-term glaucomatous progression. Therefore, the results of this preliminary study should be interpreted cautiously. Future studies involving larger sample sizes, longer observation periods, and additional structural and functional assessments are required to validate the findings of the present study. (Fernández-Albarral et al., 2024).

CONCLUSION

The findings of this study suggest that steroid-induced rabbit glaucoma models provide more stable and sustained ocular hypertension than episcleral vein cauterization methods. These models may therefore offer greater applicability for future experimental studies investigating glaucoma pathophysiology, neuroprotective therapies, and long-term ocular hypertension.

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Author Contributions

R.N conceptualized and supervised the study. R.N and A.A.D performed data collection, experimental procedures, and intraocular pressure measurements. I.C.I and A.A.D conducted data analysis and manuscript drafting. All authors reviewed and approved the final version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with institutional guidelines for the care and use of laboratory animals. Ethical approval was obtained from the appropriate institutional ethics committee prior to the initiation of the study.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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