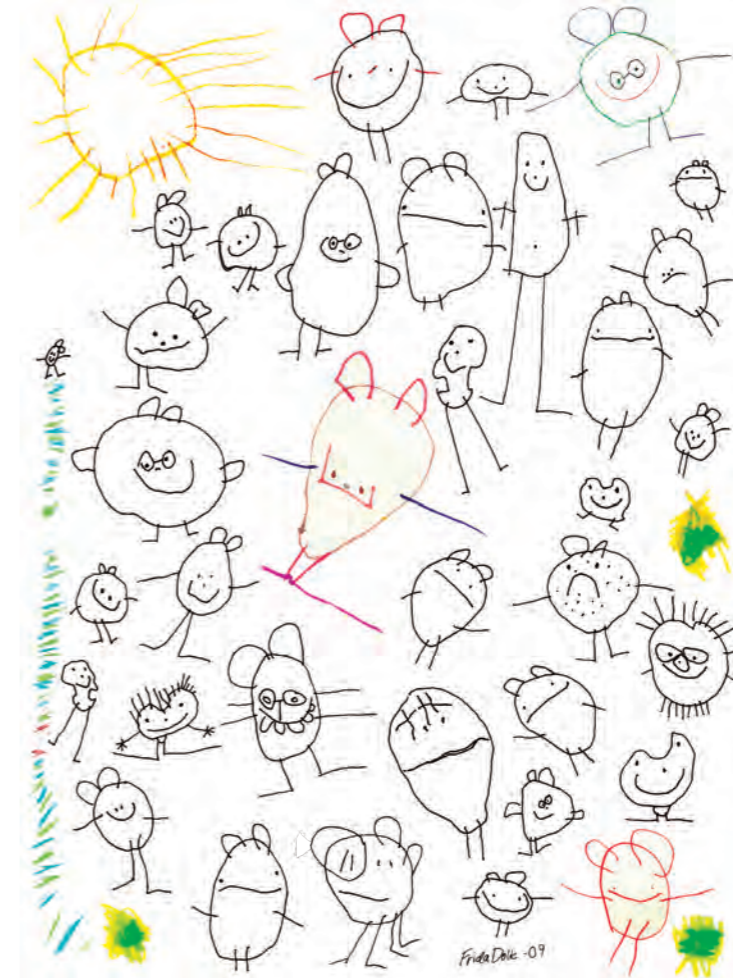


Thesis for doctoral degree (Ph.D.)
2009

AMBLYOPIA IN CHILDREN: THERAPY AND FOLLOW-UP



Pia Agervi

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Stockholm 2009

The picture on the hardcover shows different figures drawn by Theodor and Lukas Dolk at the age of 4-5 years, created by Frida Dolk.

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*To my dear mother Birgitta an in memory of
my dear father, Ted Agervi*

ABSTRACT

Amblyopia, the leading cause of unilateral visual impairment in children, is caused by inadequate stimulation of the visual system during the sensitive periods of visual development in childhood. Cataract, anisometropia and strabismus are well-known causes of amblyopia.

Bilateral congenital cataract is a common cause of treatable childhood blindness. Early surgery and intense postoperative amblyopia therapy can result in good visual acuity (VA). In the developing world, the possibilities of such postoperative care are limited. **Study I** was a prospective 2-year follow-up study. We evaluated the refractive and visual outcome after surgery for paediatric cataract in 65 children aged 3 to 15 years. No postoperative correction with spectacles or occlusion was possible due to the socioeconomic environment in the Ukraine. We found a substantial decrease in the immediate high astigmatism that developed postoperatively, and the preoperative VA improved significantly despite the lack of postoperative amblyopic treatment.

The diagnosis and follow-up of amblyopia depend on measuring the best-corrected visual acuity (BCVA) with optotypes on test charts. However, studies have shown that VA testing using conventional optotypes is insensitive for detecting subtle defects in visual function. **Study II** evaluated the foveal function in the eyes of 24 children treated for monocular amblyopia and in 25 control children. The children underwent measurement of the BCVA using a standard decimal chart, the TriVA method at different contrast levels and the Rarebit Fovea Test (RFT). The amblyopic eyes had significantly lower results when the BCVA was evaluated with the decimal chart and the TriVA test compared to the fellow eyes and the control eyes. When foveal function was evaluated with the RFT, no significant difference was found between the amblyopic eyes and the fellow eyes, although both the amblyopic eyes and the fellow eyes had significantly lower results compared to the control group. Our results agreed with those of previous studies that also reported abnormalities in the fellow eye of patients with anisometropia and/or strabismus and indicated that the RFT might provide different information about foveal function compared to the other methods.

Occlusion of the better eye has been the mainstay for amblyopia therapy. Patching might cause social stigmata, skin irritation and disruption of binocular function. Good compliance is important but sometimes difficult to achieve. Therefore, it is valuable to adjust the way we use the occlusion therapy and evaluate alternative treatments. In **study III** we prospectively randomized 80 children (age, 4-5 years) with anisometropic amblyopia to treatment with spectacles in combination with Bangerter filters or to treatment with spectacles alone. The BCVA, binocular function and refractive errors were measured repeatedly during 1 year. We found more rapid VA recovery with Bangerter filters than with spectacles alone. However, the 1-year median BCVA did not differ significantly between the treatments. The study showed an increase in the median spherical equivalent refractive error in the amblyopic eyes and the fellow-eyes. We also found a decrease in the median anisometropia in both groups. **Study IV** was a randomized prospective trial designed to compare spectacles plus patching 8 hours or more daily, 6 days a week, to spectacles plus patching 8 hours or more on alternate days as treatment for amblyopia in 40 children aged 4 to 5 years. The BCVA, binocular function, and refractive errors were measured repeatedly over the course of 1 year. There was no significant difference in the magnitude of change in the BCVA between the groups, and the BCVA at 1 year improved to a median 0.1 logMAR in both groups. Therefore, alternate-day patching might be a way to adjust occlusion treatment, especially in families in which daily occlusion is problematic.

LIST OF PUBLICATIONS

- I. Pia Agervi, Ulla Kugelberg, Maria Kugelberg, Charlotta Zetterström.
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- IV. Pia Agervi, Ulla Kugelberg, Maria, Kugelberg, Gunnela Simonsson, Monica Fornander, Charlotta Zetterström.
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LIST OF ABBREVIATIONS

BCVA	Best Corrected Visual Acuity
BL	Border Luminance
c.c.	Cum correctio, with correction
CL	Core Luminance
D	Diopter
LogMAR	Logarithm of the Minimum Angle of Resolution
MHR	Mean hit rate
PEDIG	Pediatric Eye Disease Investigator Group
RFT	Rarebit Fovea Test
s.c.	Sine correctio, without correction
VA	Visual Acuity

1 INTRODUCTION

1.1 AMBLYOPIA DEFINITION

Amblyopia is a unilateral or bilateral decrease of visual function that cannot be attributed only to the effect of a structural or pathologic abnormality of the eye or the visual pathways. Amblyopia is caused by disturbed visual experience early in life resulting from pattern vision deprivation, abnormal binocular interaction, or both, and is completely or partially reversible with therapy (von Noorden 1977). A definition of unilateral amblyopia based on visual acuity (VA) is at least a 2 logarithm of the minimum angle of resolution (logMAR)-line difference in the best corrected visual acuity (BCVA) from the fellow eye (Holmes & Clarke 2006). However, amblyopia is a spectrum of visual loss, ranging from mild to severe.

