ORIGINAL ARTICLE

Efficacy of Intravitreal Bevacizumab for the Treatment of Zone I Type 1 Retinopathy of Prematurity

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ABSTRACT

Aim: To determine the efficacy of intravitreal bevacizumab in treatment of type retinopathy of prematurity in zone I.
Study Design: Prospective study
Location and Duration: in Opthalmology department of Nishtar hospital Multan, Bahawal Victoria Hospital, Bahawalpur, and Mayo Hospital Lahore. from January 2015 to January 2018.
Methods: One hundred and eight eyes of 54 patients having Zone I ROP were included in our study. Three patients died during the follow up period. One hundred and two eyes completed the follow up period. Sample size was calculated from the reference study performed by Reza Karkhaneh et al [11]. Sample was collected using non probability consecutive sampling technique. The outcome variable assessed during the study was regression of retinopathy of prematurity after neovascularization. Mean gestational age, mean birth weight, mean PMA at first injection, percent of patients cured at 90w of postmenstrual age, percent of patients requiring reinjection, mean time of recurrence, no. of patients developing the advanced disease and mean time of the surgery were the variables measured and statistically analyzed thereafter. Statistical analysis was performed using computer SPSS vr 23.
Results: Full regression of retinopathy of was observed in 85 (83.3%) eyes at ninety weeks of postmenstrual age, after one Intravitreal Bevacizumab injection. Re-injection was required in 17 (16.7%) eyes due to recurring and persistent neovascularization. There was recurrence at a mean of 5.76±2.05 weeks. Re-injection improved the condition in eight more eyes.
Conclusion: It can be concluded that intravitreal bevacizumab is effective in the treatment of zone I retinopathy of prematurity.
Keywords: Intravitreal Bevacizumab, Retinopathy, Prematurity

INTRODUCTION

Retinal traction, retinal detachment and hemorrhage can occur in severe cases of retinopathy of prematurity due to development of peripheral neovascularization[1]. Cryotherapy was the treatment of retinopathy of prematurity but nowadays peripheral laser photocoagulation is the treatment of choice[2]. Laser photocoagulation can lead to visual field restriction as it is a destructive method of treatment in zone I retinopathy of prematurity[3]. As it is understood by the mechanism of development of peripheral neovascularization, vascular endothelial growth factor is responsible for the development of neovascularization[4].

Bevacizumab is monoclonal antibody, directed against all forms of vascular endothelial growth factor[5]. All types of retinopathies, like, proliferative diabetic retinopathy[6], age related macular degeneration [7], neovascular glaucoma [8] and retinal vascular occlusion[9], which involve the upregulation of vascular endothelial growth factors, are treatable with help of bevacizumab. Bevacizumab is effective in treatment of retinopathy of prematurity by eliminating the angiogenic threat and studies have provided the evidence of its superiority over laser photocoagulation therapy[10].

Rationale of this study is to assess the anatomical and functional outcomes of intravitreal bevacizumab in the treatment of zone I retinopathy of prematurity as very few studies have done this in past.

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MATERIAL AND METHOD

This is a prospective study performed in Opthalmology department of Nishtar Hospital Multan, Bahawal Victoria Hospital, Bahawalpur, and Mayo Hospital Lahore. from January 2015 to January 2018. One hundred and eight eyes of 54 patients having Zone I ROP were included in our study. We followed all the patients for a minimum of ninety weeks postmenstrual age. Three patients died during the follow up period. One hundred and two eyes completed the follow up period. Preterm infants with a gestational age of 34w or less and birth weight of 2Kg or less were examined beginning at postmenstrual age of 31w or chronological age of 4w whichever was later. Preterm infants with zone I retinopathy of prematurity were included in this study. Ethical approval was obtained from Hospital Ethics Committee. Sample size was calculated from the reference study performed by Reza Karkhaneh et al [11]. Sample was collected using non probability consecutive sampling technique. Infants suffering from congenital cataract, history of any other ocular disease, congenital glaucoma or previous treatment of retinopathy of prematurity were excluded from the study. All the procedure and its pros and cons were explained to the parents and informed consent was obtained.

Intravitreal bevacizumab was injected under topical anesthesia at the dose of 0.625 mg in 0.025 ml of solution by consultant ophthalmologist with more than 5 years experience. Sulfacetamide 10% eye drops were given six hourly for three days to all the infants after injection. Follow up visits were scheduled as weekly for four weeks and biweekly until 90w of postmenstrual age. The outcome variable assessed during the study was regression of retinopathy of prematurity after neovascularization. Retina

specialist performed all the follow up examinations at each follow up visit. Criteria for retreatment were set as follows, neovascularization, disease existed for more than four weeks or there was evidence of new extra retinal fibrovascular proliferation. Mean gestational age, mean birth weight, mean PMA at first injection, percent of patients cured at 90w of postmenstrual age, percent of patients requiring reinjection, mean time of recurrence, no. of patients developing the advanced disease and mean time of the surgery were the variables measured and statistically analyzed thereafter. Statistical analysis was performed using computer software SPSS version 23.

RESULTS

One hundred and eight eyes of 54 patients having Zone I ROP were included in our study. We followed all the patients for a minimum of ninety weeks postmenstrual age. Three patients died during the follow up period. One hundred and two eyes completed the follow up period. The mean gestational age of all the patients was 28.7±2.93 weeks and the mean birth weight was 1321.08±335.85 grams. Eight eyes (7.84%) had stage 2 retinopathy of prematurity and remaining ninety four eyes (92.16%) had stage 3 disease. First injection was given at the mean postmenstrual age of 34.5±1.7weeks.

