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Comparison of intravitreal injection of ranibizumab versus bevacizumab for treatment of type 1 and aggressive retinopathy of prematurity in rural Egypt. A randomized clinical trial

Ghada Mahmoud Tawfik ,[1] Ezzat A Shahein,[1] Sherif A Dabour,[1] Dina Hassanein,[2] Ahmed Mohamed Elshewy[2]

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[1]Ophthalmology Department, Zagazig University, Faculty of Medicine, Zagazig, Egypt
[2]Ophthalmology Department, Cairo University, Kasr Alainy Faculty of Medicine, Cairo, Egypt

Correspondence to
MSc Ghada Mahmoud Tawfik; ghadaeladway@zu.edu.eg

ABSTRACT

Objective The objective of this study is to evaluate the efficacy of intravitreal ranibizumab (IVR) monotherapy compared with intravitreal bevacizumab (IVB) monotherapy for treatment of type 1 and aggressive retinopathy of prematurity (ROP) in rural Egypt.

Methods 36 eyes of 18 infants with bilateral aggressive or type 1 ROP were recruited between September 2020 and September 2022. Mean follow-up duration was 16.53 months. IVB was injected in the right eye and IVR in the left eye, rescue injection of the same initial anti-vascular endothelial growth factor (VEGF) in case of ROP reactivation. Outcome measures included regression achieved either by single injection or multiple injections or additional laser therapy at 55 weeks' postmenstrual age (PMA), recurrence of ROP, total retinal vascularisation time and complications.

Results Initial regression of ROP within 1 week occurred in 11/18 eyes (61.1%) in bevacizumab group and 15/18 eyes (83.3%) in ranibizumab group (p=0.137). Primary outcome measure was achieved in 14/18 eyes (77.8%) and 16/18 eyes (88.9%) in bevacizumab and ranibizumab groups, respectively (p=0.658). Late reactivation requiring retreatment with anti-VEGF was encountered in 4/18 eyes (22.2%) and 1/18 eyes (5.6%) in bevacizumab and ranibizumab groups, respectively (p=0.338). Peripheral laser therapy on the avascular retina was done in 3/18 eyes (16.7%) in each group at mean of 55.67 weeks' PMA.

Conclusion Bevacizumab and ranibizumab proved to be effective regarding regression of acute ROP and continuing peripheral retinal vascularisation. Higher proportion of reactivation with bevacizumab, however, clinically non-significant. Laser therapy can be postponed to reduce its complications.

Trial registration number NCT05033106.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ranibizumab is the only approved anti-vascular endothelial growth factor (VEGF) for treatment of retinopathy of prematurity (ROP); however, some studies have reported that recurrence is much more common with ranibizumab than with bevacizumab.

WHAT THIS STUDY ADDS

⇒ In this prospective study, we concluded that both bevacizumab and ranibizumab can effectively reduce acute-phase ROP with no significant difference between the two drugs as regard recurrence necessitating retreatment.

⇒ Reinjection of anti-VEGF is recommended for ROP reactivation even in aggressive cases, so laser treatment can be reduced or postponed to avoid its complications.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The current study demonstrated a suggested algorithm that proved to be effective regarding initial treatment and treatment of recurrence for type 1 and aggressive ROP in rural Egypt preterm infants.

⇒ How should healthcare authorities approach the off label status of a potentially cost-saving therapy, bevacizumab, for this vision-threatening disease, ROP?

INTRODUCTION

Retinopathy of prematurity (ROP) remains a leading cause of preventable childhood blindness specifically in developing countries because of inappropriate neonatal care and lack of ROP screening programmes.[1] It is a vascular endothelial growth factor (VEGF)-driven vasoproliferative disease.[2]

Over the past decades, photocoagulation of the retina by laser was the gold standard in treating ROP.[3] Laser therapy exhibited an approximately 10% risk of retinal detachment in Early Treatment ROP (ETROP) randomised trial.[4] Anti-VEGF treatment allows normal vascularisation of peripheral retina, better refractive outcomes as well as short duration of the procedure, easy application of the injection and avoidance of the risks of general anaesthesia.[5]

Bevacizumab is a humanised full-length monoclonal antibody that binds to all VEGF isoforms. Bevacizumab molecule is approximately three times larger than ranibizumab, and its higher molecular weight results in an intravitreal half-life that is 36% higher than that of ranibizumab. Ranibizumab is a humanised recombinant antibody fragment and has nearly 10 times greater affinity for VEGF.[6] Ranibizumab is the first approved anti-VEGF treatment for the management of retinopathy and is a promising alternative to laser therapy. High treatment success rates were observed with ranibizumab 0.2 mg during the RAINBOW trial, with supporting evidence provided by the CARE-ROP trial.[7] Ranibizumab is much more expensive than bevacizumab.[8]

VEGF is vital in angiogenesis, maintaining organ health and development of various vital organs in the body.[9] The inhibition of VEGF may lead to abnormal organogenesis or neurodevelopment. The selection of an anti-VEGF drug with less systemic VEGF interference, reducing the dose or using an anti-VEGF agent only once in ROP patients seems to be safer. Intravitreal ranibizumab (IVR) was perceived as being a safer drug in premature infants due to the shorter duration of systemic VEGF suppression compared with intravitreal bevacizumab (IVB).[10] Despite the increasingly widespread use of anti-VEGF agents in the treatment of ROP in recent years, information about their systemic effects and side effects is limited.[11]

It was reported that IVB and IVR have similar treatment efficacies but relatively higher disease recurrence following IVR therapy.[12] Late recurrence at up to 70 weeks' postmenstrual age (PMA) after IVB monotherapy has been also reported.[13] So, timely detection and management of recurrence have become a major issue in anti-VEGF therapy for ROP.

Vitrectomy and/or scleral buckling (SB) are considered for stages 4 and 5 ROP. The reattachment rates with SB in stage 4A were 66%–75%,[14–16] however, recently approached 93.5%.[17 18] Lens sparing vitrectomy for stage 4A ROP has reported anatomical and functional success rates that ranged from 77% to 97%.[19–21] The anatomical success for stage 4B was only 44.4%.[22] The rates of reattachment for stage 5 ROP have been reported as disappointing, ranging between 13% and 45.5%.[23 24]

In this prospective study, we compared the efficacy of IVR and IVB for type 1 and aggressive ROP (A-ROP), as regard acute ROP regression, recurrence profile, needed additional treatment, complications, retinal vascularisation time and necessity of subsequent ablative procedures.

