Available online at www.medicinescience.org

ORIGINAL RESEARCH

Medicine Science International Medical Journal

Medicine Science 2019;8(4):1002-5

Laser photocoagulation in the treatment of retinopathy of prematurity in cases with birth weights above 1000 grams

Seyhan Dikci, Soner Demirel

Inonu University ,Faculty of Medicine, Department of Ophthalmology, Malatya, Turkey

Received 19 June 2019; Accepted 07 August 2019
Available online 13.12.2019 with doi: 10.5455/medscience.2019.08.9120

Abstract

This study aimed to evaluate the clinical features and treatment results of the cases with birth weight (BW) above 1000 grams applied for laser photocoagulation (LPC) for retinopathy of prematurity (ROP). The files of the patients who underwent laser photocoagulation due to ROP in our clinic were retrospectively reviewed. Gender, the mean gestational age, the mean BW, the mean postmenstrual (PM) age at the treatment, the mean number of laser spots for each eye, intraoperative and postoperative complications were recorded. A total of 134 eyes of 70 infants were included in the study, including 73 eyes of 37 infants in group 1 and 61 eyes of 33 infants in group 2. The mean BW of the babies was 784.3 ± 140.0 g in group 1 and 1332.4 ± 239.9 g in group 2. The mean number of laser spots for each eye was 1170.7 ± 549.8 in group 1 and 850.9 ± 362.8 in group 2. While preretinal/vitreous hemorrhage (8.2%) in 6 eyes of 6 patients and fibrotic proliferation in 8 eyes of 6 patients (11%) in group 1 were observed, preretinal/vitreous hemorrhage in three eyes (4.9%) of three patients, fibrotic proliferation in 15 eyes (24.6%) of 24 patients and tractional retinal detachment in two eyes (3.3%) of two infants in group 2 were detected. In cases with BW above 1000 g, laser therapy is an effective method, but ROP may develop in older PM age and complications such as fibrovascular proliferation, and related tractional retinal detachment may develop in these cases.

Keywords: Retinopathy of prematurity, laser photocoagulation, fibrovascular proliferation, tractional retinal detachment

Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of preventable blindness, particularly in developing countries [1]. Although various factors have been implicated in the etiology of ROP, most significant risk factors for ROP are known to be prematurity determined with a low gestational age (GA) and low birth weight (BW), as well as the administration of high levels of oxygen [2,3]. In practice, information regarding newborns is primarily concerned with birth weight and "birth weight" remains essential in the evaluation of premature newborns because of the difficulties in obtaining accurate information as to the duration of pregnancy in developing countries. Premature infants are categorized according to their birth weights as low birth weight (between 2500-1501g), very low birth weight (between 1500-1001g), and extremely low birth weight (1000g and below) [4].

The prevalence and severity of ROP have been reported to increase as birth weight, which is a parameter that affects the development of retinopathy of prematurity, decreases. Infants with birth weights below 1000g are three times more prone to ROP compared to those with birth weights between 1001-1500g [5]. A study by Ozen et al. reported that, of cases who underwent laser photocoagulation, 62.3% had birth weights below 1000g, 29% between 1001-1500g, and 8.4% above 1501g [6]. Moreover, a study by Ozdemir et al. reported that 77.7% of cases treated for ROP was comprised of infants with extremely low birth weights [7].

In conclusion, the majority of patients who require treatment for ROP is constituted by infants with birth weights of 1000g or below. This study aims to evaluate the clinical properties and outcomes of LPC used in the treatment of ROP in infants with birth weights above 1000g, who constitute a relatively limited group among infants who require treatment.