Full regression of retinopathy of was observed in 85(83.3%) eyes at ninety weeks of postmenstrual age, after one Intravitreal Bevacizumab injection. Re-injection was required in 17 (16.7%) eyes due to recurring and persistent neovascularization. There was recurrence at a mean of 5.76±2.05 weeks. Re-injection improved the condition in eight more eyes. In short, 93(91.18%) eyes were cured after one or two Intravitreal Bevacizumab injections. Nine (8.8%) patients developed advance stage disease even after re-injection. surgery was performed in these patients at a mean postmenstrual age of 50.81±3.26 weeks. Pars plana vitrectomy was performed in five eyes and scleral buckling was the procedure done in four eyes. In all the cases, retina was attached at ninetieth week of postmenstrual age. Complete peripheral retinal vascularization was seen in 75 eyes and an area of no vascularization was observed in 27 eyes, but there were no signs of active disease. No major complications such as vitreous hemorrhage, cataract or endophthalmitis were reported but there were a few cases of sub-conjunctival hemorrhage were reported.

Table-I

Variable	Results (n=102)
Mean Gestational Age (weeks)	28.7±2.93
Mean Birth weight (grams)	1321.08±335.85
Mean PMA at 1st Injection (weeks)	34.5±1.7
Patients cured at 90 weeks n (%)	85 (83.3)
Patients requiring 2nd injection n (%)	17 (16.7)
Mean time for recurrence (weeks)	5.76±2.05
Patients developing advanced disease n(%)	9 (8.8)
Mean time for surgery (weeks)	50.81±3.26

Data is presented as Mean ± S.D until mentioned otherwise

DISCUSSION

Intravitreal bevacizumab is effective in treating the retinopathy of prematurity in zone I as has been evident from the results of our research. Full regression of retinopathy of was observed in 85(83.3%) eyes at ninety weeks of postmenstrual age, after one Intravitreal Bevacizumab injection. Re-injection was required in 17(16.7%) eyes due to recurring and persistent neovascularization. In a previous study same dose of bevacizumab was used to our study and results showed that intravitreal bevacizumab is very effective in treating the zone I retinopathy of prematurity [12]. In previously performed studies overall outcomes of retinopathy of prematurity in zone I are quite poor[13].

In a study, laser photocoagulation was used to treat the retinopathy of prematurity in zone I, and retinal detachment was observed in 35.4% of the eyes included in that study[14]. It is believed that intravitreal bevacizumab might be able to improve these anatomical outcomes. Levels of vascular endothelial growth factors are usually elevated in patients with zone I retinopathy of prematurity and bevacizumab is a monoclonal antibody which acts against this growth factor. Therefore it is not wrong to believe that bevacizumab injection may regress the progression of neovascularization and thus treat retinopathy of prematurity. Mintz Hittner et al performed a study in which all the eyes with zone I or posterior zone II retinopathy of prematurity, included in the study were injected with intravitreal bevacizumab and were prevented from development of retinal detachment without the use of laser ablation[15].

In a comparative study comprising of duration of two years, Gunay M et al compared intravitreal bevacizumab with laser photocoagulation for the management of posterior retinopathy of prematurity [16]. Retreatment was required by two eyes in intravitreal bevacizumab group and by three in laser photocoagulation group of patients.

Similarly in a study by Yoon JM el al when intravitreal bevacizumab was combined with laser photocoagulation in one group, used alone in second group and compared with laser photocoagulation alone the results showed that first two groups had better anatomical outcomes and there was no need of retreatment as well as no incidence of recurrence[17]. Similar to our study another study used intravitreal bevacizumab in 238 eyes suffering from aggressive posterior retinopathy of prematurity and conclusion was made that 95.4% of the eyes had regression in the disease, 4.6% needed reinjection and four eyes required third injection [18]. Hundred percent regressions were seen after administrating third injection of intravitreal bevacizumab. A study compared intravitreal bevacizumab with laser photocoagulation in the treatment of type I zone II retinopathy of prematurity and the results were in favor of intravitreal bevacizumab in terms of success of treatment and regression of the disease and intravitreal bevacizumab was associated with better anatomical outcomes [19]. Another finding to be noticed is that, intravitreal bevacizumab is more efficient in treatment of zone II retinopathy as compared to zone I retinopathy of prematurity.

Previous studies show that, conventional laser photocoagulation was associated with progression to retinal detachment when used to treat the zone I retinopathy of prematurity as much as 70%[14]. Laser photocoagulation is a destructive process of treatment

while intravitreal bevacizumab is very simple to administer and takes less time than the former procedure. Moreover laser photocoagulation is associated with visual field restriction by ablating the peripheral retina[20,21,22]. Even though intravitreal bevacizumab is associated with lowering the levels of vascular endothelial growth factor but it is not the only growth factor produced by the avascular retina, so retinopathy of prematurity may continue to progress in spite the use of intravitreal bevacizumab injection[23].

Harder et al who performed the study to assess the efficacy and side effects of intravitreal bevacizumab in the treatment of 57 eyes with retinopathy of prematurity concluded that there were no ocular side effects associated with the use of intravitreal bevacizumab [24]. Similarly Sato et al also injected intravitreal bevacizumab for retinopathy of prematurity and the results they deducted showed that serum levels of bevacizumab increased while serum levels of vascular endothelial growth factor decreased after injecting 0.5mg or 1mg of intravitreal bevacizumab[25]. There is a possibility of development of systemic side effects because of lower levels of vascular endothelial growth factor but no such side effects have been reported in the current study. But there is need of further studies to establish this fact by following the patients for longer duration of time.

CONCLUSION

It can be concluded that intravitreal bevacizumab is effective in the treatment of zone I retinopathy of prematurity.

Conflict of interest: Nil
Funding Source: Nil

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