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Original Research Article

Retinal Thickness After Platelet Rich Plasma Injection in Glaucoma Model Rats

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Abstract

Background: Glaucoma is a disease that can lead to permanent loss of visual function that ranks as second cause of blindness in the world after cataract disease. Platelet-Rich Plasma contains high concentrations of growth factors and components that can accelerate cell regeneration, making it an alternative in minimizing the damage caused by glaucoma.

Objective: The objectives of this study were to analyze the thickness of retinal layers after increasing intraocular pressure, after injection of PRP, and to determine the most effective PRP injection route in repairing cell degeneration in glaucoma model rats.

Methods: This research employed a post-test-only control group design. Twenty-five male Wistar rats were divided into 5 groups (n = 5 each): the positive control group (without an increased IOP and PRP injection), the negative control group (increased IOP without PRP injection), and the treatment group (increased IOP and PRP injection through intravitreal, intraperitoneal, and intravitreal-intraperitoneal routes). Data were analyzed using the Shapiro Wilks test. Normally distributed data were analyzed using a parametric One Way ANOVA hypothesis test. Post-hoc analysis was performed using Duncan's multiple range test ($p < 0.05$).

Results: The results showed that there was a significant effect of PRP injection in the inner plexiform layer, but there was no significant effect of PRP injection in the rod cell layer, cone cell layer, outer nuclear layer, outer plexiform layer, inner nuclear layer, and ganglion cell layer.

Conclusion: Based on the research that has been conducted, it can be concluded that increased intraocular pressure causes thinning of the thickness of the outer nuclear layer, inner nuclear layer, inner plexiform layer, and ganglion cell layer. Intravitreal-intraperitoneal injection of PRP (P3) is a better injection route because it can increase the thickness of the inner plexiform layer.

Keywords: *Platelet Rich Plasma (PRP) Injection; Glaucoma; Intraocular Pressure; Retinal Thickness*
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INTRODUCTION

Glaucoma is a disease that can lead to permanent loss of visual function that ranks as second cause of blindness in the world after cataract disease.

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Glaucoma in Indonesia based on the Indonesian Center for Health Data and Information in 2019 has a prevalence of 0.46%, which means that 4 to 5 people out of 1000 Indonesians suffer with glaucoma. Glaucoma is a chronic degenerative optic neuropathy and most cases of glaucoma are asymptomatic until irreversible and extensive damage occurs.[1] Glaucoma can cause patients to have reduced or even lost vision which then affects their activities in daily life. Glaucoma can be caused by a variety of factors, including age, gender, genetics, as well as food and drug intake. These things can cause an increase in intraocular pressure (IOP) and neurodegenerative in retinal ganglion cells which can trigger the risk of glaucoma.[2] Intraocular pressure will affect retinal ganglion cell death and cause changes to the optic nerve and visual area.[3]

An individual who suffers from glaucoma is often unaware of their condition because glaucoma is usually asymptomatic in its early stages. Most glaucoma patients realize their condition when it is already at a severe stage. The earlier the detection of glaucoma, the greater the chance of success in preventing visual impairment, so there are many alternatives that done to reduce the damage caused by glaucoma.[4] Some of these alternatives include drugs, lasers, and surgery. However, these actions are only limited to helping facilitate the flow of eyeball fluid, but cannot repair damage to nerve cells in the eye. Therefore, the use of Platelet-Rich Plasma (PRP) is expected to be an alternative for glaucoma treatment because PRP can regenerate neurodegenerated nerve cells.[5]

Platelet-Rich Plasma is a blood platelet concentrate that contains high concentrations of growth factors and components that can accelerate cell regeneration. PRP has a platelet concentration above normal value of 94% platelets, 1% erythrocytes, and 1% leukocytes.[6] The presence of growth factor components and this high concentration of platelets, results in a high proliferation and regeneration ability, so that it can heal damaged cells.[7] The use of PRP has started since the 1980s and 1990s which proved to be an effective autologous source to treat surgical disorders.[8] PRP treated bone showed a more rapid healing effect and maturation of skin grafts. The role of PRP in bone healing is to accelerate soft tissue growth and increase bone density by 19-25% within 4-6 months.[9] PRP is often used in the dermatological field because it can heal wounds, restore damaged tissue to normal, and rejuvenate the skin.[10] Growth factors in this case also play a role in accelerating the healing of blood vessels after injury.[11]