Materials and Methods

This study was conducted after obtaining approval from the non-invasive clinical research and publication ethics committee at Inonu University Faculty of Health Sciences and by the Helsinki Declaration. Files of patients who had been treated for ROP at our clinic were retrospectively evaluated. Patients who had undergone laser photocoagulation as the primary treatment were included

***Coresponding Author:** Seyhan Dikci , Inonu University ,Faculty of Medicine, Department of Ophthalmology, Malatya, Turkey
E-mail: seyhandikci@gmail.com

in the study. Patients who had undergone intravitreal (IV) anti-vascular endothelial growth factor (VEGF) or combined laser and IV anti-VEGF as the primary treatment were not included in the study. Recorded data included patient gender, GA, BW, post-menstrual (PM) age at the time of treatment, number of laser spots per eye, and intraoperative and postoperative complications. The patients were evaluated in two groups. Infants with birth weights of 1000g or below were assigned to group 1, and infants with birth weights above 1000g were assigned to group 2. These two groups were compared with regard to the specified parameters.

Before the examination, pupillary dilation was achieved using 0.5% tropicamide and 2.5% phenylephrine drops. A fundus examination was performed with an indirect video ophthalmoscope and a 20 or 28 D lens. Patients were recorded based on the ICROP (The International Classification of Retinopathy of Prematurity) criteria [8]. The treatment decision was made based on the ETROP (Early Treatment for Retinopathy of Prematurity) rules [9]. Patients with aggressive posterior ROP (AP-ROP) or type 1 high-risk pre threshold ROP were recommended to receive treatment and no patients were detected to have threshold ROP. Laser photocoagulation (LPC) was applied to the entire avascular retina in all cases. Following LPC, moxifloxacin, and prednisolone drops were administered 8x1 and prednisolone pomade and cyclopentolate (0.5%) were administered 2x1.

Statistical analyses were conducted using SPSS 21.0 for Windows (SPSS, Inc., Chicago, IL, ABD). Quantitative data were presented as mean±SD, and categorical data were presented in the form of numbers and percentages. Continuous variables were evaluated using the Student t-test. Comparisons were made using continuity-corrected chi-square and Fisher's exact chi-square tests. The level of significance was considered as 0.05 for all analyses.

Results

This study included 134 eyes of 70 infants who had undergone photocoagulation for ROP. The study group included 37 infants (73 eyes) with a birth weight of 1000 g or below (group 1) and 33 infants (61 eyes) with a birth weight above 1000g (group 2). Among infants with a birth weight above 1000 g, six (18.2%) had a birth weight above 1500 g. Of infants in Group 1, 24 (64.9%) were female, and 13 (35.1%) were male. Of infants in Group 2, 11 (33.3%) were female and 22 (66.7%) were male (p= 0.02). Infants in Group 1 had a mean gestational age of 26.1±1.6 (23-30) weeks and a mean birth weight of 784,3±140,0 (480-1000) g. Infants in Group 2 had a mean gestational age of 29.5±2.2 (25-33) weeks and a mean birth weight of 1332,4±239,9 (1040-1980) g. There was no significant difference between the groups in terms of birth weight and gestational age (p≤ 0.01). In Group 1, 13 eyes (17.8%) were treated for AP-ROP and 60 eyes (82.8%) were treated for type 1 high-risk pre threshold ROP; while in Group 2, two eyes (3.3%) were treated for AP-ROP, and 59 eyes (96.7%) were treated for type 1 high-risk pre threshold ROP (p= 0.02). The mean number of laser spots applied to the patients was 1170,7±549,8 (420-2410) per eye in Group 1, and 850.9±362.8 (184-1550) in Group 2 (p≤ 0.01). The mean PM age at the time of treatment was 36.4±2.6 (32-44) weeks for Group 1 and 38.3±2.8 (33-45) weeks for Group 2 (p≤ 0.01). Six eyes of three infants (8.2%) in Group 1 and 19 eyes of 11 infants (31.1%) in Group 2 underwent LPC at the 40th PM week or later. Table 1 demonstrates the clinical and demographic characteristics of the patients. Five eyes of four infants (6.8%) in Group 1 and one eye of an infant (1.6%) in Group 2 underwent additional LPC (p≥ 0.05). Neither group demonstrated any intraoperative complications. Postoperative complications in Group 1 included preretinal/vitreous hemorrhage in six eyes of six patients (8.2%) and fibrotic proliferation in eight eyes of six patients (11%), whereas in Group 2, preretinal/vitreous hemorrhage was encountered in three eyes of three patients (4.9%), fibrotic proliferation in 15 eyes of 11 patients (24.6%), and tractional retinal detachment in two eyes of two infants (3.3%) (Table 2) (p≥ 0.05).

