

Continuing Medical Education:

Monitoring propranolol treatment in periocular infantile haemangioma

R Burne¹ and R Taylor²

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Learning objectives

Upon completion of this activity, participants will be able to:

1. Describe the clinical features of periocular infantile haemangioma.
2. Discuss a new tool that will determine the amblyopic risk and monitor treatment effects in the management of periocular haemangioma.
3. Assess the effects of propranolol in the treatment of periocular haemangioma, based on a case series.

Authors/Editors disclosure information

Andrew J Lotery has disclosed the following relevant financial relationships: Served as an advisor or consultant for: Allergan, Bayer, and Novartis. Served as a speaker or a member of a speakers bureau for: Novartis. Received grants for clinical research from: Novartis.

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Monitoring propranolol treatment in periocular infantile haemangioma

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Abstract

Objective To develop a tool for assessing amblyopic risk and monitoring the treatment effect of propranolol in periocular haemangioma management.

Methods We present a study of nine children with periocular haemangioma who underwent propranolol treatment at York Hospital between 2009 and 2013.

A proposed measure of amblyogenic risk based on the induced anisometropia resulting from a periocular haemangioma was calculated in the form of a single quantitative value, measured in dioptres. This calculation used published work and developed it to produce a new function, termed the delta defocus equivalent (DFE- Δ). Refraction measurements were retrospectively collected from patients' notes in order to measure the trend of DFE- Δ over the treatment period with propranolol.

Results The average DFE- Δ at commencement of propranolol was 1.54 (\pm 0.62) D. The average at the end of treatment was 0.39 (\pm 0.38) D.

Conclusion This work presents a possible tool for assessing amblyopic risk in cases of periocular infantile haemangioma. The DFE- Δ gives a measure in dioptres, which may represent the true amblyopic risk, and so be useful in supporting treatment decisions in paediatric ophthalmology.

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Introduction

Haemangiomas of infancy are common benign lesions occurring in up to 10% of children in their first year.¹ When occurring periocularly, and left untreated, their visual sequelae are common.¹ Amblyopia is the primary concern because of stimulus deprivation, induced anisometropia (mainly oblique astigmatism), secondary strabismus, or globe displacement.²

In 2008, Léauté-Labrèze *et al*³ reported a serendipitous discovery in the treatment of capillary haemangioma with propranolol. Propranolol has since been increasingly adopted as a first-line treatment for haemangioma⁴ and, while uncertainty of ideal dosage and treatment regimens still remains, 2 mg/kg/day split in three daily doses, is a frequently used regime.⁴ There is no consensus in the literature on the optimum time to start or stop propranolol therapy.

In this paper, we develop an approach using two formulae to calculate the amblyogenic risk.

Materials and methods

This is a retrospective clinical study of the first nine children who underwent propranolol treatment in our institution between 2009 and 2013 for periocular haemangioma.

Patients were started on 2 mg/kg/day propranolol by the paediatric team as per a local protocol. The cycloplegic refraction of both eyes was measured periodically. The initiation of treatment is based on the perceived risk of amblyopia from anisometropia, rather than observed difference in visual acuity.

To calculate an amblyogenic risk, the difference between the two refractions (from each eye) is calculated and expressed as a third theoretical refraction, using the Retzlaff formula.⁵ This is done by taking vector components of the cylinders in both the horizontal and vertical planes and comparing them. The formula accounts for the spherical equivalent, astigmatic power, and axis. It therefore will account for hypermetropic and myopic refractions, as well as positive and negative cylinder format. A calculation is then applied to this product, as described by Holladay *et al*⁶ to produce a single dioptre value, which Holladay termed the delta defocus equivalent (DFE), which might represent the amblyopic risk (as the DFE is proportional to the reduced visual acuity induced by that refraction⁶). Where the normal eye had an

¹Hull York Medical School, Heslington, York, UK

²Ophthalmology Department, York Hospital, York, UK

Correspondence: R Taylor, c/o R Burne, Ophthalmology Department, York Hospital, Wigginton Road, York, North Yorkshire YO31 8HE, UK
Tel: +44 07739 464022; Fax: +44 01904 726343. E-mail: richard.burne@doctors.org.uk

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oblique refraction opposite to the affected eye, this was reflected about the 90° axis before being incorporated in the equation. As this is applied to the difference between the two refractions, we have termed this DFE- δ . A Microsoft Excel (Microsoft, Redmond, WA, USA) spreadsheet was used to implement DFE- δ calculation.⁷

The following information was subsequently extracted from the patient files: lesion location, lesion type—superficial (lid) or deep (orbit), visual axis occlusion, age at initiation and termination of treatment, refractions, and visual acuity measured when treatment was discontinued (termed end visual acuity).

