

Comparative Assessment of Post-Operative Eye Pain and Ocular Surface Inflammation of 9-0 Nylon and 8-0 Polyglactin 910 Sutures Following Sclerotomy Wound Closure after Pars Plana Vitrectomy

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How to cite this paper: Wangdi, L., Halim, W.H.W.A., Yong, M.H., Naffi, A.A. and Bastion, M.-L.C. (2026) Comparative Assessment of Post-Operative Eye Pain and Ocular Surface Inflammation of 9-0 Nylon and 8-0 Polyglactin 910 Sutures Following Sclerotomy Wound Closure after Pars Plana Vitrectomy. *Open Journal of Ophthalmology*, 16, 267-278.

<https://doi.org/10.4236/ojoph.2026.163023>

Received: May 21, 2026

Accepted: July 31, 2026

Published: August 3, 2026

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Abstract

Background: In pars plana vitrectomy (PPV), three-port sclerotomy wounds are invariably created and sutured when there is leakage. Absorbable sutures such as 8-0 polyglactin 910 (Vicryl) are preferred because of their self-absorbable nature, however suture reactions can occur. The aim of this study was to compare the post-operative eye pain and ocular surface inflammation of two types of sutures following sclerotomy wound closure. **Method:** A randomized clinical trial was conducted whereby 72 patients received either 9-0 nylon or 8-0 polyglactin 910 for the sclerotomy wound closure following PPV. The participants were provided with standard post-operative care and assessed for eye pain, ocular surface inflammation, suture integrity, and suture-specific complications such as abscess formation on post-operative days (PODs) 1, 7, and 30. Their pain was measured based on the visual analog scale. Ocular surface inflammation was measured based on slit lamp biomicroscopy and scored as 1 = mild wound hyperemia-redness of surrounding conjunctiva, episcleral, or scleral tissues, 2 = moderate wound edema-subconjunctival edema, episcleral, or scleral edema, or 3 = severe wound hypertrophy or papillary or granulomatous hypertrophy of the conjunctiva, episclera, or scleral tissue. The Mann-Whitney U test was used to assess the mean and median scores for eye pain, ocular surface inflammation, and suture integrity, with a P value of <0.05 con-

sidered statistically significant at the 95% confidence interval. **Results:** The mean pain score and the ocular surface inflammation score for the patients who received the 8-0 polyglactin 910 sutures were higher than the scores for those who received the 9-0 nylon sutures during all post-operative follow-ups. Suture-induced ocular surface inflammation was significantly lower in the 9-0 nylon group, especially on POD 1 ($P = 0.007$, $U = 438$, with medium effect size; $r = 0.45$) and POD 7 ($P = 0.00$, $U = 331$ with a large effect size; $r = 0.64$). While 97.22% of the 9-0 nylon sutures were intact on POD 30, the 8-0 polyglactin 910 suture started to disintegrate as early as POD 7 and by POD 30, 33.56% of the 8-0 polyglactin 910 sutures were either loose or broken and required removal. No other suture-related complications, such as suture abscess, wound leakage, or hypotony, were observed in either group. **Conclusion:** After sclerotomy closure following PPV, 9-0 nylon sutures caused less eye pain and ocular surface inflammation than 8-0 polyglactin 910 sutures.

Keywords

Sclerotomy, Pars Plana Vitrectomy, Wound Suture, Ocular Pain, Ocular Surface Inflammation

1. Introduction

Pars plana vitrectomy (PPV) is one of the most common vitreoretinal surgeries performed for various retinal, vitreous, and choroidal disorders [1] [2]. The procedure has gained popularity for procedures such as retinopexy, membrane peeling, endo-laser, removal of traction and media opacities, retinotomies, and retinectomies [1]. During PPV, sclerotomies are created to gain access to the intraocular content. Sclerotomies are, however, associated with the risk of wound leakage, hypotony, choroidal detachment, and endophthalmitis [3]. In one retrospective study of 322 eyes that underwent 23 G PPV, the incidence of hypotony resulting in sclerotomy-associated wound leakage was found to be 3.8% on post-operative day (POD) 1, and a similar incidence of 3.39% was noted in other studies [2] [4]. In some instances, the procedure also caused post-operative endophthalmitis and recurrent vitreous hemorrhage [5] [6]. There are many known risk factors associated with sclerotomy wound leakage, including the size and types of sclerotomy wounds created during PPV, the age and gender of the patient, laterality, the surgical duration, the preoperative diagnosis (macular or non-macular), the use of endotamponade, a history of previous vitrectomy and surgeons in training [7] [8].

