Eye (2021) 35:2451–2453
https://doi.org/10.1038/s41433-021-01543-9

The ROYAL COLLEGE of OPHTHALMOLOGISTS

COMMENT

The UK practice of Anti-VEGF therapy for treatment of retinopathy of prematurity

Shahanaz B. Ahmed[1] · Aisling Higham[1] · Alan Mulvihill[2,3] · T. K. J. Chan[2,3] · Gill Adams[4,5] · Chetan K. Patel[1,5,6]

Received: 10 February 2021 / Revised: 18 February 2021 / Accepted: 6 April 2021 / Published online: 20 April 2021

A British Ophthalmic Surveillance Unit study showed 8% of babies treated for retinopathy of prematurity (ROP) had off-label anti-vascular endothelial growth factor (VEGF) used as a first line treatment between 2013 and 2014 [1]. The evidence for anti-VEGF use, both Ranibizumab (Lucentis®, Novartis, Basel, Switzerland) and Bevacizumab (Avastin, Roche, Genentech, USA), is seen within the BEAT-ROP and RAINBOW studies [2, 3], but this is not yet reflected in the Royal College of Ophthalmology ROP treatment guidelines [4].

In adults there is consensus on the intravitreal injection (IVI) administration technique [5], but there is significantly less clarity in the neonatal setting. In the absence of any formal guidelines, we performed a UK wide survey of ROP clinicians to summarise the techniques used by experts nationally. We hope these responses can contribute to a summary of standard practice and identify areas where formal guidance is needed.

All members of the ROP special interest group (SIG), an established national database of ROP screeners, were sent a questionnaire in September 2019. 23 responses were received reporting IVI anti-VEGF therapy for the treatment of ROP in 14 units. No unit treated more than 16 eyes with anti-VEGF over a 12-month period, and 8 units (57%) treated <5 eyes in the same period. Anti-VEGF is used as monotherapy or in combination with laser, but 11/13 units (85%, one unit did not provide a response) used anti-VEGF as a primary therapy in less than a third of cases, whilst two units provided primary anti-VEGF therapy in over 80% of cases.

Two units (14%) regularly perform the procedure in theatre under general anaesthetic. Five units (36%) use topical anaesthesia alone and seven units (50%) use intravenous or oral sedation. 12/14 units (86%) perform IVI in the neonatal unit: either in a treatment room (five units), or in a bay (four units), or both (three units). An injection volume of 0.025 ml is administered by 11 units (79%), with the remaining three units delivering 0.01 ml, 0.02 ml or 0.05 ml. Nine units (64%) use half the adult drug dose, whereas the other units use between 1/8th and 1/4th. Ten units (71%) have a local protocol for the procedure.

Across the UK there were clear variations in the IVI technique itself. Regarding the site of injection, the distance behind the limbus ranged from 1 to 3 mm, with a mode of 1.5 mm (six units of 13 who provided this information, 46%). The quadrant injected, where specified, included nasal, inferior, medial, temporal or varied depending on ease of access. The direction of travel of the needle included parallel to the medial orbital wall and toward the optic disc. One participant specified the needle is advanced 3 mm into the vitreous cavity.

Additional variances in the IVI technique between neonates and adults include: fixation of the globe in primary position with forceps, a two-person technique with a second person pushing the plunger on the syringe once in position and guarding of the entry point with a sterile cotton bud on needle withdrawal. Two units specified having a member of the neonatal team present during the procedure. Immediately post-IVI six (43%) units reported checking intraocular pressure and/or performing indirect ophthalmoscopy to assess for central retinal artery perfusion, with the option of

✉ Shahanaz B. Ahmed
shahanaz.ahmed@nhs.net

1 Oxford Eye Hospital, John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

2 Royal Hospital for Children and Young People, NHS Lothian, Edinburgh, UK

3 The Princess Alexandra Eye Pavilion, NHS Lothian, Edinburgh, UK

4 Moorfields Eye Hospital NHS Foundation Trust, London, UK

5 Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

6 University of Oxford, Oxford, UK

Table 1 The side effects and potential complications of intravitreal anti-VEGF therapy that are discussed during the consent process for the treatment of retinopathy of prematurity.

