Intravitreal bevacizumab to treat retinopathy of prematurity in 865 eyes: a study to determine predictors of primary treatment failure and recurrence

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Abstract

Purpose This study aimed to evaluate the rate and risk factors for primary failure and recurrence after intravitreal anti-VEGF injection in retinopathy of prematurity (ROP).

Methods This retrospective study was performed on 865 eyes from 441 patients with retinopathy of prematurity receiving intravitreal bevacizumab from 2012 to 2019. Medical records of patients were evaluated.

Results Mean gestational age (GA) and birth weight of patients were 28 ± 2 weeks and 1121 ± 312 g, respectively. Thirty-five eyes (4.04%) had a primary failure, including 18 eyes from 187 eyes in zone 1 (9.6%) and 17 eyes from 678 eyes in zone 2 (2.5%). The mean time of retreatment was 16.64 ± 13.68 days in eyes without regression ROP. The remaining 830 eyes (95.95%) were included in recurrence analysis. The recurrence occurred in 33 eyes (3.97%) of them in 20 patients, with the meantime of 77.52 days after the first treatment (IVB). The presence of plus disease, history of oxygen therapy or phototherapy, and GA less than 32 were associated with significantly increased prevalence of treatment failure. The risk factors predicting recurrence are lower birth weight, zone 1 pretreatment, history of intubation, anemia, and sepsis.

Conclusion Intravitreal anti-VEGF is a successful treatment for ROP with a low rate of primary failure and recurrence. Awareness of risk factors for treatment failure and recurrence may help clinicians to schedule more vigilant approach in susceptible cases.

Keywords Retinopathy of prematurity · Intravitreal Bevacizumab · Regression · Treatment failure · Recurrence

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the immature retina and one of the major preventable causes of childhood blindness [1]. Preterm delivery may result in inhibition of physiologic retinal vascular development and lead to the persistent avascular retina and consequent neovascular response. The abnormal vasoproliferation in some severe cases of ROP causes advanced stages, which may require treatment [2]. Laser ablation of the avascular retina is the mainstay of treatment for many years, which has significantly reduced unfavorable outcomes [3]. Nonetheless, its side effects like permanent destruction of the peripheral retina, visual field loss, and induced myopia remain a concern. Since...
BEAT-ROP study, there is an increasing trend toward less invasive intravitreal injection of anti-VEGF drugs like bevacizumab and ranibizumab, especially in zone 1 [4, 5]. Anti-VEGF treatment results in more rapid regression of abnormal vessels and is more feasible in the eyes with rigid pupils. Additionally, it has lower chance of unfavorable outcomes in type 1 ROP like high myopia [6, 7]. Furthermore, anti-VEGF administration are less cumbersome to deliver in comparison with standard laser treatment, and it allows continuous vascular development, however, side effects remain a big concern [8, 9].

Despite the advantages mentioned above, the persistence of avascular retina after treatment may act as a double edge sword. Avascular retina may result in ongoing VEGF secretion, as several studies reported significant delayed recurrence rate [10–12]. Thus, determination of risk factors for recurrence after anti-VEGF therapy is crucial. Additionally, although several studies have reported reactivation of ROP following anti-VEGF treatment, however, none of them reported risk factor of primary unresponsiveness.

In light of the abovementioned studies, early detection of primary failure and recurrence after intravitreal administration of anti-VEGF is essential to provide vigilant follow-up to ensure timely retreatment. We present the results of large case series of ROP-treated infants treated with intravitreal bevacizumab to report the rate of primary failure and recurrence in these patients and the timing of recurrence. Besides, we want to assess the primary failure and recurrence risk factors to define which patients need more frequent examination and possibly longer follow-up.

**Methods**

The current study is a retrospective case series to evaluate the variables associated with primary failure and recurrence after administering intravitreal bevacizumab for the treatment of type I ROP in zone I or II in a tertiary center Farabi Eye Hospital, Tehran, Iran. Medical documents of relevant cases were reviewed to collect data. Informed consent was obtained from the parents of the participants at the initiation of treatment for future publication of data. The ethics committee of eye research center, Farabi Eye Hospital, approved this study (https://ethics.research.ac.ir/IR.TUMS.FARABI.REC.1399.040). All procedures and interventions followed the tenets of the Helsinki declaration.

Infants with eye diseases other than ROP, such as congenital cataracts and glaucoma, or patients with a previous treatment history were excluded from this study. Infants who did not complete follow-up until 90 weeks of postmenstrual age were also excluded. Infants were examined with indirect ophthalmoscopy. All injections were performed in an operating room. Bevacizumab 0.625 mg/0.025 ml was injected under topical anesthesia (Tetracaine 0.5%) following prep with betadine 5%. The injection was done with a 30-gauge needle. In bilateral cases, injections were performed on the same day but from different vials of bevacizumab. All infants received chloramphenicol or gentamycin eye drops every 6 h for three days following injection.