METHODS

This *prospective parallel assignment, single masking (participant) randomised clinical trial* was approved by the ethical committee of Cairo University and Institutional Review Board Zagazig University. The study protocol was registered on www.clinicaltrials.gov.

The sample size was calculated to be 36 eyes of 18 infants using open Epi confidence total 95%, power of the study 80%.[25] The right eye was assigned to receive bevacizumab and the left eye to receive ranibizumab by *simple random method (by lottery)* at the beginning of the study. Moreover, in our study group, both infants' eyes were nearly of the same disease severity. Enrolled eyes were allocated in 1:1 ratio. Consort flowchart and checklist are provided in online supplemental files 1 and 2. The full trial protocol is provided as online supplemental file 3.

We informed the participants' parents about the severity of disease, treatment options and complications. Written informed consent was signed.

ROP screening was done by binocular indirect ophthalmoscope (BIO) and wide-field paediatric retinal imaging system (RetCam; Clarity Medical Systems, Pleasanton, California) according to 'American academy of paediatrics recommendations'.[26] *Inclusion criteria:* Infants with type 1 ROP and A-ROP *affecting both eyes*. Type 1 ROP, as defined by the ETROP study,[4] is zone I ROP with plus disease, zone I stage 3 ROP without plus disease or zone II stage 2 or 3 ROP with plus disease. The hallmark of A-ROP (previously known as AP-ROP) is rapid development of pathological neovascularization and severe plus disease without progression being observed through the typical stages of ROP. It may occur in larger preterm infants and beyond the posterior retina.[27] *Exclusion criteria*: eyes with previous intravitreal injections (IVIs) or laser therapy, eyes with any pathology other than ROP and eyes with ROP stage 4 or 5. Each infant was examined by an experienced paediatric ophthalmologist and a vitreoretinal surgeon independently.

Intravitreal injection (IVI) was performed within 72 hours once treatment criteria were confirmed. It was done under topical anaesthesia in standard ophthalmic operating room. Either 0.625 mg/0.025 mL bevacizumab or 0.25 mg/0.025 mL ranibizumab was injected intravitreally with a 31-gauge needle, aiming directly towards the optic nerve in direction of visual axis, at 1.0 mm posterior to the corneoscleral limbus. The IOP was checked postinjection by indirect ophthalmoscopic examination of the optic disc perfusion and central retinal artery pulsation. Topical antibiotics were given for 7 days postoperatively. Infants were examined on the next day then weekly until regression of ROP, then every (2–4) weeks until a minimum of 55 weeks' PMA or when retinal vascularisation reached zone III without an active component such as haemorrhage or clinically significant tractional elements, whichever came earlier. Follow-up was continued monthly for at least 6 months following treatment.

Failure of initial regresssion was defined as persistence of plus disease and/or neovascularisation at 3–5 days' postinjection.[7] We wait for a maximum of 5 days to state 'Failure of initial regression'. However, *reactivation/recurrence* (disease regression followed by reappearance of preplus or plus disease, extraretinal new vessels or fibrovascular ridge)[27] can occur at any time throughout the follow-up period of 55-week' PMA.

Both failure of initial plus regression or ROP recurrence were managed by rescue therapy injection of the same initial anti-VEGF.

In case of failed retinal vascularisation to approach zone III until 55 weeks' PMA, an indirect infrared diode laser (*IRIDEX, Iris Medical SL laser with laser indirect ophthalmoscope Ophthalmic Laser, 810* nm, *USA*) was used to apply photocoagulation to the peripheral avascular retina through a +22/+28 diopter condensing lens under general anaesthesia in the operating room. Retinal vascularisation was judged by both clinical examination by BIO and Retcam fundus photography at baseline and throughout the follow-up visits.

Primary outcome measures

The number of eyes achieved regression of active ROP either by single or two injections or additional laser therapy at 55 weeks' PMA and total time till full retinal vascularisation (within two disc diameter (DD) from the ora serrata).

Secondary outcome measures

The number of eyes with recurrence of ROP requiring retreatment before 55 weeks' PMA, the number of eyes that needed late peripheral laser and the number of eyes progressing to stage 4 or 5 necessitating vitrectomy with/without lensectomy.

Statistical analysis

We coded the data using the SPSS V.28 (IBM, Armonk, New York) and summarised it using mean, SD, minimum and maximum for quantitative variables, frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Unpaired t-test was used to compare groups. $\chi 2$ test was performed to compare categorical data. Exact test was used instead when the expected frequency is less than 5. P value less than 0.05 meant a statistically significant difference.

RESULTS

A total of 36 eyes of 18 infants were divided into two groups: (1) IVR group: included 18 eyes of 18 infants and (2) IVB group included 18 contralateral eyes of the same 18 infants. No significant difference between the two groups was noticed as regard demographic characteristics, duration of stay in neonatal intensive care units (NICU) and systemic condition (table 1). Patients were recruited between September 2020 and September 2022. The mean follow-up after the first procedure was 16.53 months (ranged from 12.1 to 23.8 months). The mean initial treatment time was 37 weeks' PMA (ranged from 33 to 41 weeks).

We defined treatment success as complete regression of the retinopathy with single IVI at 55 weeks' PMA and vascularisation reached zone III without any additional treatment.

In IVB group, treatment success was achieved in 14/18 eyes (77.8%). Meanwhile, in the IVR group, 16/18 eyes (88.9%) achieved the target (p=0.658). Vascularisation approached zone III in 16/18 eyes (88.9%) in both IVB and IVR groups (p=1) (table 2). Mean PMA when maximum vascularisation occurred was 51.11 weeks (table 3).