Risk of treatment	No. of units including in consent	%. of units including in consent
Local risk		
Need for further treatment	14	100
Endophthalmitis	14	100
Loss of vision	13	93
Cataract	13	93
Haemorrhage	12	86
Retinal detachment	10	71
Ocular hypertension	5	36
Subconjunctival haemorrhage	4	29
Uveitis	1	7
Corneal opacity	0	0
Systemic risk		
Adverse neurodevelopmental outcome	11	79
Adverse effects on lung development/function	6	43
Stroke	3	21
Systemic side effects not known/uncertain	2	14
Myocardial dysfunction	1	7

anterior chamber paracentesis if required. One unit routinely performs ocular massage post-procedure.

Regarding post-IVI management, 12 units (86%) prescribe post-operative topical antibiotics. The first review post-op ranged from next day (8 units, 57%) to 1-week post-procedure (4 units, 29%). Half of the units had a guideline for monitoring and/or management of endophthalmitis. Complications were rare, with one report of vitreous haemorrhage and one case of corneal clouding.

Consent is an important aspect of the treatment process, especially as the evidence base for anti-VEGF IVI in neonates is not as robust as in adults. Generally, the ophthalmic complications discussed for neonatal anti-VEGF mirrored those typically discussed with adults. There is some variability in the discussion of possible systemic side effects, however 11 units (79%) consent for adverse neurodevelopmental outcome (Table 1).

Conclusion

This survey demonstrates that there is significant variance in the specifics of neonatal anti-VEGF injection across the UK, although there are many similarities to the technique used in adults. Key factors are the anatomical differences between the two groups. The newborn pars plana is underdeveloped and in term babies around 1.7 mm. Also the lens takes up a relatively larger volume within the globe with a transverse diameter of 6.5 mm and antero-posterior diameter of 3 mm in the newborn [6, 7]. This necessitates a more posterior angulation of the needle to avoid lens touch. An iatrogenic cataract in this group often necessitates challenging surgical intervention, which increases the risk of further sight-threatening complications including aphakic glaucoma [8]. Despite a smaller globe, Obata et al., 2019 suggest that IOP does not necessarily need checking after IVI in neonates when a volume of 0.025 ml is administered [9]. The dose of anti-VEGF needs to balance the risks of potential systemic side effects, (which are not fully understood), to the intraocular benefit [10–12]. There remains uncertainty in how exactly to adapt the adult IVI technique for neonates. It is worth noting that the pre-filled Lucentis syringes allow a dose of 0.02 ml containing 0.02 mg ranibizumab to be delivered without reconstitution of the drug.

Neonatal IVI procedures are still performed infrequently, therefore there is limited data on complications and their management. We are aware of four reported cases of endophthalmitis [13–16]. Although the use of povidone-iodine, masks and a speculum reduce the risk of endophthalmitis [17, 18], the routine use of post-operative antibiotics is less clear. In adults the literature suggests no benefit and possibly increased risk of endophthalmitis with prophylactic antibiotics [19]. Moorfields found huge variability in the treatment of paediatric exogenous endophthalmitis within cases treated at the hospital over a 7 year period [20], and have subsequently developed a protocol for paediatric endophthalmitis with covers management in neonates [21].

Given the lack of consensus demonstrated in this survey, we recommend a need for formal guidelines to standardise practice and provide a framework for clinical audit to help improve outcomes.

Acknowledgements We thank all units who kindly completed the survey.

Author contributions SA: concept, drafting of the survey, data analysis, drafting of the paper. AH: data analysis, drafting of the paper. AM, TJKC and GA: review of the survey and paper. CKP: concept, review of the survey and paper. All authors read and approved the final paper.

Funding The authors received no specific funding for this work.

Compliance with ethical standards

Conflict of interest The authors have the following non-financial competing interests to disclose: Miss GA is chair of the Royal College of Ophthalmologists guideline development group on the treatment of

ROP and co-chair of the Royal College of Paediatrics and Child Health guideline group on ROP screening. Mr CKP is a member of the Royal College of Ophthalmologists guideline development group on the treatment of ROP.

