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Characterizing Parental Adherence To Amblyopia Therapy At Menelik Ii Referral Hospital In Addis Ababa, Ethiopia

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Characterizing Parental Adherence to Amblyopia Therapy At Menelik II Referral Hospital in Addis Ababa, Ethiopia

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ABSTRACT

There are limited studies completed in the East African region to assess barriers to adherence with amblyopia treatment and outcomes of this treatment. Our study aims to identify factors which are associated with higher adherence in amblyopia treatment. Institutional Review Board (IRB) approval was obtained and a hospital-based retrospective and prospective observational study was performed at the pediatric ophthalmology clinic of Menelik II Referral Hospital in Addis Ababa, Ethiopia from March 2015 to June 2015. Included in the study were Ethiopian children, between the ages of 4 and 8, with a clinical diagnosis of amblyopia defined as interocular acuity difference of at least 0.2 logMAR. We collected demographic and clinical data from charts. Parents were asked to estimate the number of hours they were able to administer patching in the past week and fill out a brief questionnaire addressing adherence, social stigma, and adverse effects associated with patching. Questions addressing parents' basic knowledge of amblyopia and its treatment were also included in the questionnaire. Fifty-three patients (25 male, 28 female) of mean age 6.4 $\pm$ 1.3 years participated. Forty-one (77.3%) of patients were residents of the capital, Addis Ababa, and 73.6% spoke Amharic, the national language. Amblyopia was associated with strabismus (n=36), anisometropia (n=6) and combined mechanism (n=11). Mean duration of treatment was 19 months. Approximately one-third of the parents (28%) were found to be non-adherent to the amblyopia treatment. Adherence was associated with parental educational level (p= 0.003) and residual amblyopia (p=0.001). Only 23.4% of patients achieved residual amblyopia of 0.19 logMAR units or less. The main factor affecting the outcome of amblyopia treatment in this study was treatment adherence.

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INTRODUCTION

Amblyopia is defined as a reduction in best-corrected visual acuity, typically monocular, in an otherwise normal eye resulting from abnormal visual experience during visual development. These abnormal visual experiences usually involve visual deprivation or abnormal binocular interaction. Often, the reduction in visual acuity cannot be entirely attributed to a structural abnormality of the eye. [1] Amblyopia is clinically defined as two-line difference in best-corrected acuity between eyes. Amblyopic eyes may also have deficits in contrast sensitivity and accommodation. [2] It remains to be the most common cause of monocular visual impairment in children with prevalence estimated at 1-5%. [3-7] In North American studies, the prevalence of amblyopia has been estimated with higher prevalence rates in the medically underserved populations; this is attributed largely to the high default rates from visual screening programs. [8,9] In contrast, the prevalence studies of amblyopia conducted in developing countries such as India, Nigeria and Ethiopia, report relatively lower rates [10-12]. Despite amblyopia being a preventable and treatable condition in childhood, the sustained vision loss contributes significantly to vision loss in adults. [5]

The most important causes of amblyopia can be broadly divided into two categories: a) visual deprivation and b) conditions that interfere with formation of vision during visual development. [13] Visual deprivation in childhood can be caused by blocking of the visual axis from light by a lenticular opacity (cataract), corneal opacity (congenital corneal disease), or eyelid malformation (congenital ptosis). In contrast, conditions such

as ocular misalignment (strabismus), a significant difference in the refractive error between each eye (anisometropia), and high refractive error causing the light not to focus due to the optics of the eye (myopia, hyperopia or astigmatism)--each of these contributes to a disruption in vision, as amblyopia can develop with the lack of stimulation of the retina. [6] The majority of children with amblyopia have strabismus and/or anisometropia; each making up about a third of the cause and a combination of the two making up another third. On average, 40-60% of children with anisometropia and/or strabismus in childhood develop amblyopia. [14] The severity of disease has been shown to be associated with the strabismic cause of amblyopia, resulting in more severe manifestation than refractive discrepancy. [5]

Amblyopia is primarily a neural disorder resulting from abnormal stimulation of the visual cortex during visual development, primarily during the first decade of life. The neurophysiologic mechanism for the development of amblyopia has not been fully elucidated. [15] Studies have not shown significant physiologic or anatomic abnormalities at the level of the retina, even with advances with OCT (optical coherence tomography). [7] However, animal studies have revealed that neurons in the primary visual cortex and lateral geniculate body show significant dysfunction when exposed to abnormal visual input during a critical period of visual development. [16] The concept of a critical or a sensitive period was based upon the feline studies conducted by Wiesel and Huble. These researchers showed that ocular dominance is established in the primary visual cortex cells of cats that underwent monocular deprivation between eye opening and several months of age. [16,17] Since the critical period is the time within which ocular dominance is

established, it is an important concept in understanding the development of amblyopia. This critical period depends upon the type of visual function, predominantly spatial resolution, being studied, and the anatomical level and the visual history of the subject, including the severity of the visual deprivation. [17]

Subsequent studies have also demonstrated the loss of particular cell types in the dorsal lateral geniculate nucleus of visually deprived cats without any observed functional deficits of neuronal signaling. [18] Therefore, there are both functional and anatomic alterations at the various anatomic levels of visual processing that appear to contribute to ocular dominance. Given that information from each eye is initially combined in the primary visual cortex, most studies support the idea that abnormal receptive field properties of V1 neurons linked to the amblyopic eye contribute most significantly to amblyopia. [15] Thus, any neuronal activity responsible for a deficit in spatial resolution and a reduction in binocularly driven neurons of the primary cortex seem to be the important pathophysiologic links to the development of amblyopia. In particular, the most profound anatomic and functional alteration in the visual system has been demonstrated in animals with early visual deprivation as compared to those with anisometropic or strabismic amblyopia. [15]

Similar to the feline studies, surgically induced strabismus in macaques has demonstrated amblyopia, with ocular dominance noted in the non-deviating (non-strabismic) eye as well as the loss of cortical binocularity. [19] Other macaque studies showing induced anisometropia with either the use of atropine penalization (with eye

drops) or a unilateral -10 diopter lens, both of these studies have demonstrated amblyopia and reduced binocularity. [14]

Given the time sensitive nature of amblyopia development and treatment, early detection is important. Delayed treatment can result in significant visual impairment. [20] The American Association of Pediatric Ophthalmology and Strabismus (AAPOS) has set recommendations regarding the age appropriate screening of children starting at infancy. In the first 6 months of life, assessment of fixation and tracking of objects can be used for vision screening. If there are any deficits regarding ocular movement or if there is an abnormal red reflex, a complete eye evaluation is recommended. Children over the age of 6 months can also be assessed for refractive error and/or strabismus by a pediatrician or a primary care physician with the use of an automated screening device such as a photo-screener. Over the age of 3 or 4 years, vision screening can be done using HOTV letters or Snellen eye chart. The tumbling E charts or the Allen or LEA figures can be used in cooperative, pre-literate child. [21]

The utility of screening all preschool children has been a controversial issue. [20] Photo-screening devices have been developed in an attempt to provide a cost-effective screening tool targeted at identifying amblyopia with good specificity at a time where treatment can be most effective. However, current devices have lower than desirable specificity to be cost effective for mass screening of preschool children. [6] Additionally, lack of randomized clinical trials to analyze the impact of screening programs upon the prevalence of amblyopia has contributed to a lack of consensus among pediatricians and

ophthalmologists on the issue of screening. [20]

However, what is agreed upon is that evaluation for amblyopia should include a complete ophthalmic exam with attention for strabismus, refractive error, lenticular opacity, and/or retinal disease as well as soliciting a family history for pediatric eye disease. [22] The diagnosis of amblyopia is achieved by detection of a two-line difference in visual acuity between the two eyes, given that best corrected vision is achieved using spectacles (correcting the refractive error). For children able to perform a quantitative visual acuity test using the eye chart, the test should ideally use either crowded or line optotypes. Amblyopic eyes display the crowding phenomenon, where HOTV letter or Snellen letter visual acuities worsen when presented with a row of images on the eye chart as opposed to an isolated individual letter. Fixation preference testing is the test of choice for those unable to perform a quantitative visual acuity test. In strabismic children, the fixating eye is determined. In children without strabismus, the induced tropia test is performed: strabismus is induced using a 10-12-prism diopter vertical prism to assess for fixation preference. [1] Bilateral amblyopia should be suspected in cases where best corrected visual acuity in either eye measures worse than 20/50 in children 3 years of age or younger, or worse than 20/40 in children older than 4 years. [22]