1.2 EPIDEMIOLOGY OF AMBLYOPIA

Amblyopia is the leading cause of unilateral visual impairment in children (Holmes & Clarke 2006). The prevalence in unscreened populations is estimated to be up to 4% depending on the population studied and the definition used (Attebo et al. 1998; Brown et al. 2000; Newman & East 2000; Robaei et al. 2006; Simons 2005; Thompson et al. 1991). In Sweden and other countries with vision screening programmes, residual amblyopia and deep amblyopia have become uncommon, with an amblyopia prevalence of approximately 1% (Jensen & Goldschmidt 1986; Kvarnström et al. 1998; Köhler & Stigmar 1973; Sjöstrand & Abrahamsson 1990).

1.3 BACKGROUND

Since the two Nobel prize-winning neurophysiologists, David Hubel and Torsten Wiesel, published their pioneering studies in the early 1960s (Hubel & Wiesel 1963; Wiesel & Hubel 1963a; Wiesel & Hubel 1963b) our understanding of the pathophysiologic mechanisms that underlie amblyopia has increased greatly, although the changes in the central visual pathways are complex and the underlying neurology in humans still remains elusive (Barrett et al. 2004).

Amblyopia can develop if the visual experience is abnormal during the sensitive periods of visual maturation (Daw 1998). The sensitive period for disruption of acuity by anisometropia or strabismus continues until approximately 8 to 9 years of age (Daw 2006). The two basic forms of abnormal stimulation that cause amblyopia are pattern deprivation (blurred retinal image) and abnormal binocular interaction (conflicting visual input from the two retinal foveae).

The amblyopic process has an effect at various levels of the visual pathway. Although the primary deficit of amblyopia is thought to be cortical in nature (Barrett et al. 2004; Hubel & Wiesel 1965a), animal research has shown repeatedly that the primary visual cortex (area V1) is affected (Crawford & Harwerth 2004; Horton & Hocking 1997; Hubel & Wiesel 1965b; Wiesel & Hubel 1963b); human research with functional imaging studies also has confirmed processing deficits in area V1 and suggest additional deficits in higher order visual areas (Anderson & Swettenham 2006; Demer

et al. 1988; Kiorpes & McKee 1999). Studies have shown a loss of binocularly driven cells, shifts in ocular dominance in the visual cortex away from the affected eye, and cell shrinkage in layers of the columns in the visual cortex (Crawford & Harwerth 2004; Horton & Hocking 1997; Hubel & Wiesel 1965b; Wiesel & Hubel 1963b). Wiesel and Hubel proposed that the changes in cortical function depend on a competitive interaction between the right and left eye afferents (Wiesel & Hubel 1965).

Furthermore, changes in neuronal size have been shown in the lateral geniculate nucleus, and functional imaging studies have suggested that the lateral geniculate nucleus is dysfunctional (Anderson & Swettenham 2006; Wiesel & Hubel 1963a; von Noorden & Crawford 1992; von Noorden et al. 1983). Retinal abnormalities also have been found (Arden et al. 1980; Westheimer 2004; Williams & Papakostopoulos 1995). Retinal involvement remains controversial since electrophysiological research and studies evaluating optical imaging technology have reported conflicting findings (Gottlob & Welge-Lussen 1987; Leone et al. 2008).

Researchers have reported a variety of visual system dysfunctions associated with amblyopia of the affected and fellow eyes, and some of these dysfunctions remains to some degree despite successful treatment (Chatzistefanou et al. 2005; Leguire et al. 1990; Simons 2005). Contrast sensitivity that is affected is one such dysfunction. Strabismic amblyopes usually need more contrast compared to normal subjects to detect higher spatial frequency stimuli whereas anisometropic amblyopes are affected at all spatial frequencies (Abrahamsson & Sjöstrand 1988). In strabismic amblyopia, reduced contrast sensitivity is described mainly in the central part of the visual field. In anisometropic amblyopia, however, the contrast sensitivity is reduced independently of visual field location (Li et al. 2007; von Noorden 2002).

1.4 CLASSIFICATION AND CAUSES OF AMBLYOPIA

Amblyopia has traditionally been classified according to the causative factors, that is, visual deprivation, anisometropia and strabismus (von Noorden 2002).

1.4.1 Visual deprivation amblyopia

Deprivation amblyopia results from obstruction of the visual axis, because the visual pathways and cortical layers require clear retinal images to develop normally.

Deprivation amblyopia usually is caused by congenital or early acquired cataract but also may be caused by corneal opacities, vitreous hemorrhage, hemangiomas, and ptosis (Figure 1). This form of amblyopia is the most damaging and difficult to treat. Amblyopia due to unilateral deprivation tends to be worse than that resulting from bilateral occlusion of the visual axis, because a competitive situation between the eyes adds to the direct developmental impact of severe image degradation. The most critical period of visual development probably extends up to about 2 to 3 months of age. Visual deprivation during this period may lead to manifest nystagmus and profound and irreversible vision loss if not managed appropriately (Gelbart et al. 1982; Rogers et al. 1981). In Sweden, the first screening for pediatric ocular disease is performed in the maternity ward, facilitating possible early detection and treatment.

1.4.2 Anisometropic and ametropic amblyopia

Unilateral or bilateral refractive errors can cause amblyopia. Anisometropic amblyopia develops when unequal refractive errors in the two eyes cause the retinal image to defocus. The amblyopia results partly from the effect of image blur and partly from interocular competitive or inhibitory interaction between neurons carrying the nonfusible inputs from the two eyes. Although anisometropia has been suggested to arise after the onset of amblyopia, anisometropia may be a result of amblyopia rather than its cause (Barrett et al. 2004).

It is unclear how large the difference in refractive error has to be to cause amblyopia and all children with substantial anisometropia do not become amblyopic (Abrahamsson & Sjöstrand 1996). Further, the decision to prescribe spectacles also depends on the age of the child and the VA. However, hyperopic anisometropia of 1.0 diopter (D) or more, astigmatic anisometropia of 1.5 D or more and myopic anisometropia of 2 D or more can induce amblyopia (Townshend et al. 1993; Weakley 2001).

Ametropic or isometropic amblyopia is a bilateral reduction in VA caused by blurred retinal images due to equal and substantial bilateral refractive errors. Hyperopia exceeding 4 to 5 D may cause amblyopia (Wallace et al. 2007). Myopia generally requires higher amounts of refractive error for amblyopia to develop. Meridional amblyopia may develop among children with substantial bilateral astigmatism if the degree of cylindrical ametropia is about 2.0 D or more (Gwiazda et al. 1984; Mitchell et al. 1973).

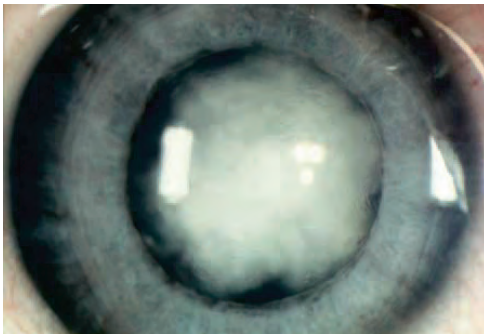


Figure 1. Congenital cataract in a child's eye.



Figure 2. On the left, a child with esotropia in the left eye. On the right, the same child with spectacles.

1.4.3 Strabismic amblyopia

Amblyopia can develop if a constant, nonalternating tropia (usually esotropia) is present early in life (Figure 2). Constant unilateral deviation causes diplopia and confusion why the visual system suppresses the retinal image of the deviating eye. Strabismic amblyopia is thought to result from interocular competition or inhibition. Strabismic and combined strabismic-anisometropic amblyopia are considered more severe than anisometropic amblyopia (Simons 2005; Woodruff et al. 1994). Nevertheless, some studies that have compared different causes of amblyopia report no differences in response to treatment (Pediatric Eye Disease Investigator Group 2003; Stewart et al. 2005).

Bilateral hyperopia increases the risk of developing accommodative esotropia. Thus, spectacles can resolve the strabismus and prevent amblyopia.