In IVB group, initial regression of neovascularization and plus disease was achieved within 1 week in 11/18 eyes (61.1%). In IVR group, this was achieved in 15/18 eyes (83.3%) (p=0.137). Failure of initial plus regression, that necessitated reinjection, occurred in 3/18 eyes (16.7%)

Table 1 Demographic characteristics of patients in the study

	Mean	SD	Minimum	Maximum
Gestational age (weeks)	31.28	2.59	25.00	36.00
Birth weight (grams)	1572.22	338.34	1200.00	2500.00
Duration of stay in NICU (days)	29.22	14.40	9.00	55.00
		Number		**%**
Multiple births		9		50.0
Sex	Male	10		55.6
	Female	8		44.4
Systemic condition	Cardiac problems, hydrocephalus	1		5.6
	Renal problems, hydronephrosis imperforate anus	1		5.6
	Respiratory distress without other comorbidities	11		61.1
	Respiratory distress, sepsis, cardiac problems	1		5.6
	Respiratory distress, transfusions	2		11.1
	Sepsis	1		5.6
	Sepsis, transfusions	1		5.6

NICU, neonatal intensive care units.

Table 2 The main ocular data in both IVR and IVB groups

		Bevacizumab		Ranibizumab		
		Number	%	Number	%	P value
ROP class	A-ROP	8	44.4	8	44.4	1
	Z II S2 +	1	5.6	1	5.6	
	Z II S3 +	9	50.0	9	50.0	
Time to resolution of plus disease after IVI	<1 week	11	61.1	15	83.3	0.137
	1–2 weeks	4	22.2	3	16.7	1
	Failed initial plus regression	3	16.7	0	0.0	0.229
Late reactivation		1	5.6	1	5.6	1
Second treatment (failed initial regression or late reactivation)		4	22.2	1	5.6	0.338
Vascularisation approached zone III		16	88.9	16	88.9	1
Need for laser intervention		3	16.7	3	16.7	1
Examination at time of laser intervention	Bilateral stage 0 post Z II, no plus	1	33.3	1	33.3	1
	Bilateral stage 0 mid Z II, no plus	1	33.3	1	33.3	
	Bilateral stage 0 ant Z II, no plus	1	33.3	1	33.3	
		Recurrence		Non-recurrence		
		Number	%	Number	%	
Zone of ROP	I	0	0.0	2	5.9	1
	Mid II	1	50.0	14	41.2	1
	Post II	1	50.0	18	52.9	1

(+), plus disease; ant, anterior; A-ROP, aggressive ROP; IVB, intravitreal bevacizumab; IVI, intravitreal injection; IVR, intravitreal ranibizumab; mid, middle; post, posterior; ROP, retinopathy of prematurity; S, stage; Z, zone.

in IVB group. On the contrary, no eyes in IVR group showed failure of initial plus regression (p=0.229).

Rescue therapy injection was defined as the need for a second dose of same initial anti-VEGF after the first injection and before 55 weeks' PMA. Time interval between initial IVI and rescue therapy injection ranged from 1 to 3 weeks in cases of failure of initial regression and 12to 13 weeks in case of recurrence.

As regard IVB group, 4/18 eyes (22.2%) needed rescue therapy injection (three eyes for failed initial regression of acute ROP as shown in figure 1 and eye for late reactivation). Meanwhile, in the IVR group, 1/18 eyes (5.6%) developed late reactivation. No significant difference was found between the two groups (p=0.338). The mean PMA of reactivation of ROP in IVB group was 40.75 weeks. While in IVR group, it was 48 weeks (p=0.305). The mean initial treatment to reactivation interval was shorter in IVB group (4.25 weeks) than in IVR group (13 weeks) (p=0.233). Demographic and ocular data for infants/eyes that needed rescue therapy injection are shown in table 4.

Late laser therapy on the peripheral avascular retina was needed in 3/18 eyes (16.7%) in both IVB and IVR groups at mean of 55.67 weeks' PMA (range from 55 to 57 weeks).

After initial IVI, no infant had intraocular heamorrhage or endophthalmitis. One infant in IVR group developed subconjunctival haematoma that totally resolved after 2 weeks. Regressed neovascularisation caused localised preretinal haemorrhage in four eyes in each group.

Table 3 PMA (in weeks) of the infants in both IVR and IVB groups at time of interventions

	Bevacizumab				Ranibizumab				
	Mean	SD	Minimum	Maximum	Mean	SD	Minimum	Maximum	P value
PMA at initial injection	37.00	1.97	33.00	41.00	37.00	1.97	33.00	41.00	1.000
PMA at time of rescue injection	40.75	5.25	36.00	48.00	48.00	0	48.00	48.00	0.305
PMA when maximally vascularised	51.11	3.18	44.00	55.00	51.11	3.18	44.00	55.00	1.000
PMA at time of laser	55.67	1.32	55.00	57.00	55.67	1.32	55.00	57.00	1.000

IVB, intravitreal bevacizumab; IVI, intravitreal injection; IVR, intravitreal ranibizumab; PMA, postmenstrual age.