The slow detection of glaucoma symptoms leads to delayed treatment, resulting in various studies to prevent and treat permanent blindness caused by glaucoma. Various methods such as laser, surgery, and medication have been used to prevent the condition of glaucoma patients from getting worse and even to cure it. However, these methods cannot reverse the degeneration of eye nerve calls. Untill now, there has been no method that can regenerate nerve cells that have undergone neurodegeneration, so researcb has been conducted on the use of the PRP method with intravitreal, intraperitoneal, and intravitreal-intraperitoneal injection in glaucoma model rats. The numerous benefits contained in PRP make it an alternative option in minimizing and treating the damage caused by glaucoma due to its high growth factor and regeneration capabilities. Therefore, this study was conducted to examine the role of PRP on retinal thickness with intravitreal, intraperitoneal, and intravitreal-intraperitoneal injection routes.

MATERIALS AND METHODS

This study employed a post-test-only control group design. Twenty-five male Wistar rats were divided into 5 groups (n = 5 each). The groups consisted of P0 (postive control), treatment without intraocular pressure (IOP) induction and PRP injection; PN (negative control), treatment with IOP induction without PRP injection; P1, treatment with IOP induction and intravitreal PRP injection 0.01 ml; P2, treatment with IOP induction and intraperitoneal PRP injection 0.3 ml; and P3, treatment with IOP induction and intravitreal PRP injection 0.01 ml + intraperitoneal injection 0.3 ml. The dosage was determined based on preliminary research and dissertation research by Hajar (2023). Intravitreal PRP injection is conducted by injecting PRP into the midvitreous cavity through the sclera, while intraperitoneal PRP injection is conducted by injecting PRP through the abdominal cavity. Observation of PRP injection was done for 8 weeks.

Ethical Research. This study has obtained ethical approval for using animals from the Research Ethics Commission of the Faculty of Veterinary Medicine, Syiah Kuala University No. 184/KEPH/XI/2022 issued on November 23, 2022.

Induction of Increased Intraocular Pressure. Induction of glaucoma in experimental animals was carried out in groups PN, P1, P2, and P3. Rats were anesthetized by intraperitoneal injection of ketamine and xylazine and in the eyes of rats were given topical anesthesia Cendo Pantocain which contains the active ingredient Tetracaine Hydrochloride. After that, the cannulation process was continued. This procedure involves injection a Ringer's lactate solution into the white part of the eye (sclera) Increased IOP pressure is done using a syringe pump. Intraocular pressure was maintained at 250 mmHg until 60 minutes, and IOP pressure is also measured using a syringe pump device Intraocular pressure was maintained until 60 minutes, then the cannula was removed from the front eye chamber so that the IOP returned to its original pressure. The rat cornea was given one drop of moxifloxacin antibiotic eye drops.

PRP Preparation. Ten donor rats were anesthetized with ether, then 2 mL of blood was taken from the heart and collected in a 9 mL tube containing anticoagulant. Samples were centrifuged at 580x g for 8 minutes at room temperature (Endoret system centrifuge). Results were collected after centrifugation, avoiding buffy coat containing leukocytes using the Endoret ophthalmology kit (BTI biotechnology institute, S.L., Minano, Alava, Spain). The supernatant was incubated at 37°C for one hour and at 56°C for 60