1.5 AMBLYOPIA THERAPY

Children in Sweden undergo vision screening at the Child Health Care Centres to detect amblyopia at 4 years of age (Kvarnström et al. 1998). Children with amblyopia will not usually complain of decreased vision why these cases generally are discovered at the screening. If an obvious abnormality such as strabismus is present, amblyopia is usually detected earlier. If amblyopia is undetected and not treated properly during childhood, irreversible visual loss may occur. Children can be treated successfully up to 8 to 10 years of age (Campos 1995; Wu & Hunter 2006). However, studies also have shown a VA improvement in older children, which is why treatment can be considered for children at least 12 years of age or those who are teenagers (Holmes et al. 2006; Scheiman et al. 2005; Scheiman et al. 2008), although the risk of developing diplopia due to occlusion therapy should be considered because of the risk of overcoming the ability for suppression. VA improvements in the amblyopic eye also were described after loss of the fellow eye in adults (Vereecken & Brabant 1984).

There are several treatments for amblyopia, all of which are aimed at increasing the VA. The treatments are used alone or in combination as required. The optimum treatment outcome is the achievement of equal VA bilaterally, since binocular vision is best promoted by equal visual input from each eye. However, many researchers define treatment success as resolution of amblyopia (interocular difference, ≤ 1 line), since the definition often used in unilateral amblyopia is 2 or more logMAR lines of interocular difference measured with best correction.

VA improvement is achieved by following strategies:

1. Presenting a clear image to the amblyopic eye by eliminating the cause of visual deprivation and by correcting refractive errors.
2. Correcting ocular dominance by making the child use the amblyopic eye through filter/optical penalization, occlusion, atropine penalization and pleoptics.

1.5.1 Surgery to treat the cause of amblyopia

When the cause of amblyopia is due to a reparable obstruction of the visual axis, such as cataract, corneal opacities, persistent vitreous opacities, or blepharoptosis, surgery is recommended to achieve a clear retinal image to the amblyopic eye. The surgical outcome depends on how soon after birth the obstruction of the visual axis is detected

and treated and on the postoperative management including adequate refractive correction and occlusion therapy with frequent follow-up (Zetterström & Kugelberg 2007). Successful outcomes in newborns with visually threatening cataract, including unilateral cases, have been achieved when the cataract is removed and optical correction is in place within 2 months of age (Birch et al. 2009; Birch et al. 1998; Birch & Stager 1996; Kugelberg 1992).

1.5.2 Refractive correction

Refractive correction alone can result in a substantial VA improvement and therefore could be considered as a separate treatment for anisometropic amblyopia before use of additional therapy (Chen et al. 2007; Cotter et al. 2006; Moseley et al. 2002; Simons 2005; Steele et al. 2006; Stewart et al. 2004a). VA also has improved in children with amblyopia due to strabismus, and therefore initial treatment with optical correction alone until the VA is stable may avoid the use of unnecessary occlusion (Cotter et al. 2007; Moseley et al. 2002; Stewart et al. 2004a). However, treatment with occlusion in combination with optical correction in strabismic amblyopia seems more effective than optical correction alone (Cleary 2000). Several studies that evaluated treatment with refractive correction alone have reported that the time to resolution of amblyopia is about 4 to 6 months (Chen et al. 2007; Cotter et al. 2006; Steele et al. 2006; Stewart et al. 2004a). Additional treatment should be offered to patients with residual amblyopia.

A recent multicenter study from the Pediatric Eye Disease Investigator Group (PEDIG) reported successful spectacle treatment of bilateral refractive ametropic amblyopia; the VA in most children improved to 0.1 logMAR or better within 1 year (Wallace et al. 2007).

1.5.3 Filter/optical penalization

The method of blurring the vision of the fellow eye to force fixation to the amblyopic eye is called penalization. The blurring of the fellow eye can be achieved by different methods. The vision of the fellow eye can be reduced to less than that of the amblyopic eye using frosted tape or translucent filters, such as Bangerter (Ryser) occlusion filters (Bangerter 1960) (Figure 3).

The filters can be used as a primary or secondary treatment in cases in which therapy for amblyopia is not providing further benefit (Iacobucci et al. 2001). Filters also can be used after treatment of amblyopia to maintain the VA in the amblyopic eye. The Bangerter filters have different grades of transparency, allowing acuity from greater than 1.0 logMAR to 0.0 logMAR. Researchers (Odell et al. 2008; Pérez et al. 2009) studied the effect of Bangerter filters on optotype VA and found that the visual degradation did not correspond to predicted levels, although a study by Mitsuyu and Zimmer (Mitsuyu & Zimmer 1984) showed that Bangerter filters did degrade acuity to predicted levels. The advantages of the filters compared to patching are that fusion is maintained during treatment, and, because the filters are cosmetically less noticeable, patient compliance might increase due to reduced social stigma. In addition, there is no skin irritation. However, there is a lack of randomised controlled trials evaluating translucent filters (Holmes & Clarke 2006). A randomized clinical trial, “Full-time Bangerter filters versus part-time daily patching for moderate amblyopia in children”, is currently ongoing in the US.

Optical penalization can be performed by changing the refractive correction of the fellow eye to induce blur for near and/or distance vision (Repka & Ray 1993).

Compliance is a concern with both filter and optical penalization, because there is a risk that the child can look over the spectacles and the filter.

Strong myopic (up to about -30 D) or opaque contact lenses can be used to treat amblyopia, although use of contact lenses in children require close follow-up due to the risk of anterior segment complications (Eustis & Chamberlain 1996).

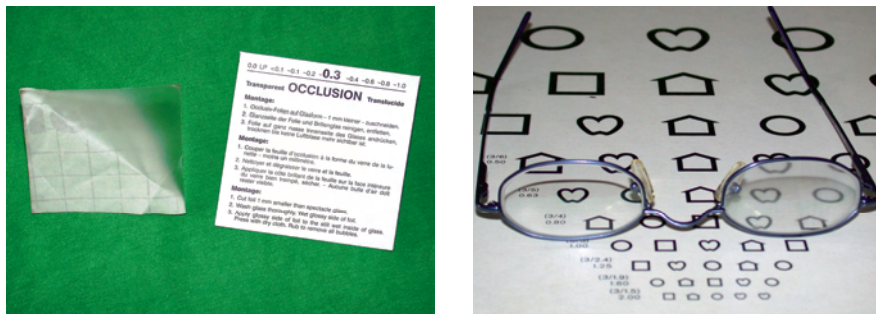


Figure 3. On the left, frosted tape and a Bangerter filter package. On the right, a 0.3 Bangerter filter attached on the back of the right spectacle lens.



Figure 4. Atropine penalization, right pupil is dilated.



Figure 5. Occlusion with a patch placed over the unaffected eye.

1.5.4 Atropine penalization

Decreased vision in the fellow eye can be achieved by using cycloplegic eye drops, usually atropine (Figure 4). Accommodation is prevented, thereby causing blurred vision at near in the fellow eye and stimulating the amblyopic eye more. Theoretically, the effect of atropine penalization should be more efficient in children with hypermetropia because a cycloplegic myopic eye still can be used at near. Atropine penalization may be used as initial amblyopia therapy or as maintenance treatment. However atropine has disadvantages such as systemic side effects, the risk of an irreversible mydriatic and atonic pupil, and blur-induced amblyopia of the fellow eye. Therefore, atropine is a further option when occlusion therapy is not tolerated.

