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Efficacy and Safety of Low Dose Intravitreal Ranibizumab for Treatment of Retinopathy of Prematurity

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Abstract

Background: Retinopathy of prematurityis a real public health problem in low and middle-income countries like Egypt. With the improvement of neonatal care and the increased survival of low-birth-weight babies, there is a real increase in the risk of vision loss from this disease, and a better understanding of the best treatment options will help to control the disease and save the sight of these babies.

Aim of Study: To evaluate safety, efficacy, and recurrence rate of lowdose intravitreal ranibizumab therapy in the treatment of type 1 retinopathy of prematurity.

Patients and Methods: Between January 2019 and December 2020, this retrospective comparative case series study was conducted on 100 eyes from fifty individuals who received intravitreal ranibizumab injections after being diagnosed with type 1 retinopathy of prematurity (ROP) and aggressive ROP. The included infants were divided into 2 groups, the first group (50 eyes) received the conventional dose (0.25mg) and the second group (50 eyes received low-dose intravitreal ranibizumab (0.12mg).).

Results: A total of one hundred eyes of fifty infants (25 in each group) were included in the study, with a mean gestational age of 31.7±1.3 weeks and a mean birth weight of 1544.2±323.9g. No intraoperative or postoperative complications were observed in either group. There was no significant difference in efficacy between the two groups in terms of post-injection complete vascularization and the absence of pathological vascular hyperplasia or retinal proliferation in the non-complete vascular retina. Concerning the post-injection recurrence rate, 2 infants in each group had a recurrence, which was treated with a second injection of the same dose of ranibizumab.

Conclusion: Intravitreal injection of low dose ranibizumab is an effective and safe method for the treatment of type 1 ROP and aggressive ROP.

Key Words: *Birth Weight – Gestational age – Ranibizumab – Retinopathy of prematurity.*

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Introduction

RETINOPATHY of prematurity (ROP) is a major factor in childhood blindness, particularly in nations with economies that are fast rising and where preterm births are becoming more and more common **[1]**. Low birth weight (BW) preterm children are more susceptible to the disease because of the interruption of the normal neurovascular development of the retina, which can result in abnormal vascular growth and blindness **[2]**. With the availability of efficient therapeutic options, it has been demonstrated that early detection and appropriate therapy of ROP can stop progression and maintain vision **[3]**. Laser treatment is the gold standard for the treatment of type 1 ROP **[4]**, but it may cause myopia, and peripheral visual field defects and traction retinal detachment **[5]**. In recent years, intravitreal injection of anti VEGF has attracted a great attention as a new treatment for ROP. VEGF inhibitors have been proven to significantly diminish the neovascular response and the incidence of refractive errors with preservation of the peripheral retina, making it more advantageous than the traditional methods of treatment as retinal cryotherapy or laser treatment **[6-10]**. However, there are several issues with anti-VEGF therapy in ROP. For instance, it is well known that intravitreally injected medicines might seep into the bloodstream. Bevacizumab administered intravitreally reduces VEGF plasma levels below the limit of detection for weeks after a single injection **[11-15]**. What negative impact such systemic VEGF suppression has on organ development is unknown. Therefore, a major issue in ROP is the systemic safety of anti-VEGF medications over the long term **[16,17]**. The second unanswered query concerns the dosage of anti-VEGF. The adult bevacizumab dose per eye was reduced by half for the BEAT-ROP trial **[18]**. Ac-

cording to a recent study [19], ROP patients can benefit from substantially lower bevacizumab dosages.

Aim of the work:

The aim of this study was to evaluate safety, efficacy, and recurrence rate of low-dose intravitreal ranibizumab therapy in the treatment of type 1 and aggressive retinopathy of prematurity.

Patients and Methods

This was a retrospective, comparative case series study, carried out by reviewing the medical records of all patients who had intravitreal injection for types 1 ROP and aggressive ROP (Fig. 1), between January 2019 and December 2020 at tertiary medical center. The study was approved by the Institutional Review Board at Tanta University and was conducted in compliance with the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Informed consent was signed by the parent or the legal guardian of the infant before enrollment. 50 patients who were included in the study divided into 2 groups according to the dose of the injected ranibizumab. 25 patients received 0.25mg. ranibizumab and the second group received 0.12mg. Baseline characteristics of the patients, including gender, gestational age at birth, birthweight, stage of ROP, presence of aggressive ROP, presence of multiple pregnancies, dose of injected ranibizumab, any complicationrelated to injection, efficacy of injection and presence of recurrence of ROP after the injection were collected from the charts. Risk factors of ROP were evaluated including oxygen therapy during admission in NICU, apnea, sepsis, exchange transfusion, thrombocytopenia, blood transfusion, and phototherapy.