Small-gauge trans-conjunctival PPV (25 G or 27 G) is generally preferred over the conventional large-gauge PPV (20 G or 23 G) because it can create self-sealing sclerotomy wounds [3] [9]. Suture-less sclerotomies save surgical time and cause less post-operative pain and ocular surface inflammation. However, when leakage is persistent after surgery, sutures are necessary to secure the wounds, especially those from large-gauge sclerotomy [10]-[12]. Endophthalmitis after PPV is un-

common but more severe than that related to post-cataract surgeries because the vitreous cavity is directly accessible to infection through sclerotomy wound. Hence, leaking wounds should be sutured. In addition, sutured sclerotomies have a lower risk of wound leakage and vitreous incarceration at the wound and lesser risk of post-operative hypotony [3]. Sclerotomy wounds are also often sutured when endotamponade agents such as silicone oil, gasses or air are used. Sutured sclerotomy wound also prevents the leakage of silicon oil into the subconjunctival or sub-tenon spaces which can result in long-term ocular redness and discomfort [13].

The use of sutures for ocular wound closure can cause post-operative pain, discomfort, irritation, suture-related toxicity, ocular surface inflammation, dry eyes, and tear film instability [14] [15]. A study comparing polyglactin 910 and nylon for pterygium graft suturing found out that polyglactin 910 caused slightly higher early-stage inflammation, whereas nylon sutures were more likely to remain stable and becomes buried over time [16]. However, no significant difference was observed between polyglactin 910 and nylon with respect to patients' discomfort levels [16]. Based on the Ocular Surface Disease Index (OSDI) assessment, sutured sclerotomies have been associated with significantly higher scores for vision-related symptoms, ocular symptoms and environmental triggers [15]. Sclerotomy wounds are usually secured with smaller size sutures with high tensile strength to prevent suture-related ocular surface inflammation and wound dehiscence. Various suture materials have been used to secure sclerotomy wounds, including absorbable sutures such as 8-0 Vicryl (polyglactin 910), non-absorbable 8-0 plain gut, synthetic polyamide (9-0 nylon), and 8-0 polypropylene [11]. The degree of ocular adverse reactions associated with sutures differs depending on the type of suture materials used [14]. One comparative study found that plain gut caused less post-operative pain and scleral inflammation at both one-week and one-month follow-ups than polyglactin 910 [17]. 8-0 Polyglactin 910, which is an absorbable and braided suture is a popular choice for scleral wound closure. Non-absorbable and non-braided nylon suture is a popular choice for cornea and limbal wounds closure. The differences between these two materials for sclerotomy closure have not been previously documented, and when sutures are necessary, patient comfort and ocular surface reactions are clearly important considerations. Accordingly, the main objectives of this study were to compare the post-operative eye ocular pain, ocular surface inflammation, and the suture-specific complications between patients who received 9-0 nylon sutures and patients who received 8-0 polyglactin 910 sutures following sclerotomy wound closure after PPV.

2. Methodology

Because the aim of this study was to document the real-world clinical profile of the patients after sclerotomy wound closure with 9-0 nylon and 8-0 polyglactin 910 following PPV, it was designed as randomized clinical trial. The study was conducted over one year, from June 1, 2024, through May 30, 2025, at Hospital

Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia. Prior to the study, ethical approval was obtained from the Research Ethics Committee of the National University of Malaysia (UKM.FPR.SPI 800-1/3/23) and written informed consents were obtained from all the participants. All patients aged 18 years and above who were scheduled for the routine elective PPV were included in this study. A minimum of one sutured sclerotomy port was used as the selection criterion, irrespective of the gauge or the size of the PPV port used. The suture materials used were either 9-0 nylon or 8-0 polyglactin 910. Those who underwent sutureless PPV or PPV following ocular trauma or infective conditions, pregnant patients and those who received sutures for purposes other than sclerotomy wound closure were excluded from the study.

