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INTRAVITREAL RANIBIZUMAB INJECTION AS TREATMENT IN PATIENTS WITH TYPE 1 RETINOPATHY OF PREMATURITY

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ABSTRACT **Aim:** To investigate the anatomic outcomes of patients treated with intravitreal ranibizumab in the treatment of type 1 retinopathy of prematurity (ROP). **Material And Method:** A prospective cohort study was done including 100 eyes of 60 patients with type 1 ROP treated with intravitreal injection of ranibizumab (IVR) (0.25 mg/ 0.025 ml) as primary treatment from June 2018 to November 2019 over a period of 18 months. The anatomic outcomes were analyzed and follow-up were done upto 6 months. **Result:** There were a total of 94 eyes (94.0%) in the positive response group and 6 eyes (6.0%) in the negative/no response group after IVR. Within the positive response group, 49 eyes (52.13%) were in the regression without laser subgroup, and 45 eyes (47.87%) were in the regression with laser subgroup. **Conclusion:** Intravitreal injection of ranibizumab seemed to be effective in treating patients with type 1 ROP.

KEYWORDS : Type 1 ROP, Intravitreal injection Ranibizumab (IVR), Prospective cohort study.

INTRODUCTION:

Ranibizumab is a humanized recombinant G1 kappa isotype antibody fragment. It is structurally derived from the light chains of bevacizumab but has approximately 10 times greater affinity for VEGF. Bevacizumab is approximately 3 times larger than ranibizumab (149 vs. 48 kDa), and its higher molecular weight results in an intravitreal half-life that is 36% higher than that of ranibizumab.[1] Ranibizumab appeared transiently in systemic circulation and was rapidly cleared. Serum VEGF levels decrease after bilateral injection of 0.2 mg of ranibizumab, reaching a nadir at approximately 2 weeks and returning to normal levels 4 weeks after injection.[2,3] Bevacizumab, by contrast, was cleared relatively slowly from systemic circulation. It was found to enter the systemic circulation 1 day after intravitreal injection of bevacizumab (IVB) and to remain detectable for 8 weeks in the patients with ROP who received 0.625 mg IVB.[4] Retinopathy of prematurity (ROP) is a proliferative disorder of the developing retina in premature infants, and it continues to be a major cause of childhood blindness worldwide.[5] The randomized trials Cryotherapy for ROP study and Early Treatment for ROP established cryotherapy for threshold ROP and laser photocoagulation for type 1 ROP, respectively.[6,7] Although cryotherapy and laser photocoagulation can cure most cases of ROP, they are relatively destructive to the peripheral retina. The role of vascular endothelial growth factor (VEGF) in pathophysiology of ROP has been intensively studied, and various antiVEGF drugs are used to treat ROP. The study trial about anti-VEGF treatment for ROP- Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity which shows bevacizumab is effective in treating ROP and was more effective than laser in case of zone I ROP.[8] Since then, other scholars have published the results of antiVEGF drugs for treating ROP.[9,10,11] Among them, bevacizumab has been the most reported thus far, and there have been only a few case reports or small case series of ranibizumab treatment. Bevacizumab is a humanized function-blocking monoclonal full-length murine antibody that binds to all VEGF isoforms.[12] We report our experience of the intravitreal injection of ranibizumab (IVR) in the treatment of ROP by collecting a large number of cases. We also discuss potential prognostic factors with regard to the outcomes after IVR.

MATERIAL AND METHOD:

Study Design-

A prospective cohort study was conducted in neonatal intensive care units (NICUs) and ROP clinic of Department of ophthalmology at Nil Ratan Sircar Medical College and Hospital, Kolkata. Patients who were diagnosed with Type 1 ROP and accepted IVR as primary treatment from June 2018 to November 2019 over a period of 18 months were included in the study. Their complete medical records were reviewed, and patients who has done followed up for less than 6 months were excluded from the study. All of the infants with ROP who required treatment were hospitalized in the NICU. The legal guardian of each patient has signed a consent form before starting examination or any treatment.

