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Ranibizumab Intravitreal Injection-Monotherapy-Treatment for Retinopathy of Prematurity in Iraq

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Abstract

Introduction: Retinopathy of prematurity is a serious blinding condition resulting from disorder of the immature retinal vasculature which causes loss of vision by means of macular dragging and retinal detachment occurring primarily in infants of low birth weight.

Patients and methods: A controlled non-randomized, prospective, interventional study was performed in the Pediatric Ophthalmology Department in collaboration with the Viteroretinal department of Ibn Al-Haithem Teaching Eye Hospital, Baghdad, Iraq between October 2015 and February 2018. Intravitreal injections of Ranibizumab (0.25 mg/0.025 ml) were given by the Vitreoretinal surgeon in the Major Vitreoretinal Operating Rooms under sterile conditions and Topical Anesthesia.

Results: A total of 116 eyes of 59 neonates with Type 1 ROP were treated with monotherapy of Raniziumab. The mean gestational age was 30 weeks. The mean birth weight was 1148 grams, 31 neonates were male and 28 were female. 105 eyes showed complete resolution after 1 week and normal vascularization of the retina was seen 4 weeks after the injection. 11 eyes from seven neonates showed recurrence.

Conclusion: The use of anti-VEGF as a monotherapy is a rapid, effective, vision saving method for Retinopathy of prematurity either as monotherapy or in conjunction with laser therapy. There should be more studies to determine the smallest effective dose of different types of anti-VEGF for treatment of ROP. Also there should be more studies in collaboration with pediatricians to evaluate the possible systemic side effects from the anti-VEGF.

Keywords: Retinopathy of prematurity; Anti-VEGF; Ranibizumab

Introduction

Retinopathy of prematurity (ROP) is a disorder of the immature retinal vasculature which was first reported by Terry as retrolental fibroplasia [1,2] which causes loss of vision by means of macular dragging and retinal detachment occurring primarily in infants of low birth weight [3].

The retina has a unique blood supply with retinal vasculature develops to meet retinal metabolic demand apart from the fovea which has a different vascular pattern. In the early stages of embryonic development the retina receives all its nutrients through the blood supply from the choroid, which is vascularized from about 6 weeks' gestational age; then vascularization of the retina begins at 16 weeks of gestation, with mesenchyme, the blood vessel precursor, growing from the disc to reach the ora nasally at 8 months and the ora temporally shortly after birth [4].

The pathogenesis of retinopathy of prematurity involves two phases: phase 1 occurs from 22 to 30 weeks' postmenstrual age, while phase 2 from 31 to 44 weeks' postmenstrual age and phase 1 involves relative hyperoxia and decreased vascular endothelial growth factors (VEGF) levels, whereas phase 2 involves relative hypoxia and increased VEGF levels. The understanding of these relationships between oxygen and VEGF has allowed for an improved strategy for managing retinopathy of prematurity [5,6].

The international classification of acute ROP [7] which was revised in 2005 involves describing ROP by four parameters; severity by stage and location by zone and extend by clock hours of retinal involvement and lastly by Plus disease, describing abnormally dilated or tortuous vessels of the posterior pole with congestion of the retinal veins close to the optic disk. Later, the vessels of the iris become engorged and the pupil fails to dilate to mydriatics. The vitreous becomes hazy. It indicates an increased likelihood of an unfavorable outcome [8].

Treatment is recommended within 72 hours for type 1 ROP including any ROP stage in zone 1 with plus disease or stage 3 in zone 1 or stage 2 or 3 in zone 2 with plus disease [9].

The aim of treatment is to remove the stimulus for vessel growth by ablating the peripheral avascular retina using either cryotherapy or laser, and, although both are effective, laser is the modality of choice by most ophthalmologists [10].

Cryotherapy is freezing from the external ocular surface, used in 1980s, then in 1990s, treatment of ROP underwent a slow transition from cryotherapy to laser therapy (in which a laser is applied through the dilated pupil to the internal retinal surface) but both these treatments destroy the majority of the cells that produce vascular endothelial growth factor (VEGF) in the retina because VEGF is a key

factor in the progression of retinopathy of prematurity [10] and this lead to inevitably permanent loss of the peripheral visual field and often induces clinically significant myopia. When multiple applications of conventional laser therapy fail to induce regression of retinopathy of prematurity, vitrectomy is required [11].

The use of anti-VEGF agents, primarily intravitreal bevacizumab is an emerging treatment for acute retinopathy of prematurity in 2000s [12]. Off-label use of intravitreal bevacizumab therapy for ophthalmologic neovascular disorders was used widely including series of cases of stage 3 plus retinopathy of prematurity, as monotherapy or in combination with conventional laser therapy [12-15]. But bevacizumab escapes from the vitreous into the general circulation and reduces systemic VEGF levels for weeks to months in premature infants which rise theoretically the systemic complication [16], while Ranibizumab is an anti-VEGF-A monoclonal antibody fragment (48 kDa) that was designed for ocular use that had no the Fc antibody region, and hence, it is cleared from the bloodstream more rapidly with shorter systemic elimination half-life of ~2 hours [17] therefore theoretically should have less systemic complications and our aim of the study is to evaluate the effectiveness of Ranibizumab on active stages of retinopathy of prematurity as a monotherapy.

