Fellow eye effects of monocular intravitreal bevacizumab (IVB) injection for retinopathy of prematurity (ROP).

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Abstract

Purpose: To evaluate if monocular IVB injection does have any far effect on the non-injected fellow eyes in ROP.

Methods: In a clinical practice setting designed as prospective interventional case series study infants having bilateral type-1(high risk) prethreshold ROP had one eye randomized to intravitreal bevacizumab (IVB) (0.625 mg /0.025 ml) and fellow eyes left untreated if had type-1 pre-threshold ROP of "zone-II stage 2 with plus" or "zone-I stage 3 without plus". Sixty eyes (30 treated 30 untreated) of 30 premature babies, 13 male 17 females, with a mean gestational age (GA) of 28,1 ± 1.69 (25 to 31) weeks and a mean birth weight (BW) of 1010.33 ± 231,03 (520 to 1530) grams were studied. All patients were followed up for a mean 29,73 ± 3,23 (24 to 36) months. Clinical course of the fellow eyes was first evaluated at the first post-injection week and determined if they were better, worse or the same in comparison to the day of monocular injection. Fellow eyes got injected if worsened during follow period.

Results: In the first post-injection week, none of the untreated eyes was found to be worsened (0/30;0%) but 19 were better (19/30;63,3%) and 11 were the same (11/30;36,7%).

During the follow up period, after the monocular injection in a mean of 2,77 ± 0,83 (2 to 4) weeks period, 13 of untreated 30 fellow eyes (43,3%) were injected and 8 over 13 injected fellow eyes were 8 over the 11 (72,7%) of the same eyes of and 5 over 13 were 5 over the 19 (26,3%) the better eyes of the first post injection week examination. Finally, infants who got monocular injection first and fellow eye injection when worsened were found to have bilateral IVB treatment rates as 43,3% (13 over 30 eyes) and all 60 eyes studied gained normal retinal maturation at the end of the follow up period.

Conclusions: Monocular IVB injection was found to have a regressing effect on the clinical course of the untreated fellow eye and for selected cases firstly monocular IVB injection can decrease the bilateral treatment rate of ROP to 43,3% in comparison to 79% reported in ETROP (Early Treatment for ROP) Study.

Keywords: Rop, Retinopathy of prematurity, Bevacizumab, Anti-VEGF

Introduction

Since then the BEAT ROP Study published in 2011 anti-VEGF treatment particularly intravitreal bevacizumab (IVB) became one of the mostly discussed topic in the area of ROP in the literature [1].Besides the debates about possible systemic risks in a premature infant firstly in the literature we have demonstrated a positive effect of IVB on the clinical course of bronchopulmonary dysplasia (BPD) and explained this effect possibly as a result of normalization of the alveolar vasculogenesis similar to retinal vasculogenesis seen in ROP [2].

In clinical practice, after IVB injection, we have always been experiencing a positive effect on the systemic course of premature infants [3] and depending upon this clinical observation and our previously presented limited laser

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treatment we have already defined and published a new hypothesis claiming and clarifying a possible single pathogenesis underlying in all main morbidities namely ROP, intracranial complications (cerebral hemorrhages and related intracranial hypertension), BPD and necrotizing enterocolitis (NEC) of a premature infant [4] and all related to vasculogenesis mainly.

On the other hand, as we published one of the largest IVB injection as well as the first re-injection series in the literature yet [5] we observed this positive effect in the fellow eye in monocular injected cases as well. To investigate and verify this clinical observation, we designed this study.

Materials and Methods

At the initiation of the study all parents signed a detailed informed consent prepared according to the Declaration of Helsinki and approved by the local ethical committee of Cerrahpasa School of Medicine. In a clinical practice setting designed as prospective interventional case series study infants having bilateral type-1(high risk) prethreshold ROP had one eye randomized to intravitreal bevacizumab (IVB) therapy and fellow eyes left untreated if having one of type-1 pre-threshold ROP either "zone-II stage 2 with plus" or "zone-I stage 3 without plus" without any masking procedure. If both eyes have these pre-threshold types arbitrarily better eyes left untreated. Sixty eyes (30 treated 30 untreated) of 30 premature babies, 13 male 17 females, with a mean gestational age (GA) of 28,1 ± 1.69 (25 to 31) weeks and a mean birth weight (BW) of 1010.33 ± 231,03 (520 to 1530) grams were included.