Follow-up schedule was at the following order: day one, weekly for 4 weeks, biweekly for 8 weeks, and then monthly until 90 weeks of postmenstrual age. RetCam photographs were repeated at 1 week after treatment, and also at 54 weeks of postmenstrual age. Any doubt regarding disease persistence or recurrence was approached with vigorous examination (every 3 days). The primary outcome was treatment failure defined as persistence of ROP as absence of the regression of neovascularization and plus, one week following treatment. Persistence of vascular tortuosity in the absence of other indicators of treatment failure was not considered as sign of disease activity. Recurrence is defined as the reappearance of any sign of plus or appearance of pathological new vessels up to the last follow-up visit until 90 weeks of postmenstrual age [13]. The persistence of vascular tortuosity in the absence of other treatment failure indicators was not considered a sign of disease activity. Once the diagnosis of treatment failure was approved by two retina specialists with expertise in the field of ROP, rescue therapy with laser photocoagulation was performed. Standard indirect laser with a wavelength of 650 nm and confluent or near confluent (separation with one-half of burn spot size) was applied at the avascular retinal periphery.

The secondary outcome was to assess the time to recurrence and risk factors for predicting primary failure and recurrence following treatment with intravitreal anti-VEGF agents.
Statistical analysis

We used mean, standard deviation, median, range, frequency, and percent to present data. Risk for primary failure is presented as prevalence ratio (PR) with its related 95% CI, which indicates the added prevalence of the outcome in the presence of the specific variable in the definite time. Because recurrence occurred in the extended time, to better present the risk of recurrence, we used hazard ratio (HR) with its related 95% CI from a shared frailty Cox regression model to compare the intensity of the recurrence in the different groups. Variables with a $P$-value less than 0.1 in this analysis entered into a shared frailty multiple Cox regression model. Then, we exclude the statistically non-significant variables using a backward approach until there is no variable with a $P$-value > 0.1 in the model. All statistical analyses are performed by Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). $P$-value less than 0.05 was set as statistically significant effect.

Results

Subjects

In this retrospective case series, 865 eyes of 252 male (57.1%) and 189 female (42.9%) infants were recruited. Mean gestational age was 28 ± 2 weeks, with a range of 22–34 weeks. Patients had a mean birth weight of 1121 ± 312 g (550–2700 g). Table 1 demonstrates the demographic characteristics of infants.

Primary failure analysis

Patients underwent treatment with intravitreal bevacizumab injection. Thirty-five eyes (4.04%) had the criteria of primary failure for whom laser therapy was applied. The first time of treatment requirement was 58.83 ± 19.19 days (21–162) after birth. In patients with regression ROP, the meantime of regression after receiving IVB and last follow-up was 13.72 ± 9.55 and 289.43 ± 257 days, respectively. The mean time of follow-up in patients with primary failure treatment was 419.33 ± 529.48 days. The rate of OD/OS was 431/434. Plus disease was observed in 861 eyes (99.5%). The situation of zone and stage included 187 (21.6%) zone 1, 678 (78.4%) zone 2, 2 (0.2%) stage 1, 33 (3.8%) stage 2, and 830 (96%) stage 3, respectively. Neovascularization of iris (NVI) was observed in 54 (6.2%) eyes. Primary failure of treatment was observed in 18 eyes from 187 eyes in zone 1 (9.6%) and 17 eyes from 678 eyes in zone 2 (2.5%). The mean time of retreatment was 16.64 ± 13.68 days in eyes without regression ROP. Retreatments included just laser in 23 eyes (65.7%), laser and then vitrectomy in five eyes (14.3%), repeated IVB and then laser in two eyes (5.7%), laser and sclera buckle in one session in two eyes (5.7%), just vitrectomy in two eyes (5.7%), and finally, laser then repeated IVB, followed by vitrectomy in one eye (2.9%).

Risk factors of primary failure

Table 2 shows the prevalence ratio of variables associated with unresponsiveness to intravitreal bevacizumab. The presence of plus disease was associated with 4% increased prevalence of treatment failure (95% CI: 1.022–1.058; $P$-value: < 0.001). Additionally, patients who had a history of oxygen therapy or phototherapy had a greater risk of treatment failure (PR: 1.045; 95CI%: 1.025–1.065; $P$-value: < 0.001; PR: 1.039; 95%CI: 1.008–1.071; $P$-value: 0.014; respectively). Patients with GA less than 32 weeks had a 4.4% increased possibility of treatment failure (95% CI: 1.024–1.065); however, birth weight was not associated with a higher incidence of failure (PR: 0.99; 95% CI: 0.92–1.06; $P$-value: 0.791).

