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Research Article

Effect of Refractive Error and Anisometropia Magnitude on Amblyopia Treatment Outcome

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Abstract

The association between amblyopia depth and amount of anisometropia remains controversial. Deeper amblyopia is generally associated with a larger magnitude of anisometropia; however, there are also many observed cases of deep amblyopia despite small amounts of anisometropia. The current standard of care in amblyopia treatment is based primarily on past research conducted on hyperopic participants. Our retrospective study reviewed the visual outcomes for forty eligible patients, ages 3-18 years old, with anisometropic amblyopia that were categorized into hyperopic, myopic, and astigmatic refractive groups. Analysis of variance comparatively analyzed the baseline and final acuity achieved by the three refractive groups. All patients responded to treatment with a group mean (\pm SD) inter ocular acuity improvement of 0.28 ± 0.20 log MAR. There was no statistical significance in amount of improvement achieved among the three groups. Final inter ocular acuity difference was strongly correlated to baseline inter ocular acuity difference ($p < 0.0001$, $r = 0.79$). Amblyopia depth was correlated with magnitude of anisometropia in the hyperopia group ($P = 0.02$, $r = 0.51$), but not the myopic group ($P = 0.27$, $r = 0.32$). The implication of differing refractive etiology in amblyogenesis is a topic that requires further study. Still our results provide evidence that therapeutic treatment should be provided for all anisometropic amblyopes since all groups, regardless of refractive nature, were able to achieve comparable visual outcomes.

Keywords

- Amblyopia
- Anisometropia
- Anisometropic amblyopia
- Refractive error
- Visual acuity

ABBREVIATIONS

VA: Visual Acuity; BVA: Baseline Visual Acuity; FVA: Final Visual Acuity; AA: Anisometropic Amblyopia; IODVA: Inter Ocular Difference in distance Visual Acuity; ANOVA: Analysis of Variance

INTRODUCTION

Amblyopia is a leading cause of monocular vision loss in childhood [1]. Uncorrected inter ocular difference or anisometropia as little as 1.00D can result in unequal cortical

input and give rise to subsequent vision deficits. The competitive advantage that the sound eye establishes over the input from the amblyopic eye disrupts the development of normal binocular vision.

Potential amblyogenic refractive errors include anisometropia greater than: 1.50D for astigmatism, 1.00D for hyperopia, and 3.00D for myopia [2]. However, some studies have demonstrated interocular thresholds as low as 1.00D astigmatism and 2.00D myopia for amblyopia to develop [3]. Anisometropia is present in 1-11% of the general children population [4-6]. However, not all these cases progress to amblyopia. A longitudinal study following 310 preschool children found that only approximately 25% of those with persistent anisometropia developed amblyopia and that over half of the children who presented with anisometropia at one year of age no longer presented with it at four years of age [1].

Prognosis for amblyopia is commonly thought to be somewhat related to the magnitude of anisometropia present. Many studies have demonstrated the success in treating anisometropia amblyopia (AA) with lower amounts of hyperopic interocular difference [7-9]. Less improvements are noted in the treatment of those with moderate and severe hyperopic amblyopia as well as those with myopia AA [9,10]. Conversely, several studies have failed to find an association between the amount of anisometropia and the depth of amblyopia [3,11]. Much of the previous amblyopia research has been subjected to a selection bias for hyperopic AA. Visual outcome comparisons between different refractive error types have been explored by few studies [8,9,11]. These studies imply a correlation between the depth of amblyopia and the absolute amount of anisometropia. The purpose of this study was to evaluate long-term outcomes in visual acuity (VA) for anisometropic amblyopia in consideration of magnitude of anisometropia and refractive error type.

MATERIAL AND METHODS

Our retrospective chart review was conducted by querying all patient charts with a diagnosis of amblyopia from 1995 to 2007 seen at the Illinois Eye Institute, an urban ambulatory eye care clinic. The study protocol was approved by the institutional review board of the Illinois College of Optometry. A total of 725 charts were reviewed and 40 patients qualified for this study. The eligibility and exclusion criteria for our subjects are listed on (Table 1). The eligibility and exclusion criteria are listed on (Table 1).

