AMBLYOPIA AND VISUAL DEVELOPMENT

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by

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Amblyopia and Visual Development

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Background
Amblyopia, 'lazy' eye is a unilateral or bilateral reduction in vision for which no organic cause is present by physical examination of the eye with a prevalence of approximately 3.5% of the childhood population. It is commonly associated with a strabismus, refractive error or both. The most common form of treatment is conventional occlusion (daily patching the good eye). Clinical studies have attempted to investigate the optimal treatment of the disease and investigate compliance, however an evidence-base for treatment is still incomplete

Methods
The study included (i) a retrospective study of 322 amblyopic children to assess current visual outcomes in comparison to clinical effort and costs; (ii) A randomised control trial (n=52) comparing prescribed treatments of 0-hours, 3-hours and 6-hours patching per day in which compliance was electronically recorded; (iii) interviews of 25 families to explore reasons behind poor compliance; and (iv) a pilot study of educational material to improve compliance.

Results
Current outcomes of amblyopia treatment are mediocre at considerable financial and time-costs. The RCT revealed poor compliance in both patching groups (3-hours and 6-hours) leading to visual improvements that were not significantly better than no patching. However, there was a clear dose-response between visual improvement and effective hours patched ($p=0.00013$). The interviews demonstrated emotional distress in families, lack of social acceptance, and confusion about amblyopia, its treatment and the role of professionals. Early findings indicate that an educational intervention could reduce the number of poor compliers.

Conclusion
Poor compliance leads to poor visual outcomes of occlusion treatment for amblyopia. However, objective monitoring of patching demonstrates that occlusion therapy is effective. An educational intervention could address some of the problems associated with poor compliance such as poor parental understanding, providing feedback of visual improvement to the family and strategies for implementing patching as a normal routine.

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PURPOSE AND OUTLINE OF THE THESIS

The main purpose of the research encompassed in this thesis is to explore the efficacy of patching therapy for improving visual function in amblyopia. I will address the role of compliance in the success of treating amblyopic children and the development of strategies to improve compliance. These studies are some of the first investigations in which compliance has been monitored objectively using electronic 'occlusion dose monitors' (ODMs).

Chapter 1: Introduction

The chapter brings to the reader a general definition and history of amblyopia treatment. It addresses the causes of amblyopia and provides a more thorough understanding of the pathophysiological processes of the disease in the visual system. The prevalence of the disease and its effect on visual function and daily life are also considered. Particular emphasis is given to describing outcomes of amblyopia treatment and the problems of compliance to amblyopia treatment.

Chapter 2: Current Outcomes Of Amblyopia Treatment: A Retrospective Study Of 322 Children

The aims of this chapter are to describe the current visual outcomes and costs in a cohort of three-hundred and twenty-two discharged amblyopic children in a UK paediatric

ophthalmology clinic. Costs were measures in terms of prescribed hours of patching, duration of treatment, number of visits as well as financial costs to the UK National Health Service. Our conclusions were that outcomes were mediocre despite considerable costs with the main issue being compliance to treatment.

Chapter 3: The Occlusion Dose Monitor (ODM).

Novel occlusion dose monitors were the means of obtaining compliance measurements in this thesis. This chapter addresses how the ODMs were implemented clinically for the young amblyopic subjects (aged between three and eight years). It also describes difficulties encountered and how they were overcome.

Chapter 4: A Randomised Controlled Trial of Mixed and Strabismic Amblyopia Using Occlusion Dose Monitors to Record Compliance

The purpose of this chapter (the main study of the thesis) was to investigate compliance with patching treatment and to describe the dose-effect relationship between improvement in visual outcome and hours patched per day. This was achieved by objectively recording the genuine patching times in a group of strabismic and mixed amblyopes (n=52). We found variability of compliance in the treatment groups prescribed 3-hours patching and 6-hours patching per day. Visual outcomes were not significantly better than in the (0-hours group). However, genuine patching times overall were significantly correlated to improvement in visual function (i.e.there was a dose-response).

Chapter 5: Problems with Compliance and the Understanding of Amblyopia and its Treatment.

To further investigate unsatisfactory outcomes to amblyopia treatment due to poor compliance (such as reported in chapter 4) a qualitative study was performed in this chapter to explore parents' perceptions and personal experiences of occlusion therapy during patching. This study highlighted that areas of concern were emotional distress due to lack of social acceptance, misunderstanding of amblyopia treatment leading to treatment not being considered credible and poor understanding of the role of professionals. Parents who used reward strategies and incentives and incorporation of patching into daily routine achieved the best success.

Chapter 6: Improving Amblyopia Treatment. A Need for an Educational Intervention Program: Pilot Study.

The results from chapter 5 led to the development of educational intervention material for amblyopia, comprising of information packs, DVD and reward systems. A description of these methods is provided in chapter 6 with a pilot study to assess their effectiveness in enhancing compliance.

Chapter 7: Discussion.

The findings of the studies are brought together and discussed in the last chapter. Future studies in improving amblyopia treatment are considered.

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Chapter 1

General Introduction

1.1. Amblyopia an overview

1.1.1. The Definition of Amblyopia

Amblyopia is a disease developing in childhood often described using the colloquial term 'lazy eye'. It is derived from the Greek term '*amblyos*' (αμβλος) meaning dull, and '*opia*' (οπια), meaning vision (from the stem 'ops'), and hence 'blunt sight'(Cynader, 1982). The most commonly cited definition of amblyopia is given by Von Noorden (Noorden, 1977):

"A unilateral or bilateral decrease of visual acuity caused by form vision deprivation and/or abnormal binocular interaction for which no organic causes can be detected by the physical examination of the eye and which in appropriate cases is reversible by therapeutic measures".

Amblyopia is difficult to define because much of the visual system, especially the eye(s), appears to be normal. Consequently, Albrecht von Graefe succinctly described amblyopia as:

> *"The condition in which the observer sees nothing and the patient very little."*

Since the vast majority of amblyopia leads to unilateral decrease in visual acuity, clinically, amblyopia is commonly detected from a difference in inter-ocular visual acuities with no organic defect. However, as Taylor states (1994) (Taylor, 1994).

"Although classic definitions stress that amblyopia is visual loss with no associated organic defect, in fact there is always an abnormality, be it strabismus, anisometric amblyopia, isoametropia, or media opacity, which predisposes the eye or eyes to amblyopia".

Practically, amblyopia is associated with common disorders of the visual function related to amblyopia. In children, these are (i) anisometropic amblyopia (difference in the refractive errors of the two eyes leading to anisometropic amblyopia), (ii) strabismic amblyopia (an eye turn leading to misalignment of the visual axis and causing strabismic amblyopia) and (iii) combined strabismus and anisometropia (called mixed amblyopia). In addition, stimulus deprivation amblyopia is a less common form of amblyopia caused by opacification of the anterior or posterior visual pathway in the eye (e.g. from congenital cataract).

These conditions interfere with a sensitive period of visual development that occurs in early childhood, sometimes referred to as 'the critical period'. Consequently, amblyopia is commonly treated within the first 7 years of life (Holmes and Clarke, 2006) although occasionally it is treated over 8 years of age (Pater, 1998).

1.1.1.1. **Variable Definitions**

No strict definition has been established with respect to the inter-ocular difference of visual acuities. This is evident from criteria used by various research groups to define amblyopia (table 1.1).

Criteria used to define amblyopia for scientific studies		
Inter-ocular line difference	**Snellen lines**	**logMAR lines**
≥1 line	Lithander & Sjöstrand (1991)	Stewart et al. (2002) LogMAR
≥2 lines	Shaw et al. (1988)	Chandna et al. (2004) LogMAR
≥3 lines	Repka et al. (1992)	Pediatric Eye Disease Investigator Group (PEDIG) (2002)

Table 1.1. *Various criteria of inter-ocular visual acuity line differences (between the amblyopic and non-amblyopic eye) are used in defining amblyopia in sci To achieve this visual acuity tests i.e.the Snellen visual acuity or the LogMAR visual acuity tests are used (logMAR denotes logarithm of the minimum angle of resolution).*

An added problem is that amblyopia is also related to many other visual functions such as contrast and motion sensitivity (Leguire et al., 1990, Simmers et al., 2003). Von Noorden (1985) (Noorden, 1985) describes this accordingly:

"The complexity of the amblyopia syndrome is symbolized as an iceberg and reduced visual acuity is the most tangible of many disturbances of visual function".

Moseley and Fielder and the United Kingdom, Royal College of Ophthalmologists have provided practical criteria to define amblyopia (2002,2006) (Moseley and Fielder, 2002, Ophthalmologists and Sub-Committee, July 2006):

1) Inter-ocular line difference in visual acuity between the two eyes.

2) Threshold of visual loss in the affected eye.

3) Usually associated with the presence of a strabismus, phoria and anisometropia.

4) Age at presentation in childhood.

5) Absence of an organic anomaly.

Holmes and Clarke (2006) highlighted that large differences in neural immaturities should be taken into account when obtaining visual acuity especially from the younger age group. They suggested that '*variations*' in the process of the neural visual maturation generally coincide with unstable clinical findings in visual acuities. Therefore, one should not enthusiastically confirm the presence of an amblyogenic condition and commence treatment immediately (Holmes and Clarke, 2006).

1.1.2 Visual Acuity Tests

The term acuity is derived from the Latin "acuitas" =sharpness. Visual acuity eye is the ability to distinguish details and sharpness of objects independantly (Pelli et al., 2006). It is crucial in diagnosing the presence of the amblyogenic defect. Age-dependant tests are widely available but it is universally accepted that it is more difficult to accurately gain visual acuity measurements from younger patients.

1.1.2.1. Preverbal Visual Acuity Testing

Several methods have been designed to measure visual acuity in preverbal infants. These include gross examination techniques such as fixation behaviour (VanderVeen et al., 2006), fix and follow behaviour (Tay et al., 2006) and forced choice preferential looking.

Fixation behaviour: Fixation behaviour is observed to assess whether fixation is central and steady or wandering. It is classified into one of three categories - "good and central", "poor and central" and "roving and eccentric" (Simons, 2005). It is also observed after removal of the cover (during cover/uncover test) to assess how long the affected eye can hold fixation.

Fix-follow-maintain (FFM): This method requires attention of the infant to fix and follow a moving target, the examiner's face or a pen torch in various positions of gaze. This type of testing method has shown to be significantly unreliable and insensitive in diagnosing the presence of amblyopia (Atilla et al., 2001, Tay et al., 2006).

Forced-choice preferential acuity tests: Pre -verbal visual acuity tests have been developed according to the infant's stage of development (Manning et al., 1982, Hopkisson et al., 1991). Forced choice preferential using grating acuity (Atkinson et al., 1982, Moseley et al., 1988) such as the Teller cards (da Cunha and Moreira, 1996, McDonald et al., 1985, Teller et al., 1986) and vanishing optotypes (Frisen, 1986) like the Cardiff vision test (Johansen et al., 2003, Adoh et al., 1992, Adoh and Woodhouse, 1994) are commonly used for detecting amblyopia. The acuity is based on the highest spatial frequency seen and the clinician is able to judge by objective responses i.e. the infant's visual behaviour when attempting to fixate to a pattern or picture of the affected eye. These types of tests have a tendency to overestimate visual acuities (Ellis et al., 1988, Breyer et al., 2003) as compared to recognition tests e.g. HOTV and are questioned regarding their reliability and validity (Atkinson et al., 1982).

1.1.2.2. Verbal Visual Acuity Testing

The Verbal pre-schooler: Several methods can be used to test vision in verbal pre-schoolers, aged 2 years or older, for example the STYCAR, the Sheridan Gardner Tests, or the (HOTV) tests which use single and/or crowded (geometrical forms) optotypes (Figure 1.1). They are based on the matching principle that require subjective responses (Hohmann and Haase, 1993). The test-retest validity and reproducibility have been shown to be more rapid (Kastenbaum et al., 1977). This means the test can be easily repeated, for example, for recording VA under monocular viewing with left and right eyes open and binocular viewing.

Figure 1.1. *Subjective visual acuity test procedure (Reproduced from Jour Comm Eye Health 1998; 11(27) 36).*

With verbal visual acuity tests, a template of the same letters on the chart is given to the subject to match the same optotype. It has been shown to increase testing performance of the subject (Merritt et al., 1996). However, single optotypes (Sprague et al., 1989) overlook the presence of amblyopia (Simons, 1983) compared to the quantitative crowded (section 1.3.1) linear optotypes (Hohmann and Haase, 1982).

Older children: Letter based systems are mainly used to measure vision in older children (aged 4 years onwards) for the detection of amblyopia. These included the Snellen chart, and more recently, the Bailey-Lovie logMAR visual acuity tests. These tests have a subjective component in that the child is required to understand the test and lettering system used.

The Snellen chart: The Snellen chart is the most widely used clinical test for visual acuity (Figure 1.2). It has been used consistently over many decades howeer, questions have arisen on the validity, reliability, reproducibility of the Snellen Chart (Davidson and Eskridge, 1977, Hussain et al., 2006) as well as the duration of testing time required (Shah et al., 2005) and its sensitivity for detecting central visual disturbances (Skalka, 1980). Although this test is the most frequently used option for detecting visual defects it has a number of weaknesses (Brant and Nowotny, 1976). The chart has different numbers of letter per line which can cause the crowding to become a confounding effect (Khamar et al., 1996). The step progression is unequal in visual acuity and not linear. There is also a risk of chart memorization during repetitive testing in older children (Johnson et al., 1998).

Figure 1.2. *The Snellen Chart*

1.1.2.3. LogMAR Visual Acuity

The logMAR visual acuity test (for older children and adults): A more refined form of vision testing compared to the Snellen chart, is the logMAR (Logarithm of the minimum angle of resolution) visual acuity test. The chart was designed by Ian Bailey and Jan Lovie-Kitchen and first introduced in 1976 (Bailey and Lovie, 1976). It was developed to achieve better threshold of vision with the crowding phenomenon compared to the Snellen vision test (Lovie-Kitchin, 1988).

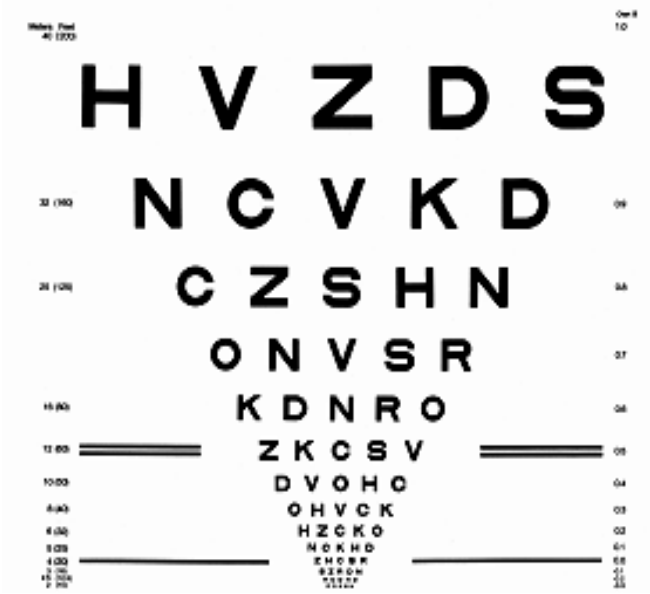
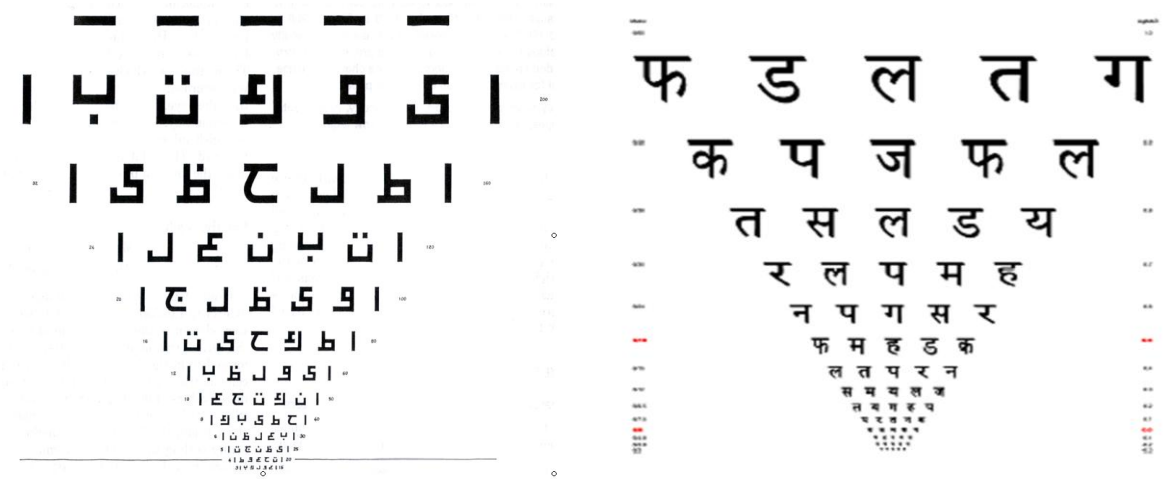


Figure 1.3 *Standardised Bailey-Lovie logMAR Visual Acuity Chart.*

It is standardized such that the letter progression from top to bottom has equal spacing in each line and size, with a Snellen conversation column on one side, Figure 1.3 (A). The overall acuity values ranges from 6/60 (20/200) to 6/4 (20/15).

The design of the Bailey-Lovie visual acuity chart has also been adapted, for use in other parts of the world in other languages. Al-Mufarrej et al. (1996) have redesigned the chart in Arabic (Figure 1.4.(A)) (Khamar et al., 1996) and Khamar et al. (1996), have reconstructed the chart in Hindi and Gujarati (Al-Mufarrej et al., 1996) (Figure 1.4 (B)) for the non-English speaking patient (Al-Mufarrej et al., 1996).



A. *Design of the Bailey-Lovie Vision Chart adapted for use in Arabic.*

B. *Design of the Bailey-Lovie Vision Chart adapted for use in Hindi and Gujarati.*

Figure 1.4: Modified versions of the LogMAR chart in national languages spoken in other countries.

The logMAR acuity test is becoming the preferred choice for acuity measurement, not only in scientific based studies, but also in clinics. The test-retest reliability is high ensuring continuous changes acuities that are easier to interpret (Stifter et al., 2004, Ferris et al., 1982).

The Glasgow logMAR visual acuity test (younger children): Keeler Glasgow Acuity-Cards are a more child friendly version of the logMAR test which requires the child to point at a card (McGraw and Winn, 1993). The test is suitable for ages 3 ½ years and upwards. It is becoming increasingly favoured over other vision tests, for its reliability, suitable for scientific research and vision screeninge. This is because the design is based on standardization of letter progression of equal legibility (equal letters per line), with surround contours retaining the crowding phenomenon around each line (Figure 1.5) (Atkinson et al., 1988).

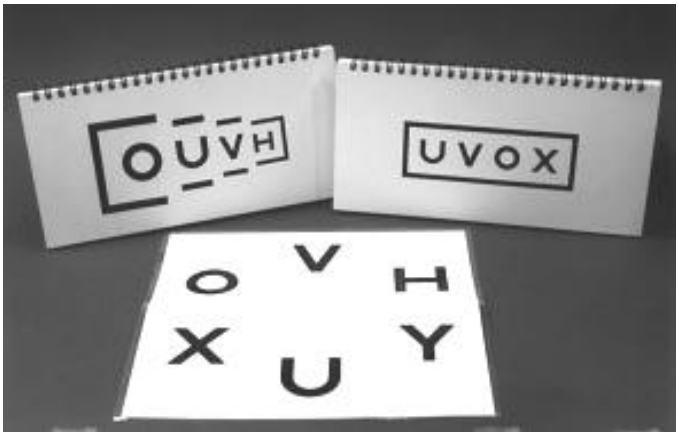


Figure 1.5. Keeler *Glasgow acuity card vision test using logMAR concept. The main measure of visual outcome in this study (Reproduced by Cleary 2000. BJO, 84 (6): 572-78)*

The Glasgow acuity card vision test gives consistent results for ages three and above with high test-retest reliability and high sensitivity of less than 0.1 logMAR units (Simmers et al., 1997, McGraw et al., 2000). It has been previously used in amblyopia research (Cleary, 2000) and will be the main measure of visual outcome for this study.

1.1.3. Contrast Sensiivity and Tests.

Mentioned in more detail (section 1.3.2) contrast sensitivity function (CSF) is also impaired in strabismic, anisometropic (Abrahamsson and Sjostrand, 1988) and deprivation amblyopia (Boothe et al., 1996). Several methods have been used to investigate contrast sensitivity (CS) such as the Pelli-Robson CS chart and the Vistech CS system.

Pelli Robson Chart: is a test based on letters rather than sine or square-wave gratings decreasing in contrast. The letters are composed of vertical, horizontal, curved and oblique square-wave targets that have been formed by whole spatial frequencies (i.e. each letter or optotype) (Elliott et al., 1990). The letters are read from top to bottom and left to right and the size of the letters subtend at an angle of 0.5 degrees at 3 meters designed for testing at 3 meters in well-illuminated conditions (Figure 1.6). The letters on each line are arranged in two groups (3 letters per group) having the same contrast. The contrast of the letters in each successive group gives the log contrast sensitivity given in the preceding group such that the letters are in proportional step from top to bottom and left to right testing each eye separately.

Figure 1.6. *An example of the Pelli-Robson, Letter Contrast Sensitivity Chart.*

CSF tests are seldom used in assessing the levels of amblyogenic deficits. Recently Moseley et al. (2006) suggested that the Pelli-Robson chart does not give an accurate measure of loss in visual function especially in dense or severe amblyopes as it tends to measure contrast sensitivity at low spatial frequencies (Moseley et al., 2006).

1.1.4. Epidemiology of Amblyopia

1.1.4.1. The Prevalence of Amblyopia.

Amblyopia is the most common cause of uni-ocular reduced visual acuity in childhood and school aged children (Ohlsson et al., 2003) with a prevalence usually stated between 0.5% to 3.5% (von Noorden and Campos, 2002). Some studies have shown incidence up to 5% (Sjostrand and Abrahamsson, 1996, Ehrlich et al., 1983). Interestingly, Wang et al. (2000) have also found amblyopia to be most frequent cause of unilateral vision loss in the age group of 49-59 year old (Wang et al., 2000). Cataract and ARMD were the most common causes of unilateral vision loss in the over sixties (Rahi and Cable, 2003)

The variations in prevalence estimates are probably due to quantitative differences in the diagnostic criterions as shown in Table 1.2 (Simons, 1996).

Studies	Sample size	Diagnostic criterion	Prevalence (%)
Adult population			
Rossman et al. (2005) (Military recruitment)	122,596	VA ≤ (20/40 - 6/12)	0.35
Brown et al. (2000)	4721	VA ≤ (20/30–6/9)	3.06
Jakobsson et al. (2002)	11,365	VA ≤ (20/40-6/9)	1.7
Attebo et al. (1998)	3654		
	. . . .*	VA ≤ (20/30-6/9)	3.2
	. . . .*	VA ≤ (20/40-6/12)	2.9
Preschool and School populations			
Kvarnström et al. (1998)	3126		
	. . . .*	VA ≤ (20/25-6/7.5)	0.6
	. . . .*	VA ≤ (20/60-6/18)	0.9
	. . . .*	VA ≤ (20/100-6/30)	1.7
Lithander et al. (1998)	6292	VA ≤ (20/40-6/12)	0.9
Ohlsson et al. (2003)	1035	VA ≤ (20/40-6/12)	2.5
Wedner et al. (2000)	1386	VA < (20/40-6/12)	0.2
Robaei et al. (2006)	1741	VA < (20/40)	0.7

Table 1.2. *A modified table of a small selection of some past prevelance studies conducted in the last decade. VA denotes visual acuity. Dots with Asterisks denotes where the same study sample has been used with different criteria sets, i.e. for studies Attebo et al. sample: 3654 and Kvarnstrom et al sample: 3126.*

Recently, Robaei et al. and Drover et al. (2006, 2008) also addressed the effect that variations in criteria (both according to a specified VA or interocular line difference) had on prevalence estimates (see Table 1.3.) (Robaei et al., 2006b).

VA Criterion for Amblyopic Eye		No Line Criterion		1-Line Difference*		2-Line Difference*	
logMAR Letters	Snellen VA Equivalent	Total Eyes, No. (%)	Treated Eyes, No. (%)	Total Eyes, No. (%)	Treated Eyes, No. (%)	Total Eyes, No. (%)	Treated Eyes, No. (%)
All VAs	All VAs	32 (1.8)†	23 (71.9)	26 (1.5)	23 (88.5)	12 (0.7)	6 (50.0)
≤45	≤20/30	24 (1.4)	17 (70.8)	21 (1.2)	16 (76.2)	12 (0.7)	6 (50.0)
≤40	≤20/40	17 (1.0)	10 (58.8)	16 (0.9)	9 (56.3)	12 (0.7)	6 (50.0)
<40	<20/40	15 (0.9)	8 (53.3)	14 (0.8)	7 (50.0)	12 (0.7)	5 (41.7)
≤35	≤20/50	9 (0.5)	4 (44.4)	9 (0.5)	4 (44.4)	8 (0.5)	4 (50.0)
≤30	≤20/60	6 (0.3)	3 (50.0)	6 (0.3)	3 (50.0)	6 (0.3)	3 (50.0)
≤25	≤20/80	4 (0.2)	2 (50.0)	4 (0.2)	2 (50.0)	4 (0.2)	2 (50.0)

Abbreviations: logMAR, logarithm of minimum angle of resolution; VA, visual acuity.
*Line difference refers to the difference in VA between the amblyopic and nonamblyopic eyes.
†Includes 8 children with a corrected VA greater than 45 letters in the amblyopic eye. Diagnosis was based on corroborative historical data.

Table 1.3. *Prevalence of amblyopia and proportion of treated case in 1739 children using different diagnostic criteria. From Robaei et al. (2006).*

The preponderance of amblyopia is higher when associated with developmental disorders such as Downs Syndrome (Tsiaras et al., 1999), cerebral palsy (Black, 1982), prematurity, low birth weight and ROP (Rudanko et al., 2003). Interestingly, a randomised controlled trial by the Avon Longitudinal Study of Parents and Children (ALSPAC) found that the amblyopia prevalence was approximately 45% lower in children that received preschool vision screening at just over 3 years than those who did not receive early screening (Williams et al., 2003). In an earlier study by the same group (2002), they found that implementing earlier and more intense intervention, in comparison to screening only, also resulted in better VA after treatment by the time the children reached 7 ½ years of age (Williams et al., 2002).

Several studies have shown a greater potential risk of visual loss in the better eye because of the defective vision in the amblyopic eye (Rahi et al., 2002, Jakobsson et al., 2002, Tommila and Tarkkanen, 1981, Vereecken and Brabant, 1984). For example, Rahi et

al. have shown in their UK population based study of amblyopes, a projected much greater lifetime risk of three times higher than normal visual impairment in the sound eye than that of the general population (Rahi et al., 2002) (Table 1.4).

Life time risk	Risk of visual impairment	Main Cause
Childhood (< 16 years)	0.03%	Trauma
Working age adults (16-64 years)	0.6%	Trauma
Older adults (by 95 years)	3.3%	ARMD

Table 1.4. *Projected lifetime risk (%) of visual impairment in the sound eye with an incidence per 100 000 total population with unilateral amblyopia. (from Rahi et al., 2002) (ARMD= age related macular degeneration).*

A number of reports indicate that trauma rather than disease is the most significant cause of unilateral visual loss in the younger age group (Simon et al., 2004, Stager et al., 1990). This was also supported in a small sample study in Finland, Tommila and Tarkkanen (1981) who suggested that trauma occurred mostly in the work place (Tommila and Tarkkanen, 1981).

1.1.4.2.. The Prevalence of Amblyopia in Undeserved Populations.

Amblyopia has been shown to be more prevalent in underserved poorer non-Western populace such as Tanzania (Wedner et al., 2000), Nepal (Thakur et al., 2004), China (Zhao et al., 2000, Zhang et al., 1992), India (Rahi et al., 1995), Saudi Arabia (Tabbara and Ross-Degnan, 1986) and also amongst those who reside in disadvantaged modern societies (Hudak and Magoon, 1997). This is due to poorer detection through

screening and less available treatment. Smith (1994) found that the amblyopic citizens from the socially deprived areas in the UK, using the Townsend deprivation score presented on average 22 months later, despite the implementation of screening services (Smith et al., 1994). Recent findings in the ALSPAC study (2008) defining parental socio-economic status (SES) showed prevalence of untreated and treated amblyopia was higher in families with lower SES compared to families with higher SES. This was because utilisation of childhood eye care services was less and seeking services were not considered important.

1.1.4.3. Prevalence Estimate Differences related to Gender, Aetiology and Ethnicity

In general most studies show no gender predilection for amblyopia (Merritt et al., 1996, Shaw et al., 1988, Brown et al., 2000, Woodruff et al., 1994a, Kohler and Stigmar, 1973) however, some studies describe greater prevalence in males (Tabe Tambi, 1993) and others in females (Garcia et al., 2005). Interestingly, one study in Leicester, UK, reported that males presented later to clinics than, than females as did Asians compared to Caucasians (Shaw et al., 1988).

Self-referrers to clinics often first presented due to a manifest strabismus rather than the suspected presence of amblyopia, (Attebo et al., 1998) with esotropia being the more common than exotropia (Friedman et al., 1980, Aurell and Norrsell, 1990, Dawson et al., 2003). However, implementation of visual screening provides greater detection of amblyopia due to anisometropia (Donahue, 2005, Brown et al., 2000, Quah et al., 1991). In general, hypermetropia (also called hyperopia) is common in amblyopia and is usually associated with a heterotopia or heterophoria (Robaei et al., 2006a). For example,

hypermetropia has been described as being more prevalent in a population based in Sydney, Australia (Attebo et al., 1998) and the lower middle class southern population of India (Kalikivayi et al., 1997). Murthy et al. have shown that hypermetropia was more prevalent amongst the females in an urban population of New Delhi (Murthy et al., 2002) with tendency of this type of refractive errors increasing further with age amongst females (Shahriari et al., 2007). In contrast, the prevalence of myopia was found to be greater, amongst female populations in China (He et al., 2007, Goh et al., 2005) and the rural older population of India (Dandona et al., 2002).

1.2. Pathophysiology

1.2.1. Causes of Amblyopia

The most common amblyogenic factors responsible for the disturbance of the visual development leading to amblyopia are:

(i) Strabismus: This is an ocular misalignment leading to different images falling on the two foveae. One image is suppressed to avoid confusion or diplopia (Figure1.7). It is a consequence of unilateral constant or decompensating unilateral strabismus, manifest in appearance, with onset in childhood. Common unilateral associated with amblyopia is esotropia (usually one eye deviating inwards towards the nose) or exotropia (usually one eye deviating outwards towards the ear) although this latter is less frequent.

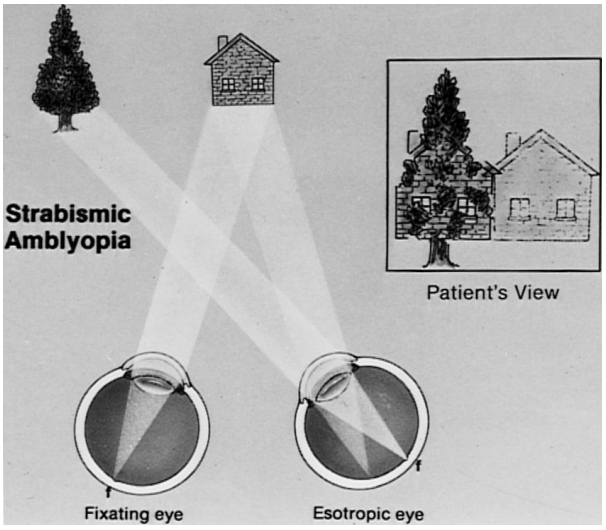


Figure 1.7.Strabismic amblyopia *leads to diplopia. Visual confusion and diplopia caused by strabismus. (from GK Von Noorden (von Noorden and Campos, 2002): Amblyopia: A Multidisciplinary Approach (Proctor Lecture). Invest Ophthalmol Vis Sci 26:1704, 1985).*

Treatment of amblyopia associated with strabismus in extended further in section 1.5.5 of the thesis.

(ii) Anisometropia: This is refractive error in one eye resulting in the foveal image in the affected eye being more blurred than the other eye (Figure 1.8) the refractive error could be hypermetropia or myopia.

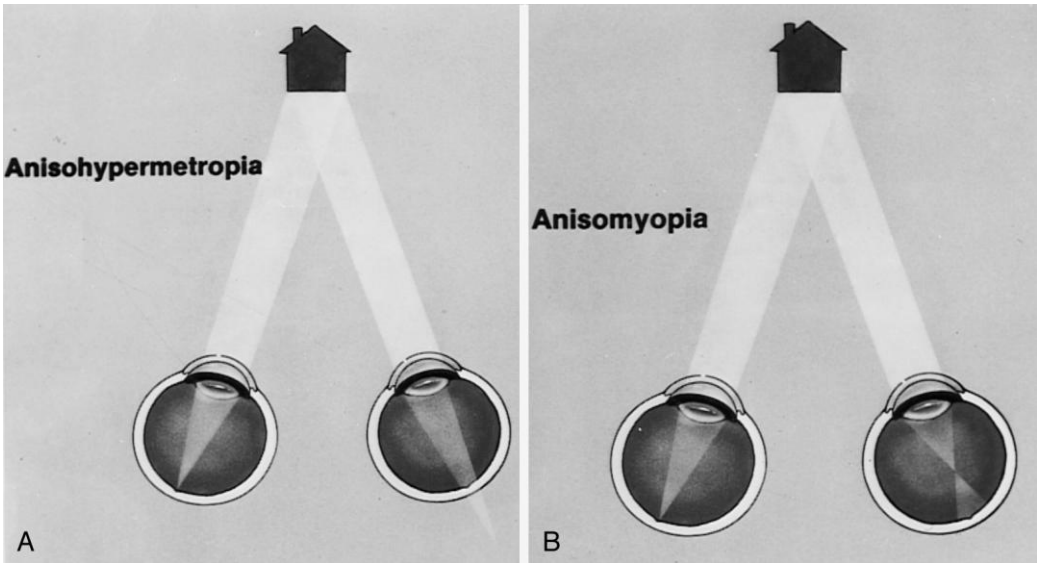


Figure 1.8. Anisometropia *where two fovea sharing the same image but one image is more degraded or blurred than the other due to the presence of a refractive error (from GK Von Noorden(von Noorden and Campos, 2002)).*

(iii) Stimulus Deprivation: is where an obstruction prevents a clear retinal image to one eye (or both eyes) for example through congenital cataract vitreous or media opacity or ptosis covering the pupil (Figure 1.9).

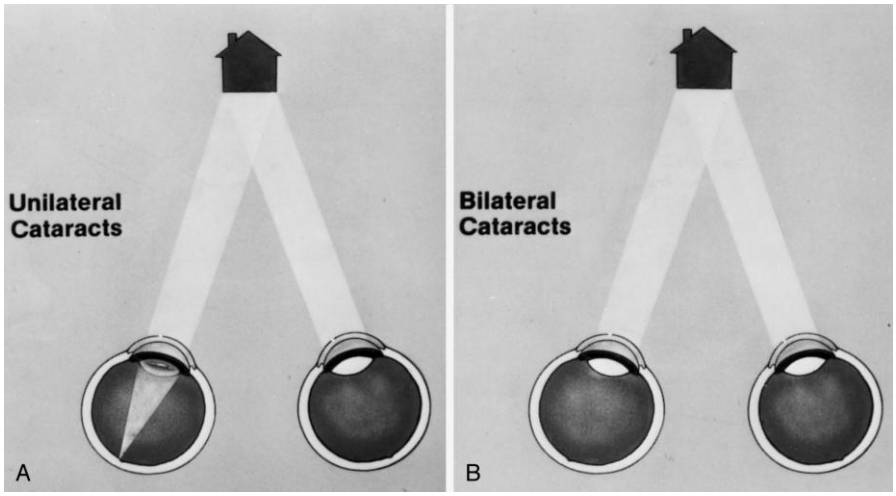


Figure 1.9. Stimulus deprivation *in one eye due to the presence of a unilateral cataract where only diffuse and reduced amounts of light enter (from GK Von Noorden (von Noorden and Campos, 2002)).*

(iv) Mixed amblyopia: is a combination of strabismus and anisometropia

(v) Ametropic amblyopia: is an uncorrected refractive error in both eyes leading to bilateral amblyopia.

Common aetiologies leading to the causes of amblyopia shown in Table 1.5.

Unilateral	Bilateral
Manifest Strabismus	**Visual Deprivation**
Esotropia	Cataracts of equal density
Exotropia (rare)	Uncorrected high ametropia
Hypertropia (rare)	Manifest nystagmus
Anisometropia	
Anisohypermetropia	
Anisomyopia	
Anisoastigmatism (meridonial)	
Anisokonia (rare)	
Visual Deprivation	
Cataract	
Complete ptosis	
Opaque cornea	
Hyphema	
Vitreous clouding	
Prolonged uncontrolled occlusion	
Prolonged unilateral atropinisation	

Table 1.5. *Aetiology of differing types of amblyopia(Reproduced by von Noorden Amblyopia. A Multidisciplinary Approach. Proctor Lecture. IOVS 26:1704-1716, 1985. (page 1705)*

Sometimes the term amblyopia has been used to describe diseases such as toxic optic nerve disease such as tobacco-alcohol toxicity (Solberg et al., 1998), nutritional deficiencies (Lessell, 1998). However, these conditions correspond to an organic toxic neuropathy and will, therefore not be included in this thesis as a form of functional amblyopia. Also, non-organic defects such as hysterical/psychogenic visual loss have been included under the term amblyopia (Weller and Wiedemann, 1989).

1.2.2. Genetics

In several families, strabismus and associated amblyopia have been found to have with inheritance through a dominant autosomal pattern with incomplete penetration (Abrahamsson et al., 1999, Dufier et al., 1979) Ziakis et al. (2002) recognised familial inheritance of complete three-generation families in different types of strabismus. They found a significant proportion of first-degree relatives were affected with hypermetropic accommodative esotropia (Ziakas et al., 2002). Their study also found that the heritability of refractive error was more significant than the presence of strabismus itself. Recent identification of a locus of the gene mutation(s) responsible for causing strabismus and amblyopia could open up a field of research in which the cause of strabismus could be explored (Engle, 2007). Parikh et al. (2003) describe a large family in which strabismus occurred in 8 relatives of the same pedigree they found the region on chromosome 7p with the risk for first degree relatives of an affected strabismic individual estimated to be between 3 to 4 members. They suggested future studies will be able to identify genes

underlying the commonest forms of concomitant (stable angle) strabismus (Parikh et al., 2003).

1.2.3. Critical Period and Plasticity

Normal visual experiences are essential to the development of visual functions usually in the first decade of life (Greenwald and Parks, 1980), usually referred to as the 'sensitive' or 'critical period' (Barrett et al., 2004). If the infant does not receive appropriate foveal cortical stimulation during this *"critical period",* it may be difficult, even impossible, to develop that function later in life (Daw, 1998).

Three periods in development of visual acuity can be distinguished as described by Simons (Simons, 2005):

- **Period 1:** *The period of development of visual acuity* ranging from birth to 3-5 years during which time the visual acuity improves from 6/60 to 6/6 (Teller et al., 1986).

- **Period 2:** *The period during which deprivation is effective in causing amblyopia* from a few months to 7 or 8 years of age (Thomas et al., 1979).

- **Period 3:** *The period during which recovery from amblyopia can be obtained* from the time of deprivation to the teenage years or even into the adult years (Liao et al., 2004, Simmers and Gray, 1999).

Simons (2005), stated that the infant's eyes begin in a state of semi-independence of the two eyes (Simons, 2005). True binocular vision and fusion of single visual percept of the images from the two eyes develops later in about the first six months of life, which coincides with the development of the primary visual cortex (Braddick et al., 1983). Initially infants experience sensory fusion in the two eyes rather than true fusion with binocularity (Eizenman et al., 1999). If fusion is absent, restoration of binocular single vision (BSV) is unlikely. The development of binocularity (termed binocular single vision (BSV), i.e. the ability to maintain a single visual percept) can be assessed using Worth's classification. Claude Worth (1869-1936) insisted that "fusion faculty" existed for the development of normal binocular vision and disruption of this was one of the causes for strabismus (von Noorden, 2002). He separated binocularity into three grades, that is clinically tested and still used in clinical orthoptics (Mein J, 1991):

Grade-I. Simultaneous perception: *Simultaneous perception of two images, one formed on each retina (Mein J, 1991).* One method for testing this grade is for example the Bagolini test (Figure 1.10A).

Grade-II. Fusion and amplitude consists of two components*: Sensory fusion:* the ability to appreciate two images, one from each eye, and interpret them as one and avoid diplopia. *Motor fusion*: the ability to maintain a single fused image during vergence movements, i.e. the amplitude (von Noorden, 2002). The degree of motor fusion during vergence is measured using amplitude. The horizontal amplitude assesses convergent and divergent components of amplitude, using prisms, and is measured in prism dioptres. The prism fusional range method is often used to test true amplitude of fusion (Figure 1.10B).

Grade-III stereoscopic vision: This is the ability to appreciate *depth perception*. Stereopsis rapidly matures to adult levels in the first 12 to 24 months of life. It relies on the ability to fuse horizontal dissimilar images, of the same object (although only within a defined band/area around corresponding retinal points to give BSV called the Panum's fusional space) resulting in binocular appreciation of depth. The Frisby Stereoacuity test or Titmus Fly Test could be used to test stereopsis (Figures 1.10C (i) and (ii)).

A

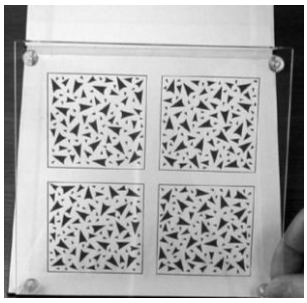
Testing Grade I. Bagolini Glasses

B

Testing Grade II. Prism Fusion Range

C(i)

C(ii)



Testing Grade III. Wirt or the Frisby are examples of stereoacuity Tests.

Figure .1.10: *Examples of orthoptic equipment used for binocularity testing used to grade on Worth's classification. (A) Bagolini glasses to test presence of sensory fusion. (B) Prisms to test for fusional range and (C) tests for stereoacuity, i.e. (i) Titmus Fly and (ii) Frisby stereoacuity tests. (Figures reproduced from orthoptic equipment supplies: Haag-Streit, UK, Keeler Orthoptic Ophthalmic Instruments, UK, and Frisby Stereotest Company, UK)*

It is usual in orthoptic practice to assess binocular functions regularly during the management of amblyopia treatment. Studies have reported improved stereoacuity following amblyopia treatment (Kraft, 1998, Daw, 1998). Lee and Isenberg (2003) describe a significant linear relationship between stereoacuity and visual acuity following amblyopia treatment in small angle strabismus (Lee and Isenberg, 2003). It is important to ascertain the strength of BSV to chart the effects of strabismus surgery or decompensating heterophoria using tests described in Figure 1.10.

1.2.4. Neural Basis of Amblyopia

Visual information follows two pathways from the retina through the cortical areas. The dorsal stream (or parietal pathway) is commonly referred to as the "where pathway" and is involved in motion processing, spatial awareness and guidance of actions such as reaching for an object (Figure 1.11). The ventral stream (or temporal pathway) is the "what pathway" involved in form recognition and object representation. The dorsal pathway is primarily driven by the highly motion and contrast sensitive cells of the magnocellular cells of the retina and lateral geniculate nucleus (LGN). Information is directed to the motion sensitive visual cortical areas of the middle temporal (MT) and medial superior temporal (MST) areas. The ventral pathway is driven by the colour sensitive high spatial acuity parvocellular cells of the retina and LGN. Information is directed through areas V2, V3 and V4 to the inferior temporal cortex. There is a high degree of crossover with these two pathways. Wurtz and Kandel (2000), stated that the inferior temporal (i.e. ventral stream) and posterior parietal pathway (i.e. dorsal stream) have shown to have interconnections of

neurons between the two (Kandel E.R, 2000) in the visual cortex. Both cortical pathways converge and diverge at the primary visual cortex (area V1 also known as striate cortex) (Kandel E.R, 2000).