Factors with a $P$-value less than 0.1 were selected for multiple variable GLM model regression analysis. GA, plus disease, history of phototherapy, and oxygen therapy still were associated with a higher rate of primary treatment failure (Table 3).

Recurrence analysis

The recurrence occurred in 33 eyes (3.97%) from 20 patients, with the meantime of 77.52 days after receiving the first treatment (IVB). Only seven (35%) of the mentioned patients got the recurrence unilaterally. Characteristic findings of patients with recurrence are given in Table 1. ROP recurred in 13 eyes (7.69%) from whom the ROP was in zone 1 and 20 eyes (3.02%) from whom the ROP was in zone 2 ($p$-value: 0.008). On the other hand, recurrence was more
common in patients with ROP in zone 1 than in zone 2 at the time of first treatment (7.69% vs. 3.02%). All of the 33 eyes with recurrence had stage 3 before the second treatment.

Risk factors of recurrence

Table 4 shows the recurrence prevalence of the ROP in the infants based on the different conditions. We calculated the hazard ratio in survival analysis with its related 95% CI from a shared frailty Cox regression model to compare the recurrence rate according to compare 16 potential risk factors between recurrence and nonrecurrence eyes. The final model (the statistically significant variables) includes BW, zone 1 pretreatment, intubation, sepsis, and anemia. Each 100 gr increase in the BW was negatively related to the hazard of recurrence (HR = 0.85, 95% CI: 0.74–0.99, \( P = 0.033 \)). Infants who got intubation (HR = 4.0, 95% CI: 1.7–9.5, \( P = 0.002 \)), history of anemia (HR = 3.1, 95% CI: 1.4–6.6, \( P = 0.004 \)), zone 1 pretreatment (HR = 2.59, 95% CI: 1.29–5.21, \( P = 0.008 \)), or history of sepsis (HR = 2.65, 95% CI: 1.30–5.39, \( P = 0.007 \)) had higher hazard for recurrence (Table 5).

From 666 eyes (80.2%) of patients with 30 weeks or lower gestational age, 30 (4.5%) eyes have recurrent ROP. Although this number was 1 in the

### Table 1 Baseline and demographic characteristics of infants

| Regression | Total | Yes | No |
|------------|-------|-----|----|
|            | Count | Percent % | Count | Percent % | Count | Percent % |
| Eye OD     | 431 (100.0%) | 413 (95.8%) | 18 (4.2%) |
| OS         | 434 (100.0%) | 417 (96.1%) | 17 (3.9%) |
| Gender Male | 496 (100.0%) | 481 (97.0%) | 15 (3.0%) |
| Female     | 369 (100.0%) | 349 (94.6%) | 20 (5.4%) |
| Zone pretreatment 1 | 187 (100.0%) | 169 (90.4%) | 18 (9.6%) |
| 2          | 678 (100.0%) | 661 (97.5%) | 17 (2.5%) |
| Plus Yes   | 861 (100.0%) | 826 (95.9%) | 35 (4.1%) |
| No         | 4 (100.0%) | 4 (100.0%) | 0 (0.0%) |
| NVI Yes    | 54 (100.0%) | 48 (88.9%) | 6 (11.1%) |
| No         | 811 (100.0%) | 782 (96.4%) | 29 (3.6%) |
| Twin Yes   | 210 (100.0%) | 204 (97.1%) | 6 (2.9%) |
| No         | 655 (100.0%) | 626 (95.6%) | 29 (4.4%) |
| O2 therapy Yes | 764 (100.0%) | 729 (95.4%) | 35 (4.6%) |
| No         | 99 (100.0%) | 99 (100.0%) | 0 (0.0%) |
| Intubation Yes | 348 (100.0%) | 333 (95.7%) | 15 (4.3%) |
| No         | 515 (100.0%) | 495 (96.1%) | 20 (3.9%) |
| Transfusion Yes | 491 (100.0%) | 470 (95.7%) | 21 (4.3%) |
| No         | 372 (100.0%) | 358 (96.2%) | 14 (3.8%) |
| IVH Yes    | 62 (100.0%) | 59 (95.2%) | 3 (4.8%) |
| No         | 801 (100.0%) | 769 (96.0%) | 32 (4.0%) |
| Sepsis Yes | 340 (100.0%) | 327 (96.2%) | 13 (3.8%) |
| No         | 523 (100.0%) | 501 (95.8%) | 22 (4.2%) |
| Phototherapy Yes | 572 (100.0%) | 541 (94.6%) | 31 (5.4%) |
| No         | 291 (100.0%) | 287 (98.6%) | 4 (1.4%) |
| Anemia Yes | 76 (100.0%) | 74 (97.4%) | 2 (2.6%) |
| No         | 787 (100.0%) | 754 (95.8%) | 33 (4.2%) |
| ARDS Yes   | 457 (100.0%) | 436 (95.4%) | 21 (4.6%) |
| No         | 406 (100.0%) | 392 (96.6%) | 14 (3.4%) |
Table 2  Prevalence ratio of risk factors associated with primary treatment failure following intravitreal bevacizumab to treat aggressive posterior retinopathy of prematurity