Best corrected visual acuity from three visits (the baseline visual acuity, or BVA, from the initial eye exam, the first follow-up after initial spectacle correction and adaptation, and the final visit upon completion of the treatment) were collected. Additional information gathered included: the patient's age, gender, and race, ocular alignment as indicated by cover test, Randot stereoacuity, cycloplegic refraction, spectacle prescription, amblyopia treatment, and final VA (FVA) at the end of amblyopia treatment. VA was measured with Snellen chart or Lea symbols and calculated into log MAR.

The amount of anisometropia was calculated from the absolute value of interocular difference between the spherical equivalence of the patient's cycloplegic refraction of both

Table 1: Eligibility and Exclusion Criteria for Anisometropic Amblyopic Children.

Eligibility criteria included:
<ul style="list-style-type: none"> • Ages: 3 < 18 years • Inter-eye Acuity Difference > 1 line • Best corrected acuity of 20/30 or worse in the amblyopic eye. • Magnitude of anisometropia: ≥ 1.50D of hyperopia or astigmatism, ≥ 3.00D of myopia • No previous refractive correction or amblyopia treatment • Completed amblyopia treatment: improved visual acuity remained within 1 line of difference over three consecutive visits
Exclusion criteria:
<ul style="list-style-type: none"> • Presence of developmental delay, neurological or systemic disease • Non-compliance to treatment

eyes. Interocular difference in VA (IODVA) was calculated at both baseline and at the final visit. Treatment type (refractive correction either alone or with the addition of occlusion and/or vision therapy) and anisometropic refractive type (myopic, hyperopic, or astigmatic) were noted. The astigmatic AA group comprised of patients with refractions that were of mixed astigmatism with spherical equivalence ≤ 1.00 D. Baseline IODVA and IODVA improvements among the three groups were subjected to analysis of variance (ANOVA) and Bonferroni comparison post test. Correlations between baseline and final IODVA and in relation to anisometropia magnitude were established using linear regression. Data analysis was performed using Graft pad Prism version 5.00 for Windows (Graph Pad Software, La Jolla California USA, www.graphpad.com). Statistical significance was set at $P < 0.05$.

RESULTS AND DISCUSSION

Table 2 lists the baseline characteristics of 40 eligible subjects categorized into the three refractive groups: hyperopic, myopic, and astigmatic AA. The mean age of the subjects at the time of their first eye exam was 8.21 ± 3.32 years old with the median age of 7.7 years. No statistically significant differences were noted in BVA among the three groups after controlling for subject's age, sex, or race.

Baseline Characteristics

A strong direct correlation between BVA and IODVA ($P < 0.0001$, $r = 0.92$) as seen in (Figure 1); thus relationships involving either variable can be implied interchangeably. For the purpose of this manuscript, amblyopia acuity improvement will be referenced in terms of IODVA.

ANOVA showed differences in baseline IODVA amongst the groups ($F(2,37) = 4.84$, $p = 0.01$). Post-hoc tests indicated this significance existed only between the myopic and astigmatic group ($p < 0.05$). The depth of amblyopia was moderately correlated with the amount of anisometropia ($P = 0.02$, $r = 0.36$). The correlation reached significance for the hyperopia AA group ($P = 0.02$, $r = 0.51$) shown on (Figure 2a), but not the myopic group ($P = 0.27$, $r = 0.32$) shown on (Figure 2b). The astigmatic AA group had too few subjects for analysis.