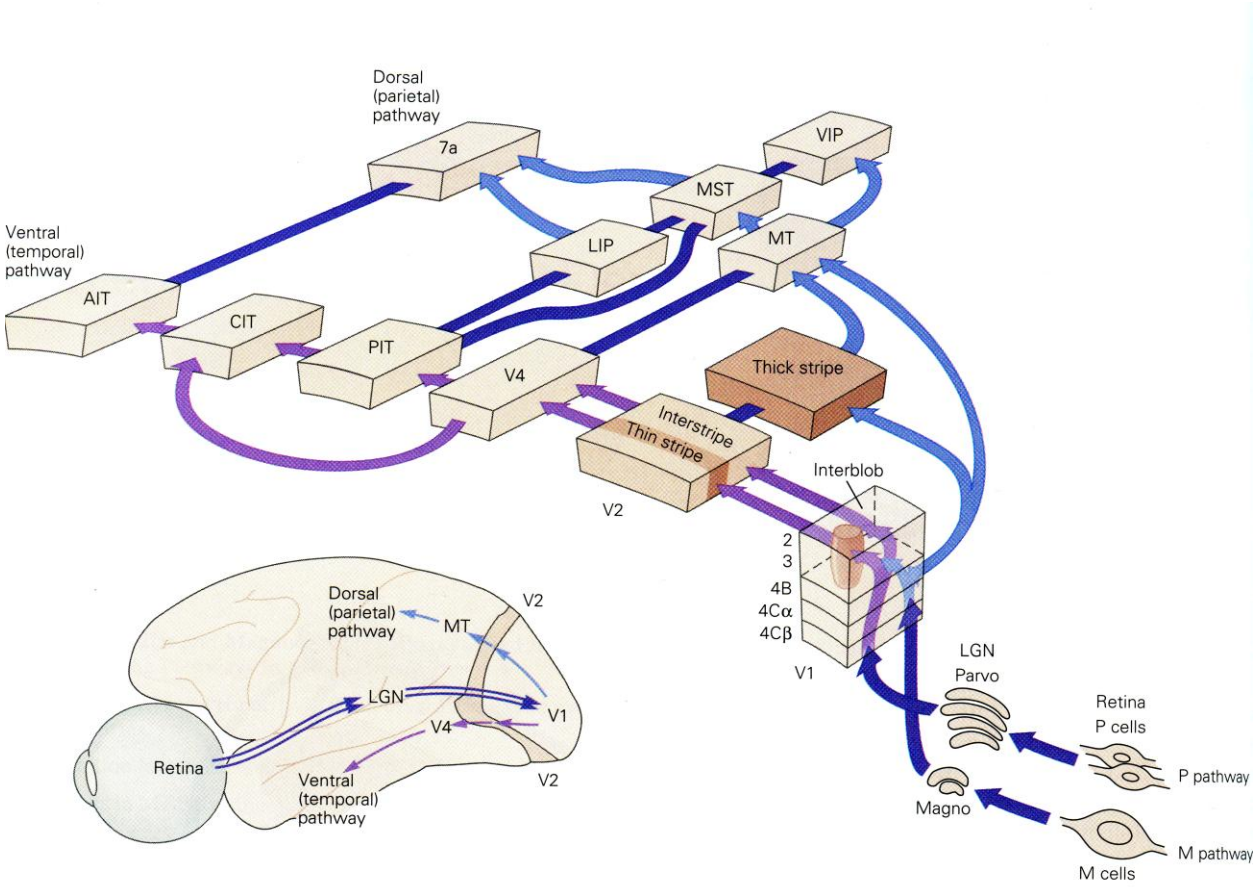


***Figure 1.11*. Dorsal and ventral pathways** *(see text for explanation). P pathway = parvocellular pathway, M pathway = magnocellular pathway, MST medial superior temporal area, MT = middle temporal area, LIP, VIP = lateral, ventral intraparietal areas, AIT, CIT, PIT = anterior, central, parietal temporal areas.*

The striate cortex is composed of vertical columns called orientation columns discovered by Hubel and Wiesel (section 1.2.4.3) that respond to all orientations in a particular area in retinotopic space. Orientation columns are then organised into ocular

dominance columns receiving information from either the right eye or left eye. The interaction between ocular dominance columns is imperative for binocular interaction necessary for fusion and depth perception. The input from each eye enters layer 4C which consists of monocular cells with circular surround receptive fields. The layers above and below layer 4C consist of binocular cells of which are two major groups, simple and complex cells, that respond to linear stimuli such as a line or bar. Thus, the primary visual cortex is involved in pattern recognition of stationary objects controlled by the parvocellular pathway of the LGN.

Whether amblyopia is caused by the loss of connections between the cortex and retina (under-sampling), or rearrangement of the connection (spatial scrambling) or neural dissaray (neurones are disordered) remains uncertain (Levi and Klein, 1990, Hess and Field, 1994, Gingras et al., 2005). The visual system in its mature and well-developed state is not immune to stimulation resulting from a late onset strabismus. If strabismus occurs when the visual system is in its mature state (i.e. late onset strabismus), the patient is likely to experience diplopia (double vision). This does not occur in the younger patient due to the brain's ability to suppress the second image (von Noorden and Crawford, 1979) and likely to lead to amblyopia (Lewerenz, 1978).

Studies have suggested that deficits can occur at numerous loci along the visual pathway prior to V1, in striate cortex and also in extra-striate cortex (V2 through to V5).

1.2.4.1. Pathophysiology defects affecting the retina

Functionally, it is known that X-cells, of the retinal ganglion cells, respond to sustained responses and linear spatial summation. The Y-cells, of the retinal gaglion cells, respond to transient movement and non-linear spatial summation (Shou and Zhou, 1989) Ikeda and Tramain (1979) found significant reduction in contrast sensitivity and poorer spatial resolution in the sustained X-cells in the area centralis of the deviating eye or blurred eye of cats compared to the X-cells in the fellow eye. Small levels of amblyopia were found in the transient Y-cells. They concluded that amblyopia is associated with inadequate or loss of stimulation in the central retinal ganglion cells (Ikeda and Tremain, 1979). More recent psychophysical studies suggested that dysfunction of vision in amblyopia includes deficits in the retina (Westheimer, 2004). Abnormalities of the optic nerve (such as myelinated nerve fibers) are also associated with anisometropic or strabismic amblyopia (Straatsma et al., 1979, Kushner, 1984).

1.2.4.2. Pathophysiology defects affecting the lateral geniculate nucleus

Sustained cells in the lateral geniculate nucleus (LGN) showed severe visual loss compared to the fellow eye. Ikeda and Wright (1976) concluded amblyopia caused by an induced squint in kittens is probably a degeneration of high spatial frequencies tuning cells in the pathway before reaching the primary visual cortex (Ikeda and Wright, 1976). However, recent advances with animal and human electrophysiological experiments suggest that the retina and the LGN are unaffected by the presence of amblyopia (Barrett et al., 2004) but this suggestion require further investigations.

1.2.4.3. Pathophysiology defects affecting the visual cortex

Animal models of amblyopia have been used to gain an understanding of the pathophysiology of the visual cortex and to serve as models for treatment in humans (Blakemore, 1976). The most important findings were the groundbreaking studies of Torsten Hubel and David Wiesel in the late 1950's and 1960's. Their Nobel prize winning studies introduced the physiological and neuroanatomical concept of cells in the lateral geniculate nucleus (LGN) and the primary visual cortices of cats and macaque monkeys being partitioned into two categories: simple and complex (Ibbotson et al., 2005). They also provided an insight into the neural basis of human amblyopia (Brendan T, 2004 Oct, Hubel and Wiesel, 1959).

Hubel and Wiesel with their associates, first described the columnar arrangement of cells in the striate cortex of cats and infant monkeys known as ocular dominance columns (Hubel and Wiesel, 1963). The ocular dominance columns of the primary visual cortex, shown by injecting one eye with the radioactive tracer proline, are apparent as 'zebra-like' alternate black and white stripes. These stripes are equally proportioned in the normal cat (Figure 1.12 (i)). By deliberately introducing monocular deprivation using surgically induced full ptosis, the cells and size of stripes in the ocular columns of infant monkeys and kittens had shrunk (Hubel and Wiesel, 1964) for the deprived eye (shown in figures 1.12 (ii) and (iii)). The loss occurred in layer IV Cβ and also the lamina of the LGN of the visual cortex. This represents a model form for deprivation amblyopia.

Hubel and Wiesel showed that occluding and depriving input into one eye during the *early* stage of the critical period, when the ocular dominance columns are segregating, leads to the axons of the LGN projecting from the occluded eye retracting. Depriving input in one eye during the *late* stage of the critical period development, when the ocular dominance columns are nearly completely segregated, leads to the axons that are already serving the non-occluded eye, developing collateral branches that extend into the territory of the occluded eye. This leads to sharing of these populations of cortical cells from either eye without overlapping in the cortex. This has the consequence of reduced stereopsis due to a lesser number of binocular driven cells in the visual cortex (Ikeda, 1979).

i. Normal **ii. Non-deprived eye** **iii. Deprived eye**

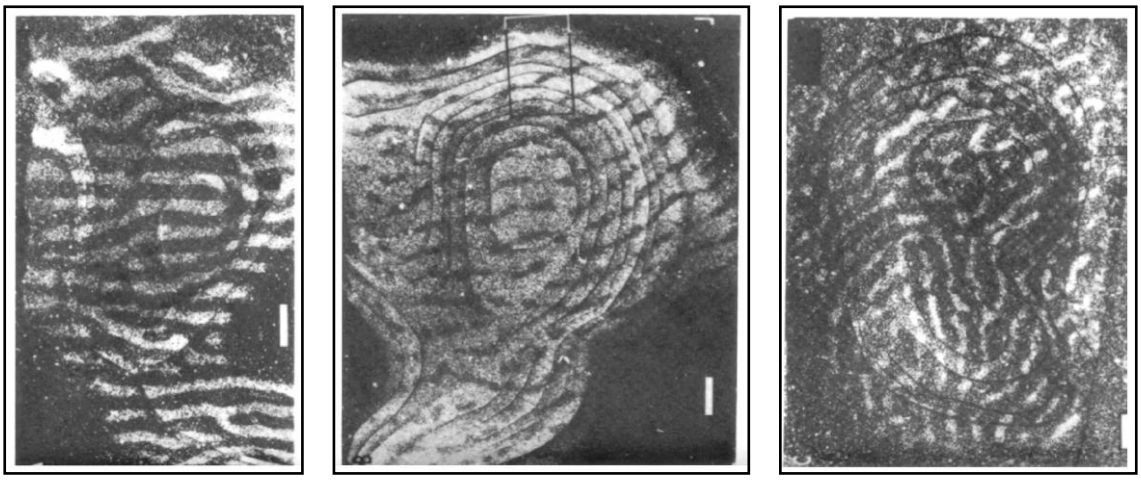


Figure 1.12: (i) *Ocular dominance columns in layer IVCβ of the visual cortex of an adult monkey.* ***(ii)*** *Ocular dominance columns in the layer of the visual cortex of an 18- month old monkey with visual deprivation with the non-deprived right eye labelled with proline.* ***(iii)*** *The pattern resulting when the deprived left eye was labelled with proline. (Reproduced from, Wiesel, T.N.: Postnatal development of the visual cortex and the influence of environment (Nobel Lecture). Nature 299: 583-591 (1982),*

Recent studies have been able to replicate in the human brain some of these findings in animal models. Horton (2006) investigated the right occipital lobe of a normal elderly deceased man (see Figure 1.13) whose left eye was enucleated 20 years prior to his death. It shows the arrangement of the ocular dominance columns (ODC) and a super-imposed image (top right hand corner) staind with cytochroe oxidase (CO) in the ight visual cortex that are very similar to the ODC in macaques (Horton, 2006).

Cytochrome oxidase is a mitochondrial enzyme which stains heavily cortical patchesin the primary visual cortex called cytochrome oxidase (CO) blobs. It is widely

accepted that CO blobs are denser in the middle of the ocular dominance bands and hence can be used to investigate ocular dominance column shrinkage and expansion. During abnormal visual experience for example, monocular deprivation, the blobs from the deprived eye have been shown to shrink (Adams and Horton, 2006, Nakagama and Tanaka, 2004)

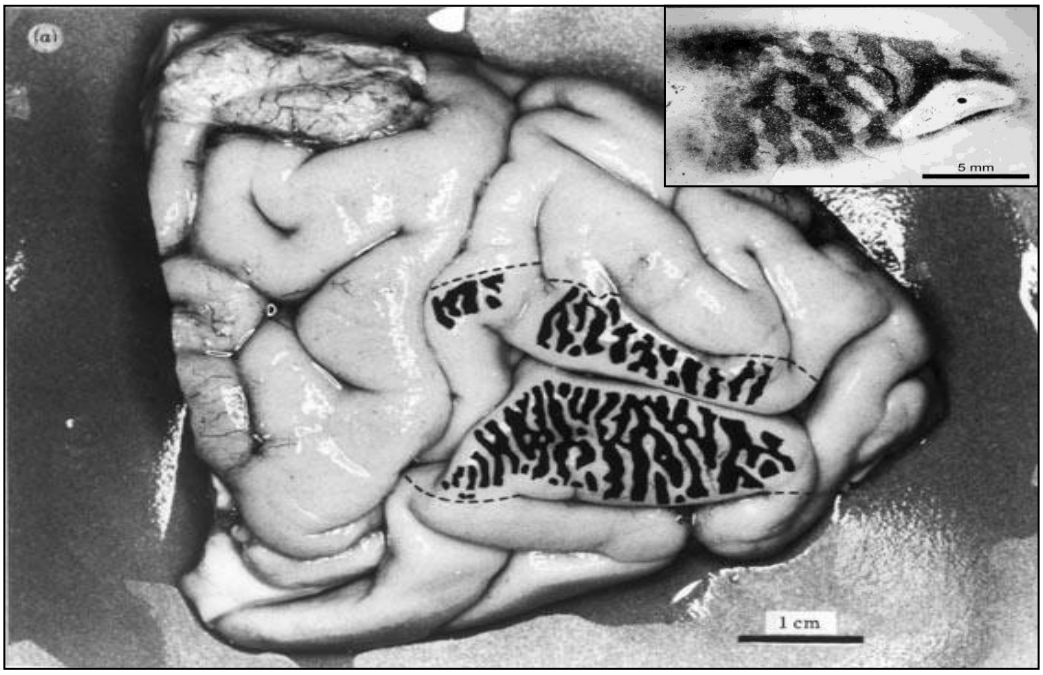


Figure 1.13. *Human ocular dominance columns in the right occipital lobe of an elderly man. Inset is a montage of photographs from individual sections, which is a reconstruction of the columns in the lower right portion of the cortex. (Reproduced from J.C. Horton. Ocular integration in the human visual cortex. Canad. J Ophthalmol 2006; 41:584-93).*

Adams et al. (2007) showed that the normal and deprved ocular dominance columns of layer 4C of the human brain resembled that of the macaque (Figure 1.14) using cytochrome oxidase staining in deceased individuals. In one case monocular visual deprivation occurred at 4 months age during the critical period of visual development and showed reduced ocular dominance columns for the deprived eye (Adams et al., 2007).

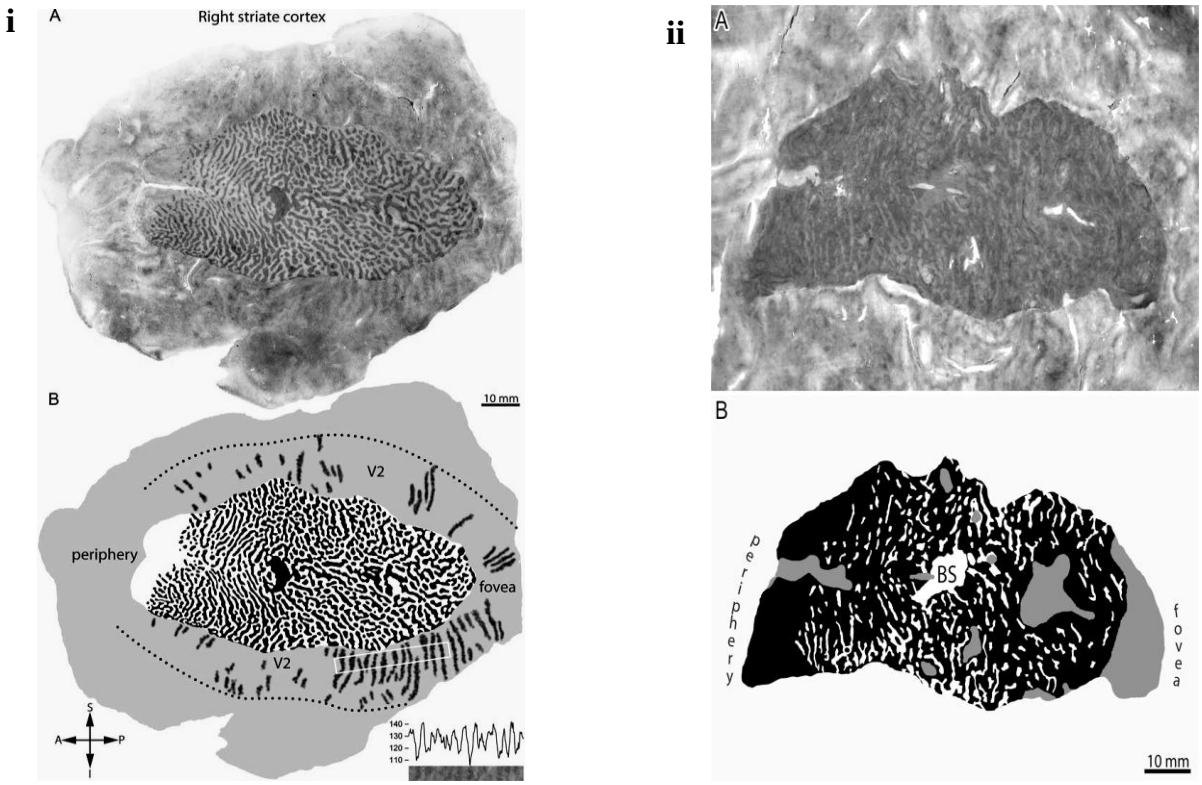


Figure 1.14. *Human visual cortex of ocular dominance columns and the reconstruction using filters.* ***Figure i-A&B,*** *shows a normal right striate cortex.* ***Figure ii -A&B,*** *shows shrinkage of ocular dominance columns caused by visual deprivation during the critical period of visual development. (Adams et al. 2007).*

1.2.4.4. Pathophysiology defects affecting the extra-striate cortex.

Magnetic resonance imaging (MRI) is othr method used for assessing the morphological changes of the visual cortex in amblyopia (Xiao et al., 2007). MRI uses a powerful magnetic field, to produce detailed pictures showing the anatomy of the human brain. It can be combined with functional magnetic resonance imagings (fMRI), which measure the tiny metabolic changes in brain activity.

Studies have confirmed reduced cortical activation by amblyopic eyes (Choi et al., 2001) compared to the sound eyes in visual area V1 (Barnes et al., 2001, Li et al., 2007b) as well as across all the higher visual areas (V2 through to V4). Figure 1.15 shows an example of anatomical images, of an amblyope with areas of cortical activation. The response to a visual stimulus of a low spatial frequency (4 cycles per degree) is shown for the fixing eye (in green) and the amblyopic eye in red with overlapping areas for both in purple. The figure shows large areas of activation of the visual cortex with the fixing eye open and little activation for the amblyopic eye open (in red).

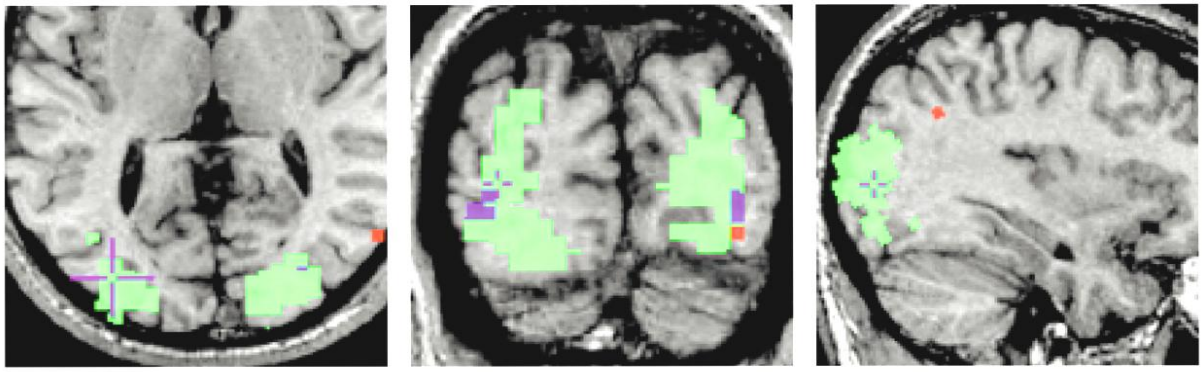


Figure 1.15. *Axial (left), coronal (middle) and sagittal (right) anatomical images of an amblyope. See text for explanation (Reproduced from Barnes et al. Journal of Physiology (2001), 533.1, pp.281–297).*

Recently, extra-striate areas have been investigated by Li et al. (2007) using functional MRI in a group of normal and amblyopic eyes showing reduced activation in amblyopes (Li et al., 2007b), Figure 1.16.

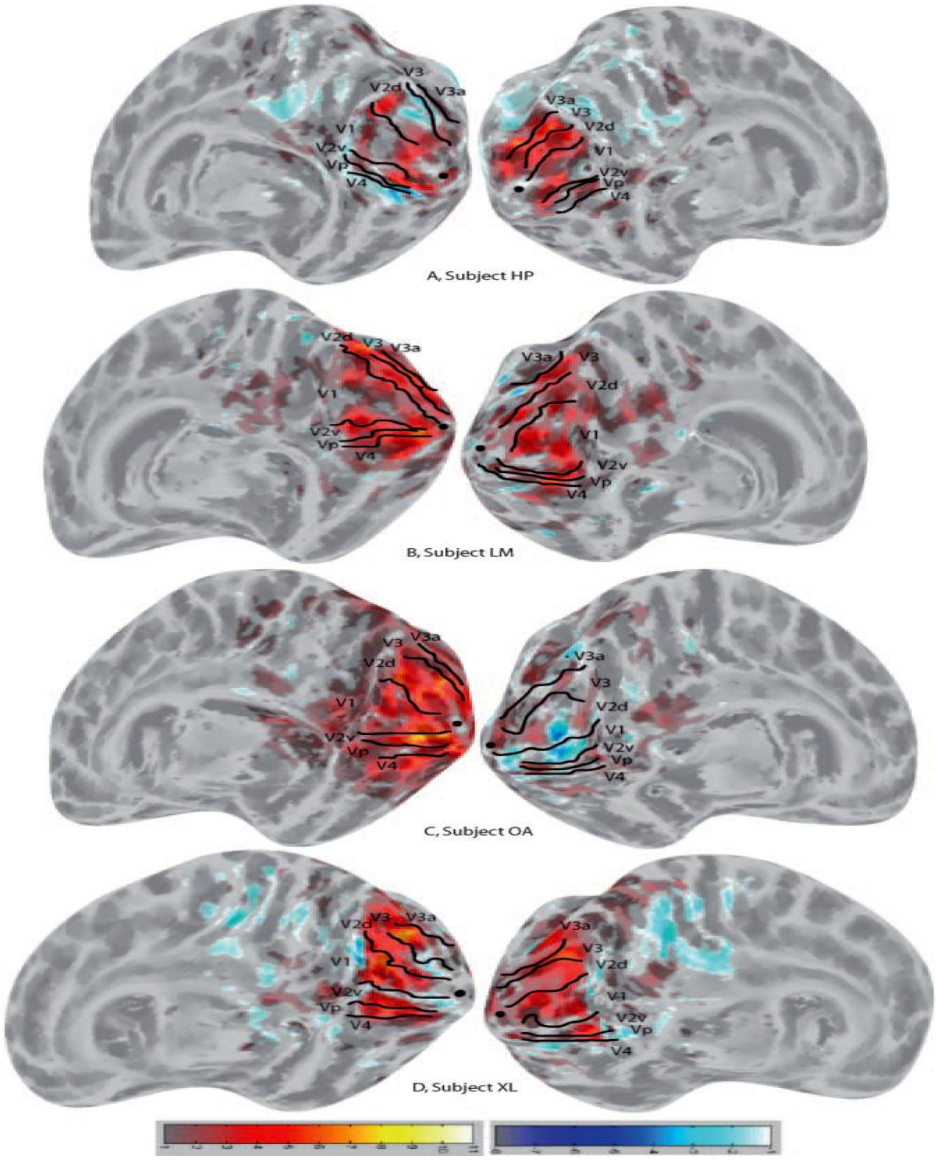


Figure 1.16. *Illustrations of an oblique view of the cortex of four amblyopes showing the reduction in activation occurring not only in V1 but extending to other extrastriate visual areas. (Reproduced from Li et al. Cortical Deficits in Amblyopia. IOVS 2007-48(4); 1575-1591).*

1.3. Visual Deficits caused by Amblyopia

As mentioned previously, amblyopia is characterised not only by the loss of visual acuity but also deficits in other visual functions.

1.3.1. Crowding Phenomenon

A characteristic of the presence of amblyopia is a deficit in visual acuity detected during linear chart acuity testing, known as the 'crowding' phenomenon (also known as separation difficulty) (Hohmann and Haase, 1993, Elliott and Firth, 2007, Pelli et al., 2004). It occurs in all amblyopes and to a much lesser degree in normal people. It is a phenomenon in which letters are much harder to identify in the presence of nearby letters (Pelli et al., 2004). Each letter or optotype is an object, Figure 1.17 (A). Additional optotypes or letters, (B) makes it harder to distinguish one letter amongst a group. It becomes more difficult to distinguish optotypes with added 'noise', i.e. with a contour surrounding the letter(s) as seen in (C). An example of visual acuity test with a "crowding arrangements" is the Keeler Glasgow visual acuity test that comprises a single line with surround contours, Figure 1.17.

A B C

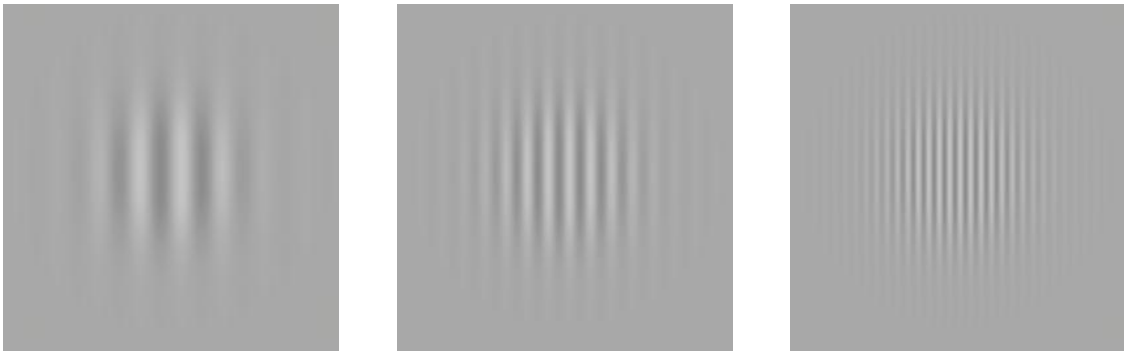
Figure 1.17. *A single optotype, B. Linear optotype and C. Linear Crowded, from the Keeler Glasgow acuity test obtain visual levels in children aged three years and older.*

1.3.2. Contrast Sensitivity

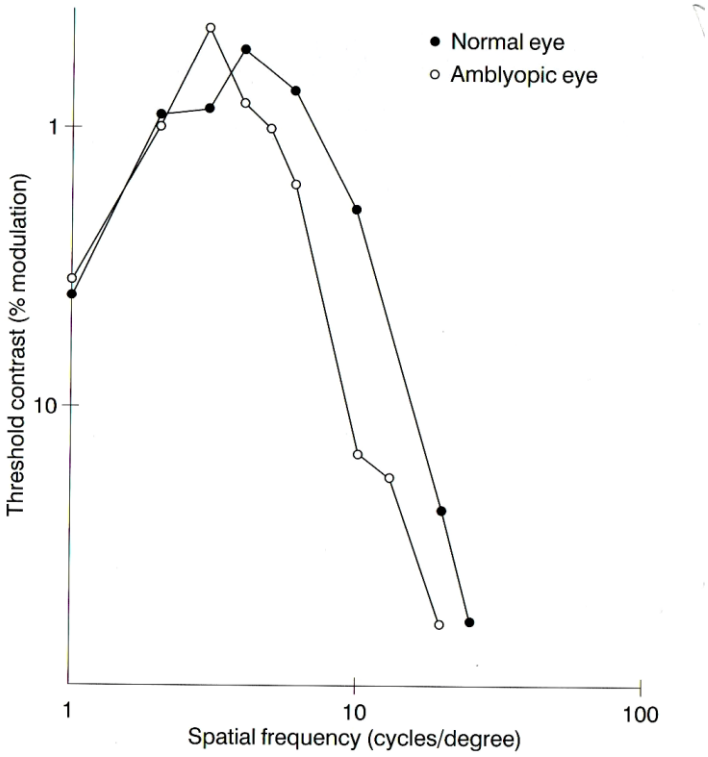
Contrast sensitivity function (CSF) is another important means of describing visual performance. CSF describes the minimal amount of contrast needed for an individual to detect sinusoidal gratings (i.e. stripes) of different spatial frequencies (i.e. widths) (Leguire et al., 1990). The contrast sensitivity function is achieved by plotting the contrast sensitivity over a range of spatial frequencies (Figure 1.18). Gstalder and Green (1971) presented the first quantitative change of CSF in amblyopia. They concluded that amblyopes needed more contrast to detect targets at higher spatial frequencies whereas the amblyopes low spatial frequency was normal (Gstalder and Green, 1971).

Loss in CSF may be present in amblyopia (Abrahamsson and Sjostrand, 1988, Yang et al., 1991) without the significant loss of visual acuity (using crowded or uncrowded letter optotypes) (Leguire et al., 1990).

Figure 1.18.



A. *Examples of contrast gratings of different spatial frequencies.*



B. *The difference in CSF in a strabismic amblyopic eye (open circles) compared with a normal eye. (Reproduced from Fielder and Moseley 2002. Amblyopia: a multidisciplinary approach, page 20).*

There is evidence that mixed (Lundh and Lennerstrand, 1983) or strabismic amblyopes (Abrahamsson and Sjostrand, 1988) have reduced contrast sensitivity at medium and high spatial frequencies (Howell et al., 1983) whereas anisometropic amblyopia (Koskela, 1986) have reduced contrast sensitivity at lower spatial frequencies. This is true before and after occlusion therapy (Leguire et al., 1990, Volkers et al., 1987). As with acuity, the reduction in CSF depends on the magnitude of the amblyopia (Bradley and Freeman, 1981).

1.3.3. Global and Second-Order Motion

Amblyopes show global motion deficits (Simmers et al., 2003) even when visual acuity is normal. This implies deficits in the dorsal pathway particularly of the MT/ MST extra-striate motion sensitive areas (Simmers et al., 2003). Ho et al. (2005) also found global motion deficits in non-amblyopic eyes of 21 amblyopes (aged 4.4 to 11.0 years) at low speeds (Ho et al., 2005). Aaen-Stockdale et al. (2007) have suggested that second-order motion (motion that is carried by texture-defined contours) is greater affected in amblyopia compared to first-order motion (motion that is carried by intensity-defined contours) (Aaen-Stockdale et al., 2007). Simmers et al. (2003) concluded that the second-order motion was affected much more in amblyopia compared to first-order motion (Simmers et al., 2003). It has been suggested that the motion-processing deficit in amblyopia is probably caused by abnormally low levels of stimuli progressing from the visual cortex to the higher extra-striate areas.

1.3.3.1. **Reading in Amblyopia**

Reading is a voluntary active cognitive process of understanding a written linguistic message. Studies have found significant differences in the reading speed between the affected and unaffected eye.

Koklanis et al. (2006) found evidence of impairment in reading speed, in the amblyopic eyes of 20 amblyopes (aged 6 to 15 years) (Koklanis et al., 2006). Monocular and binocular deficits in reading speed can result from even modest visual loss of up to 6/12 (20/40) (West et al., 2002, Stifter et al., 2005). Recent data from the Pediatric Eye Disease Investigator Group (PEDIG) (2008) study supported findings. In an observational case series of previously treated amblyopes (n=79, mean age 10.3 years) monocular oral reading ability were worse in amblyopic eyes.

1.3.3.2. **Hand-eye Co-ordination in Amblyopia**

Amblyogenic defect can result in reduced stereopsis and binocular functions (Searle et al., 2002). These functions are an advantage in performing tasks which requires fine visuomotor actions (Hrisos et al., 2006). Consequently, pointing responses were found to be more inaccurate with increased uncertainty under monocular viewing with the amblyopic eyes compared to normal eyes (Fronius and Sireteanu, 1994) and was more profound in strabismic amblyopes (Fronius and Sireteanu, 1989, Fronius et al., 2004). In contrast Hrisos et al. (2006) found that stereopsis influences performance on tasks that

require fine visuomotor skills (such as beading thread skills) irrespective of the depth of unilateral visual impairment (6/9 to 6/60) in preschool children (Hrisos et al., 2006).

1.3.3.3. **Face recognition**

Impairment of recognition of faces or objects is a result of ventral stream (temporal lobe) impairment (Dutton, 2003). Reduction in vision to 6/12 (20/40) have been shown to lead to reduced face recognition. West et al. (2002) found that loss of reading and face recognition, was considered disabling with general visual loss (West et al., 2002).

1.3.4. Detection and Diagnosis

1.3.4.1. Screening and Early Detection

Amblyopia is a public health problem. In practice, screening services are prophylactic in detecting premature impairment of visual loss in children (Gottlob, 1999) and reduce cost burden in the public health domain (Wu and Hunter, 2006). However, the deliverance of vision screening services is often governed by the local authority policy and varies depending on the quality of the orthoptic screening system. Screening methods are incorporated in health centers to detect strabismus and/or amblyopia. Assessments are usually carried out in the community by the health visitor (Thorburn and Roland, 2000, Johnson et al., 1989), the nurse screening scheme (Spowart et al., 1998, Welch et al., 1982) or orthoptists (Jarvis et al., 1991) in health centers and schools.

Differences of opinion have been shared, as to whether early versus late screening is more effective towards final outcome of treatment. In Japan, visual screening is implemented for babies aged eighteen months onwards (Matuo et al., 2007) to less than 4 years in Europe (Hard et al., 2002, Kvarnstrom et al., 2001). In the United States and South Korea favour late screening between the ages of 3 and 5 years (Wasserman et al., 1992, Lim et al., 2004). In the UK it is recommended (in the Hall Report) that all children have their vision screened between 4 and 5 years of age, by an orthoptist or a person trained or supervised by an orthoptist (Smith et al., 1994, Woodruff et al., 1994b).

A national scheme was introduced in the UK for the 3-3½ year old age group in the 1980's (Jarvis et al., 1991, Donaldson et al., 2002). However, the provision for primary

pre-school vision screening program for the younger age group was recommended to be phased out by the Department of Health when a controversial report by the Centre for Reviews and Dissemination guidelines for systematic reviews was published. Snowdon, Stewart-Brown (1997) reviewed more than eighty studies. They concluded that there was a lack of clinical evidence from randomised controlled trials of amblyopia treatment and lacked evidence that amblyopia treatment was effective. The design methodology, of many studies, contained numerous flaws (Snowdon and Stewart-Brown, 1997).

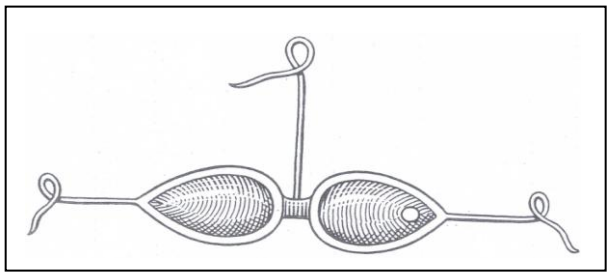
Their findings prompted numerous high quality randomized controlled trials that have now emerged in literature. A randomized controlled trial study conducted by Clarke et al. (2003) in the UK showed that delaying treatment did not hinder the prognosis of potentially achieving good visual outcomes. It did not address potential problems in ametropic amblyopia with increasing hypermetropia if treatment is delayed and most amblyopes had anisometropia (Clarke et al., 2003). The ALSPAC study group in the UK (2002) showed that children randomised into an intense vision screening group, monitoring progress from 8 to 37 months of age, had better outcomes of visual improvement once treatment was initiated earlier in comparison to the group screened at 37 months only (Williams et al., 2002). Interestingly, findings in an additional ALSPAC study, (2003), (comparing 3 year plus school entry, vs. school entry alone), that in an intention to treat analysis the outcomes were similar in the two groups-because of failure of uptake, which isn't quite the same as compliance (Williams et al., 2003). The difficulties in interpreting these studies is that poor compliance to treatment is likely to influence the visual outcome (Flynn et al., 1999).

1.4. History of Amblyopia Treatment

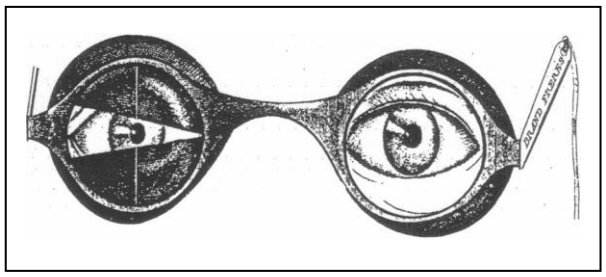
Hippocrates (460-377 BC), first used the medical term 'amblyopia' to describe "dullness or diminished acuity" (Lascaratos and Marketos, 1988) and also strabismus to describe an eye turn (from *strabos (*στραβός) meaning to turn) (von Noorden, 2002). At that time, amblyopia and strabismus were considered treatable with medicine, diet and lifestyle. The recommended medicine was a concoction of oil, vinegar, honey, water, minerals and wine, with a diet of fresh vegetables and exercise (Loudon and Simonsz, 2005). Von Noorden (2002) stated that the Hippocrates also realised that strabismus was transmitted from mother to baby. This observation was further noted by Georg Bartisch (1535-1606) (von Noorden, 2002).

Over history, numerous non-surgical devices had been created to encourage fixation in the strabismic eye and ultimately to improve the strabismus angle. The devices called strabismus or squint masks ranged from covering the entire head (with openings only for the nose and mouth) or masks for the eyes area only, to force the squinter to look straight ahead. The strabismic masks were made of different fabrics and materials, for example, walnut shells and for the wealthier patient precious stones and metals were used. Strabismus spectacles with tubes and holes were also produced later. In 1642, Di Castro devised a spectacle (see figure 1.19.A) where the dominant eye was completely covered and a small hole opened for the deviating eye to encourage fixation (von Noorden, 2002).

Figure 1.19.



A. *Di Castro spectacles with holes, 1642. (von Noorden. The History of Strabismology: p.27,2002).*



B. *Cunier's modified model of spectacle showing sector occlusion. (von Noorden. The History of Strabismology: p.31, 2002).*

Florent Cunier of Brussels (1812-1853), devised a modified version of the strabismus spectacle (Figure 1.19 B) which also occluded the dominant eye and forced fixation of the squinting eye through a small temporal triangle shaped sector.

A detailed account of occlusion for the treatment of strabismus was given by Erasmus Darwin, grandfather of Charles Darwin (1731-1802) (Fells, 1990). He stated that:

'*If the squinting eye has not been confirmed by long habit, and one eye be not much worse than the other, a piece of gauze stretched on a circle of whale-bone, to cover the best eye in such a manner as to reduce the distinctness of vision of this eye to similar degree of imperfection with the other, should be worn some hours every day. Or the better eye should be totally darkened by a tin cup covered with black silk for some hours daily, by which means the better eye will be gradually weakened by the want of use and the worse eye will be gradually strengthened by using it'*.

Occlusion treatment for amblyopia followed later in ophthalmological practice compared to treatment for strabismus. Perhaps the reason for this could have been due to the absence of a manifest strabismus for certain form of amblyopia. The introduction of occlusion for the treatment of amblyopia encouraging visual performance of the squinting eye is often attributed to the French botanist and naturalist, George Louis Leclerc Comte de Buffon (1707-1788). Buffon (1743) in his dissertation entitled *"Sur les causes du Strabisme",* describes how occlusion of the good eye strengthens the weaker eye (*"reprendre toutes ses forces"*) as strabismus was caused by poor vision in one eye leading to disruption of binocular vision (Fells, 1990). However, Charles de Saint-Yves (1677-1736) also described occlusion therapy in 1722. In his textbook he shared his clinical observations regarding detection and diagnosis of strabismus called, *"Nouveau traité des maladies de yeux"* (Loudon, 2005).

Most of the ophthalmologic literature has failed to acknowledge the much earlier work of an Arab physician and famous astronomer. Eventually discovered, by von Noorden (von Noorden and Campos, 2002, Loudon and Simonsz, 2005) Thabit ibn Qurrah ibn Marwan, [مرون] ابن [قورّه] ابن [ثبيت] is the first person to introduce occlusion or more specifically 'patching' for strabismus and amblyopia therapy (Figure 1.20). In the West, he is referred to as Thabit al-Harrani [لأ-هرّني] [بـ يت ڈ], from Mesopotamia. He was born in 836 AD in Harran (presently in Turkey) and died in Baghdad, Iraq in 901 AD. His book *'Vision and Perception'* was translated in 1991 by Z. Wafai Damascus, Syria which mentions occlusion treatment (Qurrah Ibn and $_{MZ}$, 1991).

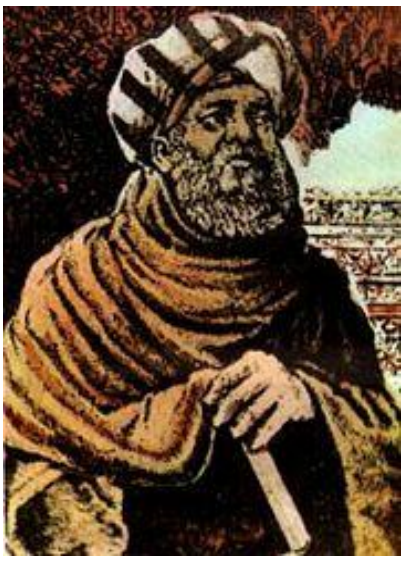


Figure: 1.20. *Thabit ibn Qurrah ibn Marwan al-Harrani*

In the copy of the original manuscript in Ancient Arabic, Thabit ibn Qurrah ibn Marwan al-Harrani stated (Figure 1.21 underlined in the lower bottom left-hand corner):

> *"Strabismus should be treated by patching the normal eye. Once you do that, the visual power will go in its entirety to the deviating eye and vision in that eye will return to normal. You should not release the normal eye until the vision in the strabismic eye has completely returned to normal".*

Figure: 1.21. *A copy of the original manuscript of Thabit Ibn Qurrah in ancient Arabic,*

Unfortunately, treatment for amblyopia was abandoned and neglected for many years until the 1920's, when occlusion was re-introduced by C.H. Sattler (1880-1958). He was based in Leipzig, Germany from where he published his clinical experience in the treatment of amblyopia between 1927 and 1940. Sattler was the first to use a glue-based (or adhesive) patch with the "*Mastisolverbänd*" (Loudon and Simonsz, 2005). Although the patch adhered to the skin around the eye for up to three days, it prevented the child from peeking around the patch. Unfortunately, it also blistered the skin.

The adhesive patch is still the preferred option of occlusion treatment for amblyopia in modern medicine (von Noorden, 2002). Adhesive occlusion was not readily available at that time so shield-type occluders, for example the Doyne occluder, or partial occluders, picture below, Figure 1.22, were used to provide better coverage.

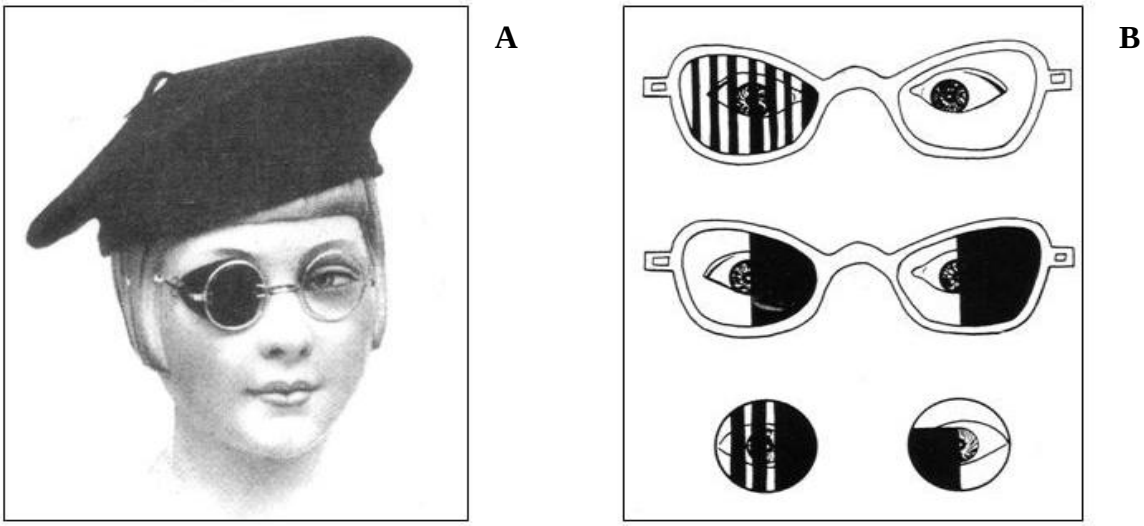


Figure 1.22 *Popular occluders****.(A)****. Doyne occluder (1939) and* ***(B)*** *partial occluders.*

Much opinion has existed over the years as to how much occlusion should be prescribed for amblyopia treatment. Claude Worth (1869-1936), an English ophthalmologist specialized in amblyopia, strabismus and binocularity developed a formula, known as Worth's fraction, for amblyopia treatment:

$$\textit{Hours of occlusion per day} = \frac{\textit{age in months when permanent turn became noticed}}{\textit{age in months when treatment began}}$$

However, Mary Maddox, daughter of Worth (1934) stated that constant and total occlusion achieved better results compared to intermittent therapy for amblyopia treatment (Fells, 1990). A year later Stenius in 1935 suggested better compliance to occlusion therapy was achieved by encouraging amblyopic children to carry out near work activities whilst patching. More recently, evidence has been emerging that poor compliance has provided the greatest obstacle in reaching an optimal regime for amblyopia treatment (Gregson, 2002, Hrisos et al., 2004).

1.5 Treatment of Amblyopia

The course of treatment, for a child, confirmed with the diagnosis of amblyopia is represented in the flow chart from Royal College Ophthalmologist, Guidelines, 2006 (Figure 1.23).

