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Intravitreal bevacizumab as a monotherapy or adjuvant therapy for retinopathy of prematurity and comparing with laser therapy

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KEYWORDS

Mulberry (Moraceae) stomatal frequency, mitosis, karyotype analysis.

A B S T R A C T

This study was carried out to evaluate the role of anti-VEGF monotherapy or adjuvant therapy and compare with conventional laser ablation therapy in patients with stage 3 retinopathy of prematurity (ROP). Medical records of premature infants with a primary diagnosis of ROP were reviewed retrospectively. Three groups of patients were considered. Group 1 include those patients who treated with laser photocoagulation (LPC) and group 2 those patients who received single 0.625mg intravitreal bevacizumab (IVB) injection. Group 3 treated with both intravitreal bevacizumab injection and laser therapy (IVB adjuvant therapy). Treatment results and complications were evaluated after treatment. 71 eyes of 36 patients were included in this study. Mean gestational age was 27 weeks and mean birth weight was 1085 ± 52.17gm. They all had stage 3 of ROP and zone 2 was most commonly involved. 10 infants enrolled in group 1. Group 2 and 3 both had 13 patients. During the follow-up period, regression of plus disease and peripheral retinal vessel development appeared significantly in all groups. There are no statistical differences between groups about treatment outcomes. No complications such as cataract, endophthalmitis or retinal detachment occurred.

Introduction

Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retinal vasculature .and it is a leading cause of possibly avoidable childhood blindness worldwide (Gilbert, 1997).

In a recent review on the incidence of ROP, the incidence of all ROP was found to be approximately 60% for infants less than 1500 g (Palmer *et al.*, 1991; Lad *et al.*, 2008). Although most cases of ROP regress spontaneously; however more severe cases need treatment to prevent blindness.

Currently standard therapy is laser therapy and cryotherapy. According to the Early Treatment for ROP (ETROP) results, these

ablative treatments reduce the incidence of blindness by 50% in infants (ETROP Cooperative Group, 2003).

Ablation of retina tissue causes permanent scar and might give rise to complications such as burns to the cornea or iris, retinal bleeding, hyphema, cataract and anterior segment ischemia (CRP Cooperative Group, 1998; Hunter and Repka, 1993).

Even with early laser treatment as suggested in the ETROP study, poor outcomes are still frequently seen in aggressive posterior form of ROP (ETROP Cooperative Group, 2003; CRP Cooperative Group, 1998; Hunter and Repka, 1993).

The role of vascular endothelial growth factor (VEGF) in the pathogenesis of ROP has been identified. It is believed that exposure to high levels of oxygen during the neonatal period leads to obliteration of vessels and ischemia which further leads to the release of vascular growth factors and neovascularization (Stone *et al.*, 1996).

Recently multiple case series studies showed that anti- VEGF therapy can be effective and safe for the treatment of retinopathy in the threshold stage.

Bevacizumab is an anti-VEGF monoclonal antibody and has been approved by the US Food and Drug Administration (FDA) for the treatment of colon cancer (FDA, 2009); also off label using of bevacizumab for ocular neovascular disease with encouraging results have recently been published.

In the present study, we have investigated the efficacy of intravitreal -bevacizumab (IVB) treatment as a monotherapy or adjuvant therapy and comparing with conventional laser therapy in ROP patients.

Materials and methods

A retrospective review of the medical records of all infants that had been treated with IVB or laser therapy or combined IVB and laser therapy at Nikoukari eye hospital from Tabriz University of Medical Sciences was performed. All cases underwent treatment from April 2011 to April 2014 by one surgeon. Inclusion criteria were all ROP infants that had treatment indication according with ETROP criteria. Exclusion criteria were ROP patients with stage 4a and upper stages and infants with systemic anomalies or disorders.

The ROP stage and plus disease were defined on the basis of the international classification scheme by indirect ophthalmoscopy.

Data included some of the demographic features of the babies such as gestational age, birth weight, age at treatment as well as pre and postoperative ophthalmologic features; pupillary dilation, iris neovascularization state, location (zone), and stage of the disease and presence of plus disease or vitreous hemorrhage.

Both IVB and laser therapy were performed in operation room. For IVB group after instillation of topical anesthesia and betadine, 0.625mg of drug injected intravitreally using a 30-gauge needle placed 1.5mm behind the limbus. After the procedure, antibiotic prophylaxis with eye drops every 3 hours for 3 days was administered. For laser group after general anesthesia peripheral and avascular zones of retina were ablated with laser spots. Infants followed in 3rd day and then weekly to determine the postoperative complication and anatomical success rate. Follow up continued until peripheral retinal vessel growth over the laser scar was noted.

Patients without resolving of ROP signs considered for re treatment.

The main evaluated outcomes including time of regression and decrease of plus signs and development of peripheral retinal vessels after treatment and absence of recurrence, final structural-anatomic outcomes compared in all groups of patients. We used kruskal wallis test and chi-square test from SPSS.18 software for statistical evaluation and P-value <0.05 was significant in this study.

Results and discussion

71 eyes of 36 consecutive patients (15 boys, 21 girls) were included in this study. Mean gestational age was 27 weeks (25–32 weeks), mean birth weight was 1085g (690–1900g).