References

1. Adams GGW, Bunce C, Xing W, Butler L, Long V, Reddy A, et al. Treatment trends for retinopathy of prematurity in the UK: active surveillance study of infants at risk. BMJ Open. 2017;7: e013366.
2. Mintz-Hittner HA. Retinopathy of Prematurity: intravitreal injections of bevacizumab: timing, technique, and outcomes. J AAPOS. 2016;20:478–80.
3. Stahl A, Lepore D, Fielder A, Fleck B, Reynolds JD, Chiang MF, et al. Ranibizumab versus laser therapy for the treatment of very low birthweight infants with retinopathy of prematurity (RAINBOW): an open-label randomised controlled trial. Lancet. 2019;394:1551–9.
4. Royal College of Ophthalmologists. UK Retinopathy of Prematurity Guideline. 2008. https://www.rcophth.ac.uk/wp-content/uploads/2014/12/2008-SCI-021-Guidelines-Retinopathy-of-Prematurity.pdf.
5. Royal College of Ophthalmologists. Intravitreal Injection Therapy. 2018. https://www.rcophth.ac.uk/wp-content/uploads/2018/02/Intravitreal-Injection-Therapy-August-2018-2.pdf [Accessed 3 February, 2021].
6. Gan NY, Lam W-C. Special considerations for pediatric vitreoretinal surgery. Taiwan J Ophthalmol. 2018;8:237–42.
7. Hairston RJ, Maguire AM, Vitale S, Green WR. Morphometric analysis of pars plana development in humans. Retina. 1997;17: 135–8.
8. Solebo AL, Rahi JS, British Congenital Cataract Interest Group. Glaucoma following cataract surgery in the first 2 years of life: frequency, risk factors and outcomes from IoLunder2. Br J Ophthalmol. 2020;104:967–73.
9. Obata S, Higashiyama T, Imamura T, Kakinoki M, Yanagi T, Maruo Y, et al. Short-Term Changes in Intraocular Pressure After Intravitreal Injection of Bevacizumab for the Treatment of Retinopathy of Prematurity. Clin Ophthalmol. 2019;13:2445–9.
10. Kaushal M, Razak A, Patel W, Pullattayil AK, Kaushal A. Neurodevelopmental outcomes following bevacizumab treatment for retinopathy of prematurity: a systematic review and meta-analysis. J Perinatol. 2020. https://doi.org/10.1038/s41372-020-00884-9 [Accessed 30 January 2021].
11. Tsai C-Y, Yeh P-T, Tsao P-N, Chung Y-CE, Chang Y-S, Lai T-T. Neurodevelopmental Outcomes after Bevacizumab Treatment for Retinopathy of Prematurity: a Meta-analysis. Ophthalmology. 2020. https://doi.org/10.1016/j.ophtha.2020.11.012 [Accessed 30 January 2021].
12. Sankar MJ, Sankar J, Chandra P. Anti-vascular endothelial growth factor (VEGF) drugs for treatment of retinopathy of prematurity. Cochrane Database Syst Rev. 2018;1:CD009734.
13. Wang J, Xiang D. Early clinical characteristics of bacterial endophthalmitis in retinopathy of prematurity after intravitreal bevacizumab injection: a case report. Exp Ther Med. 2017;13: 3563–6.
14. Chandra P, Kumawat D, Tewari R, Azimeera S. Post-Ranibizumab injection endophthalmitis in aggressive posterior retinopathy of prematurity. Indian J Ophthalmol. 2019;67:967–9.
15. So JM, Richards AB. Bilateral endophthalmitis from bevacizumab intravitreal injections in type I retinopathy of prematurity. J Am Assoc Pediatr Ophthalmol Strabismus {JAAPOS}. 2019;23:e55.
16. Suren E, Cetinkaya E, Kalayci M, Özkan SEÖ, Kucuk MF, Erol MK. Endophthalmitis in Retinopathy of Prematurity after Intravitreal Aflibercept Injection. Case Rep Ophthalmol Med. 2020;2020:8861435.
17. Friedman DA, Mason JO, Emond T, McGwin G. Povidone-iodine contact time and lid speculum use during intravitreal injection. Retina. 2013;33:975–81.
18. Doshi RR, Leng T, Fung AE. Reducing oral flora contamination of intravitreal injections with face mask or silence. Retina. 2012;32:473–6.
19. Bande MF, Mansilla R, Pata MP, Fernández M, Blanco-Teijeiro MJ, Piñeiro A, et al. Intravitreal injections of anti-VEGF agents and antibiotic prophylaxis for endophthalmitis: a systematic review and meta-analysis. Sci Rep. 2017;7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5741717/ [Accessed January 17, 2021].
20. Parvizi S, Papadopoulos M, Panteli V, Brookes J, Soothill J, Bloom J, et al. Paediatric endophthalmitis: a UK retrospective study. Eye (Lond). 2020;34:553–61.
21. Moorfields Eye Hospital NHS Foundation Trust. Paediatric Endophthalmitis. 2019. https://viewer.microguide.global/MOOR/EMGUIDE#content,c384ec91-e564-403f-af0d-2e49110effbb [Accessed 3 February, 2021].