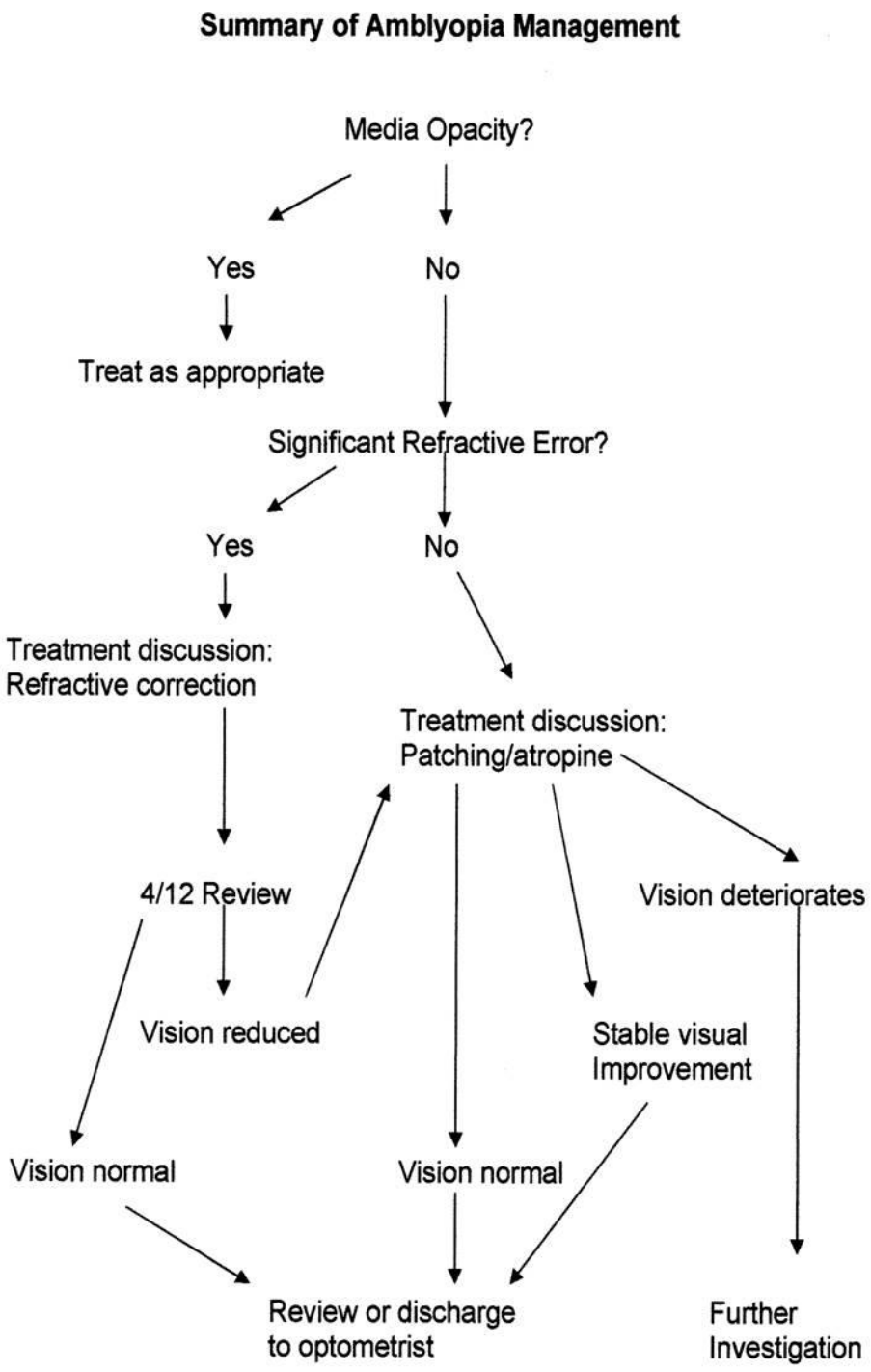


Figure1.23. *A simplified course of treatment progression for an amblyope. -(Produced by Royal College Ophthalmologist Guidelines 2006. (www.rcophth.ac.uk/docs/publications/GuidelinesfortheManagementofAmblyopia.pdf).*

This is a gross outline of treatment usually applicable upon confirmation of strabismus and/or anisometropia amblyopia. Other forms of amblyopia for example, stimulus deprivation, occurring from congenital cataract or ptosis, strabismus would follow a slightly different route according to the patient's age, density of visual loss at initiation, age of onset and the clinician's decision of when to operate.

1.5.1. Refractive Correction and Adaptation

Many factors influence the decision to prescribe refractive correction directly associated with amblyopia. One key issue in relation to optical correction for refractive error is emmetropisation. Emmetropisation is a phenomenon in which the axial length and spherical equivalence of the eyeball changes shape naturally. This leads to a reduction in the magnitude of refractive error in children aged between nine months and four years (Atkinson et al., 1996). Ingram et al. (2003) found that emmetropisation was deficient in both eyes when the spherical equivalent of the fixing eye was > +2.75D than in normal children without strabismus. It has been found that hypermetropia increased in 53% of patients associated with a strabismus in a cohort of 2920 infants (Ingram et al., 2003) whereas, Abrahamson and Sjostrand (1996) found hypermetropia depletes or vanishes. They concluded hypermetropia equal or greater to 3.00 dioptre spheres (DS) is a risk factor for developing amblyopia (Abrahamsson and Sjostrand, 1996). Full cycloplegic refraction and correction should be performed before amblyopia treatment is diagnosed and initiated by reassessing the vision in either eye again with the best-corrected refractive error worn. The correction of refractive error has shown that variations exist in the amount of

prescribed spectacle correction (Donahue, 2005) given to the potential amblyope. Less than +3.00 D spherical equivalent (SE) are usually prescribed in full for myopia, anisometropia, astigmatism and hypermetropia.

Hypermetropia (hyperopia) is generally more common than myopia especially in strabismus and anisometropia associated to amblyopia. Usually a spherical equivalent or greater prescription of +4.00DS hypermetropia is either fully corrected or symmetrically under-corrected, at the discretion of the clinician, although by not more than 1.50 dioptres under corrected in either eye (Cotter et al., 2007, Cotter et al., 2006) is sensibly accepted irrespective to the level of visual acuity found. In a sample study of 1742, six year old Australian children, most amblyopic eyes (58.7%) were significantly hypermetropic (SE > or = +3.00 D), using their defined criteria of 20/40 vision or less for amblyopia (Robaei et al., 2006b). In the absence of a strabismus, clinicians' opinions are variable due to insufficient evidence of when 'best' to prescribe refractive correction especially in the very young age groups as this information is based purely on clinical judgment (O'Connor, 2008).

In practice it has been accepted that the period of spectacle wear requires only a few weeks to overcome any refractive error deficit, yet the 'window' of continuous spectacle wearing time has shown discrepancies ranging from 4 weeks to 18 weeks as presented in the list of studies below.

- Lithander et al., (1991): 8 weeks
- Fielder et al., (1995), 4 weeks
- PEDIG studies, (2002-2004), 4 weeks
- Clarke et al., (2003), 6 weeks
- MOTAS studies, (2004, 2006), 18 weeks

Consequently, the effect of full correction with glasses alone on visual improvement is important in evaluating whether the visual deficit is purely refractive (Moseley et al., 2002, Cotter et al., 2007, Steele et al., 2006, Wutthiphan, 2005). This has been explored by Moseley et al. (2002). Their findings suggested that extending the period of refractive correction leads to significant improvement of refractive deficit, increasing vision and reducing the visual deficit. Graph, Figure 1.24 shows significant improvements in the visual acuity over a period between four and twenty-four weeks.

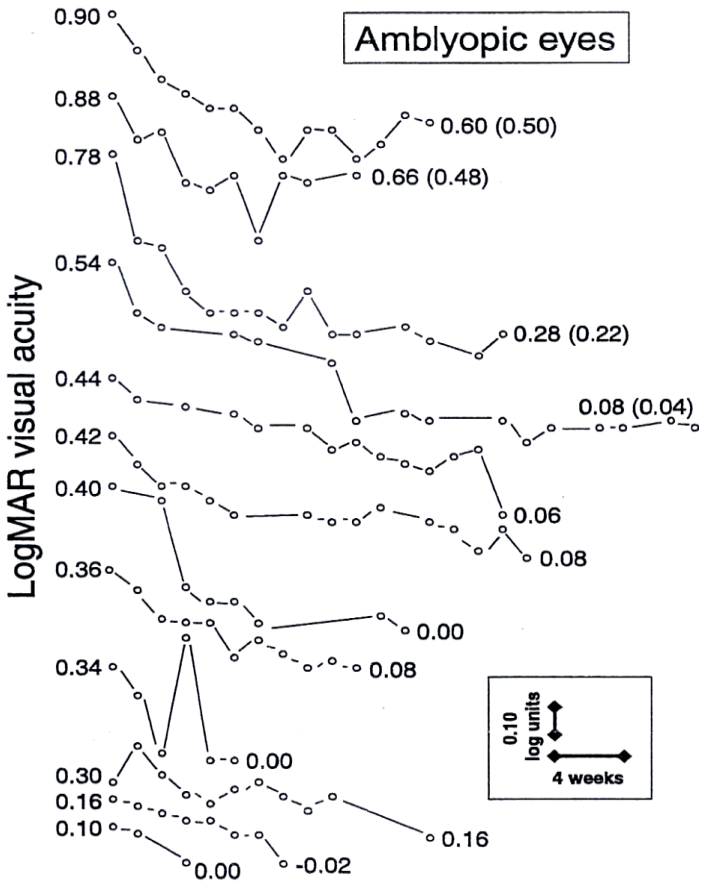


Figure 1.24*. Changes in visual acuities over time from individual patient data. Poor acuities at the top to least on Y-axis. Initial and final acuities with refractive correction respectively, on the left to right of each plot line. (Reproduced from Moseley et al. Ophthal. Physiol.Opt. 2002.22:296-99)*

Moseley et al. (2002) have described this as *"refractive adaptation"*, a period during which the visual acuity improves and reaches a plateau, usually within 18 weeks (Moseley et al., 2002). After this period occlusion is started although in some cases occlusion may not be necessary (Clarke et al., 2003). Several other studies have suggested that amblyopia treatment should be postponed until a 'refractive adaptation' period has been completed (Stewart et al., 2002, Stewart et al., 2004a). Consequently, treatment for

amblyopia studies have recently included extended 'refractive adaptation' periods for up to 25 weeks and longer before patching (Clarke, 2006, Cotter et al., 2007).

The MOTAS study group (2004) modified the refractive adaptation and showed a significant improvement in acuity in the amblyopic eye by increasing the duration of refractive adaptation to 18 weeks and the mean visual improvement recorded was 0.24 logMAR in the amblyopic eyes of the group of 65 amblyopic children (Stewart et al., 2004a).

Recently, the Amblyopia Treatment Study, (ATS) of the Pediatric Eye Disease Investigator Group (PEDIG), reported results of its prospective randomised controlled study in a group of 409 amblyopic subjects, with spectacle correction alone in the 3-7 year age groups. It resulted in visual improvement of ≥ 2 lines or more in 77% of the patients and amblyopia resolved in 27% in their cohort. The average improvement in visual function was 3-lines with spectacle correction alone. The difference in the duration and stabilisation of visual acuity improvement was 30 weeks in comparison to the MOTAS study group. Clarke et al. (2003), randomised controlled trial study found a mean increase of 0.21 logMAR in vision wearing spectacle correction alone for the initial duration of 52 weeks with an additional improvement of 0.19 logMAR (Clarke et al., 2003) within the first 6 weeks of wearing spectacles. However, no studies have directly compared the visual outcome and time course of increase in visual acuity with or without refractive adaptation

As well as accurate prescription at the outset of treatment it is also important to monitor and adjust (if required) the child's refractive error at regular intervals as it usually changes due to emmetopization (Ehrlich et al., 1997). This is especially in cases for higher

hypermetropes (of +5.00 DS or more) with strabismus (Abrahamsson et al., 1990, Eibschitz-Tsimhoni et al., 2007). Although refraction is difficult to conduct in infants and younger children an effective refractive adaptation period is likely to be beneficial and probably reduce the need to patch making it less arduous especially in the slightly older amblyopic subject (Stewart et al., 2004a).

1.5.2. Occlusion

Occlusion of the better eye has been the mainstay of amblyopia treatment for more than two centuries for which treatment traditionally involves complete total occlusion of the non-affected eye. The aim of occlusion is to degrade vision in the dominant eye. This forces the amblyopic eye or eyes to view, equalise the vision, attain an optimum level of VA and centralise fixation. The most common method is total occlusion of which there are two types:

- *Total occlusion, all light and form,* applied to the peri-orbital skin of the non-affected eye made form usually hypoallergenic materials (Rubin and Nelson, 1993). This is most common and the preferred choice of treatment. Such examples are hypo-allergenic adhesive skin patches or spectacle-mounted occlusors that fit around the spectacle lens in cases of skin irritation to skin patches (PEDIG et al., 2003a). Coverlet and Opticlude patches are used widely. Rarely the use of an opaque contact lens is used to treat the condition. Problems of irritation, poor fitting lens and anterior segment complications are documented (Eustis and Chamberlain, 1996).

- *Total occlusion excluding form,* which allows penetration of some light. This type requires the use of opaque patches that are generally adhered to the spectacle lens, for example blenderm or Bangerter foils. Charman (1983) used transpeal occlusion, a form of partial occlusion that typically uses an adhesive material applied to the spectacle lens (Charman, 1983). Another method using 'occlusive contact lenses' and 'a high powered soft contact lenses' (Calcutt, 1983). These studies are few and susceptible to speculations that require further investigation.

Conventional occlusion has contributed significantly to the treatment of amblyopia, as it is convenient and cost-effective. There is no consensus, however, regarding the amount of prescription required for treatment. Examples of regimens include:

- 'minimal occlusion' (15 minutes to 20-60 minutes/day) (Schor and Wick, 1983)
- 'part-time' (1-6 hours/day) (Fielder et al., 1995)
- 'full-time' (6 -8 hours/day) (PEDIG, 2002),
- 'constant' (all waking hours) (Keech et al., 2002)

Other prescription methods include a ratio according to the age of the amblyopic patient. Keech et al. (2002) applied the 1 week per age of child ratio, for example, 5 weeks of constant occlusion would be prescribed for a 5 year old amblyope (Keech et al., 2002). Lithander and Sjostrand (1991) applied 1 day per age of child with 1 day free, for example, 2 days of constant occlusion for a 2 year old amblyope with 1 day free or 5 days of constant

occlusion for a 5 year amblyope (Lithander and Sjostrand, 1991) with 1 day free. The suggested duration of visual reassessment in the clinic is also variable, ranging from days (Dorey et al., 2001) to weekly follow-ups (Fronius et al., 2006) or assessment at monthly intervals (Keech et al., 2002). Studies have also yielded disparities in the total duration of patching treatment required in achieving the best corrected visual acuity ranging from 16 weeks (Oto et al., 2002) more than 52 weeks (Clarke et al., 2003) to 31 months (Hiscox et al., 1992) and longer. Prescribed regimens may be influenced by the threshold of visual acuity at the start of treatment, the type of diagnosis and compliance to treatment. For example more intense patching regimes, in general are prescribed for more severe amblyopia

In general, suggestions have lead that more intense patching regimes, irrespective of amblyopia type, should be prescribed for severe amblyopia (Hussein et al., 2004, Dorey et al., 2001, Elder, 1994, Cobb et al., 2002) in order to achieve at least 1 or more lines of successful visual improvement regardless of the acuity at the start of treatment.

The side effects of occlusion are occlusion amblyopia of the dominant eye (Kutschke et al., 1991), precipitation of strabismus or decompensation of an existing strabismus (Holbach et al., 1991), occurrence of diplopia and allergies to using skin adhesive patches. Other concerns is the appearance associated to patching (Nucci et al., 1992, Holmes et al., 2003), impact on quality of life with poorer vision whilst occluding. These all have an impact upon family life that leads to poor compliance (Webber and Wood, 2005).

1.5.3. Penalisation

Conventional total occlusion method are more frequently used than other occlusion modalities. Methods such as optical and pharmacological penalisation, although not widely used have been documented as alternatives to occlusion therapies for the treatment of strabismic and anisometropic amblyopia.

The American Pediatric Eye Disease Investigator Group (PEDIG) performed a randomised controlled trial of ordinary conventional occlusion versus pharmacological occlusion, using the cycloplegic drug atropine sulphate (1%) in the non-affected eye. This mydriliate prevents accommodation at near. There were gains of 3 lines in moderate amblyopes with pharmacological occlusion which were very similar to occlusion using patches (PEDIG, 2002). Similar visual improvements were reported in studies investigating optical penalisation, using an additional convex lens over the non-affected eye to create blur. In contrast to atropine occlusion , tolerance to blur in the distance was difficult for some amblyopic children (Repka and Ray, 1993). Less common in literature is the use of high-powered extended wear soft contact lens in the treatment of strabismic amblyopia. Response to this form of occlusion was effective in the visual outcome by 13 weeks, however the problems associated with this form of occlusion was loss of lenses, fitting problems, deposits on lenses and occurrence of conjunctivitis (Elmer et al., 1981). Penalisation methods, especially atropine, were more favourably accepted by parents as the primary treatment for amblyopia, showing overall better compliance and effectiveness, with low risks of developing occlusion amblyopia (Repka and Ray, 1993, Foley-Nolan et al., 1997, Tejedor and Ogallar, 2008). However, these studies are small compared to conventional occlusion and require further investigations.

1.5.4. Pharmacological Treatment

When long-term conventional occlusion has failed to achieve visual improvements in the treatment for amblyopia, pharmacological treatment may be used to augment the restoration of vision. Various investigations have explored the ability of using the neurotransmitter dopamine (DA) to augment occlusion treatment by administering levodopa (L-dopa) (Leguire et al., 1992, Gottlob et al., 1995, Algaze et al., 2005). Gottlob et al. (1990) stated that DA is the primary cathecholoamine in the retina and is involved in several physiological functions. This was the first study to use DA to improve visual acuity for amblyopia (Gottlob and Stangler-Zuschrott, 1990).

Following oral administration of a dose of L-dopa, Leguire et al (2002) found mean improvements of visual acuity in the amblyopic eye by 1.7 lines when combined with additional conventional occlusion (Mohan et al., 2001, Leguire et al., 1998b, Leguire et al., 1998a). In addition, visual acuity appeared to stabilise longer after cessation of treatment. In contrast, some studies had observed regression of visual acuity in the amblyopic eye following termination of administration of L-dopa when compared to the visual acuity at pre-treatment levels (Leguire et al., 2002).

1.5.5. Aetiology Associated With Amblyopia

1.5.5.1. Strabismus

Strabismus associated with amblyopia is one of the most common form of constant unilateral strabismus with an onset in childhood, often referred to as strabismic amblyopia (PEDIG, 2002), or less frequently "functional strabismic amblyopia" (Godde-Jolly et al., 1983). Godde-Jolly et al. (1983) described the condition as *"a loss of functional parallelism of the two visual axes that disrupts the functional balance between the images received from the two eyes."* The absence of bifoveal fixation means the two eyes receive different images and leads to diplopia and confusion. Therefore, one image is suppressed to eliminate these problems (Godde-Jolly et al., 1983).

The competition and inhibition of active cortical spatial responses interfering with normal fusion over time causes reduced vision (Bedell and Flom, 1981) if left untreated. As a consequence the off-fovea point is used as the point of monocular fixation (Hess and Howell, 1977) in the turning eye. Early and active occlusion treatment is imperative to encourage steady foveal fixation and restoration in visual acuity. Selenow and Ciuffreda (1983) found application of active vision therapy with patching in a 6½-year-old child with mixed amblyopia attained marked improvements with monocular fixation and binocular vision. Initial visual acuity improved from 20/400 to 20/30 and greater (Selenow and Ciuffreda, 1983). In intermittent strabismus the added advantage is that the depth of visual loss may be minor as the eye is able to receive and maintain normal visual functions before it decompensates into a manifest deviation (Flom and Bedell, 1985).

1.5.5.1.1. Strabismus Angle

There has been debate concerning intervention of strabismus surgery for ocular alignment querying whether it should be carried out prior to amblyopia treatment to encourage binocular recognition, or after amblyopia treatment to reduce potential risk of post-operative diplopia (Haase et al., 1979). Usually treatment for amblyopia is carried out first to avoid degradation in the binocular status of the patient following surgery (Fawcett and Birch, 2003). Repka et al. (2005) reported that ocular alignment following atropine or occlusion therapy that had deteriorated or improved did not require surgical involvement, with the effect of amblyopia treatment however, 32 patients required surgery during the 2 year follow-up after cessation of amblyopia treatment (Repka et al., 2005).

1.5.5.2. Anisometropia

Anisometropia is one of the most common forms of amblyogenic factors related to amblyopia (Majeed et al., 2008) and generally responds to treatment. Donahue (2006), found that the severity of ambyopia rises with age and the progression of the visual deficit is already levelled off by the time vision screening is intervened, therefore, it becomes too late (Donahue, 2006). Generally, the responses to occlusion treatment are better especially in cases of moderate degrees of amblyopia. Wallace et al. (2006), found that with 2 hours of daily occlusion with continued spectacle wear and 1 hour of near visual activities, the mean improvement in vision was 1.1 line from base-line to 5-weeks (Wallace et al., 2006). In a similar study, Cotter et al. (2006) found in their group of 84 moderate anisometropic amblyopes, improvements in visual acuity averaged by 3 lines with occlusion (Cotter et al., 2006).

1.5.5.3. Mixed Amblyopia

Mixed amblyopia is a combination of both anisometropic and strabismic amblyopia. In general, treatment in this type of condition would imply same procedures as would anisometropic and strabismic.

The VA outcomes following treatment shows improvement of visual gain however, in contrast to the anisometopic or strabismic types it shows the least improvement (Woodruff et al., 1994a). Perhaps comparative studies to investigate findings purely on the treatment and outcome of mixed amblyopia should be explored.

1.5.5.4. Ametropic Amblyopia

Ametropic amblyopia is more uncommon is comparison to other forms of amblyopia. In literature, reference to this condition is sometimes called isoametropic amblyopia in the United States. It is caused by high insuperable uncorrected bilateral refractive error such that a blurred image on the retina is constantly present (Ansons and Davis, 2000). It is frequently associated with hypermetropia, which is in excess of 6DS or more with astigmatism in some cases of 2.50DS or greater that cannot be compensated by accommodation (Mein J, 1991). The presence of high hypermetropia requires the constant wearing of full-time refractive correction. Kilmek et al. (2004) found, in their amblyopic child population study, visual acuity improved and responded well with occlusion and glasses, based on their criterion of high hypermetropia > or = 4.5 D or more. Although the strength of hypermetropia does influence outcome of vision improvements can be achieved

as shown by Moseley et al (1997) (Moseley et al., 1997). In some cases gradual improvements could take place over a period of 1-2 years or longer (Fern, 1989).

1.5.5.5 Stimulus-Deprivation Amblyopia

Usually the cause of unilateral stimulus-deprivation is initially treated before additional therapy can be initiated in the infant and very young patient. Extraction of a unilateral congenitial cataract results in aphakia and treatment with full optical correction is usually administered first. In bilateral cases, the second eye would be operated on within a few weeks to minimize inhibition of active binocular neurones within the visual system.

Intensive occlusive therapy is implemented to restore residual visual in these patients and outcomes have resulted in fair achievements. Yamamoto et al. (1998) and Lambert (1996) found that diligent rehabilitation with occlusion therapy with long-term follow up should be monitored closely following congenital cataract surgery (Lambert and Drack, 1996, Yamamoto et al., 1998). In support of these findings, compliance to occlusion regimes not only resulted in successful visual rehabilitation but also evidence of binocularity functions was sometimes successfully attained in a few cases (Brown et al., 2000).

1.5.5.6. Ptosis

Drooping of the upper lid or ptosis can affect one or both eyes. In cases of congenital ptosis, treatment should be sought immediately to avoid permanent poor vision.

Patients treated for severe ptosis (for example, the brow suspension procedure), have shown outcomes of poor vision due to post-operative outcomes related to deficient levator function of the lids (Finsterer, 2003). Similarly, to infantile cataracts studies, treatment for the primary cause is imperative (Doshi and Rodriguez, 2007).

1.6. Outcomes of Amblyopia Treatment

1.6.1. Measuring Outcome

The interpretation of success of amblyopia treatment is approached either by quantifying the improvement from the initial level to the post-treated level (i.e. the number of lines gained), or by the final threshold of acuity achieved, usually ≥ 20/40 or near to equal vision in the fellow eye. The problem of adopting these methods is that it does not highlight the proportion of the deficit corrected and defining success has not been established to define success. Worth documented a quantitative method of visual outcome (section 1.1.2). Another methods suitable for assessing improvements in VA was previously described by Westheimer (1979) and later modified by Neumann et al.(1989) (Neumann et al., 1989)

$$\%\ Improvement = \frac{VA^*\ (final) - VA\ (initial)}{log\ (20/20) - VA\ (initial)} \quad X\ 100$$

Method of quantifying visual improvement. VA denotes visual acuity (logarithmic scale). "VA (final) – VA (initial)" represents the child's actual improvement. "log (20/20) – VA (initial) represents the maximum visual improvement possible for the child to achieve. The percentage improvement was obtained by calculating the two proportions of the equation and multiplying it by 100.*

Fielder et al. (2003) suggested using a quantitative method described as the proportion of change (or the deficit resolved). Fielder's research group recommended a quantitative method in describing the outcome of visual acuity as proportion of change

$$\text{Proportion of change} = \frac{VAas - VAae}{VAas - VAfe}$$

The groups method of quantifying improvements in visual acuity in the amblyopic eye using logMAR for easier interpretation and standardisation of results. VA_{as} *and* VA_{ae} *denotes the difference of VA of the amblyopic eye at the start and at the end of treatment and the VA of the fellow eye at the end of treatment was signified by* VA_{fe}.

The proportion of change score 1.0, would represent the optimal outcome of vision reached and the deficit resolved and acuities in either eye of the amblyopic eye would be equal.

Various references have been made in literature regarding the non-amblyopic eye. It is sometime referred to as the "dominant" (Wali et al., 1991), "sound" (PEDIG, 2002), "better seeing" (Brown et al., 2003) or "fellow" (Stewart et al., 2003) eye. For the purpose of this study, the contralateral eye will be referred to as the "dominant" eye.

Flynn et al. (1999) conducted a study comparing visual outcomes in two pooled data sets (both of 961 amblyopic patients) performed at different times. Using the definition of 20/40 or better as the successful outcome to treatment achieved from the

initial acuities in the amblyopic eye. The two study groups were adjusted to conform to the definitions in (group 1, from an English establishment) and (group 2, from an American establishment) the data, from the study groups were aligned of which nine-hundred and sixty-one patients were then retrospectively studied. Presentation of visual success rates were 73.7% in study group 1 and 59.9% in study group 2. It is also worth noting that the duration of occlusion therapy in study group-2 was longer, 41.4 weeks versus 23.3 weeks in study group-1 thus, supporting that the longer the duration of treatment the higher the failure rate (Flynn et al., 1999). Conversely, in related studies, Flynn and Cassady (1978), showed poor visual outcomes with the presence of eccentric fixation remaining eccentric with poor visions at the start of treatment (Flynn and Cassady, 1978) in their group of 439 treated amblyopes.

1.6.2. Time Course of Improvement

Neumann et al. (1989) have charted the time course of improvement in a prospective study in a group of 103 amblyopic children aged between 3 and 7 years. Visions were monitored every three months for the duration of one year. Types of amblyopia recruited for the study were strabismic, micro-strabismus, anisometropic and mixed. Three groups of initial acuities of the amblyopic eye are defined as: (group-1) $\leq$ 20/200, (group-2) 20/100-20/80 and (group-3) 20/70-20/60. At the twelve-month follow-up, the visions in the amblyopic eye improved to: 20/35, 20/35 and 20/33, respectively as shown in the graph (Figure 1.25). Their study concluded that, regardless of the initial

visual acuity presented and the type of amblyopia all groups attained very similar levels of final acuities ≥ 20/40 at final outcome.

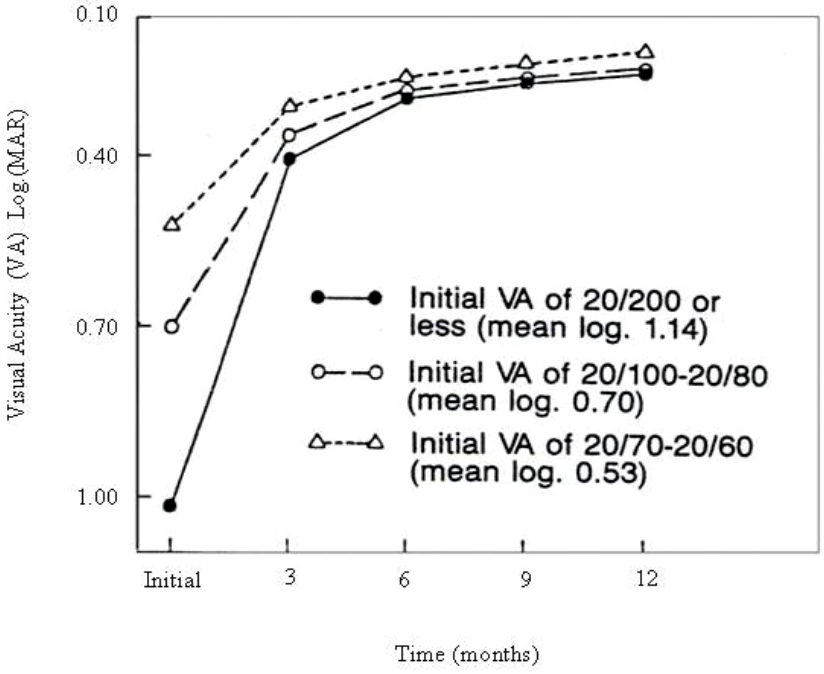


Figure 1.25. *Mean comparison of final visual acuity attained from three groups with different initial visual acuities. (Reproduced from Neumann et al. Chibret Inter Jour of Ophthalmol.1989:Vol 6 (3). page22-27)*

The significant increase especially within the first assessment could possibly be due to the requirements of full cooperation of patients in the study

1.6.3. Outcome For Different Types Of Amblyopia

On the other hand, pure anisometropia showed better outcomes to occlusion treatment compared to the strabismic and mixed groups (Beardsell et al., 1999) that supports findings in a cohort of 961 amblyopic children requiring treatment in different clinical English establishments. Shotton et al.,Cochrane Report, (2008) found visual improvements in strabismic amblyopies with at least 20/40 or better levels achieving both equal VA and foveal fixation in the amblyopic eye (Shotton and Elliott, 2008). Hiscox et al. (1992), ascertained better outcomes for pure anisometropic amblyopia, intermediate outcomes in the strabismic groups and least improvement in the mixed amblyopia showing final acuities of 6/10.2, 6/12.8 and 6/14.8 respectively with an average length of 31months of follow-up.

1.6.4. Sustainability of Visual Outcome

An important concern is the sustainability of visual acuity after cessation of treatment and possible deterioration of vision in the amblyopic eye. Table 1.6 shows results from four studies describing the maintenance of vision following cessation of treatment. Visual acuity following amblyopia therapy was found to deteriorate when adult amblyopes visual acuities were re-assessed later in their lives (Ohlsson et al., 2002, Thompson et al., 1991, Simonsz-Toth et al., 2007). Residual amblyopia was also present in the 12-13 year age group following cessation of treatment (Ohlsson et al., 2001) and in military recruits (Hopkisson et al., 1982). Scheiman et al. (2005) found recommencing

occlusion showed a better response in the older age group than when compared to amblyopes who never received previous therapy (Scheiman et al., 2005).

Post- treatment decrease in the acuity occurred more in the mixed group (Simonsz-Toth et al., 2007), and was less common in mild amblyopes (Clarke et al., 2003). However, Levartovsky et al. (1995) in a group of 94 amblyopes (mean follow-up 6.4 years) concluded that patients with low VA at the start of treatment and mixed amblyopes are at risk of deterioration in VA in the long term. Average deterioration of vision was 79% in the mixed groups, 46% in the strabismic group and 36% in the anisometropic group (Levartovsky et al., 1995). Recent studies indicate that most children sustain good levels of achieved vision pending upon their study design following cessation of treatment (Hertle et al., 2007). Precautionary measures such as weaning occlusion towards the end of therapy reduce residual deficit (Holmes et al., 2006).

Studies	**Sample size**	**Average Follow-up (yrs)**	**Visual Acuity Maintained (%)**
Sparrow and Flynn,*1977*	439	5.4	40
Levartovsky et al *1992*	104	6.4	45
Ohlsson et al. *2002*	26	10.4	50
Leiba et al. *2001*	54	21.5	66.7

Table 1.6. *Showing visions maintained in the amblyopic eye following cessation of treatment in different studies.*

Studies	Sample size	Average Follow-up (mos/yrs)	% Recurrence of Amblyopia	Lines Regressed (number)
Gregerson & Rindziunski (1965)	53	10 yrs	75	2.4 Snellen lines
Kutschke *et al.*(1991)	124	37.9 mos	24.2	≥ 2 or more lines
Levartovsky *et al.*(1998)	86	6.4 yrs		
Group 1	(74)	..... *	51	≥ 1 or more Snellen lines
Group 2	(12)	..... *	75	≥ 3 or more Snellen lines
PEDIG (2004)	145	12 mos	24	≥ 2 log MAR lines
King *et al.*(2007)	74	≥ 5 yrs	14	2.6 Snellen lines

Abbreviation, mos denotes months and yrs denotes years.
Dots with Asterisks denotes different criteria used in one study sample above.
Levartovsky *et al.* Group 1; spherical equivalent difference between the two eyes ranged 0 and +1.50 dioptres
Group 2; spherical equivalent difference between the two eyes ranged +1.75 or greater.

Table 1.7. Outcome of Amblyopia Treatment. *Presentation of results attained from different studies showing deterioration in vision in the amblyopic eye following cessation of treatment.*

Many authors have studied the recurrence deterioration in vision (Table 1.7) over a short-term and longer-term follow-up following cessation of treatment. It is worth mentioning that each study had a different set of criteria in their investigations, regarding age at initiation of treatment and age at final visual outcome, occlusion practice and duration of treatment.

Levartovsky et al. (1998), Table 1.7, evaluated the extent of visual outcome in patients with anisometropic hypermetropia. Twelve of eighty-six patients, in group 2, (hypermetropia, ranging from 0 and +1.50 dioptres) and group 1 (+1.75 dioptres or greater) showed visual deterioration in anisometropic hypermetropia with more than +1.75 dioptres, spherical equivalent between the two eyes, although, relapse in visual acuities was not significant between the two groups overall. The efficacy of occlusion has an influence on the ocular alignment treated for strabismic amblyopia amblyopia (Holbach et al., 1991, Chun et al., 2007). Chun et al. (2007), in a group of 22 patients, found a significant correlation in the reduction in the angle of deviation with glasses from 19.45 PD to 12.14 PD with an increase in vision following occlusion in 15 (68%) patients with strabismus at 2 years following occlusion therapy (Chun et al., 2007).

1.6.5. How Much Treatment?

These studies have addressed the important aspect that occlusion treatment is crucial for the treatment of amblyopia. However, the question remains regarding how much dose of occlusion is necessary for an optimum outcome. A related issue is also the degree of of compliance for different prescribed regimens.

1.7. The Problem of Compliance

Compliance with treatment is one of the main factors in management of amblyopia that could influence the decision to either continue or end treatment. Prior to the current study and others where compliance has been measured objectively using electronic monitors, several studies estimated compliance using non-objective means such as diaries.

A nine year retrospective historical cohort study by Smith et al. (1995) investigated compliance using missed clinical appointments in 961 previously treated amblyopic children seen at seven different English clinics in Leicestershire. They determined that overall that compliance was low in that 41% of children from the most deprived areas were compliant, compared to 61% least compliant from the poorer deprived areas. In the same study, the frequency of attended follow-up appointments had better compliance, when arranged by some clinics in the first year of treatment though these results were not significant (Smith et al., 1995b).

Searle et al. (2002) reported that 105 parental questionnaires revealed that compliance with eye patching recommended by the treating orthoptists was only followed in 81(54%) of parents (Searle et al., 2002). They deduced that poor compliance to patching was due to the limitation incurred in their child's activities. Consequently, patching was perceived as negative (Searle et al., 2002). The study also found that compliance was a greater problem in children diagnosed with mixed amblyopia having worse visions before treatment commenced (Woodruff et al., 1994a, Nucci et al., 1992, Loudon et al., 2006b).

Another major issue in relation to compliance is the age of the amblyopic child at occlusion phase. Lithander (1991) demonstrated that in a group of forty-four amblyopic children, in the age group younger than two years, compliance, using the number of days, to achieve visual restoration was much faster than the 4-year age group (Lithander and Sjostrand, 1991). However other literature suggests that compliance to treatment was more successful in children aged seven to eight years or more with a significant increase in visual gain (Oliver et al., 1986, Smith et al., 1995b, Mintz-Hittner and Fernandez, 2000) compared to children aged 1-2 years (Nucci et al., 1992).

1.7.1. Impact of Amblyopia

1.7.1.1. Functional Impact of Amblyopia

In the amblyopic adult, poor residual vision following cessation of patching treatment affects the functional ability to perform everyday visual tasks such as driving or reading small print (Keeffe et al., 1999). To assess these problems, questionnaires have been used to obtain measurements that focus on daily living. Quality-of-life questionnaires (QOL) are useful tools to assess changes in the vision- specific quality in life inflicted by visual loss for example, issues related to cataract surgery or glaucoma. Keeffe et al. (1999) used the questionnaires and asked how much their eyesight had interfered with each of their activities for example 'reading a sign across the street'. Some people reported having difficulty in social and consumer interactions as well as household and personal care (Keeffe et al., 1999). Interestingly, Rahi et al. (2006) compared people with normal vision in each eye to those with amblyopia from the 1958 British Birth Cohort. They concluded

that there was no significant difference, both functionally and clinically, in these two groups of people in educational achievements, in paid employment or occupation based social class trajectories. They also did not find significant differences related to social engagements or exlucusions (Rahi et al., 2006).

Another group conducted patient-based interviews and found patients had specific problems related to visual tasks such as difficulty seeing black cars when crossing the road and judging perspective in oil paintings. The more general comments received was blurred vision, distortion and glare (Frost et al., 1998). In others interference with school, some level of work and life-style was affected (Packwood et al., 1999). Majority of studies have focused on the emotional and psychological impact related to amblyopia treatment however, to date, there a few published reports directly addressing the problems of functional impact in amblyopic children.

1.7.1.2. Quality of Life with Amblyopia

Suboptimal visual acuity and high grade binocularity have hindered amblyopic adults from being recruited for military assignments (Rosman et al., 2005, McAlister and Wingert, 1995) causing distress and interpersonal sensitivity at work and socially (Packwood et al., 1999). In a small sample study in Finland, Tommila and Tarkkanen et al. (1981) found higher incidence of trauma occurred commonly in the work place in which members had lost the vision in their healthy eye (Tommila and Tarkkanen, 1981). In education, it was found in the younger study population base study, that reading and

mathematic scores of 10 year olds with moderate to severe amblyopia was significantly worse (Stewart-Brown and Butler, 1985) compared to their normal counterparts.

1.7.1.3. Emotional Impact of Treatment

In children, toleration to occlusion is difficult in the amblyopic child as they are forced to experience abnormal visual perceptions during the treatment phase of the disease. Studies have demonstrated that eye patches are poorly tolerated compared to other forms of occlusion by patients and parents as the patch is exposed during treatment causing distress and anxiety amongst family and friends (Hrisos et al., 2004, Holmes et al., 2003, Sabri et al., 2006, Williams et al., 2006).

To understand problems related to visual impairment, psychological and psychosocial impacts have been assessed and measured on health related quality of life questionnaire (HRQOL) in adults (Chia et al., 2003) and in children (Packwood et al., 1999, Searle et al., 2002). The psychological impact scores relate to amblyopia, wearing glasses and an obvious strabismus. The visual function 14 questionnaires (VF-14) had been utilised to measure scores related to general daily living with a weaker eye. The VF-14 questionnaire comprised a series of questions designated to 14 different activities which are purely vision-dependant (Sabri et al., 2006). Sabri et al. (2006) investigated the psychological impact related to visual function in a group of 120 amblyopic teenagers, aged 16-18 years, with residual amblyopia by administrating the VF-14 questionnaire. Results in this study exhibited a negative impact on general daily living-with mean scores of 18.2% for the controls and 37.2% for the amblyopes (where a high score is detrimental) (Sabri et

al., 2006). It concluded that amblyopia and/or strabismus caused distress and subjective visual function.

Similarly, Packwood et al. (1998) found amblyopic patients experienced a greater degree of depression, anxiety, interpersonal sensitivity compared to controls using the Hopkins Symptom Checklist (KSC) in their cohort of 25 patients with amblyopia with no obvious manifest strabismus (Packwood et al., 1999). An attempt to reduce potential psychological impacts in amblyopia treatment was addressed by the ALSPAC study group, (2006) focused on bullying and victimisation. It highlighted that early intervention of preschool vision screening reduced bullying by 50% (Williams et al., 2006). In summary, occlusion treatment for amblyopia is effective in restoring visual loss but it also creates a negative impact on the child's behaviour and on the family, influencing compliance. The negative impact could be addressed when occlusion is prescribed (Webber and Wood, 2005, Clarke et al., 2003).

1.7.1.4. Parent/Patient Attitude to Treatment

There is strong evidence to support the hypothesis that parental input is vital in achieving satisfactory vision through successful compliance. Newsham (2000) reported non-compliance in a group of 57 patients with amblyopia using questionnaires and diaries. The questionnaires identified gaps in the parents' understanding in areas of amblyopia, occlusion therapy, critical period, and prognosis. They also revealed parents' own personal experiences towards compliance to treat were limited. Evidence suggested that parents had limited knowledge about the critical period. Some parents had misconceptions that

occlusive patching would straighten the strabismic eye. Others took a more casual approach to patching as they were unaware of the impact of amblyopia to the child and felt that the treatment was not credible (Newsham, 2002). Similarly, questionnaires identified problems with the clinicians' role in delivering information, instructions to the parent and patients and building confidence in their ability to patch (Oto et al., 2002).

The problem of compliance is the difficulty in getting a child to patch. Tripathi et al. (2002) suggested, "Letting the parents decide." They should be given a choice to manage and establish a successful daily regime of patching according to their personal circumstances and letting them decide how best to achieve compliance to treatment (Tripathi et al., 2002). Strategies devised by parents for good compliance have shown that rewarding children (Rubin and Nelson, 1993) to augment patching treatment is effective (Loudon et al., 2006b). On the other hand, language barriers, inadequate parental education and social deprivation can hinder in compliance (Smith et al., 1995b, Loudon et al., 2006b, Majeed et al., 2008). Rahi et al. (2003) carried out a cross-sectional survey of parents or caregivers who attended the ophthalmology clinics for a period of one-week using questionnaires. Of the 58 patients participating, only 46% (27 patients) were able to correctly diagnosis their child's condition and understood the impact of the disease. The study shows the importance of relaying knowledge and instructions to parents by health professionals and other allied sources. Thus, increase knowledge towards the management of amblyopia and reduce any misconceptions regarding treatment (Rahi et al., 2003).

1.7.2. The Need to Objectively Monitor

1.7.2.1. Measuring compliance

Establishing an optimal regimen of occlusion has been hindered in the past by difficulties in knowing levels of compliance to patching treatment in amblyopic children. The definition of compliance, according to the Report for the National Co-coordinating Centre for NHS Service Delivery and Organisation R & D, " is the extent to which patient's behaviour matches the prescriber's recommendations" (Horne et al., 2005).

Before electronic monitoring devices made contributions towards measuring compliance, studies used different methodologies, listed below.

- Smith, et al. 1995 used clinical attendance in the first year as a surrogate measure of compliance from patients residing in more or less deprived areas of the county (Smith et al., 1995b).
- Newsham 2000 used a daily diary to monitor concordance and total hours of prescribed occlusion (Newsham, 2000).
- Cleary 2000 used self-reports from parents to record compliance, i.e., the daily number of hours occlusion was worn. (Cleary, 2000).
- Oto et al. 2002 used a schematic diary based in which the parent entered the number of hours occlusion and a measure of the child's attitude during patching with 'smiley' and 'sad' images (Oto et al., 2002).

All these studies are subjective and are not direct measurements in either patient recording or related measures.

1.7.2.2. Dose response-without objective monitoring

Previous studies suggested that efficacy of treatment is greater in the first few months after initiation of treatment, see Table 1.8.

Studies	Sample	Amblyopia (type)	Treatment (mos) (most effective)	Duration (yrs)
(Lithander and Sjostrand, 1991)	44	Strabismus Anisometropia	3 mos	4.5
(Woodruff et al., 1994a)	961	Strabismus Mixed Anisometropes	3 mos	10
(Cleary, 2000)	136	Strabismus	6 mos	1

Table 1.8. *Average duration of treatment as most effective for occlusion*

Woodruff et al. (1994), using cumulative dose, demonstrated shorter hours of occlusion was more effective than the longer hours of patching, see graph (Figure 1.26) in all patching groups (strabismus, anisometropes and mixed) overall (Woodruff et al., 1994a).