Amblyopia is a relatively well-understood disease with an established treatment modality. Recent studies conducted by the Pediatric Eye Disease Investigator Group (PEDIG) have aimed to provide randomized clinical trials over the last 17 years for evidence upon which to base treatment decisions. The PEDIG is funded by the National Eye Institute with more than a 100 participating sites and has completed over 17

Amblyopia Treatment Studies (ATS). [22] Treatment for amblyopia has three important components: a) providing a clear retinal image for the amblyopic eye, if deprivation exists, b) correction of significant refractive errors, and c) forced use of the amblyopic eye by occluding or penalizing the fellow eye. [22]

The role of accurate refraction in children is of great importance both in the diagnosis and treatment of amblyopia. The refractive error requires a measurement obtained with adequate cycloplegia (the pupil dilated at its maximum). The role of glasses alone in treating amblyopia was one of the study questions explored by PEDIG. Eighty-four patients between ages of 3 and 7 participated in a study lasting 30 weeks. Results demonstrated that 77% of amblyopic eyes improved by 2 or more lines of vision by using optical correction alone. Of these patients, 27% showed complete resolution of amblyopia with spectacle correction alone. [23] This emphasizes the need for accurate refraction and the improvement of vision using spectacles alone.

Occlusion, although introduced for children over 250 years ago, remains to be the mainstay of treatment for amblyopia. [24] The role of occlusion in the management of amblyopia was established by numerous prospective and retrospective studies. PEDIG conducted the first such randomized clinical trial comparing occlusion after a stable improvement with glasses alone compared to patients treated with only glasses. A total of 180 patients between ages of 3 and 7 were followed for 5 weeks. Patients in the glasses plus occlusion group were treated with 2 hours of patching per day combined with 1 hour of near visual tasks. Vision improved by 1.1 lines in the treatment group compared with 0.5 lines in the control group. [25] This demonstrates that there is a significant role for

occlusion therapy in amblyopia management, including children with refractive amblyopia.

In the early 1970s, total and continuous occlusion during all waking hours was thought to be valuable in treating amblyopia. Since then, there have been wide ranges of occlusion treatment regimens. [24] PEDIG trials were conducted addressing this question of dosage for occlusion therapy necessary for an optimal visual outcome. The studies found that there was no significant difference in outcome between patients with moderate amblyopia patched for 6 hours per day versus patients patched for 2 hours per day. [26] Similarly, in patients with severe amblyopia, there was no significant difference in treatment outcome between the full time occlusion group and the part-time occlusion group. These studies demonstrated that for initial treatment of amblyopia due to strabismus, anisometropia or combined mechanism, starting with a lower dosage of occlusion does not decrease the chance of success for improving vision. [26,27] It is possible that there might be a treatment adherence benefit to decreasing occlusion time without compromising treatment outcome.

Compliance with patching treatment has been shown to be a significant contributor of successful treatment. Lack of compliance leads to further deterioration of visual acuity in the amblyopic eye. [28] The need for an objective measure of compliance to assess the dose-dependent nature of occlusion therapy led to the development of Occlusion Dose Monitors (ODM). Patients were given an ODM, which consisted of a patch modified with electrocardiogram, battery and data logger to objectively monitor compliance. Fielder and colleagues found objective monitoring to be technically feasible

and clinically informative especially in cases where non-compliance had to be ruled out as a possible explanation for poor outcome. The ability to monitor compliance allows for the precise titration of occlusion to prevent loss of visual function. [29]

Other researchers also used ODM measurement to help establish a relationship between visual acuity improvement and compliance in children being treated with patching. Here, the results showed that there is a significant relationship between increased visual acuity and measured compliance. [30] There have been similar studies establishing compliance as one of the most important factors affecting outcome of amblyopia treatment. [31,32] At the same time, non-compliance rates to occlusion have been shown to be as high as 50%. [24]

Given how critical occlusion compliance is to the outcome of visual acuity, several studies have been completed to address the factors associated with better compliance. A retrospective study by Nucci and colleagues reviewed the charts of 496 amblyopic subjects to identify factors associated with lower compliance using patient report and records of missed appointments to measure non-compliance. The study found that lower initial visual acuity, age (less than 2 years old), and poor parental understanding to be significantly correlated with less complaint patients. [33] On the other hand, another retrospective study conducted in Australia evaluated the patching compliance in 127 children for amblyopia management. [34] In this study, there was no difference in compliance among the genders, across diagnostic class or treatment duration, with younger and older children showing better compliance compared with children at 15-30 months reporting significantly worse compliance. [34] There are some contrasting ideas concerning which factors are more meaningfully associated with

compliance. However, despite the variation in results regarding which factors truly influence compliance, studies have demonstrated that non-adherent parents have significantly poor understanding of the amblyopic critical period and confusion regarding which eye needed to be patched. [35]

Atropine penalization is an alternative approach to patching occlusion for amblyopia therapy. This eye drop treatment prevents the treated eye from accommodating, resulting in blurred vision at near; thereby allowing the amblyopic eye to be used preferentially. Its use is usually advocated when the amblyopic eye has vision better than 20/100, since this level of visual acuity might not give the amblyopic eye a preferential advantage over the atropinized, better seeing eye.[36] The first PEDIG study evaluated at the efficacy of Atropine 1% (1 eye drop daily) as compared to patching for 6 hours daily in 419 patients between the ages of 3 and 7 with moderate amblyopia. [36] At 6 months, 75% of both groups achieved approximately 3 lines improvement in vision with a faster improvement rate seen in the patching group.[36] At the 2 year follow- up, visual acuity outcome in both patient groups were similar, suggesting that both treatments are equally efficacious. [36,37]

Subsequent PEDIG investigations point to a potential benefit of using atropine penalization over patching when it comes to improving rates of treatment compliance. At the same time, another PEDIG study assessed the quality of life and psychosocial impact of amblyopia treatment on the child and family using a standardized questionnaire called Amblyopia Treatment Index (ATI). [38] Parents completed the questionnaire at 5 weeks into the treatment period. Results from the ATI showed that both treatment groups, atropine penalization and patching occlusion, tolerated the treatment. However, the

children in the patching group performed worse than the children in the atropine group on all three subscales of the questionnaire including compliance, social stigma and/or adverse effects.[38]

There are limited studies performed in the East African region looking at the outcomes of pediatric eye disease. Even less research has been performed to address the epidemiology, characterization, management and compliance of amblyopic children in the region. In 2008, a study addressing amblyopia in Ethiopian children examined the clinical profile of patients presenting to the Ethiopia's main pediatric ophthalmology referral center.[39] This study, *Profile of Amblyopia at the Pediatric Ophthalmology Clinic of Menelik II Hospital, Addis Ababa,* evaluated at the magnitude and clinical profile of amblyopia among children presenting to the pediatric ophthalmology clinic of Menelik II Referral Hospital. Data collected over a five month period included visual acuity, refractive status and fixation pattern of all patients presenting to the clinic. From the 1,660 children examined, 183 (9.1%) were amblyopic with approximately equal divide between the genders. The mean age of presentation was 6.9 years with strabismic amblyopia being the most common subtype seen at 39.3%. Regionally, 72.1% of children lived in the capital, Addis Ababa while the other children, 27.9%, came from other parts of Ethiopia.[39] The average age of initial presentation for amblyopia was 6.2 years for combined mechanism amblyopia, 6.8 years for strabismic amblyopia and 7.4 years for anisometropic amblyopia. The problem of amblyopia was detected during evaluation for strabismus in 69.4% of the children.[39] In this hospital-based study, the delay to initial presentation is likely to have contributed to the high prevalence rate reported.