Screening And Treatment-

Infants were examined for ROP to check whether they were born at gestational age (GA) < 32 weeks and birth weight (BA) < 2000g. The first screening was at 4 after birth or at 31 to 32 weeks postmenstrual age (PMA), whichever came first as according to The International Classification of Retinopathy of Prematurity (ICROP)2005. Pupils were dilated with Phenylephrine 2.5% and Tropicamide 0.5%. One drop of Tropicamide will be instilled every 10-15 minutes for 4 times starting 1 hour before the scheduled time for examination. This will be followed by Phenylephrine, one drop just before examination. 10% concentration Phenylephrine is available; dilution should be done 4 times before use in neonates' patient. Repeated instillation of Phenylephrine is avoided for the fear of hypertension Screening of ROP shall be done by indirect ophthalmoscopy by an experienced single ophthalmologist in our ophthalmology OPD and NICU. After instilling a topical anesthetic drop like Proparacaine, a wire speculum will be inserted to keep the eye-lids apart. anterior segment of eye should examine first to check for tunica vasculosa lentis, dilation of pupillary, and clarity of lens/media which is followed by the posterior pole to check for disease plus; also, sequential examination should follow for peripheral retina of all clock hours. A scleral depressor is used to indent the eye externally to examine areas of interest, rotate and stabilize the eye. Notes should be made for after each ROP examination, zone detailing, stage and terms of clock hours extension of any ROP and to ruled out of pre-plus or plus disease. These notes include a recommendation for the timing of next examination and are kept with medical record. After screening, the cases are classified as per ICROP.[6] ICROP describes vascularization of the retina and characterizes ROP by its position (zone), severity (stage), and extent (clock hours). The indications for IVR as a primary treatment were patients who met the criteria for type 1 ROP used in the Early treatment for Retinopathy of Prematurity study.[3] A 0.25 mg/0.025 ml dose of ranibizumab (half of the dose administered intravitreally in adults for ocular neovascular diseases)[8,13,14] was injected into each eye, using the following technique: topical anesthesia, sterile gloves, insertion of a lid speculum, instillation of topical povidone-iodine, injection of ranibizumab with a sterile 30-gauge 0.5-inch needle at 0.5 to 1 mm posterior to the limbus, removal of the needle with simultaneous compression using a sterile cotton tip, instillation of topical tobramycin, and removal of the speculum. If the other eye was to be treated, new equipment was used. After injection, the patients underwent binocular indirect ophthalmoscopy to assess the lens clarity, retinal breaks, and retinal artery or optic nerve perfusion.[10,15] The patients were re-examined the next day and then every week to monitor the progression of the disease until full vascularization was noted or additional treatment was given. The IVR injection, laser

treatment, lensectomy, and vitrectomy were all performed by the same experienced surgeon. Treated infants were kept hospitalized for at least 2 weeks after IVR in the NICU, where the systemic conditions of the infants were evaluated before and after injection, including the oxygen saturation, complete blood count, renal and liver function tests, chest x-rays, and abdomen and head ultrasound examinations.

Classification Of Patients:

Patients were classified all eyes into 2 groups according to their response to a single IVR: the positive response group and the negative/no response group. Furthermore, the positive response group was classified into 2 subgroups :(1) the regression without laser subgroup and (2) the regression with laser subgroup. The positive response group was defined as follows: Ridge and venous dilation and arteriolar tortuosity of the posterior retinal vessels (plus disease)[16] regressed after IVR, and retinal vessels continued to develop into the peripheral area. The negative/no response group was defined as follows: ROP worsened after IVR and developed into Stage 4A, 4B, or 5, or plus disease and ridge did not show any change 1 week after IVR. The regression without reactivation subgroup was defined as plus disease, ridge regressed after IVR without reoccurrence, and flat retina was achieved at the last visit. The regression with laser subgroup was defined as eyes with reoccurrence of plus disease or ridge during follow-up and treated with laser.