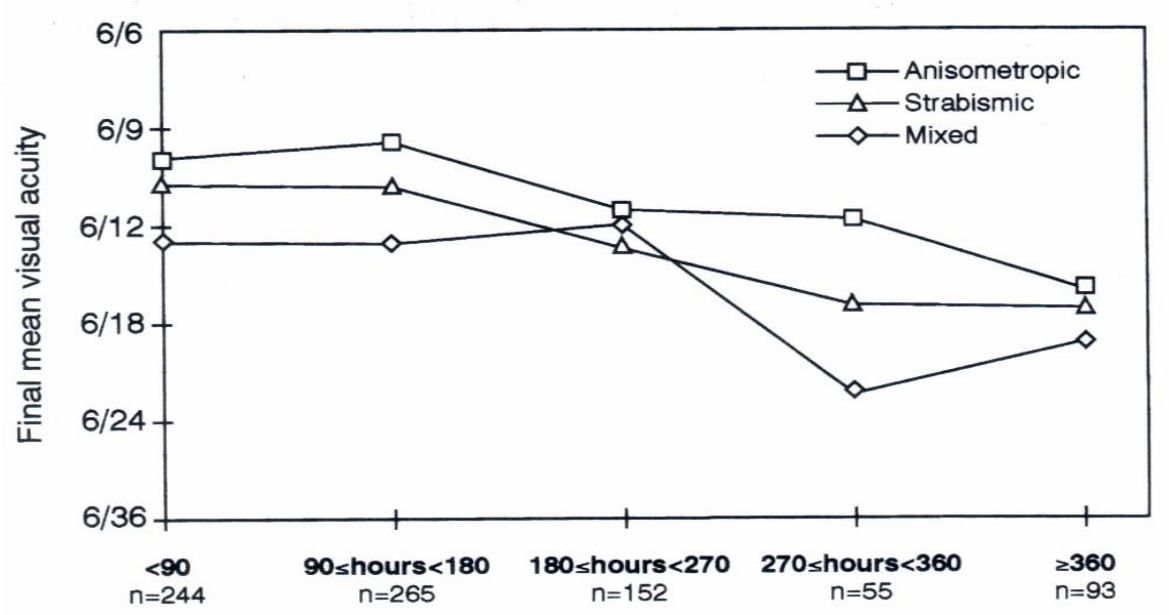


Figure 1.26. *Mean final acuities versus hours of patching during the first 3 months of treatment. In 809 of 961 children (80%) attained VA significantly lower in > 360 hour group compared to <90 hour group. On average children given less than 90 hours of occlusion reached 6/10.8 VA (n=244) compared to 360 hours or more reaching an overall VA 6/16.7 (n=93) in the first three months of initiation of treatment. (Reproduced from Woodruff et al. Eye 1994 8,627-631).*

The difference in improvement in vision could be attributed to longer hours of prescribed for greater levels of visual loss at the start of treatment in all amblyopes. In agreement with Woodruff et al. (1994), Hiscox et al. (1994) reported better VA 61%

(n=70) of the 114 patients were prescribed up to 100 hours achieved VA 6/9 and 28% (n=18) of the 95 subjects prescribed over 500 hours of occlusion achieved VA 6/9 in a cohort of 368 children. One of the problems with the study is non-randomisation of subjects to dose. Therefore, it is impossible to determine dose response since compliance was not actually measured with dose. It is possible that the children with better initial visual acuity were more compliant and responded faster.

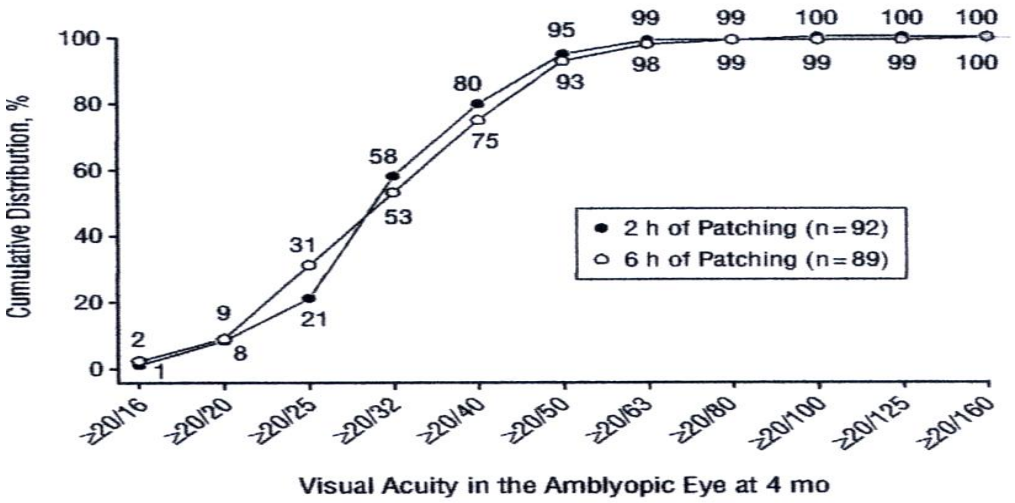
1.7.2.3. Studies Investigating Patching Treatment without Monitoring Occlusion Objectively.

A number of large studies performed by the American Study, Pediatric Eye Disease Investigator Group (PEDIG), funded by the National Eye Institute, directly address the importance of visual improvement following occlusion treatment from a range of base-line acuities and several paradigms of treatment. Reference to the contralateral eye is referred to as the normal eye however, measurable changes in visual function over the treatment period is evident (Simons, 2005, Fielder et al., 1995).

The Amblyopia Treatment Studies (ATS) of the (PEDIG) conducted two comparative randomised trials comparing visual outcome for the treatment of moderate (VA 20/40 to 20/80) and severe (VA 20/100 to 20/400) amblyopia in children aged less than 7 years (PEDIG et al., 2003a, PEDIG et al., 2003b). In the moderate amblyopia study, children were assigned to receive either 2 versus 6 hours of occlusion and in the severe group were assigned to receive either 6 versus 12 hours of occlusion. VA in both

groups was monitored over a four-month trial period. Observing cumulative distribution of visual acuity in the amblyopic eye, improvements in visions were revealed in each of the two treatment groups Graphs A and graph B (Figure 1.27) show cumulative distribution of VA in the amblyopic eye. Figure 1.27 (A) shows little separation and (B) shows separation at 20/40 and worse suggesting difference in visual outcome.

A



B

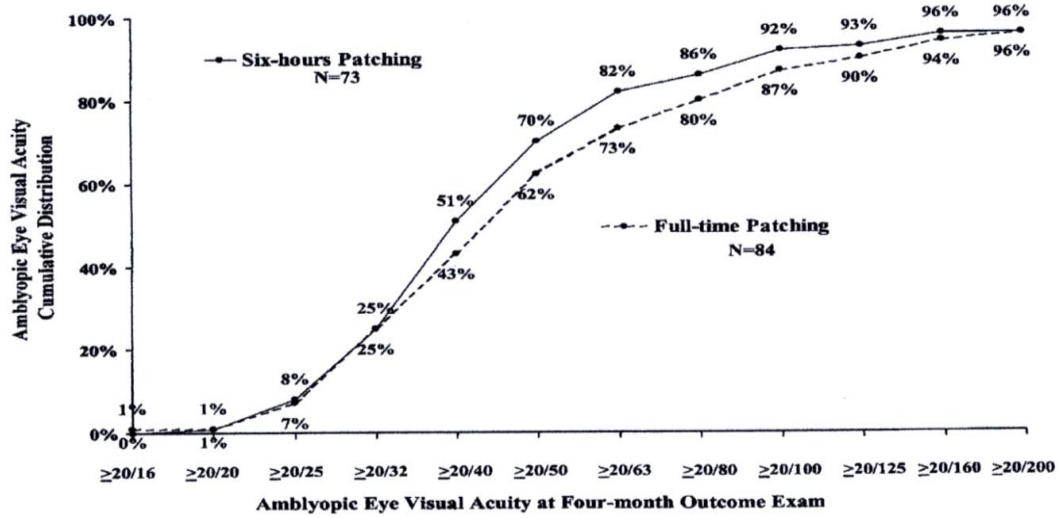


Figure 1.27. *Comparative studies, from the PEDIG group. Both studies, showing cumulative distribution (sigmoid curve) in VA outcome in the amblyopic eye at end of the four months. The two treatment groups: (**A):** Group 1. Moderate amblyopia. (**B):** group 2 severe amblyopia. (Reproduced from the PEDIG studies: Arch Ophthalmol 2003; 121:603-611 & Ophthalmology 2003; 110:2075-87 respectively)*

The average number of lines increased at the end of the trial period, in the two study groups and four treatment arms are shown in table 1.9. This shows VA gains overall were no different between 2 versus 6 hours and 6 versus 12 hours in the moderate and in the severe amblyopes. However, there was greater improvement for the severe ambyopes prescribed 6 hours of occlusion than there was for the moderate amblyopes prescribed 6 hours. No difference between the two prescribed groups are shown in Table 1.9 below.

Treatment Groups (hrs)	**Moderate amblyopia (20/40- 20/80) (mean number of lines gained from baseline acuity)**	**Severe amblyopia (20/100 – 20/400) (mean number of lines gained from baseline acuity)**
2	2.4	
6	2.4	4.8
12		4.7

Table 1.9. *Number of lines gained in the two treatment groups from the base-line acuities to completion of follow-up at four months (Produced by main author)*

The baseline acuity in the study groups were variable, as the study criterion was at least 0.30 logMAR interocular line difference between the two eyes. The group did not analyse the efficacy of occlusion treatment, as ODMs were not available but focussed on the effect of using two different prescription regimens. The study only had a short period of refractive adaptation at four-week glasses wearing. Visual improvements during the occlusion phase may have been due to visual improvements from refractive adaptation.

1.8. Enhancing Compliance

Occlusion therapy is problematic (von Noorden, 2002) and compliance can be improved by involving the patient in some form of positive visual activity during patching treatment under a controlled environment (Foley-Nolan et al., 1997, Hiscox et al., 1992, Williams et al., 2002). Visual activities include colouring, tracing, video games, and other forms of hand-eye coordination may also assist by improving the effect of patching when the child is being compliant.

Clorfein et al. (1992) suggested the use of a transparent film dressing to strengthen compliance during the therapy, to prevent child from peeking over or removing the patch during treatment (Clorfeine and Parker, 1992) (Figure 1.28). The use of this type of patch is invisible when applied over the conventional skin adhesive occlusion patch. However, in real life the tape is likely to have caused much distress in a child, unable to remove the patch.

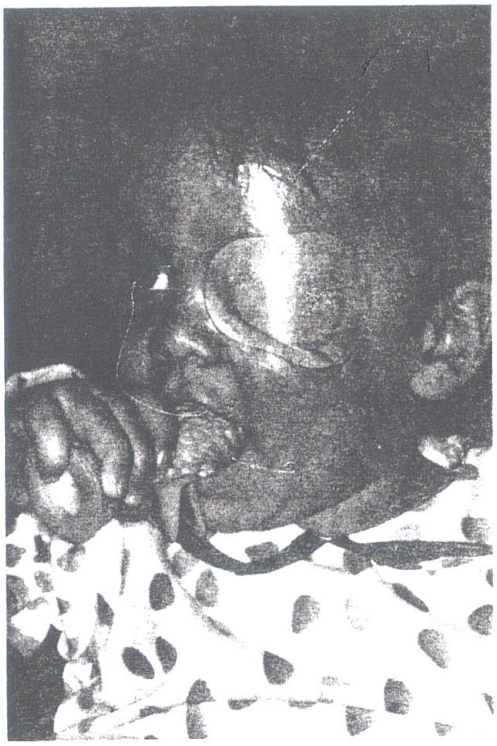


Figure 1.28 *amblyopic patient with a transparent film dressing placed over the conventional adhesive occlusive patch. The patch blends with the skin. It was only visible with light made by the flash from the camera that reflected presence of the dressing.*

Recently, Li et al (2007) found substantial visual restoration using a course of intense perceptual learning combined with occlusion (Figure 1.29). The task was to identfy misalignment of three pairings of two groups of eight Gabor patches (Li et al., 2007a).

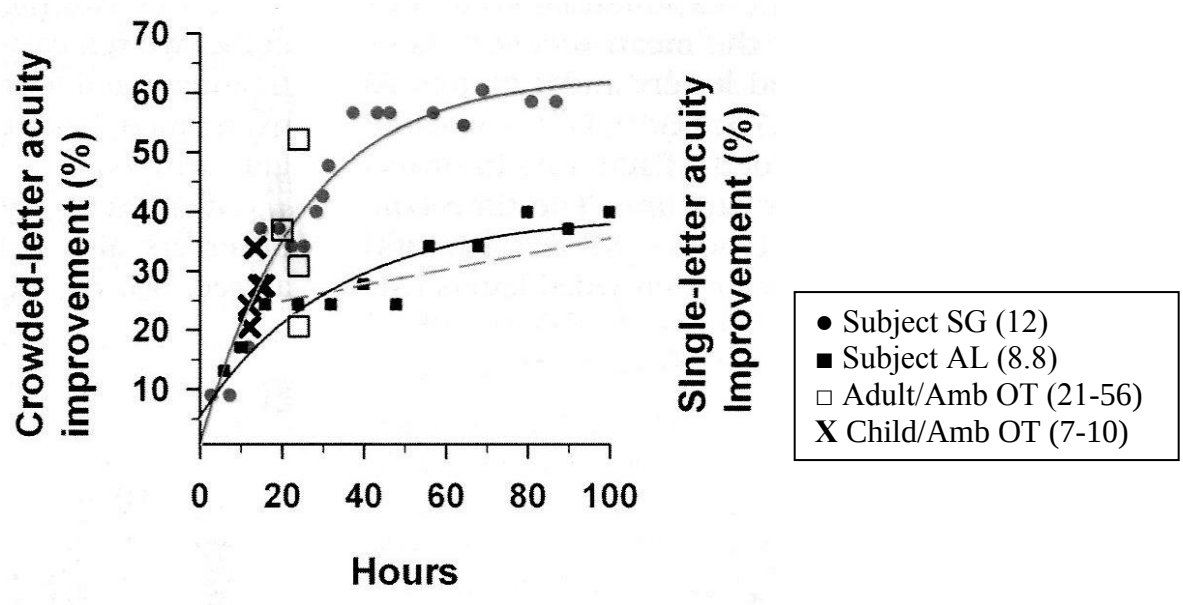


Figure 1.29. *Fast recovery of visual acuity. Percentage improvement in VA logMAR, in relation to cumulative therapeutic hours of the two juvenile subjects compared to data from previous subjects. Filled circles denotes subject aged 12 years. Filled squares denotes subject age 8.8 years. Fifty hours of treatment dosage showed a marked increase and plateau in VA than that of previous amblyopes that received occlusion therapy (cross) and adults (squares). The grey dashed line is a comparison of the dose response following occlusion treatment in the study of 93 ambyopes children (aged 3-8 years). (Reproduced by Li et al IOVS 2007; 48(11)5046-5051)*

Li et al. (2007) investigated amblyopia on two juvenile amblyopes aged 8.8 and 12.0 years with no previous history of occlusion therapy with data from twelve subjects in their previous studies of the same age group. Fifty hours of in-house occlusion and training showed positive results compared to occlusion performed outside of the clinic (Li et al., 2007a). However, further exploration is required to verify findings and prove that perceptual learning as enhancing treatment for amblyopia is cost-effective on the health service.

Another means of improving compliance is in providing information to the parents of amblyopes. Newsham (2000, 2002) presented evidence that lack of information, in understanding amblyopia and the critical period contributed towards non-concordance with occlusion treatment-(Newsham, 2000, Newsham, 2002).

1.8.1. Objective Monitoring of occlusion

In recent years, applied researchers have become increasingly interested in monitoring compliance (Kass et al., 1986, Kass et al., 1984). Electronic recordings of compliance have been used in other research fields in the 1980s to monitor administration of eye drops. Kass et al. (1984, 1986) measured compliance in adult patients who administered pilocarpine eye drops for treating glaucoma. The compliance monitors were found to be reliable methods of detecting patients who default from treatment (Kass et al., 1986, Kass et al., 1984). Monitoring occlusion in children is even more challenging.

At the commencement of this study, two European research groups used occlusion dose monitors (ODMs) for their studies on amblyopia. At this point the UK based group Fielder et al. were the first to develop an ODM and utilised their monitor investigating on the effectiveness of occlusion therapy and visual outcome (Fielder et al., 1995, Stewart et al., 2002, Fielder et al., 1994). The Rotterdam Group developed an ODM to investigate and measure visual outcome and compliance to the treatment prescribed (Simonsz et al., 1999, Loudon et al., 2003, Loudon et al., 2002). The extensive literature on electronic monitoring devices for amblyopia is reviewed in chapter 3 of the thesis.

1.9. Aims.

The aim of this thesis is to investigate ways of improving patching therapy for the treatment of amblyopia. I will in particular explore the role of compliance and ways of improving it. Compliance will be objectively measured using electronic occlusion dose monitors.

1.9.1. Establish Current Outcomes in Relation to Costs.

In the first study (chapter 2) we aim to determine the current visual outcome of patching treatment for amblyopia in relation to the costs, i.e, clinical effort and financial costs. Information will be gathered from previously discharged amblyopes, from a UK clinic. I will focus on the age at presentation, type of amblyopia, visual acuities prior to, immediately at the end and at discharge, total number of clinical visits (consultant, orthoptist and optometrist) including non-attended visits, duration of treatment received from the hospital, hours prescribed and costs incurred to the NHS.

1.9.2. Can ODMs be used to provide reliable measurements of compliance.

For many years, the visual outcome of amblyopia treatment has been investigated. However, evidence for the actual effect of occlusion has been recently questioned. A European research group developed novel occlusion dose monitors (ODM) to investigate

the efficacy of occlusion therapy for amblyopia. Following permission, I will utilise some of these monitors to carry out the relevant studies described in the thesis.

To test reliability of the occlusion dose monitor (ODM) I will use the assistance of colleagues in the research department and their children to ensure the ODM are capable of recording patching times reliably. I will modify the patches required for the research described in the following chapters to ensure that reliability of patching is achieved, loss of data is minimised, the patches look cosmetically acceptable and are comfortable to wear. These "pocket" patches will be used in the two patching studies. However, in the latter experimental study I have modified the "pocket" patch further to suit the design of the educational informational package used for this purpose.

1.9.3. The Efficacy of Occlusion for the Treatment of Amblyopia and Observe Compliance to the Treatment Prescribed.

The aim of the main study in this thesis (described in chapter 4) is to perform a randomised control trial (RCT) to explore compliance to different patching regimes of occlusion treatment in a group of strabismic and mixed amblyopes. The patients will be randomised into three treatment groups of 0-hour, 3-hours and 6-hours patching with absolute patching times monitored using a novel occlusion dose monitor (ODM) over a 3-month treatment period. A description of the ODM and its validation is described in chapter 3. A comparison of effective patching times and improvement in vision will allow us to describe the dose-effect relationship for patching therapy in this group of patients.

1.9.4. A Qualitative Approach to Explore Amblyopia Treatment and the Difficulties Entailed in the Therapy.

Since the findings of the RCT indicate that compliance is a vital factor in determining the success of occlusion therapy, the aim of the next study (chapter 5) is to explore reasons for poor compliance using semi-structured interviews. In particular questions I will ask is to explore the child's well being during treatment, social acceptance of patching, the perceived credibility of the treatment, visual appearance of the patch, understanding the different roles of professionals involved in the care of amblyopia and also the knowledge of parents concerning amblyopia, for example, the difference between a strabismus and amblyopia. Additional questions focus on strategies families use to achieve successful treatment such as school and family support and rewards systems.

1.9.5. Enhancing Amblyopia Treatment Using an Educational Intervention Program.

The aim of the final study in the thesis involves preliminary testing of an educational intervention that was designed based on knowledge given by the earlier studies. The aim of the study that will follow this preliminary testing is to investigate whether the educational intervention improves compliance and hence improves visual outcome. Newly diagnosed amblyopes are randomly recruited into one of two patching groups, i.e. a group that received the educational interventional and a group that did not. Ten hours of patching will be prescribed and compliance is recorded with ODMs. The longer hours of patching will also provide data on the dose-response characteristics at higher patching rates.

Chapter 2

The Outcome of Amblyopia Treatment: A retrospective study of 322 children

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2.1. Aims

Our aim was to retrospectively investigate modalities for occlusion treatment for amblyopia, the outcome of amblyopia treatment and estimate costs (clinical obligation and financial) in a cohort of amblyopic children who attended a single National Health Service (NHS) ophthalmology clinic in the United Kingdom treated for occlusion.

2.2. Introduction

Amblyopia is usually treated by patching the non-amblyopic eye; however, treatment practice shows extensive variation (Simons, 2005). Occlusion treatment for amblyopia has been practiced for over three centuries; however, an effective protocol or regime for patching has not been established. The lack of evidence for amblyopia treatment and contradictory data on dosage for the best treatment and duration has recently led to a large amount of studies aiming to clarify best treatment options (Holmes and Clarke, 2006, PEDIG et al., 2003b, PEDIG et al., 2003a, Stewart et al., 2007b, Stewart et al., 2007a, Loudon et al., 2006b). However, little is known about the current treatment modalities such as treatment duration or hours of patching prescribed in patients treated in hospital settings who are not enrolled in studies. It is possible that unnecessary efforts and costs for patients, their families, health professionals and hospitals currently occur during amblyopia treatment.

2.3. Methods and Materials

A retrospective analysis was conducted on random selected patients receiving occlusion treatment between 1996 and 2008 from the Leicester Royal Infirmary, UK. Only patients detected with amblyopia that had prresented before the age of 8 years and subsequently discharged from the hospital were included in the study.

The sample size (n=322) was based on the number required to estimate the 95% ± 5% confidence interval of the current treatable population of amblyopes in Leicester (i.e. 49 168 individuals in Leicestershire between 3-8 years based on the 2001 UK Census of which 4% were assumed to be amblyopic). Inclusion and exclusion criteria were as follows:

Inclusion Criteria:

- Newly diagnosed amblyopes
- Aged < 8 years of age
- Strabismic amblyopia (mainfest deviation of the eyes)
- Anisometropic amblyopia (difference of refraction of both eyes of at least 1.50 dioptre spheres and/or 0.5 dioptres of cylindrical error)
- Mixed amblyopia (combination of both anomolies)
- Stimulus deprivation amblyopia

Exclusion Criteria:

- Absent amblyopia (VA < 6/9)
- Absent or nil recorded visions at the time occlusion commenced
- Missing or incomplete notes of all visits to the Ophthalmology Deprartment at initiation of treatment to discharge
- Treatment continued elsewhere
- Continued receiving amblyopia treatment once the study ceased (2008)
- Presence of an organic pathology

Notes were randomly selected (from patients listed electronically in the orthoptic database that commenced treatment in 1996) by the main author MA until 322 notes of patients that fulfilled inclusion criteria were suitable Collection of data included:

- The age at first clinical presentation in the ophthalmology department.
- Best corrected visions at the beginning of treatment.
- Type of amblyopia.
- VA at initiation of treatment, immediately at cessation of treatment and at discharge.
- The total numbers of prescribed hours of patching,
- The total duration of patching treatment.
- Number of alterations made to the glasses prescription during the treatment phase for occlusion.
- Number of visits attended and failed to attend during the treatment period.
- Number of orthoptists involved in the treatment.

This was an observational study. The sample frame used to select patients was an orthoptic electronic database created in 1996 kept to the present date. Patients details entered in the database were full name and date of birth entered at the date of their first presentation. Details of every orthoptic visit attended and non-attended were also entered including clinical assessments of visual acuity, ocular motility, cover testing, binocularity testing and convergence (minimum standards). The main author (MA) selected the patients from the database in order (of visit date omitting patients already included), in batches of 30 from each year 1996-2001 cyclically until 322 that met the inclusion criteria and notes were obtained.

Data were manually entered predominantely by the main author. The process was slow in obtaining data therefore junior ophthalmologists of the ophthalmology department, (IC) and (DG) participated. To ensure all data was entered correctly in specified fields of the spreadsheet, I ensured and overlooked the spreadsheets entered by (IC) and (DG). All data was entered into individual block spreadsheet created by (FP). Appropriate information needed to create relevant fields in the spreadsheet was a group participation between the authors (MA), (IG), (FP) and (NS).

VA measurements were carried out by orthoptists using tests that were age appropriate for the age and compliance. Valid tests documented were Cardiff Acuity Cards, Kay Pictures, Sheridan Gardner and Keeler Glasgow LogMAR Cards for the younger age group and predominantly and Snellen optotypes for the more compliant and older children. VA measurements for most patients were performed using different tests according to the age range between first clinical presentation and the time of discharge.

Ninety-eight patients, where patching was given, were too young to have the above visual acuity tests and were excluded from the analysis of VA related outcomes.

Costs for the National Health Service (NHS) UK were estimated from prices paid for examinations from Primary Care Trusts in Leicestershire (£110 for the first visit and £53 for follow up visits). For patients who did not attend examination appointments the same tariffs as follow up costs were used. To estimate the costs of glasses, prices were based on the General Ophthalmic Services voucher scheme (prices range from £34.60 to £173.70 depending on sphere and cylinder of the strongest lens). Costs of patches were calculated from the ordering price for the orthoptic department (£6.50 per pack of 50). Costs occurring for the patients were not included in this study.

Group comparisons were made using Kruskal-Wallis (KW) tests since most measures were not normally distributed. Percentages of patients reaching certain VA thresholds were compared using the Gamma statistic. Univariate analysis was used to investigate significant predictors of visual outcome including age, number of orthoptists examining the children, prescribed hours, number of visits not attended as covariates and type of amblyopia as fixed factors. SPSS v14 was used to perform the statistical analysis.

2.4. Results

At presentation the 322 patients were aged between 5 months and 8.9 years of age (mean age 4.10 years, SD 1.73 years), of which 123 (38.2%) patients were diagnosed with strabismic amblyopia, 103 (32.0%) with anisometropic amblyopia, and 95 (29.5%) with

mixed amblyopia. One patient diagnosed with stimulus deprivation was excluded from analysis.

Of the 922 patients listed between 1996 and 2001 we estimated that 485 patients were eligible between these years who met the inclusion criteria. The biggest group who were not eligible had suspected amblyopia but achieved visual gain on clinical follow-up. Others were not classified as being amblyopic or were misdiagnosed. Also, there were incomplete or unreliable notes and a small group of patients were not discharged. These groups were excluded from the study. Therefore, the proportion of eligible patients in the database included in the study was 322/485 = 66.4%.

Figure 2.1A shows the mean number of attended vsits and failed visits with ophthalmologists, orthoptists and optometrists. All amblyopes underwent more visits (including failures to attend) with orthoptists compared to ophthalmologists or optometrists. The anisometropic amblyopes necessitated less clinical appointments. Non attended visits were proportionally lower for optometry visits (2.0%), compared to 11.4% for ophthalmologists and 12.6% for orthoptists.

The mean duration of hospital care were similarly for the strabismic and mixed amblyopes (approximately 40 months) but shorter for the anisometropic amblyopes (KW, χ^2=58.7, p=1.8x10^{-13}, Figure 2.1B). On average patients were patched for 51.3% of the time for hospital care. Mean prescribed patching times were highest in the mixed group, followed by the strabismic group and then anisometropes (KW, χ^2=36.2, p=1.4x10^{-8}, Figure 2.1C).

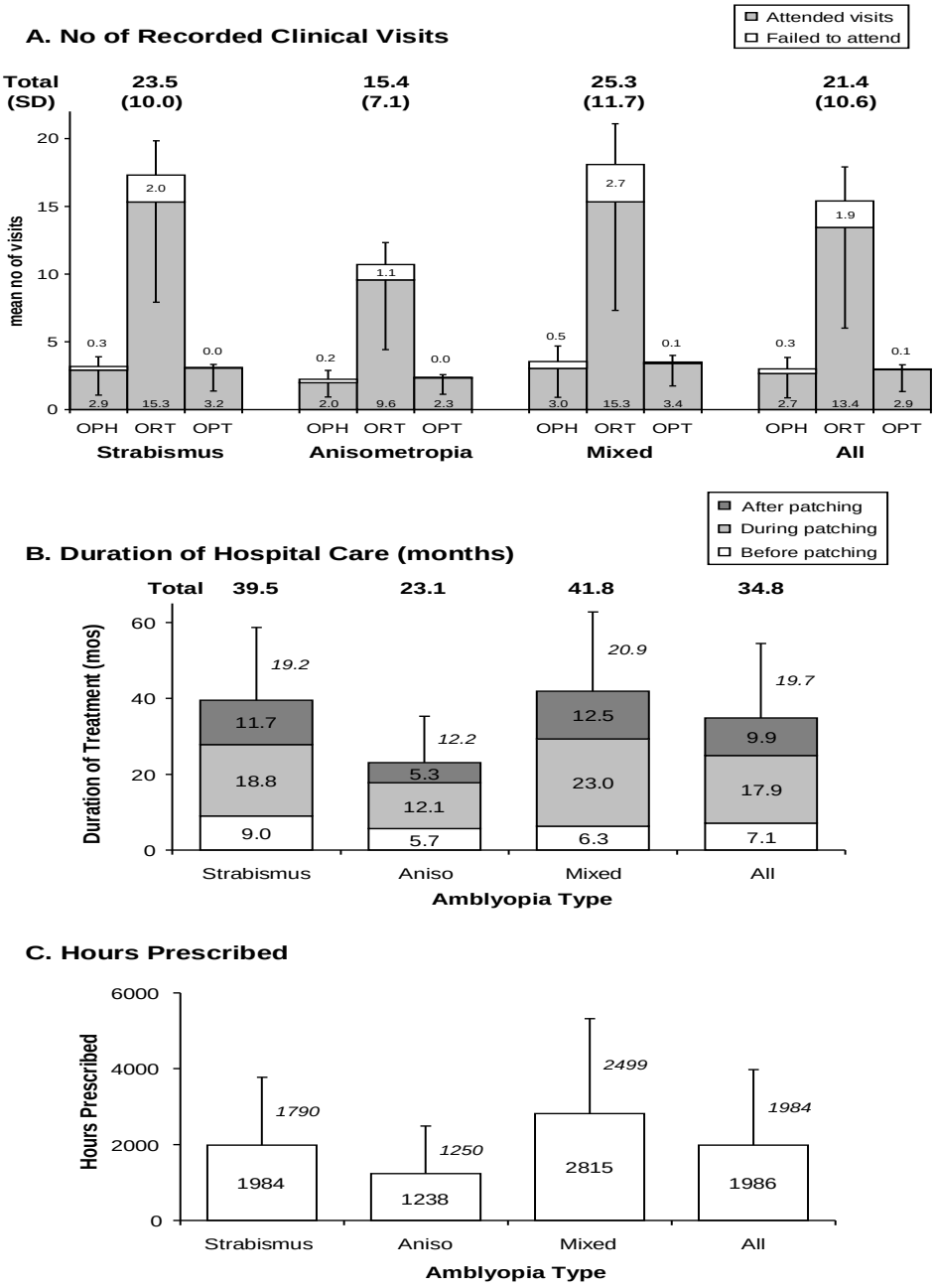


Figure 2.1: (A) *Mean number of visit and standard deviations attended and failed to attend with the ophthalmologists (OPH), orthoptists (ORT) and optometrists (OPT).* ***(B)*** *Mean duration of hospital care in months (±SD).* ***(C)*** *Hours prescribed for each group and collectively. Means are inserted in figures (see Y-axis for units). For figure A and B standards deviations are also inserted.*

Figure 2.2 shows the mean number of alterations made to the glasses prescribed and number of patches estimated used during occlusion treatment. For both, the number was highest for mixed amblyopia and lowest for anisometropic amblyopia (KW, χ^2=32.6, p=8.2x10^{-8} for number of glasses used and χ^2=37.3, p=17.8x10^{-9} for number of patches used).

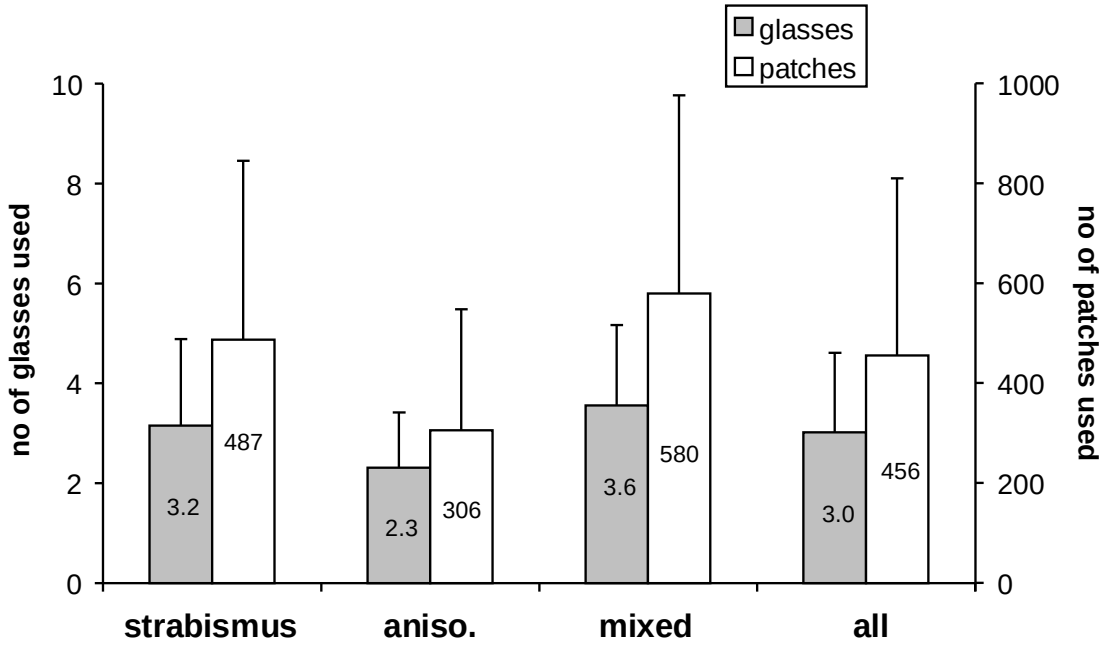


Figure 2.2: *Estimates of mean number of glasses and patches used in each amblyopic group. Numbers inserted in boxes represent mean values.*

Low initial visual acuity (F=362.8, p=4.78x10^{-48}), low age at presentation (F=11.1, p=0.0010) and high number of failed appointments (F=9.5, p=0.0023) were significant predictors of the improvement in logMAR visual acuity in the amblyopic eye. However, type of amblyopia (F=0.14, p=0.86) and number of different orthoptists seen (F=0.023,

p=0.87) were not. Prescribed hours of patching was also a significant predictor of visual improvement in the amblyopic eye (F=25.0, p=1.18x10^{-6}) although the correlation was negative with longer prescribed hours leading to poorer visual outcome.

This was a retrospective study there was, therefore, no control on the test type used for each patient. All recorded visual acuities, regardless of test type, were converted into logMAR for analysis. Cardiff cards were excluded as a measure of VA as these are uncrowded that rely on diminishing vision (Figure 2.3). The use of different visual acuity tests was acknowledged as a weakness (page 121 and 122).

Figure 2.3 shows the proportions of patients with VAs of 6/6, 6/9 and 6/12 in the amblyopic eye before and after treatment. Group comparisons (Gamma statistic) show VAs were less in the mixed group before (p=0.003) and after treatment (p=0.049) for volunteers with VA measures prior to patching (n=223) and p=0.036 for all data after treatment (n=321)).

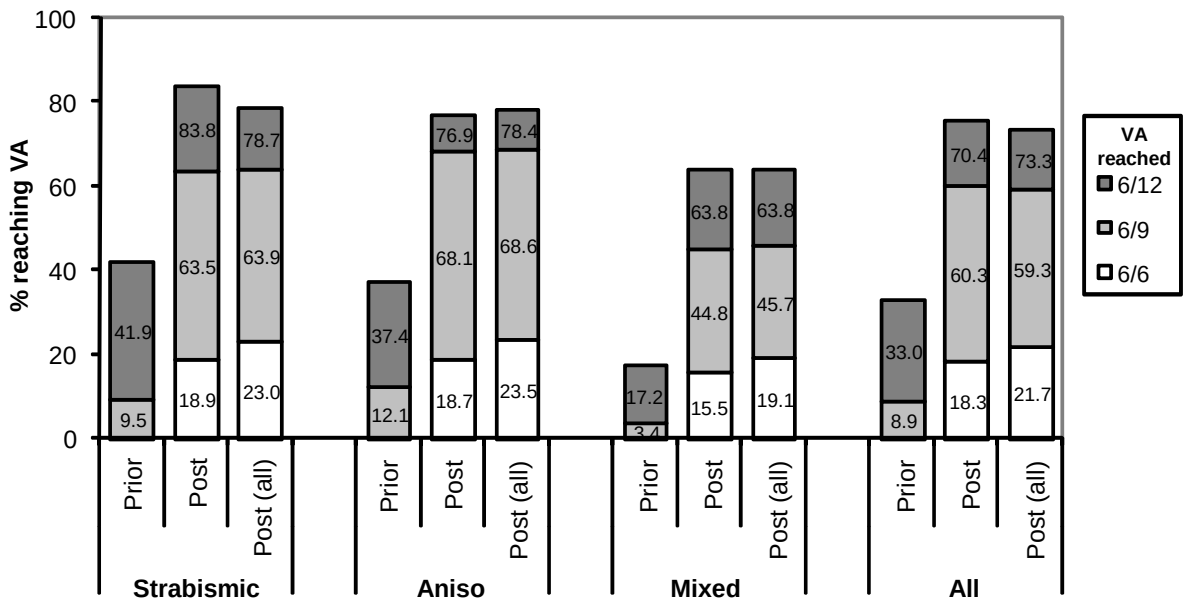


Figure 2.3. *Percentage of improved visual acuity reached before and after treatment for strabismic, anisometropic, mixed amblyopia and all patients. The first two bars in each group represent patients where visual acuities were recorded before and after patching (n=223). The last bar represents VA of all subjects after patching. Inserted numbers represent cumulative mean percentages for each acuity level.*

The VA of all patients before and after occlusion and at the last visit before discharge is represented in Figure 2.4 for the three different groups of amblyopia. There was no significant change between the VA at last patching and at discharge (p=0.76 for strabismics, p=0.22 for anisometropes and p=0.53 for mixed).

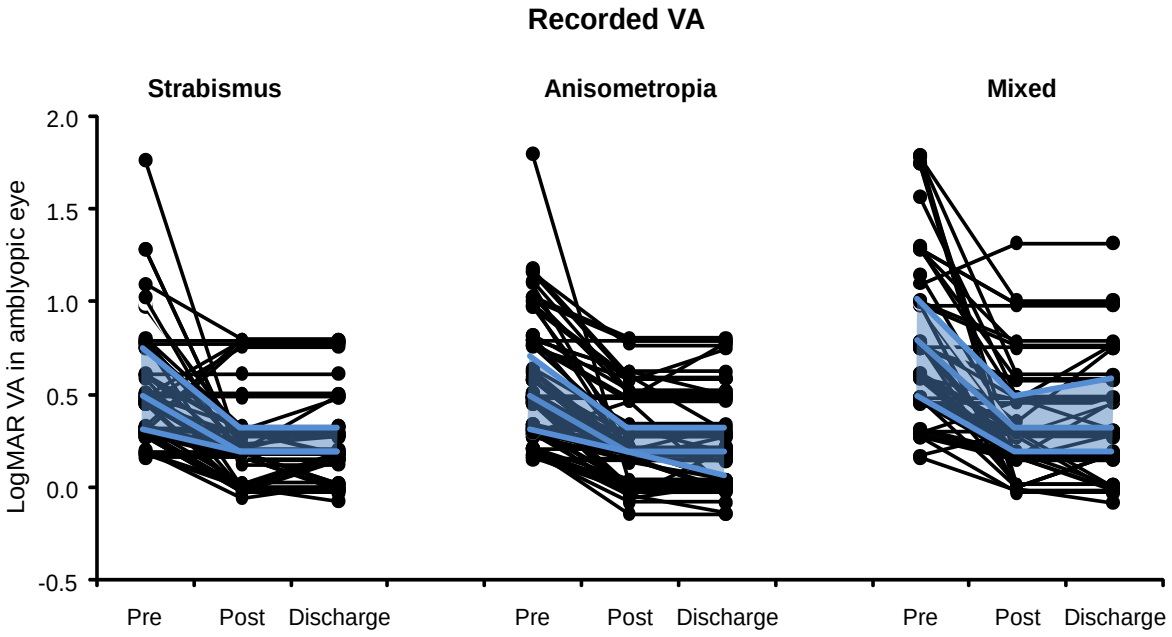


Figure 2.4: *Change of LogMAR visual acuity in the amblyopic eye at the start, immediate end of occlusion and at discharge for strabismic, anisometropic and mixed amblyopia. Overlying data points have been spread. Thick blue lines and shaded area represent median and quartiles.*

The costs estimated for treatment are represented in Figure 2.5 (A). There were significant differences between amblyopia types (KW, χ^2=61.0, p=5.7x10^{-14}) because of lower costs for treating anisometropic amblyopia. Figure 2.5 (B) represents the frequency distribution of costs. Treatment of a significant number of patients exceeds £2000. In anisometropia, the costs were lowest peaking between £800 to £1000. In other amblyopia forms, costs were more spread out and higher.

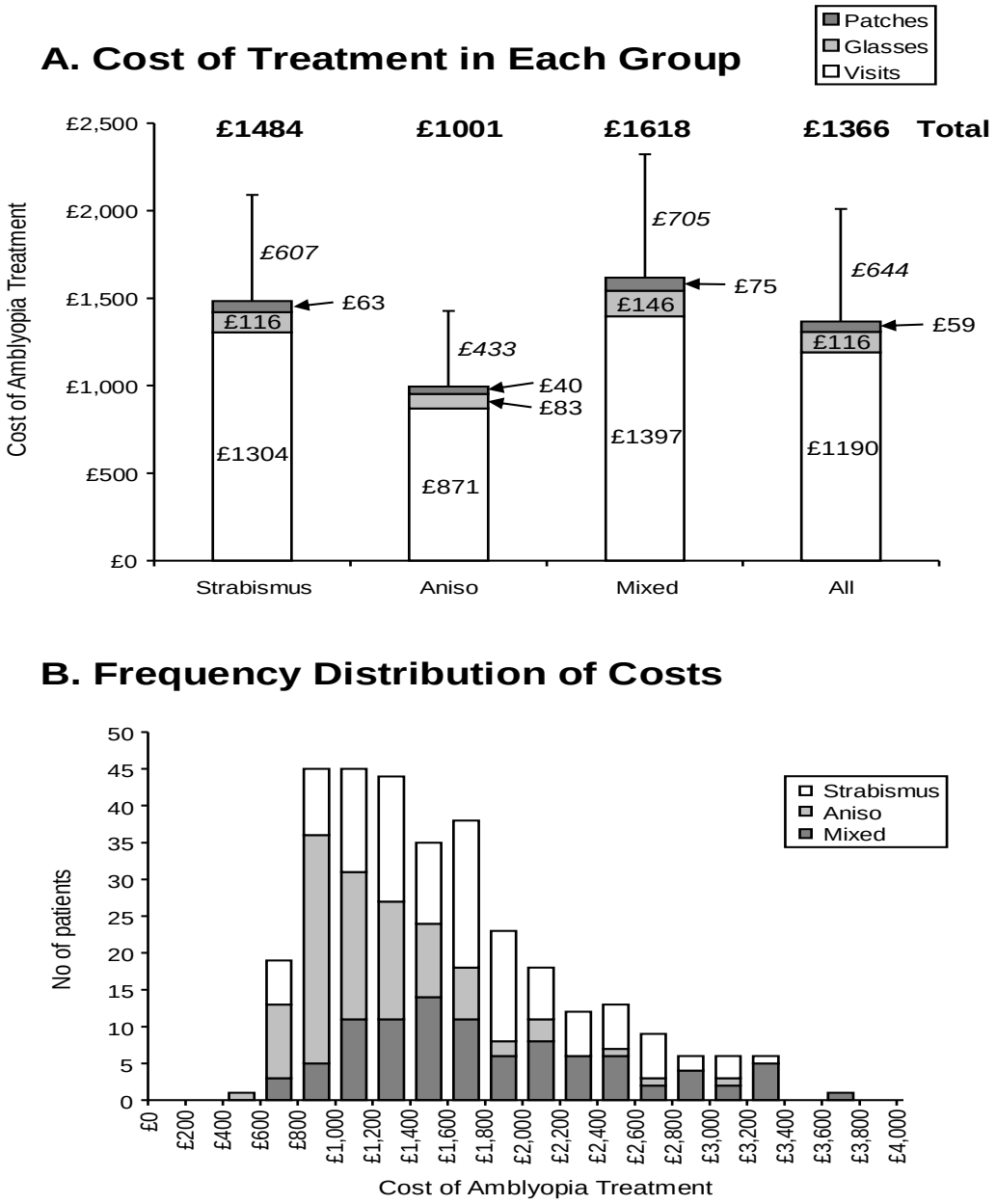


Figure 2.5: (A) *a breakdown of the costs to NHS for treating amblyopia in each group (inserted numbers represent mean costs, standard deviations are for total treatment costs) and* ***(B)*** *frequency histogram of costs for individual patients.*

2.5. Discussion

In this study we investigated treatment modalities and visual outcome of occlusion therapy for amblyopia in a hospital setting (National Health Service) in the UK. The mean time under hospital care was considerable lasting on average 35 months in which patching treatment lasted 18 months. The mean duration under hospital care and duration of patching were similar for strabismic and mixed amblyopia but shorter for anisometropia. Hospital visits were frequent with an average of 21.4 (SD 10.6) visits. Visual outcome was correlated to age at patching commencement and the hours of patching prescribed. Visual outcome was the best for anisometropic amblyopia and the worst for patients with mixed amblyopia. Treatment costs were accordingly the highest for mixed amblyopia and lowest in anisometropic amblyopia.

The times of occlusion we found were very long compared to optimal patching times found in recent studies. There is evidence that much shorter periods of patching and total amount of hours patching can achieve optimal improvement. In strabismic amblyopia, Cleary (2000) found occlusion only effective in the first 400 hours within the first 6 months (Cleary, 2000). Stewart et al. found when effective hours patched (measured with the occlusion dose monitors) were used that even less hours of patching are necessary with most children achieving best visual acuity between 170 hours of patching in children up to four years of age and 236 hours in older children (Stewart et al., 2007a). In this study, using a protocol in which children were patched until VA ceased to improve, only 9 children out of 72 found were patched for more than 400 hours. These studies stand in

contrast to very long patching times observed in our study suggesting that in current UK practice duration of patching treatment is too long with too many hours are prescribed.

Flynn et al. (1999) using a similar design to this study found 59% to 73% patients achieved a VA of 6/12 with a reverse relationship between duration of patching and success as in our study (Flynn et al., 1999). It is possible that very long patching causes demotivation and loss in belief for families of amblyopic children. Another possible explanation of the reverse relationship is that some children do not have the visual potential to reach full VA but patching has been continued for long time without progress.