Learning from this 2008 Ethiopian amblyopia study, we conducted our clinical research to better understand the barriers to optimal management of amblyopia in children presenting to the ophthalmology department at Menelik II Referral Hospital, Addis Ababa, Ethiopia. Our study aims to identify factors which are associated with higher compliance in the treatment of amblyopia and thus improved visual acuity outcomes. As strabismic and anisometropic amblyopia are the most frequent causes of amblyopia in children, our study focuses upon the treatment of strabismus and refractive error as the main etiologies of amblyopia. In addition, we plan to identify factors that lead to improved compliance with amblyopia treatment and this will allow physicians to anticipate possible barriers to improved visual outcomes.

Hypothesis

We hypothesize certain determining factors which are associated with better compliance in the treatment of amblyopia in children presenting to the ophthalmology department at Menelik II Referral Hospital, Addis Ababa, Ethiopia will: (1) help pediatric ophthalmologists to better anticipate barriers to treatment of amblyopia and (2) improve visual acuity outcomes. We anticipate that parents' educational level, their understanding of the rationale for treatment recommended, and the duration of treatment will play a significant role in compliance with amblyopic management.

Specific Aims

Primary Aim:

1. To determine the rate of non-adherence to amblyopia treatment in this patient population
2. To determine the demographic and clinical factors that are associated with higher rates of non-adherence to amblyopia treatment

Secondary Aims:

1. To determine the visual outcome from patching occlusion treatment in this patient population
2. To determine the factors associated with improved vision outcome

METHODS

Recruitment, Inclusion and Exclusion Criteria

Our study was a hospital-based cross-sectional, observational study at the pediatric ophthalmology clinic of Menelik II Referral Hospital in Addis Ababa from March 2015 to June 2015. Institutional review board (IRB) approval was obtained. It was designed to include children between ages 4 to 8 years old. This age range was chosen because these children could provide a more reliable and consistent visual acuity. Additionally, at the time of recruitment, we believed there would be a sufficient number of children at the clinic within this age group meeting inclusion criteria for our study.

Our study examined patients with a clinical diagnosis of strabismic, anisometropic or a combined mechanism of amblyopia undergoing patching treatment. These three causes of amblyopia were selected because they constitute the majority etiology of amblyopia and share similar diagnostic, therapeutic, and prognostic features as compared to sensory deprivation amblyopia. Strabismic amblyopia was defined as an ocular misalignment and associated with an interocular visual acuity difference of at least 0.2 logMAR units in verbal and cooperative children. Anisometropic amblyopia was defined as a refractive difference of greater or equal to one diopter in any meridian.

Patients were excluded if they had neurologic, traumatic or other structural ocular disease, or previous ocular surgery. In addition, patients with sensory deprivation amblyopia and manifest nystagmus were also excluded.

Study Procedure

The clinical charts of patients were screened daily throughout the study period to determine eligibility. Verbal consent was requested and obtained from parents for participation in our study. As previously noted, we obtained permission to review patient's medical records.

Demographic information, medical and surgical history, family history pertinent to eye disease, and social history were collected on the initial patient encounter. Results from the eye exam which characterized the presence and severity of amblyopia as well as measures of refractive error, ocular motility and ocular alignment were collected from enrolled patients.

Typically, an initial assessment of patients presenting to this clinic with the risk factors for amblyopia were evaluated with a detailed history related to the age of onset as noticed by the parent or guardian, age at presentation to the hospital, and any previous treatments for amblyopia. The uncorrected and best-corrected visual acuity were measured for children over the age of 4 years. For children presenting at less than age 4 years, fixation preference using corneal light reflex was recorded. A completed eye exam was performed including the assessment of ocular alignment and ocular motility. Slit lamp examination and fundus examination for the assessment of anterior segment and posterior segment pathology was performed, respectively. The determination of refractive

error was performed from cycloplegic refraction and retinoscopy.

Initial and Final Visual Acuity

Visual acuity was obtained using the 5-letter tumbling E visual acuity chart. Visual acuity was recorded as the smallest complete line of five letters read, plus the number of letters correctly identified in the line below while wearing proper spectacle correction. We only recorded visual acuities obtained before start of treatment (from chart review) and at the final counter with the treating clinician.

Treatment protocol

The selection of a treatment regimen, such as the number of hours needed for occlusion therapy, was based upon the treating physicians' preferences. In particular, the time necessary for occlusive patching was primarily based on the patient's degree of amblyopia, although individual patient flexibility was applied in order to promote compliance. Full time occlusion was avoided in our study in order to avoid disruption from schoolwork. Part time occlusion consisted of an average of 4 hours of occlusion patching per day after school during weekdays and 10-12 hours per day during the weekend. A nurse gave parents instructions on how to make a one- time patch using an adhesive tape at the time when patching was initiated.

Patient follow- up

The length of time between follow-up visits for an amblyopic patient undergoing occlusion therapy at Menelik II Referral Hospital was determined by the treating physician, using the patient's age as a guideline. A maximum patching interval of 1 week was implemented for every year of the patient's age, with the initial interval not longer than 4 weeks, regardless of age.

Administered questionnaire

Data on each enrolled patient was collected from the parents using a semi-structured interview consisting of a) Basic parental information, b) Amblyopia Treatment Index survey, and c) Parental awareness of amblyopia and knowledge of occlusion therapy, critical period, visual prognosis and treatment regimen.

The basic parental information portion of the questionnaire addressed the following: whether the respondent was responsible for the child's treatment administration the majority of the time, what prompted the parent to first seek an ophthalmologic consultation, the family's city of residence, preferred language, and educational level.

The Amblyopia Treatment Index (ATI) was developed by the PEDIG group for assessing the impact of amblyopia treatment on 3- to 6-year old children and their parents. [40] The items on this questionnaire have three subscales intended to independently assess compliance, adverse events and social stigma. The ATI consists of

20 Likert-type items with 6 response choices ranging from “strongly agree” to “strongly disagree.” The ATI was slightly modified for our study purposes to 4 response choices which included “0 = all of the time,” “1 = most of the time,” “2 = some of the time,” and “3= none of the time” so as to make the questionnaire more accessible to the parents of our patient population. This was based upon consultation with treating physicians at the pediatric ophthalmology clinic at Menelik II Referral Hospital. Of note, the modified questionnaire was translated by a professional language translator into Amharic, the national language of Ethiopia.

Scores for the three subscales of the ATI were calculated from the sum of each response item within the subscale. Compliance was calculated out of a total of 12 points with higher points indicating better compliance. Similarly, social stigma and adverse effects of occlusion therapy were calculated out of a total of 9 and 18 points, respectively, with higher scores indicating lower stigma and minimal adverse effect with treatment.

The third component of our questionnaire consisted of questions clarifying parental awareness of amblyopia, knowledge of occlusion therapy, critical period, visual prognosis and treatment regimen. Parents were asked if their child had decreased vision in one eye and what treatment the child was receiving for the ocular condition. They were asked basic questions addressing the appropriate time for amblyopia treatment, the current regimen of treatment and what they found to be most challenging about treating their child. Parents were also asked to estimate the number of hours they were able to

administer patching in the previous week. Non-adherence was then calculated as a ratio of the difference between prescribed and administered hours to prescribed hours.

$$\text{i. e. Non-adherence} = \frac{\text{Prescribed hours} - \text{Administered hours}}{\text{Prescribed hours}}$$

All research activities, including protocol development, recruitment, screening, enrollment, interviews, data collection and data management were completed by the author.

Statistical Analysis

The association between non-adherence and gender, age at initial presentation, parental education, parental awareness of amblyopia, social stigma, and adverse effects of amblyopia treatment was studied. Preliminary analysis by single variable regression was applied and then further by multivariate regression analysis. All estimation will be adjusted for other variables, along with crude estimation reported. Further exploratory analysis was conducted for factors associated with treatment outcome, evaluated by residual amblyopia. Due to our study's small sample size, calculations with a p-value greater than 0.01 will be considered for further study.

RESULTS

Recruitment Process

Parents of fifty-nine patients with amblyopia undergoing occlusion (patching) therapy were approached for screening to determine eligibility. All parents agreed to participate. Six of these patients were under the age of four, and thus were excluded. Of the remaining fifty-three patients, seven patients had incomplete charting of initial visual acuity and were excluded from the visual outcome analysis, but were included for non-adherence analysis. All study participants spoke sufficient Amharic and language translators were not required to conduct our semi-structured interviews.