| Parameter          | Level | Total       | Regression | PR  | 95% CI       | P   |
|--------------------|-------|-------------|------------|-----|--------------|-----|
|                    |       | No          | Yes        |     | Lower        | Upper| P     |
| Eye                | OD    | 431 (49.8%) | 413 (95.8%)| 18  | 4.2%         | 1.002| 0.998 | 1.007 | 0.316 |
|                    | OS    | 434 (50.2%) | 417 (96.1%)| 17  | 3.9%         | 0.978| 0.943 | 1.014 | 0.230 |
| Gender             | Male  | 496 (57.3%) | 481 (97.0%)| 15  | 3.0%         | 0.987| 0.943 | 1.024 | 0.146 |
|                    | Female| 369 (42.7%) | 349 (94.6%)| 20  | 5.4%         | 1.029| 0.995 | 1.064 | 0.092 |
| Zone pretreatment  | 1     | 187 (21.6%) | 169 (90.4%)| 18  | 9.6%         | 1.029| 0.995 | 1.064 | 0.092 |
|                    | 2     | 678 (78.4%) | 661 (97.5%)| 17  | 2.5%         | 0.990| 0.960 | 1.023 | 0.548 |
| Plus               | Yes   | 861 (99.5%) | 826 (95.9%)| 35  | 4.1%         | 1.040| 1.022 | 1.058 | < 0.001* |
|                    | No    | 4 (0.5%)    | 4 (100.0%) | 0   | 0.0%         | 0.997| 0.966 | 1.032 | 0.066 |
| NVI                | Yes   | 54 (6.2%)   | 48 (88.9%) | 6   | 11.1%        | 1.074| 0.964 | 1.196 | 0.198 |
|                    | No    | 811 (93.8%) | 782 (96.4%)| 29  | 3.6%         | 1.074| 0.964 | 1.196 | 0.198 |
| Twin               | Yes   | 210 (24.3%) | 204 (97.1%)| 6   | 2.9%         | 0.985| 0.950 | 1.022 | 0.430 |
|                    | No    | 655 (75.7%) | 626 (95.6%)| 29  | 4.4%         | 0.985| 0.950 | 1.022 | 0.430 |
| Oxygen therapy     | Yes   | 764 (88.5%) | 729 (95.4%)| 35  | 4.6%         | 1.045| 1.025 | 1.065 | < 0.001* |
|                    | No    | 99 (11.5%)  | 99 (100.0%)| 0   | 0.0%         | 0.997| 0.966 | 1.032 | 0.083 |
| Intubation         | Yes   | 348 (40.3%) | 333 (95.7%)| 15  | 4.3%         | 1.005| 0.969 | 1.041 | 0.803 |
|                    | No    | 515 (59.7%) | 495 (96.1%)| 20  | 3.9%         | 1.005| 0.969 | 1.041 | 0.803 |
| Transfusion        | Yes   | 491 (56.9%) | 470 (95.7%)| 21  | 4.3%         | 1.006| 0.972 | 1.042 | 0.736 |
|                    | No    | 372 (43.1%) | 358 (96.2%)| 14  | 3.8%         | 1.006| 0.972 | 1.042 | 0.736 |
| IVH                | Yes   | 62 (7.2%)   | 59 (95.2%) | 3   | 4.8%         | 1.009| 0.943 | 1.070 | 0.789 |
|                    | No    | 801 (92.8%) | 769 (96.0%)| 32  | 4.0%         | 1.009| 0.943 | 1.070 | 0.789 |
| Sepsis             | Yes   | 340 (39.4%) | 327 (96.2%)| 13  | 3.8%         | 0.997| 0.962 | 1.032 | 0.846 |
|                    | No    | 523 (60.6%) | 501 (95.8%)| 22  | 4.2%         | 0.997| 0.962 | 1.032 | 0.846 |
| Phototherapy       | Yes   | 572 (66.3%) | 541 (94.6%)| 31  | 5.4%         | 1.039| 1.008 | 1.071 | 0.014* |
|                    | No    | 291 (33.7%) | 287 (98.6%)| 4   | 1.4%         | 0.985| 0.935 | 1.037 | 0.570 |
| Anemia             | Yes   | 76 (8.8%)   | 74 (97.4%) | 2   | 2.6%         | 0.985| 0.935 | 1.037 | 0.570 |
|                    | No    | 787 (91.2%) | 754 (95.8%)| 33  | 4.2%         | 0.985| 0.935 | 1.037 | 0.570 |
| ARDS               | Yes   | 457 (53.0%) | 436 (95.4%)| 21  | 4.6%         | 1.012| 0.977 | 1.048 | 0.503 |
|                    | No    | 406 (47.0%) | 392 (96.6%)| 14  | 3.4%         | 1.012| 0.977 | 1.048 | 0.503 |

