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ARTICLE

Clinical outcome following reinjection of Ranibizumab for reactivation of retinopathy of prematurity

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BACKGROUND: To assess reactivation after initial intravitreal injection of ranibizumab (IVR) for type 1 retinopathy of prematurity (ROP) or worse and the outcome following reinjection of ranibizumab for this reactivation.

METHODS: This retrospective study was performed on infants screened for ROP between March 2013 and February 2020 in Mansoura University Children Hospital, Mansoura, Egypt. Infants treated with ranibizumab 0.25 mg/0.025 mL were identified for review of their clinical outcomes. Data of infants with reactivation and IVR re-injection were analysed.

RESULTS: A total of 2318 infants were screened for ROP, 115 (5%) infants (216 eyes) with a mean gestational age of 30 ± 2.5 weeks and mean birth weight of 1290 ± 355.2 g received IVR at mean postmenstrual age (PMA) of 38 ± 3.1 weeks. All treated eyes demonstrated initial regression of ROP. However, ROP reactivation occurred in 5 (2.3%) eyes of 3 patients, at an average of 9.6 ± 2.9 weeks after treatment. None of these eyes had retinal detachment. A second dose IVR was administered and all five eyes showed regression with complete retinal vascularisation, at a mean PMA of 60 ± 5.1 weeks.

CONCLUSIONS: IVR is beneficial as an initial and subsequent treatment for type 1 ROP or APROP. A long-term follow-up until complete retinal vascularisation is recommended to avoid disease reactivation.

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INTRODUCTION

Retinopathy of prematurity (ROP) is a neovascular disorder of the developing retinal blood vessels of preterm infants. It is considered as a leading cause of childhood blindness all over the world, especially in middle-income countries [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]. Over the past several decades, retinal ablation by cryotherapy or laser has been the gold standard in treating severe ROP [3, 4]. However, they exhibit complications such as peripheral visual field defect and myopic shift. Moreover, there is an approximately 10% risk of retinal detachment or other unfavourable structural outcome despite laser treatment in Early Treatment ROP (ETROP) randomised trial [5]. This encouraged researchers to use (anti-VEGF) for treatment of ROP, enabling continuous vascularisation of the retina without destroying it and potentially minimising the risk of retinal detachment.

The most commonly used VEGF inhibitors are bevacizumab and ranibizumab. However, the safety and efficacy of both remain uncertain [6, 7]. Furthermore, some studies describing pharmacokinetics of anti-VEGF assumed that their VEGF suppression effect may be transient [8, 9]. This might explain reactivation of ROP after a single treatment with an anti-VEGF agent, either with bevacizumab or ranibizumab [10, 11]. Therefore, timely detection and management of reactivation has become a major concern in anti-VEGF therapy for ROP. This study was carried out to assess the reactivation after initial intravitreal injection of ranibizumab (IVR, Lucentis®) for type 1 ROP or worse and the outcome following reinjection of ranibizumab for this reactivation.

METHODS

A retrospective review of medical records of preterm infants screened for ROP in Mansoura University children hospital, Mansoura, Egypt during the period from March 2013 to February 2020 was performed. This included infants admitted to neonatal intensive care unit or referred from other hospitals participating in the Egyptian Neonatal Network for ROP screening. We included records of infants with type 1 ROP or aggressive posterior ROP (APROP), who received IVR as initial monotherapy according to ETROP study [12]. In our hospital, the policy for ROP treatment is to use ranibizumab, not laser as a primary line of treatment. Records with incomplete data or patients with a follow-up of less than 6 months after initial IVR injection were excluded. The study followed the Declaration of Helsinki. It was approved by Mansoura faculty of medicine Institutional Review Board (code No R.20.08.985) and registered on www.clinicaltrials.gov (NCT04539106).

Data extracted included gestational age (GA), birth weight (BW), type of pregnancy (single or multiple), laterality of eye involvement, stage and zone of ROP and post menstrual age (PMA) at initial injection and at

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complete regression. Fundus examination of preterm babies was performed using binocular indirect ophthalmoscopy under topical anaesthesia, and fundus photographs were obtained with a RetCam III digital fundus camera. ROP was diagnosed and classified according to the International Classification of ROP [13]. Diagnosis was confirmed independently by at least two paediatric retina specialists.