Study participants characteristics

The mean age of study participants was 6.4 $\pm$ 1.3 years (range = 4 to 8 years). The mean age at the start of treatment was 3.7 $\pm$ 1.6 years (range = 0.4 to 7 years). Demographics included that 45% (n=21) of participants were male and 54% (n=25) were female. Strabismic amblyopia was identified in 68% (n=36) of the patients, anisometropic amblyopia was identified in 11.3% (n=6) of the patients, and a combined mechanism was identified in 20.7% (n=11) of the patients. A majority of the patients, reported at 77.3% (n=41) as residents of the capital city, Addis Ababa; in contrast, 22.6% (n=12) of the patients travelled variable distances, frequently over 50 miles, from regions outside Addis Ababa.

More than half of our patients' parents interviewed, at 62.3% (n=33), were the primary care taker of the child and administered the patching treatment the majority of the time. Of these parents, 35.8% (n= 19) administered treatment about half of the time, sharing the responsibility with others in the house hold. Of note, one parent administered the patching treatment rarely. The task of administering occlusion treatment was performed mainly by parents: either mothers (52.8%) or the fathers (33.9%). To a lesser extent, older siblings and other extended family members were involved in administering the occlusion therapy. A summary of the distribution of demographic and clinical variables of our recruited study participants by types of amblyopia is shown in Table 1.

Table 1. Distribution of demographic and clinical variables within the amblyopic groups

Factors Assessed	Types of Amblyopia			Total N=53
	Strabismus (N=36)	Anisometropia (N=6)	Combined (N=11)	
Age (months)				
4-6	22.6 % (12)	2.77% (2)	5.66% (3)	32.1% (17)
6-8	45.2% (24)	7.55% (4)	15.1% (8)	67.9% (36)
Gender				
Male	35.8% (19)	5.66% (3)	5.66% (3)	43.4% (25)
Female	32.1% (17)	5.66% (3)	15.1% (8)	52.8% (28)
Duration of Treatment (months)				
1-3	7.55% (4)	2.77% (2)	1.89% (1)	13.2% (7)
3-6	0	0	0	0
6-12	11.3% (6)	0	1.89% (1)	13.2% (7)
12-24	13.2% (7)	5.66% (3)	2.77% (2)	22.6% (12)
24-48	18.9% (10)	0	9.43% (5)	28.3% (15)
>48	1.89% (1)	0	1.89% (1)	2.77% (2)
Initial Visual Acuity (LogMaR)				
Mild (0-0.3)		1.89% (1)	0	2.77% (2)
Moderate (0.4- 0.7)	1.89% (1)	5.66% (3)	7.55% (4)	45.3% (24)
Severe (0.8-1)	32.1% (17)	1.89% (1)	5.66% (3)	17.0% (9)
	9.43% (5			
Glasses				
Y, Y	47.2% (25)	5.66% (3)	15.1% (8)	67.9% (36)
Y, N	9.43% (5)	5.66% (3)	5.66% (3)	20.7% (11)
N,N	9.43% (5)	0	0	9.43% (5)
Age at First presentation				
<6 months	0	0	0	0
6-12 months	7.55% (4)	0	1.89% (1)	9.43% (5)
1-2 years	13.2% (7)	1.89% (1)	2.77% (2)	18.9% (10)
2 – 4 years	28.3% (15)	2.77% (2)	5.66% (3)	37.7% (20)
4-6 years	15.1% (8)	5.66% (3)	2.77% (2)	24.5% (13)
>6 years				
Dose of occlusion (hours/day)				
< or = 28	34.0% (18)	7.55% (4)	5.66% (3)	47.2% (25)
28-44	32.1% (17)	2.77% (2)	15.1% (8)	50.9% (27)
>44	1.89% (1)	0	0	1.89% (1)
Parental education level				
Primary or none	28.3% (15)	5.66% (3)	9.43% (5)	43.4% (23)
High school	20.7% (11)	2.77% (2)	11.3% (6)	35.8% (19)

College	15.1% (8)	1.89% (1)	0	17.0% (9)
Graduate	2.77% (2)	0	0	2.77% (2)
Residence				
Addis Ababa	52.8% (28)	7.55% (4)	17.0% (9)	77.3% (41)
Non-Addis Ababa	15.1% (8)	2.77% (2)	2.77% (2)	22.6% (12)
Language				
Amharic	50.9% (27)	9.43% (5)	13.2% (7)	73.6% (39)
Non-Amharic	17.0% (9)	1.89% (1)	7.55% (4)	26.4% (14)

Notably, distribution of patients with regards to severity of amblyopia measured by their initial visual acuity showed that 45.3 % (n=24) of patients fall into the moderate amblyopia group with LogMaR visual acuity measures between 0.4 to 0.7. At initial presentation, the largest age group of patients was between the ages of 2 and 4 years (37.7%) (n=20) with 68% of all patients presenting with an ocular misalignment. The classification of ocular misalignment among patients treated for strabismus and combined mechanism amblyopia (n=47) is described for 42 of these patients in Table 2.

Table 2. Classification of ocular misalignment for children with strabismic amblyopia

Type of strabismus	Frequency	Percent
Infantile Esotropia	2	4.76
Accommodative esotropia	35	83.3
Acquired non-accommodative esotropia	1	2.38
Infantile Exotropia	4	9.52
Total	42	100

Duration of treatment for our patients varied widely: from 1 month of follow-up to 68 months of follow-up. The mean duration of treatment was 19 months with an average of 11 clinic visits. In 15 patients (28.3%) with either strabismic or combined

mechanism amblyopia, the most common treatment time was within the 24-48 months duration.

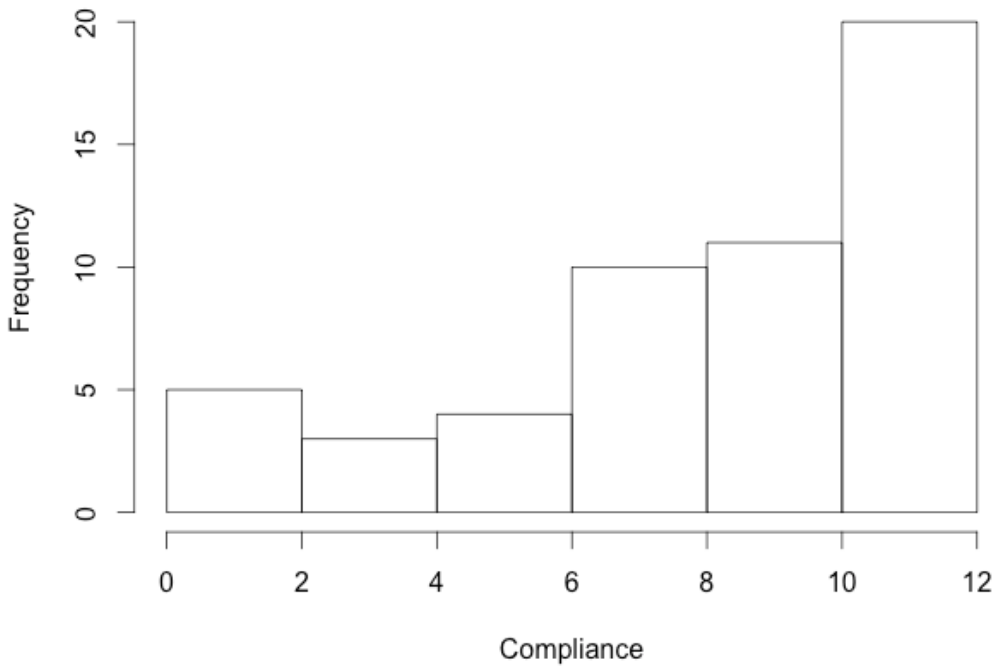
The most common dosage of occlusion reported by parents was in the strabismic amblyopia patients, with 28-44 hours per week and ≤ 28 hours per week reported in 17 patients (32.1%) and 18 patients (34%), respectively. Of note, 25 patients (53.2%) were patched up to 44-hours per week (4 hours during the week day and 10-12 hours during the weekends), especially the patients with strabismic amblyopia. The second largest dosage group was 14-hours per week (2 hours daily) with 31.9% of patients (n=15) in this group.