In the PEDIG American studies where patching lasted only 4 months, 43% and 51% of patients with severe amblyopia, and 75% to 80% with moderate to mild amblyopia, reached a VA of 6/12 for the two patching regimens tested (PEDIG et al., 2003a, PEDIG et al., 2003b). Our study 73.3% of patients reached overall VA of 6/12 observed over longer patching periods. However, VA outcomes appear relatively similar despite the much longer patching time in our patients. As there is no established consensus when amblyopia is considered "cured." (Stewart et al., 2005). An optimal result would be if the VA is equal to the dominant eye or achieves the acuity level of 6/6. Only 21.7% of children reached 6/6 vision in the amblyopic eye in our study.

The reasons for very long treatment periods in our study and the relatively poor outcome are numerous. This possibly includes poor compliance, suboptimal treatment regimens (although currently the best treatment regimen is unknown with diverse regimens reported in different European countries (Tan et al., 2003, Loudon et al., 2004)), patching

without the amblyopic eye being visually challenged or insufficient brain plasticity to restore vision in an amblyopic eye. Using occlusion dose monitors, substantial evidence is emerging that compliance to occlusion therapy is poor (Loudon et al., 2006b, Awan et al., 2005), a probable reason for prolonged treatment and poor outcome in our study. Loudon et al. (Loudon et al., 2006b) showed that compliance decreases with treatment duration, from approximately 50% in the first three months to 10% after 18 to 21 months of patching. In our study, it is likely that with extensive duration of treatment children and their families became discouraged leading to poor compliance after several months and even years of patching. Loudon et al. demonstrated that interventional methods could improve compliance (Loudon et al., 2006b) however, such methods are not currently incorported as routine in the NHS.

Semi-quantitative interviews have shown that occlusion therapy for amblyopia is often difficult causing distress and emotional impact for children and parents. There is increasing evidence that patching is associated with a negative emotional impact and bullying (Koklanis and Georgievski, 2007, Sabri et al., 2006) although earlier treatment resulted in fewer reports of bullying (Williams et al., 2006). Past unpleasant experience during patching had an unpleasant psychological impact in teenagers (Sabri et al., 2006). Because of the negative impact of patching on the wellbeing of children, it is important to carefully balance the benefit of patching and the possible psychological impact of the child. Patching of short duration is likely to help to reduce the psychological impact related to amblyopia therapy.

In agreement with several studies we find that visual outcome is correlated to age at presentation (PEDIG et al., 2003a, Stewart et al., 2007b) (in contrast to other investigators (PEDIG et al., 2003b, Clarke et al., 2003, Awan et al., 2005)) and type of amblyopia with best to worst ranking of anisometropic, strabismic and mixed amblyopia (Simons, 2005). Anisometropic amblyopia has the best visual outcome with the least amount of patching. This indicates the importance to adjust treatment regimens to the type of amblyopia.

In our study, after cessation of treatment patients were followed in the hospital on average for 9.9 months without patching. During this time, no mean deterioration of vision was stable. This is in agreement with findings in a study investigating the VA after one year of cessation of patching which was sustained in most children aged 7 to 12 years (Hertle et al., 2007). Possibly the long treatment times in our study contributed to the stable effect after cessation of patching.

There are a number of potential sources of bias:

1. It is possible that patient notes may not be missing at random. For example, using incomplete notes as exclusion criteria could lead to exclusion of poor compliers to treatment if this is related.
2. Measurement bias: This study has indicated that there was no consistent method used for visual acuity testing to assess patients with amblyopia, especially in the younger age group. Tests chosen depended on the treating orthoptist, the child's intelligence and the cooperation to the test. These can be considered as a possible weakness as we analysed the overall visual acuity from the beginning to the end of treatment and not concentrated on specific vision tests used (Pocock, 1983).

However, we excluded preferential looking (Cardiff Acuity Cards) from analysis as these test have shown to provide a poor estimate of visual acuity.

3. Selection bias: Since not all eligible patients were not included (only 66.4%) there is a possibility that the selection is not representative of the database as a whole. For example the fact that patients were selected starting in January of each year could lead to bias. However the use of multiple samples taken over a period of eight years, rather than analysing a cohort of amblyopes who presented in one year should lead to the sample being more representative of this period of time (Craig et al., 2008, Pocock, 1983).
4. Bias could result from the Leicester demographic being different to other parts of the UK.
5. Another possible bias to this study is confounding bias. The statistical model used to find predictors of improvement in vision in the amblyopic eye include a number of predictors such as patient's age, no of orthoptist seen, type of amblyopia that may not be independent of each other.

Since amblyopia is the most frequently treated paediatric eye disease its treatment represents a significant contribution to NHS costs. We found that the average costs of treatment for the hospital for all amblyopia types were £1,366. This figure is only a gross estimation not taking into account, for example, costs arising for patients and families during the frequent visits. The costs per patients are lower than for example those of strabismus surgery (Beauchamp et al., 2006) but, considering the high incidence of amblyopia and the uncertainty of the impact of amblyopia on the quality of life (Konig and

Barry, 2004) a reduction of costs using shorter and more intense treatment would significantly reduce NHS costs.

Although recent studies have shown that patching treatment of less than 400 hours and 6 months are optimal for obtaining best VA outcome, the current treatment in a hospital setting (NHS) is significantly longer. Similar studies would be interesting in other NHS trusts and other clinical settings. Longer periods of treatment are likely to inflate costs, increase the psychological burden for patients, and decrease compliance. The main reasons for protracted treatment times are firstly because optimal treatment regimens are not known, and secondly, because compliance to treatment is poor due to lack of motivation especially with prolonged treatment. Consequently, a priority should be placed on increasing amblyopia research into (i) determining optimal patching regimens, (ii) providing realistic guidelines for ophthalmologists and orthoptists for determining the point at which therapy should be stopped, and (iii) improving methods to increase compliance, for example through educational/motivational interventions.

Chapter 3

The Occlusion Dose Monitor (ODM)

3.1. Occlusion Dose Monitor (ODM)

3.1.1. History of the ODM

Occlusion dose monitors (or ODMs) were first developed and used for amblyopia investigations by Fielder, Moseley and associates in England in 1991 (Figure 3.1 (A)) and later modified (Figure (B)), using two electrodes connected to a battery powered datalogger

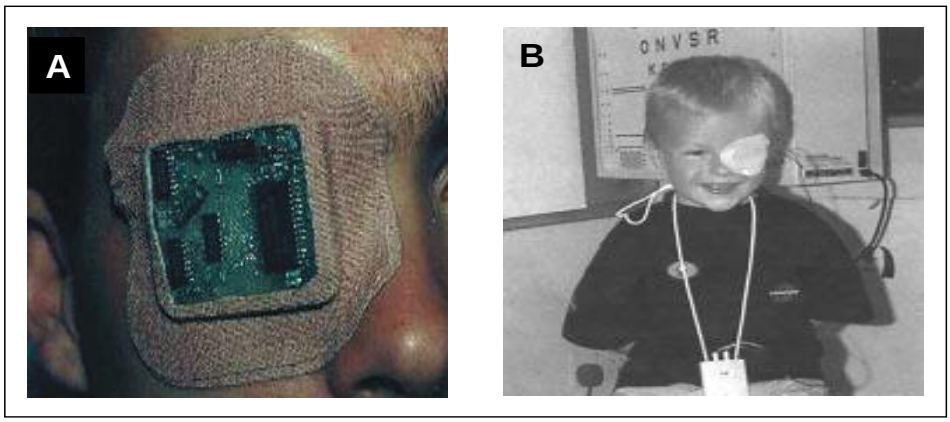


Figure 3.1: (A) *The first occlusion dose monitor (ODM) developed by Fielder and Moseley (1991), Birmingham, UK (Chopovska et al., 2005). The ODM had a miniature data-logger, which records the patch skin resistance every 46 seconds.* ***(B)*** *Modified version of the ODM (2002) designed by the same group. The prototype has two electrodes attached to the under surface of the patch and a battery powered datalogger by a lead which the child carries*

(Stewart et al., 2002) (Reproduced from Chopovska, Loudon et al. Graefe's Arch Clini Exp Ophthalmol (2005) 243:539-544 and Stewart et al).

Later the Academic Medical Centre in Amsterdam developed ODMs in 1997 for use by Simonsz and associates (Fielder et al., 1994, Simonsz et al., 1999, Fielder et al., 1995) (Figure 3.2 (A). Again, these were later modified as a smaller version Figures (B) and (C). The first protype (figure 3.2 (A)) was used in this study.

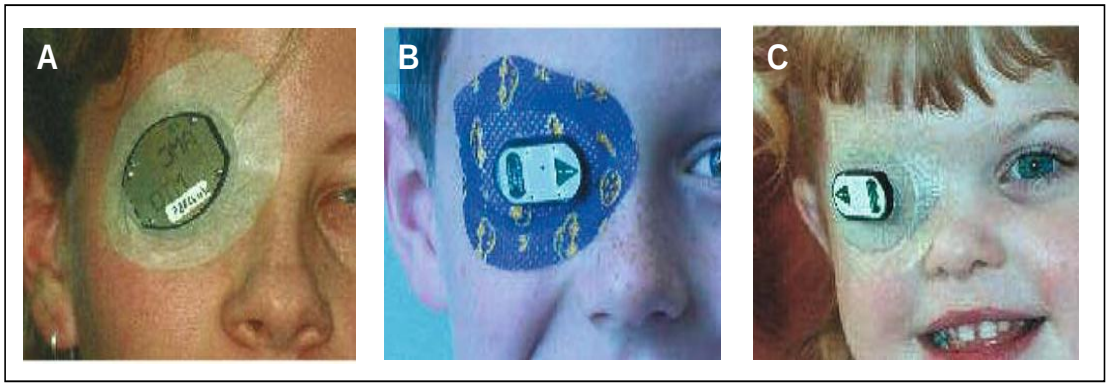


Figure 3.2: (A) *The first ODM prototype produced by the Academic Medical Centre, Amsterdam (1997) used by Simonsz and colleagues, The Hague. The ODM had two thermistors connected to the front and back of the ODM. Dimensions of this version were 35×23×4 mm and weight 6 g.* ***(B)*** *Version 2 of the ODM (2001) (24×12×3.6 mm, 1.8 g used in the Netherlands.* ***(C)*** *Version 3 of the ODM (2002) (31×15×3.6 mm, 2.3 g) (Chopovska et al., 2005). NOTE: (A) was used in the experimental study, Chapter 4, of the thesis.*

3.2. Technical Specifications

The Occlusion Dose Monitor (ODM) used in this study was provided through collaboration with Huibert Simonsz of The Hague Research Group, Netherlands. It is an electronic temperature sensitive miniature data logger *(Figure 3.3)*. Its dimensions are

35mm x 23mm x 4mm and it weighs approximately 6 grams. It is composed of two separate temperature sensors (or thermistors) connected to the back and the front of the device, a 24-hour clock, a microcontroller chip, an EEPROM memory, a 3Volt CR1220 coin battery, and a connector to download the recorded data onto the personal computer. The ODM used was developed and validated by The Medical Technical Development Department at the Academic Medical Centre in Amsterdam, Netherlands.

Figure 3.3.*Occlusion Dose Monitor developed in Amsterdam (1997)*

3.3. The Function and Initiation of the ODM

The devices record the temperature difference between the sensors at the front and back of the ODM every 2-5mins. For the purpose of this study, the ODM was initiated to record the temperature difference at 5-minute intervals for minimum period of 21 days. A small green LED light would indicate that the ODM was ready to initiate and record once a new lithium coin cell battery was inserted. Initiation was carried out by connecting the ODM to the PC and activating the ODM through Easy View software package. The

sensitivity was permanently set at 1/16°C. The data, stored in the EEPROM memory[1], (Figure 3.4) was downloaded onto the PC after use and simultaneously the data was erased and the ODM was ready to reuse.

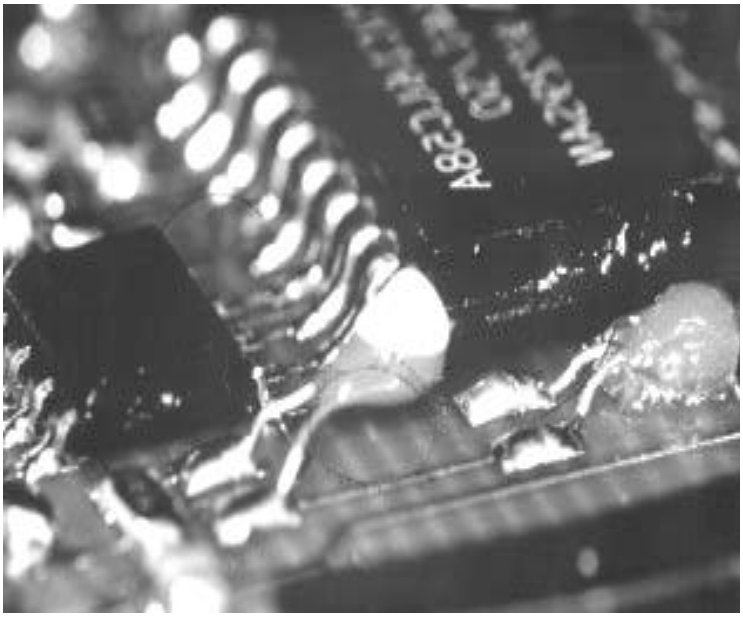


Figure 3.4*. Inside the ODM shows the thermistor and EEPROM memory device.*

3.3.1. The Battery

Small miniature lithium, non-rechargeable Manganese Dioxide coin cell battery (CR1220, 3.1Volts), size DL 1220 was required to operate the ODM. For the trial the required recording time per cycle was 504 hours (21 days) recording at 5-minute intervals. To ensure minimal loss of information over the three-week recording period, a new battery were use each time the ODM was initiated.

[1] EEPROM - Electrically Erasable Programmable Read-Only Memory. It instantly erases and rewrites at the byte level, whenever a significant amount of non-volatile, solid-state storage data is required

Several types of the lithium, non-rechargeable coin cell batteries were tested, (see Section 3.4). This was to ensure that the battery could maintain a voltage output capable of driving the recording circuitry over the duration of the recording. The "Duracell" CR1220 battery showed best reliability. On average, it was able to maintain discharge at a sufficient capacity to record over 504 hours continuously.

3.3.2. Reliability and Validity of the ODM

The reliability of the ODMs was tested before the study commenced. All normal volunteers were from the Ophthalmology Group at the University of Leicester or the Leicester Royal Infirmary. They were colleagues or friends, with families of children aged 3-8 years who cooperated by performing recordings in which participants accurately recorded application of an ODM to patch to their own child or children (mean, 53.4 minutes). The mean difference between ODM and participant-recording times (SD) was 0.85 minutes (± 3.1 minutes) giving an accuracy of 99.4% (79%). In addition, eight participants were instructed to make an accurate recording of the wearing times of the ODM on their arms over a 21 day period between 1 and 8 hours each day (mean, 5 hours 7 minutes) the mean error was 5.7 minutes (± 3.5 minutes) over the whole 21 day period. The Leicestershire Ethics Committee approved of the protocol of the main study, (chapter 4) and confirmed that a seperate ethics approval for testing and getting callibration of the equipment was not required.

3.3.3. Administering the ODM

The initiated ODM was placed inside the 'pocket' patches, modified by the author (MA). When the patient wore the patch on their eye, (Figure 3.5) the temperature recorded from the back of the monitor was higher than that recorded at the front of the device. The device was entirely patient / parent control free. The only exception was to apply new patches each day when occlusion was carried out and the supervising adult was responsible to remove and insert the ODM inside each new patch daily during the monitoring period for 21-days per cycle.

The subject was required to wear the ODM each day during the hours of prescribed occlusion for a minimum period of twenty-one days per cycle of recording. At the end of each recording, the parents/guardians were instructed to place the ODM inside an insulated Tupperware plastic box with a lid provided and store in a cool dry place. This was to reduce the temperature fluctuations when the ODM was not in use. At each assessment, the ODM was replaced. Recordings were repeated on four consecutive visits for a period of 12 weeks or 84 days in total.

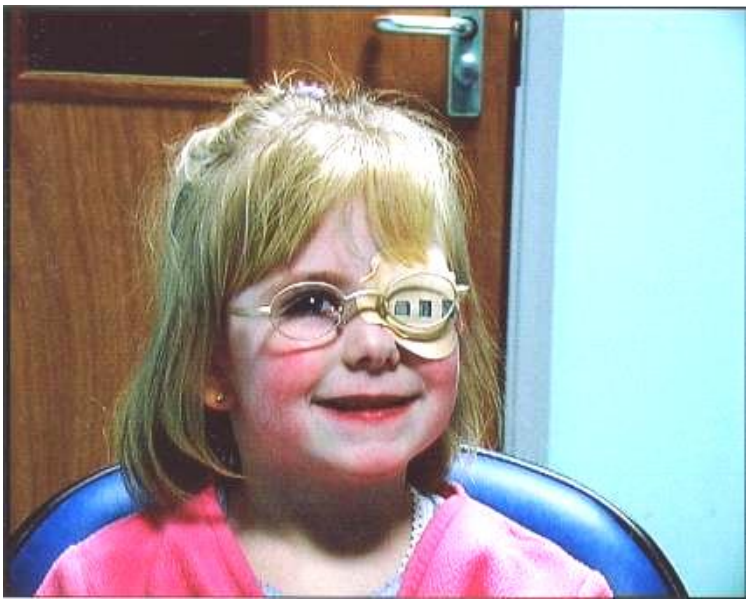
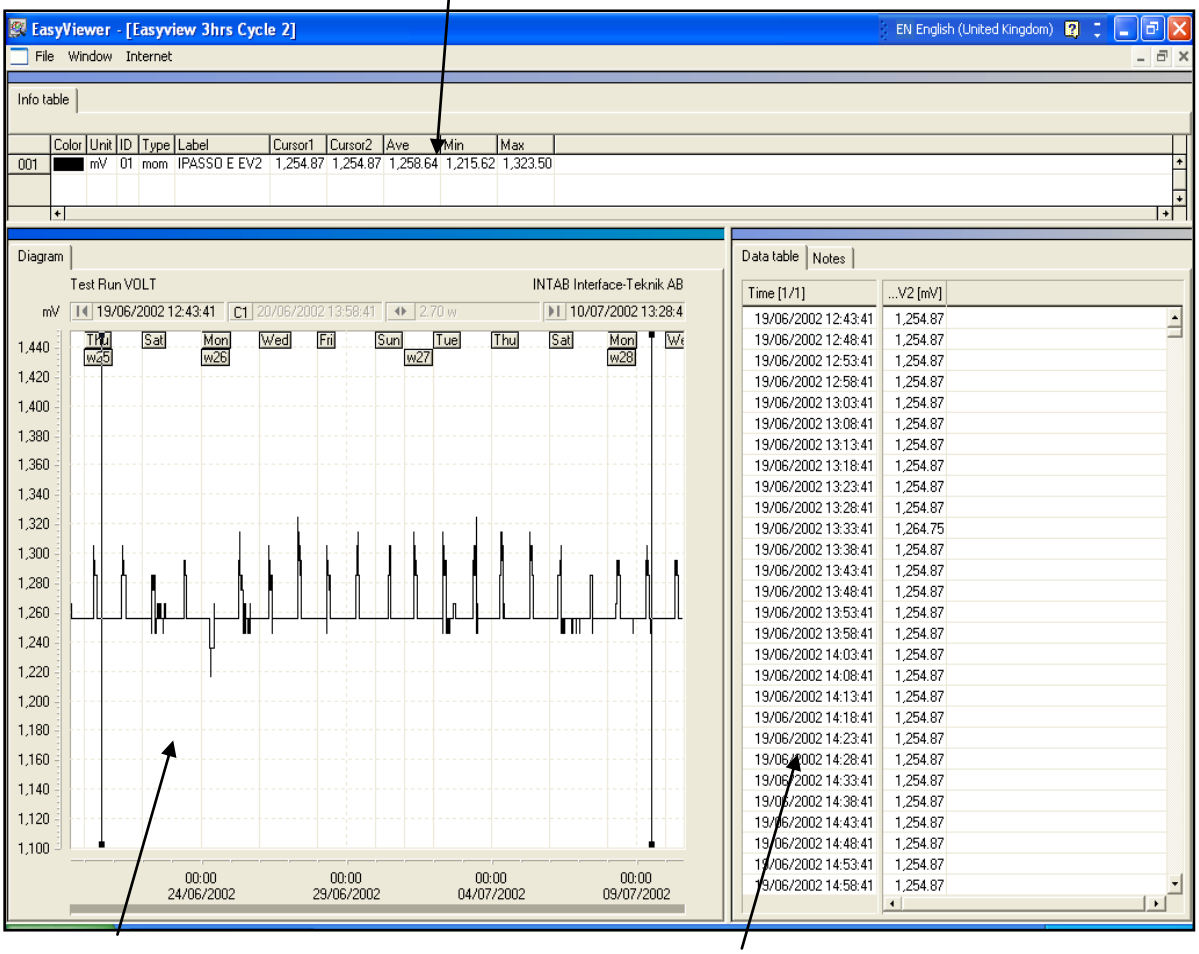


Figure 3.5: *A subject wearing the ODM with the modified 'pocket' type eye patch.*

3.3.4. Obtaining Data

The data was retrieved by connecting the ODM to a PC. Easy view software (version 5.6, INTAB Interface-Teknik AB, Stenkullen, Sweden) was installed to communicate and transfer data. The data was then exported into a Microsoft Excel© Spreadsheet for analysis. The Easy view 5-Pro-software is specifically designed for obtaining graphical presentations from the PC-data logger (ODM) (Figure 3.6) with a cycle of absolute patching obtained, is shown in Figure 3.7.

Information table showing voltage (mV)



Graph
An example of a patient's ODM recording during one cycle of patching.

The Data table
It contains the numeric data (mV) that makes up the shown graph

Figure 3.6. *Data showing information and graph retrieved once the ODM was downloaded using The Easy view 5-Pro-software.*

Once downloaded, the data consisted of an information table with the time format situated on the left side of the data table and the readings (in Volts) on the right side of the table illustrated pictorially as a graph situated on the left hand side of the screen.

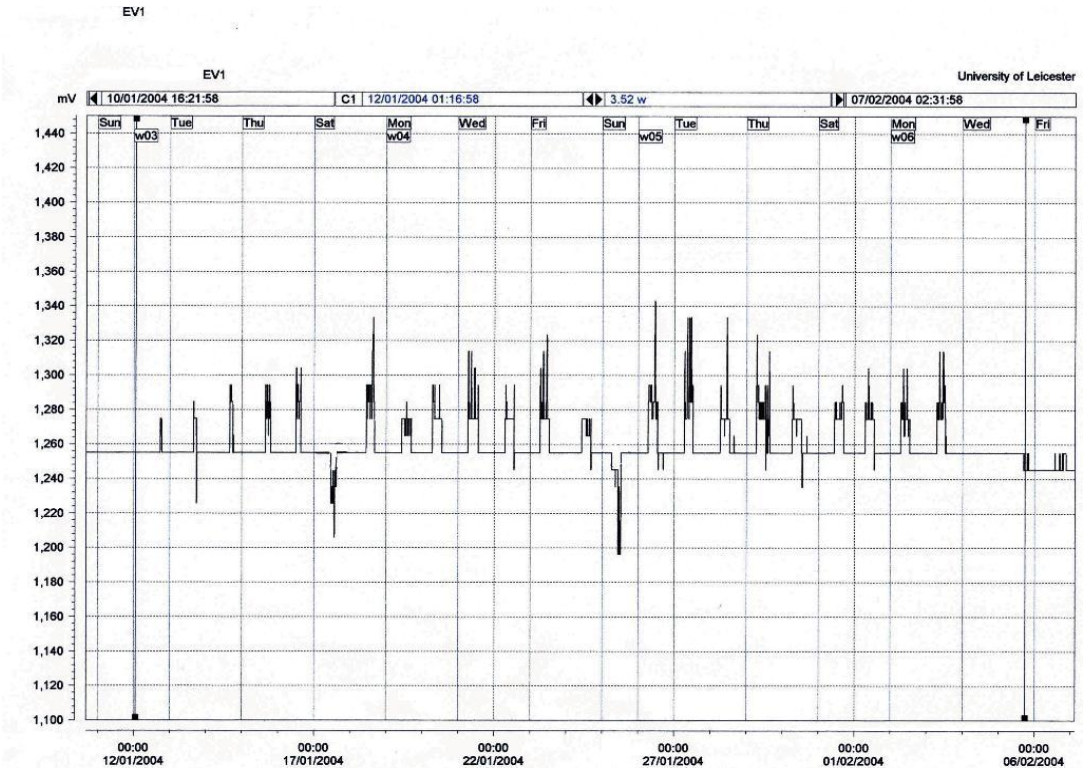


Figure 3.7. *Recording of original data downloaded from the ODM after a three-week recording. The date and times are shown on the X-axis (abscissa) and the temperature difference on the Y-axis (ordinate). The voltage difference at the baseline was 1,260mV, i.e. the value when the child did not patch. The shift away from the base line value shows the time when occlusion had taken place. This subject complied well with patching. On two separate occasions, the ODM was worn the wrong way, shown as downward peaks on the dates shown on 17/01/2004 and 25/01/2004. The spikes were caused by handling the ODM. The downward peaks were reversed using the Spike2 Software.*

3.3.5. The Eye Patch

Hypoallergenic skin coloured sterile eye patches were used to accommodate the ODM during patching. Different brands were tested with departmental colleague's children to ensure comfort and minimal loss of ODM. The final design for accommodating the ODM (developed by MA) was a pocket-like design. This was to ensure minimal ODM loss

and a better coverage and appearance was acceptable when worn for the child. The modified 'pocket' patch required adhering two regular sized Coverlet patches (Biersdorf Master-Aid Ortopad Eye Patches, USA).

The innermost patch was meticulously cut with a sharp blade, to a slightly smaller size to house the ODM. Foam of the outermost patch was removed to make it comfortable and less bulky for the child. Holes were cut on both sides to improve the temperature gradient across the ODM. Figure 3.5 shows the patient wearing the patch with the monitor. This was the final type of "pocket" patch. It showed to be most suitable and well tolerated during the experimental phase in the following chapter and in the pilot study (chapter 6) of the thesis.

3.4. Problems Encountered with Using the ODMs.

3.4.1. Batteries

Various brands of CR1220 lithium manganese dioxide 3Volt bateries were tested for performance and their reliability. These included Duracell, Maxell, Renata, Varta, Energizer and Panasonic. Most of these batteries could not maintain a voltage output capable of driving the recording circuitry over the duration required and stopped recording after between 14 and 20 days. Duracell batteries were the most consistent batteries to last the full 21 days.

3.4.2. ODMs

No loss of data (full or partial) was evident during the experimental period when the ODMs were returned from use However, of the two patients recruited into the patching groups, one patient accidentally dropped the ODM in the water and the second patient's ODM was white washed in the family's washing machine. After ensuring all components were completely dry, data was *still* saved and retrieved. Another five patients lost the ODM whilst at school or at home. The ODM was immediately replaced as soon as it was reported, lost and this required a home visit, by main investigator (MA) or parents or guardian visiting the clinic.

3.4.3. Eye Patches

Initially an Opticlude patch (by 3M) and a Coverlet patch (by Beiersdorf) sticky patch available in the junior (under age 4 years) and regular (above 4 years of age) were used. The ODM was attached to the patch using a double-sided strong sellotape. This method was unreliable and uncomfortable for the wearer (adult and/or child) and frequently reported that the ODM was becoming lose and falling off the patch. Consequently, I produced a 'pocket' type patch by adhering two same sized or one Junior and one Regular eye patches of the same brands (3M or Biersdort, Master-Aid) together. This was done by sticking the outerside of the inside patch that then becomes the inside part forming a 'pocket' to the outside patch child's eye that will conceal the ODM when worn. The method was unreliable as the weight of the ODM was uncomfortable for the child with a greater risk of losing the ODM. This was frequently reported when using the Ortopad from 3M. Thirdly, I attempted to join one regular and one junior patch (Biersdorf Opticlude eye-patch). Although the stickiness was better, wearing and loss of or losing the ODM

remained a concern. Colleagues and friends of the main investigator cooperated with wearing the device. Feedback provided by colleagues and friends about the ODM and patches were used to further improve the methods.

Chapter 4

A Randomised Controlled Trial of Mixed and Strabismic Amblyopia Using Occlusion Dose Monitors to Record Compliance

4.1. Aims

In chapter 3, I referred to the first prototypes of electronic devices for monitoring occlusion. In this study, in collaboration with co-workers (Professor Irene Gottlob (IG) and Dr Frank Proudlock (FP)), we performed the first randomised controlled trial (RCT) of patching therapy for strabismic and mixed amblyopia in which occlusion was objectively monitored. The trial included a baseline group who did not patch in comparison to patients who were prescribed either 3-hours or 6-hours patching per day. The ODMs allowed us to compare compliance rates for patients who were prescribed these two speific regimens. The ODMs also provide information concerning the correlation between the patching dose and the improvement in visual function (i.e. the dose response). The hypothesis under test is that higher dosage of prescribed treatment (6 hours compared to 3 hours) leads to lower compliance leading to lack of improvement in visual outcome (compared to 0-hours and 3-hours group).Our secondary hypothesis is that measured occlusion is strongly related to improvement in visual outcome.

The primary outcome of the study was absolute patching prescribed monitored with an electronic datalogger. The secondary outcome is to investigate visual outcome measured using percentage improvement in visual acuity (Fielder et al).

4.2. Introduction

A retrospective study carried out in a single NHS clinical establishment of 322 amblyopic children was discussed in chapter 2 of the thesis. Following analysis of the pooled data, the main findings showed that the mean duration of occlusion treatment for amblyopia was long, requiring many clinic visits with variable visual outcomes. Credibility of treatment was unsatisfactory and unnecessarily expensive without an established regimen to adhere too.

There are extensive variations of clinical conduct for treating amblyopia. A recent survey of practices and outcomes of amblyopia treatment in Europe shows wide variation between and within countries with German speaking countries patching with more intensity and for longer (Tan et al., 2003) with variation in treatment regimen varying between numbers of hours prescribed with different orthoptists (Loudon et al., 2004).

A major review by Snowdon-Stewart Brown (1997) has concluded that no study has yet provided sufficient evidence that patching treatment is beneficial in a condition that is non-fatal and recommended discontinuing primary preschool screening for amblyopia for the 3 and 3 ½ year olds only (chapter 1) (Snowdon and Stewart-Brown, 1997). Their findings, stated that dose–effect and adherence to occlusion have not been adequately investigated. Since then, one recent study has shown that glasses and/or patching significantly improve vision in moderate (VA, 6/36–6/18) anisometropic amblyopia compared with no intervention (Clarke et al., 2003).

These studies question whether a dose–effect relationship exists in amblyopia and suggest that less intensive patching might be preferable. However, the success of visual rehabilitation has not been optimal in these studies, due to lack of monitoring device, and only prescribed patching was analysed. Most importantly, the rate of compliance to treatment had not been taken into account as addressed by Kushner (Kushner, 2005).

4.3 Materials and Methods

This study included mixed and strabismic amblyopes from one clinic. The inclusion criteria were newly diagnosed amblyopes aged 3-8 years competent to perform the Glasgow Acuity Card Test, (chapter 1) and capable of using the ODM, (chapter 3) with parental/guardian instruction. A list of patients' inclusion and exclusion criteria are listed below for the study

Inclusion Criteria

- Amblyopes 8 years and under
- Diagnosed with mixed or strabismus amblyopia
- An intraocular acuity line difference of ≥ 2 Snellen lines that persisted after 6-weeks on continuous glasses wear.
- Competent to perform the Keeler Glasgow vision test.
- No evidence of pathological or neurological anomaly

Exclusion Criteria

- Unable to perform the Keeler Glasgow Acuity Test
- Absence of a strabismus
- History of previous occlusion
- Strabismus induced by trauma
- Evidence of pathological or neurological anomaly

The role of the author was to initially set up and perform all experiments from the start of study to the end of trial period for every patient recruited, involvement n writing paper and present data at national and international meetings as paper and poster presentation.

Possible amblyopes attending the ophthalmology outpatient clinic were approached by the author (MA) or by (IG) to verbally discuss the nature and possible consequences of the study. Once parents had consented, they were followed up after the 6 weeks refractive adaptation period as potential amblyopes. The Leicestershire ethics committee approved of the protocol, informed consent forms and information leaflets. The research adhered to the tenants of the Declaration of Helsinki.

Following confirmation and suitability in meeting the recruitment criteria the patient, already randomised into the patching groups, were given the ODM home-kit on the first visit. The author also undertook a full orthoptic assessment at this time. The home kit contained the initiated ODM, 'pocket' patches and a three-week empty diary and information leaflets for the child and supervising adult. Refer backwards to (section 3.3.5)

relating to how the patches were made. The function of the ODM, application of the device, wearing the patch with the ODM was fully explained by MA.

All visual acuities measurements and orthoptic assessment was conducted by the main author within the clinical office at three week intervals. If situations arose where the patient missed or could not attend the allocated appointment therefore, a home visit was made (by the main author) to avoid unnecessary data loss from the ODM. The main author performed all preparation of home packs, initiation of ODM recordings and download of ODM data following patching. All patient details and monitoring visual function were stored onto the Microsoft Excel database initially created by FP and MA carried out reliability of the information transferred from the ODM and the PC. All ODM and diaries times were entered manually also by the man author.

The study was conducted in one single institution with the main researcher (MA) involved in the selection of patients. Patients with suspected amblyopia and attending the eye department were selected. Once parents of patients verbally agreed to participate with the study they were randomised using a randomisation procedure. The procedure was composed of allocation tickets in a series of shuffled sealed envelopes with each envelope containing the name of the next allocated treatment group. The allocation tickets had been prepared by another researcher completely independent from the study of the Ophthalmology group. The patients were sub-randomised into two groups according to age, under 4 years and 4 years and over. This form of randomisation ensured equal distribution between each of the three groups with similar characteristics, thus minimising

differences among groups. The main researcher (MA) opened the next envelope in the sequence when the patient agreed to participate in the study.

For patients with presence of refractive errors, following cycloplegic retinoscopy, full refractive adaptation of six weeks with glasses was dispensed. Thereafter, upon return to clinic, if subjects were still suitable the study was commenced. The three treatment groups were as follows:

- Group 1: no patching
- Group 2: 3-hours patching
- Group 3: 6-hours patching

The study timeline is illustrated in Figure 4.1, showing patient management and procedure of the three allocated treatment groups

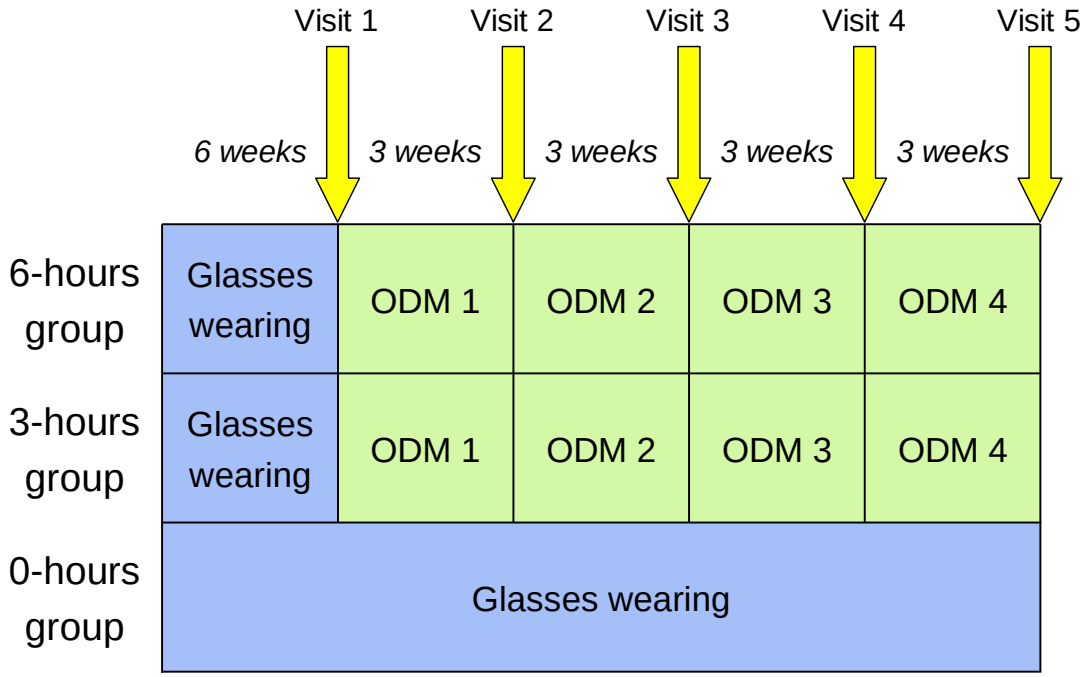


Figure 4.1. *The study timeline indicating administration of ODMs and clinic visits in the three treatment arms.*

For patients allocated into the 6-hour or 3-hour patching group, ODMs were administered with the temperature resolution fixed at 1/16 ºC with the difference in temperature between the two sides of the ODM recorded at 5-minute intervals. Diaries, to record compliance were given in addition to the parents/carers and they were requested to fill in the daily patching times for the duration of patching treatment. At each three-week cycle, the ODMs and diaries were collected and exchanged for a new kit with more patches. Data from the ODM was downloaded onto the PC.

The sample size calculation was based on estimating the dose response curve rather than determining the difference in visual outcome between the groups since previous studies have shown little difference exists between treatment groups (e.g. the PEDIG

studies) (PEDIG et al., 2003a, PEDIG et al., 2003b). With a correlation coefficient of at least 0.5 and a dropout rate of 10%, sample size of approximately 60 subjects would be required to determine a significant correlation with 90% power *(two-tailed, $P<0.01$).* Through vision screening and hospital referrals, from general practitioners and/or optometrists, school nurses and health visitors, seventy-seven patients were referred to the orthoptists or ophthalmologists department within the Leicestershire County and observed for possible recruitment into the study (Figure 4.2).

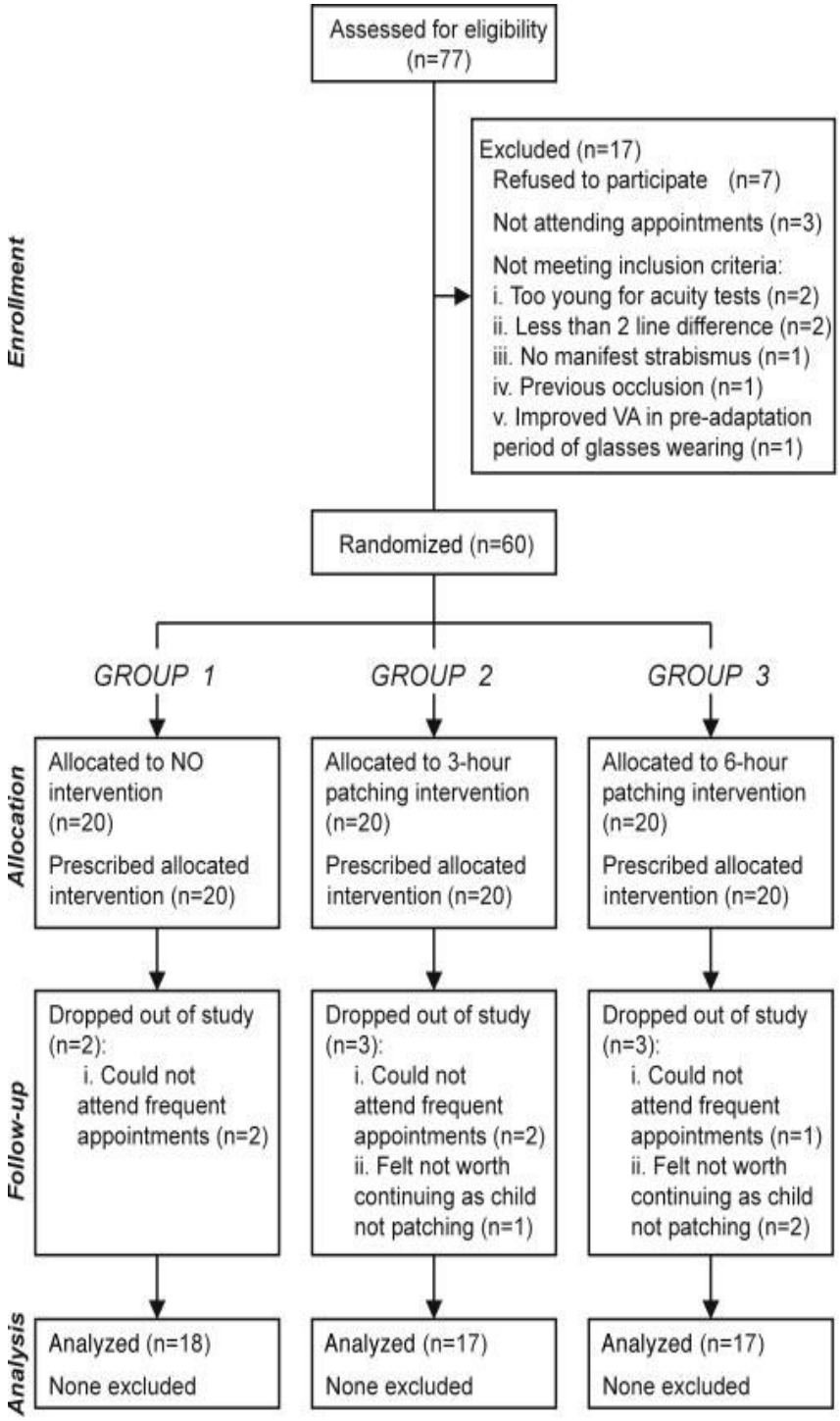


Figure 4.2. *Flow chart of patient's progression through the study.*

Out of seventy-seven subjects, seventeen were not recruited for reasons stated. Seven sets of parents refused to partake with the study, three amblyopic subjects failed to attend consecutive appointments, two subjects were too young for reliable measurements with the Glasgow Acuity Card (Mrugacz et al.) vision test, two subjects had less than the two inter-ocular line difference in vision in both eyes. One did not present with a manifest strabismus, one had previous occlusion treatment and one subject improved in vision during the first stage of refractive adaptation by wearing glasses for a period of six weeks as required for the study. Recruited and randomized were sixty newly diagnosed children with strabismic and mixed (anisometropia and strabismus) between December 2001 and November 2003.

Groups were created to investigate the compliance to treatment and the efficacy of patching therapy. Collectively they were used to looking at the dose–effect response to treatment. The compliance to treatment was determined by the percentage of the absolute time during with the subject was wearing the patch measured by the ODM compared to the diaries.

The secondary outcome was the improvement in the visual function. To measure this we used the quantitative equation suggested by Stewart et al. (2003) measured as a percentage of outcome refer backwards to section 1.6.1. The information was used to achieve accurate proportions of visual improvement in relation and achieve near to equal vision to that of the dominant eye.

The percentage change in amblyopia $= (VA_{as} - VA_{ae}) / (VA_{as} - VA_{de}) \times 100\%$

where, VA_{as} and VA_{ae} denotes the difference of VA of the amblyopic eye at the start and at the end of treatment and the VA of the dominant eye at the end of treatment was signified by VA_{de}. This formulae proposed by Stewart et al. (Stewart et al., 2003) is to measure the outcome of treatment for amblyopia as it grades improvement of vision in the amblyopic eye as the proportion of change in VA with respect to the absolute potential of improvement i.e. (VA of the dominant eye at the end of treatment). Only if the visual acuities reached were equal between the two eyes would the result be classed as one-hundred percent. The correlation of prescribed patching time and visual improvement was calculated to determine whether the dose-effect relationship existed for patching treatment. Analysis was performed to compare effective patching of the 3 and 6 hours group (n=8) with no patching.

Univariate general linear model was used for statistical analysis. Comparisons in the group were made using the Bonferroni post hoc analysis. Absolute patching time, gender and age were included as explanatory variables for compliance and for the final visual outcome. Absolute and prescribed patching times were not introduced concurrently in the analysis, as they are not independent variables.

4.4. Results

The study design required 60 newly diagnosed patients with strabismic and mixed amblyopia and twenty subjects were randomly allocated in groups 1, 2 and 3. Patients with strabismic and mixed amblyopia, respectively were, 11 and 7 in group 1, 6 and 11 in group 2 and 10 and 7 in group 3. Raw data of patients details and amblyopia are presented in Appendix A. Absolute data retrieved per ODM usage was graphically presented and visual progression to treatment over the 12-week period was observed as shown in Figure 4.3.