Table 1. The clinical and demographic characteristics of the patients in both groups

	Group 1 n (%)	Group 2 n (%)	p value
Gender F/M	24/13	11/22	**0.02**
Tip 1 ROP	60 (82.2)	59 (96.7)	**0.02**
AP-ROP	13(17.8)	2(3.3)	**0.02**
Additional LPC	5(6.8)	1(1.6)	≥ 0.05
BW (g) mean±SD	784.3±140.0	1332.4±239.9	**≤ 0.01**
GA mean±SD	26.1±1.6	29.5±2.2	**≤ 0.01**
Applied laser spot numbers, mean±SD	1170.7±549.8	850.9±362.8	**≤ 0.01**
The mean time at the treatment (PM week), mean±SD	36.4±2.6	38.3±2.8	**≤ 0.01**

AP-ROP: Agressive posterior retinopathy of prematurity, BW: Birth weight, F: Female, GA: Gestational age, LPC: Laser photocoagulation, M: Male, PM: Postmenstrual, SD: Standard deviation

Table 2. Comparison of groups according to anterior and posterior complications

	Group 1 n (%)	Group 2 n (%)	p value
Cataract	0	2 (3.3)	≥ 0.05
Preretinal/Vitreous hemorrhage	6(8.2)	3(4.9)	≥ 0.05
Fibrovascular proliferation	8(11)	15(24.6)	≥ 0.05
Tractional Retinal Detachment	0	2(3.3)	≥ 0.05

Discussion

Low birth weight is one of the most important determining factors that must be considered in the development of retinopathy of prematurity [10]. In the multi-center CRYO-ROP (Cryotherapy for Retinopathy of Prematurity) study, the prevalence of ROP at any stage was detected as 47% among those with birth weights between 1000-1250 g, 78% among those with birth weights between 750-999 g, and 90% among those with birth weights below 750 g [11]. In the study by the Early Treatment study group (ETROP), treated infants were determined to have a mean GA of 25.3 and a mean BW of 703 g [12]. Ozen et al. reported that treated infants had a mean birth week of 27.3±2.5 and a mean birth weight of 991.1±314.7 g [6]. In our study, infants in Group 1 were determined to have a mean GA of 26.1±1.6 and a mean BW of 784.3±140.0 g, while infants in Group 2 had a mean GA of 29.5±2.2 and a mean BW of 1332.4±239.9 g. Mean GA and BW of infants in Group 2 in our study were higher compared to those of both infants in Group 1 and other studies in the literature.

In ROP, which is a vasoproliferative disease, whether healthy or pathological retinal vascular development will take place is closely related to the postmenstrual (PM) age [13]. In the acute phase, ROP peaks at approximately 35th-39th PM weeks and 90% of cases emerge before the 44th PM week [2,3,14]. In the ETROP study, the mean PM age at the time of treatment was determined as 35.2 (30.6-42.1) weeks [12]. In the study by Ozdemir et al., patients were treated at 36.7±2.9 (30-48) weeks PM age on average [7]. In rare cases, ROP may be encountered after the 40th PM week due to a late-onset or delayed examination [3,15]. In the CRYO-ROP study, the acute phase appeared in those older than a PM age of 41.5 weeks at a rate of 5% and in those older than 46.3 weeks at a rate of 1% [2]. In a study conducted in our country with 121 infants who had undergone treatment, 11 patients were reported to be older than 40 weeks [7]. In our study, the mean PM age at which patients underwent treatment was determined as 36.4±2.6 weeks for Group 1 and 38.3±2.8 weeks for Group 2. Six eyes of three infants in Group 1, and 19 eyes of 11 infants in Group 2 had undergone LPC after the 40th PM week. There is less information about the natural history of severe ROP that develops at an advanced PM age [13]. Moreover, most studies have investigated the outcomes of ROP treatments before the 40th PM week, and the effectiveness and anatomical outcomes of the treatment of severe ROP at more advanced PM ages remain unclear [15-17].