In addition to occlusion therapy, refractive correction with glasses was part of the amblyopia management for 88.6% of patients (n=47) in the study. Of these patients wearing spectacles, 67.9% (n=36) patients were adherent with their current prescriptions at the time of our encounter, while 20.7% (n=11) patient were not adherent.

Educational level of parents had a wide range of distribution: no formal education, only primary education (1st to 8th grade), up to high school (12th grade), college, and graduate level. The largest group of parental education level was noted as only primary education or none, with 43.4% (n=23) parents represented.

Summary of questionnaire results

Results from our modified ATI questionnaire were divided into the compliance, adverse effects, and social stigma subscales. Numerical results from each subscale were the sum of individual questions within each subscale. The mean value for the compliance subscale (calculated out of a total of 12 points with higher score representing better compliance) for all study participants was 8.57 ± 3.51. The mean value for social stigma subscale (calculated out of a total of 9 points with higher score representing lower social stigma of treatment) was 7.26± 2.28. The mean value for the adverse effects subscale (calculated out of a total of 18 points with higher values representing least treatment associated adverse effects) was 16.08± 2.30. A graphical representation for the distribution of the scores for each subscale is show in Figure 1.



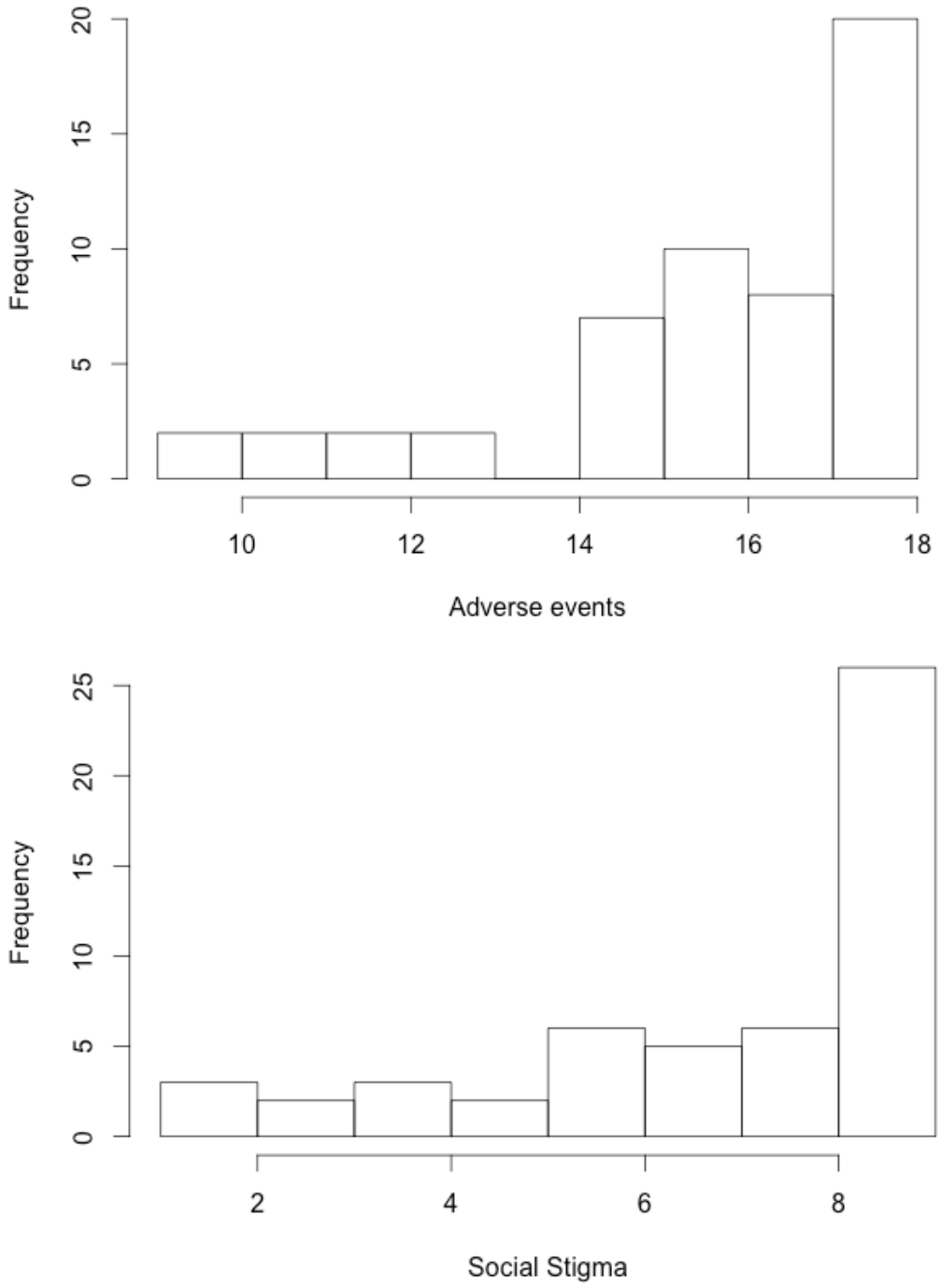


Figure 1. Distribution of ATI subscale scores in participants. A. Compliance; B. Adverse events; C. Social Stigma.

Parental Knowledge

Table 3 is a summary of the responses obtained from parents regarding their basic knowledge of amblyopia and its treatment. The results showed that parental understanding was generally poor in important areas such as critical period, as shown by responses to questions addressing age limit to treatment and the preferred age of administering treatment. We noted that 13% (n=7) of parents were found to be patching the incorrect eye. This subset of patients had a median duration of follow-up of 16 months. Given this length of treatment duration, this error in implementing amblyopia treatment is particularly striking.

Table 3: Parental awareness of amblyopia and knowledge of occlusion, critical period, visual prognosis and treatment regimen

Questions	*Number (%) of parents giving the correct answer (N=53)*
Does your child have reduced vision in one eye?	42 (79)
What is the treatment for reduced vision in one eye?	37 (70)
Does the treatment have to be carried out by a certain age?	23 (43)
Would it be easier to correct weak vision in one eye at age 2 years or 6 years?	24 (45)
Which eye are you putting the patch on?	47 (87)

Non-Adherence

All 53 enrolled parents completed our questionnaire and provided an estimate of the number of hours of prescribed amblyopia treatment they were able to administer the week prior to their follow-up appointment. Non-Adherence was then calculated as a ratio of missed hours (difference between prescribed and administered hours) to prescribed hours. The distribution of calculated non-adherence score for our cohort is graphically presented in Figure 2. The median non-adherence score was 0.41 with 25% and 75% percentiles of 0.21 and 0.625. Patients with greater than 0.5 calculated non-adherence were considered to have poor adherence to treatment. This group constituted 28% of our study participants.

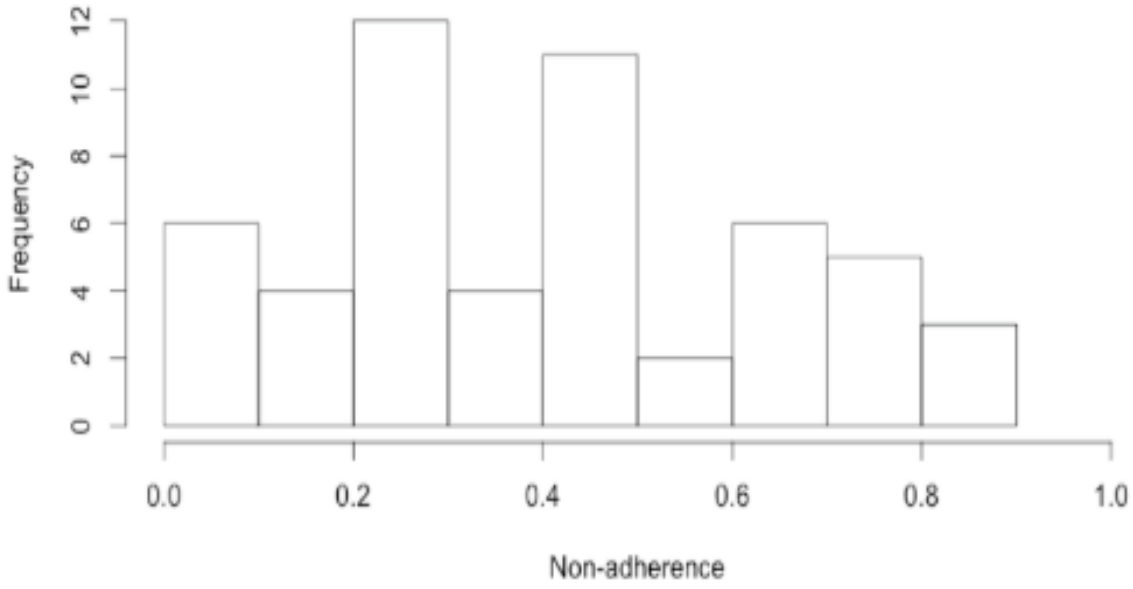


Figure 2: Distribution of patients in relation to calculated non-adherence.