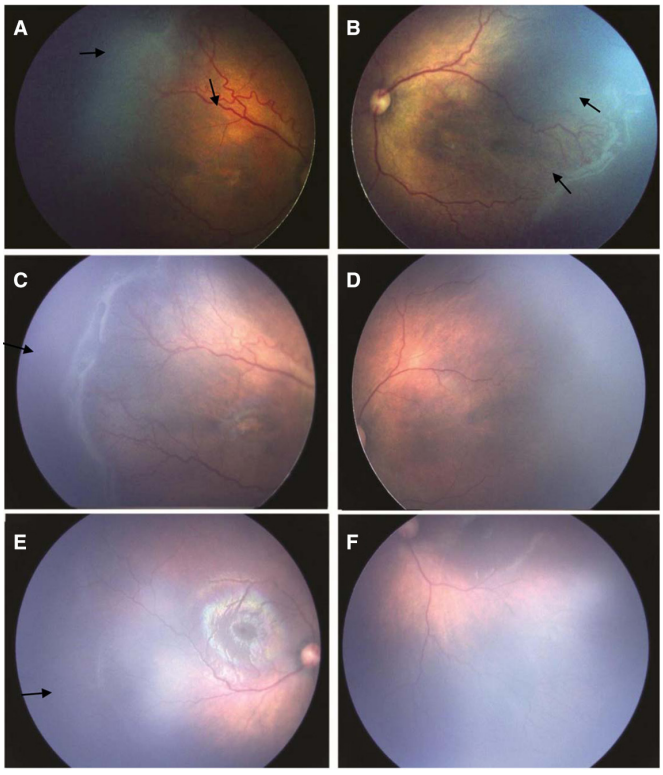

Figure 1 Retcam fundus photographs of a female baby (GA 28 weeks, BW 1200 grams). (A)Temporal fundus photograph of the right eye obtained at 36 weeks' PMA before IVB showed type 1 ROP with severe plus disease in zone I, stage 3. (B) Temporal fundus photograph of the left eye before IVR showed A-ROP with plus disease in zone I, stage 3, double ridge, retinal neovascularisation. (C) Temporal fundus photograph of the right eye, obtained one week after IVB, showed failed initial plus regression, even aggravated plus disease, extensive retinal neovascularisation, aggravated ridge and arteriovenous shunts. (D) Temporal fundus photograph of the left eye, obtained one week after IVR, showed better initial plus disease regression, regression of a ridge and retinal neovessels completely. (E) Temporal fundus photograph of the right eye 49 weeks' PMA, after reinjection of avastin showed faint line at the site of old ridge with vessels crossing it to the periphery, continued anterior retinal vascularisation. (F) Inferotemporal fundus photograph of the left eye at 49 weeks' PMA showed disappearance of active ROP, but still avascular retina at anterior zone II. GA, gestational age; BW, birth weight; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; PMA, postmenstrual age; ROP, retinopathy of prematurity.

These haemorrhages resorbed within 3 weeks without any sequalae. An infant in IVB group developed localised lens opacity in the right eye after the second IVB. It was away from the visual axis, did not affect fixation and did not progress till the end of follow-up period. Through the follow-up visits, no eyes showed progression to stage 4 or 5. In all infants, the macula was intact without macular fold, or foveal dragging.

As regard systemic adverse events, two infants showed delay in growth and motor milestones. One of them was diagnosed as hydrocephalus. He is still being followed

Table 4 Demographic and ocular data for eyes that needed rescue therapy injection in IVR, IVB groups

Patient number	Drug injected	GA (weeks)	BW (grams)	PMA at first IVI (weeks)	PMA at rescue injection (weeks)	Time interval between initial IVI and rescue injection (weeks)	ROP class at intial IVI	Full vascularisation achieved	Rescue therapy injection done	Indication of rescue IVI	Late peripheral laser done
1	Bevacizumab	28	1200	37	38	1	Z II S3 +	Yes	Yes	Failed initial plus regression	No
2	Bevacizumab	33	2500	33	45	12	A-ROP	No	Yes	S 0, mid Z II Recurrent plus	Yes
3	Bevacizumab	32	2000	39	42	3	Z II S3+	Yes	Yes	Failed initial plus regression	No
4	Bevacizumab	28	1300	36	37	1	A-ROP	No	Yes	Failed initial plus regression	Yes
5	Ranibizumab	33	2500	33	46	13	A-ROP	No	Yes	S 0, mid Z II recurrent plus	Yes

(+), plus disease; A-ROP, aggressive ROP; BW, birth weight; GA, gestational age; IVB, intravitreal bevacizumab; IVI, intravitreal injection; IVI, intravitreal ranibizumab; mid, middle; ROP, retinopathy of prematurity; S, stage; Z, zone.

in the neurosurgery clinic and the rehabilitation department, as he underwent repeated ventriculoperitoneal shunt surgeries. The other infant was diagnosed as spastic cerebral palsy of prematurity. We believe that these presentations are considered known complications of prematurity, therefore not associated with our intervention.

There was no correlation between the need for rescue therapy and BW, GA, PMA at initial treatment (p=0.249, p=0.658, p=0.627, respectively). 4/5 eyes, that needed rescue therapy, were treated with bevacizumab. But this did not reach statistical significance to correlate the type of drug injected to the need for rescue injection (p=0.338). A-ROP was found in 3/5 eyes, that needed rescue therapy, still no significant correlation between staging of ROP and the need for rescue injection (p=0.740). There was no statistically significant correlation between zone of ROP and the recurrence rate (p=1.0) as shown in table 2.

DISCUSSION

The third epidemic of ROP mostly involves middle income countries, like Egypt where wider NICU availability is increasingly supporting the survival of infants, but suboptimal care and improper oxygen administration and monitoring are resulting in higher rates of ROP among older and heavier infants.[25 28] This is especially true in rural settings where higher rates of more severe forms of the disease are reported.[29 30] Intravitreal anti-VEGF agents are currently used as a first-line therapy for the treatment of ROP, rather than an adjunctive or supplemental therapy. Despite their ocular advantages, prolonged follow-up is required because of incomplete retinal vascularisation.[31] In the current study, we prospectively reported the outcomes of 36 eyes of 18 infants with type 1 ROP (20 eyes) and A-ROP (16 eyes) who received IVB (18 eyes) and IVR (18 eyes). Every patient was his own control, which greatly minimised the effect of the systemic condition, gestational age (GA), birth weight (BW) and weight gain on the results.

We used a second IVI of the same initial anti-VEGF drug for ROP reactivation or failed regression of acute ROP. This helps to purely assess the effect of the two different anti-VEGF drugs without any overlap that may occur due to cross treatment[32] or combined treatment.[33] We believe that a second injection represents a better alternative to rescue laser photocoagulation[34] for ROP recurrence.

Gunay *et al*[35] collected the data of 134 infants (264 eyes) retrospectively. Type 1 ROP or AP-ROP cases received either IVB (55 infants), IVR (22 infants) or diode laser photocoagulation (57 infants). All eyes showed complete resolution of neovascularisation after single injection but recurrence of ROP occurred in 3 of 55 infants (5.5%) treated with IVB, 11 of 22 infants (50%) treated with IVR and 1 of 57 infants (1.7%) treated with laser photocoagulation. The mean time to recurrence after IVR was 8.8±1.5 weeks compared with 14±2.7 weeks with IVB. All infants with recurrence in IVB group required bilateral retreatment. While only 3% with recurrence in IVR group required bilateral retreatment, no difference in retreatment rates.

Unlike our study results in which 4/18 eyes (22.2%) needed reinjection in the IVB group. Meanwhile, 1/18 eyes (5.6%) developed late reactivation after IVR monotherapy. Failed initial plus regression in the IVB group in our study may be explained by deterioration of the intrinsic properties of the molecule or the potency of the drug as a result of the repackaging into plastic syringes[36] or duration of the storage.[37] Alliquoting of bevacizumab is challenging. It needs to be done with complete aseptic precautions by the compounding pharmacies. Even so, the risk of contamination, degradation of the molecule cannot be completely ruled out. In the absence of compounding pharmacies, the risk is higher.