The efficacy of atropine as initial treatment for mild to moderate anisometropic and strabismic amblyopia has been reported in randomized controlled trials (Pediatric Eye Disease Investigator Group 2002; Repka et al. 2005). After 6 months the studies have reported success rates (achievement of VA to 0.2 logMAR or VA improvement of the amblyopic eye by 0.3 logMAR) in 74% of children treated with atropine compared to 79% of children treated with patching at least 6 hours daily. Further, daily instillation of atropine results in an improvement in VA similar in magnitude to that provided by weekend atropine (2 days a week) (Repka et al. 2004). In addition, undercorrecting the hypermetropic refractive error in the atropine-treated fellow eye does not enhance the treatment effect of atropine (Pediatric Eye Disease Investigator Group 2009). Patching resulted in an initially faster VA improvement compared to atropine (Pediatric Eye Disease Investigator Group 2002); however atropine had a slightly higher degree of acceptability in terms of compliance and social stigmata (Holmes et al. 2003).

1.5.5 Occlusion

Patching of the eye with better vision has been the centuries-old mainstay of therapy for treating amblyopia in children (Loudon & Simonsz 2005) (Figure 5). The effectiveness of occlusion therapy has been questioned. However, two randomized controlled trials have reported that occlusion therapy is effective for treating amblyopia (Clarke et al. 2003; Williams et al. 2002).

The side effects of patching include skin irritation, risk of social stigmata, disruption of binocular function, increasing angle of deviation in strabismus, diplopia and occlusion amblyopia of the fellow-eye.

Studies have reported successful amblyopia treatment in 19% to 96% of patients (Flynn et al. 1998; Repka et al. 2003; Scott et al. 2005; Simons 2005; Stewart et al. 2004b), with the wide range probably due to differences in defining treatment outcomes, patient selection, treatment modalities and follow-up periods. Further, the PEDIG studies have shown that daily prescribed patching of 2 hours generates a final improvement similar to that with 6 hours of treatment of moderate amblyopia ($VA < 0.7 \log \text{MAR}$) (Repka et al. 2003), and that 6 hours produces an improvement of a magnitude similar to that of full-time patching to treat severe amblyopia ($VA \geq 0.7 \log \text{MAR}$) (Holmes et al. 2003). In addition, no benefit was found for undertaking near activities with occlusion when treating anisometropic, strabismic, or combined amblyopia (Pediatric Eye Disease Investigator Group 2008), although Scott et al. (Scott et al. 2005) reported that full-time

occlusion (24 hours daily) produced excellent VA outcomes (achievement of VA ≤ 0.17 log MAR) with a success rate of 96%. However, higher dose of patching might achieve the best outcome faster but at risk of accumulating excessive non-therapeutic hours of occlusion (Stewart et al. 2007a). Since less patching time reduces the treatment burden for the child and the parent, fewer hours of prescribed patching per day might be preferable.

Researchers who evaluated patching with objective occlusion dose monitors have reported individual variability to a particular patching dose (Awan et al. 2005; Stewart et al. 2004b) and suggested that as little as 1 hour of patching daily is effective for treating some children (Stewart et al. 2005). However, Awan et al. found that only children who used the patches for more than 3 hours had significant VA improvement compared with no occlusion (Awan et al. 2005). Researchers also have found a dose-effect relationship between the number of hours patched daily and the VA increase (Awan et al. 2005; Moseley & Fielder 1995; Stewart et al. 2004b; Stewart et al. 2007a; Stewart et al. 2007b). Stewart et al. showed a positive, almost linear, dose response up to 400 hours (Stewart et al. 2004b; Stewart et al. 2007b) with a plateau in the improvement at about 4 hours of patching daily (Stewart et al. 2007a); they also found that most VA improvement occurs in the first 6 weeks of patching (Stewart et al. 2004b). Other studies also have shown that the major effect of occlusion occurs in the first weeks to months of treatment (Cleary 2000; Holmes et al. 2003; Repka et al. 2003; Simons 2005; Stewart et al. 2004b).

In summary, based on the reports from several studies, it seems likely that reduced patching doses are as beneficial as substantial or maximum patching in amblyopia due to strabismus and/or anisometropia. Nevertheless, the prescribed amounts of occlusion still vary widely and many clinicians have not changed their traditional treatment methods (Tan et al. 2003; Wagnanski-Jaffe 2005; Wagnanski-Jaffe & Levin 2007).

1.5.6 Active therapy and pleoptics

Active stimulation of the amblyopic eye has been suggested to improve the VA.

The Cambridge Amblyopic Vision Stimulator (CAM) is a method that uses a high-contrast spinning disc with square-wave grading.

Pleoptics is a technique of treating amblyopia with eccentric fixation. Originally, bright light was flashed around the fovea to stimulate foveal fixation, and later different training devices have been added to the treatment method.

Neither the CAM treatment nor the treatment with pleoptics is more effective than standard occlusion therapy, which is why they are rarely used (Fletcher et al. 1969; Lennerstrand & Samuelsson 1983; Nyman et al. 1983).

Video display-based treatment has been tried to stimulate vision among amblyopes (Simons 2005).

1.5.7 Drugs

Levodopa and carbidopa improve VA in amblyopia (Leguire et al. 1993; Leguire et al. 1995). However there are questions regarding the VA stability after treatment (Pandey et al. 2002). Researchers also have reported that citicoline (CDP-choline) improves VA in amblyopia (Campos & Fresina 2006; Fresina et al. 2008).

Recently, animal experiments have shown that the antidepressant fluoxetine restores plasticity in the adult visual cortex (Maya Vetencourt et al. 2008). Therefore, fluoxetine may have a future clinical application in adult amblyopia treatment (Brodsky 2009).

1.6 WHY DOES AMBLYOPIA THERAPY FAIL?

Researchers have suggested that only about 50% of children achieve normal vision after treatment of the amblyopic eye (Repka et al. 2005; Woodruff et al. 1994). What could be the possible explanation for this?

The prognosis for achieving normal vision in the amblyopic eye depends on many factors, including the cause and initial severity of amblyopia and the age of the child at the onset of amblyopia and at the start of treatment (Flynn et al. 1998; Stewart et al. 2005; Stewart et al. 2004b; Stewart et al. 2007a; Stewart et al. 2007b; Woodruff et al. 1994). Studies have reported that children younger than 4 years required less occlusion than older children when evaluated with objective occlusion dose monitors (Stewart et al. 2007a; Stewart et al. 2007b). Nevertheless, there was no effect of age in the PEDIG study that evaluated children 3 to 7 years (Pediatric Eye Disease Investigator Group 2003) and also by other researchers using occlusion dose monitors (Awan et al. 2005). Other studies have shown that the presence of binocularity might be prognostic of a favourable outcome (Birch et al. 2004; Gregersen & Rindziunski 1965; Stewart et al. 2005).

A recurrence risk of 17 to 27% within the first year in children successfully treated with patching for amblyopia has been reported (Bhola et al. 2006; Holmes et al. 2004; Nilsson et al. 2007). In addition, long-term studies have found that the VA was maintained in 67-83% of patients (Leiba et al. 2001; Ohlsson et al. 2002; Scott & Dickey 1988). Researchers have found an increased risk of recurrence with strabismus (Levartovsky et al. 1995; Nilsson et al. 2007), combined strabismic-anisometric amblyopia (Tacagni et al. 2007), dense amblyopia (Rutstein & Fuhr 1992), and a decrease in the risk of recurrence with increasing age (Bhola et al. 2006). The PEDIG recently reported that the recurrence risk was higher in the most successfully treated children, and there was no protection from orthotropia and excellent random dot stereoacuity (Holmes et al. 2007).

Another factor in failure of therapy is inaccurate refractive correction. The refraction during childhood changes due to emmetropization. Adequate refraction is by itself an effective amblyopia therapy (Chen et al. 2007; Cotter et al. 2006; Moseley et al. 2002; Simons 2005; Steele et al. 2006; Stewart et al. 2004a). Therefore, the child's spectacles should be changed if there are any changes in the refractive state.