Regression Analyses for non-adherence

The association between calculated non-adherence scores and the various demographic and clinical factors including: age at the start of treatment, gender, type and severity of amblyopia at the start of treatment (categorized as mild: <0.4 logMAR in the amblyopic eye; moderate: ≥0.4 to <0.7 logMAR; or severe: ≥0.7 logMAR), prescribed hours for occlusion therapy, duration of treatment for occlusion, number of clinic visits, compliance with glasses, parental educational level, place of residence, primary language spoken, questionnaire results addressing compliance, adverse effects of occlusion therapy, social stigma of occlusion therapy, parental knowledge of amblyopia and its treatment, and residual amblyopia were statistically interrogated by single variable and multivariate regression analysis. The resulting final model is summarized in Table 4. Validity of underlining model assumptions were assessed graphically and analytically.

Parental education level ($p= 0.003$) and residual amblyopia ($p=0.001$) were found to be significantly associated with non-adherence. Compared to parents with a college level education or higher, parents with a high school education or less were more likely to be non- adherent to patching. With regards to residual amblyopia, those children with smaller level of residual amblyopia, i.e better treatment outcome, were found to be more adherent to treatment by occlusion therapy.

Although statistical significance was not reached, initial visual acuity (severity of disease) and adverse effects of treatment were also marginally associated with non-adherence. Patients with worse initial visual acuity or more severe disease had worse adherence to therapy. Patients with lower adverse effect subscale scores (suffered greater adverse effect from treatment) also demonstrated worse adherence to patching. All other variables were not significantly associated with the calculated non-adherence scores.

Table 4: Summary of Multivariate Analysis for Calculated Non-Adherence Scores

Variables	Unadjusted Coefficient			Adjusted Coefficient		
	Estimate	SD	p-value	Estimate	SD	p-value
Parental educational level						
College and above	0	-	-	0	-	-
High school and below	0.240	0.076	0.003	0.226	0.0705	0.002
Adverse Events	0.027	0.014	0.064	-	-	-
Initial Vision Acuity	0.173	0.095	0.075	-	-	-
Residual amblyopia	0.317	0.093	0.001	0.293	0.0855	0.001

Reasons for parental non-adherence

All 53 parents were asked to provide their family's primary reason for non-adherence and 88.7% (n=47) were able to provide at least one reason. The most common reason for non-adherence given by 37.7% (n=20) of all parents was lack of cooperation from the child. Parents indicated that the child disliked the patch and often resisted or tried to avoid being patched. Competing priorities and other life stressors, including busy work and home life, was the next most sited reason (30.2%) for non-adherence to treatment. Difficulty finding patching material (n=6) and forgetting to administer

treatment (n=5) constituted the primary reason for non-adherence to occlusion therapy for the remaining parents.

Visual outcome of treatment

Given our small cohort of patients (N=53), especially within the anisometropic and combined mechanism amblyopia groups, it is difficult to make associations between visual outcome and our clinical or demographic variables by diagnostic grouping. Therefore, children within the three diagnostic types of amblyopia (strabismic, anisometropic and combined mechanism) were considered together. The initial and final visual acuity was recorded by the tumbling E-chart in 46 (86.8%) of the children. Of these patients, 4.35% achieved 6/9 or better, 23.9% 6/18 or better and 71.7% achieved less than 6/18. Visual outcome for each group is shown graphically in Figure 3. Outcomes were not shown to be better for any given diagnostic groups ($p \geq 0.1$).

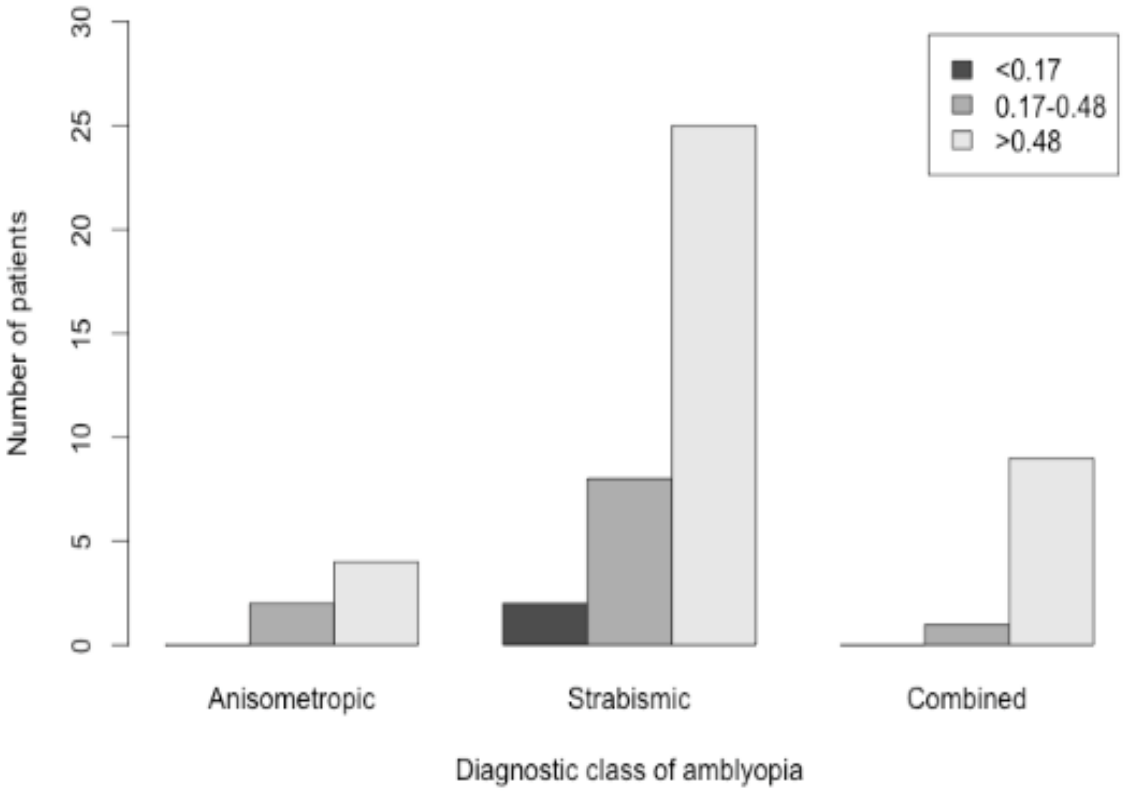


Figure 3: Summary of final visual acuity for each diagnostic type of amblyopia.

Neither age at the start of treatment (Figure 4) nor duration of treatment (Figure 5) were associated with final visual outcome ($p=0.158$ and $p=0.151$, respectively). Similarly, severity of disease as measured by the initial visual acuity of the patients was not found to be associated with visual outcome ($p \geq 0.1$).

In contrast, the final visual acuity in our cohort of patients was found to be significantly associated with calculated non-adherence score ($p = 0.00132$) and the compliance subscale of the ATI questionnaire ($p=0.00137$). Patients who were more adherent to prescribed hours of occlusion demonstrated better final visual acuity as

compared to those who were less adherent. All other variables were not significantly associated with the final visual acuity.