Alyamac *et al*[38] recorded retrospectively a review of 45 infants (90 eyes) with type 1 ROP-affecting zone I or posterior zone II. IVB group included 44 eyes and IVR group included 46 eyes. Recurrence occurred in 14/23 infants (61%) treated with ranibizumab and 6/22 infants (10%) treated with bevacizumab. 2/6 infants (33%) with recurrence in IVB group required laser photocoagulation was needed as additional treatment for 2/6 infants (33%) with recurrence in IVB group at 43 weeks' PMA and 2/14 infants (14%) with recurrence in IVR group at 42.5 weeks' PMA.

Although the reactivation rate in IVR group was much higher than IVB group according to Alyamac *et al*, the rescue therapy was needed at a higher rate in IVB group in partial agreement with our results. Laser photocoagulation was done for 33% in IVB group, which is higher rate than the current study, mostly because it was done earlier (43 vs 55.67 weeks' PMA).

Alyamac *et al*[38] revealed that complete retinal vascularisation was detected in the 55.9 weeks' PMA in IVB group and in the 56.3 weeks' PMA in IVR group. In the current study, the time of full retinal vascularisation was 51.11 weeks' PMA in both groups. This 5-week difference is mostly due to the fact that total retinal vascularisation is defined in our study as perfusion within 2 DD from the ora serrata. However, according to Alyamac *et al*, it was defined as retinal vessels reaching the ora serrata.

Lin and Tsai[39] noted that 15/25 eyes (60%) treated with ranibizumab and 7/15 eyes (47%) treated with bevacizumab showed complete retinal vascularisation. The authors assumed that the IVR could achieve more complete retinal vascularisation than IVB because IVR has shorter intravitreal VEGF suppression.[39]

Kimyon and Mete[34] reported a higher recurrence rate (7.1%) than our study, although near similar GA and BW. Several studies with lower GA and BW revealed a higher reactivation rate (20.8%–83%).[32] Other studies noted high reactivation rate despite average GA or BW.[40] The lower reactivation rate in our study (5.6%) was mostly due to relatively mature infants (later GA and higher BW) than some other studies. Those infants of a younger GA and lower BW would have been more ill with a more serious ROP necessitating earlier intervention, so an

early PMA at initial therapy is a risk factor for ROP reactivation.[32]

Kabatas *et al*[41] analysed the reports of 54 infants (108 eyes) with type 1 ROP who received IVB (24 eyes), IVR (12 eyes) or diode photocoagulation (72 eyes) retrospectively. Recurrence occurred in 2/12 eyes (16%) treated with ranibizumab and 2/24 eyes (8.3%) treated with bevacizumab. According to Kabatas *et al*,[41] complete vascularisation in IVB group was detected at 73±10.1 weeks' PMA and 61.8±6.6 weeks' PMA in IVR group.

The number of cases in IVB group is two times that in IVR, so the recurrence rate appeared higher in the latter although two eyes in both groups experienced recurrence of ROP. This explained the different results when compared with ours.

Unlike the current study, mean PMA when maximally vascularised in both IVR and IVB groups was 51.11 weeks. That was a shorter time than Kabatas *et al*[41] mostly because 55.5% of our cases were of type 1 ROP-affecting zone II. While in Kabatas *et al*[41] type 1 ROP, affecting zone I represented 22.2% of eyes in ranibizumab and bevacizumab groups. It is logic that more time is needed to achieve full vascularisation for zone I compared with zone II ROP.

Feng *et al*[42] found that more aggressive forms of ROP at initial IVR injection were significantly correlated with ROP recurrence. Recurrence was detected in 67% eyes with APROP, 38% eyes with threshold ROP and 16% eyes with type 1 prethreshold ROP. Higher recurrence rates in APROP have been noted in premature infants treated with either IVR[43] or IVB.[35] This is in agreement with our results in which recurrence, that necessitated rescue therapy injection, was seen in 3/16 eyes (18.75%) with APROP, 2/20 eyes (10%) with type 1 ROP.

In the current study, the initial treatment to reactivation interval in IVR group was 13 weeks and 4.25 weeks in IVB group. Wong *et al*[44] noted the shortest reactivation interval (5.9 weeks) after IVR, this might be due to smaller GA (23.48 weeks) and lower BW (620 g) in their study population. Zhang *et al*[45] reported the longest reactivation interval of (12.62±7.93 weeks), and this may be attributed to using a higher dose of ranibizumab (0.3 mg in 0.03 mL).

In this study, it was obvious that IVR was associated with better initial regression of plus (less venous diameter, less arterial toursousity), regression of neovascularisation and straightening of closed vascular loops as early as few days after injection. Also, it promotes better and earlier growth of normal retinal vasculature towards the retinal periphery than IVB. This may be due to shorter intravitreal half-life of ranibizumab. It can theoretically decrease the supplementary laser spots needed and the subsequent destruction of peripheral visual fields, which might offer potential vision benefits.

Still our results were contradictory to previous studies that reported more and faster recurrence with IVR. Most of these studies have been conducted on European,[46] Asian[46 47] or American population.[48] To our knowledge, few studies were conducted among African (Egyptian) infants. So, there may be different levels of VEGF expression, ROP severity and treatment responses in different ethnic groups.[45 49]

The strength of our study appears as all cases were treated in a prospective manner, minimising the risk of missing data or incomplete examinations. Moreover, all cases were evaluated before and after injection, so that even minute changes are detected and analysed using coloured RetCam-saved photos and clinical examinations by the indirect ophthalmoscopy.

In many studies which compare the two medications in infants with ROP, one group of patients received IVR and a different group received IVB. In this study, the patient was his own control, receiving one drug in one eye and the other drug in the contralateral eye. This greatly minimises the effect of the systemic condition, birth weight, gestational age and weight gain on our results.

