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RESEARCH ARTICLE

Evaluation of Outcomes and Regression after Neovascularization Treatment for Non-type 1 Retinopathy of Prematurity

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Abstract:

Introduction:

To study the unfavorable outcomes and regression after neovascularization treatment for non-type 1 retinopathy of prematurity (ROP) in a tertiary care facility in Thailand.

Methods:

A retrospective study was done of all infants undergoing screening and treatment for ROP at a tertiary referral center between July 2018 and June 2021 with follow-up for 60 weeks postmenstrual ages (PMA). The outcomes measured were unfavorable outcomes, including macula involving posterior retinal folds, macula involving retinal detachment, retrolental cicatrix formation, or a mass obscuring the view of the posterior pole, and the regression of ROP after treatment. The infants received neovascularization treatment (stage 3 ROP) within 72 h of diagnosis. The study also compared the unfavorable outcomes and regression between neovascularization in type 1 ROP and non-type 1 ROP subgroups.

Results:

There were 58 eyes of 31 infants that received neovascularization treatment that were included in the study. Of these 58 eyes, 41 had non-type 1 ROP, and 17 had type 1 ROP. 92.68% of the eyes treated for non-type 1 ROP had stage 3 ROP in zone II with pre-plus disease and 74.47% of the eyes treated for type 1 ROP had stage 3 ROP in zone II with plus disease. The mean gestational age and birth weight of the enrolled infants were 28.48 ± 1.99 weeks and 1165.32 ± 394.57 g, respectively. Unfavorable outcomes after neovascularization treatment occurred in three eyes (17.65%) in the type 1 ROP group, but there were no unfavorable outcomes in the non-type 1 ROP group (p=0.022); these three eyes were treated with laser indirect ophthalmoscopy (LIO) combined with Intravitreal bevacizumab (IVB). The non-type 1 ROP treated with laser LIO alone group had 100% regression, whereas type 1 ROP treated with LIO or combined LIO and IVT bevacizumab group had 82.35% regression. Progression after treatment without regression occurred in five eyes (29.41%) with type 1 ROP, but no progression occurred in eyes with non-type 1 ROP (p=0.001).

Conclusion:

Neovascularization treatment in non-type 1 ROP is useful for preventing unfavorable outcomes and achieving the regression of neovascularization, especially for diseases less severe than type 1 ROP. Moreover, neovascularization treatment in non-type 1 ROP can reduce the progression of ROP disease.

Keywords: Retinopathy of prematurity, Non-type 1 retinopathy of prematurity, Treatment for retinopathy of prematurity, Outcomes, Regression, Peripheral non-vascularized retinal ablation.

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1. INTRODUCTION

Retinopathy of prematurity (ROP) continues to be a largely preventable cause of blindness and severe visual impairment globally in preterm infants, especially in middle-income regions such as Latin America, China, India, Vietnam, the Philippines, and Thailand [1 - 3]. Currently, the occurrence of preterm birth and survival is increasing, which is the leading cause of ROP blindness [4, 5]. In 2008, approximately 50,000 children were blind from ROP worldwide [6]. There were approximately 13,101 cases of blindness or low vision in Thai children in 2006-2007 [7]. The National Survey of Blindness, Low Vision, and Visual Impairment in Thailand in 2006-2007

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showed that the prevalence of blindness in children aged 1-14 years was 0.11%, and 67% of blindness in children was due to ROP [8].

ROP is a vasoproliferative disease affecting the retina of preterm infants; the major risk factors are low birth weight and low gestational age (GA) [9]. Other risk factors are oxygen therapy (higher oxygen concentration, long duration, and prolonged mechanical ventilation), pulmonary complications (apnea, respiratory distress syndrome, and bronchopulmonary dysplasia), intraventricular hemorrhage, sepsis, anemia, thrombocytopenia, administration of blood products, patent ductus arteriosus, necrotizing enterocolitis, and double volume exchange transfusion [4, 10, 11]. The key pathological change in ROP is retinal neovascularization. Preterm infants have incomplete blood vessel development. The peripheral incompletely vascularized immature retina causes ischemia, with subsequent retinal neovascularization. The growth of abnormal neovascularization involves fibrous tissue and abnormal vessels (stage 3 ROP), which may contract and bleed. The end stages of the disease involve retinal detachment, traction, distortion of the retina, and scarring, which are the main causes of severe vision impairment and blindness from ROP.