ARDS Acute respiratory distress syndrome; IVH Intraventricular hemorrhage; NVI Neovascularization of iris, PR Prevalence ratio, P p-value tested by..., *: statistically significant.

31–33 weeks group and 2 (6.4%) in the 34 weeks group, the calculated HR did not significantly increase with decreasing gestational age (P-value: 0.23). Of 40 patients with documented iris neovascularization, three eyes (7.5%) have the recurrent disease; however, it was not significantly higher than the patients without NVI (30 eyes (4.6%), P-value: 0.47). All 33 patients with recurrent disease have a history of oxygen therapy. The HR ratio for ARDS was marginally insignificant (HR: 0.53, P-value: 0.078). Other systemic factors which we assessed in this regression model were history of sepsis, intraventricular hemorrhage, phototherapy, and being twin did not significantly increase this risk of ROP recurrence.

Factors with a P-value less than 0.1 were selected for multiple variable GLM model regression analysis. Intubation is the only factor that was associated with a higher rate of recurrence (Table 6), while zone 1 pretreatment was marginally insignificant.
Table 3  Multiple variables regression analysis of parameters associated with primary treatment failure following intravitreal bevacizumab to treat type 1 retinopathy of prematurity

| Parameter               | Level | PR  | 95% CI   | P-value |
|-------------------------|-------|-----|----------|---------|
|                        |       | PR  |          |         |
| Zone pretreatment       | 1     | 1.029 | 0.995   | 1.064   | 0.189  |
|                        | 2     |      |          |         |        |
| Plus                    | Yes   | 1.040 | 1.022   | 1.058   | <0.001*|
|                        | No    |      |          |         |        |
| NVI                     | Yes   | 1.074 | 0.964   | 1.196   | 0.218  |
|                        | No    |      |          |         |        |
| Oxygen therapy          | Yes   | 1.045 | 1.025   | 1.065   | <0.001*|
|                        | No    |      |          |         |        |
| Phototherapy            | Yes   | 1.039 | 1.008   | 1.071   | 0.020* |
|                        | No    |      |          |         |        |
| GA                      | <32w  | 1.049 | 1.023   | 1.077   | <0.001*|
|                        | 32–34w| 1.027 | 0.989   | 1.067   | 0.159  |
|                        | >34w  |      |          |         |        |

PR Prevalence ratio; NVI Neovascularization of iris; GA Gestational age, *: statistically significant

Table 4  Demographic data of patients with recurrence of retinopathy of prematurity

| GA (weeks) | BW (grams) | Gender | Time first treatment from birth date (days) | Laterality of recurrence | Severity of ROP at the time of first treatment | Retreatment |
|------------|------------|--------|---------------------------------------------|--------------------------|-----------------------------------------------|-------------|
| Case 1     | 30         | 670    | Female 74                                   | Bilateral                | Z1-S3-Plus                                    | IVB         |
| Case 2     | 34         | 1400   | Male 51                                     | Unilateral               | Z1-S3-Plus                                    | Laser       |
| Case 3     | 27         | 1220   | Male 48                                     | Unilateral               | Z2-S3-Plus                                    | Laser       |
| Case 4     | 28         | 900    | Female 124                                  | Bilateral                | Z2-S3-Plus                                    | Laser       |
| Case 5     | 26         | 700    | Female 53                                   | Bilateral                | Z2-S3-Plus                                    | IVB         |
| Case 6     | 30         | 1300   | Male 34                                     | Bilateral                | Z1-S3-Plus                                    | Laser       |
| Case 7     | 22         | 815    | Female 67                                   | Unilateral               | Z1-S3-Plus                                    | LVB         |
| Case 8     | 26         | 820    | Female 73                                   | Bilateral                | Z2-S3-Plus                                    | Laser       |
| Case 9     | 28         | 830    | Female 50                                   | Bilateral                | Z2-S3-Plus                                    | Laser       |
| Case 10    | 27         | 700    | Female 54                                   | Bilateral                | Z2-S3-Plus-NVI                                 | Laser       |
| Case 11    | 28         | 1120   | Male 38                                     | Bilateral                | Z2-S3-Plus                                    | Laser       |
| Case 12    | 29         | 1360   | Female 27                                   | Bilateral                | Z2-S3-Plus                                    | Laser       |
| Case 13    | 34         | 2010   | Female 34                                   | Unilateral               | Z2-S3-Plus                                    | Laser       |
| Case 14    | 31         | 1600   | Male 76                                     | Unilateral               | Z2-S3-Plus                                    | Laser       |
| Case 15    | 25         | 720    | Male 71                                     | Bilateral                | Z1-S3-Plus                                    | Laser       |
| Case 16    | 26         | 930    | Female 61                                   | Bilateral                | Z2-S3-Plus                                    | Laser OD    |
|            |            |        |                                              |                          | Laser and lensectomy                          |             |
| Case 17    | 28         | 980    | Male 57                                     | Bilateral                | Z1-S3-Plus                                    | Laser       |
| Case 18    | 27         | 1100   | Male 61                                     | Unilateral               | Z2-S3-Plus                                    | Laser       |
| Case 19    | 26         | 960    | Female 45                                   | Unilateral               | Z1-S3-Plus-NVI                                 | IVB         |
| Case 20    | 26         | 620    | Bilateral OD:77, OS:53                      | Bilateral                | Z2-S3-Plus                                    | IVB         |