Eyes detected to have ROP after the 40th PM week were found to demonstrate abnormal vascular activity and increased fibrotic proliferation. The observational findings reported in the same study included a thicker, wide, flatter, and whitish ridges for cases encountered at more advanced weeks, whereas situations encountered at earlier weeks had ridges with a more reddish appearance and blurred edges [18]. Ho et al. reported that four of the 18 eyes with ROP (nine patients) manifested typical fundus symptoms including a fibrotic ridge and vascular traction in older prematurely born infants [15]. In a case series by Gupta et al. fibrotic activity, vitreous hemorrhage, and retinal traction were found in 10 of the 13 eyes detected to have ROP less severe than type 1 after the 40th PM week [19]. In our study, fibrotic proliferation was detected in eight eyes of six patients (11%) in Group 1 and 15 eyes of 11 patients in Group 2 (24.6%). Although Group 2 demonstrated a higher rate of fibrotic proliferation, this difference was not statistically significant ($p \leq 0.05$). However, fibrotic proliferation occurred in 11 (57.9%) of 19 eyes treated with LPC after the PM 40 week in Group 2 and one eye of those showed tractional retinal detachment. Figure 1 shows fibrotic proliferation occurred in a patient who underwent a laser treatment at PM 44 week.

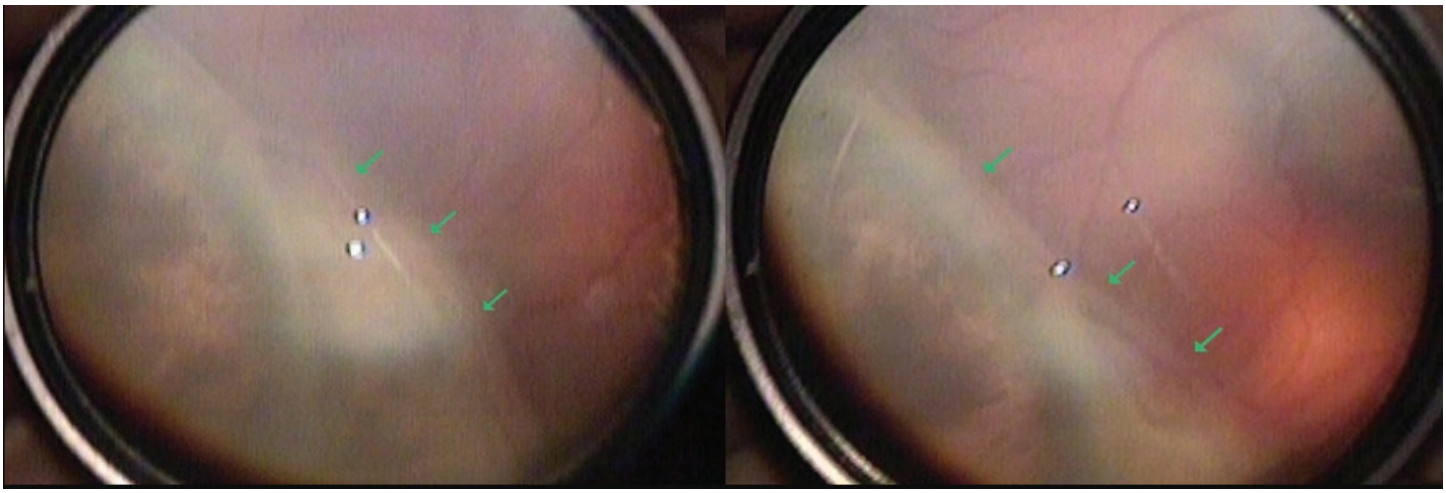

Figure 1. In a patient who underwent a laser treatment at PM 44 week, there is an increase in fibrotic proliferation after treatment.