Surgical technique:

Prophylactic antibiotic eye drops used for 3 days before intravitreal injection which was done in a sterile operating room. Before injection, anesthetic eye drops were used for surface anesthesia of the injected eye, and a 10% povidone-iodine solution was used to disinfect the skin around the eye. Then, push the drug to the dose scale of the required injection in advance. Open the eye with a pediatric eye speculum, instill 5% povidone-iodine eye drops into the conjunctival sac of the eye. After 1.5 minutes, the conjunctival sac was rinsed with normal saline. Ranibizumab was injected at 1.5mm posterior to the limbus in the inferior-temporal quadrant. After the injection, a sterile cotton swab was used to press the injection site for 60 seconds. If the other eye was to be treated, all surgical instruments were replaced. After the operation, quinolones was given for 5 days post operatively and the operated eye covered with gauze, which was removed at the end of the day of injection [20].

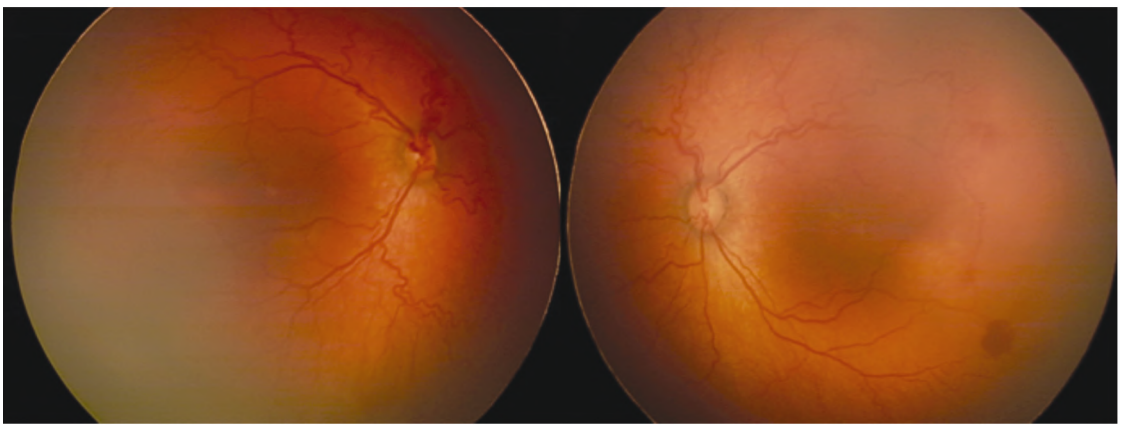

Fig. (1): Showing fundus photos of both eyes of case number 2; a preterm male patient with GA of 31 weeks and birth weight of 1000g showing aggressive retinopathy of prematurity.

Follow-up after injection:

An indirect ophthalmoscope was used on the first postoperative day to check for any signs of central retinal artery occlusion, retinal or vitreous hemorrhage, retinal tear or detachment, or lens damage. Then the fundus was examined weekly in the first month, once every two weeks in the second month and once a month from the third month.Follow-up was conducted for 65 weeks post menstrual age or until clinical examination confirmed complete retinal vascularization to ora serrata, whichever came first. The same ophthalmologist (RG) performed the procedure and the examinations that followed.

Outcome measures:

The primary outcome measures were safety of low-dose intravitreal ranibizumab therapy, which was detected by the presence of any early or late post injection complications, the efficacy of injection which was defined as post injection complete vascularization or the retinal vessels in zones II or III had terminated without pathological vascular hyperplasia or retinal proliferation, and recurrence which has been defined as reappearance of plus disease, neovascularization, extraretinal fibrovascular proliferation, new ridge after prior initial regression, or progression of disease despite prior treatment **[21]**.

Statistical analysis:

Data was collected and stored in a spreadsheet. Descriptive continuous variables are normally distributed; therefore, they were presented using the mean and standard deviation, whereas categorical variables were reported as proportions (%). Statistical analysis was carried out using SPSS version 23.0 (SPSS, Inc, Chicago, IL). For all hypothesis tests, 2-sided p-value of <0.05 was considered as statistically significant.

Results

Baseline characteristics:

A total of 100 eyes of 50 infants were included in the study (25 infants in each group) with mean gestational age of 31.7±1.3 weeks and mean birth weight 1544.2±323.9g. Baseline characteristics are displayed in Table (1). Demographics and baseline characteristics were comparable between the two groups.

Table (1): Demographic and baseline characteristics for both groups.