Successful amblyopia treatment is dependent on good compliance (Lithander & Sjöstrand 1991; Loudon et al. 2003; Simons & Preslan 1999). However, difficulty with compliance is a well-known problem associated with patching in children (Awan et al. 2005; Gregson 2002; Newsham 2000; Stewart et al. 2004b; Stewart et al. 2007a; Woodruff et al. 1994). Difficulty in keeping the patch in place is addressed by various strategies for patching, that is, hand socks, inflatable water wings, benzoin tincture, occlusive dressings, glued patches and sewing the patch to the brow and cheeks (Arnold

et al. 2008; Hacker & O'Hara 1991; Rubab et al. 2008). Compliance has with objective occlusion dose monitors been shown to be as low as 48% (Stewart et al. 2004b). Motivating parents or caregivers is an important factor in attaining compliance (Newsham 2000). Parental education with written information has been shown to change the attitude and significantly increase compliance to treatment (Göransson et al. 1998; Newsham 2002).

A subtle pathology in the eye and the brain can result in failure to respond to treatment. Amblyopia without media opacity, unequal refractive error, or strabismus is rare. If an obvious cause is not present or if the amblyopia is resistant to therapeutic interventions, a careful search for an alternate diagnosis should be undertaken. Optic nerve abnormalities such as hypoplasia are missed easily and should be excluded (Lempert 2000; Lempert 2004).

Nevertheless, there are compliant children in whom VA initially respond to treatment and then seems to plateau. It is not always known why VA does not improve further with therapy; the children might have functional or physical deficits making the achievement of equal vision impossible.

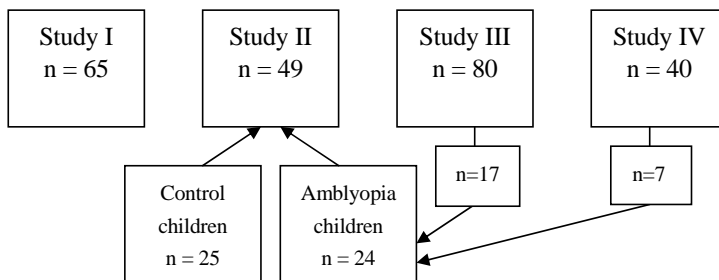
2 AIMS OF THE STUDY

1. To describe the refractive results and the visual outcomes of paediatric cataract surgery in the Ukraine where postoperative correction with glasses or occlusion therapy was not possible (study I).
2. To evaluate foveal function in children treated for monocular amblyopia using conventional high contrast optotype BCVA testing, BCVA at two different contrast levels, and the RFT (study II).
3. To conduct prospective randomized clinical trials to evaluate different amblyopia treatments such as translucent Bangerter filters or spectacles alone and different amounts of prescribed patching regimens and to describe the refractive outcomes (studies III and IV).

3 PATIENTS

Patients were recruited for study I from the Filatov Institute in Odessa, Ukraine. The patients in study II were recruited from studies III and IV. The control children for study II were recruited mainly from one school class in Sundbyberg, Sweden. Patients for studies III and IV were recruited consecutively from the Department of Paediatric Ophthalmology and Strabismus, St. Erik Eye Hospital, Stockholm, Sweden.

The parent or guardian of each child in studies II, III and IV provided a signed informed consent form agreeing to participation.



3.1 ETHICS

The Local Ethics Committee at the Karolinska Institutet approved studies I, II, III and IV. The studies followed the tenets of the Declaration of Helsinki.

4 PATIENTS AND METHODS

The VA in the presented studies is usually expressed in logMAR units. For the readers convenience a conversion table to decimal VA is presented (Table 1).

Table 1. Conversion table.

LogMAR	Decimal VA (1/MAR)
- 0.3	2
- 0.2	1.6
- 0.1	1.25
0	1.0
0.1	0.8
0.2	≈ 0.6
0.3	0.5
0.4	0.4
0.5	≈ 0.32
0.6	0.25
0.7	0.2
0.8	0.16
0.9	0.125
1	0.1
1.1	0.08
1.2	0.063
1.3	0.05

4.1 REFRACTIVE AND VISUAL OUTCOME OF PAEDIATRIC CATARACT SURGERY IN THE UKRAINE (STUDY I)

4.1.1 Study design

This prospective study was performed in the Ukraine where 65 children aged 3 to15 (mean 7.8 ± 3.7) years underwent cataract surgery.

4.1.2 Inclusion criteria

Children with unilateral (n= 21) or bilateral (n = 44) congenital or developmental cataract.

4.1.3 Surgery

Cataract surgery was performed by one surgeon (CZ). Before surgery, the axial length and corneal curvature were measured for intraocular lens power calculation. Anterior and posterior capsulorhexes was performed, and all eyes were implanted with a single-piece Acry-Sof ® SA30AL intraocular lens. Intracameral antibiotic prophylaxis with 1 milligram of cefuroxime was administered during surgery. Postoperative wounds were closed firmly with tight sutures. Topical dexamethasone 0.1 % was prescribed postoperatively.

4.1.4 Preoperative visit and follow-up

Examinations were performed preoperatively and postoperatively on 1 day, 6 months and 2 years after surgery. The examination included measurement of the VA, objective

refraction using retinoscopy after dilatation of the pupil with a combination of 1.5% phenylephrine and 0.85% cyclopentolate, intraocular pressure, and examination of the media and fundus with a handheld ophthalmoscope. The VA was tested with a Lea symbols chart (Hyvärinen et al. 1980) without optical correction at all visits except at the final 2-year control when the VA also was measured with optical correction by retinoscopy. All testing was performed monocularly, with the non-viewing eye occluded. Strabismus was estimated with cover testing.

4.1.5 Primary and secondary outcome measures

Primary outcome measure was the VA 2 years postoperatively in the eye that underwent surgery. The secondary outcome measure was the refractive outcome of the amblyopic eye measured at 2 years postoperatively.

4.2 FOVEAL FUNCTION IN CHILDREN TREATED FOR AMBLYOPIA (STUDY II)

4.2.1 Study design

In this prospective study, 24 children with treated amblyopia and 25 control children underwent measurement of the BCVA using a standard decimal (KM) chart, and at 50% and 10% contrast levels, using the TriVA test and the computerized RFT. In the amblyopic group, the fellow eye was tested first. To evaluate a possible learning effect, the testing order between the right and left eyes in the control children was randomized. A mixed control group consisting of both first and second tested eyes was created by randomizing among the control eyes. The ratio of first to second tested eyes in the randomized control group was 13: 12. Table 2 show the age and gender distribution.

Table 2. Clinical data from the tested groups.

	Amblyopic group (n=24)	Control group (n=25)
Age (years)	8 (7-9)	8 (7-9)
Gender M/F	11/13	8/17

Age is expressed as the median (range)

M = male; F = female; n = number

4.2.2 Inclusion criteria

To be eligible for study inclusion, the children had to have been previously treated for amblyopia with a BCVA of 0.3 logMAR or more in the amblyopic eye and a BCVA of 0.1 logMAR or less in the fellow eye before treatment and were otherwise generally healthy and had no other ocular diseases.

4.2.3 Visual acuity measurement

Monocular BCVA was measured with the line letter KM-chart, based on seven letters of similar legibility, in 13 lines with three to 12 letters on each line (Hedin & Olsson 1984; Moutakis et al. 2004). The testing distance was 4 meters. The BCVA was defined according to clinical practice as the line on which 70% or more of letters were read correctly.