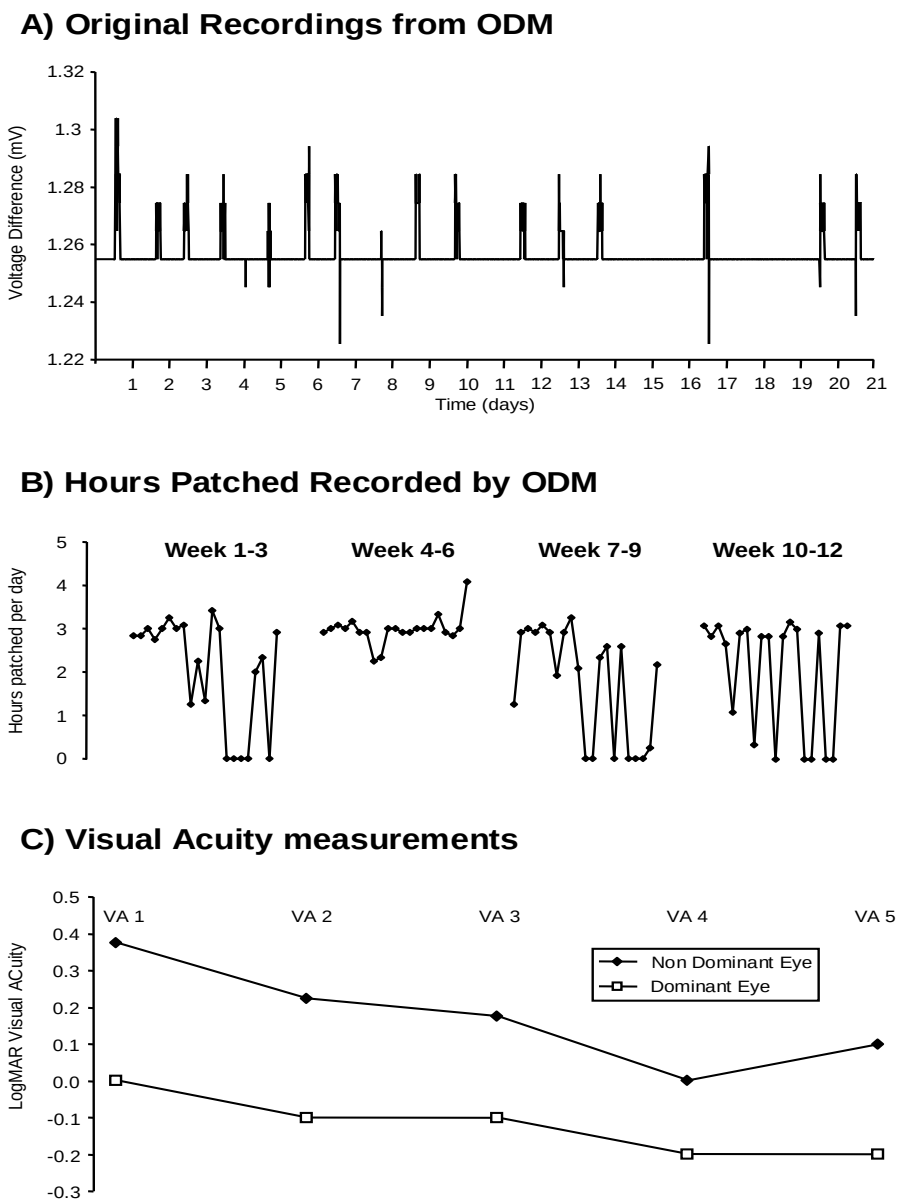


Figure 4.3: Shows the original recordings in a patient randomised into the 3-hour patching group in which one cycle of recordings have been obtained in (A) and the absolute data of recordings retrieved from the ODM between 1 and 12 weeks (B). In (C) the improvement of visual acuity was monitored over the study duration in both the amblyopic eye and in the dominant eye from the first assessment at the start of the study to the end of the experimental period.

Out of 60 amblyopic subjects, 52 had completed the study. (n=18 in group 1; n=17 in group 2; and n=17 in group 3). The mean (± standard deviation) ages in each of the three groups respectively were 4.6 years (±1.5); 4.4 years (±1.0) and 4.7 years (±1.3). Eight patients had dropped out of the study for reasons stated. Due to the commitment and frequency of appointments, 5 parents could not fully commit to the study design (2 in group 1; 2 in group 2, and 1 in group 3). Three sets of parents did not feel that there children would fully comply with treatment (1 in group 2 and two in group 3). The visual acuities before patching in the respective groups [UK Snellen equivalents in square brackets] were 0.59 [6/19] (±0.23), 0.63 [6/24] (± 0.17) and 0.69 [6/24] (±0.22) in the amblyopic eyes and 0.03 [6/6] (±0.12), 0.03 [6/6] (±0.05), and 0.00 [6/6] (±0.09) in the dominant eyes, for groups 1, 2 and 3, respectively.

Figure 4.4 shows the wide spread of absolute patching times in both the 3- and 6-hour groups. The mean (±SD) compliance in the 3- and 6-hour groups was 57.5% (±30.8%) and 41.2% (±30.9%), and the mean effective patching time per day was 1 hour 43 minutes (±55 minutes) and 2 hours 33 minutes (±1 hour 52 minutes), respectively. There was no significant difference between the 3- and 6-hour groups for compliance with patching ($P = 0.33$).

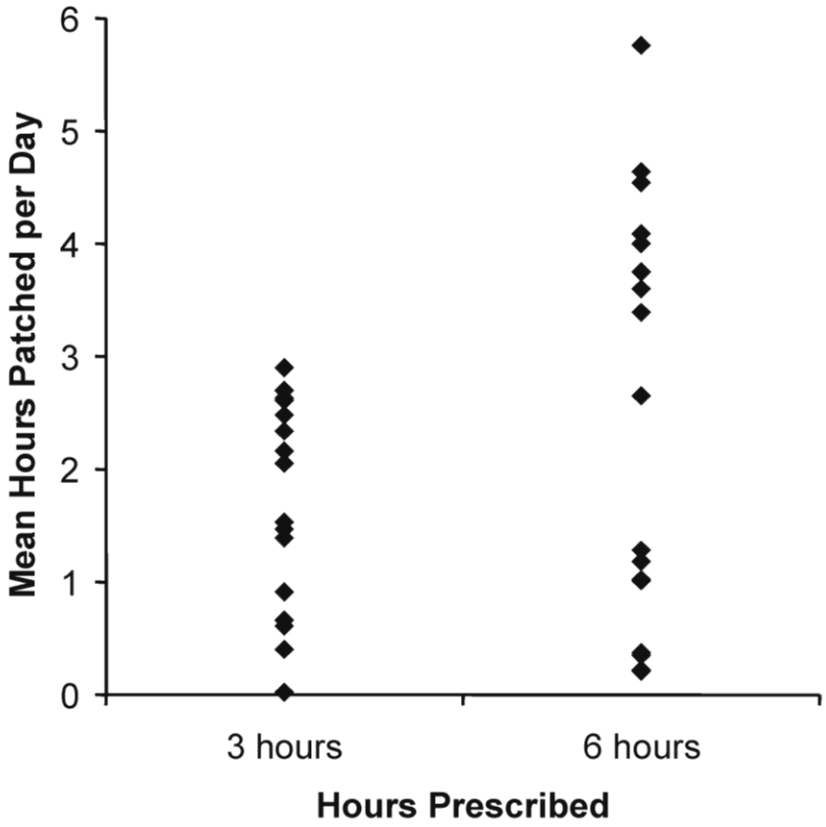


Figure 4.4. *Absolute patching times for each individual in the 3 and 6-hours patching groups.*

Neither age nor gender had a significant influence on compliance (P = 0.22 and 0.30, respectively) although initial amblyopia (VAas-VAde) was a significant effect, as children with worse VA were less likely to wear the patches (P = 0.03). The mean (SD) improvement in logMAR VA of amblyopic eyes over the 12-week period was 0.24 (±0.17), 0.29 (±0.14), and 0.34 (±0.19) [approximate Snellen equivalents: 1.6 lines (±0.12), 1.9 lines (±1.0), and 2.3 lines (±1.2)] for groups 1, 2, and 3, respectively signifying a higher dose-effect produces an effective and rapid response. VA improvement in amblyopic eyes was

steady in the three groups over the 3-month period, with a slightly larger increase in the first 3 weeks in the 6-hour group (Figure. 4.5).

The number of subjects showing improvement in VA in each of the three treatment groups and overall using different criteria is shown below (Table 4.1).

Success Criteria	***0 hours***	***3 hours***	***6 hours***	***p value***
> 0%	88.9	100.0	94.1	0.370
> 10%	83.3	100.0	94.1	0.171
> 20%	77.8	82.4	82.4	0.924
> 50%	27.8	35.3	52.9	0.294

Table 4.1: *The number of subjects improving in VA in each of the three treatment groups using different criteria (p values were determined using Pearson's Chi-square test.*

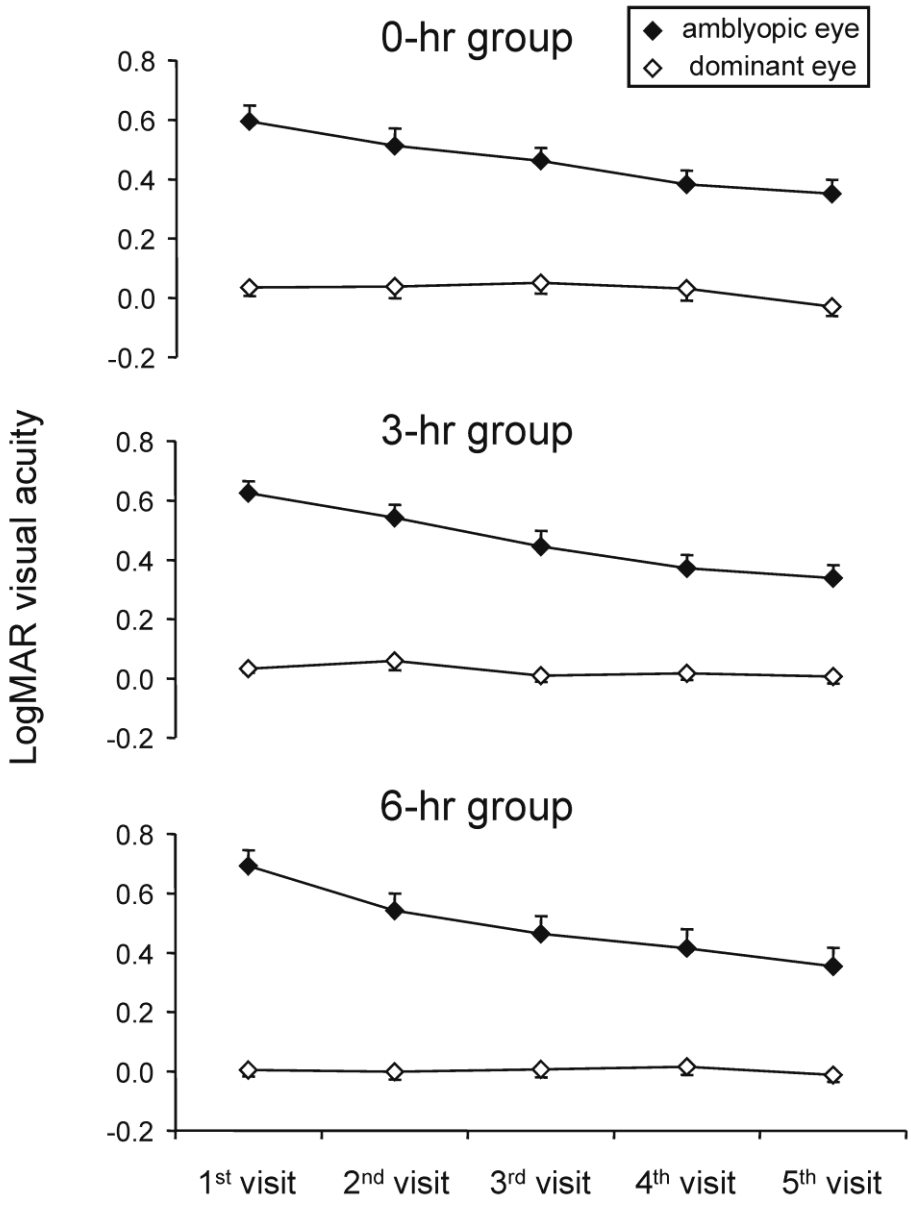


Figure 4.5. *Mean VA of amblyopic and fellow eyes in each treatment group at each examination time.*

The visual outcomes for groups 1, 2, and 3 were 34.5% (±27.7%), 46.0% (±19.8%), and 51.8% (±27.6%), respectively. Recorded patching was a strong predictor of visual outcome (P =0.0002), whereas there was no influence of age (P = 0.77) or gender (P=0.86). Initial amblyopia (VA_{as} - VA_{de}) was a strong predictor for greater improvement in the amblyopic eye (VA_{as} _ VA_{ae}, P = 0.0002). Although the visual acuity at the start appears to be higher in the 6 hours group, these were not significant between the three treatment groups (ANOVA, F=1.06,p=0.35).

Figure 4.6 shows ODM-monitored patching time plotted against the percentage of change in amblyopia. The relationship between effective hours patched and the percentage of change in amblyopia was highly significant (F = 17.1, *P* = 0.00013, *r* = 0.50) with VA outcome increasing by 8.3% (SE 2.0%) for each hour patched per day over the 12-week period.

The mean and SD percentage change in amblyopia in groups 1, 2 and 3 were 34.49% (± 27.73%), 46.00% (±19.77%) and 51.48% (27.61%). There were no significant differences in the percentage of change in amblyopia between groups 1 and 2 (*P* = 0.43), 1 and 3 (*P* = 0.16), or 2 and 3 (*P* = 0.99). However, effective patching of 3 to 6 hours (*n* = 8) was significantly better than no patching (*n* = 18, *P* = 0.02), whereas 2 to 3 hours of effective patching (*n* = 10) was not (*P* = 0.1). None of the patients had a major adverse effect, such as inverse amblyopia or patch allergy in this study.

Excluding the 0-hour group from the analysis there was still a strong and significant association between percentage improvement in visual acuity and mean hours effectively patched (F = 17.2, P = 0.00032, r = 0.59).

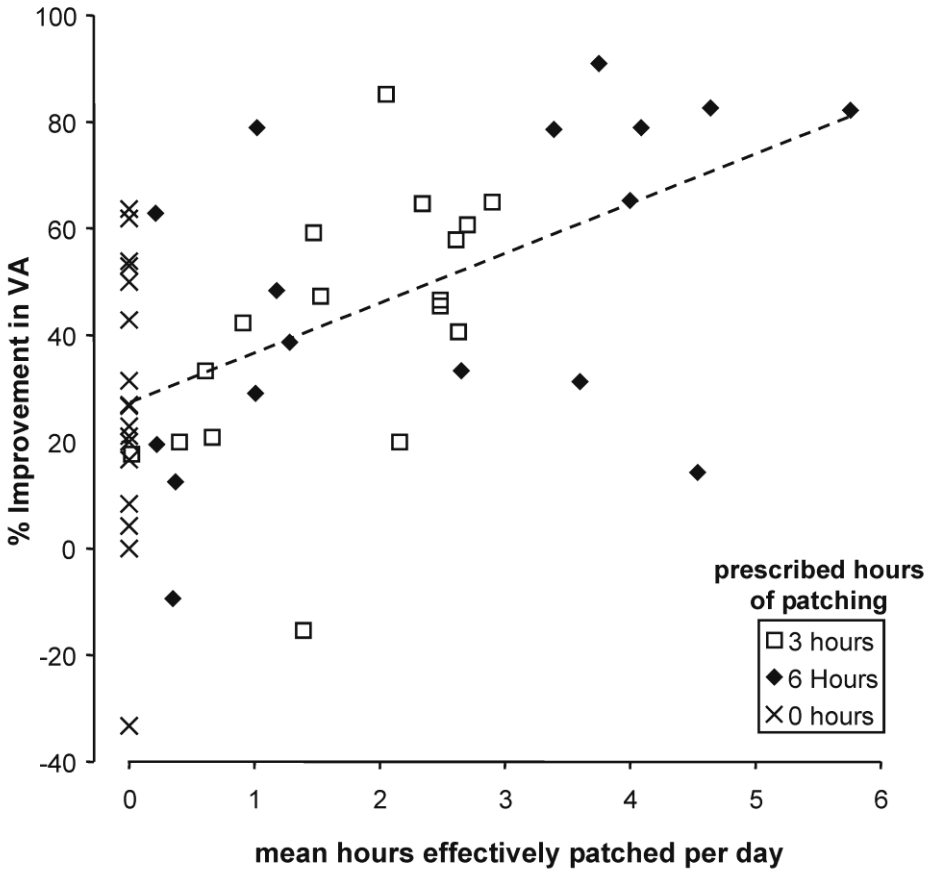


Figure 4.6. *Percentage change in amblyopia, using the formulae from Fielder et al research group, versus mean hours effectively patched (measured with ODMs) in the 3 groups showing a significant relation between effective hours patched and improvement in amblyopia. Only one patient achieved 6 hours of effective patching.*

An analysis was performed on the time of day when each patient patched in the 6-hour group (figure 4.7). The majority of high compliers (towards the rear of the graph) commenced patching at about 8am with the end of patching tailing off between 3-6pm. Patients who patched predominantly in the evening (numbers 1, 3, 4, 7 and 9) were characterised by lower compliance. More patients would be required to investigate this systematically.

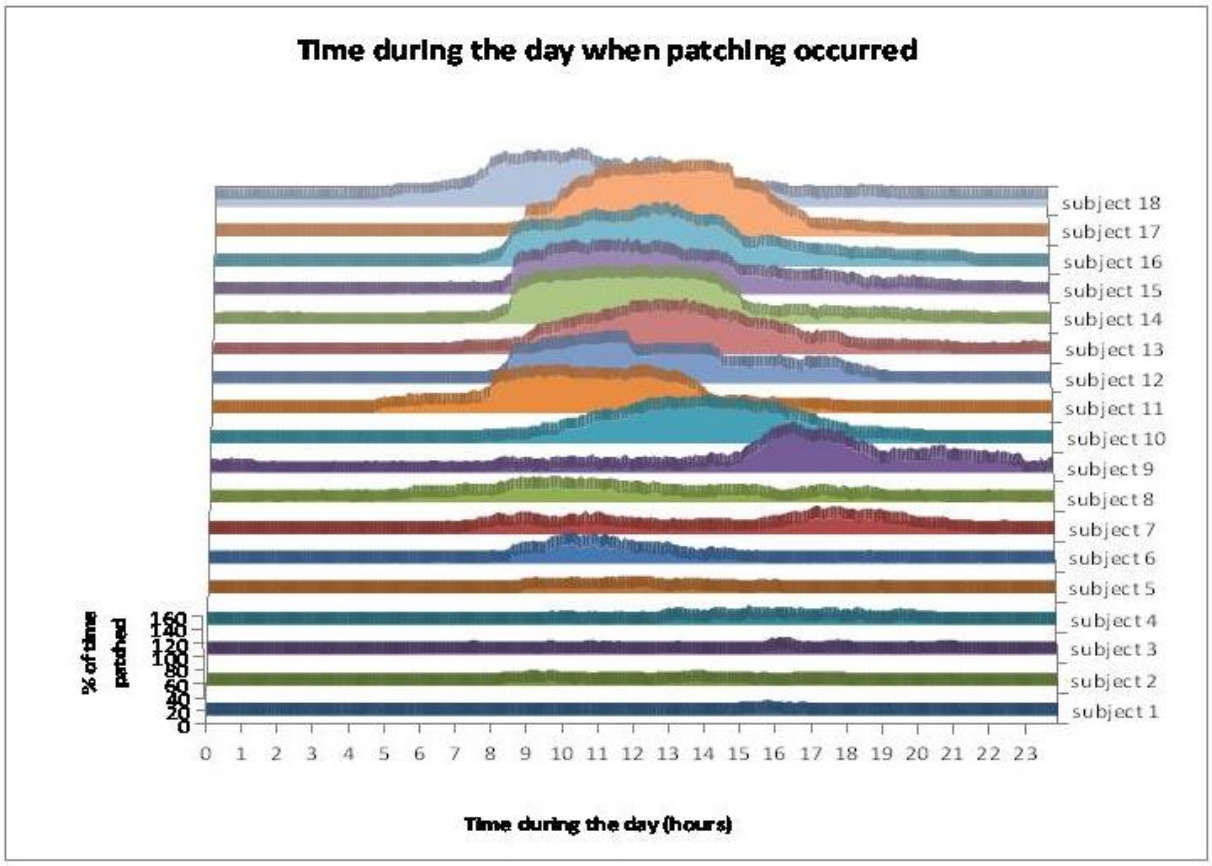


Figure 4.7. *A Waterfall plot of individual subjects showing times during the day when patched (hours). Abscissa denotes times during the day patched in hours and the ordinate denotes percentage of time patched in scale.*

A comparison of the ODM and diary times of one patient in the 3-hour patching group illustrates that the differences between the two throughout the duration of the study period (Figure 4.8).

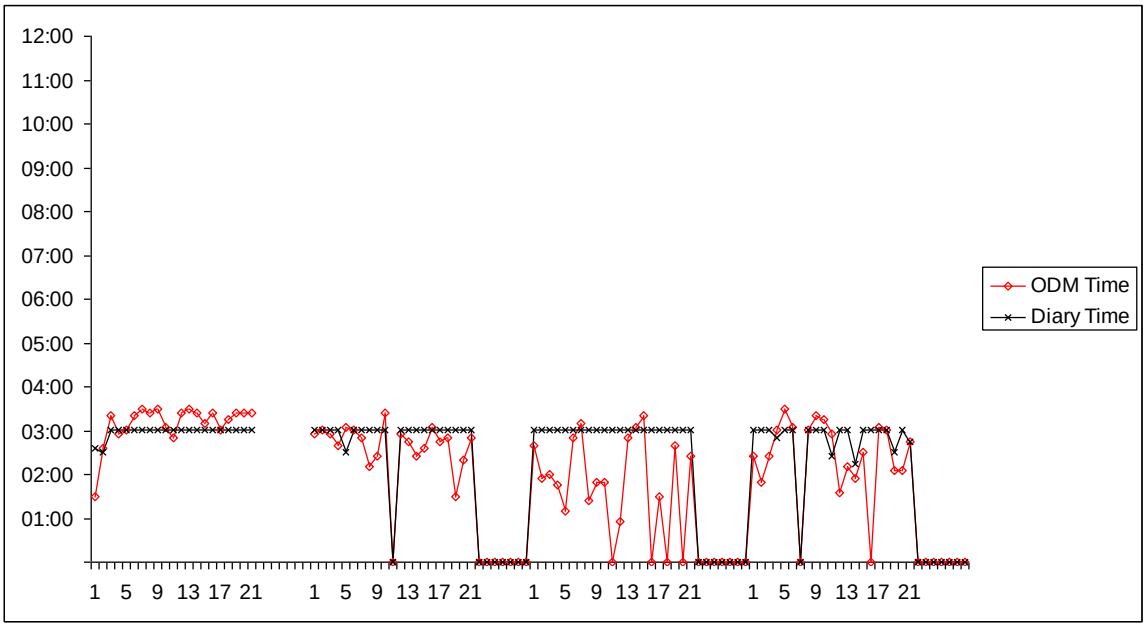


Figure 4.8. *Comparison of the ODM (solid red circle and line) and diary times (solid black circle and line) of the patient treated in the 3-hour group, throughout the experimental period.*

The mean diary times in hours were 1.95 (± 0.92) in group 2 and 2.92 (± 2.04) in group 3 with an overall mean of 2.43 (± 1.63). The mean differences in the recorded diary versus absolute ODM times in groups 2 and 3 were 0.42 (± 0.89) and 0.45 (± 1.15) respectively, with an overall mean of 0.33 (± 0.84) in both groups (Figure 4.9) shows that the recorded data between the absolute and subjective recordings i.e (the diaries and ODMs) were similar.

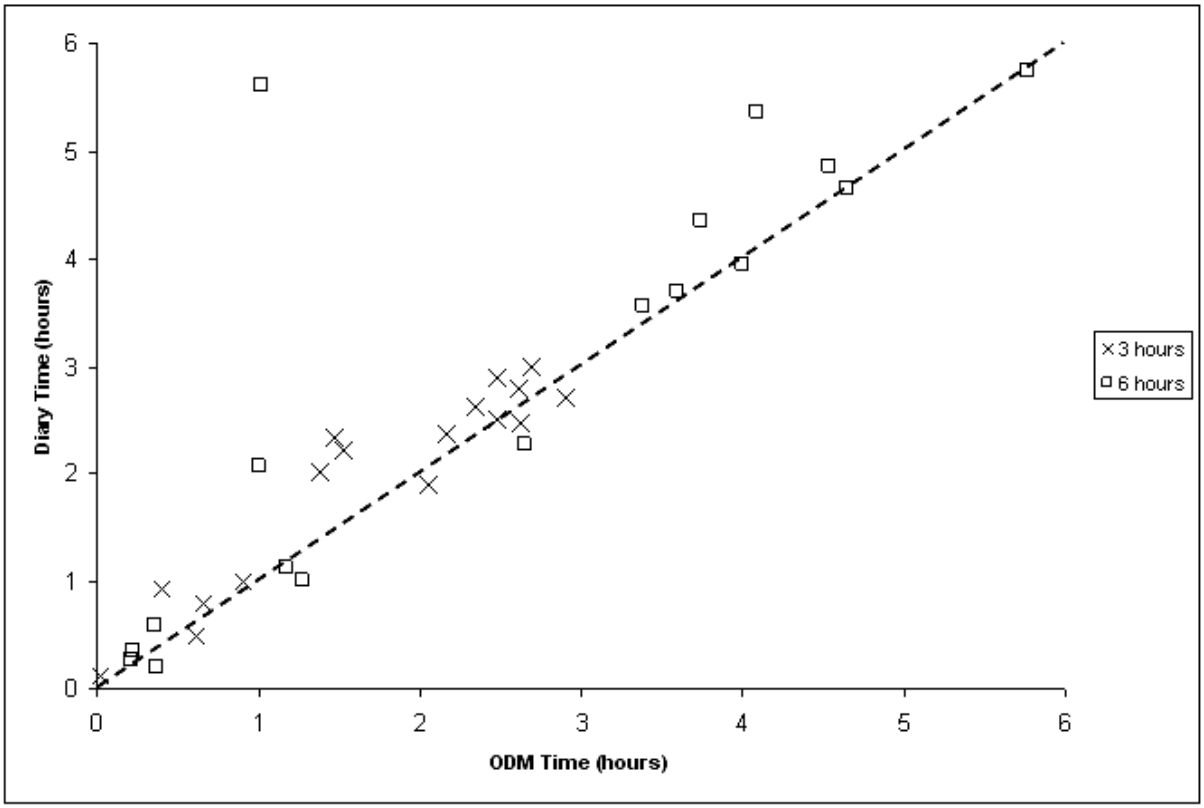


Figure 4.9. S*hows the difference in diary time (Y-axis) and absolute patching times using the ODM X-axis.*

4.5 Discussion

There was low compliance with patching therapy in amblyopia, with a mean of 57.5% for the 3-hour prescribed patching (1 hour 43 minutes mean effective patching time per day) and 41.2%, for the 6-hour prescribed patching (2 hours 33 minutes mean effective patching time per day). Poor compliance explains our findings that prescribed regimens of 3 or 6 hours of patching did not significantly differ in effectiveness compared with no patching. The VA increase was not different regardless if patients were asked to wear only

glasses (0-hour group) or to wear the patches 3 or 6 hours per day. If the effective hours patched per day were taken into account, it showed that the dose relationship between hours patched per day and increase in the vision of the amblyopic eye was highly significant. A similar dose–effect relationship has also been found by other studies using the ODM (Stewart et al., 2004b).

In a RCT study that compared "no treatment" with "glasses only" and "glasses combined with patching" in mild to moderate amblyopia, Clarke et al. found that treatment with glasses and/or patching had little effect in children with mild amblyopia however, moderate amblyopes would have benefited with earlier treatment. It is difficult to compare directly this study with Clarke et al. (2003) since all amblyopes recruited in this investigation were strabismic and mixed whereas in their analysis children diagnosed were mainly anisometropic amblyopes (Clarke et al., 2003). In addition, all patients in the "no treatment" group were prescribed glasses.

The observed improvement of vision in the no patching group as shown in figure 4.6, probably indicates that refractive adaptation continues to progress longer than 6 weeks. Although there is variability in the data, it shows that visual acuity can improve even beyond 50% in some patients during the 12-week period. This suggests that compliance to glasses wearing during refractive adaptation is a factor that needs further investigation.

In an RCT for moderate amblyopes performed by the PEDIG, the prescription groups of both 2 hours and 6 hours showed a similar magnitudes of visual improvement (PEDIG et al., 2003b). One difficulty in interpreting their study is that they did not include

a patient group treated with glasses only. Therefore, comparisons could not be made with the improvement in visual gain during the period of refractive adaptation. It is also worth mentioning that the subjects recruited in this analysis, had a slightly lower VA at the beginning of the study compared with the ATS (0.59 vs. 0.48 mean logMAR VA). Hence, these numbers are not directly comparable.

Another possible explanation that there was no difference in VA change between the different periods of patching prescribed is poor adherence to treatment. This is supported by our results showing no difference between effective hours patched, whether 3 or 6 hours were prescribed. Although, diaries have previously been used to monitor compliance their reliability are questionable. The ATS, moderate and severe amblyoia studies, indicated fewer adherences to treatment especially in the longer hours of prescribed patching groups (PEDIG et al., 2003b, PEDIG et al., 2003a), in their diaries.

In this study, our diary recordings were relatively reliable. However, a possible explanation for this is that parents were aware that occlusion was monitored using the ODM. This could have also influenced the overall compliance rate in these patients. An alternave explanation of the lack of significant difference in change in VA between the 3- and 6-hour groups would be that the effect of patching is saturated after, for example, 3 hours' patching per day. The results in the eight subjects who effectively ptched for > 3 hours daily suggest that there is no plateau effect up to 6 hours' patching per day, although more data for between 3 and 6 hours patching per day are needed to substantiate this finding. To determine whether a dose–effect response continues beyond 6 hours per day of

effective patching, a future study would be needed including a prescription of greater than 6 hours of occlusion per day.

In this study, there was no influence of age on visual outcome. These findings are similar to previous studies (chapter 2). However, consistent with our data, as in most studies, patients with worse amblyopia at onset of treatment, showed a larger increase in VA (Cleary, 2000, Clarke et al., 2003, Woodruff et al., 1994a). Our recent survey showed that the mean duration of patching prescribed in the United Kingdom is ~3 hours per day (6) The results of the present study indicate that only the group of patients who effectively used the patches for >3 hours significantly improved in VA, compared with no patching. Therefore, if ≤ 3 hours are prescribed, the current practice should be changed by increasing effective patching times through longer prescribed patching hours and improved compliance. Surveys of clinical treatment of amblyopia have shown poor outcome despite lengthy treatments, often over several years (Awan et al. 2004) (Flynn et al., 1999).

In conclusion, for the first time, at the time of analysis, we presented a randomized controlled trial including a non-patching group, in which effective patching was monitored. Poor adherence to treatment was evident but we found evidence of a significant dose–effect relationship if effective patching hours are taken into account. It is important to devise methods that could improve compliance, and reduce unnecessary long-term treatment such as developing an educational program for amblyopia treatment.

CAPTER 5

Problems with Compliance and the Understanding of Amblyopia and its Treatment

5.1. Aims

Patching treatment for amblyopia is routinely prescribed to restore the reduced visual loss. The previous chapter (chapter 4) concluded that although patching was effective when monitored objectively, the compliance to treatment was poor especially in the longer hour groups. The variability in compliance is often mediocre probably due to the emotional impact and distress involved of wearing an obvious eye patch to cover the dominant eye (Holmes et al., 2003). This section describes interviews that were conducted to explore reasons as to why compliance to occlusion is poor. It has different points of view of how patching is percieved and do parents feel that the disease is worth treating.

5.2. Introduction

It is becoming clear that the continuing uncertainty over patching treatment is that many studies fail to address, perhaps the main factor of compliance, which may influence outcomes of treatment (Hussein et al., 2004, Cleary, 2000, Nucci et al., 1992). This study used qualitative methods to investigate and explore families' experiences of attempting to patch children who had been diagnosed with amblyopia and possible reasons why compliance could have been affected during treatment. The study was in collaboration with Professor Irene Gottlob and Mary Dixon-Woods of University of Leicester.

5.3. Methods

The main author (MA) approached twenty-eight families, where a child was prescribed patching at the Leicester Royal Infirmary, Leicester, England, in the eye outpatient department. A range of hildren's treatment, ages, ethnicity, and social class were

selected. Informed verbal consent was obtained from participants after explanation of the study was given by the research orthoptist (MA). Eight families opted not to participate with the study as parents did not wish to be interviewed. The study commenced once parents/guardians signed a formal consent before interviews were conducted. Questions for the interviews were discussed using published work and feedback from patients of study chapter 4 primarily to interview parents of amblyopic children. See prompt guides in Appendix (C). We had composed a small series of questions in case older children wanted to participate. This was to minimise interruption or avoid incomplete interviews. This was optional and only carried out with parental or guardian consent.

Semi-structured interviews were performed on the parents choice of place either in their home or at the clinic and one or both parents could participate with the interviews. Interviews were specifically addressed to explore parents' and patients understanding, perceptions and treatment of amblyopia, and their experiences of patching, using a prompt guide that had been developed following a review of published reports, pilot interviews, and discussions within the study team. The research ethics committee of Leicester approved the study.

To avoid contention or bias, the prompt guide was flexibly used in response and direction according to how the participants wished to take the interview. All interviews were tape recorded with permission and subsequently transcribed verbatim. Qualitative analysis began with open codes describing each unit of meaning within the transcripts, and included the use of in vivo codes based on the terms used by participants themselves, as well as more conceptual codes (Appendix C). Through careful comparison across

transcripts, the open codes were developed and refined into organising themes or categories, which provided the coding frame for analysis. QSR N5 software was downloaded onto the PC used to assign data to codes and was validated by MDW.

5.4. Results

Twenty-eight families were approached for the study at the Leicester Royal Infirmary, and twenty-five consented to participate. Of the families interviewed with amblyopic children prescribed patching, ten were male and fifteen were female. Subjects comprised a spread of ages (range 2 to 8 years, mean 5.72 years, SD 1.4 years) with several ethnicities (Caucasian n=18 Asian n=7). Nineteen interviews were conducted with mothers, one interview with a father, and five interviews with both parents. Five families were single parent and in 20 families, two adults were living together. The mean duration of patching at the time of interview was 18.7 months (range 3 months to 5 years). Outcome of patching therapy was variable.

Difficulty in patching

For both children and their carers, patching was reported to be generally a difficult experience, especially at the first cycle at initiation of occlusion treatment. Attempts to make children wear the patch were reported to result in often-extreme emotional reactions between the parent/carer and child. A prominent problem was the visual impact of wearing the patch, which caused children to struggle with everyday life activities, and schoolwork. Wearing the patch was perceived to have significant social impact, including an increased risk of teasing and changes in confidence and personality. *(Direct quotations in italics).*

She used to cry every morning because she wouldn't wear it. […] was very upset, she didn't want it done at all (participant 13).

She's in school. When she is doing a lesson, when she is playing with her friends, she's not normal. We can see by her face… she thinks that she's disabled, so she can't do everything that she wants to do (participant 12).

Accepting the Patch

To comply with the treatment, parents had to tolerate their child's present experience to some degree of emotional distress with the anticipation of a promising visual improvement in the future. Consequently, many parents reported that persistence would overcome resistance with patching but this resulted in significant distress on the direct relationship between parent(s) and their child.

Took us weeks to get him used to keeping the patch on, it wasn't a good experience to me seeing my child disturbed (Participant 15).

Well, at first she would not wear it. I couldn't force her. I mean, I tried everything to try to get her to wear the patch to school, but she wouldn't…[…] well, at first it was hard, so I used to put it on for like, a couple of hours before school and then sort of two or three hours after school. 'Cause she wouldn't wear it for school. (Participant 13)

Evidence of Visual Improvements

Evidence that their efforts were being rewarded with demonstrable improvements in the child's vision at clinic visits encouraged parents to persevere. However, if no improvements were evident, parents were at risk of becoming alienated.

It's not getting any, there's no improvement after the three years, so she couldn't see what more the patches would do. And he's getting frustrated, I mean, because he's been wearing them for three years now and you know and his eye's getting no better' But we just made a decision as parents He just, you know, and that's why we've come to a decision couple of week ago to stop it because it's not fair at school either (Participant 14).

Otherwise, like she says, 'improvement is good'. Because all the time I am going, and you know alphabet chart and so M is sitting in the chair, and I am say, 'One line, two lines, three lines, four lines.' And it is in the same position. So, why take, uh, why do I go all the time because not improved it is always in the same position, and at the hospital and sitting near the chart and that's it, the alphabet, and uh, ten, fifteen minutes, they say, 'Not improved.' […] Yeah, I keep going because I am worried about him, you know? So, I am all the time, I keep going and I keep going, but it is in the same position (Participant 7).

Credibility of Treatment

Participants found supporting their child through the initial stages of patching time consuming, especially because children often required additional supervision and attention while patching. The problems associated with compliance meant that it was important to parents that the treatment plan appeared believable.

Just to strengthen the…they said just to strengthen the…we put the patch on the good eye to strengthen the weaker eye they said. […]I weren't bothered, I was willing to do it, but C was very upset, she didn't want it done at all. (Participant 7)

It's just keep patching him, I mean, that's sort of about all we got and when he was wearing his patch, like to do stimulating things with him, that's all we told about. […]We decided as parents and I discussed it with her and she said, 'Well, keep patching because that's what the consultant would say. […] Even to this day we don't know exactly know why (Participant 14).

Rejecting Patching Treatment

Some parents who were unable to see improvements in their child's vision decided to abandon patching altogether. Importantly, parents' accounts emphasised that whether or not they complied with the prescribed treatment, they felt they were doing their best for their child.

Because he didn't seem to have liked a childhood, he couldn't play with other children outside because he kept falling over. […] So, basically it's just a decision because on our back, because I don't want his schoolwork to slip. […] I think patching for him has not worked. Doesn't matter how long you patched him for, just him. It's just his eyes not responded to that. And we've lost hope (participant 14).

Misunderstanding Amblyopia and its Treatment

Some parents had difficulty in understanding the meaning of amblyopia or accepting the rationale behind the treatment and the need to patch. They were perplexed by different explanations given by the professionals in the clinic.

I don't really … I don't really understand … er … 'cos … lazy eye doesn't really mean m… nothin' to me … unless … it's what she's … what she had … which it moves to one side but I w … I don't know … really (Participant 5).

Then we've been told again, the same things, squint and connected with the lazy eye and all that, lazy eye means a squint and we understand, we've been cleared by that as well. And then that was it. […] I haven't been given anything to read. I have to do my own research and at some point because I wasn't feeling comfortable… (Participant 15)

They've only really said that um, he's got a lost vision, lost vision really that's basically all we know. […] he's had some diagnosis but I'm not sure what they've actually said (Participant 19).

Inadequate Information and Explanation

Improvisation on information and clearer explanation about the disease and its management was often not clearly understood and the parents felt disabled to deliver justification of treatment to their child. It was difficult for parents whose first language was not English.

Um, no I think they could make um, us understand it a bit more. Maybe by you know, using plain English. (Laughs) 'Cause some of us don't understand the big words they like to use. […] I think from the start they should have made it clearer, like said that your son's got you know, a certain condition and this is what it's called and we'll do this or this and then from there, so at least you know sort of what he's got and how you're gonna go about it (Participant 19).

I had been given the information, but it wasn't sink in becasue myabe English being my second language can difficult. I haven't been given leaflet to read....(Participant 15)

Role of Different Professionals within Ophthalmology

These parents had trouble in understanding the role of different professionals in the clinic, and sometimes did not recognise or accept that an authoritative individual was giving either the diagnosis or the treatment.

I don't really know their names but…I didn't really get personnel with them like…just …er..I know there was a doctor an optician and em….what do you call a lady who has them glass bit?? (pause) its like em…she just checks what lenses is good for her eyes? That the…(pause) optometrist. Oh the optometrist (Participant 6).

Personal Modifications of Managing Patching Treatment

Similarly, emphasising the status as ''good'' parents some participants modified the prescribed treatment anticipating to achieve a balance between their child's current medical status in line with the child's other important future needs.

I wouldn't take him to school in it. […] He probably would [go to school with patch on] but I myself wouldn't want him to.[…] 'Cause you can get some kids who are really spiteful, and I don't want him to go through that when he doesn't really need to (participant 11).

M: Um, I think my main concern with M being patched at school would be, um, she's feel, um, odd. Um, and that she'd fall behind with her work, 'cause her work wouldn't be up to the normal standard it normally is when she's using both her eyes. I feel that uh, that she'd fall behind and wouldn't be able to make it up (Participant E).

Social Acceptance of the Patch

Acceptance of the patch in society was not only the concern for the parent but significantly for the child. Peer group pressure and school environment was avoided by preference of the parent(s). Wearing the patch became emotionally taxing outside of home and consequently invited a negative impact within the home.

I felt sorry for him, we just do it in the house, and we don't go out (Participant 11).

With the patch. Alright M, he doesn't like it because, you know, friends are coming and the friends are laughing, saying he is blind, like this. […]Yeah, because uh, of my son's experience, he's a clever boy and bright, but uh, sometimes he comes home, and uh, like uh, do you know, like uh, disabled. Like, sitting in the sofa and nothing talk, nothing like this, like uh, he thinking likes uh, 'I'm not good person.' Like this (Participant 7).

Amblyopia and the Child's Educational Welfare.

Pressure within the classroom environment hindered successful patching due to the set up and strain involved in running the class and presented a misconception of the child's academic progress.

M: ...I don't know actually, I think they just try and muddle through, 'cause she really hasn't got any time just for that one, just for M, when she's teaching a class of thirty-odd. Um, you know, she has to, you know, move on, um, the only thing that she said that she wasn't prepared for M to wear it during P.E. […] Um…when she last tried it at school, she got a poorly eye, because uh, she couldn't read the blackboard, uh, she got tired of the work. She got upset 'cause she's good at English, not so good at maths and she struggled with her handwriting and her teacher wasn't very happy (Participant E).

He won't wear it at school, he's been picked on a little bit and I've tried to talk to the teachers about it, but they can't be there every second of the day sort of thing (Participant 20).

Patching created Incentives to Learn

For some parents patching was an educational tool to dissuade the emotion involved with the treatment and encourage learning.

Is it my patching today?' 'Is it my patching today?', so in some terms, she didn't like it but she expressed her view about it every day, but it taught her the days of the week as well, and she learned what days she was having the patch, so, you know (Participant B).

Explaining Amblyopia and its Treatment to their Child

Many parents attempted to provide explanations to their children (especially older children) about why patching was necessary, and to tell them about improvements in vision.

We just told her it was for her own good and she'd benefit from it and that's it really [important]. Because they want to know why they've got to wear it, don't they? (Participant 9).

Because there is something wrong with my eye. Because my other eye, with my other eye I can't see properly (Participant 8).

Gifts and Rewards

Gifts and treats or reward charts were popular methods of encouraging children to wear the patch. Some parents encouraged their child with attention and praise, some parents promised sweets or a toy. Turning occlusion treatment into a game was another incentive to ensure compliancy throughout whilst others preferred not to make a ''big deal'' out of the patch.

At the moment because he's wearing all day for school, he is having a reward system, we're putting money in his box so as he can buy himself an engine for his train (Participant 4).

I was telling her that I'd go and buy her a nice toy at the end of the week if she wore it. Something that she'd actually want, you know like a sweet or something, you know just something that she'd wanted just to try to make her wear it a bit more…(Participant 13).

Incorporating Patching Treatment as Routine to Home Life

Parents reported attempting to normalise the patch by wearing a patch themselves, or getting siblings, friends or using a favourite cuddly toy to wear a patch. However, what appeared to make wearing the patch most acceptable to the children was being with other children who were wearing a patch such as siblings.

We got the other girls wearing them…(laughs) the other day all the others girls were wearing one for a bit (Participant 1).

when she first started wearing patches … it was … she used to 'ave a teddy that she put a patch on as well … as … well when they're young anyway … it made it so … she weren't the only one with' a patch on the teddy used to 'ave one on … so she was fine … as long as you make it so it's not a big deal … they don't mind (Participant 5).

The Appearance of the NHS Patch

Many children and parents disliked the appearance of the standard patch, describing it looked dated and pinky-beige skin colour that resembled a larger version of a band-aid sticking plaster.

The old, boring patch. […] they're just plain (Participant 11).

Allowing children to choose a different type of patch or a sticker to put on the patch was found to be very helpful in giving children a measure of leadership and ownership.

[…] she's a lively little girl, she don't really care, and when she started school she didn't really care, she jumped on the bus and went, ''Look I'm a pirate'' an' the stickers, you know, the stickers they get for the chart, she always put one on, on her patch, and so everybody wanted a sticker… (Participant 5).

Integrating Patching as Routine

Parents who reported being able to patch successfully had been able to integrate the wearing of the patch into well-structured routines, particularly outside the home.

So what we did was we introduced the patching to coincide with her starting date at the nursery. […] Just to have it integrated as part of her daily routine and to be in a situation where she had a lot going on, once she'd got the patch on (participant 16).

There was a couple of times when she was a bit awkward, she didn't want to wear it, but other than that, she was all right. I think that as long as she was at school and, you know, just in her classroom, she was all right […] But, we persevered with her and she did it. (Participant 9).

Additional Support from Other Amblyopic Families

Other than the authorization of parents support network of teachers and childcare workers provided a stimulus to integrate patching into a routine outside the home. These individuals were important in the compliance of patching which included: setting and adhering a routine for the child; application and removal of the patches; preventing teasing

amongst peers and establishing a reward system. Awareness of the eye condition at school brought attention to classroom teachers to lessen the visual problems caused by patching, for example, by moving the child to the front of the class or providing additional specialist help.

And they kept the patches there and put them on for her, 'cause we used to put them on about one o' clock in the afternoon I think. And then it came off, well, she used to take it off herself. 'It's time to take it off,' she'd say. (laughs) […] And with it being a bit like that, she went to a special class that helped her bring herself out of herself, 'cause she got a bit introverted (Participant 9).

Well there was always seeing if I was OK and mostly it was Mrs. K or Mrs. S because erm they were my two helpers and another teacher on Tuesday. […] Yeah they made me move right to the front (Participant 3).

5.5. Discussion

Often, the most preferred and first choice for treating amblyopia is conventional patching, i.e., covering the good eye with a sticky patch, but, results on the improvement of vision attained is mediocre. Failure rates of patching are probably influenced by poor or limited compliance with the treatment prescribed. This study was conducted in a single establishment. The qualitative data provides insights into the reasons why parents and their amblyopic children find patching difficult.