Peripheral non-vascularized retinal ablation is the mainstay of ROP treatment. In 1988, the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP) Study suggested cryotherapy treatment for threshold ROP (defined as stage 3 ROP in zone I or II with plus disease extending for 5 contiguous clock hours (150 degrees) or 8 cumulative clock hours (240 degrees), where threshold ROP is the point of progression of neovascularization leading to retinal detachment, which brings a high risk of blindness. The treatment resulted in a reduction in unfavorable outcomes by nearly 50% (21.8% in eyes treated with cryotherapy compared to 43.0% in untreated eyes) [12]. However, the long-term outcomes of treated eyes have been frequently poor. A recent report of CRYO-ROP in children (age 15) showed that almost half of the treated eyes (44%) had a visual acuity of 6/60 or worse despite their improved retinal outcomes after treatment [13]. After the CRYO-ROP study of 1988, many ophthalmologists believed that earlier treatment before the development of threshold ROP might benefit some premature infants with severe ROP. In 2003, the benefits of earlier treatment of ROP infants were evaluated in the Multicenter Early Treatment for Retinopathy of Prematurity (ETROP) study. This study randomly allocated the patients to early laser photocoagulation treatment or conventional management groups. The results demonstrated reductions in unfavorable visual acuity outcomes from 19.5% to 14.5% (p=0.01) and unfavorable structural outcomes from 15.6% to 9.1% (p<0.001), with early laser treatment done in type 1 ROP (high-risk pre-threshold ROP) compared to threshold ROP [14]. Thus, Criteria for laser photocoagulation treatment (peripheral retinal ablation *via* laser indirect ophthalmoscopy [LIO]) before the occurrence of threshold ROP became the gold standard and universal worldwide for ROP treatment.

The role of vascular endothelial growth factor (VEGF) in normal retinal vascular development and pathogenic retinal neovascularization has been recognized [15]. VEGF inhibitor drugs are applied in ROP treatment, especially in cases of ROP in zone I. In 2011, the benefits of anti-vascular endothelial growth factor (anti-VEGF) treatment in ROP infants were studied in the "Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity" study (BEAT-ROP) [16]. This study was a prospective multicenter randomized controlled trial to assess the benefits of using intravitreal bevacizumab (IVB) monotherapy for posterior stage 3 ROP in zone I or zone II with plus disease. The participants were randomly assigned to receive intravitreal bevacizumab (0.625 mg in 0.025 mL of solution) or conventional laser photocoagulation treatment. The outcome was the recurrence of ROP requiring retreatment before 54 weeks postmenstrual age. The results showed ROP recurring in zone I and posterior zone II at 4% in the intravitreal bevacizumab group and 22% in the conventional laser photocoagulation treatment group (p=0.002). There was a significant treatment effect in stage 3 in zone I with plus disease ROP (p=0.003) but not for zone II disease (p=0.27) [16]. The study also showed a lower rate of recurrent neovascularization for zone I ROP with intravitreal bevacizumab compared with conventional laser photocoagulation therapy. There was a study to compare the efficacy of intravitreal ranibizumab (IVR) monotherapy and laser photocoagulation for treatment-requiring ROP in Zone II (*i.e.*, Stage 2 or 3 ROP in Zone II with plus disease). The results showed 52% developed ROP recurrence after a single-dose injection in the IVR monotherapy group. Meanwhile, 4% developed ROP recurrence after laser photocoagulation in the laser therapy group (p=0.001) [17]. There was a study that used the intravitreal anti-VEGF injection as an adjunct to LIO in some conditions of ROP [18].