Our study had a relatively small sample size. The follow-up period was enough to document ocular efficacy of the two drugs, but relatively short to document systemic safety. The study targeted the assessment of ocular efficacy of the two anti-VEGF drugs, of which one holds a clear price advantage. Ranibizumab (Lucentis) is up to 50 times more expensive than bevacizumab (Avastin)[50] so health services in our developing countries could make significant savings by using bevacizumab (Avastin). Though fundus fluorescein angiography is a useful tool in observing retinal vascular morphology and development, it was not used in our study. Our study population characteristics of higher BW and older GA were different compared with the previous publications. So, the results cannot be generalised especially for highly developed countries.

CONCLUSION

The current study demonstrated a suggested algorithm that was effective regarding initial treatment and treatment of recurrence for type 1 and A-ROP in preterm infants in rural Egypt. Following this algorithm, only 5/36 eyes (13.89%) needed a second IVI of anti-VEGF drug. Also, only 6/36 eyes (16.7%) needed peripheral laser after 55 weeks' PMA. This greatly minimised the peripheral visual field defect and myopic shift and allow for improvement of the general condition in a physically compromised preterm newborn. Still, there is a dire need for larger randomised trials that analyse risk versus benefit regarding repeat anti-VEGF or minimal peripheral laser treatment especially for ROP reactivation-affecting anterior zone II.

Contributors GMT, AME: data collection, examination and manuscript writing; EAS: data analysis, manuscript revision and editing; SAD; DHH: data extraction, manuscript revision and supervision of the study process; DHH: study design, data analysis and manuscript editing; AME: data analysis, interpretation and manuscript revision. GMT: responsible for the overall cotent as guarantor. All authors contributed to the article and approved the submitted version.

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Disclaimer All methods were performed in adherence to the relevant guidelines and regulations.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by 1-IRB, Faculty of Medicine, Zagazig University ZU-IRB#6269/22-7-20202—Research Ethical Committee D-9-2020. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

ORCID iD

Ghada Mahmoud Tawfik http://orcid.org/0000-0003-2228-6452

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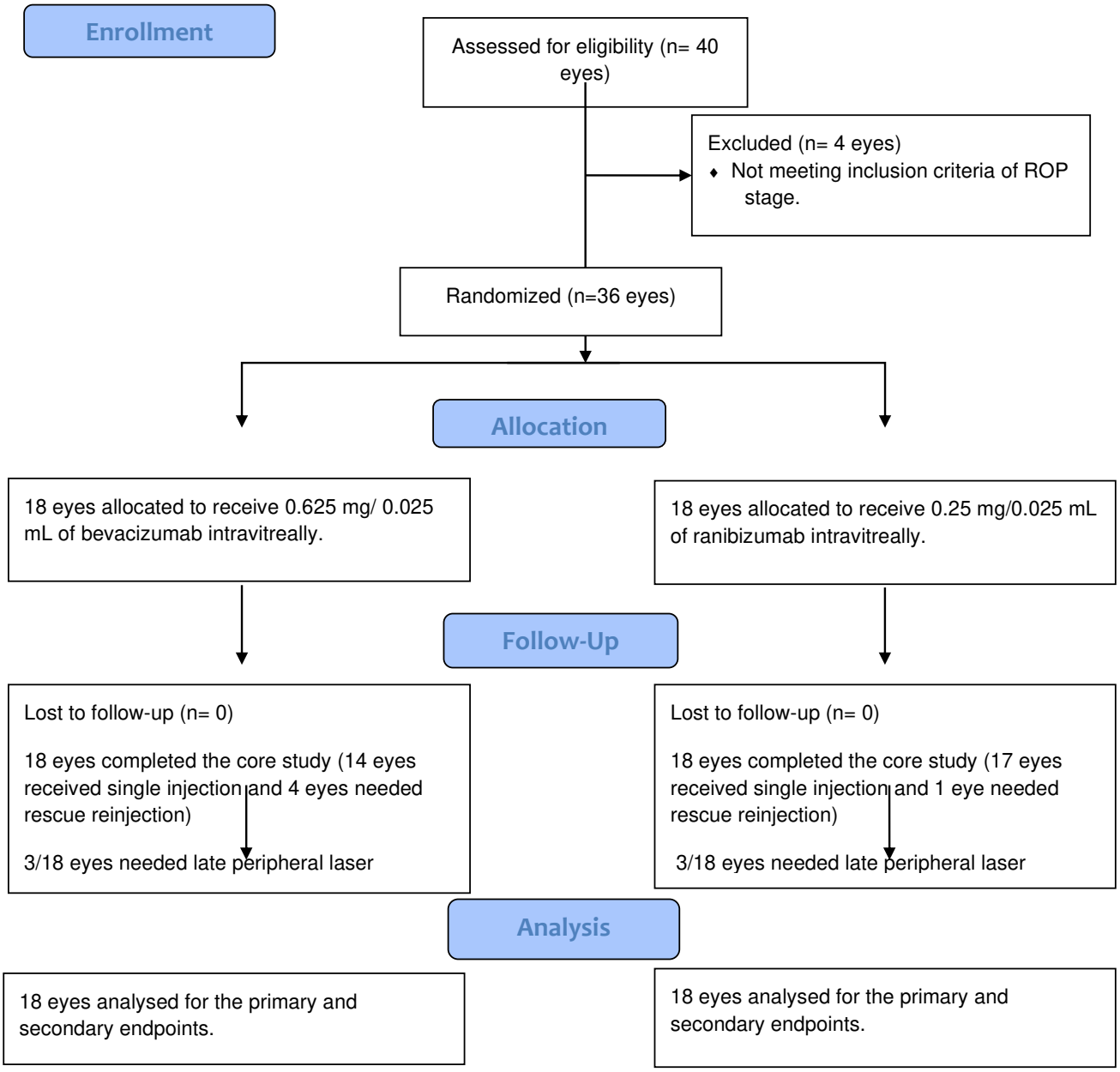
CONSORT Flow Diagram of Comparison Of Intravitreal Injection Of Ranibizumab Versus Bevacizumab For Treatment Of Type 1 And Aggressive Retinopathy Of Prematurity



CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	4
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	5
	4b	Settings and locations where the data were collected	5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	5, 7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	6
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	5
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	5