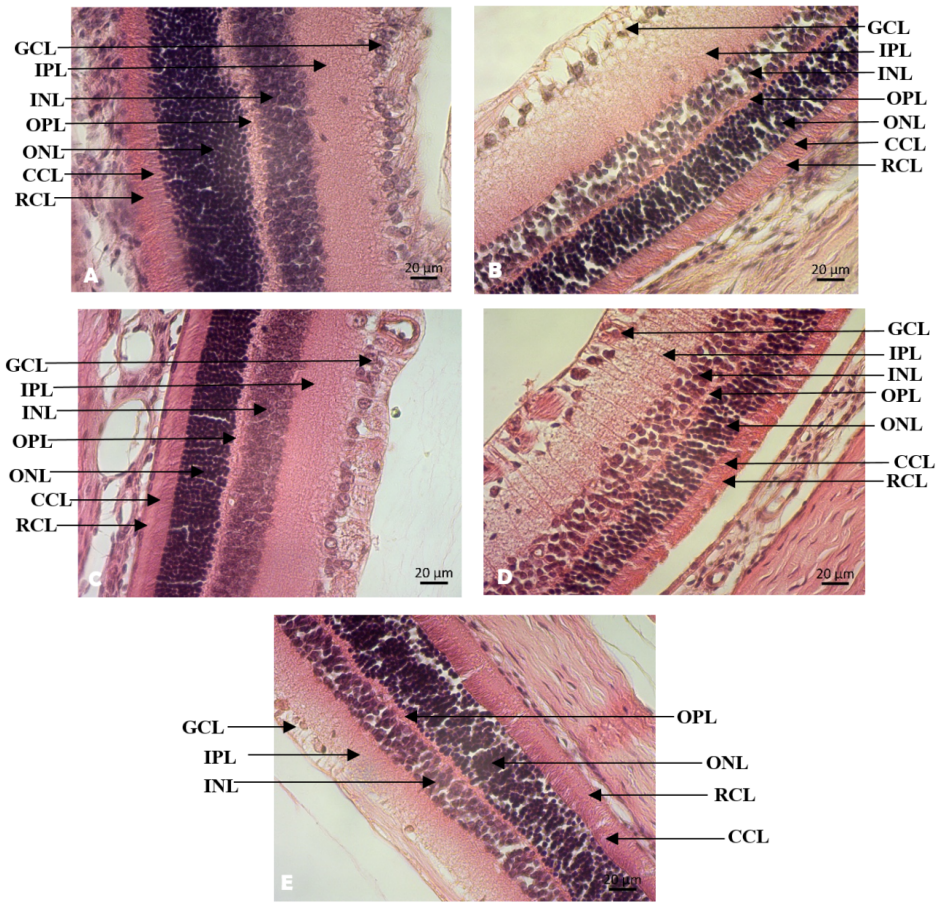

Figure 1. Histology structure of retinal layer of rats eye glaucoma model after platelet rich plasma injection. Notes: Based on the figure, it can be seen that the ONL, OPL, INL, and IPL in normal control group (A) are thicker and the cells are tightly packed compared to PN (B), P1 (C), P2 (D), and P3 (E). (RCL = Rod Cell Layer; CCL = Cone Cell Layer; ONL = Outer Nuclear Layer; OPL = Outer Plexiform Layer; INL = Inner Nuclear Layer; IPL = Inner Plexiform Layer; and RGC = Retinal Ganglion Cell) 400x magnification, HE staining.

minutes. The supernatant plasma was filtered, separated, and stored at -20°C until use.[12]

Sample Collection and Histological Preparation. On the 61st day of observation, rats were sacrificed and enucleated in the eyes of the treated and untreated group. The collected organs were the eyes more precisely on the optic disc to the peripapillary retina which were then immersed in 10% NBF and Davidson's solution. The collected organs were dehydrated using graded alcohol and paraffin block preparation. Then staining was performed on histological preparations using Hematoxylin Eosin staining.

Data Analysis. The retinal thickness measurement data that has been collected is processed statistically by first testing the normal distribution using the Shapiro Wilks test. Normally distributed data were analyzed by One Way ANOVA parametric hypothesis test. Post-hoc analysis was performed using Duncan's multiple range test ($p < 0.05$). Data analysis using SPSS Statistic 25.

RESULTS

The normality test results show that the data is normally distributed (sig>0.05). the homogenity test results (sig>0.05) showed that the data came from a population with homogeneous variations. The results of the ANOVA test on the thickness of retinal layer show the effect of PRP injection on the outer nuclear layer, inner nuclear layer, inner plexiform layer, and ganglion cell layer. The complete data can be seen in Table 4.1.