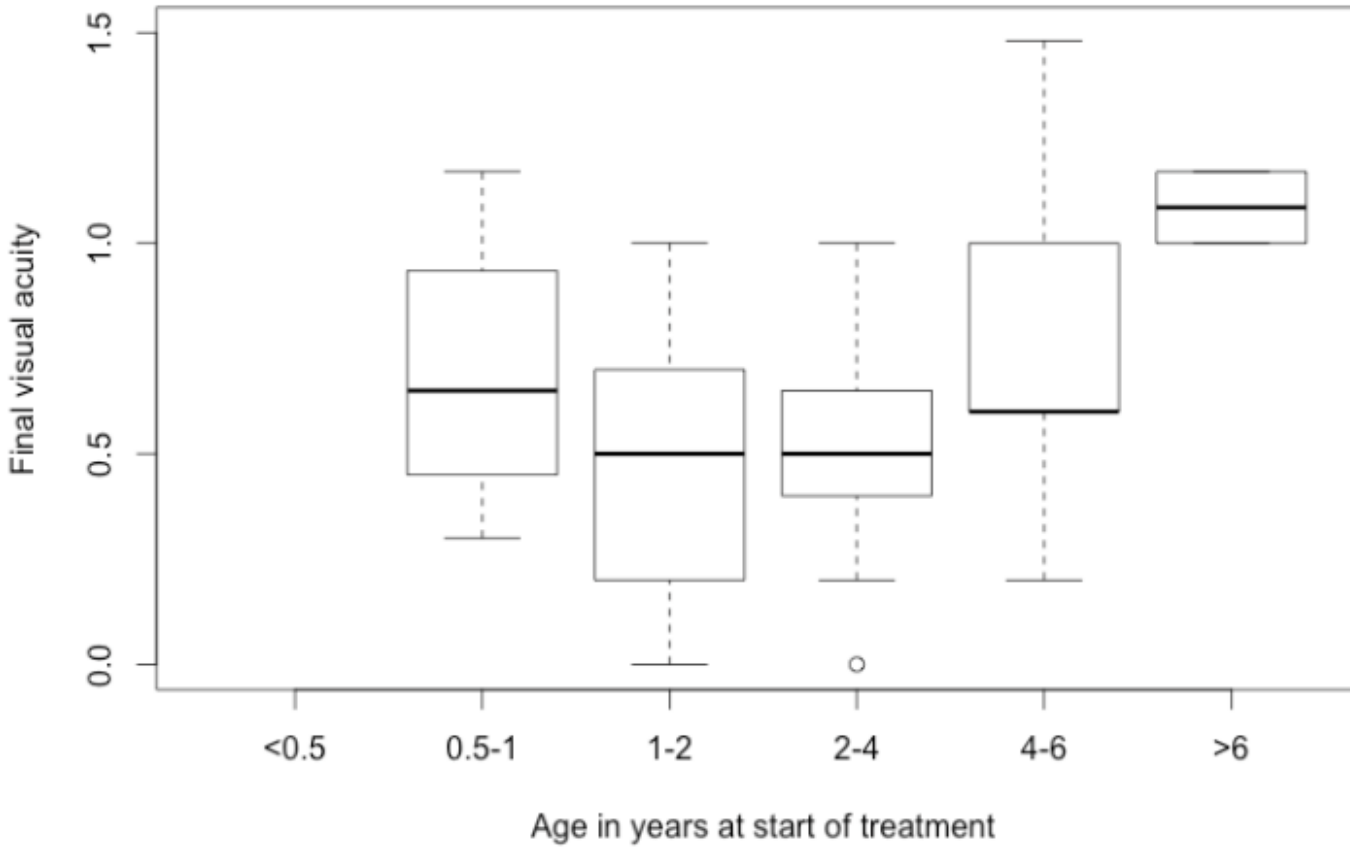


Figure 4: Distribution of final visual acuity in patients by age at first clinical presentation.

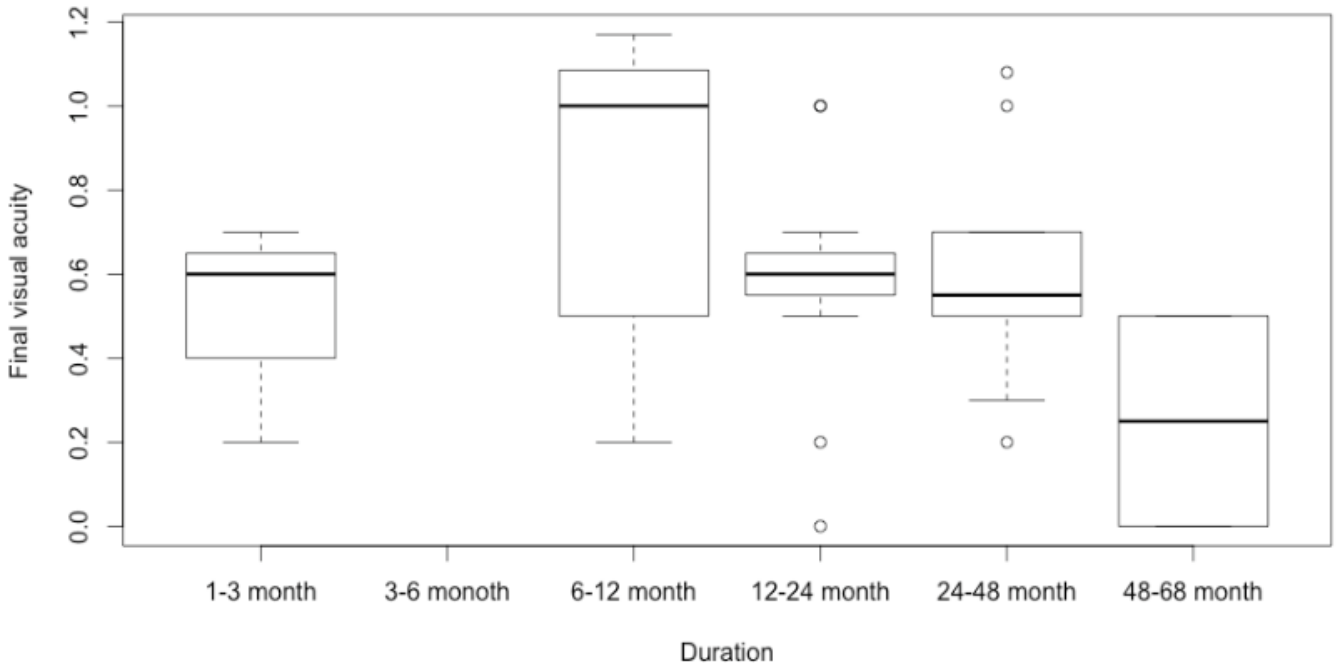


Figure 5: Distribution of final visual acuity in patients by duration of treatment.

DISCUSSION

Our study has explored the effects of various demographic and clinical parameters upon adherence to amblyopia treatment at the pediatric ophthalmologic referral hospital in Addis Ababa, Ethiopia. Approximately one-third of the parents (28%) were found to be non-adherent to the amblyopia treatment. Our reported level of non-adherence is significantly lower than levels determined by Newsham et al (54%) because non-adherence in their study was determined using an 80% threshold to divide non-adherence from adherence as compared to a threshold of 50% for our study.[35] If an 80% threshold were to be used, the percentage of non-adherent parents in our study would be calculated at 58.5%. This is a higher level of non-adherence than cited by most studies.[41,42] The variation in adherence rates across the literature can be partly explained by the variation in methodology adopted.

Most studies, like the Newsham study, determine adherence to amblyopia treatment and factors influencing adherence to treatment with the use of a diary, in addition to the use of an occlusion dose monitor, which is attached to the occluding material.[36] This is a major drawback for our study since we had to rely solely on parental recall and self-report of treatment administration the week prior to our clinical encounter. Therefore, it is likely that the true percentage of non-adherent parents in our study may be higher than calculated. In turn, parents are likely to overestimate their adherence to amblyopia treatment in order show that they are following through with the treating

physicians recommendation, and thus reluctant to disclose the full extent of their non-adherence. It should be noted that an effort was made to use non-judgmental language in obtaining information about non-adherence and in relating to parents that information obtained for the study would in no way affect their follow-up care at the clinic. It is also important to consider that our study only looked at non-adherence as a snap shot, during a period of one week, with participating parents at different lengths of treatment duration. It is very likely and expected that the level of parental adherence to treatment may vary during treatment period, especially given the limitation of evaluation of our four-month period.