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	7
	13b	For each group, losses and exclusions after randomisation, together with reasons	-
Recruitment	14a	Dates defining the periods of recruitment and follow-up	2,7
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	13,14
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	7,8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	11
Other information			
Registration	23	Registration number and name of trial registry	5
Protocol	24	Where the full trial protocol can be accessed, if available	Supplement 3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Comparison Of Intravitreal Injection Of Ranibizumab Versus Bevacizumab For Treatment Of Type 1 And Aggressive Retinopathy Of Prematurity

Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of visual loss in children by means of macular dragging and retinal detachment. The first known description of the condition was in the 1940s. It occurs primarily in infants of low birth weight (≤1250 g) or gestational age of 30 weeks or less.[1] The disease process is associated with high levels of vascular endothelial growth factor (VEGF) secreted by the avascular retina which in turn leads to neovascularization, retinal detachment, and permanent visual loss.[2]

A committee for ROP classification was formed in1984, which proposed an international classification of ROP (ICROP) by dividing the retina into three zones, extending from posterior to anterior retina and describing the extent of ROP in clock-hours of involvement (International Committee for the Classification of Retinopathy of Prematurity 1984). [3]

However, with the advances in retinal imaging techniques, a revised ICROP classification was put forth which described the zones better (International Committee for the Classification of Retinopathy of Prematurity revisited 2005). For the purposes of localizing the disease, the retina is divided into 3 zones. Zone I, the posterior pole, is the retina within a circle centered on the optic disc with a radius equal to twice the disc-macula distance; zone II is concentric with zone I, whereas its radius extends to the distance from the disc to the nasal ora serrata; and zone III comprises the remaining crescent of temporal retina. Staging of ROP is based on the appearance of the clinically visible demarcation between the vascularized and avascular retina. This demarcation is a flat line in stage 1, a raised ridge in stage 2, and extraretinal neovascular proliferation overlying the ridge in stage 3. [4]

In more severe ROP, plus disease occurs which means that the blood vessels of the retina have become engorged and tortuous, indicating worsening of the disease. This is thought to be due to shunting through the areas of neovascularization. Presence of stage 3 ROP with plus disease in either 5 contiguous or 8 total clocks hours within zones I or II indicates ‘‘threshold disease’’—disease with a 50% chance of progression to retinal detachment and very poor visual prognosis (International Committee for the Classification of Retinopathy of Prematurity 1984). Retinal detachment is divided into subtotal (stage 4 ROP) or total detachment (stage 5 ROP).[5]

The Early Treatment for Retinopathy of Prematurity (ETROP) study defined type 1 ROP as cases with zone I ROP with plus disease, zone I stage III ROP, and zone II stage 2-3 with plus disease. The earlier treatment, within 72 hours, of those carefully selected cases results in an overall improved visual outcome. [6]

The Cryo-therapy for Retinopathy of Prematurity randomized trial demonstrated the efficacy of cryotherapy (vs. observation) as a treatment for threshold ROP, and it showed a marked reduction in the rates of unfavorable retinal structural outcomes and blindness (Cryotherapy for Retinopathy of Prematurity Cooperative Group 1988).[7]

Laser photocoagulation of the peripheral retina using indirect delivery system has proved to be an effective method of treatment according to the Early Treatment for Retinopathy of Prematurity (ETROP) study [8], however, in the same trial 9.1% of the patients had unfavorable structural outcomes. In addition,

a large area of peripheral retina is destroyed in the ablative process and normal vascularization generally cannot be achieved.[9,10]

A previous study reported significantly increased vitreal vascular endothelial growth factor (VEGF) levels in ROP patients. In the same study, an excess production of VEGF was shown to play an important role in ROP pathogenesis.[11] Bevacizumab treatment was found to be more effective than laser photocoagulation for ROP treatment, particularly in patients with zone 1 and 2 posterior disease (BEAT-ROP). [12] Moreover, other anti-VEGF therapies, macugen and ranibizumab, demonstrated efficacy in the treatment of ROP when used alone or in combination with laser photocoagulation. [13-15]

Bevacizumab is a larger, full-length immunoglobulin G (IgG) molecule with slower retinal clearance and therefore prolonged diffusion into the systemic circulation.[16] In contrast, the systemic half-life of a Fab molecule, such as ranibizumab, is a few hours, whereas that of a full-length IgG is up to 3 weeks in the general circulation. [17] Because of these structural differences, a much longer systemic half-life has been noted with bevacizumab compared with that of ranibizumab after intravitreal injection (20 days vs. 2 hours for bevacizumab and ranibizumab, respectively).[18,19]

The inhibition of VEGF raises concerns that these important physiologic effects associated with VEGF will be inhibited, leading to abnormal organogenesis or neurodevelopment. Based on our current data, the selection of an anti-VEGF with less systemic VEGF interference or reducing the dose of anti-VEGF agent or using an antiVEGF agent only once in ROP patients seems to be a safer choice because of the concerns mentioned above. [20-23]

In this prospective study, we compare the efficacy and reliability of bevacizumab and ranibizumab treatments for type 1 ROP, namely pattern of disease regression, recurrence of ROP, necessity of subsequent ablative procedures.

Rationale

Retinopathy of prematurity continues to be a major cause of childhood blindness worldwide. ROP has become a growing problem because of the increasing number of surviving preterm infants and the awareness of screening issues.

Although cryotherapy and laser photocoagulation can cure several cases of ROP, being relatively destructive to the peripheral retina, associated with high myopia, retinal dragging, anterior segment ischaemia, and vitreous heamorrhage, other lines of treatment have been tried.

Recently there is a shift of treatment to VEGF inhibitors which can regress ROP without destroying the peripheral retina. Yet, the best drug has not been identified.

Research question

Is the intravitreal ranibizumab monotherapy as effective in treatment of type 1 ROP as intravitreal bevacizumab monotherapy as regard disease regression, recurrence after single intavitreal injection and timing of total retinal vascularization?

Hypothesis

Intravitreal bevacizumab injection is better than intravitreal ranibizumab for treatment of type 1 ROP. Bevacizumab is a larger, full-length immunoglobulin G (IgG) molecule with slower retinal clearance and therefore prolonged diffusion into the systemic circulation, up to 3 weeks. In contrast, the systemic half-life of a Fab molecule, such as ranibizumab, is a few hours. Intavitreal ranibizumab is associated with higher chance of reactivations, need for additional laser therapy or more doses of IVR.