Patients and Methods

A controlled non-randomized, prospective, interventional study was performed in the Pediatric Ophthalmology Department in collaboration with the Viteroretinal department of Ibn Al-Haithem Teaching Eye Hospital, Baghdad, Iraq between October 2015 and February 2018.

The study was approved by The Scientific committee of Ibn Al-Haithem Teaching Eye Hospital. Infants with a birth weight of 1500 g or less and a gestational age of 30 weeks or less were examined, beginning at 4 weeks' chronologic age or 31 weeks' postmenstrual age, whichever was later.

Examination was performed by the pediatric ophthalmologist in the Minor surgeries operating room under topical anesthesia (Alcaine) pupillary dilatation was done using (Tropicamide 0.5% cyclopentolate 0.5%+phenylephrine 2.5%) in order to achieve a good dilatation. RetCam II unit from (Clarity Medical Systems, CA) was used for examination and documentation of retinopathy of prematurity for all patients.

Indirect Laser was out of service in our hospital and was not available throughout the country. So this left us with only one treatment option, the Intravitreal anti-VEGF Ranibizumab which was provided by the MOH to our hospital and delivered to the patients free of charge. 116 eyes of 59 neonates with Type 1 ROP were included for the treatment trial.

After diagnosis and documentation, the neonates with type 1 ROP were referred and referred to the Viteroretinal department in our hospital and scheduled for Intravitreal injections of anti-VEGF Ranibizumab (lucentis).

A data information form and informed consent was taken from the family after explanation of the nature of the pathology and the role of anti-VEGF injections for control of the disease.

Intravitreal injections of Ranibizumab (0.25 mg/0.025 ml) were given by the Vitreoretinal surgeon in the Major Vitreoretinal Operating Rooms under sterile conditions and in the presence of the anesthesiologist. Topical Anesthesia with ALCAINE (proparacaine hydrochloride ophthalmic solution, USP 0.5%) was used along with a lid speculum to open the lids and a povodine iodine 5% for disinfection.

Postoperative Antibiotic drops (ofloxacin 0.3%) were given every 4 hours and a postoperative examination visit by the pediatric ophthalmologist was scheduled after 1 week. Examination was done with the Retcam II and IOP measurement was taken with the indentation tonometry using the Perkins tonometer.

Subsequent visits were scheduled after 2 weeks, 4 weeks and 8 weeks after the date of the injection. Subsequent follow up included a monthly visit for the next 4 months and every 2 months for the following 6 months till the age of 2 years. Annual follow up till the age of 3 years was done. For Visual acuity and Cycloplegic refraction along with a retinal fundus examination, results were obtained.

Results

A total of 116 eyes of 59 neonates with Type 1 ROP were treated with monotherapy of Ranibizumab. The mean gestational age was 30 weeks. The mean birth weight was 1148 grams. 31 neonates were male and 28 were female. 105 eyes showed complete resolution after 1 week and normal vascularization of the retina was seen 4 weeks after the injection. 11 eyes from seven neonates showed recurrence.

4 eyes from 2 neonates showed progression after 1 week from the injections and were given a second injection with close weekly follow up. Resolution was achieved after 1 week and complete vascularization after 3 weeks weekly follow up continued for 8 weeks then every 2 weeks for 4 weeks then every month for 3 months.

4 eyes from another 2 neonates showed recurrences after 4 weeks and they were given a second injection with close weekly follow up. Resolution was achieved after 1 week and complete vascularization after 3 weeks weekly follow up continued for 8 weeks then every 2 weeks for 4 weeks then every month for 3 months.

3 eyes from 3 neonates showed progression to stage 4 and were referred to the Vitreoretinal surgery department and a pars plana vitrectomy was performed and they have been put on a follow up plan by the vireoretinal department.

After 8 months 3 neonates who had complete resolution showed myopic shift in their Cycloplegic refraction (-4, -5.5, -7) Diopters respectively. The children who had undergone pars plana vitrectomy had navigating vision in their eyes (Figures 1 and 2).

There were no ocular side effects and systemic side effects, apnea, renal dysfunction were not reported.

Discussion

Retinopathy of prematurity is a serious blinding condition. Sophisticated screening programs for high risk newborns should be applied for prevention of ROP and its serious complications.

In Iraq, screening programs have been established over the last three years In Collaboration between the neonatal care units around the country and Ibn Al-Haithem Teaching Eye Hospital/Baghdad (The Largest Tertiary ophthalmology hospital in Iraq).

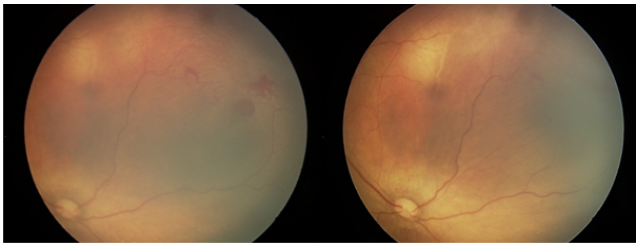

Figure 1: A Retcam picture showing the retina of a neonate with stage 2 zone 1 plus ROP before and after intravitreal Ranibizumab, Stage 2 zone 2 plus before injection 1 week after injection showing complete resolution.