Amblyopia Treatment Outcome

IODVA was reduced as treatment progressed seen in (Figure 3). Marked IODVA improvement was seen by the first follow-up

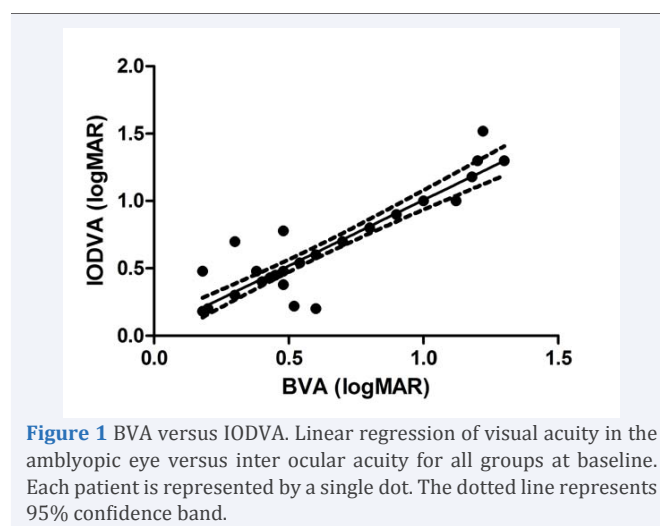
Table 2: Baseline Characteristics of the 40 Eligible Participants with Anisometropic Amblyopia.

	Myopic AA (n = 14)	Hyperopic AA (n = 22)	Astigmatic AA (n = 4)	Total (n = 40)
Sex, F	10 (71)	9 (41)	2 (50)	21 (53)
Age*				
3 to < 7	6 (42)	10 (45)	2 (50)	18 (45)
7 to < 11	4 (29)	8 (36)	2 (50)	14 (35)
≥ 11	4 (29)	4 (18)	0	8 (20)
Mean (year ± SD)	8.7 ± 3.30	8.1 ± 3.42	7.1 ± 3.35	8.21 ± 3.32
Median (year)	8.5	7.2	6.6	7.7
Race				
Caucasian	1 (7)	5 (23)	1 (25)	7 (18)
African American	11 (79)	12 (55)	1 (25)	24 (60)
Asian	1 (7)	3 (14)	1 (25)	5 (13)
Hispanic	1 (7)	2 (9)	1 (25)	4 (10)
Cause of Amblyopia				
Refractive Anisometropia	12 (86)	20 (91)	4 (100)	36 (90)
Anisometropia & Strabismus	2 (14)	2 (9)	0	4 (10)
Treatment Type				
OC	1 (7)	4 (18)	1 (25)	6 (15)
OCPT	3(21)	6 (27)	2 (50)	11 (28)
OCPTVT	10 (71)	12 (55)	1 (25)	23 (58)
Mean VA in Non-Amblyopic eye (log MAR± SD)	0.10 ± 0.16	0.07 ± 0.09	0.20 ± 0.18	0.09 ± 0.13
Mean VA in Amblyopic eye (log MAR± SD)	0.86 ± 0.33	0.57 ± 0.24	0.50 ± 0.09	0.67 ± 0.30
Mean Interocular VA Difference (log MAR± SD)	0.76 ± 0.38	0.50 ± 0.26	0.30 ± 0.10	0.57 ± 0.33
Refractive Error, Non-Amblyopic Eye				
0.00 to < 2.00D	10 (71)	16 (73)	4 (100)	30 (75)
2.00 to < 4.00D	2 (14)	3 (14)	0	5 (13)
4.00 to < 6.00D	0	3 (14)	0	3 (8)
6.00 to < 8.00D	2 (14)	0	0	2 (5)
≥ 8.00D	0	0	0	0
Mean (SE ± SD)	-2.54 ± 3.68	+1.63 ± 1.36	+0.06 ± 0.55	
Refractive Error, Amblyopic eye				
0.00 to < 2.00D	0	1 (5)	4 (100)	5 (13)
2.00 to < 4.00D	0	5 (23)	0	5 (13)
4.00 to < 6.00D	0	10 (46)	0	10 (25)
6.00 to < 8.00D	4 (29)	4 (18)	0	8 (20)
≥ 8.00D	10 (71)	2 (9)	0	12 (30)
Mean (SE± SD)	-10.8 ± 3.4	+5.01 ± 1.99	0.00 ± 0.89	
Mean Inter ocular SE Difference	8.27 ± 3.74	3.38 ± 1.74	0.44 ± 0.43	4.80 ± 3.70