	Both groups (50 infants)	Group 1 (Conventional dose Lucentis)	Group 2 (Low dose Lucentis)	*t*-value	*p*-value
Gender (male)	28	15	13	0.3	0.56
Mode of Delivery (normal vaginal delivery)	2	0	2	2	0.1
GA	27-35 w (31.42±1.6)	31.7±1.3	31.1±1.8	1.3	0.1
Birth weight	1200-2400 g (1544.2±323.9)	1561±325	1527±328	1.3	0.1
Respiratory distress	50	25	25		
Nasal cannula	50	25	25		
CPAP	49	25	24	1.02	0.3
MV	49	24	25	1.02	0.3
Apnea	41	21	20	0.13	0.7
Sepsis	5	2	3	0.2	0.6
Thrombocytopenia	4	2	2	0	1
Blood transfusion	8	4	4	0	1
Exchange transfusion	1	0	1	1	0.3
Phototherapy	29	16	13	0.7	0.3
Type 1 ROP	43	20	23	1.5	0.2
APROP	7	5	2	1.4	0.2

APROP: Aggressive posterior Retinopathy of prematurity. MV : Mechanical ventilation.
CPAP : Continuous positive airway pressure. ROP: Retinopathy of prematurity.

Clinical outcome measures:

The clinical outcome measures in the two study groups are displayed in Table (2). No intraoperative or postoperative complications were observed in in either group. Regarding the efficacy of low dose intravitreal ranibizumab group there was no significant difference between both group regarding the post injection complete vascularization (Fig. 2) and the absence of pathological vascular hyperplasia or retinal proliferation in the non-complete vascular retina. Concerning the post injection recurrence rate, two infants in each group had a recurrence which was treated with a second injection of the same dose of ranibizumab.

Table (2): Clinical Outcome for both groups.

	Group 1	Group 2 (Low dose Lucentis)	X^2	*p*-value
Intraoperative complication postoperative complications.	0	0		
Post injection complete vascularization	0	0		
Retinal BV terminated in zone 2-3	46	45	0.12	0.7
without pathological vascular hyperplasia or retinal proliferation	4	5	0.12	0.7
Recurrence	2	2		

BV: Blood vessels.

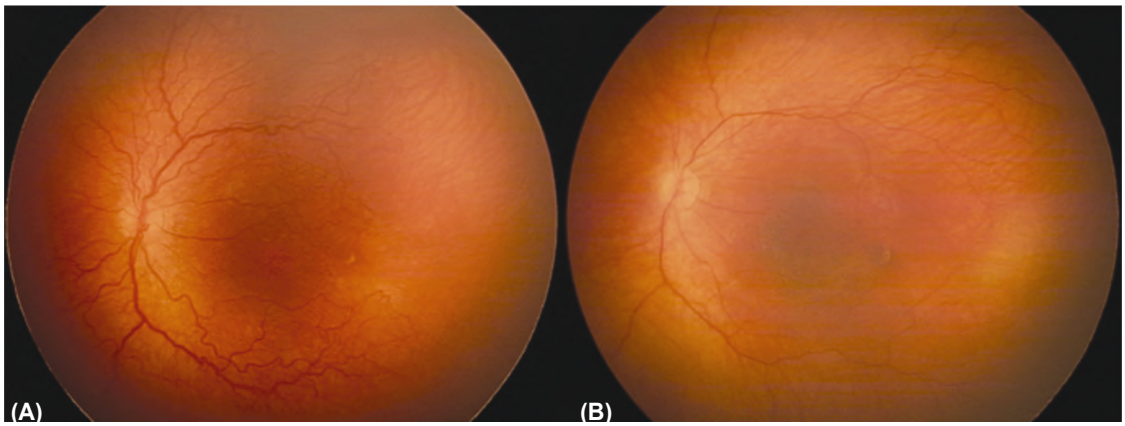

Fig. (2): Showing fundus photos of the left eye of case number 3; a preterm male patient with GA of 32 weeks and birth weight of 1200g: (A) Aggressive retinopathy of prematurity, (B) Fundus photo of left eye of the same infant 2 month after treatment with intravitreal low dose ranibizumab showing regression of the active ROP signs and progression of the normal vascularization to the peripheral retina.

Discussion

Ranibizumab is a recombinant humanized monoclonal antibody fragment which can bind and inhibit all biologically active isoforms of human VEGF. Although the European Commission approved in 2019 the use of intravitreal injection ranibizumab as a method of treatment of retinopathy of prematurity, the optimal dose of anti VEGF medications for ROP treatment is not clear especially there is an essential role of VEGF in development and maturation of many organsas in the lungs, kidneys, and brains of neonates **[22]**. The BEAT-ROP trial, **[18]** recommended the use of 0.625mg of bevacizumab for children, which is half of the adult dose. Compared to bevacizumab, ranibizumab has a higher affinity for binding to VEGF. Therefore, hypothetically, in terms of therapeutic benefit and adverse effects following systemic absorption, ranibizumab is preferable to bevacizumab for preterm newborns **[23]**.