Data Analysis:

Statistical analysis has been done using IBM SPSS 22 (SPSS Inc., Chicago, IL). Kolmogorove-Smirnov tests were used to analyze the distribution of the samples, and chi-square and Fisher exact tests were performed to compare categoric data**.**

RESULTS:

A total of 100 eyes of 60 patients were included in the study, 40 males and 20 females. As per our classification, there were a total of 94 eyes (94.0%) in the positive response group and 6 eyes (6.0%) in the negative response group after IVR (fig 1).

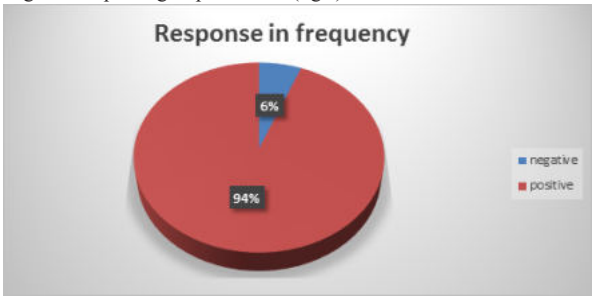

Fig.1

Within the positive response group, 49 eyes (52.13%) were in the regression without laser subgroup, and 45 eyes (47.87%) were in the regression with laser subgroup**.** There were significant differences among the BW, PMA, and PNA at IVR of the positive response group and the negative/no response group using the independent Kruskal Wallis test, and there were significant differences between the mean BWs of the regression without laser subgroup and the regression with laser subgroup using the independent t test (Table 1).

Table 1: Patient Characteristics Compared Within Different Groups

	Positive response group	Negative response group	Regression without laser group	Regression with laser group
Eyes	94 (94%)	6(6%)	49 (52.13%)	45 (47.87%)
GA (in weeks)	29.4+-2.2	28.6+-1.6	30.0+-2.1	28.5+-1.6
BW (in g)	1377.5+-395.6	1578+-592.3	1460.9+-436.5	1288+-324.2
PMA (in weeks)	35.8+-1.9	37.2+-5.3	36.3+-2.1	35.4+-1.8
PNA at IVR (in days)	47.2+-13.4	62.2+-15.4	46.2+-13.2	47.8+-12.9

BW: birth weight; IVR: intravitreal injection of ranibizumab; PMA: postmenstrual age; PNA: postnatal age; SD: standard deviation.

The time between laser and the initial IVR was 14 to 100 days, with an average of 58.4+-18.7 days (8.4+-2.8 weeks). The laser rate was 46.8% in APROP, 57.9% in zone I, and 35.3% in zone II. All reactivation eyes received laser treatment. The plus disease and ridge regressed, and retina remained flat after laser treatment.

Of the 6 eyes that had negative/no response, 2 eyes were APROP, 3eyes were zone 1 stage 3þ, and 1 eye was zone 2 stage 3þ ROP at screening. One eye progressed to stage 4A, 2eyes progressed to stage 4B, 1 eye progressed to stage 5, 1 eye had marked posterior fibrosis, and 1 eye had no response after IVR. At the last visit, 98 eyes (98%) had attached retinas, and 2 eyes (2%) had retinal detachment.

The major ocular complications associated with IVR in our study included cataract in 1 eye (1%) and vitreous and preretinal hemorrhage in 1 eye (1%). The cause of cataract in 1 infant was not related to possible trauma during the injection operation. The vitreous and preretinal hemorrhage resolved eventually without any additional treatment. No notable systemic adverse event subsequent to IVR was observed in our series. No patient died or experienced pulmonary dysfunction after IVR.