Intravitreal ranibizumab injection was performed as follows; topical anaesthetic drop application, lid speculum insertion, standard aseptic eye preparation with 5% betadine and intravitreal injection of 0.25 mg/0.025 ml ranibizumab with a 30-gauge needle 1.5 mm from limbus [14]. In cases with bilateral ROP, both eyes were injected in the same session. Infants were examined on the next day, the next week after injection, then follow up was scheduled according to "American academy of pediatrics recommendation in 2013" until full retinal vascularisation was observed [15]. An informed consent was obtained from the parents of all infants before IVR injection. All cases were injected by the same surgeon (RB) under similar circumstances

Fundus photos taken by Retcam III, were reviewed before and after treatment. Data of infants with reactivation of ROP and IVR re-injection were analysed. Reactivation of ROP was defined as any of the following: recurrent plus disease, recurrent neovascularization at initial or new advancing ridge despite treatment [11].

A systematic literature search was performed involving studies that used IVR as an initial monotherapy for ROP treatment and different modalities for treatment of reactivation, in comparison with the current study.

Statistical analysis

Data was analysed with SPSS (Statistical Package for Social Science) V 21.0. Qualitative data was described using number and percentage. Continuous variables were presented as mean ± SD (standard deviation) for parametric data.

RESULTS

From March 2013 to February 2020, 2318 preterm infants were screened for ROP, out of which 132 (5.7%) infants had treatment requiring ROP according to ETROP classification. Twelve infants were excluded due to incomplete data as well as 5 infants with follow-up examinations not extending to 6 months. One hundred fifteen (5%) infants were included in the study, of which 101 (87.8%) infants had bilateral disease and 14 (12.2%) had unilateral disease. Demographic data and baseline characteristics of treated infants are demonstrated in (Table 1).

A total of 216 eyes had received IVR as an initial monotherapy at (PMA) of 38 ± 3.1 weeks; out of which 211 (97.7%) eyes showed disease regression with complete retinal vascularisation, at a mean PMA of 53.6 ± 5.1 weeks, while 5 eyes (2.3%) of 3 infants showed reactivation at a mean PMA of 46.7 ± 5.1 weeks, with treatment to reactivation interval of 9.6 ± 2.9 weeks. None of these five eyes had vitreoretinal traction or retinal detachment as a result of reactivation. All eyes with ROP reactivation had APROP in zone I at first diagnosis and received initial IVR at mean PMA of 36.7 ± 2.08 weeks. An adjunctive treatment with second dose IVR was administrated, and all five eyes showed regression and were followed up till complete retinal vascularisation, which occurred at a mean PMA of 60 ± 5.1 weeks. Profile of eyes with ROP reactivation is illustrated in (Table 2). A typical series of fundus photographs for right eye of infant (2) is shown in Fig. 1. A comparison among different studies showing reactivation after initial monotherapy of IVR and how it was managed is summarised in (Table 3).

Table 1. Baseline characteristics of all infants receiving initial IVR.

Infants receiving initial IVR ($n = 115$)	
Sex (M/F)	(70/45)
GA (mean ± SD)	30 ± 2.5 w
BW (mean ± SD)	1290 ± 355.2 g
Multiple birth [no (%)]	
Single	55 (47.8%)
Twin	47 (40.9%)
Triplet	13 (11.3%)

IVR intravitreal ranibizumab, *M/F* Male/Female, *GA* gestational age, *w* weeks, *BW* birth weight.

DISCUSSION

Reactivation of ROP is a serious problem that may result in vitreoretinal traction or retinal detachment. It has been reported following initial treatment with either laser photocoagulation or intravitreal anti-VEGF treatment with either bevacizumab or ranibizumab [10, 11, 16, 17].

Reactivation of ROP following IVR has been related to short systemic half-life and rapid clearing of ranibizumab from the vitreous [18]. However, reactivation rate reported in literature is variable. Some authors reported a relatively low reactivation rate [7], while others found a relatively high reactivation rate of ROP [19]. We reported the lowest reactivation rate (2.3%) after IVR compared to previous studies as shown in (Table 3). This could be due to a relatively mature infants (later GA and higher BW) than some other studies. In Egypt, we still have no guidelines regarding which preterm babies have to be screened. Being a middle-income country with different socioeconomic standards and limited health facilities, we screen all preterm infants (less than 37 weeks of gestation) in order not to miss ROP cases until establishment of an Egyptian screening protocol.

In 2018, Kimyon and Mete in Turkey reported similar GA and BW to ours, albeit a higher recurrence rate (7.1%) [20]. Similarly, several

Table 2. Profile of Infants/eyes with ROP reactivation.