During the closure of PPV, the sclerotomy ports were sutured with either 9-0 nylon or 8-0 polyglactin 910 based on a simple random sampling method. The participants were assigned to either the 8-0 polyglactin 910 group or the 9-0 nylon group based on a computer lottery program to ensure equal chance of receiving either type of suture [18]. The participants were blinded regarding the type of sutures that they received but the assessors were not. Three vitreoretinal surgeons who had worked together and used similar techniques for creating sclerotomies performed the surgeries. The sample size for the study was calculated using the power and sample size software version PS.3 [19]. Since the study involved two independent groups of equal size, an unpaired t-test was used for sample size calculation. To detect a 10% difference between the two groups using a standard deviation of 15%, with $\alpha = 0.05$ and a power of 80% based on previous similar studies [17], and considering 10% drop-out and non-response rate, the total sample size calculated was 80. However, 4 participants from each group defaulted and were lost to follow-up, so a total of 72 samples, 36 from each group were analyzed in this study.

Participation in this study did not influence the nature of the surgery or the standard post-operative care that the patients received. After the surgery, each participant was reviewed on PODs 1, 7, and 30. During all the PODs, eye pain, integrity of sutured sclerotomy wounds and ocular surface inflammation were assessed. All the post-PPV patients had visual acuity measured with the Snellen eye chart, intraocular pressure (IOP) measured with a Goldman applanation tonometer and underwent thorough slit lamp examination. During the slit lamp examinations, the integrity of the sclerotomy wounds and the presence of ocular surface inflammation were noted, followed by routine anterior and posterior segment examination of the operated eyes. The operated patients received, standard regime of 2-hourly topical steroid and antibiotic with combined steroid-antibiotic ointment at night, with or without oral acetazolamide for control of IOP to ensure that it has no direct influence on ocular pain or inflammation. At the end of POD 30, the sutures were removed from the sclerotomy site using a fine needle and forceps.

Assessment of Post-Operative Eye Pain

During each visit, eye pain was assessed using a visual analog scale (VAS), which

is a validated scale for rating the degree of pain that can be assessed with either a traditional paper-based scale or a digital-based scale, both of which have been found to be equally effective [20]. The eye pain scores were determined using a paper-based VAS. Each participant received a VAS to mark the level of pain during each clinic visit. The severity of ocular pain was recorded using the VAS score as 0 = no pain, 1 - 3 = mild pain and a minimal impact on daily life, 4 - 6 = moderate pain and a moderate impact on activity of daily life, or 7 - 10 = severe pain and a major impact on daily life.

Assessment of Post-Operative Ocular Surface Inflammation

The measurement of suture-related inflammation of the ocular surface was based on a similar previous comparison of nylon and polyglactin sutures following pterygium surgery [16]. The ocular surface inflammation of the wounds was scored as 0 = absence of hyperemia, edema, or hypertrophy, 1 = mild hyperemia with redness of the surrounding conjunctiva (episcleral or scleral tissues), 2 = moderate subconjunctival, episcleral or scleral edema, or 3 = severe papillary or granulomatous hypertrophy of conjunctiva, episclera, or scleral tissues.

Assessment of Suture-Specific Complications

During each clinic visit, suture-specific complications were assessed for the members of the 9-0 nylon and 8-0 polyglactin 910 groups, specifically, suture integrity (whether the sutures were intact, loose, or broken) and suture infection (suture abscess). The scores assigned for suture integrity were 1 = broken sutures, 2 = loose sutures, or 3 = intact sutures.