Results

Nine cases of periocular capillary haemangioma were treated in this study. None of the children had occlusion

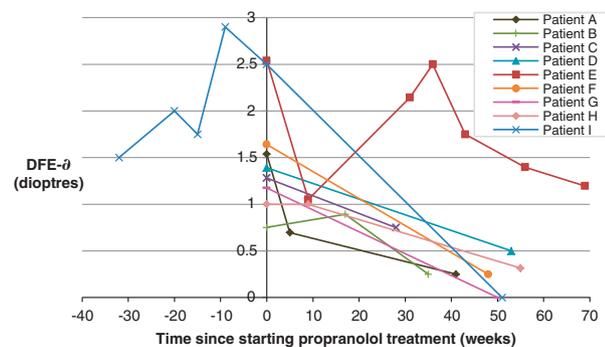


Figure 1 Change in DFE- δ with respect to time for all the nine patients.

of the visual axis. The average DFE- δ at commencement of propranolol was 1.54 (± 0.62) D. The average at the end of treatment was 0.39 (± 0.38) D (Table 1).

Figure 1 shows the DFE- δ over the period of treatment for all the nine participants. It also demonstrates the DFE- δ trend in patient I prior to initiating propranolol treatment.

Of note is the DFE- δ rise corresponding to rebound haemangioma growth in patient E whose propranolol treatment was stopped prematurely. Patient E's initial response to propranolol is represented by a drop from 2.54 to 1.06 after 9 weeks of treatment. After 20 weeks, the propranolol was tapered down as his mother had concerns that the treatment was contributing to breath-holding attacks. Refraction measurements were not taken at 20 weeks; however, the DFE- δ calculations at 31 weeks (2.14 D) and 36 weeks (2.5 D) correlate to the clinically observed re-bound growth. At 36 weeks, 2 mg/kg/day propranolol was re-started and the DFE- δ began to fall once more ending at 1.20 D.

Discussion

This work demonstrates a useful application of the Retzlaff formula and DFE as a tool for assessing amblyopic risk and monitoring treatment effect in infantile haemangioma management.

Measurement of the treatment effect from propranolol varies widely in the literature. Qualitative approaches have included the use of visual analogue scales to assess the lesion with respect to its colour, size and growth.⁸

Table 1 Table showing data extracted from patient files. Patients ordered based on the age they started propranolol treatment from youngest to oldest

Patient	Sex	Lesion Location	Start age (weeks)	End age (weeks)	Total weeks treatment	Start refractions — Right eye — Left eye	End refractions — Right eye — Left eye	Cylinder power difference at start	Start DFE- δ (dioptres)	End DFE- δ (dioptres)	End Visual Acuity	Method for acuity measurement at end
A	M	Right orbit	8	36	28	+1.25/ +2.00 \times 45	+1.00 DS	1.00	1.54	0.25	6/6	Kay's
B	M	Left orbit	9	47	38	+1.25/ +1.00 \times 85	+1.25 DS	0.25	0.75	0.25	6/6	CC
C	F	Left lid	11	43	32	+1.25/ +2.25 \times 90	+0.50/ +0.75 \times 90	1.00	1.28	0.75	NR	CC
D	F	Right orbit	12	66	54	+0.25/ +3.00 \times 90	+1.50	2.00	1.39	0.50	6/9.5	CC
E ^a	M	Right orbit	15	69	54	+0.25/ +4.00 \times 100	+0.75/ +1.00 \times 90	3.00	2.54	1.20	6/12	CC
F	F	Right orbit + Lid	22	70	48	-1.25/ +4.00 \times 105	+0.50/ +1.50 \times 120	0.50	1.64	0.25	6/12	CC
G	F	Cheek lesion encroaching right orbit	30	74	44	+1.25/ +1.00 \times 95	+0.75/ +0.25 \times 180	1.50	1.18	0	6/6	SSG
H	F	Left lid	34	83	49	-2.00/ +3.00 \times 120	+0.75/ +1.25 \times 180	1.00	1.00	0.32	6/6	CC
I	M	Right orbit	50	73	23	-2.00/ +2.50 \times 90	+0.75/ +1.00 \times 180	1.75	2.50	0	6/6	SSG
		Mean (SD)	21.2 \pm 14.2	62.3 \pm 16.2	41.1 \pm 11.4	+0.50/ +1.00 \times 90	+1.75 DS		1.54 \pm 0.62	0.39 \pm 0.38	6/6	

Abbreviations: BEO, both eyes open; CC, Cardiff cards; Kay, Kay pictures; NR, not recorded; SSG, Sheridan Gardner Singles.