Infant/eye	**Infant 1 OD**	**Infant 1 OS**	**Infant 2 OD**	**Infant 3 OD**	**Infant 3 OS**
GA (w)	31		31	28	
BW (g)	1400		1000	985	
Type of pregnancy	Single		Twin	Twin	
ROP grade	APROP, Z1	APROP, Z1	APROP, Z1	APROP, Z1	APROP, Z1
PMA at first injection	36		39	35	
PMA at reactivation	48		51	41	
Treatment- reactivation Interval (w)	12	12	12	6	6
ROP grade at reactivation	S2+, ant Z2	S3+, ant Z2	S3 Z1	S2+ post Z2, A-V shunt	S3+, post Z2, A-V shunt
Age of complete retinal vascularisation(w)	55		67	58	

GA gestational age, *w* weeks, *BW* birth weight, *APROP* aggressive posterior ROP, *PMA* postmenstrual age, *S* stage, *Z* zone, *(+)* plus disease, *ant* anterior, *post* posterior.

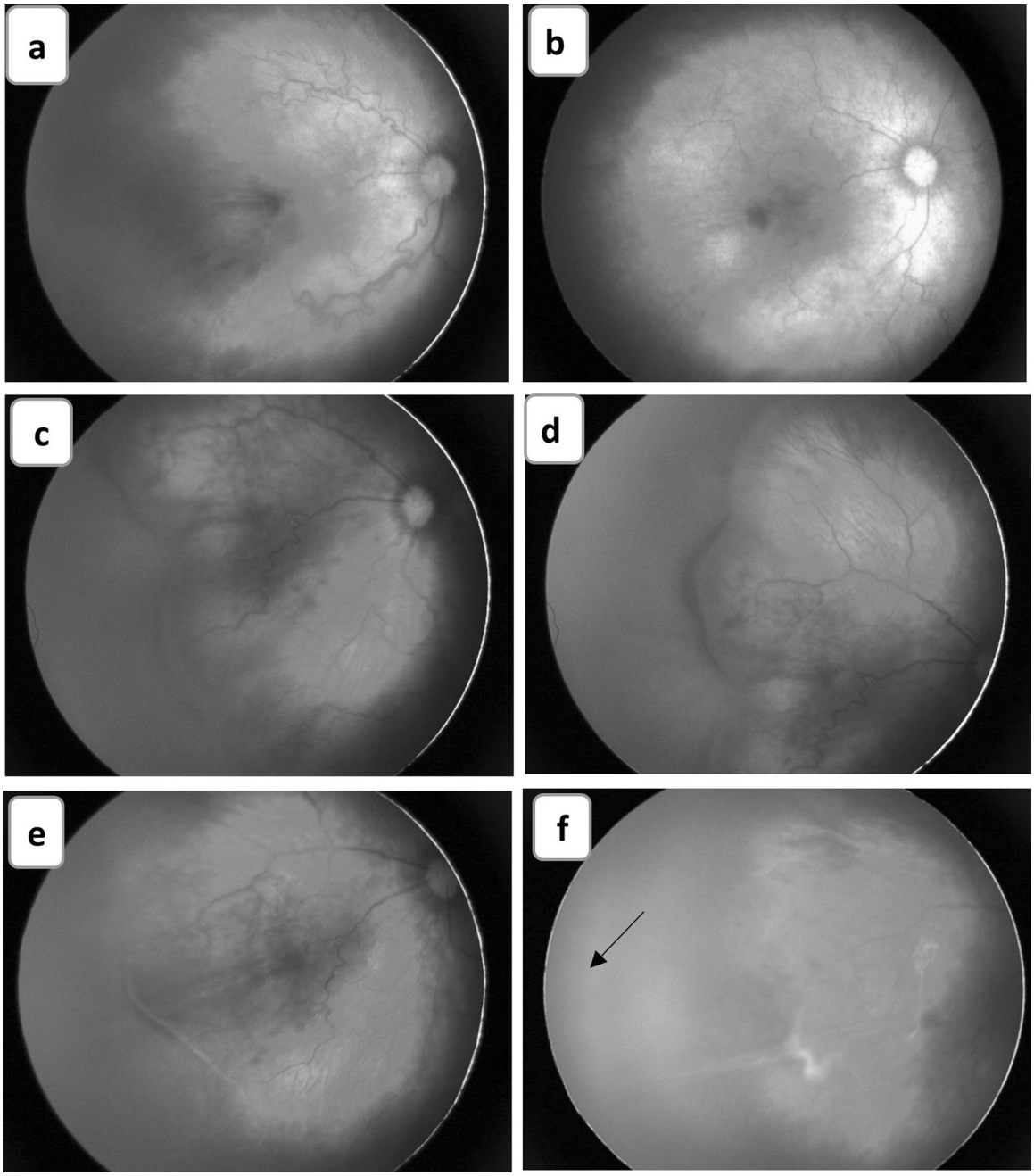

Fig. 1 Fundus photographs of the right eye of infant (2) who received IVR as an initial and subsequent monotherapy for ROP. a First visit before any intervention: there is APROP in Zone 1. **b** First week following initial IVR representing improvement of plus disease. **c**, **d** Twelve weeks after initial IVR: posterior and temporal fundus representing appearance of neovascularization and haemorrhage upon ridge (S3 in posterior Zone2). **e** One week after second IVR: regression of ridge and retinal neovascularization. **f** The temporal fundus photograph obtained at last visit shows complete regression with total retinal vascularisation (black arrow pointed to ora serrata).

studies with lower GA and BW reported a higher reactivation rate (20.8–83%) [10, 21–23]. However, other studies reported high reactivation rate despite average GA or BW [19, 24–26]. Another explanation of the lower reactivation rate in our study may be the older PMA (36.7 ± 2.08 weeks) at initial therapy, compared to that reported in previous studies [21, 23, 27]. An early PMA at initial therapy is a risk factor for ROP reactivation, as those infants would have been more ill with a more serious ROP necessitating earlier intervention [21].

In this study, all eyes that had reactivation of ROP were diagnosed initially as APROP in zone I. This is consistent with the results of previous studies [11, 25, 28–30]. Feng et al. [28] found that zone I ROP had higher reactivation rate when compared to zone II. Moreover, the extent of retinal neovascularization has been identified by Lyu et al. [25] as an important predictor for prognosis of ROP.