GA Gestational age, BW Birth weight, Z Zone, S Stage, NVI Neovascularization iris, IVB Intravitreal Bevacizumab
Discussion

ROP is a VEGF-driven vasoproliferative disease. Although retinal photocoagulation is the mainstay of ROP treatment, some authors suggest anti-VEGF agents for treating some ROP cases, like ones with media opacity, meiotic pupils, or the APROP. It has several advantages over conventional laser therapy. It is easier and less expensive without any need for
expensive equipment. Also, it does not induce visual field loss which frequently occurs with laser therapy.

To our knowledge, none of the previous investigations have provided evidence regarding risk factors for primary treatment failure in patients treated initially with anti-VEGF therapy alone. Thirty-five eyes from 865 eyes treated with intravitreal bevacizumab (4.04%) meet the criteria of primary failure. Our results demonstrated that infants with younger age and plus disease who have a history of phototherapy and oxygen therapy harbor a greater risk of treatment failure following injection of bevacizumab to treat type I ROP in zone I or II.

Nevertheless, ROP recurrence is a significant concern about anti-VEGF agents because it can devastate outcomes, like vitreoretinal traction and retinal detachment [14]. Notably, it may recur after a more extended period compared with laser therapy [14]. Off-label usage of bevacizumab for regression of abnormal retinal vessels is acceptable. Its relatively large molecular size which provide longer half-life in the eye suggests that a single intravitreal injection may be adequate for the ROP treatment [5].

In this study, we used intravitreal bevacizumab injection to treat ROP in zone 1 and zone 2. All of the 830 eyes that were treated successfully showed primary regression after receiving IVB, but ROP recurred in 33 eyes. Thereby, intravitreal bevacizumab treatment is an effective modality in inducing regression in treatment required type 1 ROP, but recurrence is an important factor.

The art of managing IVB-treated ROP patients is to differentiate treatment failure from recurrence, chiefly because the mainstream of treatment failures signifies a misdiagnosis [15]. Currently, evidence on response patterns to IVB, primary failure rate, and risk factors is scarce. Chen and colleagues described a spectrum of regression, including full vascular maturity, vascular arrest alone, or vascular arrest with persistent tortuosity following injection of bevacizumab [16]. They evaluated 92 eyes of 42 infants, of whom 16 eyes (18%) experienced reactivation. Areas of ischemia were greater in eyes with reactivation. They found younger age at IVB treatment was associated with vascular arrest accompanied by tortuosity; however, their results do not provide data about primary treatment failure.

On the other hand, recurrences need to be carefully assessed in order to avoid overtreatment. In the light of the importance of recurrence, many studies reported the incidence of recurrences after initial treatment with intravitreal injections. The incidence of recurrence reported varies from 4 to 10%. On the other hand, IVB monotherapy led to persistent avascular retina [13, 17] and delayed recurrence of ROP (even three years after IVB) [12, 18, 19]. BEAT-ROP study demonstrated a 4% risk of recurrence at a mean time of 16 ± 4.4 weeks post-IVB injection [5]. This is relatively similar to our results showing 3.9% recurrence.