In the management of ROP in our tertiary care hospital, we treat all preterm infants who develop neovascularization (stage 3 ROP) in any zone with or without plus disease because previous studies found that earlier treatment for ROP yields better structural and visual outcomes. Neovascularization treatment in non-type 1 ROP occurs earlier than that for type 1 ROP (high-risk pre-threshold ROP). Neovascularization treatment involves laser photocoagulation monotherapy or a combination with intravitreal bevacizumab. In this study, we analyze treatment in terms of unfavorable outcomes, regression of ROP, and progression of ROP after ROP treatment.

2. SUBJECTS AND METHODS

Our study collected data for all preterm infants who underwent screening and treatment for ROP at the neonatal intensive care unit, the prematurity unit, and referral cases from another hospital between July 2018 and June 2020. The institutional review board of Sawanpracharak Hospital approved the study, which followed the World Medical Association Declaration of Helsinki. The enrolled preterm infants had been examined by retina specialists with ROP expertise until retinal vascular maturity or complete disease regression was achieved. Data were collected using a case recording form, which included body weight (BW), gestational age (GA), sex, screening time, ROP examination findings (staging, zone, and presence of plus or pre-plus disease) using the International Classification of Retinopathy of Prematurity

(ICROP) [19], all types of treatments, number of treatments and repeated treatments, postmenstrual ages at treatment, regression timing after treatment and regression rate, sequelae, and outcome. All treated eyes were classified as either type 1 ROP or non-type 1 ROP, according to the ETROP definitions.

The Treatment followed ETROP study specifications: near-confluent gray-white ablation at peripheral avascular retina by LIO.14 Intravitreal bevacizumab injection (IVB) followed BEAT-ROP study: 0.625 mg bevacizumab in 0.025 ml of solution (AVASTIN, 100 mg/4 ml, Roche, Switzerland) [16].

The primary outcomes were unfavorable outcomes and regression of ROP after neovascularization treatment.

The operational definitions used in this study are as follows:

1. Neovascularization treatment is defined as the treatment for all stage 3 ROP in any zone with or without plus disease within 72 hours by using laser indirect ophthalmoscopy (LIO) or a combination of LIO and intravitreal bevacizumab (IVB).

2. Unfavorable outcomes are defined as posterior retinal folds involving the macula, retinal detachment involving the macula, and retrolental cicatrix formation or mass obscuring the view of the posterior pole.

3. ROP regression is defined as retinal vessel growth into the retinal avascular area, a decrease in the height and width of the intraretinal ridge; and the regression of the neovascularization.

4. ROP progression is defined as the increasing extent of neovascularization or progression to the next stage of ROP after neovascularization treatment.

The data were analyzed by using descriptive statistics of various aspects, such as demographic data for frequency and percentage, mean, and standard deviation, and comparison between subgroups using an independent t-test to compare the 2 independent groups. Data on the unfavorable outcomes, ROP regression after treatment, and progression after ROP treatment were collected and analyzed for frequency, percentage, and comparison between subgroups using a chi-squared test and Fisher's exact test to compare the 2 independent groups.

3. RESULTS

There were 58 eyes of 31 infants with neovascularization (stage 3 ROP) in any zone, with or without plus, that received neovascularization treatment for ROP. Twenty patients were male (64.52%), and 11 patients were female (35.48%). The mean gestational age and birth weights were 28.48 ± 1.99 weeks and 1165.32 ± 394.57 g, respectively. The patient demographics are shown in Table **1**.

Of the 41 eyes that were treated for non-type 1 ROP, 38 (92.68%) had stage 3 ROP in zone II with the pre-plus disease, and 3 (7.32%) had Stage 3 ROP in zone II ROP with no plus disease. Of the 17 eyes that met the ETROP criteria for type 1 ROP, 4 (23.53%) had stage 3 ROP in zone I with plus, and 13 (76.47%) had Stage 3 ROP in zone II with plus disease. The ICROP diagnoses for these eyes are presented in Table **2**. The majority of treated eyes (65.52%) had stage 3 ROP in zone II with the pre-plus disease. The mean gestational age and birth weight of non-type 1 ROP were 28.63 ± 1.58 weeks and 1186.67 ± 358.89 g, respectively. The Type 1 ROP had mean gestational age and birth weight of 28.67 ± 3.08 weeks and 1232.78 ± 566.111 g, respectively (Table **3**). The two groups did not differ significantly with respect to BW, GA, or sex. LIO was used to treat 46 eyes (79.31%), and combined LIO and intravitreal bevacizumab were used in 12 eyes (20.69%).