Aim of the Work

To evaluate the efficacy of intravitreal ranibizumab monotherapy compared to intravitreal bevacizumab monotherapy for treatment of type 1 ROP.

Objectives

- To report and compare the percentage of eyes achieving regression in each group (defined as: Regression of the ridge and venous dilation and arteriolar tortuosity of the posterior retinal vessels (plus disease)) after single intravitreal injection at one week post-injection and 55 weeks' postmenstrual age.
- To report and compare the percentage of eyes with relapse which necessitates additional treatment.
- To report and compare the percentage of eyes achieving regression at 55 weeks' postmenstrual age either by multiple intravitreal injections or additional laser therapy in each group.
- To detect, record and analyze any complications either related to the disease (progression into stage 4 or 5) or to the inravitreal injection procedure during the follow-up period of 6 months after initial injection.

Subjects and methods

Before initiating this study, all parents or guardians of the recruited infants will be provided with informed written consent. The investigator will explain to the parents the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks, benefits and the follow-up schedule.

The participants' parents will be informed that participation is voluntary, that he or she may withdraw from the study at any time and without giving reasons. The withdrawal will not affect the subsequent medical or conservative treatment or relationship with the treating surgeon. The participants' parents will be informed about the severity of disease, treatment options, and complications.

Technical Design

Setting: Abulreesh Children's Hospital Kasr Alainy, Cairo University and Zagazig University Hospitals.

Design: A prospective randomized clinical trial.

Subjects: Patients screened at neonatal intensive care unit (NICU) of Cairo University and Zagazig University Hospitals meeting the inclusion criteria of the study.

Sample size:

The sample size is calculated to be 36 eyes of 18 infants using open Epi confidence total 95%, power of the study 80% according to the following: the mean ±SD of axial length of patients with stage 3 ROP using bevacizumab versus ranibizumab (20.3±1.16 versus 19.4±0.36 mm).[24]

Inclusion Criteria:

Infants with a birth weight of ≤ 1500 g or geststional age of ≤ 30 weeks and selected infants with birth weight between 1500 and 2000 g or gestational age of more than 30 weeks with an unstable clinical course, including those requiring cardiorespiratory support. Patients with bilateral disease who will receive bilateral injections, are only included. Aggressive ROP (A-ROP) and Type 1 ROP according to ETROP study [6] which is defined as:

- Zone I ROP with plus disease.
- Zone I, stage 3 ROP without plus disease.
- Zone II, stage 2 or 3 ROP with plus disease.

Exclusion Criteria:

- Eyes with previous intravitreal injections.
- Eyes with previous laser therapy.
- Eyes with any other pathology, other than ROP.
- Eyes with ROP stage 4 or 5.
- Infants who will not be able to comply to the follow-up schedule.

Operational design:

Initial clinical evaluation:

History:

Data will be collected for each baby regarding date of birth, sex, single or multiple pregnancy, gestational age at birth, birth weight, age at which ROP is detected. Other data include oxygen and surfactant given or not, presence of common problems of prematurity, presence of intrauterine growth retardation, and duration of stay of infant in the Intensive Care Unit of the Neonatology Department.

Examination:

The stage of ROP, the affected zone, and presence or absence of plus disease are recorded by binocular indirect ophthalmoscope and digital fundus images by RetCam.

Interventional procedure:

Dilating drops, 0.5% tropicamide and 2.5% phenylephrine, are instilled twice, 10 minutes apart, at least 30 minutes before the treatment.

Intravitreal injection will be performed under general (light inhalational anaesthesia) or topical anesthesia (Benoxinate hydrochloride 0.4%) in standard ophthalmic operating room under strict sterile

conditions. Povidone iodine 10% swab will be applied on the eyelids and eyelashes and sterile speculum will be inserted. Then, 5% povidone-iodine disinfectant for 3 minutes before intavitreal injection.

A dose of 0.25 mg/0.025 mL ranibizumab (Lucentis; Novartis, Basel, Switzerland) is injected in the left eye of the infant and 0.625 mg/0.025 mL bevacizumab is injected into the vitreous cavity of the right eye. The two injections are done sequentially on two consecutive days starting with the eye of more advanced disease.

A 31-gauge needle is used, aiming the needle directly toward the optic nerve in direction of visual axis 1.0 mm posterior to the superior/ inferior temporal limbus. Removal of the needle with simultaneous compression using a sterile cotton tip. All injections are done by the same surgeon.

Fundus examination will be conducted after injection with an indirect ophthalmoscope and a 28-D lens. The central retinal artery and the lens will be evaluated in addition to whether a retinal tear is present.

Postoperative moxifloxacin 0.4% drops will be prescribed 4 times daily for three days. Patients will be seen 24 hours after first injection, to monitor for any signs of infection. Risks of injection include endophthalmitis, lens injury, heamorrhage, retinal detachment and elevation of IOP.

Follow-up:

The follow-up period: at clinics is for six months after initial intravitreal injection.

Follow-up regimen:

All infants will be followed up weekly until the regression of ROP, after that every 2 weeks until full vascularization (vascularization reaching to the temporal ora serrata without an active component such as heamorrhage or exudation or clinically significant tractional elements) or additional treatment is given. Follow up is done by binocular indirect ophthalmoscope and digital coloured fundus images by RetCam (Clarity Medical Systems, Pleasanton, CA).

Primary and secondary outcome measures:

The primary outcome measurements include:

- The number of eyes that achieved regression either by single injection or multiple injections or additional laser therapy at 55 weeks' postmenstrual age.
- Total retinal vascularization time.

The secondary outcome measurements include:

- The number of eyes with recurrence of ROP (recurrent plus disease, recurrent neovascularization, or reformation of ridge despite treatment) in one or both eyes requiring retreatment before a postmenstrual age of 55 weeks.
- The number and kind of adverse events, the number of patients progressing to stage 4 or 5.

- The number of reinjections or laser spots and the number of eyes that need vitrectomy with/without lensectomy.

Results

Data were coded using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, minimum and maximum for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired t test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. *P*-values less than 0.05 were considered as statistically significant**.**

Discussion

Discussion will be done on results compared to relate relevant literatures and scientific researches to explain the reasons for getting such results.

Conclusion and Recommendation

They will be derived from the findings of the study.

References

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