\[HR\] Hazard ratio; \(GA\) Gestational age; \(*\): Statistically significant

### Table 6

| Parameter                  | Level | aHR   | 95% CI     | P-value |
|----------------------------|-------|-------|------------|---------|
|                            |       | Lower | Upper      |         |
| Zone pretreatment           | 1     | 1.87  | 0.91       | 3.86    | **0.089** |
|                            | 2     | 1     |            |         |           |
| ARDS                       | Yes   | 0.73  | 0.32       | 1.70    | 0.470    |
|                            | No    | 1     |            |         |           |
| Anemia                     | Yes   | 2.12  | 0.81       | 5.58    | 0.126    |
|                            | No    | 1     |            |         |           |
| Sepsis                     | Yes   | 1.44  | 0.65       | 3.18    | 0.371    |
|                            | No    | 1     |            |         |           |
| Intubation                 | Yes   | 3.70  | 1.50       | 9.11    | **0.004** |
|                            | No    | 1     |            |         |           |
| GA                         | < 32w | 0.98  | 0.83       | 1.17    | 0.854    |
|                            | 32–34w|       |            |         |           |
|                            | > 34w |       |            |         |           |

**HR** Hazard ratio; **GA** Gestational age; *: Statistically significant.
at a mean of 18 weeks and 3 days. More recently, in a large cohort of IVB-treated ROP patients, they demonstrate, 2.5% (17 patients) failed treatment and a recurrence rate of 6.8% within the first 12 ± 4 weeks [15]. They found initial misdiagnosis as the main culprit for unresponsiveness. However, in our study, cases of misdiagnosis are not included, and the remaining infants with primary failure have been re-examined by two experts in the field to assure correct diagnosis. Another explanation for discrepancy could be the inclusion of patients with different baseline demographic factors such as GA and birth weight which were lower in our study (1450 ± 750 g vs. 1121 ± 312 g; 30 ± 2 weeks vs. 28 ± 2 weeks; respectively), as well as different ethnic.

Additionally, a lack of widely accepted criteria for practice patterns after initial treatment with IVB may lead to different approaches in various centers, which some may attain a more aggressive and cautious approach. Furthermore, experts in ROP describe plus disease differently, but they tend to be internally consistent [20]. On the other hand, other studies on ranibizumab have demonstrated an earlier and higher risk of recurrence [14, 21].

Some authors propose laser photocoagulation for the treatment of such recurrences, while others advocate for repeat injections. In retreatment required patients, based on our experience, we recommend laser photocoagulation. Repeat anti-VEGF was done in cases with recurrence of retinopathy of prematurity when the border of the vascular–avascular area was posterior (posterior zone 2).

In terms of primary failure, our results demonstrated that younger age and plus disease, history of phototherapy, and oxygen therapy harbor a greater risk following injection of bevacizumab to treat type I ROP in zone I or II.

GA is the strongest risk factor for developing severe ROP. In cryotherapy for ROP study (CRYO-ROP), younger age was associated with the development of threshold ROP [22]. This finding has been replicated in other studies [23–26]. Lower GA was a common risk factor among various studies to be associated with recurrence after successful initial treatment [13, 27, 28]. Infants with lower GA are more ill, have a higher grade of retinopathy, and additionally lower capacity to produce anti-oxidant enzymes. Our result implies that GA under 32 weeks imposes a 4.4% increased possibility of primary treatment failure. Therefore, it is crucial to maintain vigorous follow-up examination in the early phase after therapy to detect signs of treatment failure in these subsets of infants.

Our results demonstrate that plus disease, defined as vascular tortuosity and dilatation, is associated with a 4% increase in the prevalence of treatment failure. Excessive signaling through VEGF-VEGFR2 is involved in the features of plus disease. Therefore, regulation of VEGFR2 signaling through anti-VEGF treatment combats this condition and prevents progressive neovascularization. On the other hand, the presence of plus disease indicates a more severe form of the disease [2]. Additionally, primary failure indicates an overabundance of VEGF, which is not completely controlled with single-dose treatment. So, it is rational that those infants suffering from a more severe form of the disease are prone to treatment failure and might require further therapy throughout the course of the disease. However, 99.5% of infants in our study had plus disease. This issue underscores the necessity for a standard grading scale of vascular abnormality in ROP. Recently, efforts have been made to apply vascular severity scores for patients with ROP [29–31]. These investigations showed variability in plus disease. In fact, eyes with higher severity scores may be prone to unresponsiveness to treatment or recurrence. This hypothesis requires further prospective studies to evaluate objective vascular scores to differentiate the severity of plus disease and its association with treatment response.