Based on Table 1, the results of the Analysis of Variant (ANOVA) test show the effect of PRP injection ($P<0.05$) on the inner plexiform layer and ganglion cell layer, but there is no PRP injection effect on the rod cell layer, cone cell layer, outer nuclear layer, outer plexiform layer, and inner nuclear layer. The results of further tests on the inner plexiform layer showed a significant effect between treatment P0 (45,496 ± 14,055) and P3 (40.640 ± 6.098) with PN (28.963^{a} ± 3.745), but P0 and P2 were not significantly different from P1 (33.669^{ab} ± 3.598), and P2 (34.478^{ab} ± 2.449). The treatment of PN (28.963 ± 3.745) showed no significant effect with the treatment of P1 dan P2. The P0 dan P2 treatments were significantly different from PN, indicating a significant effect on the treatment of intraocular pressure induction and PRP injection through the intravitreal-intraperitoneal route.

DISCUSSION

Based on Table 1, it was found that there was no effect between treatments on the photoreceptor cell layer. This indicates that the treatment of increased

Table 1. Mean values of retinal layer thickness measurement in various platelet-rich plasma (PRP) treatment.

Layer Type	Groups				
	P0	PN	P1	P2	P3
Rod Cell Layer	7.757 ± 2.193	7.984 ± 1.493	6.008 ± 2.054	7.164 ± 1.602	8.447 ± 2.305
Cone Cell Layer	9.561 ± 2.757	9.579 ± 2.424	9.353 ± 2.704	8.208 ± 0.783	9.949 ± 3.222
Outer Nuclear Layer	43.086^{b} ± 3.209	38.491^{ab} ± 7.098	35.601^{a} ± 4.639	39.787^{ab} ± 3.923	42.407^{ab} ± 5.621
Outer Plexiform Layer	7.051 ± 2.927	4.844 ± 2.924	4.408 ± 2.195	4.826 ± 0.832	4.525 ± 2.598
Inner Nuclear Layer	37.295^{b} ± 4.796	27.669^{a} ± 5.407	28.286^{a} ± 6.530	31.522^{ab} ± 3.490	31.747^{ab} ± 6.524
Inner Plexiform Layer	40.187^{b} ± 4.446	28.963^{a} ± 3.745	33.669^{a} ± 3.598	34.478^{a} ± 2.449	40.640^{b} ± 6.098
Ganglion Cell Layer	26.647^{b} ± 6.737	18.856^{a} ± 4.899	23.273^{ab} ± 3.551	20.743^{ab} ± 3.515	22.514^{ab} ± 6.153

Note: Different superscript letters (a and b) indicate significant differences ($P<0.05$), which means there is a significant treatment effect on the outer nuclear layer between P0 and P1, on the inner nuclear layer between P0 with PN and P1, on the inner plexiform layer between P0 and P3 with PN, P1, and P2, on the ganglion cell layer between P0 and PN, and there is no significant treatment effect on the rod cell layer, cone cell layer, and outer plexiform layer. (P0 = treatment without IOP induction and PRP injection; PN = IOP induction treatment without PRP injection; P1 = IOP induction treatment and 0.01 ml intravitreal PRP injection; P2 = IOP induction treatment and 0.3 ml intraperitoneal PRP injection; and P3 = IOP induction treatment and 0.01 ml intravitreal + 0.3 ml intraperitoneal PRP injection.

intraocular pressure and PRP injection via intravitreal, intraperitoneal, and intravitreal-intraperitoneal routes does not affect the thickness of the rod cell layer and cone cell layer. The unaffected treatment on both photoreceptor layers indicates that the treatment of increased intraocular pressure (IOP) has no impact on black white and color vision. It is suspected that the damage to the photoreceptor layer du to increased IOP is still at a very early stage, so the damage has not yet had an impact on the photoreceptor cells. There was no significant difference in the value of retinal photoreceptors among the three groups of primary open-angle glaucoma patients, but there was a difference in density, namely a decrease in photoreceptor cell density in primary open-angle glaucoma patients when compared to patients with healthy eyes.[13]

Furthermore, based on Table 1, it is found that P0 is significantly different from P1, but P0 is not significantly different from PN, P2, and P3. P1 is not significantly different from PN, P2, and P3. P0 which is not significantly different from PN and PN which is not significantly different from P1 indicates that the treatment of increasing intraocular pressure and injection PRP does not have an impact on the thickness of the outer nuclear layer. This can also be seen from P2 and P3 which are not significantly different from P0. Tong et al also found that there was no change in the Outer Retinal Complex (ORC) in glaucoma patients, including the outer nuclear layer and the outer plexiform layer located in it.[14]