*Age is the age of the child when he or she first presents to the clinic for their initial eye exam

Abbreviations: AA: Anisometropic Amblyopia; VA: Visual Acuity; OC: Optical Correction; OCPT: Optical Correction and Patching Therapy; OCPTVT: Optical Correction, Patching Therapy, and Vision Therapy; SE: Spherical Equivalence

after initial spectacle correction and continued to progress over time. (Figure 3b) shows the mean final IODVA improvement for myopic, hyperopic, and astigmatic groups achieving 0.32 ± 0.22 , 0.27 ± 0.20 , and 0.21 ± 0.17 log MAR, respectively. There was no statistical significance in amount of IODVA improvement among the three groups ($F(2,37) = 0.54$, $p = 0.59$). The mean IODVA improvement of 0.28 ± 0.20 log MAR corresponding to a mean VA improvement in the amblyopic eyes of 0.36 ± 0.19 log MAR among all groups. Out of the 40 subjects, 2, 7, and 3 subject from the myopic, hyperopic, and astigmatic group (a total of 30%), respectively, achieved a final IODVA of 0.10 logMAR (Snellen: 20/25) or better. There were 2 subjects, 1 each from the hyperopic group and myopic group, who had increases IODVA at the completion of treatment due to acuity changes in both eyes. No significant difference in IODVA improvement was found between younger subjects (< 7 years old) and older subjects (> 7 years old) in all three groups.



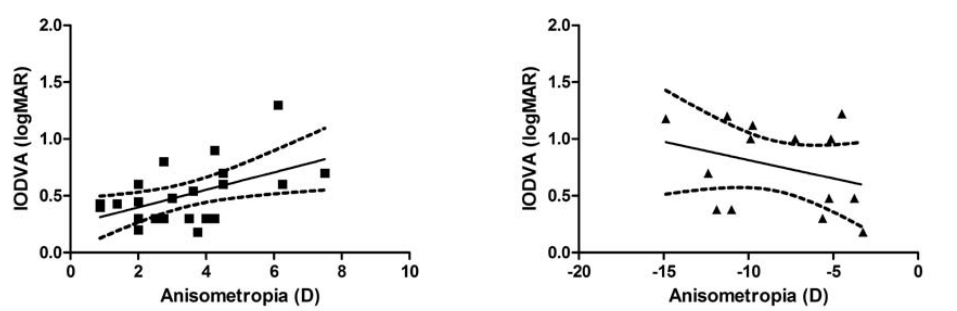


Figure 2 Baseline IODVA versus Anisometropia. Linear regression of interocular acuity versus amount of anisometropia in the hyperopic group (a) and the myopic group (b).

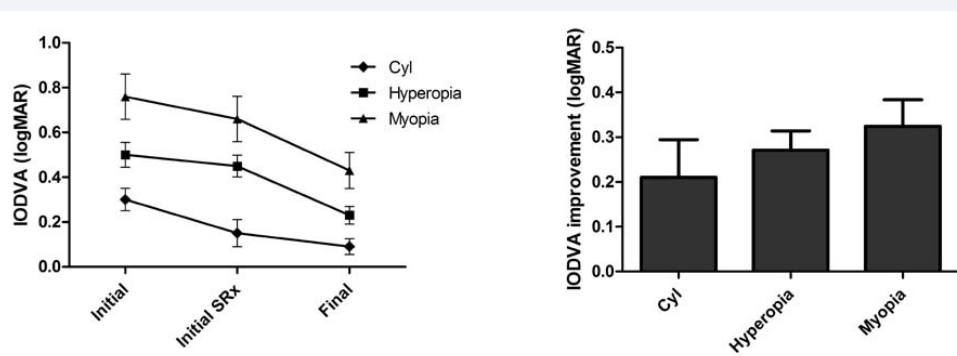


Figure 3 Treatment reduces IODVA. Inter ocular acuity improvement was seen by the first follow-up after initial spectacle adaptation in all three refractive groups (a). No statistically significance difference was seen in the amount of IODVA improvements among all three refractive groups (b).