4.2.4 The TriVA test

The BCVA also was tested at 50% and 10% contrast levels, using the TriVA test. This test is a rapid, computerized VA test applied at different contrast levels using Y-shaped, high-pass spatial frequency filtered (vanishing) targets, with three prongs of different widths (Figure 6) (Malmer & Martin 2005; Martin 1999). The operator sets the contrast levels, but the orientation and size of the test target can be selected at will and adapted to the child's response during the examination. The child must indicate whether he or she perceives one, two or all three prongs. The size of the Y is decreased as long as the child sees all three prongs. The goal of the examination is to find the smallest discernible test prong size. Prong sizes are given as visual angles for the prong cores. In this study, the step factor between prong widths was 1.26 (based on a decibel scale). Luminance was calibrated such that the core luminance (CL) and border luminance (BL) of the test target were set at equal amounts above and below the background level, respectively, with the aid of a luminance meter (Hagner EC-1; B. Hagner AB, Solna, Sweden). Contrast was defined as $(CL - BL) / (CL + BL)$. VA was expressed in MAR (minimum angle of resolution), and was converted to logMAR values for descriptive purposes. The highest measurable VA was -0.05 logMAR. The test was performed monocularly in a dark room at a testing distance of 2 m. The children were given appropriate correction for refractive errors.

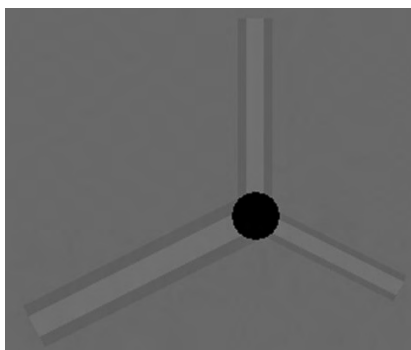


Figure 6. TriVA optotype at 10% contrast. The tested subject is asked whether he or she perceives one, two or three prongs. Perception of the actual test procedure can be simulated by changing the viewing distance and counting the number of visible prongs.

4.2.5 The Rarebit fovea test (RFT)

Foveal function also was evaluated with the computerized RFT test (Malmer & Martin 2005; Nilsson et al. 2006), which is included in the Rarebit perimetry program package (Frisén 2002) and which tests the central 4 x 3 degrees of the visual field. The principle is to briefly present no, one or two bright and very small dots, separated by 1 degree and with a size equal to or less than - 0.3 logMAR in the tested area, against a dark background with the contrast kept constant. The Rarebit technique was developed to detect small, subtle defects in the neural detector system. The child is asked to fixate a small flickering cross in the middle of the screen and to respond by making one or two mouse clicks when one or two of the presented test stimuli are detected. A total of 10% of the presentations contain either one or no dot and are used for control purposes (i.e., if the subject clicks when no dot is presented or double-clicks when only one dot is presented, this is regarded as an error). The RFT result is expressed as a percentage as a Mean Hit Rate (MHR) which is, the number of targets seen relative to targets presented (Figure 7). In the study, RFT Version 4.0 was used. The RFT and the TriVA test were performed with the same equipment, a personal computer with a 17-inch liquid crystal

display. The test was performed monocularly in a dark room at a testing distance of 2 m. The children used appropriate correction for refractive errors.

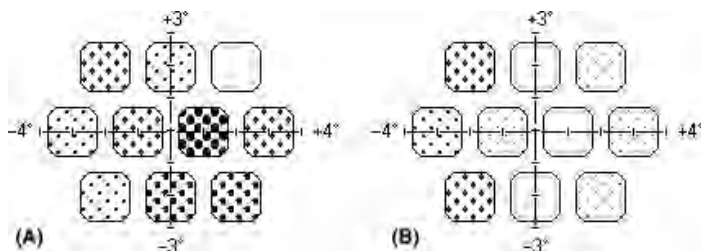


Figure 7. RFT results from an amblyopic (A) and fellow eye (B) in an 8-year old girl with logMAR BCVAs of 0.1 and 0.0 and mean hit rates of 72% and 88%, respectively. The open squares indicate that all dots were perceived. The fraction of missed targets is proportionally depicted by a grey scale within the test area.

4.2.6 Primary and secondary outcome measures

The primary outcome measure was the MHR of the amblyopic eye measured with the RFT. The secondary outcome measures included monocular BCVA measured with the line letter KM-chart and BCVA at 50% and 10% contrast levels using the TriVA test.

4.3 TREATMENT OF ANISOMETROPIC AMBLYOPIA WITH SPECTACLES OR IN COMBINATION WITH TRANSLUCENT BANGERTER FILTERS (STUDY III)

4.3.1 Study design

In this prospective study, 80 children were randomized to either spectacle correction alone ($n = 40$) or spectacle correction with Bangerter filters ($n= 40$) as treatment for anisometropic amblyopia. The Bangerter filter (Ryser Optik AG, St Gallen, Switzerland) had a density of 0.3 and was attached to the back of the spectacle of the fellow eye and worn full time. The children were randomly allocated to treatment by drawing a numbered allocation ticket provided by the researchers.

4.3.2 Inclusion criteria

To be eligible for the study, the children were 4 to 5 years of age, had a BCVA of 0.3 logMAR or more in the amblyopic eye and a BCVA of 0.1 logMAR or less in the fellow eye, had amblyopia in the presence of anisometropia defined as an interocular spherical refractive error difference of 1.0 D or more or a cylindrical difference of 1.5 D or more, and were otherwise healthy with no other ocular diseases or strabismus.

4.3.3 First visit and randomization

During the first visit, the children underwent monocular VA testing with the Lea symbols 15-line folding distance chart (Hyvärinen et al. 1980) without optical correction at distance and near, a cover test, a prism cover test, a 4-D prism test, evaluation of the binocular function with the Lang stereo test II, and examination with Bagolini glasses at distance and near. In addition, a detailed ophthalmologic examination was performed with objective refraction using cycloplegic retinoscopy, cycloplegic autorefractometry (Topcon Corporation Model RM-8000B, Tokyo, Japan), examination of the anterior segment with a slit lamp and examination of media and fundus with a handheld ophthalmoscope (Table 3).

Table 3. Visits and examinations

Time	First Visit (Study Entry + Randomization)	Baseline Visit (Start of Treatment)	Months after Baseline									
			0.5	1.5	2.5	3.5	4.5	5.5	6.5	9	12	
Uncorrected VA	X											
Corrected VA		X	X	X	X	X	X	X	X	X	X	X
Cover test	X	X	X	X	X	X	X	X	X	X	X	X
Prism-cover test	X	X	X	X	X	X	X	X	X	X	X	X
4-diopter prism test	X	X										
Lang stereo test	X	X	X	X	X	X	X	X	X	X	X	X
Bagolini glasses	X	X	X	X	X	X	X	X	X	X	X	X
Retinoscopy	X							X				X
Autorefractometry	X							X				X
Ophthalmoscopy	X							X				X

4.3.4 Follow-up

A baseline examination was performed. Follow-up visits were scheduled at 0.5, 1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 9, and 12 months. The visits involved an orthoptic examination as described at the first visit, but VA testing with Lea symbols chart was performed with the prescribed spectacles. The visits at 4.5 and 12 months included a detailed ophthalmologic examination as described at the first visit (Table 3). Table 4 shows the baseline characteristics of each group.

Table 4. Baseline characteristics according to treatment group

	Spectacles	Spectacles + Bangerter filter
	n=33	n=33
No. female/male	18/15	24/9
Age (years)		
Mean \pm standard deviation (range)	4.5 \pm 0.3 (4.1-5.1)	4.5 \pm 0.3 (4.1-5.5)
BCVA amblyopic eye		
Median (range) logMAR	0.4 (0.3-0.9)	0.4 (0.3-0.8)
BCVA fellow eye		
Median logMAR (range)	0.1 (0.0-0.1)	0.1 (-0.1-0.1)
Difference in BCVA between amblyopic and fellow eyes (log units)		
Median (range)	0.3 (0.2-0.9)	0.3 (0.2-0.8)
Type of anisometropia		
Spherical no. (%)	22 (67%)	26 (79%)
Cylindrical no. (%)	11 (33%)	7 (21%)
Severe amblyopia BVCA \geq 0.7 logMAR		
No. (%)	3 (9%)	4 (12%)

4.3.5 Primary and secondary outcome measures

The primary outcome measure was the time course to resolution of the amblyopia (interocular difference, \leq 1 line). Secondary outcome measures included the BCVA, change in BCVA, and binocular and refractive outcome of the amblyopic eye measured at 1 year. We also evaluated visual gain by considering the visual development of the fellow eye according to the formula of Stewart et al. (Stewart et al. 2003). The proportion of the amblyopic deficit that was corrected = (VA of amblyopic eye at baseline - VA of amblyopic eye at trial end) divided by (VA of amblyopic eye at baseline - VA of fellow eye by trial end).