DISCUSSION:

In this study, we found that IVR as primary treatment resulted in a positive response in 94% of ROP eyes. Compared with reports of bevacizumab use in ROP, such as the Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity study and the report of Wu et al,6 our reactivation rate was higher.[4,17] Chen et al[17] reported that 151 eyes that received IVR had a reactivation rate of 33.1%, which is a similar value to ours. Wong et-al[14] also demonstrated that ranibizumab treatment had a higher chance of reactivation when compared with infants treated with bevacizumab. The differences may be related to the different ROP types enrolled. In our study, there were high proportions of zone I ROP and APROP, and zone I ROP and APROP require more time to achieve full vascularization after IVR. Reactivation occurs at any time if there is an increase in VEGF levels. The fact that the reactivation rate in zone I ROP in our study (57.8%) was higher than that in zone II (35.4%) confirmed this finding. Incomplete vascularization and vascular abnormalities were observed in our study. Approximately 3% of eyes (3eyes) had incomplete vascularization without reactivation after IVR. A large avascular area was found in the peripheral retina. Within those eyes, abnormal vessel shunting and branching also were observed according to fundus photography. These results confirm that there may be serious and lasting ocular structural abnormalities in eyes with ROP treated with ranibizumab. These phenomena also were reported in patients treated with bevacizumab. Tahija et al[18] showed that in their series of 20 eyes, complete normal peripheral retinal vascularization was not achieved in half of the patients. Lepore et al[19] studied the fundus fluorescein angiography results of 23 eyes and found that all eyes treated with bevacizumab injection had abnormalities at the periphery (large avascular area, abnormal branching, shunting) or the posterior pole (hyperfluorescent lesion, absence of foveal avascular zone). These posterior and peripheral lesions were not observed in the majority of the lasered eyes.[20] Considering the potential risk of retinal holes or tears in the avascular retina, we performed laser treatment on these eyes. The long-lasting implications of these abnormalities for the visual function of the child need to be studied. Although most ROP eyes showed a positive response to IVR, 5.7% of eyes still progressed to stage 4 or 5 and required vitrectomies or laser treatment to reattach the retina. Retinopathy of prematurity deterioration after ranibizumab or bevacizumab treatment has been reported,[21,22,] but has not been analyzed statistically.

We found that the PMA and PNA in the negative/no response group were larger than those in the positive response group. These findings indicated to us that delayed IVR treatment may lead to a negative or no response. In the vasoproliferative phase, relative hypoxia peripheral avascular retina stimulates secretion of VEGF. Unlike other ocular neovascular conditions such as exudative age-related macular degeneration, in which there is continual release of VEGF, there is a single burst of VEGF that promotes neovascularization in ROP[23]The delayed IVR treatment given at a period when VEGF levels are decreasing may promote fibrosis driven by connective tissue growth factor.[24,25]Traction from fibrosis may cause retinal breaks or detachments. The minimum effective dose of IVR for infants with ROP remains undetermined. The dose we used in this study was half of the dose administered intravitreally in adults for ocular neovascular diseases. This dose is the same that has been used in many reported cases. However, it has been argued that this dose might be relatively

high for infants with ROP, considering their vitreous volume and body weight compared with those of adults.[26] It is certain that IVB and IVR can enter systemic circulation after intravitreal injection in both animal models and humans.[27,28] A case series has been reported in which one third of the adult dose of IVB produced the regression of retinal neovascular changes.[29] The bilateral effects of unilateral injections of both IVB and IVR have been described for both adults and children.[30,31] Ranibizumab is considered safer for premature infants than bevacizumab, because the systemic VEGF suppression seems to last for less time than that with bevacizumab.[32]

CONCLUSION:

Intravitreal injection of ranibizumab seemed to be effective in treating patients with type 1 ROP. Future studies of the optimal dose and unilateral anti-VEGF treatment in certain infants with ROP should be performed. Treatment with IVR is less time-consuming and risky than conventional laser treatment, and it allows further retinal vascularization, whereas laser treatment can lead to permanent destruction of the peripheral retina**.**

Limitation Of The Study:

It was a single-center study and a very limited according to an Indian population. No systemic complications were observed or reported to us from the neonatologists; however, this finding does not mean that there were none but rather that we did not detect any complications. Long term outcome and complications of IVI need to be studied.

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