Additionally, we noted that reactivation occurred in the form of stage 2 or 3 with plus disease. Similar observation was made by Ling et al. [21] who found that reactivation after initial anti-VEGF monotherapy mostly involved the return of plus disease and reappearance of neovascularization at the original site of the ridge and/or the advancing edge of retinal vascularisation.

In this study, the treatment to reactivation interval was 9.6 ± 2.9 weeks. A longer mean time of relapse (16 weeks) was reported

Table 3. Summary of different studies that used IVR as initial monotherapy for ROP treatment.

Authors	Study design	Total no of screened infants	Total no of eyes treated initially with IVR	GA of treated infants (w) (mean ± SD)	BW of treated infants (g) (mean ± SD)	Criteria for intervention
Current study	Retrospective	2318	216	30 ± 2.5	1290 ± 355.2	Type 1 ROP or APROP
Ling et al. [21]	Retrospective	176	48	26.2 ± 1.6	827.9 ± 187.3	Type 1 ROP
Stahl et al. (RAINBOW Study) [17]	RCT	225	298 eyes; 0.2 mg group: 73 infants (bilateral injection), 0.1 mg group: 76 infants (bilateral injection)	0.2 mg group: 25 0.1 mg group: 26	0.2 mg group: 791 ± 244 0.1 mg group: 886 ± 299	Type 1 ROP or AP-ROP except for Z2, S2+
Yang et al. [31]	N/A (Oct. 2014–Jan. 2017)	46	86	28.18 ± 1.67	1070.57 ± 226.85	Z2, S3+
Kimyon and Mete [20]	Retrospective	37	28	30.1 ± 2.4	1389 ± 406.3	Type 1 ROP in Z1
Arámbulo et al. [24]	Retrospective	43	85	29.7 ± 2.0	1276 ± 302	APROP orS3+ in Z1 or posterior Z 2.
Hu et al. [32]	Retrospective	42	80	29.4 ± 2.2	1204.09 ± 321.36	Z2, S3+
Lyu et al. [25]	Retrospective	59	50	29.4 ± 1.7	1369 ± 338	Type 1 ROP or APROP
Huang et al. [19]	Retrospective	84	168, Symmetric gp:150, Asymmetric gp: 18	Symmetric gp: 29.4 ± 2.1, Asymmetric gp: 29.6 ± 1.8	Symmetric gp: 1412.2 ± 335.6, Asymmetric gp: 1222.2 ± 216.6 g	Type 1 ROP or APROP
Zhang et al. [26]	Prospective	50	50	28.96 ± 1.59	1220 ± 320	Z2, S2 or S3 ROP with plus
Yi et al. [27]	Retrospective	33	66	29.8 ± 1.6	1291 ± 211	Type 1 ROP or APROP
Chan et al. [22]	Retrospective	138	8	24	576.7	Selected cases of Type 1 ROP, e.g. APROP, poor pupil dilatation
Wong et al. [10]	Retrospective	142	6	23.48	620	S2 or S3 with plus in Z1 or posterior Z2
Erol et al. [23]	Retrospective	20	15	26.2 ± 2.7	853 ± 120	Type 1 ROP