Table 1. Demographic information for preterm infants receiving neovascularization treatment.

Patients Demographics	Neovascularization Treatment for Retinopathy of Prematurity Patients
Number of patients	31
Number of eyes	58
Sex - Male - Female	 20 (64.52%) 11 (35.48%)
BW, g, mean ± SD	1165.32 ± 394.57
GA, weeks, mean ± SD	28.48 ± 1.99

Table 2. ICROP classification of 58 eyes receiving neovascularization treatment for ROP.

ETROP Type	ICROP Classification	No. Eyes
Non-type 1	Stage 3, zone II, pre-plus Stage 3, zone II, no plus	38 (65.52%) 3 (5.17%)
Type 1	Stage 3, zone I, plus Stage 3, zone II, plus	4 (6.90%) 13 (22.41%)

Table 3. Comparison information for preterm infants receiving neovascularization treatment for non-type 1 ROP and type 1 ROP.

Patients Demographics	Infants Receiving Neovascularization Treatment for Non-type 1 ROP	Infants Receiving Neovascularization Treatment for Type 1 ROP	p-value
Number of eyes	41	17	
BW, g, mean ± SD	1186.67 ± 358.89	1232.78 ± 566.111	0.740
GA, weeks, mean ± SD	28.63 ± 1.58	28.67 ± 3.08	0.708
Treatment - LIO - Combine LIO and intravitreal bevacizumab	41 (100%) -	5 (29.4%) 12 (70.6%)	< 0.001

The treated eyes had non-regression after treatment in 3 eyes (17.65%) in the type 1 ROP group, which occurred with unfavorable outcomes, but none in the non-type 1 ROP group were statistically significant according to Fisher's exact test (p=0.022) (Table **4**). All eyes in the non-type 1 ROP group revealed 100% regression after treatment (41 eyes). Two eyes with unfavorable outcomes were at stage 3 ROP in zone I with plus, and one eye was at stage 3 ROP in zone II with plus; all three eyes had developed macula involving retinal detachment and were treated with combined LIO ablation at all peripheral

avascular retina area and intravitreal bevacizumab (0.625 mg in 0.025 ml of solution). All of the non-type 1 ROP eyes were treated with LIO ablation at all peripheral avascular retina areas only. Five eyes progressed after neovascularization treatment in the type 1 ROP group, but none progressed in the non-type 1 ROP group (p=0.001). All five eyes were treated with combined LIO and intravitreal bevacizumab. Two of the above-mentioned five eyes subsequently caused unfavorable outcomes that progressed to the proliferation of neovascularization and led to the development of retinal detachment (stage 5 ROP). The other eye with unfavorable outcomes developed ROP recurrence after combined LIO and intravitreal bevacizumab treatment.

Table 4. Comparison of outcomes between non-type 1 ROP and type 1 ROP eyes.

-	Infants Receiving Neovascularization Treatment for Non-type 1 ROP	Infants Receiving Neovascularization Treatment for type 1 ROP	P value
Unfavorable outcomes (%)	0	3 (17.65%)	0.022
Regression after treatment (%)	41 (100%)	14 (82.35%)	0.022
Progression after ROP treatment (%)	0	5 (29.41%)	0.001