2.1. Data Management

The participants' demographic profiles, including their age, gender, and ethnicity were recorded. The details of the surgery including; indications for surgery, the size of the PPV gauge used, the type and number of the sutures used to close the sclerotomy wounds, and the use of silicone oil or another tamponade agents were noted. The compiled data were maintained and stored in a password-protected system by the principal investigator. Later, the data were exported to Statistical Package for Social Sciences for Windows (SPSS; SPSS Inc., Chicago, IL, USA) (version 26) for analysis.

2.2. Statistical Analysis

The SPSS Program was used for the statistical analysis. The descriptive statistics were used to characterize the demographic and clinical characteristics of the patients. The data distribution was checked for normality and for outliers using the Shapiro-Wilk test of normality at a 0.05 significance level, which revealed a non-normal distribution of the data. In addition, the scores for ocular pain, ocular surface inflammation, suture integrity, and suture abscess followed an ordinal scale rather than continuous values. Therefore, the Mann-Whitney U test was used for the analysis, with $\alpha = 0.05$. The rank-biserial correlation (r) was also reported as an effect size to validate the significance (P) values. At the 95% confidence in-

terval (CI), a P value of less than 0.05 was considered statistically significant. The interpretation of *r* was based on Cohen's benchmark of effect size (small = 0.1, medium = 0.3, large $\geq$ 0.5).

3. Result

72 participants who were enrolled in this study were divided equally into 8-0 polyglactin 910 and 9-0 nylon groups. The participants ranged in age from 23 to 97 years; their mean age was 61.16 years. Forty-four of the participants (61.11%) were local residents belonging to the Malay ethnic group, 28 (29.17%) were ethnic Chinese, and 7 (9.72%) were ethnic Indians, as shown in **Table 1**.

Table 1. Patient demographics.

Demographic profile	8-0 Polyglactin 910 (n)	9-0 Nylon group (n)	Total n (%)
Gender:			
Male	15	13	28 (38.89%)
Female	21	23	44 (61.11%)
Mean age (years):	63.16	59.77	61.47
Ethnicity:			
Malay	22	21	43 (59.72%)
Chinese	10	11	21 (29.17 %)
Indian	4	4	8 (11.1%)

Among the participants, 66.67% underwent 25 G PPV, and 31.94% underwent 23 G PPV, as shown in **Table 2**. In both suture groups, 25 G PPV was the most common surgery performed: in the 8-0 polyglactin 910 group, 25 of the 36 participants (69.44%) underwent 25 G PPV surgery; in the 9-0 nylon group, 23 of the 36 participants (63.89%) had 25 G PPV surgery; **Figure 1**. Overall, the most common indications of PPV surgery were retinal detachment (RD), in 31 (43%) of the cases, followed by vitreous hemorrhage (VH), in 10 (14%) of the cases, as shown in **Figure 2**. During the PPV surgery, the most common endotamponade used were gas, in 25 cases (34.72%), and air in 20 cases (27.78%), whereas 16 cases (22.22%) involved no endotamponade as shown in **Table 2**. In both suture groups, again, the most common endotamponade was gas, followed by air. The types of endotamponade were not equally divided between the two suture groups.

Table 2. Size of PPV and the usage of endotamponade between the two suture groups.

	9-0 Nylon (n)	8-0 Polyglactin 910 (n)	Total; n (%)
PPV G size			
23 G	12	11	23 (31.94%)
25 G	23	25	48 (66.67%)
27 G	1	0	1 (1.39%)

Continued

Endotamponade			
Air	11	9	20 (27.78%)
Gas	15	10	25 (34.72%)
Silicon oil	4	6	10 (13.89%)
Densiron	0	1	1 (1.39%)
None	6	10	16 (22.22%)