In the past, most cases of ROP presented in advanced stages and beyond treatment. After the development of the screening program early stages were identified and treated successfully. There have been several treatment options for ROP. The recent development of anti-VEGF and its applications to different retinal vascular diseases has given a new hope in the treatment of ROP.

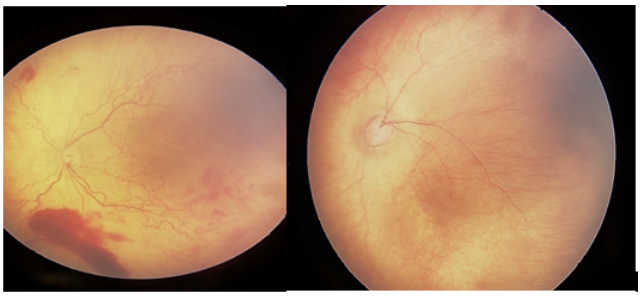

Figure 2: Stage 2 zone 1 plus, 1 week after injection showing complete resolution.

Anti-VEGF Drugs

Ranibizumab is a humanized monoclonal antibody to VEGF-A. It inhibits VEGF-A-induced ocular neovascularization. Its half-life is 9 days (vitreous) while the peak plasma time is 1 day and the peak plasma concentration is 0.3-2.36 ng/mL.

While bevacizumab is a recombinant humanized monoclonal antibody to VEGF, it blocks the angiogenic molecule VEGF thereby inhibiting tumor angiogenesis, starving tumor of blood and nutrients. The half-life is 20 days (range 11-50 days). The safety of Bevacizumab has been questioned as it has been found in the systemic circulation long after intravitreal injection. However Ranibizumab has a shorter half-life and smaller peak plasma time and concentration.

(BEAT-ROP) Cooperative Group conducted a prospective, randomized, multicenter trial to assess intravitreal bevacizumab monotherapy for zone I or zone II posterior stage 3+ (i.e., stage 3 with plus disease) ROP. Infants were randomly assigned to receive bilateral intravitreal bevacizumab (0.625 mg in 0.025 mL of solution) or conventional laser therapy. The results of this study have led to a dramatic change in treatment of ROP. However, concerns about the safety of bevacizumab have been an issue. Reported ocular complications of anti-angiogenic therapy for ROP include vitreous hemorrhage, retinal detachment, extension of an existing retinal detachment, and choroidal rupture. Concerns over systemic safety of anti-angiogenic therapy include the possible effects on infant development, and these have prevented widespread use of bevacizumab for ROP in the United States.

VEGF is essential for maturation of the developing brain, lung, and kidneys, and the anti-VEGF effects on these organs in the newborn are not known. Apnea and renal dysfunction or potential side effects to be watched for.

In the BEAT-ROP study five deaths were reported in the bevacizumab group and the rate of systemic intubation were more than that in the laser group.

In our study 116 eyes of 59 neonates with TYPE 1 ROP were treated intravitreal Ranibizumab as it was available in the Hospital, Most of the newborns showed complete resolution with full normal retinal vascularization within the first 2 weeks after injection and the rest improved 3-4 weeks after the injection.

There were no reported systemic ocular or systemic complications from Ranibizumab.

Similar to our results, Baumal et al. [18] concluded Intravitreal Ranibizumab induces rapid, complete regression of high-risk posterior ROP.

As noted in the results recurrence was minimal 11 eyes had progression 8 needed a second injection, 3 eyes progressed to stage 4 and were referred to the Vitreoretinal department where Pars Plana vitrectomy was performed.

It was noted that recurrence rate was higher among zone 1 or posterior zone 2 disease and Sankar et al. [19] showed that anti-VEGF monotherapy reduced the risk of myopia and recurrence in type 1 ROP.

Chen et al. [20] showed similar efficacy between Bevacizumab and Ranibizumab.
With significant differences in mean refractive errors at 1 year of corrected age, though there was a higher risk of myopia in the Bevacizumab treatment group.

ROP 4 eyes had recurrences between 2 to 4 months and those had plus disease at their initial diagnosis which means that those with plus disease should be monitored more closely and frequently.

Moreover, neonates with zone 1 disease and those with stage 3 ROP need an early intervention with very close follow up. In Taiwan, Lin et al. [21] found that Intravitreal Ranibizumab injections were effective with no short-term systemic or major ocular side effects.

Conclusion

The use of anti-VEGF as a monotherapy is a rapid, effective, vision-saving method for retinopathy of prematurity either as monotherapy or in conjunction with laser therapy. There should be more studies to determine the smallest effective dose of different types of anti-VEGF for treatment of ROP. Also there should be more studies in collaboration with pediatricians to evaluate the possible systemic side effects from the anti-VEGF.

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