Intravitreal anti-VEGF and LPC have been shown to be effective in the treatment of retinopathy of prematurity [3,16,17]. The vascular response obtained with laser treatment is delayed compared to that obtained with IV anti-VEGF because it decreases intravitreal VEGF levels indirectly [20]. Compared to laser photocoagulation, anti-VEGF therapy may cause ROP to regress more rapidly and allow complete retinal vascularization. However, IV anti-VEGF procedures may lead to complications such as recurrent neovascularization, persistent peripheral avascularity, and retinal detachment due to fibrotic proliferation [16,17,21-23]. In the ETROP study, 63 (89 eyes) of the 401 patients who had undergone laser treatment developed retinal detachment [22]. In eyes with active vascularization, laser ablation may result in excess inflammation by destroying the blood-retinal barrier, inducing fibrosis and cicatrix [20]. Another study has recommended the combined use of laser ablation and intravitreal anti-VEGF treatments at advanced PM ages to promote fast regression of neovascularization and induce retina-RPE adhesion to minimize undesired outcomes [18]. In our study, patients who had undergone IV anti-VEGF as the primary treatment were not included in the research and tractional retinal detachment was encountered in two eyes (3.3%) with fibrovascular proliferation in Group 2.

Certain studies have reported that male premature infants are at a higher risk of ROP and impaired vision [23,24]. Accordingly, our study determined a higher rate of male infants in Group 2, which consisted of infants with BW above 1000 g. In our study, there was a significant difference between Group 1 and Group 2 concerning rates of AP-ROP and type 1 high-risk pre threshold disease. Moreover, the mean number of laser spots applied to each eye was lower for Group 2 than Group 1 ($p \leq 0.01$). This finding shows that smaller retinal regions were affected in Group 2. Weaknesses of our study include its retrospective design and the heterogeneous distribution of treated ROP types, gender, and sizes of affected retinal regions in the posterior segment across the groups. Also, the preferred treatment for eyes with zone 1 disease in infants with

birth weights below 1000 g because of high rate of AP-ROP was IV anti-VEGF therapy and this might have affected the results of laser therapy we encountered in the first group.

Conclusions

In this study, the outcomes and clinical properties of LPC in the treatment of ROP were evaluated in infants with birth weights above 1000g in comparison to infants with birth weights of 1000 g or below. In patients with birth weights above 1000 gr; the meantime of laser therapy is later, required number of laser spots is fewer and increased fibrotic proliferation may develop more. Also, in selected patients who require treatment at a more advanced PM age, combined laser and IV anti-VEGF treatment must be considered as an option to provide a more effective treatment. Further studies with larger patient populations are needed on this matter.

Competing interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee 2019 / 10-8 and the number of decisions was approved.