The result obtained that the thickness of P1 is lower than that of PN is suspected to due to the intravitreal injection of PRP in P1, which is given directly to the eye which is a very sensitive area, so it can cause excessive stress and side effects. Intravitreal injection can cause irritation, conjunctival bleeding, corneal abrasion, and iritis.[15] Intravitreal injection can cause retinal inflammation and vasculitis which can cause significant vision loss.[16]

Although there is no effect between treatments, it can be seen that the thickness value of the three layers (Outer Nuclear Layer, Outer Plexiform Layer, and Inner Nuclear Layer) is higher in P0 than the other treatment groups. The average thickness of the outer retinal layer where the outer nuclear and outer plexiform layer are included, is thicker in the early stage glaucoma group compared to the moderate and severe stage glaucoma groups. However, the thickness of the outer retinal layers in the early stage glaucoma group was thinner than the normal control group. The outer plexiform layer found that there was no difference superscripts, indicates that there is no effect of PRP treatment, meaning that there is no healing effect from PRP on this layer. This indicates that increasing intraocular pressure and PRP injection had no impact on the thickness of the outer plexiform layer. In addition, it is suspected that the outer plexiform layer is not sensitive to IOP increased treatment. Furthermore, based on Table 1, it can be seen that the highest thickness value of the outer plexiform layer is found in P0, which is 7.051 μm. The thickness of the outer retinal layer was thicker in the control group than in the glaucoma group.[17]

The inner nuclear layer showed that P0 was significantly different from PN and P1, but not significantly different from P2 and P3. P2 and P3 were not significantly different from PN and P1, so it can be said that increasing IOP and PRP injection did not have a significant effect. However, when compared between

PRP treatments, the lowest inner nuclear layer thickness was obtained in P1 compared to P2 and P3 at 31.522 and 31.747 µm. It is suspected that P1 has an injection route that has a higher risk of causing excessive stress than other injection route treatments. The lowest inner nuclear layer thickness was obtained in PN which is an IOP increase treatment without PRP injection. Research conducted by Shen et al, in the group that was given high intraocular pressure, it was seen that in the inner nuclear layer (INL), the core shrank and the arrangement became sparse.[18] This can be seen in Figure 1. (B) which shows the retinal layers after increasing IOP without PRP injection. Based on the figure, it can be seen that the cell density is reduced and the arrangement of cells becomes more sparse when compared to other treatments, especially P0 which has a higher density and a tighter arrangement.

The inner plexiform layer showed that P0 and P3 were significantly different from PN, P1, and P2, so there was a significant effect between the normal control treatment (P0) and P3 with the negative control treatment (PN), P1, and P2. This indicates that the increase in IOP and the injection of PRP have a significant effect, where intravitreal-intraperitoneal injection of PRP can repair damage due to increased IOP by increasing the layer thickness. The thickness of inner plexiform layer in P3 of 40.640 µm is quite different from PN which is 28.963 µm. Based on this, it is suspected that the inner plexiform layer is quite sensitive to an increase in IOP. This can be because IPL is a layer where there are dendrites from ganglion cells. Structural and functional changes in the Inner Plexiform Layer (IPL) are early stages in a disorder such as glaucoma, before the loss of ganglion cell soma.[19] IPL thinning is associated with Retinal Ganglion Cell (RGC) injury in pre-perimetric glaucoma (PPG), early glaucoma, and advanced glaucoma. Research by Kalloniatis et al. (2013) based on Optical Coherence Tomography (OCT) also showed a reduction in thickness at IPL indicating that retinal ganglion cells are impaired due to glaucoma.[20]