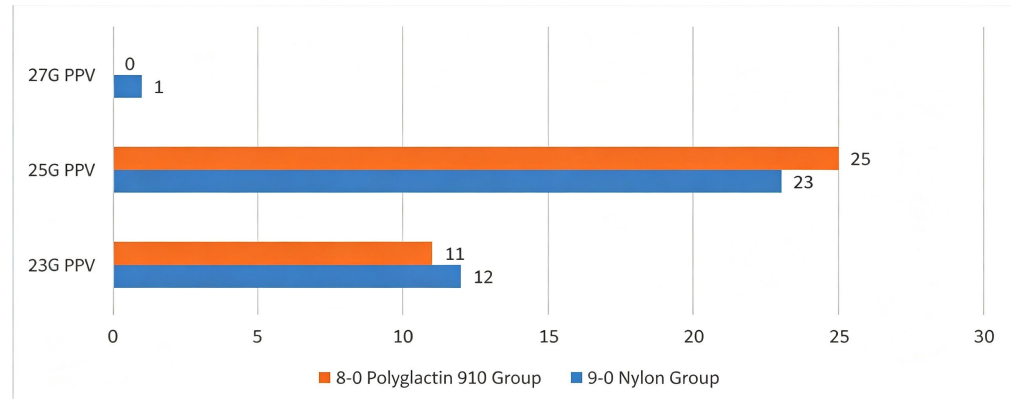


Figure 1. Types of PPV between the two suture groups. PPV: pars plana vitrectomy; G: gauge.

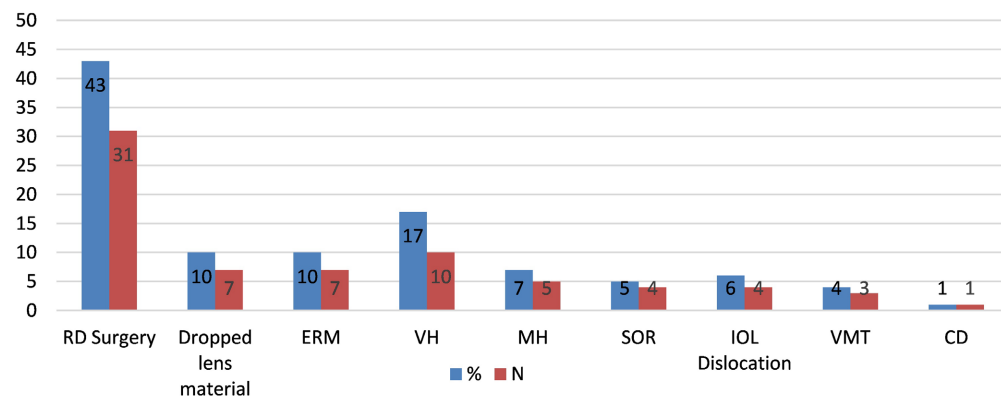


Figure 2. Indications of pars plana vitrectomy. CD: choroidal detachment; ERM: epiretinal membrane; IOL: intraocular lens; MH: macular hole; RD: retinal detachment; SOR: silicone oil removal; VH: vitreous hemorrhage; VMT: vitreomacular traction.

The comparative analysis revealed that the post-operative mean score of eye pain in the 8-0 polyglactin 910 group was higher than that in the 9-0 nylon group on PODs 1, 7, and 30. However, the difference in the pain scores between the two suture groups during all of the post-operative follow-up days were not statistically significant, as shown in **Table 3**. The results of the Mann-Whitney U test indicated that the mean and median scores for ocular surface inflammation in the 8-0 polyglactin 910 group were higher than those in the 9-0 nylon group throughout the post-operative follow-up. At a 95% CI, the difference in the ocular surface inflam-

mation was statistically significant on POD 1 ($P = 0.007$, $U = 438$), with a medium effect size ($r = 0.45$), and on POD 7 ($P = 0.00$, $U = 331$), with a large effect size ($r = 0.64$). However, on POD 30, the inflammation scores were not statistically different, as shown in **Table 3**.

The suture integrity assessment revealed that both the 9-0 nylon and the 8-0 polyglactin 910 sutures had similar integrity on POD 1; however, by POD 7 and thereafter, the mean score for the integrity of the 9-0 nylon sutures was higher than the mean score for the 8-0 polyglactin 910 sutures. Thus, on POD 30, the 9-0 nylon sutures were more intact than the 8-0 polyglactin 910 sutures, and the difference was statistically significant ($P = 0.001$; $U = 486$ at 95% CI). Also by POD 30, 11 (33.56%) of the 8-0 polyglactin 910-sutured sclerotomies had either broken or loose sutures requiring removal, whereas all of the 9-0 nylon-sutured sclerotomies were intact except for one suture. Neither the 8-0 polyglactin 910 group nor the 9-0 nylon group showed suture abscess until the end of POD 30. While the 8-0 polyglactin 910 sutures were left to degrade, the 9-0 nylon sutures were removed on POD 30 with a fine needle. The removal of the 9-0 nylon sutures was not difficult because the nylon-related local tissue inflammation was less than the inflammation associated with the 8-0 polyglactin 910 sutures.