4.4 RANDOMIZED EVALUATION OF SPECTACLES PLUS ALTERNATE-DAY OCCLUSION TO TREAT AMBLYOPIA (STUDY IV)

4.4.1 Study design

In this prospective study 40 children were randomized to either spectacles plus prescribed patching 8 hours or more daily 6 days per week (n = 20) or spectacles plus prescribed patching 8 hours or on alternate days (n = 20) as treatment of amblyopia. The children were randomly allocated to treatment by drawing a numbered allocation ticket provided by the researchers.

4.4.2 Inclusion criteria

To be eligible for the study the children had to be 4 to 5 years of age, had a BCVA of 0.3 logMAR or more in the amblyopic eye and a BCVA of 0.1 logMAR or less in the fellow eye, had amblyopia in the presence of heterotropia at distance and/or near fixation indicating strabismus and/or a positive 4-D prism test indicating microstrabismus with or without identity, and were otherwise healthy and no other ocular diseases.

4.4.3 First visit and randomization

The first visit was performed as described in 4.3.3 (Table 3).

4.4.4 Follow-up

The follow up was performed as described in 4.3.4 (Table 3). Table 5 shows the baseline characteristics of each group.

Table 5. Baseline characteristics according to treatment group

	Daily-Patching Group n=18	Alternate-Day Group n=20
No. female/male	9/9	8/12
Age (years)		
Median (range)	4.3 (4.1-5.2)	4.3 (4.1-4.6)
BCVA amblyopic eye		
Median (range) logMAR	0.7 (0.3-1.3)	0.9 (0.4-1.5)
BCVA fellow eye		
Median logMAR (range)	0.1 (0.0-0.1)	0.1 (0.0-0.1)
Difference in BCVA between amblyopic and fellow eyes (log units)		
Median (range)	0.7 (0.2-1.2)	0.9 (0.3-1.4)
Severe amblyopia BVCA ≥ 0.7 logMAR		
No. (%)	10 (56%)	16 (80%)
No. anisometropia	12	14

4.4.5 Primary and secondary outcome measures

The primary outcome measure was the median change in BCVA of the amblyopic eye after 1 year. Secondary outcome measures included the time course to resolution of the amblyopia (interocular difference of ≤ 1 line), BCVA, binocular and refractive outcome of the amblyopic eye measured at 1 year. We also evaluated visual gain by considering the visual development of the fellow eye according to the formula of Stewart et al. (Stewart et al. 2003) as described in 4.3.5.

5 RESULTS AND DISCUSSION

5.1 REFRACTIVE AND VISUAL OUTCOME OF PAEDIATRIC CATARACT SURGERY IN THE UKRAINE (STUDY I)

Seven children were lost to follow-up. In the group with bilateral cataract, 41 eyes were evaluated according to refraction and 40 children according to VA. Among the children with unilateral cataract 16 eyes could be evaluated at the final visit.

The VA improvement was statistically significant ($p < 0.05$) when comparing the uncorrected median logMAR VA preoperatively vs. 2 years postoperatively among the children with bilateral cataracts and those with a unilateral cataract. The median decimal VA in the bilateral group increased from 0.12 (0.9 logMAR) without correction preoperatively to 0.4 (0.4 logMAR) with correction at the final visit (Figure 8). Our results agreed with other studies that reported similar or better outcomes (Lundvall & Kugelberg 2002a; Magnusson et al. 2002; Neumann et al. 1993; Taylor 1998; Wright et al. 1992).

Among the unilateral cases the median decimal VA improved from 0.05 (1.3 logMAR) without correction preoperatively to 0.13 (0.9 logMAR) with correction 2 years after surgery (Figure 9). Previous studies have shown varying functional results among children with unilateral cataract (Beller et al. 1981; Cheng et al. 1991; Kushner 1986; Lundvall & Kugelberg 2002b; Neumann et al. 1993; Wright et al. 1992). However, complete comparisons with other studies are difficult because of differences in patient selections, surgical methods, postoperative care and presentation of visual outcome.

Both groups in our study showed unexpectedly favourable visual development over time despite the lack of occlusion therapy or spectacles. This is surprising since other studies have shown the importance of occlusion therapy with intensive patching of the phakic eye and adequate optical correction to obtain a good visual outcome (Bradford et al. 1994; Elsas 1990; Fallaha & Lambert 2001; Gelbart et al. 1982; Hiles & Wallar 1977; Taylor 1998; Taylor et al. 1979). The results in our study are probably due to the reduced postoperative astigmatism and decreased amblyopia as a response to a clear optical axis. The good visual outcome and the few cases ($n = 4$) with nystagmus might indicate that the cataract in most cases was developmental and not congenital (Zetterström et al. 2005). However, the number of esotropia ($n = 19$) implies that there were more cases with congenital cataract. Initially, the cataracts in these cases were probably not so dense.

Preoperative strabismus was present among 53% (31 of 58) of the children in our study and 11 of them achieved straight eyes at the final visit. Other studies have reported a prevalence of strabismus of 40% to 70% of children with cataract (Fallaha & Lambert 2001; France & Frank 1984; Hiles & Sheridan 1977). Esotropia is more common in congenital cataracts, while exotropia is more commonly associated with acquired cataracts (Fallaha & Lambert 2001; France & Frank 1984). In our study esotropia occurred more often than exotropia (19 vs. 12 patients) as described by Hiles and Sheridan (Hiles & Sheridan 1977).

Manifest nystagmus was present preoperatively and postoperatively in four cases among the 58 children examined at the final 2-year control visit (Figure 8 and 9). Dense congenital cataract often leads to sensory nystagmus, which is irreversible and often obvious at 3 months of age (Gelbart et al. 1982; Rogers et al. 1981). Some authors have suggested that preoperative sensory nystagmus indicates a poor visual outcome after cataract surgery, while others report that good visual acuity can be achieved in some cases (Bradford et al. 1994; Gelbart et al. 1982; Leinfelder 1963; Rabiah et al. 2002; Rogers et al. 1981; Wright et al. 1992). In our study, all children with nystagmus except one had improved VA 2 years after surgery, with a final median VA of 0.1 decimal (1.0 logMAR) with correction.