Severity of ROP disease were as 22 "Zone-II Stage 2 with plus", 8 "zone-I stage 3 without plus" in total 30 untreated eyes and 15 "Zone II stage 2 with plus", "7 zone II stage 3 with plus", 8 "zone-I stage 3 with plus" in 30 treated eyes respectively.

Clinical course of the fellow eyes was first evaluated at the first post-injection week and depending upon the examination findings they were categorized as better, worse or the same in comparison to the day of monocular injection. Regression in plus and/or stage and any increase in the normal vascularized retinal area were evaluated as "better" signs but new onset or increase in plus and/or stage were evaluated as the signs to classify the eyes as "worse" and no change in plus and/or stage meant to classify the eyes in "the same" category.

Depending upon each examination findings follow up examination was continued with 1 to 6 week intervals till complete retinal vascularization occurred clinically, determined by binocular indirect ophthalmoscopy (BINO). Fellow eyes got injected if worsened as either stage 2 increased to stage 3 or stage 3 w/o plus gained plus, during the follow up period.All patients were followed up for a mean 29,73 ± 3,23 (24 to 36) months.

Intravitreal bevacizumab injection procedure (Dr. Hüseyin Yetik's Injection Technique): After the eyes prepared with 5 % povidone–iodine in a standard fashion, the surgeon wears binocular indirect ophthalmoscope and turns the light on and looking through the oculars of the BINO and visualizing the tip of the needle through the dilated pupil under binocular indirect ophthalmoscopic illumination, using a 30-G needle, 0.625 mg (0.025 ml) bevacizumab (Altuzan 100 mg/4 ml flacon, Roche, Turkey) was injected into the vitreous cavity approximately 1 mm behind the limbus via pars plicata under topical anesthesia. An experienced nurse helped to secure the infant during the procedure. All injections were performed by the same surgeon (Dr. H.Y). After the injections, retinal artery patency was checked. Topical steroid and antibiotic mixture drugs were administered for 5 days [5].

Results

In the first post-injection week, none of the untreated eyes was found to be worsened (0/30;0%) but 19 were in better (19/30;63,3%) and 11 were in the same (11/30;36,7%) category (Figure 1).All the 19 of the first post injection week better and 3 of the same category untreated eyes were "Zone II stage 2 with plus" and the rest 8 of the same category were "zone-I stage 3 without plus" preoperatively (Figure 1).

During the follow up period, in a mean of 2,77 ± 0,83 (2 to 4) weeks after the monocular injection, 13 of untreated 30 fellow eyes (43,3%) were injected as well; 8 over 13 injected fellow eyes were the 8 over 11 (72,7%) of the same category and 5 over 13 were the 5 over 19 (26,3%) of the better category of the first post injection week examination. Of Untreated 30 eyes, 5/22 (22,72 %) "Zone II, Stage 2+" and 8/8 (100%) "zone-I stage 3 without plus" were injected during follow up period (Figure 1).

Figure 1. Intravitreal Anti-VEGF Injections Appear Safe with Regard to RNFL Thickness

Finally, infants who got monocular injection first and fellow eye injection when worsened were found to have bilateral IVB treatment rate as 43,3% (13 over 30 infants). At the end of the follow up period all 60 eyes studied were found to have a normal retinal maturation determined by BINO in a mean 21.63 ± 7,29 (12 to 38) weeks of duration (Figure 1). Neither first nor fellow eyes needed re-injection or additional laser and none found to have late reactivation till the end of the follow up period.

Discussion

It is well known that after intravitreal injection, bevacizumab can be detected in serum within 1 day, and serum VEGF levels are suppressed for at least 8 to 12 weeks [6].

Despite the fact that effects of lowering systemic VEGF levels on the developing organ systems of premature infants are unknown, and there are limited long-term data on potential systemic and neurodevelopmental effects after anti-VEGF use for ROP treatment, in our experience we observe positive effects on the systemic course of the premature infants without exception (5). We have already demonstrated and published these relieving effects particularly on the clinical course of bronchopulmonary dysplasia (BPD) [6]. Furthermore, we claim that all main morbidities of a premature infant can be explained by a single vasculogenesis hypothesis and our observation of relieving effects on the systemic course cannot be explained by chance as we have already published [4].

Besides this a new experimental study on the new born rabbits did not reveal any significant functional or histological changes in major organs and neurons in the central nervous system (CNS) as well as in complete blood count, biochemistry and several other measurable vital parameters after either one or two IVB injections (0.625 mg) [7]. On the other hand, since anti-VEGF agents can be observed in bloodstream after intravitreal injection an expectation of a more or less far effect on the fellow eye after monocular injection is not unreasonable and we observe this clinically in practice. This study was designed to research this expectation and clinical observation scientifically.