Table 3. Comparative analysis of 9-0 Nylon and 8-0 Polyglactin sutured sclerotomy groups for ocular pain and ocular surface reaction using the Mann-Whitney U test.

POD	Clinical characteristic	8-0 Polyglactin 910 mean rank	9-0 Nylon mean rank	8-0 Polyglactin 910 median	9-0 Nylon median	U value	P value (95% CI)	<i>r</i>
Day 1	Ocular pain	37.89	35.11	2	2	598	0.42	0.13
	Ocular surface inflammation	42.33	30.67	3	2	438	0.007	0.45
	Suture integrity	36.50	36.50	3	3	648	1	0
Day 7	Ocular pain	37.67	35.33	2	2	606	0.59	0.09
	Ocular surface inflammation	45.31	27.69	3	2	331	0.00	0.64
	Suture integrity	36	37	3	3	630	0.317	0.17
Day 30	Ocular pain	38.06	34.94	1	1	592	0.31	0.17
	Ocular surface inflammation	40.85	32.15	2	1	491.5	0.052	0.32
	Suture integrity	31.50	41.50	3	3	468	0.001	0.57

U: Mann-Whitney test; P: probability; *r*: effect size; CI: confidence interval.

4. Discussion

PPV requires a minimum of three sclerotomy ports, all of which must be properly closed after the surgery. Small-gauge PPV with tunnel technique sclerotomy is usually self-sealing. However, with prolonged surgery, closure is often necessary. Sclerotomy wounds are prone to leakage, vitreous incarceration, infection, and seepage of silicone oil endotamponade under subconjunctival tissues. Various in-

traoperative interventions have been attempted to prevent the sclerotomy from leaking, including hydration, glue, clots, or plugs and sutures, with variable success rates [21] [22]. The decision to close sclerotomies with sutures is based on the prevailing risk factors, the size and type of the sclerotomy wounds and the nature of the endotamponade used. The risk of sclerotomy wound leakage is higher when endotamponade agents are used, and the sutures used for sclerotomy wounds are invariably kept for a prolonged period after PPV. Weeks after the surgery, when the sclerotomy wounds have healed, the sutures are either removed or, when absorbable sutures are used, it is left to degrade. During this period, sutured sclerotomy wounds are at risk of suture-induced ocular surface inflammation, which causes ocular pain and discomfort to patients, and complications such as suture abscess formation or tissue granulation.

8-0 polyglaction 910 is braided, is thicker, softer, and less stiff than 9-0 nylon, which is a slender monofilament. In this study, the mean eye pain score for the 8-0 polyglaction 910 group was higher than that for the 9-0 nylon group, though the difference was not statistically significant. Currently, vitreo-retinal surgeons tend to use 9-0 or 8-0 polyglaction 910 to suture sclerotomy wounds because it is soft and easy to use during surgery. However, Sridhar *et al.* reported that 8-0 polyglaction 910 was associated with higher pain scores and more inflammation than other types of sutures, such as plain gut [17]. In the present study, 8-0 polyglaction 910 was associated with higher mean eye pain scores and significantly higher ocular surface inflammation scores than 9-0 nylon, especially during the first two weeks after PPV. In this period, some of the ocular conditions, which can aggravate the post-surgical eye pain, can be attributed to the surgical wounds itself, the use of an endotamponade and the associated raised IOP. In both suture groups, the IOP was well-controlled throughout the study period, and both groups received the same post-operative medications and care. The comparative analysis revealed that the use of 9-0 nylon for sclerotomy wound closure was associated with lower ocular surface inflammation scores than 8-0 polyglaction 910 up to POD 30. The slender and monofilament suture characteristics of 9-0 nylon were thus associated with less suture-induced ocular surface inflammation.