In our study, we evaluated safety of a low dose of ranibizumab (quarter the adult dose) in treating type 1 and aggressive ROP, none of the infants had intraoperative complications, such as retinal hemorrhage, central retinal artery occlusion, vitreous hemorrhage, or iatrogenic cataract, or postoperative systemic complications. This coincides with the results of Castellanos et al., **[24]**. Who used ranibizumab for ROP treatment and followed-up the patients for 3years, and their findings proved the efficacy and safety of ranibizumab and the BEAT-ROP study did not show any increase in children mortality after intravitreal injection of anti VEGF. Also, we found no clinically significant difference between the conventional dose group and low dose group regarding the efficiency and recurrence rate. Complete vascularization was reached in 46 eyes in group 1 and 45 eyes in group 2. All eyes without full intraretinal vascularization are being followed-up beyond 65 weeks. 2 eyes in each group shows signs of recurrence which have been treated by second dose of ranibizumab. Our results are consistent with CARE-ROP study, Stahl et al., **[25]** compared 2 different ranibizumab doses (0.12mg and 0.20mg) in infants with bilateral ROP and assessed the number of infants who required rescue therapy at 24 weeks. A total of 14 of 16 (88%) infants achieved control of ROP without the need for more treatment. Two infants in each group showed signs of recurrence and another dose of

ranibizumab was given. Another retrospective case series evaluated the low dose ranibizumab in treatment of type 1 ROP showed regression of the disease in all infants without the need of another dose of ranibizumab **[26]**.

There are some limitations in our study, including the retrospective nature of the study and the assessment of efficacy of ranibizumab and recurrence of ROP without measurement of VEGF level in serum. Based on our results, we advise taking into consideration a lowering of the ranibizumab dose for the treatment of retinopathy of prematurity.

Conclusion:

Type 1 ROP and aggressive ROP can both be effectively and safely treated by intravitreal injection of low dose ranibizumab.

Financial support and sponsorship:

Nil.

Conflicts of interest:

None declared.

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فاعلية وسلامة الجرعة المنخفضة من عقار الرانيبيزوماب داخل الجسم الزجاجى للعين لعلاج مرض اعتلال الشبكية الخداجى

الهدف من الدراسة : لتقييم السلامة والفعالية ومعدل تكرار العلاج بجرعة منخفضة من عقار الرانيبيزوماب داخل الجسم الزجاجى فى علاج اعتلال الشبكية الخداجى من النوع الأول.

المرضى وطرق الدراسة : بين يناير ٢٠١٩ وديسمبر ٢٠١٠، أجريت دراسة مقارنة بأثر رجعى على ١٠٠ عين من خمسين طفل حديثى الولادة تلقوا حقن رانيبيزوماب داخل الجسم الزجاجى بعد تشخيص إصابتهم باعتلال الشبكية الخداجى من النوع الأول واعتلال الشبكية الخداجى العدوانى.

تم تقسيم الأطفال المشمولين إلى مجموعتين، المجموعة الأولى (٥٠ عيناً) تلقت الجرعة التقليدية (٠.٢٥مجم) من عقار الرانيبيزوماب داخل الجسم الزجاجى والمجموعة الثانية (٥٠ عيناً) تلقت الجرعة المنخفضة (١٢.٠) من عقا ر الرانيبيزوماب داخل الجسم الزجاجى.

نتائج الدراسة : تم تضمين مائة وخمسين عين رضيعاً فى الدراسة (٢٥ رضيعاً فى كل مجموعة)، بمتوسط عمر حمل ٣.١±٧.٣١ أسبوعاً ومتوسط وزن عند الولادة ٢.١٥٤±٩.٣٢٣ جم.

لم يلاحظ أى مضاعفات أثناء العملية أو بعد العملية الجراحية فى أى من المجموعتين. لم يكن هناك فرق ذو قيمة إحصائية بين المجموعتين من حيث إكتمال الأوعية الدموية بعد الحقن أو فى تضخم الأوعية الدموية أو النمو غير الطبيعى للشبكية فى الشبكية ذات الأوعية الدموية غير المكتملة. وفيما يتعلق بمعد لتكرار المرض فيما بعد الحقن، حدث ارتجاع للمرض فى رضيعين فى كل مجموعة ، وتم علاجهم بحقنة ثانية من نفس جرعة رانيبيزوماب.

الاستنتاج : الحقن داخل الجسم الزجاجى بجرعة منخفضة من عقار رانيبيزوماب هو طريقة فعالة وآمنة لعلاج النوع الأول من اعتلال الشبكية الخداجى واعتلال الشبكية الخداجى العدوائى.