To simplify the evaluation of the far effects on the fellow eyes first we aimed to categorize the fellow eyes as “better”, “worse” or “the same” at the end of the first week after the monocular injection and none of the untreated fellow eyes was found to be worsened (0/30; 0%) and 19 were in better (19/30;63,3%) and 11 were in the same (11/30;36,7%) category. This first week effect, particularly non-worsening of any eyes was evaluated as the first clue of systemic or far effect of monocular injection. It should be kept in mind that for a progressing disease like ROP particularly with a treatment indication, after one week without treatment if it is not worse then it should be better and this non-worsening should be attributed to the far effect of monocular injection. Therefore, assessment at the first week even qualitatively demonstrated an early relieving effect on all untreated eyes without exception.

On the other hand, all the 19 of the first post injection week better and 3 of the same category untreated eyes were “Zone II stage 2 with plus” and the rest 8 of the same category were “zone-I stage 3 without plus” preoperatively. This finding was also consistent with the possible far effects of monocular injection because the eyes with less degree of severity of ROP i.e. “Zone II stage 2 with plus” were found to be more responsive in comparison to the eyes with higher degree of severity i.e. “zone-I stage 3” to monocular IVB injection.

Further supporting this determination although in a mean of 2,77 ± 0,83 (2 to 4) weeks after the monocular injection, 13 of the untreated 30 fellow eyes (43,3%) were injected; 8 over 13 were the 8 over 11 (72,7%) of the same category and 5 over 13 were the 5 over 19 (26,3%) of the better category. Besides this when it comes to pre-injection status of the fellow eyes, 5 over 22 (22,72 %) “Zone II, Stage 2+” and 8 over 8 (100%) “Zone I, stage 3 without plus” eyes needed injection during follow up period. These results altogether mean that after monocular IVB treatment for the untreated fellow eyes becoming better or non-worsening at the end of the week does not guarantee a non-injection throughout the follow up period but for the eyes with “Zone II, stage 2 without plus” almost 77% of the cases will not need any further treatment and for the eyes with “Zone-I, stage 3 without plus” almost all will need an injection in next 2 to 4 weeks.

Although we experience and claim that anti-VEGF treatment makes the infant to go in better in short and long term systemically as well we also agree that anti-VEGF agents should be used judiciously and with awareness of the known and unknown or potential side effects. Because of the risk benefit debate and indispensable usefulness of the treatment nowadays in the literature low-dose even ultra-low-dose intravitreal bevacizumab studies started be seen [8,9].In ultra-low-dose study 0,16mg IVB alone applied to severe posterior ROP cases was reported to be successful (primary success where no additional treatment required) in 23/29 eyes (79.3%) (8). In low dose (0.25 mg) IVB study authors found no difference in the short-term clinical outcomes of stage 3+ ROP in zone I or II between the eyes with low dose and conventional dose of IVB [9]. In comparison to our study disease as being zon-I and –II posterior Stage 3+ severity of the cases in both low-dose and ultra-low-dose studies were more severe than our cases. Results of these studies also support our study results that even lower doses of bevacizumab seem to regress the disease successfully and we go one step forward and claim that if the disease severity is convenient normal dose monocular IVB injection may emerge a beneficial effect on the fellow eye as well. Furthermore, for selected suitable cases monocular IVB treatment can decrease the bilateral treatment rate of ROP

to 43,3% in comparison to 79% reported in ETROP (Early Treatment for ROP) Study [10].

At the end of the follow up period all 60 eyes studied were found to have a normal retinal maturation determined by BINO in a mean 21.63 ± 7,29 (12 to 38) weeks of duration and these results are concordant with our previously published results [5]. Neither first nor fellow eyes needed re-injection or additional laser and none found to have late reactivation till the end of follow up period of mean 29,73 ± 3,23 (24 to 36) months. We think this follow up period is enough to conclude this result. In summary results of this study set forth that for suitable cases monocular IVB treatment alone may be enough to induce disease regression in the untreated fellow eyes as well.

Conclusion

Monocular IVB injection was found to have a regressing effect on the clinical course of the untreated fellow eye and for selected cases firstly monocular IVB injection can decrease the bilateral treatment rate of ROP to 43,3% in comparison to 79% reported in ETROP (Early Treatment for ROP) Study.

Conflict of Interest

There is no conflict of interest for any author. Authors have no proprietary interest in any material described in the article

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