9-0 nylon suture, being non-absorbable, requires a second setting for removal, and its removal can be challenging, especially when the sutures lie beneath inflamed conjunctival tissue during the first two weeks after surgery. In this study, 9-0 nylon-induced ocular surface tissue inflammation decreased by three weeks after PPV surgery, and its removal became easy by the end of the fourth week. Nylon caused less local tissue inflammation than 8-0 polyglaction 910; thus, on POD 30, it was easily removable under a slit lamp with a fine needle. On the other hand, 8-0 polyglaction 910 is absorbable and self-degrading which may take up to six weeks to absorb, during this time there is a risk of inflammation and discomfort, especially when sutures loosen or break. Among the patients in this study, by 30 days after PPV, most of the 8-0 polyglaction 910 sutures were either loose or broken and thus required removal. The mean integrity scores for the 9-0 nylon sutures were higher than those for the 8-0 polyglaction 910 sutures from POD 7

onward, and the 9-0 nylon sutures showed greater integrity at POD 30. Accordingly, 9-0 nylon sutures may be the preferred choice when sclerotomy wound integrity is essential, especially when an endotamponade is used after the PPV. The other suture-specific complications related to 8-0 polyglaction 910 and 9-0 nylon were not significant in this study: none of the patients in either group experienced wound leakage, hypotony, or suture abscesses.

The limitations of this study included the fact that it was not a true randomized clinical trial as it did not involve identical samples. The comparative analysis of the two suture groups was based on the two equal groups, but the size of PPV gauge surgeries, the number of sutured sclerotomy wounds and the use of endotamponade between the suture groups were unequal. The use of an endotamponade such as silicone oil or gas may have contributed indirectly to the eye pain scores, especially through endotamponade-related increases in IOP.

5. Conclusion

This study was designed as a randomized clinical trial to assess patients' eye pain and ocular surface inflammation following the closure of sclerotomy wounds with either 8-0 polyglaction 910 or 9-0 nylon after PPV in a real-world scenario. In this trial, the 9-0 nylon sutures had a more favorable outcome in terms of being associated with lower eye pain scores and significantly less ocular surface inflammation compared with the 8-0 polyglaction 910 sutures. A true randomized clinical trial with identical suture groups involving similar PPV sizes, numbers of sutures, and endotamponade usage is needed to determine the clinical differences between the two types of sutures.

Author Contributions

Research conceptualization; Lhacha Wangdi, Mae-Lynn Catherine Bastion and Mein Hsien Yong. Methodology; Lhacha Wangdi, Mae-Lynn Catherine Bastion and Mein Hsien Yong, Wan Haslina Wan Abdul Halim. Research Proposal write-up; Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong and Ainal Adlin Naffi. Ethical review and clearance: Lhacha Wangdi, Mae-Lynn Catherine Bastion and Mein Hsien Yong. Formal analysis: Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong, Ainal Adlin Naffi and Wan Haslin Wan Abdul Halim. Data Collection: Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong, Ainal Adlin Naffi and Wan Haslin Wan Abdul Halim. Data entry; Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong, Ainal Adlin Naffi and Wan Haslin Wan Abdul Halim. Data analysis; Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong, Ainal Adlin Naffi and Wan Haslin Wan Abdul Halim. Writing—original manuscript draft; Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong, Ainal Adlin Naffi and Wan Haslin Wan Abdul Halim. Manuscript review and editing; Lhacha Wangdi, Mae-Lynn Catherine Bastion, Mein Hsien Yong, Ainal Adlin Naffi and Wan Haslin Wan Abdul Halim. Supervision; Lhacha Wangdi and Mae-Lynn Catherine Bastion.

Project administration; Lhacha Wangdi and Mae-Lynn Catherine Bastion. Funding acquisition; Lhacha Wangdi and Mae-Lynn Catherine Bastion. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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