In our study, we identified parental level of education and residual amblyopia as statistically significant predictors for non-adherence. Adverse effects of treatment and initial visual acuity were also found to be marginally associated with non-adherence. Age of onset of therapy, gender, type of amblyopia, duration of treatment, use of spectacles, parental awareness of amblyopia, and social stigma as measured by the ATI questionnaire did not appear to be significant predicators of non-adherence. Given our small sample size, further sub-group analysis is not warranted and a larger cohort of patients may yield different results.

Parental level of education was found to be a significant predictor of adherence in a study conducted in the Netherlands by Loudon et al. In this study, the 310 participating children and their families had a diverse socioeconomic, ethnic, and educational

background-- enabling the investigators to asses the role of these demographic factors on adherence.

The study also found parental fluency in Dutch and parental country of origin to be associated with adherence. [43] Although a smaller cohort, our study participants' educational level ranged from no formal education to graduate level education. Parents with only high school level education or less demonstrated poorer adherence than those with exposure to college education and beyond. Thus, parents with limited education require greater attention with regards to explanation of the treatment regimen in appropriate terminology for improved understanding of the importance of amblyopia treatment practices.

As in our study, the benefit of improved visual acuity (as measured by reduced residual amblyopia) in significantly influencing adherence has been previously demonstrated. Studies have demonstrated the importance of "self-efficacy "as a factor in determining parental adherence to patching treatment. In a research conducted by Searle et al, parents who believed treatment to be bringing about change in the functional vision of their child were more likely to adhere to treatment. This led to the finding that there is a benefit to emphasize the evidence of visual acuity improvement of children to their parents during follow up visits in order to encourage adherence. [44] Similarly, a qualitative study in Great Britain by Dixon-Woods et al used interviews with families of children with amblyopia to better characterize the challenges associated with occlusion therapy.[44] These researchers found that parents were more likely to abandon treatment when improvement in vision was not apparent and when the child suffered socially or

educationally.[45] These findings can plausibly be expected as parents who are more aware of the improvements being gained from therapy would proceed to treat better than those parents who are not seeing or understanding the benefits of occlusion therapy. The importance of addressing the improvement in vision as amblyopia treatment progresses could make a significant difference in motivating parents to continue adhering to the treatment regiment prescribed.

Initial visual acuity has been shown to be an important predictor of treatment adherence in a study of 496 amblyopic patients conducted by Nucci et al. [33] A more recent study has also demonstrated that initial visual acuity is the only clinical factor most significantly associated with adherence.[43] This has been attributed to the fact that children with worse initial visual acuity in the affected eye resist patching more than those with better initial acuity. Thus, parents would find themselves having to do more work to convince and apply occlusion treatment regularly. Understandably, adherence also suffers further if parents perceive amblyopia treatment as having a deleterious effect on their child's ability to perform educationally or socially.[45]

In our cohort, parents have demonstrated a very poor understanding of amblyopia, its treatment and visual prognosis. For this reason, we had anticipated that parental awareness as assessed through our questionnaire would significantly be associated with adherence to amblyopia treatment. Although parental comprehension did not emerge as a significant predictor of treatment adherence in our cohort analysis, other studies have demonstrated that it is highly associated with treatment adherence.[35] Furthermore,

research in other areas of medicine have certainly demonstrated that the understanding level of patients with regards to their condition or diagnosis can have a direct and profound effect on their adherence to therapy.

Parental knowledge of both the critical period in amblyopia and the preferred age at which occlusion treatment should be started were quite poor in our study. Approximately 56.6 % of parents were unsure about the most favorable time to administer treatment and only 20% of parents scored 5 out of 5 with regards to their basic knowledge of amblyopia while 13% of the parents were patching the incorrect eye. This lack of knowledge suggests that parents do not fully appreciate the urgency of treatment, which can lead to further non-adherence. A better understanding of amblyopia, the importance of treating early, and the goals of amblyopia treatment can reinforce the urgency and efficacy of the treatment to parents. In our study, 26.4 % of parents did not have a clear understanding of what patching was intending to treat. Some parents communicated the expectation that the surgery planned at the end of the patching therapy to be the most important aspect of the management, and in turn, making patching less of priority. Other parents related their understanding that patching was intended to treat the ocular misalignment rather than the decreased vision.

Our study also exposed a significant deficiency in parental understanding of the role of glasses in treating amblyopia. Out of a subset of 18 parents who were specifically asked if they applied the glasses on their child after patching, the majority of parents, that is 10 out of the 18 parents, said that they were not applying the glasses once the child was

patched. This exposes a gap in the information related to parents regarding the role that glasses play in the management of amblyopia.

An RCT study by Newsham et al looked at the role of intervention in the form of education material provided to parents to improve their understanding of amblyopia and patching and thereby increase adherence. Patients were randomized to a leaflet group or a control group. In the leaflet group, they were issued written educational material whereas in the control group, additional educational material was not provided. Patients were paired and matched for age and occlusion time prescribed.[45] The study found the level of knowledge in key areas of amblyopia and adherence to occlusion therapy to be significantly greater in the leaflet group; moreover, only parents in the control group were patching the incorrect eye.[45] This study suggested that providing educational material for parents helps clarify the concept of the amblyopia critical period, the importance of patching and the consequences of not treating. At the same time, researchers concluded that providing educational material to improve parental understanding of amblyopia could lead to improved adherence to amblyopia treatment.[46]

Given low literacy rates in Ethiopia, especially in patients coming from a rural setting outside of Addis Ababa with very limited or no exposure to formal education, more creative ways should be used to communicate the importance of better adherence and timely treatment for preventing amblyopia. In a Dutch study conducted by Tjiam et al, they describe the effectiveness of an educational cartoon shown in a clinical setting, without using words, in explaining why amblyopic children should wear an eye patch.

This research showed improvement in electronically-measured adherence to patching and clinic attendance.[46] It also demonstrated an improvement with adherence following the implementation of the cartoons being more pronounced in patients of low socioeconomic status, with a large portion of these patients being immigrants who spoke Dutch poorly.[47] Similarly, for our study population, educational material prepared in a leaflet format, not requiring words, could provide greater awareness of the importance of treating amblyopia in their children and improve adherence in both illiterate parents and parents who do not understand or speak the national language fluently.

There was a wide range of reasons described by the parents in our study as the primary challenge to administer occlusion therapy: unwillingness of the child to tolerate the patching, competing socioeconomic priorities associated with poverty, challenging family dynamics, lack of resources including the simple materials required for occlusion patching. While improving parental understanding is expected to increase compliance, it is also important to emphasize that treating physicians address the particular challenges families face with regard to implementing treatment. A study by Tripathi et al investigated the role of parental preference in planning occlusion treatment and thereby improving adherence.[47] The study showed that parents had strong preferences for one occlusion regimen over another, based upon their particular circumstance and family situation.[48] It is intuitive that by empowering parents to voice their preferences and determine what patching treatment regimen works best for their families, there will be an improved adherence to amblyopia treatment. Such discussions would also help find solutions to other practical challenges associated with patching, such as finding

appropriate occlusive material, which in our study was noted by parents as one of the reasons for non-adherence to treatment.

In summary, our 14-week retrospective and prospective cohort study demonstrated that non-adherence to patching treatment was associated with worse initial visual acuity and lower parental education level. While there was not a significant difference between the initial visual acuity and final visual acuity in our cohort of patients, this factor represents two facets. One facet is that a 14-week period of time is difficult to achieve lasting and transformative results regarding improved visual outcomes, especially in amblyopia associated with accommodative esotropia, as this was the diagnosis in the majority of our patients with strabismic amblyopia. A second facet is that worse initial visual acuity represents a deeper loss of binocular vision and compounded with non- adherence to amblyopia treatment, it is difficult to achieve improved final visual outcome. Our study of this cohort of children at the pediatric ophthalmology clinic at Menelik II Referral Hospital serves as a springboard to further studies to help treating physicians better communication with parents for a better understanding of their childrens' amblyopia diagnosis and the long-term benefits of treatment adherence.

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