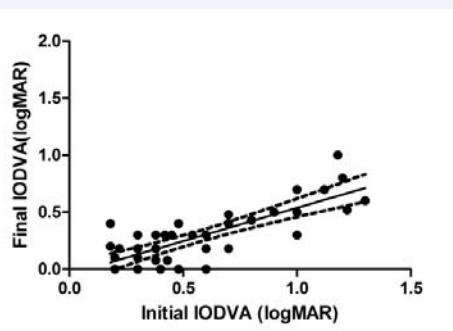


Figure 4 Baseline versus final IODVA. Linear regressions of baseline versus final inter ocular acuity in all refractive groups.

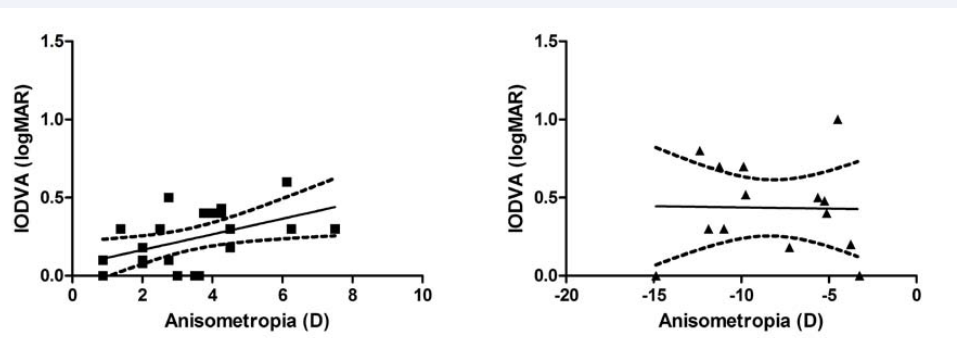


Figure 5 Final IODVA versus Amount of Anisometropia. Correlation between final IODVA and amount of anisometropia in the hyperopic group (a) and the myopic group (b).

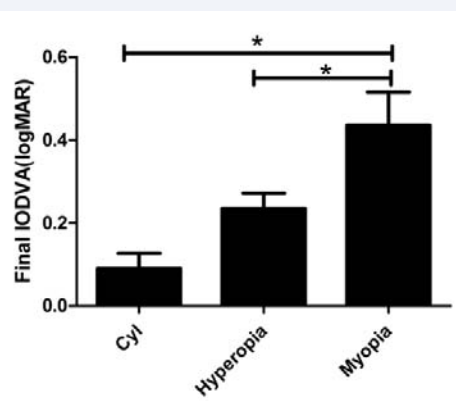


Figure 6 Final IODVA for all three refractive groups. Asterisks indicate a statistical significant difference ($p < 0.05$) between the refractive groups.

Figure 4 shows how final IODVA was strongly correlated to baseline IODVA ($p < 0.0001$, $r = 0.79$). A moderate correlation between final IODVA and the amount of anisometropia was significant for the hyperopic AA group ($p = 0.02$, $r = 0.49$) seen in Fig 5a, but not the myopic AA group ($p = 0.95$, $r = 0.025$) seen in (Figure 5b).

The final IODVA for the myopic, hyperopic, and astigmatic groups were 0.43 ± 0.30 , 0.23 ± 0.18 , and 0.09 ± 0.07 log MAR, respectively seen in (Figure 6). Post hoc multiple comparison test shows this difference was significant between the astigmatic and the myopic group ($p < 0.05$), and the hyperopic and myopic group ($p < 0.05$), but not between the astigmatic and hyperopic group ($p \geq 0.05$).