During the interview, parents of children prescribed patching treatment found themselves to be leaders to facilitate their own strategic management of the treatment inbetween hospital visits. Many parents felt pressure to endure patching, which caused distress and other possible negative outcomes, including relationship strain and disturbances between family members especially if they had insisted on persisting with the treatment. Parents were highly sensitive to the reliability of the treatment, and there was evidence that they were likely to abandon treatment if no visual improvement could be detected or the child continued to suffer socially, disturbance in the child's confidence or threatened their child's academic progress. Credibility seemed particularly reliant on demonstrations of improved vision observed during clinical assessments. These findings provide some possible indications that compliance may in part be a marker for amblyopia that is treatable. Our study suggests that a focus on psychological wellbeing and distress may not capture all dimensions of the experience of caring for a child with amblyopia. Parents' accounts in our study showed that they sought to avoid the stigma and teasing by refraining from patching outside of the home environment.

Parents found themselves positioned as "alert assistants" (Charmaz, 1991) acting to protect their child's identity. This tension between ensuring their child's welfare in the present and their role as the guardians of their child's future (McKeever and Miller, 2004) was fraught with difficulty and resulted in some parents abandoning or modifying the regimen. These findings suggest that efforts to improve compliance must take account of the difficulties and tensions experienced by parents and their child (Holmes et al., 2003) rather than simply treating non-compliance as resulting from information deficits.

This study does have its limitations such as this qualitative study based on interviews in which subjects were selected without a formal randomisation procedure. Families who had seen a treating orthoptist were contacted directly by the main researcher to obtain verbal consent for study participation. This is a possible source of bias which has been acknowledged in the strengths and weaknesses section (page221). The relationship between socioeconomic background and motivation/compliance is interesting and would provide a useful further study. We have added this as a possible future study (page 224).

Sample size was small and it relied heavily on accounts of behaviour rather than direct observation. We were unable to test directly whether parents' accounts of successful strategies did result in improved visual outcomes. The study was designed not to assess findings on how much depth of understanding parents had on the disease and its treatment as in previous literature (Newsham, 2000, Newsham, 2002) but, to point out some of the ways how compliance could be enhanced, by indicating some of the strategies that parents acquired themselves related to their personal experiences during patching.

These included explanations, attempting to incorporate patching as being normal activity of daily activity, establishing routine, strategies encouraging rewards, accepting additional help of previous treated amblyopes and improving the appearance of the patch. All of these strategies are practical forms of support that can be provided by professionals who treat amblyopia. For example, it may be very useful for parents to offer ways of making the patch more attractive and personal to children, and professionals can help with this by ensuring that alternatives to the standard patch are provided within the department. Addressing clear written information for those who become involved in patching, translated

into other languages, would help the child and propose guidance on strategies to increase compliance for the parent(s) or guardian(s) (Gregson, 2002).

Chapter 6

Improving Amblyopia Treatment. A Need for an Educational Intervention Program: Pilot Study

6.1. Aims

Amblyopes respond to occlusion treatment as demonstrated in chapter 4. To avoid unnecessarily extending the duration of patching treatment and needless hospital visits more rigorous treatment plans to achieve a better visual outcome would improve the final visual outcome. In the previous chapter, we explored the reasons related to poor compliance and the credibility of occlusion treatment. This section of the thesis describes an educational intervention pack specifically designed to (i) improve explanation of treatment, (ii) overcome difficulties of patching at school and/or home and incorporating patching as normal routine, (iii) provide a reward system during the patching phase, (iv) improve the visual appearance of the patch and (v) pilot the educational material during patching. The hypothesis under test is that additional educational intervention improves compliance to occlusion treatment.

The primary outcome of the study is absolute patching monitored with an electronic datalogger. The secondary outcome is the percentage improvement of vision using the formula proposed by Fielder (Stewart et al., 2003) **.**

6.2. Introduction.

Since the first monitoring of occlusion conducted in 1994, for amblyopia therapy using the occlusion dose monitor (ODM), it is evident from our studies and the studies of other groups that visual success is related to compliance of patching (Smith et al., 1995b, Stewart

et al., 2004b, Oto et al., 2002). Factors such as lack of understanding of the disease by the parents influenced the treatment of the child. A structured educational program could give valuable support during treatment.

The objectives were to explore the effect of the new educational intervention on compliance. The aims of this section required investigation of the following questions:

1) Does compliance improve with the provision of additional educational material?
2) Does poor visual outcome relate to poor compliance?
3) What is the maximum dose-effect that can be achieved with increasing the prescription for occlusion?

6.3. Study Design.

6.3.1. Educational Intervention Material

In collaboration with Professor Irene Gottlob, Mary-Dixon Woods (University of Leicester), Professor Jacqueline Collier and Sarah Redsell of the University of Nottingham an educational interventional amblyopia treatment pack were developed.

The package consisted of four information booklets, one advice booklet, one story book, one quotation book, a passport of attendance, sticker charts and stickers and a video tape or DVD Entitled “Patching” . The video was produced to clarify the problem and facilitate an understanding between the clinician and families of the disease and was

entitled “Patching”. The recordings of the video or DVD was taken from an old eye patch presentation, for amblyopic families, produced and edited by Biersdorf, USA (originally known as Coverlet) and an English patching presentation for parents with amblyopic children from the orthoptic video library in Leicester (produced by Roger Hickinbotham, University Hospitals of Leicester, UK).

The booklets provided scientific information regarding the aetiology and diagnosis of amblyopia, understanding the disease, common misconceptions between a squint and a lazy eye, importance of detecting and treating the disease, treatments available for amblyopia treatment and timing of treatments. Scientific information for the booklets were undertaken by MA and IG. Several reviews of versions were carried out to ensure that the clinical information was correct. The quotations booklets were real-life accounts of patching for amblyopia that were obtained from the interview study (chapter 5). The story booklet, was an illustrated story of a ‘potato head’ boy and his family were written by Jacqueline Collier and designed by I.Crooke (Showme Multimedia Ltd) and revised for scientific corrections by IG and myself. MA presented all the components of the educational pack in clear plastic folders. The monitoring device, patches and diary for the study were presented in gender insulating lunch bags commercially available for children.

6.3.1.1. Components of the Educational Intervention Pack Booklets:

A series of booklets sharing advice on patching for parents and also providing information for teachers and children were provided (front covers shown in Figure 6.1 (A), (B) and (C).

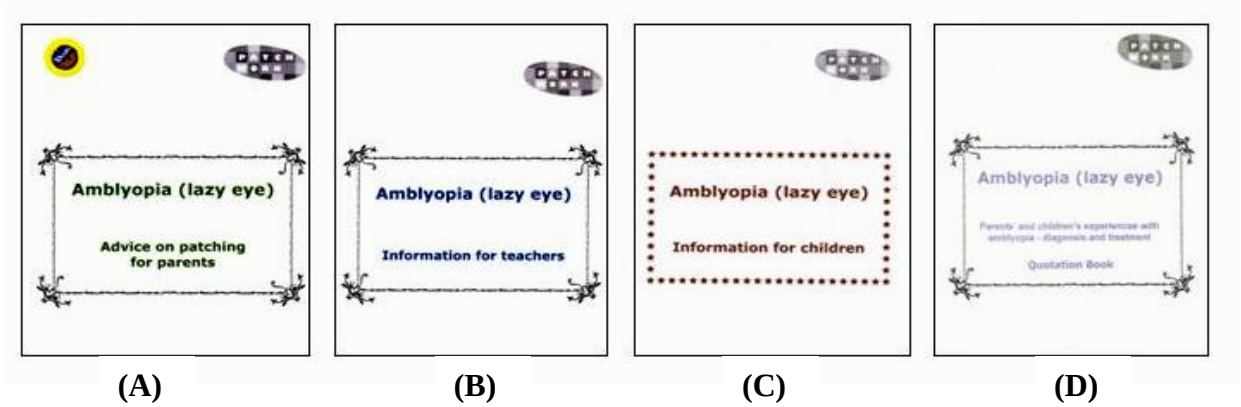


Figure 6.1 *Advice on patching, information and a quotation booklet.*

The advice on patching for parents: gives information about the disease and why patching for amblyopia is important. It also provides advice on how to encourage your child to patch successfully, and gradually increase timings of the patch for the poor or non complier and how to deal with problems and question that the child may ask.

Information for parents: gives more detailed information about the disease, how a lazy eye is different from a squint, common misconceptions, what causes amblyopia, its diagnosis, treatment, the timing of treatment in the child's life and availabilities of different methods for treatment.

Information for children: is similar to the parents' booklets however, the language is simpler and made more personal by using the personal pronouns 'I' and 'you'.

Information for teachers: The information in this booklet includes the same content as the parent's booklets with additional information on how teachers could help with amblyopic

children when patching at school, in the classroom and helpful activities, such as reading, writing, hand-eye coordination or other visual work.

A quotation booklet (Figure 6.1 (D)): shares accounts from families of patients previous treated for amblyopic. It contains actual quotations from parents' experiences, sharing their child's 'journey' from the time of diagnosis, understanding the condition and treatment involved, overcoming difficulties wearing the eye patch, making patching treatment as a daily routine and support from other families.

A children's' story book: entitled "Eye don't want to work!" is a story related to a boy named Kieran who was diagnosed with amblyopic and invites the reader to share his experiences and journey of wearing an eye patch and achieving good visions at the end of treatment. It focuses on the two eyes talking to each other as illustrated in Figure 6.2. Kieran's right eye is called "Rara" and his left eye, "Lala". It tells how "Rara" was a lazy eye and preferred to sleep most of the time whilst "Lala" was doing all the hard work of seeing for Kieran. Key issues raised in the story, include explanation and treatment of patching, incorporating patching treatment as a daily routine at home, reward strategies, and support from others.

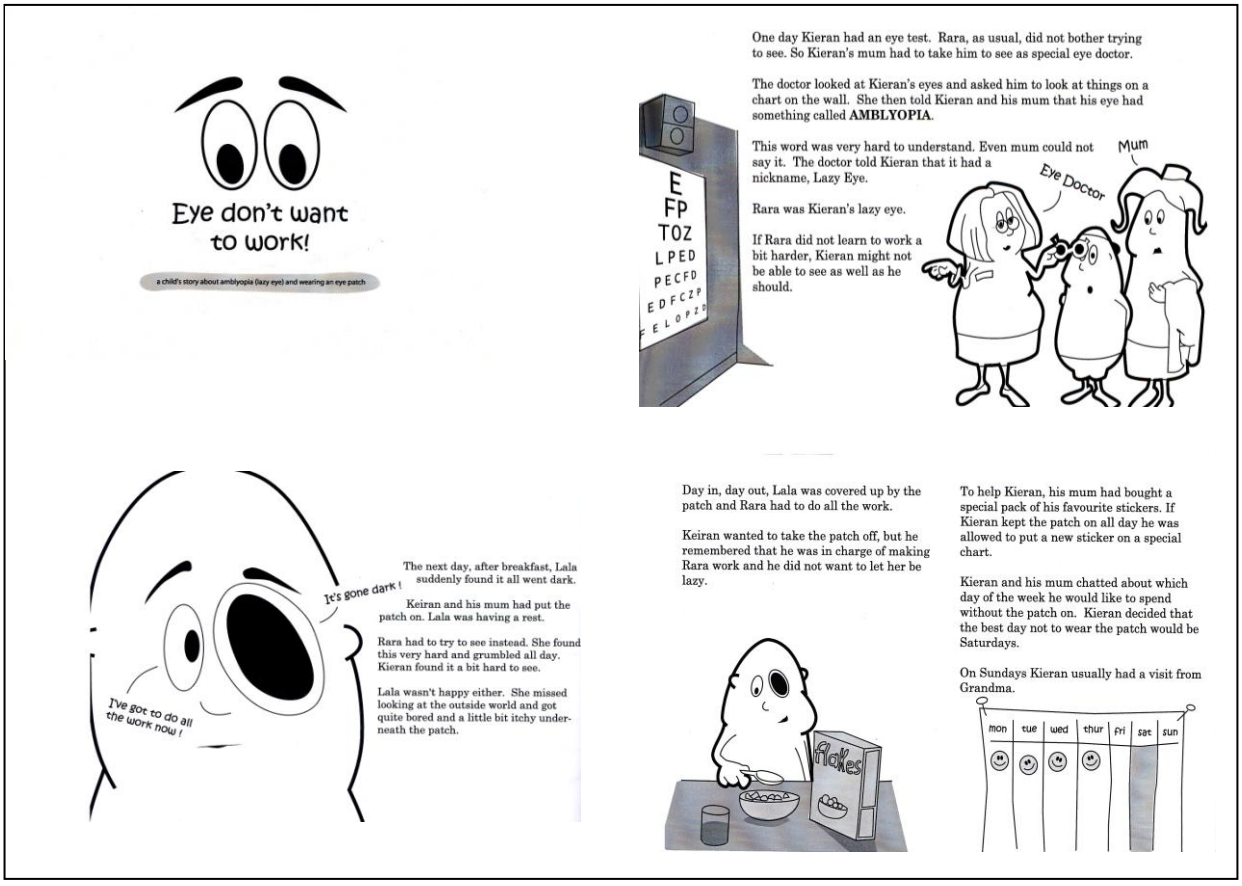
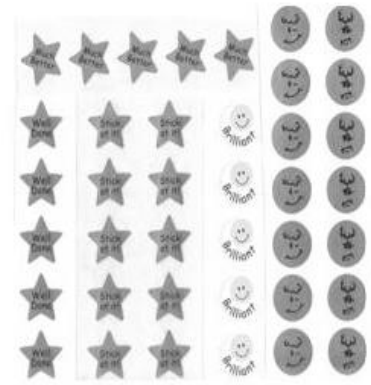
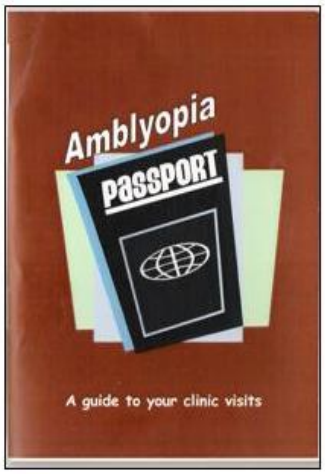


Figure 6.2. *The storybook entitled, "Eye don't want to work", shows examples of the book that convey a boys journey for the treatment of amblyopia and its success.*



A



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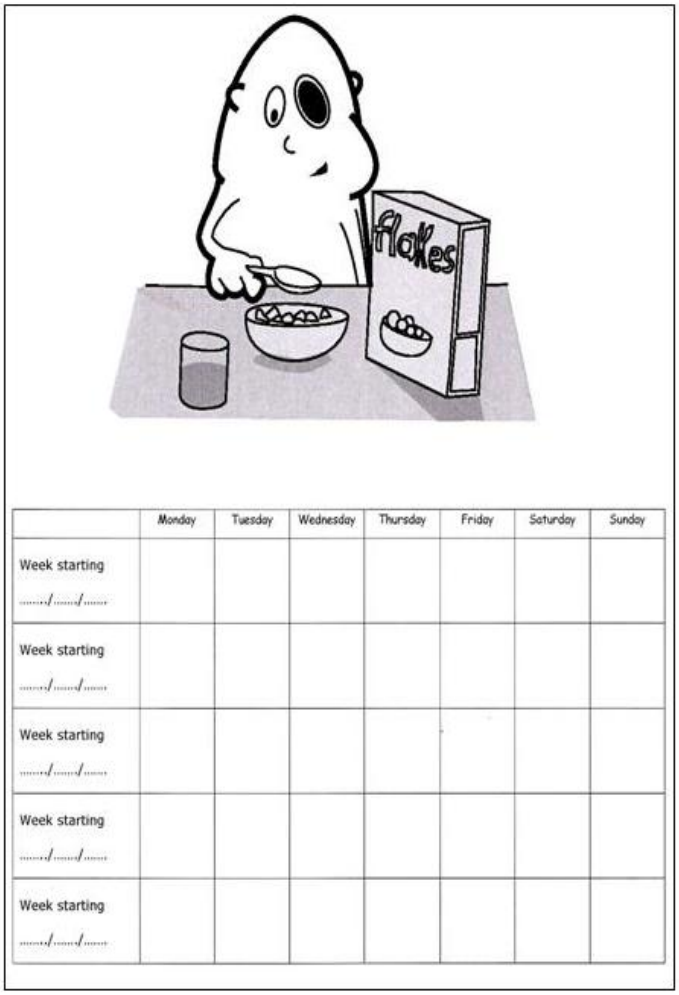


C

Figure 6.3: *(A) and (C), reward stickers and sticker charts with illustrations from the story book. (B), was the amblyopia passport comprised part of the educational intervention material for the intervention group.*

Amblyopia Passport: As different members of staff within the ophthalmology clinic regularly assess the amblyopic child an amblyopia passport with stickers was produced for the parent and child to take home (figure 6.3 (B). It includes written statements by the ophthalmologist, orthoptist and/or optometrist during the clinical visit that required inputting information into the passport with visual acuity recordings and any comments from the clinician. A specific sticker was adhered inside the page indicating whether an ophthalmologist, orthoptist or optometrist saw the child.

Sticker Chart: To encourage compliance of the child, during patching a sticker chart was created with reward stickers (Figure 6.3, (A) and (C)), showing illustrations from the storybook. This was to maintain consistency and build up the anticipation of the child with the hope of improving compliance. At every three-week visit, a new sticker chart with stickers was sent to the patient.

Patches: The intervention group received more visually appealing patches manufactured (Masteraid by Ortopad, USA). Patches were provided according to the gender of the child. Figure 6.4, shows patches for boys in the left hand side with designs based on ball sports, space and planes. The girls' patches were designed with hearts, musical notes and flowers on the right hand side of the picture. In addition, the colour of the patch was brown and blue for boys and reds, pinks or pastel colours for girls. These patches were also modified into pockets (refer to section 3.3.5) by MA to accommodate the ODM whilst patching to monitor the effectiveness of the intervention.

Figure 6.4. *Boy and girl patches supplied by Master-Aid Ortopad Company, UK, used only for the interventional group. The control group were given plain patches as were used in RCT study of mixed and strabismic amblyopes, chapter 4.*

6.4. Methods

All potential amblyopes were verbally approached regarding the study. Once the parents' consented, and signature to participate in the study was obtained the amlyopes were randomised into one of two treatment arms:

For the educational intervention group, more patches that are attractive were used as part of the study design. The use of more attractive looking patches in this study was considered because of parental views and concerns regarding the types of patches for amblyopia treatment, highlighted in chapter 5. The hypothesis was that more attractive patches would increase compliance and was included as part of the intervention material.

Group-I. Educational intervention group receiving the educational pack and more visually appealing eye patches.

Group-II. Control group receiving hospital leaflets and neutral skin coloured patches. Both treatment groups were prescribed 10-hours of patching for 6 days and monitored using the ODM for newly diagnosed amblyopic children aged 3 and 8 years of age.

Randomisation tickets were allocated, with sub-randomisation of age and severity of amblyopia, by dividing envelopes into:

- Younger group aged 3 and 4 years and an older group aged 5 and above.
- mild to moderate amblyopia(VA $\geq$ 0.300 - 0.675) and severe amblyopia (VA$\geq$ 0.700).

An independent researcher not involved in the study placed tickets in relevant envelopes. Patching was measured with the electronic skin conducting ODM provided by Huibbert Simonsz research group (Chapter 3). To maintain consistency with the former RCT mixed and strabismic amblyopia study (chapter 4) the inclusions and exclusion criteria for recruitment of amblyopes were similar. The study conformed to the approval by ethics department of Leicestershire Research and Development and Declaration of Helsinki.

Visual outcome was monitored consistently every three-weeks over the duration of twelve weeks as shown in the timeline (Figure 6.5).

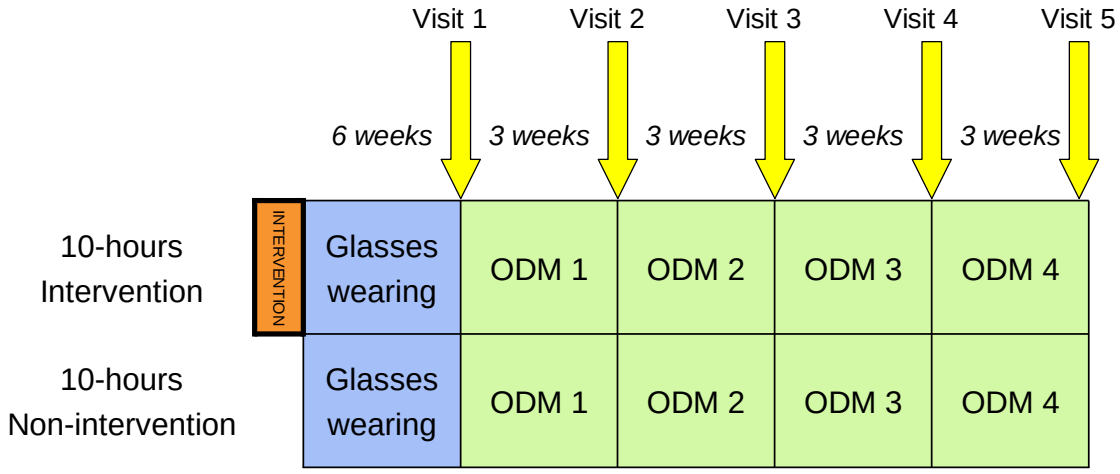


Figure 6.5 *Timeline of the Educational Intervention for Amblyopia Treatment Study.*

At visit 1, patients randomised into the educational intervention group were given all materials regarding amblyopia, gender-specific patches, and the ODM. Allowance of time in the clinic was given to explain the use of the pack, video or DVD, explanation of the ODM and how to apply into the pocket patches.

At visit 2, a one-to-one session was held between the parents, patients and the research orthoptist (MA) to allow extra clinical time discussing problems of patching, clarity of the information provided, exchange of the ODM and a supply of new patches.

At visits (3, 4 and 5) involved exchange of ODM, supply of patches and opportunity to discuss any concerns or questions during the course of treatment.

The logMAR VAs in the amblyopic eyes were recorded by the research orthoptist (MA) using the Keeler Glasgow Acuity Card Test, as in the RCT study (chapter 4). A

second recording was taken by an independent orthoptist, at the hospital. The visual acuities were written on a separate sheet and sealed in a separate envelope. Marking of the patients name, visit number, and initials of the second orthoptist was forwarded to the research orthoptist MA. The independent orthoptist was not aware which treatment group the research patients were randomised. All sealed visual acuities collated from the second measure would to be opened once the study had ceased and data compared for analysis later. At this point this research study was still ongoing and data were too few to perform for reasonable statistical analysis.

6.5. Results of Pilot Study

Amblyopes were recruited and randomised into the pilot study between May and July 2006 (Figure 6.6). Of the 24 amblyopes that were randomised, four patients did not qualify as vision improved during the six-week refractive-adaptation period, two could not perform the Keeler Glasgow logMAR acuity card test competently. Of the three drop-outs, one patient relocated to another city and two did not wish to pursue using the ODM.

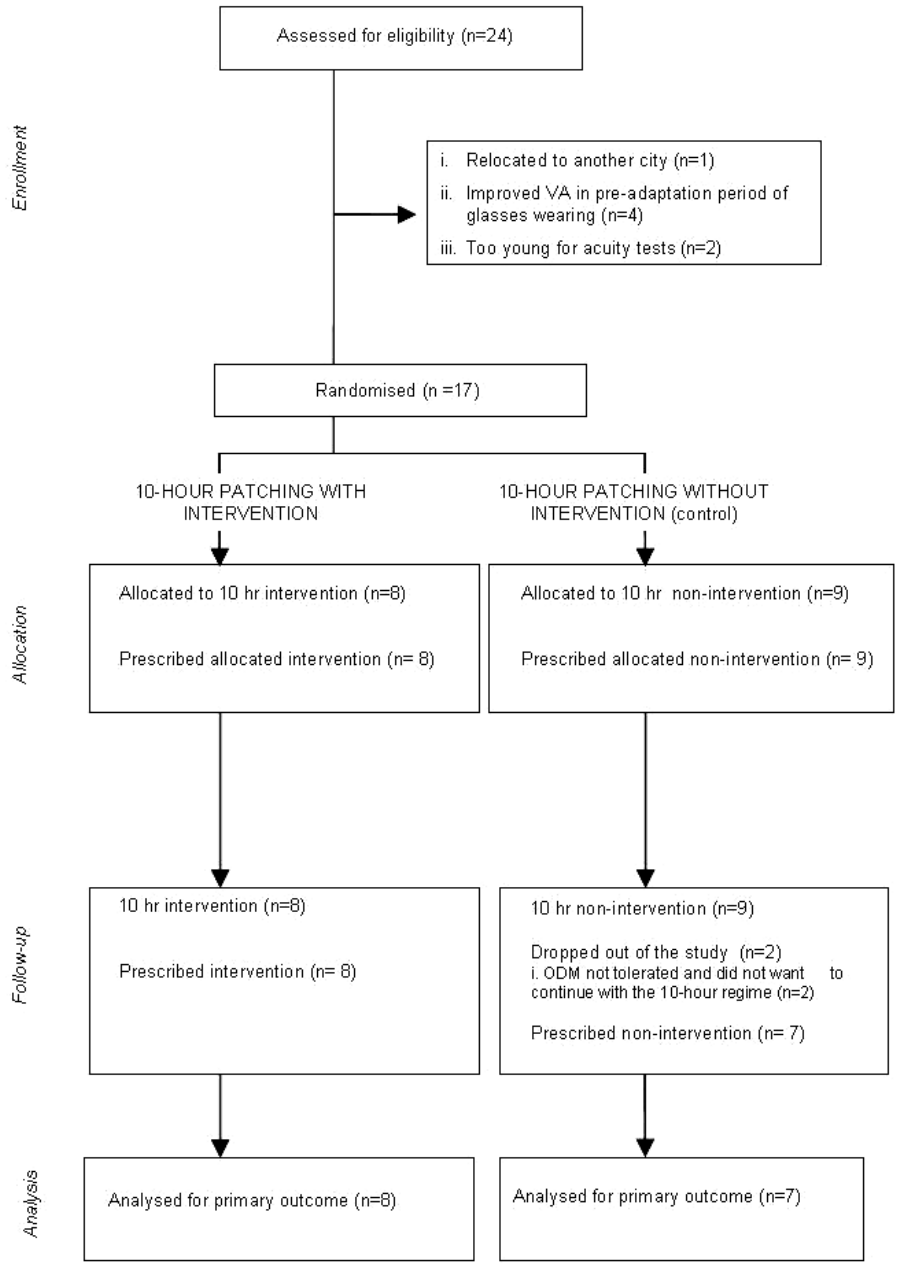


Figure 6.6. *Flow chart of patients randomised and recruited for the study.*

The randomisation resulted in eight amblyopes in group I: Intervention, with strabismus (n=2), mixed (n=5) and anisometropic (n=1) amblyopia and seven in group II: Non-intervention, with strabismus (n=1), mixed (n=4) and anisometropia (n=2) (Figure

6.7). The mean age (±SD) recruited in group I and group II respectively were 5.0 (±0.9) and 5.5 (±1.5).

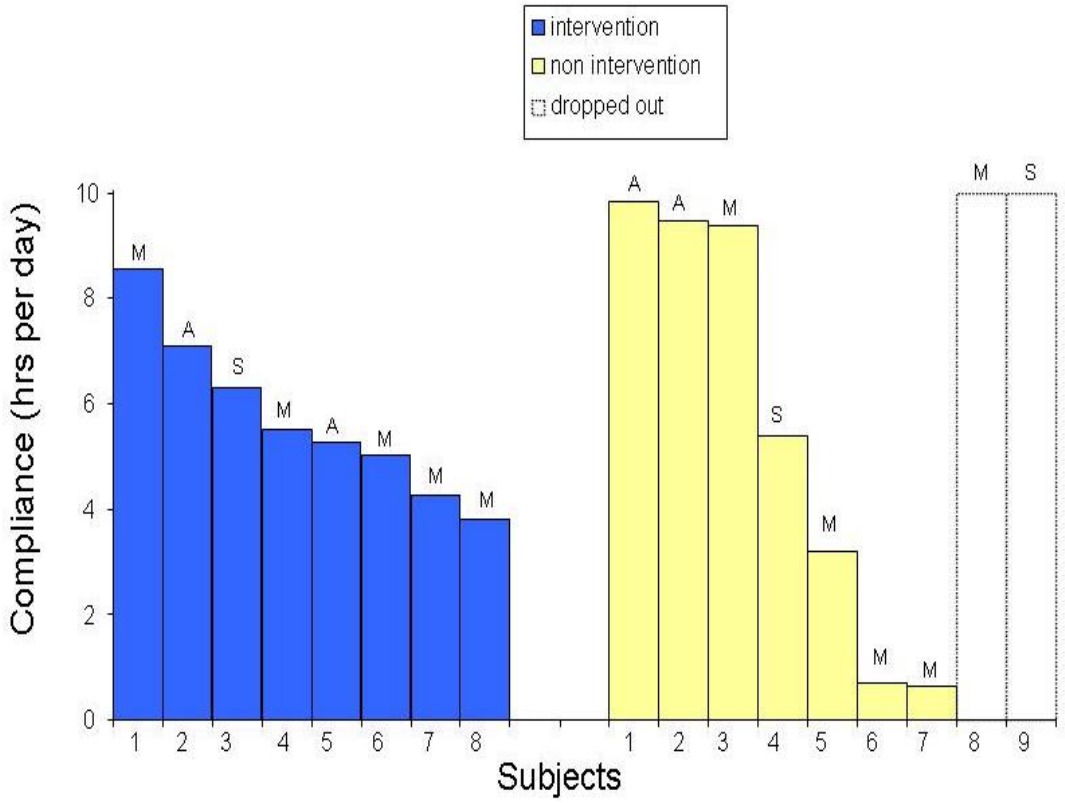


Figure 6..7. *Histogram Pilot data of compliance hours per day per each subject recruited into the two study arms. Light blue bars denotes intervention group and yellow bars denotes control group. Clear bars represents drop outs of the study.*
Amblyopia: S= strabismus. A=anisometropia, M=mixed

Mean LogMAR visual acuities (±SD) before patching in group-I and group-II were 0.72 (±0.16) and 0.75 (±0.40), respectively. LogMAR VAs in the fellow eyes before patching were; 0.12 (±0.08) and 0.14 (±0.11). The logMAR VAs (±SD) at the end of the

trial period in the amblyopic eyes in groups I and II were 0.38 (±0.17) and 0.29 (±0.26), respectively. In the fellow eyes acuity at the end of the trial period were 0.09 (±0.10) and 0.07 (±0.10), respectively.

With respect to primary outcome the total hours of patching, the total hours of patching were 257.56 (±84.09) in group-I and 259.62 (±188.12) in group-II. This was equivalent to 4.91 (±1.32) and 4.73 (±3.53) daily hours of patching, respectively. High levels of occlusion, using the ODM, showed that actual hours of patching were highly variable in these small numbers of 15 amblyopic patients over the twelve-week trial period in both study groups as shown in the histogram (Figure 6.7). However, full collection of data is required before a conclusion can be drawn from the study.

Surprisingly, in the non-intervention group, 4 out of 7 subjects patched more than half of the prescribed time of which 3 of the 4 patched near to ten hours of the prescribed patching time given. In the intervention group, a slight reduction of visual gain of less than one logMAR line in comparison to the control group was detected. However, the overall compliance in the intervention group was better where nearly all but 2 subjects patching for more than half the prescribed time with no drop outs compared to the control group.

The study has now been completed and has included 62 patients (31 in each arm) of which 16 patients dropped out (although visual acuity data was collected for all but 7 patients). The final results are shown below (figure 6.8).

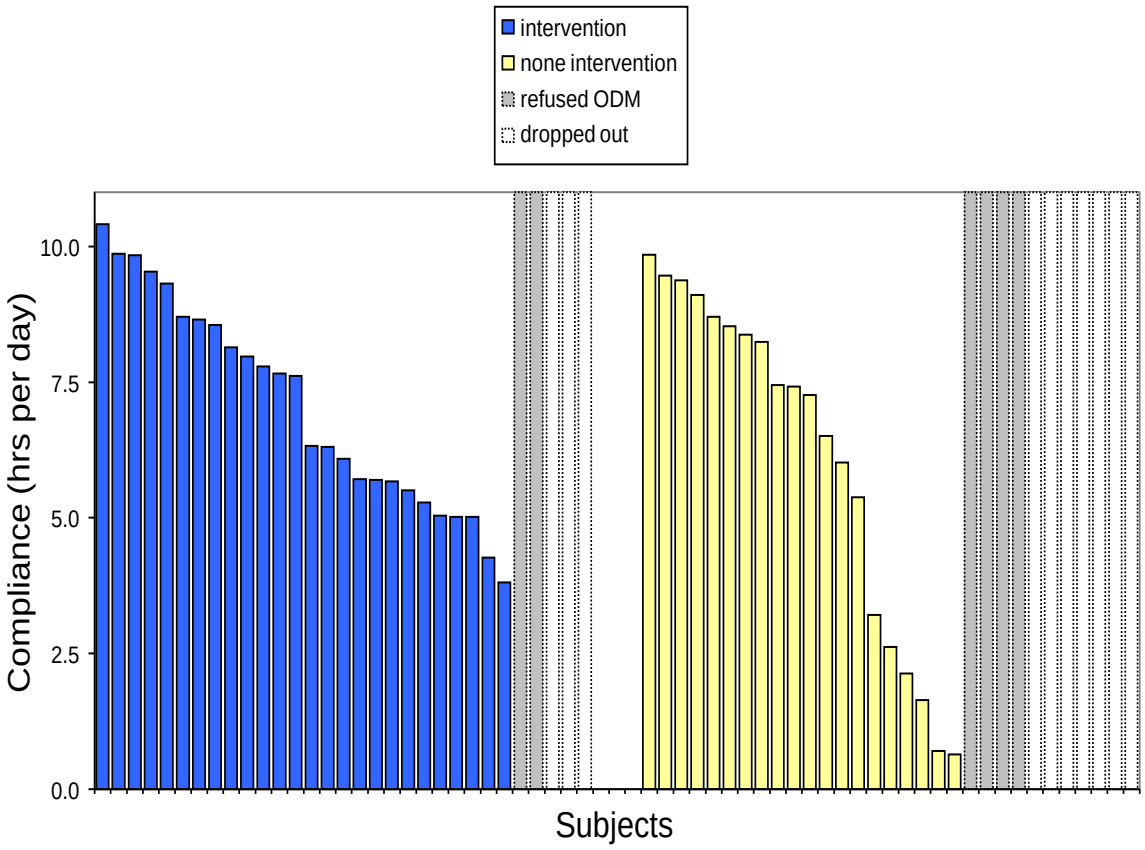


Figure 6.8. *Histogram Pilot data of compliance hours per day per each subject recrulted into the two study arms. Light blue bars denotes intervention group and yellow bars denotes control group. Grey shaded bars represents refusal to useODM and clear bars represents drop outs of the study.*

The researcher who continued this study will publish the results of this study in future.

6.6. Discussion:

In general, it has been found that compliance for amblyopia therapy is poorer in amblyopes with severe visual loss (PEDIG et al., 2003a, Woodruff et al., 1994a) at initiation of treatment regardless of the type of occlusion administered (Repka et al., 2004, Repka and Ray, 1993). Several strategies have been employed in an attempt to improve compliance. Factors known to improve compliance have previously been attempted, (section 1.8, page 100) such as increasing near visual activities and supplying additional information to enhance understanding of the disease and its treatment. Smith, et al. (1995) found that compliance had increased in patients when invited to follow-up more regularly in their first year during treatment (Smith et al., 1995a). Compliance of occlusion therapy (Fielder et al., 1995, Smith et al., 1995b, Fletcher et al., 1969) showed a rapid response to treatment when children were patched under a more controlled environment where supervision was constant, such as hospitalisation methods (Elder, 1994).

Loudon et al. (2006) E-Abstract 4312, administered a compliance-enhancing program with compliance measured to using the ODM (Loudon et al., 2006a). In their Electronic Recording of Patching for Amblyopia Group (ERPAG) study, non-compliance were predominantly caused by the lack of understanding the disease and deficient communication between the clinician, parent-patient (Loudon et al., 2006a).

More data for analysis is required to verify findings as absolute from the ODM recordings. However, this study addresses that implementing rigorous treatment over a shorter duration, with effectiveness in visual gain, could probably reduce the financial burden on the health service of needlessly employing long-term treatment plans.

Chapter 7

General Discussion

7.1. Summary of Findings

7.1.1. Analysis of Current NHS Treatment for Amblyopia with Occlusion Therapy.

A retrospective analysis of 322 amblyopic children treated and discharged for amblyopia from a UK clinic was analysed. We found that outcome of visual acuity was mediocre and incurred significant costs of patients care and financial burden to the NHS. For example, the overall percentage of improved visual acuities was 59.3% reaching visual acuity of 6/9 and only 21.7% reaching an optimal visual acuity of 6/6 in the amblyopic eye. Overall, the mean of total recorded visits was 21.4 and the overall total treatment duration for the treatment of amblyopia was and 34.8 months. In relation to the total hours prescribed the mixed group were prescribed the most 2815 hours compared to the anisometropes 1238 hours. Measures such as number of missed visits strongly suggest that poor compliance is a key factor leading to residual amblyopia at discharge.

7.1.2. A Randomised Controlled Trial of Mixed and Strabismic Amblyopia Using Occlusion Dose Monitors to Record Compliance.

A quantitative study of fifty-two newly diagnosed strabismic and mixed amblyopes were recruited to investigate compliance to the treatment prescribed and the efficacy in visual improvements in relation to patching. Patching was observed using occlusion dose monitors to objectively record the actual hours patched. Visual outcomes in the 3 treatment groups (0-hour, 3-hour and 6-hour) was 34.5%, 46.0% and 51.8% respectively thus, demonstrating visual improvements in logMAR of 0.24, 0.29 and 0.34 logMAR lines

(Snellen equivalents: 1.6 lines, 1.9 lines and 2.3 lines) in the amblyopic eye. There was no significant difference between the three groups. Our evidence based study with objective measurements of patching showed that the lack of difference between the groups was due to the effective patching time which were only 1 hour 43 minutes in groups 1 (compliance of 57.5%) and 2 hours 33 minutes (compliance of 41.2%) in group 2. There was a large range of compliances with some very poor compliers. Sub-optimal visual outcomes evident in this study raise a concern about current treatment modalities.

7.1.3. Problems with Compliance and the Understanding of Amblyopia and its Treatment.

A qualitative study of interviews of 25 amblyopic families was conducted to explore reasons for poor compliance. Prompted questions were asked which focussed on parents personal experiences of occlusion therapy. Main areas investigated were parental concerns, their experiences of amblyopia treatment, whether parents understood what amblyopia means, and the common differences between a lazy eye and a squint. Parents felt that little or no evidence of visual improvement influenced the credibility of the treatment. The emotional anxiety involved during patching related to the outward appearance of the NHS patch and disturbance in the child's normal activities. Rewards together with patching as a part of daily routine were effective at achieving good compliance.

7.1.4. Improving Amblyopia Treatment. A Need for an Educational Intervention Program: Pilot Study

Information based on the interviews led to the development of an educational interventional package to overcome difficulties with patching therapy and enhance occlusion therapy. The intervention was tested with a pilot RCT study analysed 15 newly diagnosed amblyopes of which eight were randomised into the interventional group and seven into the non-interventional group. Occlusion was monitored using occlusion dose monitors. There is preliminary evidence that the intervention reduces the numbers of poorer compliers.

7.2. Is Patching Treatment Effective?

Evidence provided in chapter 2, assessing patching treatment in a single UK hospital, support the belief that outcomes in VA are poor. Similarly, other literature shows less than optimal improvements in visual gains to various patching regimens (Loudon et al., 2006b, Stewart et al., 2004b, Simonsz et al., 1999, Fielder et al., 1994, Fielder et al., 1995). Our data showed that the overall percentage of patients who reached 6/12 in the amblyopic eye was 78% occuring in both anisometropes and strabismic amblyopes and 64% in the mixed group and the overall percentage who reached 6/6 in the amblyopic eye was 23% in both the anisometropia and strabismus groups and 19% in the mixed group. In an earlier comparative study, Flynn et al (1999) used two pooled data sets of 961 patients (their own data and that used by Woodruff et al. (1994), i.e. study group 2), using the same threshold of visual success of 6/12. Findings showed that subjects reaching 6/12 in study group 1 (Flynn data) and study group 2 (Woodruff data) were 73.7% and 59.9%, respectively

(Flynn et al., 1999, Woodruff et al., 1994a). This was less in the study by Hiscox et al. (1992) with a success rate 33% of patients reaching ≤ 6/12 (Hiscox et al., 1992).

This is comparable to the ATS (PEDIG) studies where the proportion of subjects reaching visual acuities of 6/12 were, 75% and 85% in the moderate group (for 2-hours versus 6-hours, respectively) and 43% and 51% in the severe group (6-hours versus 12-hours, respectively) in the two seperate prescribed patching groups (PEDIG et al., 2003b, PEDIG et al., 2003a). The Clarke et al. (2003) and ATS American studies reported that visual outcomes were better in the mild amblyopes, compared to moderate amblyopes however, their findings were not directly comparable. The ATS involved a fixed treatment period of four months with fixed base-line acuities (20/40-20/80) with a refractive adaption groups whereas, the study by Clarke et al. used a wider baseline criteria of 6/9 to 6/36 (20/30-20/120). They show that most of the deficit resolved in the mild amblyopia group, even when treatment was delayed (Woodruff et al., 1994a, Flynn et al., 1999, Flynn et al., 2000, Clarke et al., 2003). They also highlight that amblyopia with initial low visions usually show poor visual outcomes that would necessitate early intervention. However, their main outcomes with diaries have been shown to be unreliable (Simonsz et al., 1999). The ATS differed from ours in that they used fixed base line acuities. As their studies main investigation was prescribed hours of two treatment groups and not absolute hours patched, no results of actual patching were demonstrated. In addition, the duration of patching used in the ATS was 4 months in contrast to 3 months used in this study. However, overall similar results to our sample of amblyopes treated in Leicester (chapter 2) achieved similar visual acuities in years what many groups observed in a matter of months. In comparison to studies performed over a decade ago conducted by Flynn and Woodruff from the same

institution (Leicester Royal Infirmary Ophthalmology Department), visual outcomes have not significantly improved but remain mediocre as shown in our findings in chapter 2 (Flynn et al., 1999, Woodruff et al., 1994b).

This literature and our own data from chapter 2 agrees with the report published in (1997) by the NHS Centre for Reviews and Dissemination (NHS CRD), that there is poor evidence for the effectiveness of patching for amblyopia and hence the value of preschool vision screening. It is worth highlighting, that large variations in base-line acuities (initial VAs) and visual thresholds achieved interpreted as success (VA at the end) (Stewart et al., 2003, Evens and Kuypers, 1967, Gottlob, 1999) may have influenced their overall conclusions (Stewart et al., 2003). This also indicates that a consensus needs to be reached to establish criterion to define amblyopia (level of visual acuity) at the start of treatment and the VA level attained that is described as a "cure".

Our findings in chapter 4 present evidence that poor compliance to patching is a major cause of poor visual outcomes (supported by ODMs). It also highlighted that compliance is reduced when longer hours of patching are prescribed (41.2% in the 6-hour group compared to 57.5% in the 3-hour group). Evidence from the literature also shows that lack of compliance to patching determines the poor visual outcome of treatment (Leiba et al., 2001, Loudon et al., 2002, Loudon et al., 2003). One study showed mean compliance of 50% even though parents were aware that patching was being monitored (Stewart et al., 2004b). One of the causes of poor outcomes is lack of standardisation of treatment.

Regarding visual outcomes related to the type of amblyopia our findings (chapter 2) showed a greater residual deficit in the mixed amblyopes although treatment duration was

longer, whereas the anisometropic amblyopes had the best level of visual outcome with the shortest duration of treatment. It is possible that poor initial visions at the start leads to poor outcome (Woodruff et al., 1994a, Woodruff et al., 1994b, PEDIG et al., 2003a). The presence of high hypermetropia (Levartovsky et al., 1998, Ingram, 1977) in strabismic and mixed amblyopia and also the presence of eccentric fixation could also lead to reduced outcomes (Sparrow and Flynn, 1977, Stewart et al., 2005). Since anisometropia show better improvements in visual outcomes, Phillips (1959) suggested that long-term occlusion in anisometropic amblyopes up to the age of thirteen years is appropriate to ensure maximum restoration of vision in these groups of patients (Phillips, 1959).

Longer periods of occlusion treatment with mediocre outcomes is not only a concern in terms of visual potential in the amblyopic adult but the costs (clinical efforts and financial) can be high as shown in chapter 2. The average cost for all amblyopes was higher than necessary, in terms of prescribed hours, duration clinic visits and financial costs to the NHS totaling £1366.00. Considering the deficit is such a common childhood condition, this implies a huge burden to the NHS and more cost-effective methods are required (Konig et al., 2003). Further studies are required to understand the impact of amblyopia on the quality of life and achieve more cost-effective treatment methods to treat amblyopia (Konig and Barry, 2004).

Importantly, detecting amblyopia and strabismus crucially depends upon who is actually performing the visual test and basic ocular assessment and also if the child is old enough to cooperate with testing (Simons, 2005). In most cases, referral via the health visitor, general practitioner and/or optometrist performance in detecting the disease is inadequate leading to high numbers of false positive and false negatives detections

(Thorburn and Roland, 2000, Donaldson et al., 2002) compared to orthoptic screening (Smith et al., 1995a) or combined orthoptic and optometrist expertise (Donaldson et al., 2002). With variations between treating clinicians or different clinical establishments (Tan et al., 2003, Loudon et al., 2004, Mazow et al., 2000, Clarke et al., 2003) it was evident in our study (chapter 2) that the type of amblyopia and different numbers of orthoptists seen did not significantly affect the final visual outcome.