Seyhan Dikci ORCID: 0000-0003-2062-3515
Soner Demirel ORCID: 0000-0001-6293-9492

References

1. Gilbert C, Field A, Gordillo l, et al. Characteristics of infants with severe ROP in countries with low, moderate, and high levels of development: implications for screening programs. Pediatrics. 2005;115:518-22.
2. Palmer E, Flynn J, Hardy R, et al; Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. Ophthalmology 1991;98:1628-40.
3. Good WV, Hardy RJ, Dobson V, et al. The incidence and course of retinopathy of prematurity: findings from the early treatment for retinopathy of prematurity study. Pediatrics. 2005;116:15–23.
4. Nelson W., Nelson Textbook of Pediatrics, 16.th ed., Sounders com., 2000;93: 474-85.
5. Campbell PB, Bull MJ, Ellis FD, et al. Incidence of retinopathy of prematurity in a tertiary newborn intensive care unit. Arch Ophthalmol 1983;101:1686-8.
6. Özen Tunay Z, Özdemir Ö, Ergintürk Acar E, et al. Clinical features of treated infants for severe retinopathy of prematurity 8 years study from a large tertiary neonatal intensive care unit in Turkey. Turk J Med Sci 2016;46:42-7.
7. Özdemir Ö, Tunay ZÖ, Acar DE, et al. Prematüre Retinopatisi Nedeni ile Tedavi Edilen İnfantların Doğum Ağırlıklarına Göre İncelenmesi. Turkiye Klinikleri J Ophthalmol 2016;25:51-6.
8. International Committee for the Classification of Retinopathy of P. The international classification of retinopathy of prematurity revisited. Arch Ophthalmol. 2005;123:991–9.
9. Early Treatment For Retinopathy Of Prematurity Cooperative G. Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol. 2003;121:1684–94.
10. Lundgren P, Kistner A, Andersson EM, et al. Low birth weight is a risk factor for severe retinopathy of prematurity depending on gestational age. PLoS One. 2014;9:109460.
11. Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Arch Ophthalmol. 1988;106:471-9.
12. Good WV. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomized trial. Trans Am Ophthalmol Soc 2004;102:233-48.
13. Blencowe H, Lawn JE, Vazquez T, et al. Preterm-associated visual impairment and estimates of retinopathy of prematurity at regional and global levels for 2010. Pediatr Res. 2013;74:35-49.
14. Repka MX, Palmer EA, Tung B. Involution of retinopathy of prematurity. Cryotherapy for retinopathy of prematurity cooperative group. Arch Ophthalmol. 2000;118:645-9.
15. Ho LY, Ho V, Aggarwal H, et al. Management of avascular peripheral retina in older prematurely born infants. Retina. 2011;31:1248–54.
16. Mueller B, Salchow DJ, Waffenschmidt E, et al. Treatment of type I ROP with intravitreal bevacizumab or laser photocoagulation according to retinal zone. Br J Ophthalmol. 2017;101:365-70.
17. Mintz-Hittner HA, Kennedy KA, Chuang AZ, et al. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. N Engl J Med. 2011; 364:603-15.
18. Lyu J, Zhang Q, Chen C, et al. Ranibizumab injection and laser photocoagulation to treat type 1 retinopathy of prematurity after 4weeks post menstrual age: a retrospective case series study. BMC Ophthalmology 2019; 19:60.
19. Gupta MP, Chan RV, Anzures R, et al. Imaging, Informatics in ROPRC. Practice patterns in retinopathy of prematurity treatment for disease milder than recommended by guidelines. Am J Ophthalmol. 2016;163:1-10.
20. Mintz-Hittner HA, Kuffel RR Jr. Intravitreal injection of bevacizumab (avastin) for treatment of stage 3 retinopathy of prematurity in zone I or posterior zone II. Retina. 2008;28:831–8.
21. Zhang G, Yang M, Zeng J, et al. Comparison of intravitreal injection of Ranibizumab versus laser therapy for zone ii treatment-requiring retinopathy of prematurity. Retina. 2017;37:710-7.
22. Repka MX, Tung B, Good WV, et al. Outcome of eyes developing retinal detachment during the early treatment for retinopathy of prematurity study. Arch Ophthalmol. 2011;129:1175-9.
23. Hu J, Blair MP, Shapiro MJ, et al. Reactivation of retinopathy of prematurity after bevacizumab injection. Arch Ophthalmol. 2012;130:1000-6.
24. Tan Z, Chong C, Darlow B, et al. Visual impairment due to retinopathy of prematurity (ROP) in New Zealand: a 22-year review. Br J Ophthalmol. 2015; 99:801–6.
25. Ying GS, Quinn GE, Wade KC, et al. Predictors for the development of referral-warranted retinopathy of prematurity in the telemedicine approaches to evaluating acute-phase retinopathy of prematurity (e-ROP) study. JAMA Ophthalmol. 2015;133:304-11.