DISCUSSION

Acuity deficit from amblyopia can be described in two ways: either by inter ocular acuity difference or by the acuity of the amblyopic eye alone, the latter being the more traditional method found in literature. Few studies have noted the acuity change in both eyes over the course of treatment, sometimes leading to increased inter ocular differences; hence, these studies also accounted for inter ocular difference progression in addition to the traditional method [11-13]. This study observed slight increases in IODVA following treatment in a small subset of patients; however, a vast majority proceeded with decreased IODVA as expected. A strong positive correlation between acuity and inter ocular difference was evident; hence, the relationship between these entities appears interchangeable.

A relationship between anisometropia magnitude and amblyopia depth has been difficult to establish. Weakley demonstrates an amblyopia development threshold of $\geq 1.00D$ interocular difference between meridians for hyperopia and astigmatism and $\geq 2.00D$ for myopia [3]. Mechanistic difference between hyperopic and myopic AA may account for AA development being twice as likely to occur in hyperopes versus myopes given the same amount of anisometropia [14]. The same study also noted deeper fall-off acuity for hyperopes with large amounts of anisometropia compared with myopes. Kiorpes and Wallman found that in hyperopic AA, the more hyperopic eye,

which experiences constant defocus, becomes the amblyopic eye; conversely, the more myopic eye becomes the amblyopic eye for myopic AA [15]. Our study illustrates the amblyopia development threshold between amblyopes of different refractive nature with significantly greater correlation between amblyopia severity and anisometropia in the hyperopic group compared with the myopes. We are limited to defer correlative relationships with our astigmatic group due to the small sample size. Mounting evidence suggests that the refractive etiology behind the amblyopia is different between myopes and hyperopes, but the exact mechanism remains unclear.

No significant difference in the amount of inter ocular VA improvement was seen among the three refractive groups in this study. Children with myopic AA who started with larger amounts of anisometropia finished with the larger residual inter ocular differences after treatment compared with other refractive types. Initial IODVA was strongly correlated with final IODVA. Hence, this study was able to concur with past research that implied lesser rates of treatment success with myopic AA. Our finding of an average three-line VA improvement of the amblyopic eye was comparable to the results of other studies [9,11,13]. Despite therapeutic intervention, only 30% of patients in this study reached a final inter ocular acuity ≤ 0.1 log MAR. The possible presence of microtropia can affect the amount of correctable acuity. Up to 45% of those with AA can have coexisting microtropia, which accounts for residual acuity deficit, anomalous correspondence, and poor stereoacuity after treatment [16,17].

This study is limited by its retrospective nature, selection bias, and a small sample size. Acuity measurement was age-appropriate and measures either with Lea Symbols or Snellen acuity by various examiners. Treatment protocol involving vision therapy, in addition to patching, was not randomized but instead subjected to examiner preference. Similar to other studies [7,9], this study demonstrated that optical correction alone is able to resolve many AA cases. However, due to the retrospective nature of this study, the first follow-up with optical correction subjected patients to different lengths of spectacle adaptation. Stewart et al showed continual VA gain for up to 15-18 weeks following the introduction spectacle wear; hence, a truncated spectacle adaptation period may have potentiated unnecessary further intervention [18].

CONCLUSION

In summary, the association between amblyopia depth and anisometropia magnitude appears contingent on the refractive basis of the amblyopia. Deeper amblyopia was associated with larger amounts of anisometropia in hyperopic amblyopia, but this relationship was less evident in myopic amblyopia. Future studies are needed to delineate the mechanistic differences behind are fraction's ability to induce amblyopia. Final visual outcome was highly correlative with baseline acuity. However, the comparable acuity improvement potential demonstrated among all refractive groups warrants the standard of care treatment for all anisometropic amblyopes.

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