Mean gestational age at the time of treatment was 35.2 ± 0.35 weeks. Sex, age and weight distribution was similar in all groups. Demographic data for each group are presented in Table 1.

All of the patients were on stage 3 ROP and Zone 2 was most commonly involved. Plus disease was seen in 23 patients and one patient had vitreous hemorrhage.

13 patients treated with LPC (group 1) and 10 patients received IVB injection (group 2) and 13 patients treated with both LPC and IVB (group 3).

Regression of plus disease and peripheral retinal vessels development appeared significantly in all groups (IVB group: 90%, LPC group: 84%, both IVB and LPC group: 100%) and difference was not statistically significant (Table 2).

Of all newborn infants who were treated with IVB one required further treatment with LPC and in LPC group two infants need retreatment. Of patients who received both treatments no patient required retreatment.

No systemic or significant ocular complications, such as vitreous hemorrhage, retinal detachment or endophthalmitis, were noted during follow-up after treatment.

Although ROP is a benign disease and spontaneous regressing of proliferative retinopathy occurs in about 90% and only10% of ROP requiring treatment, but current standard treatments (cryotherapy and laser therapy) are aggressive procedure, furthermore treatment results are not favorable always (CRP Cooperative Group, 1998; Hunter and Repka, 1993).

Knowledge of the molecular mechanisms of the pathogenesis of ROP has become the basis for current therapeutic approaches and studies using bevacizumab for the treatment of ROP with encouraging results have recently been published.

The BEAT-ROP study is a randomized controlled Phase II multicenter trial exploring the safety and efficacy of IVB for stage 3 ROP in severe Zone I or posterior Zone II in 150 premature neonates. Comparing intravitreal monotherapy of bevacizumab with conventional laser therapy investigators found no difference between laser and anti-VEGF treatment for zone 2 diseases, but a statistically significant benefit of anti-VEGF therapy for zone 1 disease. 70% of patients of this study were Hyspanic and it is common knowledge that ROP in Hispanic infants is more difficult to treat (Mintz-Hittner *et al.*, 2011).

Table.1 Demographic characteristics of patients with retinopathy of prematurity

		Group 1(N=13)	Group 2(N=10)	Group 3 (N=13)	p-value
Mean gestational age		26.39±0.59	27.40±0.37	27.31±0.56	0.12*
Range		25 to 32	25 to 29	25 to 32	
Mean gestational age at the time of treatment		35.08±0.45	35.70±1.04	35.08±0.42	0.93*
Range		31 to 38	31 to 43	33 to 37	
Birth weight		1057.69±56.37	1314.00±104.82	1056.92±85.47	0.08*
Range		710 to 1400	900 to 1900	800 to 1830	
gender	Female	61.5%(8)	50.0%(5)	61.5%(8)	0.82**
	Male	38.5%(5)	50.0%(5)	38.5%(5)	

Group 1: laser ablation group.

Group 2: IVB group.

Group 3: treated with both IVB and lase group.

* Kruskal Wallis Test

** Chi-Square Test

Table.2 Treatment outcomes between groups

		Groups		
		Group 1(N=13)	Group 2(N=10)	Group 3(N=13)
Treatment outcomes	Treated ROP	92.3%(12)	90.0%(9)	100.0%(13)
	Failed treatment	7.7%(1)	10.0%(1)	0.0%(0)

Ozdek and associates in a retrospective study showed the addition of IVB after the laser ablation slightly decreased the progression rate in severe AP-ROP eyes. limitations of this study is retrospective nature, absence of a control group and a small number of patients and limited functional results (Uzdek *et al.*, 2013).

In another prospective study Adjuvant intravitreal anti VEGF injection, in patients with stage 3+ ROP in zone I and posterior zone II as compared with conventional laser or cryotherapy, showed significant benefit in terms of better final anatomic outcome, induction of prompt regression, rapid development of peripheral retinal vascularization and decrease of recurrence rate of neovascularization. They also showed in ROP patients IVB is a safe and well tolerated (Autrata *et al.*, 2012).

Tahija and associates evaluate vascularisation of the peripheral retina using fluorescein angiography of infants who had been treated with IVB, they concluded although bevacizumab appears effective in bringing resolution of zone I and posterior zone II ROP and allowing growth of peripheral retinal vessels, complete normal peripheral retinal vascularisation was not achieved in half of the patients (Tahija *et al.*, 2014).

According to these studies and multiple other reports anti-VEGF therapy as a

monotherapy or adjuvant therapy leads to regression of ROP with promising results. It is consistent with pathophysiologic bases of ROP that VEGF has important role (Lee *et al.,* 2010; Bancalari *et al.,* 2014; Ahmed et al 2010; Wu *et al.,* 2011; Roohipoor *et al.,* 2011).

In the present study we have investigated the efficacy of IVB monotherapy and comparing with laser therapy alone and adjuvant therapy (IVB and LPC) in ROP patient. We selected infants with stage 3 ROP because IVB therapy in higher stages can leads to development of fibrotic tissue and causing traction of retina.

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