Authors	Dose of IVR	PMA at initial IVR (w)	Recurrence rate no. (%)	Treatment—reactivation interval (w)	PMA at reactivation (w)	Subsequent treatment	Response to retreatment
Current study	0.25 mg/ 0.025 mL	36.7 ± 2.08	5 (2.3%)	9.6 ± 2.9	46.7 ± 5.1	IVR	Regressed complete retinal vascularisation
Ling et al. [21]	0.25 mg/ 0.025 mL	34.0 ± 1.0	10 (20.8%)	8.3 ± 1.6	42.3 ± 2.0	(IVB/IVR) 4 eyes, laser 5 eyes, vitrectomy 1 eye	Regressed attached retina after vitrectomy
Stahl et al. (RAINBOW Study) [17]	0.2 mg: 146 eyes 0.1 mg: 152 eyes	0.2 mg group: 36.7 (30.3–51.9) 0.1 mg group: 36.9 (31.9–54.9)	0.2 mg group: 49 (31%) 0.1 mg group: 55 (31%)	8	45	0.2 mg group: IVR: 11 infants Laser: 11 infants 0.1 mg group: IVR: 12 infants Laser: 10 infants	45/68 (66%) infants for laser therapy 56/70 (80%) infants for ranibizumab 0.2 mg 57/76 (75%) infants for ranibizumab 0.1 mg
Yang et al. [31]	0.25 mg/ 0.025 mL	38.32 ± 2.99	15 (17.4%)	5.96 ± 3.22	N/A	IVR: 6 eyes Laser: 7 eyes Combined: 2 eyes	Regresses attached retinas no macular dragging

Table 3. continued

Authors	Dose of IVR	PMA at initial IVR (w)	Recurrence rate no. (%)	Treatment—reactivation interval (w)	PMA at reactivation (w)	Subsequent treatment	Response to retreatment
Kimyon and Mete [20]	0.25 mg/ 0.025 mL	N/A	2 (7.1%)	N/A	N/A	Laser	N/A
Arámbulo et al. [24]	0.25 mg/ 0.025 mL	37.2 ± 2.2	43 (53.6%)	7.1 ± 3	43 ± 3.2	Laser	6 patients had persistent peripheral avascular retina in Z2 for >6 months
Hu et al. [32]	0.25 mg/ 0.025 mL	N/A	18 (22.5%)	8.5 ± 5.7	45.7 ± 6.1	IVR (11, 61.1%), Laser (4, 22.2%), combined (1, 5.6%), spontaneous regression (2, 1.1%)	Regressed
Lyu et al. [25]	0.25 mg / 0.025 ml	35.5 ± 1.3	32 (64%)	7.9 ± 2.7	43.1 ± 3.3	Laser	-5 eyes blood vessels not reaching ora seratta. -vitrectomy: 1 eye
Huang et al. [19]	0.25 mg/ 0.025 ml	Symmetric gp: 35.9 ± 2.3 asymmetric gp: 37.0 ± 2.4	Symmetric gp: 60 (40%) and 4 (2.7%) progressed asymmetric gp: 8 (44.4%)	8.11 ± 2.4	43.4 ± 3.4	Symmetric gp: laser in 60 eyes Surgery in 4 eyes / asymmetric gp: laser:1 eye surgery: 1 eye	Symmetric gp: all eyes had flat retinas asymmetric gp: attached retina in 16 eyes (88.9%)
Zhang et al. [26]	0.3 mg/ 0.03 mL	N/A	26 (52%)	12.62 ± 7.93	N/A	Laser	Regressed
Yi et al. [27]	0.25 mg/ 0.025 ml	34.8 ± 0.5	8 (12.1%)	6.9 ± 1.8	41.5 ± 1.5	IVR: 4 eyes (one eye had 2 injections), Laser: 4 eyes	Regressed
Chan et al. [22]	0.25 mg/ 0.025 ml	36 ± 1.9	3 (37.5%)	7.6	44	Laser	Regressed
Wong et al. [10]	0.25 mg/ 0.025 ml	N/A	5 (83%)	5.9	41.86	Laser	N/A
Erol et al. [23]	0.25 mg/ 0.025 ml	34.4 ± 1.0	6 (40%)	8	41 ± 3	Laser	Regressed