^aPropranolol treatment stopped and re-started (see results).

Imaging with ultrasound, MRI⁹, and photographic surface area measurement¹⁰ have also been used. Ophthalmic quantitative measurements have mainly focused on calculating an amblyogenic astigmatic error from the difference in cylinder power between the affected and unaffected eyes.^{10–12} Where cylinder axis and spherical equivalent are similar, the proposed formula for calculating the amblyogenic risk will have little advantage. However, this will ignore oblique axes induced by the haemangioma (eg patients A, B, and F) as well as over playing the cylinder power significance if the spherical equivalent is similar (eg patient D). We suggest a DFE- $\hat{\delta}$ calculation ultimately will be more accurate as all components of the refraction are included; however, we accept cylinder power alone will act as a guide. Larger studies will be needed to compare the two.

The decision to begin propranolol treatment was always made clinically; however, our results suggest a DFE- $\hat{\delta}$ of 1.5D could be an appropriate guide, particularly if it is increasing over time, in support of the treatment decision.

This clinical study also adds to the increasing body of evidence⁴ in support of propranolol as a first-line treatment for periocular haemangioma.

Summary

What was known before

- Propranolol treatment in periocular infantile haemangioma has produced good results in relation to reducing visual sequela.
- International consensus regarding an appropriate dose of propranolol for use in treatment is becoming clearer.
- There is neither a consensus on when to start or stop treatment for periocular haemangioma nor on the best way to monitor its treatment effect.

What this study adds

- We have developed a method to calculate a value, in dioptres, which may be proportional to the amblyogenic risk from a haemangioma.
- We demonstrate its use in a case study of nine patients.
- We propose that it can be used to assist in treatment decisions in periocular haemangioma treatment.

Conflict of interest

The authors declare no conflict of interest.

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- Your patient is an 8-month-old boy thought to have periocular haemangioma. According to the case series by Burne and Taylor, which of the following statements about the clinical features of infantile haemangioma is **correct**?
 - Haemangiomas of infancy are usually malignant.
 - Haemangiomas of infancy occur in less than 1% of children younger than 1 year.
 - Visual complications of untreated periocular haemangioma are rare.
 - Amblyopia is the main risk associated with periocular haemangioma because of stimulus deprivation, induced anisometropia (mainly oblique astigmatism), secondary strabismus, or globe displacement.
- According to the case series by Burne and Taylor, which of the following statements about a new tool (delta defocus equivalent [DFE- δ]) to determine amblyopic risk in the management of periocular haemangioma is **correct**?
 - To calculate amblyogenic risk, the investigators used refraction measurements only from the affected eye.
 - DFE- δ is based on the induced anisometropia resulting from a periocular haemangioma and is calculated in the form of a single quantitative value, measured in dioptres.
 - The formula used accounts for the spherical equivalent, but not for astigmatic power or axis.
 - The formula used accounts for hypermetropic, but not myopic, refractions.

- According to the case series by Burne and Taylor, which of the following statements about the effects of propranolol in treatment of periocular haemangioma would **most likely** be correct?
 - Propranolol is used only as second-line treatment of haemangioma.
 - The ideal dosage regimen is 1 mg/kg/day, split into two daily doses.
 - The average DFE- δ at initiation of propranolol was 1.54 (± 0.62)D, and the average at treatment completion was 0.39 (± 0.38)D.
 - There was no evidence of rebound haemangioma growth when propranolol treatment was stopped prematurely.

Activity evaluation

1. The activity supported the learning objectives.				
Strongly disagree				Strongly agree
1	2	3	4	5
2. The material was organized clearly for learning to occur.				
Strongly disagree				Strongly agree
1	2	3	4	5
3. The content learned from this activity will impact my practice.				
Strongly disagree				Strongly agree
1	2	3	4	5
4. The activity was presented objectively and free of commercial bias.				
Strongly disagree				Strongly agree
1	2	3	4	5