Based on our findings, oxygen therapy is associated with a 4.5% increase in the prevalence of primary treatment failure. A historical trial published in 1956 found that the incidence of ROP is higher in infants treated with > 50% oxygen [32]. Additionally, the period of oxygen therapy, fluctuation in oxygen saturation, and mechanical ventilation are independent risk factors for the development of severe ROP [33–35]. Although lower oxygen saturation may decrease the incidence of severe ROP, an increase in mortality has been observed in BOOST II collaborative group study [36]. So the optimum root of oxygen delivery is still controversial, and due to the relatively small sample size for subgroup analysis of methods of oxygen therapy, our data do not have sufficient power to determine this detail.

Previous retrospective and observational studies define various risk factors for the prediction of recurrence of ROP after IVB treatment. Previously
reported risk factors for recurrent ROP after anti-VEGF therapy includes lower GA, lower BW, longer duration of hospitalization, extensive retinal neovascularization, supplemental oxygen requirement after treatment, and preretinal hemorrhage before treatment, as long as multiple birth [13, 14, 21, 27]. In the current study, we assessed the risk factors for recurrence of ROP after treatment with bevacizumab. From 16 factors we assessed, lower birth weight, zone 1 pretreatment, history of intubation, anemia, and sepsis were associated with increasing recurrence chance in univariate analysis, while only intubation is significant in multivariable analysis.

Unlike the abovementioned studies, we did not find gestational age an independent risk factor of recurrence. Although earlier gestational age at initial treatment may show illness of these infants and had more severe retinopathy that required earlier treatment, likely because two of 20 patients who suffered recurrence after IVB were in 34 weeks of gestational age. It implies that vigilant follow-up for IVB-treated patients requires all treated patients independent of gestational age. Main ROP risk factors include low gestational age and birth weight [37, 38]; in our study, we mentioned that maybe birth weight is a more independent risk factor that implies prematurity than gestational age. Moreover, the history of ARDS was marginally an insignificant risk factor. Lyu et al. reported an 11-fold increased risk of ROP recurrence in patients with a history of oxygen therapy [27].

History of intubation and sepsis in infants implies more severe ocular hypoxia and higher oxygen requirements. Then, systemic hypoxia during this period may exacerbate the retina’s hypoxia and block retinal maturation, increasing the risk of recurrent neovascularization. Moreover, zone 1 pretreatment implies a more aggressive nature of retinopathy which requires more vigilant follow-up.

Similar to previous studies on this subject, our study’s limitations include its retrospective nature, data collection from a single institution as long as we did not perform fluorescein angiography in our recurrent cases. In order to accurately diagnose persistent disease or recurrence of ROP in IVB-treated ROP, the cautious approach is to do fluorescein angiography to confirm the extent of retinal vascularization. As a result, our results cannot be generalized to all eyes with type 1 ROP, as only eyes with more aggressive forms of ROP whereby laser would be suboptimal or not possible were offered IVB in our series. On the other hand, a large sample size and being treated at the same hospital with standardized treatment protocols are significant strengths of the study.

Our results help incorporate risk factors into practice patterns and devise a plan for early detection of treatment failure and recurrence. Although over examination following treatment can prevent dreadful sequels of ROP, it is worthy of note that ROP examinations, despite their medical cost, can induce morbidity in neonates, including decreased oxygen saturation, increased heart rate, and apnea events [39]. Attention to risk factors accompanied by special care to patterns of treatment failure, and recurrence, helps to achieve both objectives.

In conclusion, intravitreal bevacizumab is an effective treatment in inducing ROP regression, low rate of primary failure, but the effect may be transient in some cases. Post-IVB treatment, recurrence can occur later in the course than with conventional laser therapy. The risk factor for predicting primary failure in our study is infants with younger age and plus disease who have a history of phototherapy and oxygen therapy. The risk factor predicting recurrence is a history of intubation. Future studies on the definition of primary failure, recurrence and screening criteria, treatment-type recommendations, and time should be done.

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**Authors’ contributions** FB and HRE involved in conception and design, definition of intellectual content, data acquisition, analysis and interpretation, manuscript review, and guarantor. KF and MH and MMB involved in analysis and interpretation, literature search, data acquisition, manuscript preparation, manuscript editing, and manuscript review. AA and ADF involved in definition of intellectual content, literature search and manuscript review, consistent criticism. All authors read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**Availability of data and materials** The datasets analyzed during the current study are available from the corresponding author on reasonable request.

**Code availability** Not applicable.
Declarations

Conflict of interests The authors declare that they have no competing interests.

Ethical approval Human subjects were included in this study. The ethics committee of eye research center, Farabi Eye Hospital, approved this study (https://ethics.research.ac.ir/IR.TUMS.FARABI.REC.1399.040).

Consent to participate The study was conducted according to the tenets of the Declaration of Helsinki. Any procedure was done after providing parents with informed consent.

Consent for publication Written informed consent was obtained from the patient’s parents (that his fundus photographs were used in the Figure1) for publication of any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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