IVR intravitreal ranibizumab, *GA* gestational age, *w* weeks, *BW* birth weight, *PMA* postmenstrual age, *N* number of eyes, *RCT* Randomized controlled trial, *S* stage, *Z* zone, *(+)* plus disease, *APROP* aggressive posterior ROP, *N/A* not available.

by the BEAT-ROP study [6], which could be due to different pharmacokinetics of both ranibizumab and bevacizumab and different population included in both studies. Using IVR, Wong et al. [10] observed the shortest reactivation interval (5.9 weeks), that might be related to smaller GA (23.48 weeks) and lower BW (620 g) in their study population, while Zhang et al. [26] recorded the longest reactivation interval of (12.62 ± 7.93 weeks) and this might belong to using a higher dose (0.3 mg in 0.03 mL) of ranibizumab than all other studies.

We noticed that reactivation in both eyes of infant 1 occurred in anterior zone II with treatment to reactivation interval of 12 weeks and occurred in both eyes of infant 3 in posterior zone II with an interval of 6 weeks. This is in agreement with the work by Lyu et al. [25], where reactivation at or near to the initial site of neovascularization occurred significantly earlier than reactivation at a new vascular advancing edge.

For reactivation after initial IVR, some authors used laser photocoagulation [10, 19, 20, 22–26] or IVB [21] as alternative therapy. Their rationale was that using a different treatment modality than the initial one would give a better response. Moreover, laser following intravitreal injection of anti-VEGF provides retreatment on less avascular retina, thus reducing extent of its scar. On the other hand, some authors performed additional IVR either as single therapy [21, 31, 32] or combined with laser photocoagulation [31, 33]. Martínez-Castellanos et al. [33] recommended anti-VEGF re-injection for flat vessels and anti-VEGF re-injection combined with laser for neovascularization. In our practice, we prefer to use IVR as a single retreatment for ROP reactivation after initial IVR therapy. We believe that primary response to the initial treatment with signs of regression indicates success of this treatment modality and disease responsiveness. Reactivation noticed might be due to persistence of risk factors or exposure to a new risk factor that might increase VEGF in the avascular part of the retina, for example poor weight gain and sepsis. In addition, pharmacokinetics of anti-VEGF might explain reactivation following initial regression. Ranibizumab is a small molecule with a relatively short vitreous half-life (5.6 days) [34]. In this study, following IVR reinjection, all five eyes showed regression with successful retinal vascularisation without traction or dragging. Despite the small number of eyes, this result is encouraging and adds to the relatively limited data available on the safety and efficacy of anti-VEGF treatment for ROP. All previous studies have been conducted on European, Asian, or American population. To our knowledge, this is the first study conducted among African (Egyptian) infants. However, our study encountered some limitations, including its retrospective nature. We also acknowledge that being a single centre study may render its results less representative. However, our centre is a large tertiary referral centre and the study had a relatively large sample size.

In conclusion, this study demonstrated that IVR is beneficial as an initial and subsequent treatment for type 1 ROP or APROP. Reactivation is more common with APROP. It can occur as long as there is incomplete retinal vascularisation. Thus, we suggest a long-term follow-up until complete retinal vascularisation to observe any signs of disease reactivation.

Summary Table

What was known before

- Intravitreal injection of ranibizumab (IVR) has been reported as alternative to conventional laser in primary treatment of severe retinopathy of prematurity (ROP).
- However, reactivation of the disease has been documented in some studies, and researchers shifted back to laser as a treatment for reactivation.

What this study adds

- In this study the reactivation rate after initial IVR for type 1 ROP or worse were assessed and the efficacy of reinjection of ranibizumab in reactivated cases were reported.
- We believe this could be a better alternative to laser photocoagulation for reactivated ROP as it avoids the development of peripheral visual field defect or myopic shift following laser.

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AUTHOR CONTRIBUTIONS

The study idea and design were conceived by RMB, WMG and MRB. Material preparation, data collection and analysis were performed by RMB, AEN, EAA and AGE. Preparation of the first draft of the manuscript was written by RMB and AGA. Final review of the manuscript was performed by WMG, AEN, AGA and MRB. All authors approved the final version of the manuscript that was submitted for publication.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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