The damage that occurs in the IPL is thought because the IPL contains part of the ganglion cells, which is the dendrite. Glaucoma will cause damage to ganglion cells and all its parts, including the dendrites located in the IPL. In addition, the IPL also contains cells that receive and process visual information before being forwarded to the ganglion cell layer. Damage due to glaucoma does not only occur in the RGC, but also in the IPL. Glaucoma-induced damage to the RGC will cause axonal and somatic changes as well as dendrites accompanied by morphological changes in RGC dendrites found in the IPL. This indicates that damage to the dendrites precedes other ganglion cell parts.[21] Dendrites are the first structure to be damaged in the early stages of glaucoma.[22] Opposite to the decrease in IPL thickness, there was a significant increase in visual field disability, but there was no significant decrease in the overall thickness of the RGC.[23] Glaucoma effects on IPL layer thinning associated with horizontal hemifield visual field disability. The horizontal hemifield is the part of the visual field that can be seen with both eyes.[24]

The treatment of PRP on the thickness of the inner plexiform layer found that P3 was significantly different from P1 and P2. This indicates that P3 showed the best results compared to P1 and P2. P3 is an IOP increase treatment and a combination of intravitreal and intraperitoneal PRP injection. The combination of PRP injection through two different routes of injection is thought to be more effective in increasing cell regeneration. PRP injection that is rich in growth factors can increase the ability of tissue regeneration. The high platelet content in PRP plays a role in cell regeneration derived from secretion of growth factors by platelets. Growth factors will signal to injured cells to proliferate and differentiate to the repair themselves.[25]

PRP is also believed to reduce intraocular pressure, preventing further damage from occuring. A decrease of the intraocular pressure in glaucoma patients after the injection of Plasma Rich in Growth Factor (PRGF) eye drop therapy. PRGF contains Platelet-Derived Growth Factor (PDGF), Fibroblast Growth Factor (FGF), and Transforming Growth Factor (TGF) which can accelerate injury healing time, increase cell proliferation, and reduce scar formation.[12] Furthermore, the ganglion cell layer showed that P0 was significantly different from PN. This indicates that an increase in IOP has a significant effect on the ganglion cell layer, which decrease the thickness of the ganglion cell layer. The decreased retinal thickness is thought to be caused by damage experienced due to the application of increased IOP. Increased IOP is one of the main causes in the development of glaucoma. Increased IOP is believed to cause a reduction in retinal thickness. In the eye group that had high intraocular pressure, had a lower thickness of the retinal nerve fiber layer.[26] In the various treatments of PRP injection, there was no significant difference in the thickness of the ganglion cell layer. This indicates that the injection of PRP has not been able to repair damage due to increased IOP in the ganglion cell layer. It is suspected that this layer is a layer that is difficult to repair because in this layer, there is a collection of nerve cells so it is more susceptible to damge. Among all neurons, ganglion cell are neurons that require the highest energy so they are more prone to mitochondrial dysfunction which causes apoptosis.[27]

In addition, the injetion of PRP through various routes that do not have significant differences is thought to be related to the frequency of PRP injection which is still quite low, which is only given once. PRP that injected to rats to heal injured bone marrow showed that PRP improves locomotor recovery, promotes angiogenesis and nerve regeneration, and modulates blood vessel size. In addition, the therapeutic effect was found to be better in the group with continuous PRP injection for six days than in the group with a single dose of PRP injection.[28]

The decrease in thickness of the ganglion cell layer, inner plexiform layer, inner nuclear layer, outer plexiform layer, and outer nuclear layer seen in PN indicates that the IOP inrease treatment has an impact on layer thickness, which is a decrease in layer thickness in the group induced by increased IOP. Increased IOP is thought to cause mechanical stress that

cause damage to cells which then leads to apoptotic mechanisms. High intraocular pressure is the main cause of glaucoma, especially in ganglion cells which will lead to apotosis. Apoptosis can be caused by various things, including neurotrophin deficiency, excitoxicity, ischemia, oxidative stress, and others, where in this study, the increase in IOP is thought to be the cause of apoptosis because it causes cell damage and ultimately death.[29]

CONCLUSION

Based on the research that has been conducted, it can be concluded that increased intraocular pressure causes thinning of the thickness of the outer nuclear layer, inner nuclear layer, inner plexiform layer, and ganglion cell layer. Intravitreal-intraperitoneal injection of PRP had a significant effect on the thickness of the inner plexiform layer. Intravitreal-intraperitoneal injection of PRP (P3) is a better injection route because it can increase the thickness of the inner plexiform layer.

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