7.3. Why are Outcomes to Patching Treatment Poor?

Novel ODMs now provide new ways to monitor compliance, which in turn allows us to determine the efficacy of patching for amblyopia. Previous reports have shown evidence that amblyopes respond to occlusion treatment with variable dose rates (Loudon et al., 2007, Stewart et al., 2005). Our evidence based study (chapter 4) demonstrated variable outcomes in vision in the three treatment groups 0-hour (0.24 logMAR), 3-hours (0.29 logMAR) and 6-hours (0.34 logMAR). However, using ODMs we were able to demonstrate that these findings could be easily explained through measured compliance. Mean effective patching time per day in the 3-hour and 6-hour groups (with percentage compliance) was 1 hour and 43 mins (57.5%) and 2 hours and 33 minutes (41.2%), respectively with no significant differences between the groups.

In a recent RCT study that has been published since the completion of our RCT, Stewart et al. (2007) also used ODMs to objectively measure compliance and compared two prescription rates of 6-hours versus 12-hours. They also found similar mean improvements in vision to 0.26 logMAR and 0.24 logMAR respectively. An improvement

of similar magnitude of 2.4 Snellen lines was found in the ATS in moderate amblyopes (both 2-hours and 6-hours) (PEDIG et al., 2003b). Stewart et al. (2007) showed that the lack of difference between the two groups in the studies is due to poor compliance which were 66% and 50% in the 6-hour and 12-hour groups, respectively. The Electronic Recording of Patching for Amblyopioa Group (ERPAG) studies by Simonsz et al.(2006) found compliance of 57% with similar outcomes (Loudon et al., 2006b, Loudon and Simonsz, 2007). In their earlier study, by the same group, (2004) overall compliance was 48% with a prescription of 6 hours of patching (Stewart et al., 2004b).

Our own data and previous literature suggests that outcomes are particularly poor in mixed and strabismic amblyopes. For example, in our first study (chapter 2) the mixed and strabismic groups had the worst visions and the mixed required longer duration of patching treatment. These results were supported in previous studies (Simons, 2005). The level of the initial deficit has also been shown to lead to poor outcomes in visual gain. Clarke et al. (2003) found that mild amblyopes respond regardless of delaying treatment on visual outcome (Clarke et al., 2003). Woodruff et al. (1994) also suggests that poorer initial vision leads to poor outcomes regardless of time of detection (Woodruff et al., 1994a).

Late detection has also been shown to lead to poorer outcomes in visual gain (Kutschke et al., 1991). This was evident from the study by Clarke et al. (2003) in the moderate groups with inital VA loss or more than two Snellen lines that were treated (Clarke et al., 2003, Hiscox et al., 1992). Probable reasons were the presence of refractive errors and small angle strabismus where there are no apparent clinical signs of any visual defect and amblyopia continued to become established (Kvarnstrom et al., 2001, Ingram, 1977).

7.4. Is Patching Treatment Efficacious?

There is evidence, from the literature of a lack of standardisation in the treatment of various types of amblyopia in different European countries (Tan et al., 2003, Loudon et al., 2004). Practice patterns for management ranges from a few minutes to longer hours, in some cases all waking hours with a large variety of dose rates (Stewart et al., 2004b). The level of visual acuity before treatment is initiated is very variable ranging from being extremely poor vision (6/60 – 20/200) to being mildly better (6/9-20/30) (Mintz-Hittner and Fernandez, 2000, PEDIG et al., 2003b). In establishing guidelines for the treatment of amblyopia, it is important to establish the dose-response characteristics of visual improvement to hours patched. Our own findings and that of previous studies such as the MOTAS and ATS studies suggest that increasing prescribed dose has little effect in significantly improving visual outcome.

Using occlusion dose monitors it is now becoming clear, however, that in contrast to prescribed patching, percentage change in amblyopia showed a clear relationship with effective hours patched. This was highly significant from our data with reduction in the visual deficit by 8.3% for every hour patched daily over the duration of 12-weeks. This is also being verified from other emerging studies using ODMs.

Recently, Stewart et al. (2007) found a significant increase in the proportion of deficit in the amblyopic eye corrected with increases in dose rates up to 4 hours. Beyond this, the improvement plateaus (Figure 7.2). However, all types of amblyopes are included in the figure in contrast to only strabismus and mixed groups used in our study.

Consequently, they suggest that 4 to 6 hours of occlusion treatment is adequate for effective treatment (Stewart et al., 2007b). In contrast, to our figure (chapter 4, Figure 4.6) shows no clear evidence of plateauing beyond 4 hours patching per day. On the contrary, our prelininary recent dose-response graph showing absolute dose rates in relation to percentage of visual acuity gain exceeded beyond what Stewart et al stated (Figure 7.1). Substantitative data is required to confirm these findings.

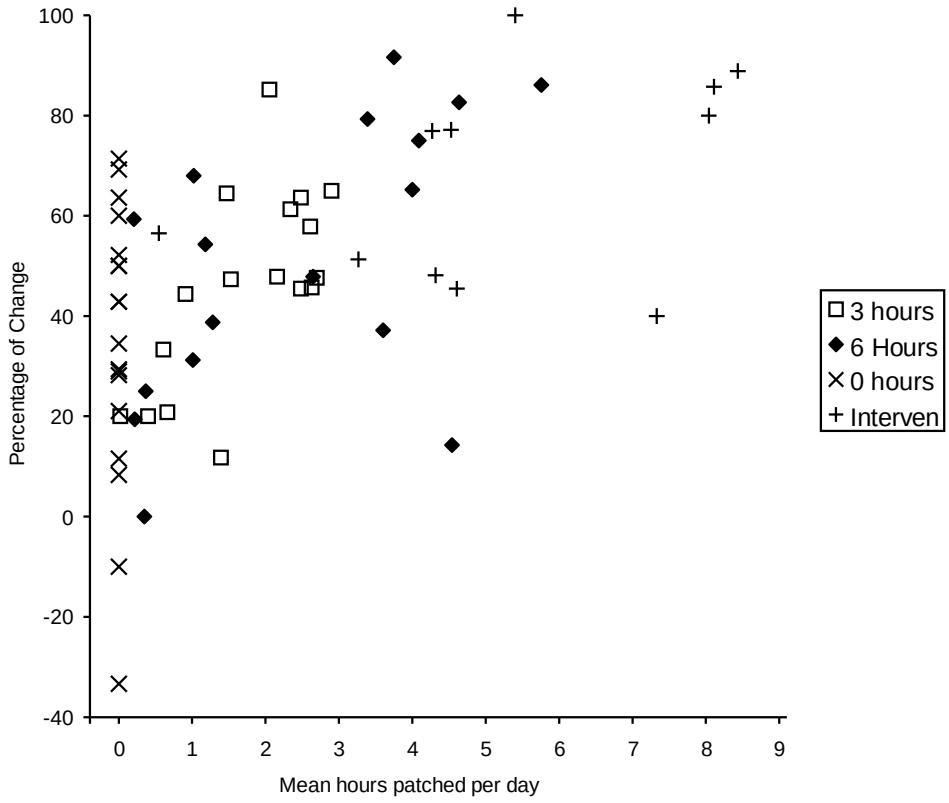


Figure *7.1 dose response of effectual patching in relation ot the percentage visual improvement with occlusioon. Open squares, filled diamonds and crosses represent data from our RCT study (chapter 4) with additions plots of the in educational interventions study represented in crosses.*

Discrepencies between their study and ours is the variable duration of patching in the study by Stewart et al. study compared to our fixed amount of 12 weeks patching in our study. The mean duration of patching in their study overall at 9 weeks compared to 12 weeks in our patching phase. It would be important to establish whether dose-response curves differ for different types of amblyopia. This is an important area of future research.

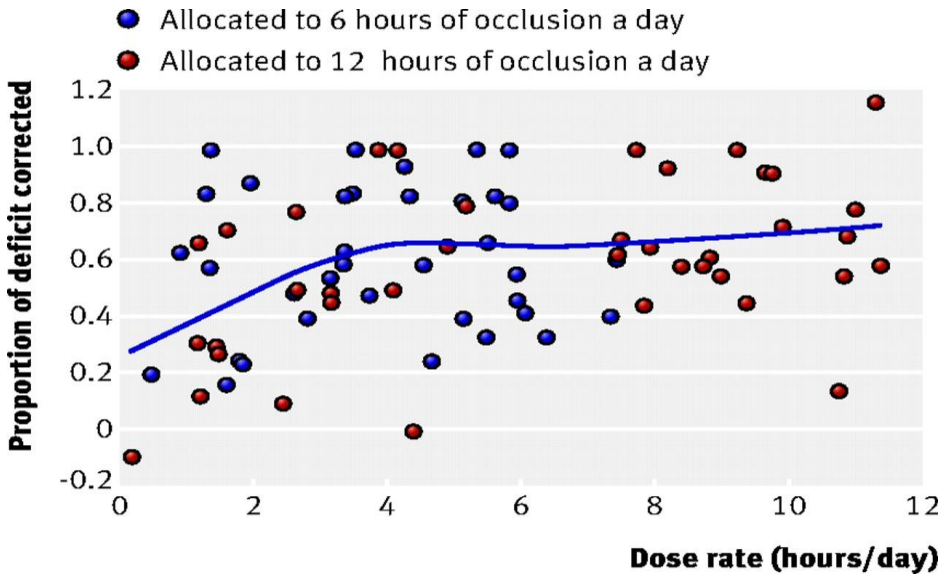


Figure 7.2 *proportion of deficit corrected in relation to dose rate to prescribed patching hours. (Reproduced Stewart et al. (2007) BMJ 335 (7622):707-13)*

Regarding cumulative dose response to patching, (Stewart et al (2007, IOVS) found only 9 children out of 72 were patched for more than 400 hours. This compared to other studies that varied between 50 hours (Woodruff et al., 1994a, Stewart et al., 2005) and 400 hours (Cleary, 2000). The lack of established regimens continue to undergo variable amounts of prescribed occlusion where for example in some studies, age is not relevant to treatment.

In an earlier ODM study conducted by Stewart et al. (2004) they found that increasing the dose rate beyond 2 hours per day did not result in further visual improvement in the final visual outcome compared to longer hours (Stewart et al., 2004b). Whereas, in their later study (2007) the same group demonstrated a plateauing effect beyond 4 hours in

the two longer groups (Stewart et al., 2007b, Stewart et al., 2004b). A possible explanation for a plateau in the dose–effect relationship is that the VA increases up to a certain level beyond which saturation occurs. The existence of a plateau needs to be clarified with further research since most patients included in the study by Stewart et al. are anisometropes.

Menon et al. (2005) has suggested that successful treatment would require a total cumulative dose of 1,089 hours including maintenance patching (Menon et al., 2005) to reduce majority of the amblyogenic deficit. However, this study lacked objective evidence as they did not use an occlusion dose monitor and analysis was based on treatment regimens rather than actual hours patched.

Several studies show more rapid improvement at beginning of treatment. Our study illustrated a slightly greater rate of increase in visual acuity in the first 3-weeks after commencing treatment. Other studies found greater effectiveness in patching occured within the first two months (Wallace et al., 2006, Stewart et al., 2007b, Holmes et al., 2005), in the first three months (Neumann et al., 1989, Oliver et al., 1986, Lithander and Sjostrand, 1991) or within the first six months (Cleary, 2000) of treatment. This implies that possibly a more effective way to treatment amblyopia would be to implement a more intense patching regimen within the first few weeks. This would also shorten treatment, hence minimise costs, and reduce psychological impact of patching.

Clarke et al. found that delaying treatment until the age of five years did not significantly affect visual outcome since their randomised study was designed with the intention to delay treatment with glasses or patching or both. However Clarke did not find

a signficant difference in mild amblyopes (Clarke et al., 2003). Although previous studies found age was a factor of final visual outcome (Stewart et al., 2007b), our RCT study (chapter 4) found that age was not a factor affecting final visual outcome. This also contradicted the study conducted in chapter 2. This could possibly be due to the smaller sample size used in chapter 4. In their later study, Stewart et al. (2007) found that in contrast, age was a factor of significant increases in vision due to the change in plasticity in the visual system. They suggest that different levels of effective hours of patching are required according to age group (used occlusion monitors) stating achievable visual acuity is best (0.20 logMAR gain of visual improvement) with 170 hours of patching in children at age 48 months and longer with 236 hours at 72 months (Stewart et al., 2007b, Stewart et al., 2007a).

Refractive adaptation in our study was 6 weeks compared to the longer periods of refractive adaptation in other studies (Stewart et al., 2004a, Clarke et al., 2003). Most of the literature now recommends an extended refractive adaptation period before the second stage of patching treatment begins. It is still not clear, however, whether it is more beneficial to commence patching during this refractive adaptation period since the nervous system may be more plastic during this time and compliance may be better as the parents perceive that vision is improving. Studies involving different refractive adaptation periods for each amblyopia type using objective monitors designed to monitor glasses wearing would assist in establishing the role of refractive adaption for amblyopia treatment.

The use of diaries to assess compliance are more limited compared to ODMs (Nucci et al., 1992, Cleary, 2000). In other disciplines, electronic monitoring of asthma in children demonstrated that mean compliance was 58% whereas diaries greatly exaggerated

compliance to treatment reporting more than 90% compliance (Milgrom et al., 1996). However, in our RCT study (chapter 4) the diary times recorded were fairly reliable. A reason for this is that parents/guardians may be aware that occlusion treatment was being monitored (Fulton and Mayer, 1988, Leiba et al., 2001).

7.5. How can we Improve Compliance?

We performed interviews to investigate reasons as to why compliance is poor that ultimately lead to deficits in final visual outcome. One of the main factors affecting compliance was the level of distress imposed on the child and family to ensure adherence to patch. Implementations used by the parents were strategies such as rewards (stickers, sweets or a favourite toy). Parents also achieved success by incorporating patching regimes as a normal everyday activity. Encouragement by siblings was important or putting a patch on a favourite cuddly toy. In our intervention study (chapter 6) we developed a sticker chart supported with stickers and the Amblyopia Passport to use everday of the week. The use of stickers would encourage the child to patch as they could see their own compliance towards treatament and the information from the clinic visits would give necessary feedback to parents regarding improvements in visions thus creating a positive control towards the therapy.

The lack of understanding of amblyopia and the rationale behind treatment influenced patching treatment (Loudon et al., 2006b, Newsham, 2000, Smith et al., 1994, Gillum and Barsky, 1974). There was also deficient communication between the clinician, parent and child (Wilis, 1980 - 1981). To overcome these problems suitable booklets were

produced (chapter 6) that describes the disease to the parent, child, teacher and siblings. Areas covered included, questions and answers related to what amblyopia (referred to as a lazy eye in booklets) is and the common misconception between a lazy eye and a squint. Possible aetiologies of amblyopia and how the disease can be treated. Parents in the interviews highlighted problems and strategies to overcome difficulties, especially when they felt treatment was not working, the distress, patching as daily routine, stickers for patches as a positive activity, this information was used as feedback to develop useful information in the booklets entitled "Advice on Patching for Parents" and in the quotation booklet (chapter 6)

Parents perceived 'self-efficacy' (i.e. that they see the effects on vision of their own patching) as positive whereas disruption in the child's activities was perceived as negative (Searle et al., 2002). Incorporating patching as routine during school time was difficult as parents felt the teachers could not fully supervise. Therefore, information booklets for teachers were designed with additional information such as helpful activities involving hand-eye coordination such as reading, writing, drawing, computer work and physical activities such as playing catch. We also used a storybook with pictures and text of information that could be understood by the child and send a postive message (chapter 6).

Initiating these new methods of improving compliance by creating informative leaflets to generate awareness of amblyopia and an understanding of its treatment (Newsham, 2000, Newsham, 2002, Nucci et al., 1992) may contribute towards better prognosis in achieving a better visual outcome. Our preliminary study suggests that using

educational intervention for amblyopia reduces the number of poor compliers and drop-outs (Figure 6.7, chapter 6).

The appearance of wearing the eye patch has known to influence the child's well being as was clear when we interviewed parents in our study. Some parents felt their children were subjected to teasing and became isolated from family and peer group for fear of victimisation. The ALSPAC group, found that early detection and intervention of occlusion treatment could reduce the likelihood of the child being a victim of verbal abuse and bullying by almost 50% (Williams et al., 2006, Horwood et al., 2005). These findings imply that effective strategies need to be implemented not only to ensure the achievement of good vision but also to lessen the psychological distress involved (Rahi et al., 2002). The ALSPAC study group found that early pre-school vision screening reduced the deficit considerably (Williams et al., 2002, Williams et al., 2003). Similarly, detection below four years of age has been shown to be effective in reducing the deficit (Williams et al., 2001, Oliver and Nawratzki, 1971) possibly because of the psychological effect of patching later in life.

Simonsz et al. (1999) performed an investigative study of compliance to patching treatment using ODMs showed that treatment was mediocre and infrequent ranging from as low as five minutes using ODMs (Simonsz et al., 1999, Chopovska et al., 2005). They have also developed educational material composed of a story booklet without text in black and white, coloring plates and sticker chart for their diaries. In the same study, the group found that poor level of parental education, with limited or no use of the national language and level of parental education were strong predictors of the final visual outcome (Loudon et al., 2006b).

The Rotterdam Group conducted studies using their compliance-enhancing programe (2006, 2007) (Loudon et al., 2006b, Loudon et al., 2007, Loudon et al., 2006a). They demonstrated a significant improvement in compliance (78%). They also suggested good interaction between the parent, patient and clinician with continuous positive reinforcements, counselling (Menon et al., 2005) coping mechanisms (Wackerhagen and . 1990) is important. Our study design commited extra one-to-one clinical time, between the treating therapist (the main author MA) and the parent to discuss problems and queries related to patching as a positive reinforcement. The Rotterdam group (2006) demonstrated that patching significantly improved using educational intervention treatment packs for amblyopia treatment. In the first week of objective monitoring the intervention and reference group patching groups showed compliances of 78% and 32%, respectively (Loudon et al., 2006b).

Searle et al. (2002) investigated the distress associated with the physical appearance and psychological distress associated with a manifest strabismus in adults using the Protection Motivation Theory. They found that, following strabismus surgery, psychological well-being improved as a sense of their appearance improved (Searle et al., 2002).

Another form of enhancing occlusion therapy is to administer highly demanding visual tasks while patching under a controlled environment. The visual tasks have been developed using a computer based reality system known as the interactive binocular treatment (I-BiT) system. The system involves binocular training using 3D games and videos (Waddingham et al., 2006). It requires therapy to be performed within allocated hospital appointment times. Cleary (2007) in a small study found visual improvement in 7

of 12 (58%) patients using this method (Cleary et al., 2007). Alternative provisions enhance amblyopia trreatment suggested in literature is appointing an 'Amblyopia Nurse', or organising a 'Patch Club' for parents and patients to meet and discuss their experiences (Donnelly et al., 2005). However, thes studies require further investigation of effective use, especially since deliverance of such implementations in the management of amblyopia is likely to be expensive for the health service.

Preliminary investigations of methods used to improve effective patching for amblyopia using educational programs show promising results. Improved amblyopia educational packs to reinforce knowledge supported with clear instructional dialogue from clinicians could play an important role in the future in improving compliance and visual outcomes of treatment .

7.6. Strengths and Weaknesses of Each Study in the Thesis

7.6.1. Chapter 2. Outcome of amblyopia treatment:

Strengths:

1) Large sample size.
2) Data collection was representative of an eight years period.
3) Comprehensive collection of data that included all visits from the date of first presentation to clinic. Data collected included number of prescription changes for glasses, number of different orthoptists seen.

4) Repeatability of visual acuities over longer treatment duration may have sustained visual acuity.

Weaknesses:

1. It is possible that patient notes may not be missing at random. For example, using incomplete notes as exclusion criteria could lead to exclusion of poor compliers to treatment if this is related.
2. Measurement bias: This study has indicated that there was no consistent method used for visual acuity testing to assess patients with amblyopia, especially in the younger age group. Tests chosen depended on the treating orthoptist, the child's intelligence and the cooperation to the test. These can be considered as a possible weakness as we analysed the overall visual acuity from the beginning to the end of treatment and not concentrated on specific vision tests used. However, we excluded preferential looking (Cardiff Acuity Cards) from analysis as these test have shown to provide a poor estimate of visual acuity. Several testing methods of visual acuities were used, over the course of treatment, to achieve an overall outcome in vision.
3. Selection bias: Since not all eligible patients were not include (only 66.4%) there is a possibility that the selection is not representative of the database as a whole. For example the fact that patients were selected starting in January of each year could lead to bias. However the use of multiple samples taken over a period of eight years, rather than analysing a cohort of amblyopes who presented in one year should lead to the sample being more representative of this period of time (Pocock, 1983) .

4. Bias could result from the Leicester demographic being different to other parts of the UK.
5. Another possible bias to this study is confounding bias. The statistical model used to find predictors of improvement in vision in the amblyopic eye include a number of predictors such as patient's age, no of orthoptist seen, type of amblyopia that may not be independent of each other.

7.6.2. Chapter 4. The RCT of strabismic and mixed amblyopia using occlusion dose monitors to record compliance

Strengths:

1) The study aimed to follow the stringent requirements laid down by the CONSORT agreement (see ref)
2) Random allocation of patients to specific treatment groups.
3) Use of a control group with only glasses wearing.
4) Absolute occlusion measured using novel electronic dataloggers.
5) The study design involved frequent visits.
6) Consistency in using one examiner (MA) to perform visual acuity measurements.
7) Subrandomisation of two age groups into each category.

Weakness:

1) Randomisation to allocation was carried out using shuffled envelopes rather than a formal randomisation e.g. using a computer or permutated blocks. Although subjects were allocated to specific treatment groups, the subjects were not randomly selected from a sample frame in the first instance
2) Relatively small sample size.
3) Initial vision may have been an important predictor of increased visual acuity and should be sub-randomized.
4) Information bias: Patients may have been more inclined to comply as they were aware that recordings of patching times were made. However, the data between the diary and absolute patching times were similar.
5) Electronic data logger failure in some recordings (a more reliable ODM is required).
6) Drop out bias: Patients were not lost at random
7) Placebo affect was impossible, as patients knew what type of treatment they were having.
8) Repeatability bias: Repeatability of VA, every three weeks may have shown improvements in vision due to patients being more likely to cooperate with testing and being more used to testing procedure.
9) Ascertainment bias: Study was not masked. Examiner (MA) was not blind to the study and no other visual acuity measurements was taken using an independent examiner.

7.6.3. Chapter 5: Problems with compliance and the understanding of amblyopia and its treatment

Strengths:

1) This study was carried out using semi-structured interviews. This gave potential to be able to share information more easily at different times during the interview rather than having strict criteria to the process in asking questions.
2) Conducting interviews at home, parents were more likely to be honest about their experiences of the treatment inside their own home.
3) Thorough analysis (although time consuming) carried out required sifting and scrutinizing data with the qualitative analysis software QSR, N5.

Weakness:

1) Detection bias: No formal randomisation process was carried out. Therefore patients were selected based on ad-hoc selection by the main researcher attending the eye department.
2) Recall bias: Information gathering required recall from the memory of parents. Many parents also had the condition themselves during childhood which could lead to a bias based on their own personal experiences.
3) Bias during interview. The interviewer is more assertive in finding and classifying exposure as the responses are directly from the affected population (Bayona M and C, 2004).

7.6.4. Chapter 6: Improving amblyopia treatment: A need for an educational intervention program: Pilot study

Strengths:

1) Randomised controlled trial study using electronic data loggers (see points mentioned in chapter 4).
2) Measurement bias minimised, as it is a single-masked study. An independent orthoptist provides a second measure of VA unaware which treatment group the patient was randomly allocated to.
3) Intervention materials based on results of interviews.

Weakness:

1) Randomised controlled trial study using electronic data loggers (see points mentioned in chapter 4).
2) Complex intervention. Difficult to ascertain which component of the study was more influential towards treatment i.e. booklets or patches (Craig et al., 2008).
3) Intervention pack comprised with booklet based on the findings from one study.
4) Unconscious bias: Intervention required a one on one session on the second visit with the orthoptist. The additional clinic time allocated and nicer treatment of the patients could have led to better compliance to treatment in the intervention group.
5) Sample size is too small although only a preliminary study.

7.7 Future Studies

Our pilot RCT of preliminary study, using a more intensive educational program will perhaps provide objective evidence of dose-response in over a rigorous course of treatment to increase compliance to occlusion once final data is published.

Future studies that could be advantageous in providing evidence-based treatment could include:

- Use of interventional materials on larger sample cohort
- Investigate ideal dose for patients with different age groups, different levels of visual acuities thresholds in the amblyopic eye and type of amblyopia
- Prescribe longer hours of patching supplementing treatments of the educational intervention material
- Evidence based studies for optimal refractive periods for depth of visual loss at initiation of treatment, age, amblyopia type
- Other modalities such as amblyopia treatment investigating binocular functions
- Producing smaller ODMs
- Comparative investigation for refractive adaptation in relation to patching. What is better as the first line of treatment?
- The relationship between socioeconomic background and motivation / compliance.

7.8 SUMMARY

Amblyopia is a common disorder in childhood affecting up to 5% of the childhood populace (Attebo et al., 1998) that, if not treated will continue into adulthood (Rahi et al., 2002). Amblyopia rarely occurs in isolation but is commonly associated with a strabismus, refractive error or a combination of both. The disease is reversible. However, outcomes to treatment are currently sub-optimal as shown in our study of 322 previously treated amblyopes with only 73% of subjects reaching visual acuity of 6/12 overall and only 64% in the mixed group whereas figures reaching visual acuity levels of 6/6 overall was 22%. Our randomized controlled study demonstrated insignificant differences in visual outcomes in the three treatment groups: 0-hour (0.24 logMAR), 3-hours (0.29 logMAR) and 6-hours (0.34 logMAR). This was due to poor compliance, where mean effective patching time per day in the 3-hour and 6-hour groups (with percentage compliance) was 1 hour and 43 mins (57.5%) and 2 hours and 33 minutes (41.2%), respectively. However, there was evidence of a dose-effect response to patching treatment with an improvement of 8.3% for every hour patched.

We explored issues as to why compliance is poor using questionnaires. Some parents expressed the lack of information, emotional anxiety induced, teasing, the overall appearance of the patch and lack of credibility of treatment. To overcome these problems we developed an educational intervention package to enhance amblyopia treatment. The package contains useful information suitable for parents, children and teachers to assist with understanding the disease and to send a positive messages of patching. The preliminary result of this study looks promising.

Our findings have been part of a new and exciting wave of research using objective measurements of compliance to provide invaluable new evidence for the value of amblyopia treatment. The development of new methods to enhance treatment could potentially change current practice nationally and internationally.

APPENDICES

APPENDIX A: List of Abbreviations

ATS	Amblyopia Treatment Studies
DS	Dioptre Spheres
ERPAG	The Electronic Recording of Patching for Amblyopia Group
ODM.....	Occlusion Dose Monitor
LogMAR	Logarithm of the Minimal Angle of Resolution
MOTAS	Monitored Occlusion Treatment of Amblyopia Study
PEDIG	Pediatric Eye Disease Investigator Group
QSR N5	Qualitative Data Analysis Software (Ned 5)
SE	Spherical Equivalent
VA	Visual Acuity
VA*as*	Visual Acuity of amblyopic eye at the start
VA*ae*	Visual Acuity amblyopic eye at the end
VA*de*	Visual Acuity: dominant eye at end
VA*fe.*	Visual Acuity of fellow eye at the end

APPENDIX B:

Group	Patient	Age	Deviation	Amblyopia	Refraction	Refraction	Amblyopic Eye VA	Amblyopic Eye VA	Dominant Eye VA	Dominant Eye VA
	ID			Type	Amblyopic Eye	Dominant Eye	Visit 1	Visit 5	Visit 1	Visit 5
0 hours	1	3.0	RCS	Strabismus	+2.00-0.50x180	+2.50-0.50x180	0.875	0.625	0.000	0.025
	2	5.4	LCS	Mixed	+8.25-3.00x5	+6.25-1.75x180	0.600	0.100	0.175	-0.100
	3	3.9	RCS	Strabismus	+5.50	+5.50	0.725	0.475	0.075	0.000
	4	5.0	RCS	Strabismus	+7.00-1.50x145	+7.50-2.50x45	0.275	0.300	0.000	0.025
	5	4.6	RDS	Mixed	+2.25-1.00x165	plano	0.300	0.100	-0.100	-0.100
	6	4.5	RCS	Strabismus	+2.75	+2.00	0.475	0.375	0.000	0.000
	7	4.1	LCS	Mixed	+4.50-2.25x170	+2.25-1.00x30	0.875	0.500	0.275	0.000
	8	3.1	RCS	Strabismus	+5.25+0.75x80	+5.50	0.300	0.275	0.000	0.000
	9	6.4	RCS	Strabismus	+3.00+0.25x90	+2.25	0.275	-0.025	-0.100	-0.300
	10	5.4	RCS	Mixed	+3.25-1.00x180	+1.50-0.75x180	0.800	0.400	0.000	0.000
	11	5.7	LCS	Strabismus	+1.50-1.00x170	+1.25-0.75x180	0.550	0.100	0.000	-0.100
	12	8.7	LCS	Mixed	+3.75+2.25x95	+0.25	0.775	0.500	-0.100	-0.200
	13	4.8	LCS	Mixed	+6.50-0.50x25	+5.25-0.50x160	0.650	0.575	0.050	0.000
	14	3.6	RCS	Strabismus	+2.50-0.50x180	+2.25-0.75x180	0.300	0.400	0.000	0.000
	15	3.5	RCS	Strabismus	+1.50-0.50x180	+1.00-0.50x180	0.875	0.600	0.000	-0.075
	16	4.8	RCS	Mixed	+4.75-1.50x10	+3.25-0.75x180	0.525	0.300	0.000	0.000
	17	4.8	RCS	Strabismus	+3.25-0.75x180	+2.50-0.75x170	0.650	0.200	0.000	-0.100
	18	2.9	RCS	Strabismus	+3.00-0.75x90	+2.50-0.75x90	0.875	0.525	0.350	0.325

Raw data of patient details analysed in the study Chapter 4 (0-hour group).

Group	Patient	Age	Deviation	Amblyopia	Refraction	Refraction	Amblyopic Eye VA	Amblyopic Eye VA	Dominant Eye VA	Dominant Eye VA
	ID			Type	Amblyopic Eye	Dominant Eye	Visit 1	Visit 5	Visit 1	Visit 5
3 hours	1	3.4	LCS	Mixed	+8.00	+6.50+1.50x90	0.775	0.275	0.100	0.000
	2	3.1	LCS	Strabismus	+4.00+2.25x90	+3.50+1.00x90	0.850	0.375	0.000	0.075
	3	4.0	LCS	Strabismus	plano	plano	0.475	0.200	0.000	0.000
	4	4.5	LCS	Mixed	+4.25-0.75x10	+1.50	0.550	0.300	0.000	0.000
	5	3.8	LCS	Strabismus	+1.25	+1.25	0.500	0.175	0.000	0.000
	6	3.6	LCS	Mixed	+6.50-2.00x180	+4.00-1.00x180	0.875	0.475	0.075	0.000
	7	3.8	RCS	Strabismus	+1.50	+1.25	0.450	0.100	0.075	-0.100
	8	6.6	LCS	Strabismus	plano	plano	0.375	0.100	0.000	-0.200
	9	5.4	LCS	Strabismus	+3.50-1.75x165	+3.25-1.00x15	0.425	0.375	0.100	0.000
	10	4.0	LCS	Strabismus	+7.50+1.00x90	+7.50+1.00x90	0.800	0.550	0.100	0.275
	11	4.2	LCS	Strabismus	+4.00-0.50x15	+3.00-0.50x10	0.575	0.475	0.075	0.075
	12	3.5	LCS	Strabismus	+2.75	plano	0.600	0.475	0.000	0.000
	13	6.1	RCS	Strabismus	+3.50	+3.00	0.475	0.250	0.000	0.000
	14	4.4	LCS	Strabismus	+2.50+0.75x177	+2.00+0.50x91	0.775	0.550	0.100	0.100
	15	4.6	RCS	Mixed	+5.50-1.25x80	+2.50	0.875	0.700	0.025	0.000
	16	4.4	RCS	Mixed	+3.75	+1.50	0.675	0.100	0.000	0.000
	17	6.2	RDS	Mixed	+5.00-0.75x90	plano	0.575	0.275	-0.075	-0.100

Raw data of patient details analysed in the study Chapter 4 (3-hour group).

Group	Patient	Age	Deviation	Amblyopia	Refraction	Refraction	Amblyopic Eye VA	Amblyopic Eye VA	Dominant Eye VA	Dominant Eye VA
	ID			Type	Amblyopic Eye	Dominant Eye	Visit 1	Visit 5	Visit 1	Visit 5
6 hours	1	6.6	LCS	Mixed	+3.75	+0.75	0.375	0.100	-0.075	-0.200
	2	5.2	RCS	Strabismus	+3.00	+2.50	0.700	0.600	0.000	0.000
	3	3.2	RCS	Mixed	+5.50-1.50x90	+1.25+0.50x90	0.875	0.550	0.075	0.000
	4	5.3	RCS	Strabismus	2.75	2.25	0.275	0.000	0.000	-0.025
	5	4.7	LCS	Mixed	7.25	5.75	0.875	0.400	0.100	0.000
	6	4.5	LCS	Strabismus	0.25	0.25	0.800	0.225	0.100	0.075
	7	5.8	LDS	Mixed	+3.00-0.75x180	plano	0.500	0.325	-0.100	-0.200
	8	4.3	RCS	Strabismus	+3.50-1.50x5	+3.00-1.25x175	0.575	0.100	0.000	0.000
	9	3.2	RCS	Strabismus	plano	plano	0.900	0.725	0.000	0.000
	10	4.3	LCS	Strabismus	+9.00-0.75x160	+9.00-0.75x165	0.575	0.200	0.000	0.000
	11	4.0	RCS	Mixed	+8.75-2.00x180	+5.00-0.50x180	0.875	0.400	0.000	0.075
	12	4.5	LCS	Strabismus	+6.25-0.75x170	+5.25-0.50x20	0.775	0.475	0.000	0.000
	13	3.3	LCS	Strabismus	+3.00	+2.75	0.875	0.100	0.175	-0.025
	14	4.0	LCS	Mixed	+3.25	+1.00	0.875	0.875	0.075	0.000
	15	8.0	LCS	Strabismus	+1.75	+1.75	0.300	0.000	-0.175	-0.100
	16	5.0	LCS	Mixed	+10.75-0.50x180	+9.00-0.50x180	0.775	0.525	0.000	-0.025
	17	3.6	LCS	Strabismus	+2.50	+2.25	0.850	0.425	-0.100	0.225

Raw data of patient details analysed in the study Chapter 4 (6-hour group).

APPENDIX C:

Interview Questions/Prompts & QSR N5 Software,. (chapter 5)

Can you tell me how you came to be asked to patch you child?

How was the diagnosis made that your child needed patching?

Can you tell what they did and who was involved?

When was the diagnosis made?

How did you feel about being asked to patch?

What are the achievements of patching your child?

What do you think of the information you received from the clinic about the reasons for patching?

Were you told what the condition was or what it is called?

Can you tell me what you were told about why patching was advised?

How long (weeks, months or year) will you have to patch you child for?

What would you expect from the treatment?

How do you think the treatment works?

How many hours have been prescribed?

How have you managed with the patching?

How many hours do you manage to achieve per day?

Do you think the results depend on how many hour you patch? Do you think the results depend on how regularly you patch?

What would happen if you did not patch at all?

What is a lazy eye?

What is a squint?

What have your experiences of patching been like for your child and yourself?

What attempts did you do to manage the treatment?

Interview Questions/Prompts for children

Which eye is your bad or poorly eye?

Do you know why you have to wear a patch?

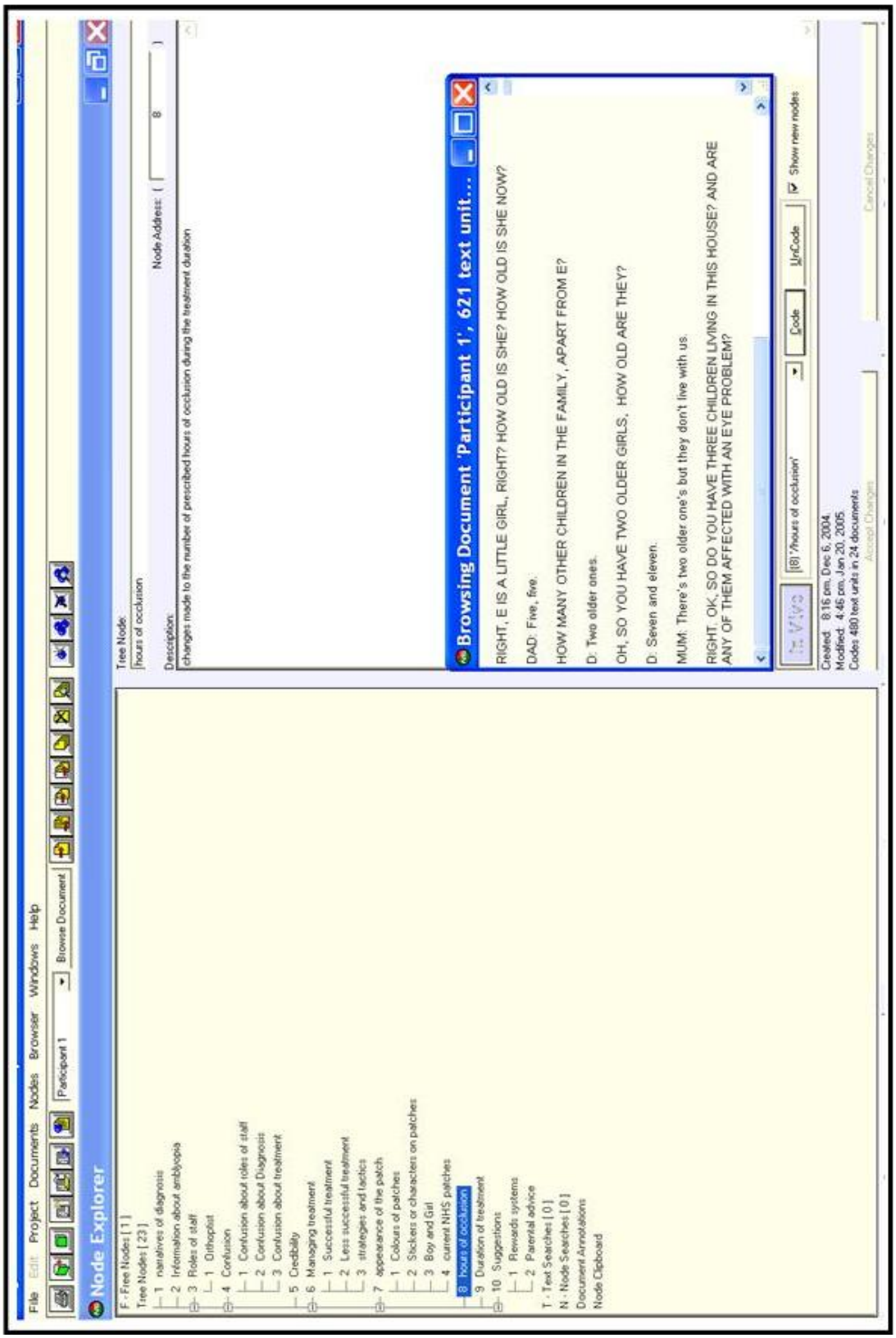
Do you patch at school or at home?

Does the school help you?

Do you want to see other kinds of patches?

Which ones would you like to wear?

QSR N 5 software



APPENDIX D:

List of Publications

(A) **Awan M**, Proudlock F, Grosvenor D, Chaudri I, Sarvananthan N, Gottlob I. The Outcome of Amblyopia Treatment: A Retrospective Study of 322 Children. British Journal Ophthalmology *(in press)*

(B) Dixon-Woods M**, Awan M,** Gottlob I. Why is Compliance with Occlusion Therapy for Amblyopia So Hard ? A Qualitative Study. **Archives of Disease in Childhood.** 2006; 91(6): 491-4.

(C) **Awan M,** Proudlock FA, Gottlob I. A Randomised Controlled Trial of Unilateral Strabismic and Mixed Amblyopia Using Occlusion Dose Monitors to Record Compliance. **Investigative Ophthalmology & Visual Science** 2005; 46(4):1435-9.

APPENDIX E:

Meetings (National and International) attended

Posters and Papers Presented at Scientific Meetings

Pradeep A, **Awan M,** Bush G, Proudlock F, Gottlob I. Oral Presentation. Interventional Program to Improve Amblyopia Treatment: Results from a Randomised Controlled Study. 8th Alcon Research Symposium, 11th April 2008, UHL, Leicester, UK

Awan M, Proudlock F, Gottlob I, Oral Presentation. The Occlusion Dose Monitor Research Project. The British and Irish Orthoptic Society (Northern Branch), 4 Oct 2006, Warrington, UK

Awan M, Proudlock F, Gottlob I, Oral Presentation. A RCT of Unilateral Anisometropic Amblyopia Using Occlusion Dose Monitors to Record Compliance. The Association for Research in Vision and Ophthalmology (ARVO) 30 Apr – 4 May 2006. E-Abstract 4311, Fort Lauderdale, Florida. USA

Awan M, Proudlock F Gottlob I, Oral Presentation. A RCT of Anisometropic Amblyopia Compared with Strabismic Amblyopia Using the Occlusion Dose Monitor. Alcon Research Symposium. 3 Mar 2006, UHL, Leicester. UK

M. Awan, M. Dixon-Woods, I. Gottlob. Poster Presentation. Can Patching Be Improved in Amblyopia Treatment? May 1-5 2005: The Association for Research in Vision and Ophthalmology (ARVO) E-Abstract 5707, Fort Lauderdale, Florida. USA

M. Awan, M. Dixon-Woods, I. Gottlob. Oral Presentation. Can Patching Be Improved in Amblyopia Treatment?. Orthoptic In-Service Training Day, Apr 2005, Leicester, UK

M. Awan, M. Dixon-Woods, I. Gottlob. Oral Presentation. Can Patching Be Improved in Amblyopia Treatment?. Alcon Research Symposium Mar 2005, Leicester, UK

Awan M, Proudlock F Gottlob I, Oral Presentation. "The Effect and Compliance of Strabismic Amblyopia Monitored With the Occlusion Dose Monitor. ESA (European Strabismological Association), 1-4 June 2004, Izmir, Turkey

M.B. Awan, F.A.Proudlock, I.Choudhuri, D.Grosvenor, N.Sarvananthan, I.Gottlob. Poster Presentation. Outcome of amblyopia treatment The Association for Research in Vision and Ophthalmology (ARVO)April 25-29 2004 45: E-Abstract 4998, Fort Lauderdale, Florida. USA

Awan M, Gottlob I, Proudlock F. Oral Presentation. The Effect and Compliance of Strabismic Amblyopia Monitored with the Occlusion Dose Monitor.. Alcon Research Symposium Feb 2004, UHL, Leicester, UK.

Awan M, Proudlock F, Sarvananthan N, Gottlob I, Poster Presentation. Outcome of Amblyopia Treatment. 8th Nottingham Eye Symposium and Research Meeting, Jan 2004, Nottingham, UK

Awan M, Orthoptic Treatment of Accommodative Esotropia, Oral presentation. Sept 2003, Dept of Ophthalmology. UHL, Leicester, UK

Awan M, Gottlob I, Proudlock F. Poster Presentation. The effect and compliance of strabismic amblyopia monitored with the occlusion dose monitor. Royal College of Ophthalmologist Annual Congress 20-22 May 2003, Birmingham, UK

Awan M, Proudlock F, Gottlob I. Poster Presentation. The Effect and Compliance of Strabismic Amblyopia Monitored with the Occlusion Dose Monitor.. The Association for Research in Vision and Ophthalmology (ARVO)May 4-9 2003 44: E-Abstract 4797, Fort Lauderdale, Florida. USA

Awan M, Gottlob I, Proudlock F. Oral Presentation. The effect and compliance of strabismic amblyopia monitored with the occlusion dose monitor. Alcon Research Symposium Jan 2003, UHL, Leicester,UK

Awan M. "My Saudi Arabian Experience". Oral Presentation. South West Thames and In-service Meeting 8 May 2001. Surrey and Crawley Hospital, Crawley. UK

M Awan. Oral Presentation. The Graphical Presentation of the Post-Operative Diplopia Test. Oct 1999. Saudi Ophthalmology Congress, Riyadh, Saudi Arabia.

APPENDIX F:

PRIZES AWARDED BASED ON THESIS

Awards:

M.Awan, M Dixon-Woods, I Gottlob. Oral Presentation. Can Patching be Improved in Amblyopia Treatment?. *Awarded* ***Vernon's Trophy Research Award*** *for "Best Ophthalmologic Clinical Research Presentation",* 9th Nottingham Eye Symposium and Research Meeting, Jan 2005 Nottingham, UK

Awan M, Gottlob I, Proudlock F. Poster Presentation. The Effect and Compliance of Strabismic Amblyopia Monitored with the Occlusion Dose Monitor. Awarded; ***Ernest Frizelle Prize*** *for "Best Research Poster Presentation".* Sept 2003. UHL NHS Trust, Leicester, UK

Awan M, Gottlob I, Proudlock F Oral Presentation. The Effect and Compliance of Strabismic Amblyopia Monitored with the Occlusion Dose Monitor. *Awarded* ***Vernon's Trophy Research Award*** *for "Best Ophthalmological Research Presentation",* 7th Nottingham Eye Symposium and Research Meeting, Jan 2003 Nottingham, UK

Pradeep A, **Awan M,** Bush G, Proudlock F, Gottlob I. Oral Presentation. Interventional Program to Improve Amblyopia Treatment: Results from a Randomised Controlled Study. 8th Alcon Research Symposium, 11th April 2008, UHL, Leicester, UK. ***Best Clinical Research Presentation (Awarded to the first author of this presentation)***

APPENDIX G:

PUBLICATIONS

Addenda attached

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