4. DISCUSSION

Of the 58 eyes treated for ROP neovascularization (stage 3 ROP) between July 2018 and June 2021, 70.69% had an ROP diagnosis that did not meet the criteria for type 1 ROP. 92.68% of the eyes treated for non-type 1 ROP in our study had stage 3 ROP in zone II with the pre-plus disease, and the standard early ROP treatments in type 1 ROP were based on the ETROP study. The peripheral retinal laser photocoagulation remains the current gold standard care for treatment-requiring ROP in Zone II [14]. First, the CRYO-ROP study suggested treatment for threshold ROP, which was defined as contiguous 5 clock hours or 8 cumulative noncontiguous clock hours of stage 3 ROP in zones I or II with plus disease [12]. The results showed that unfavorable outcomes occurred in 21.8% of eyes in the treatment group. The ETROP study considered a treatment for type 1 ROP, which was treated earlier than threshold ROP. The results showed unfavorable visual outcomes in 14.5% and unfavorable structural outcomes in 9.1% of eyes in the treatment group [14]. In this study-treating all neovascularization (stage 3 ROP) in any zone with or without plus disease within 72 hours of diagnosis-most patients were treated for non-type 1 ROP, which occurred earlier than treatment for type 1 ROP and threshold ROP. All cases of neovascularization (stage 3 ROP) in any zone with or without plus disease were treated with either LIO or combined LIO and intravitreal bevacizumab. There was a study that found infants with Zone II treatment-requiring ROP had a higher recurrence rate after treatment with intravitreal anti-VEGF monotherapy than laser photocoagulation therapy, so this study used the intravitreal anti-VEGF injection as an adjunct to LIO in some patients with type 1 ROP [17]. However, the study also had some cases that met the type 1 ROP criteria at the first visit; therefore, we compared the results between the non-type 1 ROP group and the type 1 ROP group. No unfavorable outcomes or non-regression occurred in non-type 1 ROP, whereas 17.65% of type 1 ROP cases had unfavorable outcomes and non-regression.

The data from the BEAT-ROP study showed that intravitreal bevacizumab was significantly more effective than LIO for stage 3 ROP with plus in zone I but not in zone 2 [16]. The rate of recurrence of ROP with zone I disease was 42% in the LIO group compared with 6% in the intravitreal bevacizumab group (p=0.003), but with zone II, the posterior disease was not significantly different between the two groups [16]. However, The rate of recurrence of ROP with zone II, the posterior disease still was found at 12% in the LIO group and 5% in the intravitreal bevacizumab group [16]. The results of this study showed no recurrence in the non-type 1 ROP group, and all eyes of the non-type 1 ROP group were stage 3 ROP in zone II without plus or pre-plus, which were treated earlier than type 1 ROP and threshold ROP. There were no cases in which intravitreal bevacizumab was used for the treatment of non-type 1 ROP; these were treated for neovascularization with LIO treatment only. One eye in the type 1 ROP group had a recurrence of ROP, which was treated with LIO and intravitreal bevacizumab combined. Currently, there is an absence of long-term data on the effects of intravitreal bevacizumab on the ocular outcomes and systemic side effects of children [20]. The LIO treatment proved to be effective in preventing ROP-related blindness, but with significantly fewer side effects.

In the ETROP study, it was found that 22.1% of type 2 ROP cases progressed to type 1 ROP [21]. The results of this study found that if ROP was stage 3 in zone II without plus or pre-plus disease, after receiving LIO treatment, there was no progression to type 1 ROP.

CONCLUSION

In summary, this study suggests that the earlier treatment of stage 3 non-type 1 ROP had favorable outcomes and complete regression. Moreover, the earlier treatment of stage 3 non-type 1 ROP could reduce the progression of ROP after treatment. Further prospective studies involving longer-term outcomes of ROP treatment of non-type 1 ROP would provide solid evidence for the benefits of ROP treatment.

LIST OF ABBREVIATION

ROP = Retinopathy of Prematurity

ETROP = Multicenter Early Treatment for Retinopathy of Prematurity

LIO = Laser Indirect Ophthalmoscopy

PMA = Postmenstrual Ages

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The institutional review board of Sawanpracharak Hospital approved the study.

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from the guardians of neonates involved in the study.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are provided within the article.

STANDARDS OF REPORTING

STROBE guidelines were followed.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest financial or otherwise.

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Declared none.

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