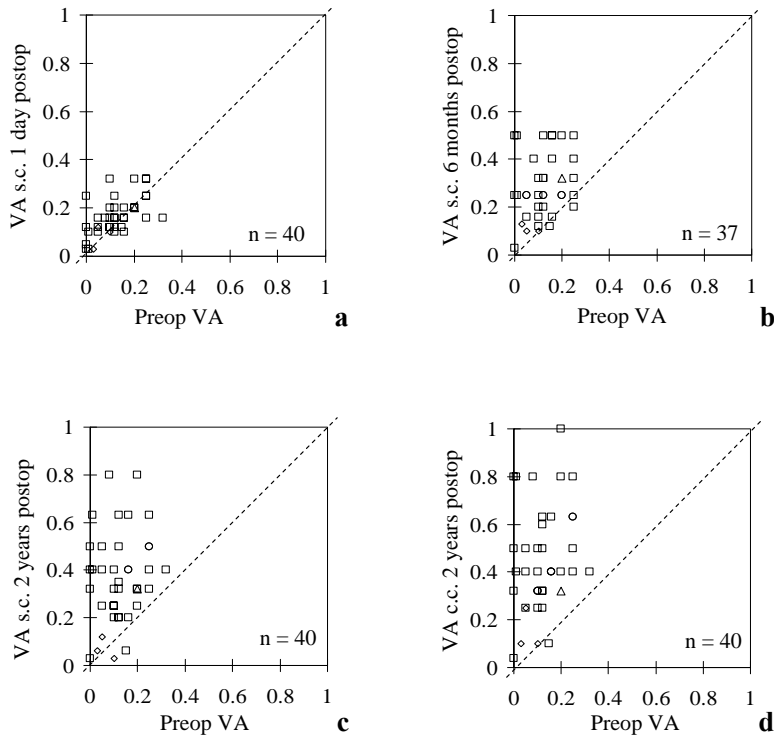


Figure 8. Decimal VA in children with bilateral cataract measured (a) at 1 day without correction, (b) at 6 months without correction, (c) at 2 years after surgery without correction, and (d) at 2 years after surgery with correction. VA s.c. = VA without optical correction; VA c.c. = VA with optical correction; □ = one patient, ○ = two or more patients, Δ = optic atrophy, ◇ = nystagmus.

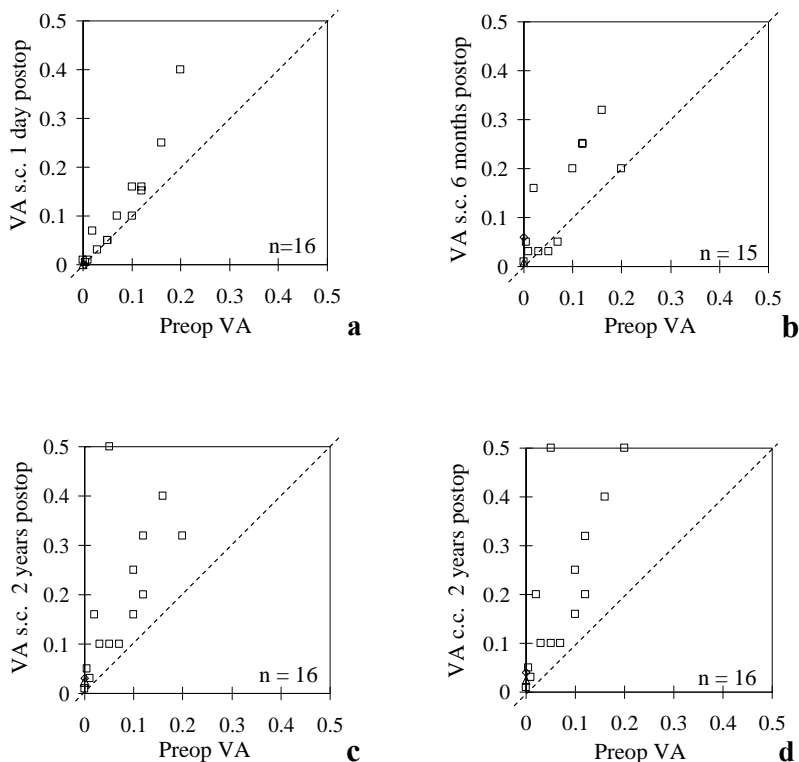


Figure 9. Decimal VA in children with unilateral cataract measured (a) at 1 day without correction, (b) at 6 months without correction, (c) at 2 years after surgery without correction, and (d) at 2 years after surgery with correction. VA s.c. = VA without optical correction; VA c.c. = VA with optical correction; \square = one patient, \circ = two or more patients, Δ = optic atrophy, \diamond = nystagmus.

We found a substantial postoperative reduction in the mean astigmatism in both groups, among the bilateral cases from 3.9 D (1 day postoperatively) to 0.6 D (2 years postoperatively) and among the unilateral cases from 4.2 D (1 day postoperatively) to 0.4 D (2 years postoperatively) ($p < 0.001$ for both comparisons) (Figure 10). The astigmatic axis was 0 degrees in most children; 86% of children one day postoperatively and 75% of children at the final 2 year control. Other studies also have shown that large amounts of suture-induced astigmatism spontaneously decrease in children without suture cutting (Brown et al. 2001; Spierer & Bar-Sela 2004; Spierer & Shelah 1999). The postoperative changes in astigmatism after cataract surgery in children differ from those in adults, in whom only small spontaneous changes in suture-induced astigmatism occur and suture removal is often necessary (Spierer & Bar-Sela 2004). Children usually require general anesthesia to remove sutures, whereas sutures can be removed in adults under topical anesthesia. Severe astigmatism in children might affect visual development and cause amblyopia (Abrahamsson & Sjöstrand 2003; Fulton et al. 1980; Spierer & Bar-Sela 2004); hence, Spierer & Bar-Sela recommend precise refractive optical correction as soon as possible.

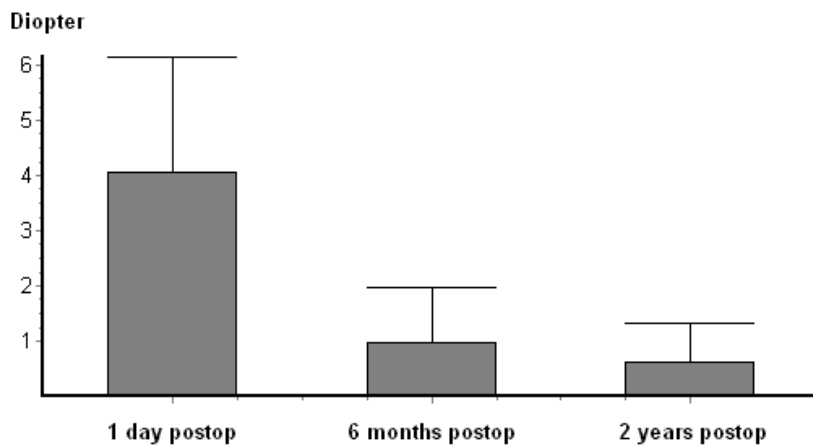


Figure 10. Change in postoperative astigmatism in D (mean \pm standard deviation) during the study period in all children.

During the study, 23 of 65 patients presented with after-cataract and surgery was performed. This was published elsewhere (Kugelberg et al. 2005). No other complications developed.

In summary, our study showed that good postoperative VA was achieved, especially in the group with bilateral cataracts, but even in the group with unilateral cataract a satisfying increase in VA was found despite the lack of postoperative correction with spectacles or occlusion therapy. We also found that postponed surgery in bilateral or unilateral cataract of undetermined onset may result in visual improvement. Therefore we recommend that almost all children with significant cataract irrespective of age should undergo cataract surgery if possible.

5.2 FOVEAL FUNCTION IN CHILDREN TREATED FOR AMBLYOPIA (STUDY II)

The amblyopic eyes had a significantly lower median BCVA when evaluated with the KM chart compared to the fellow eyes and the control eyes ($p < 0.001$ for both comparisons). In addition, the amblyopic eyes had a significantly lower median BCVA when evaluated with the TriVA test at 50% contrast, both compared to the fellow eyes and the control eyes ($p < 0.05$ and $p < 0.001$, respectively). At 10% contrast, we also found that the amblyopic eyes had a significantly ($p < 0.05$ for both comparisons) lower median BCVA compared to the fellow eyes and the control eyes (Table 6). Other authors have reported reduced contrast sensitivity in previously treated amblyopic eyes, which agreed with the findings in our study (Huang et al. 2007; Rogers et al. 1987). However, we found no significant differences in median BCVA with the TriVA test at different contrast levels between the fellow eyes and the control eyes. Other studies have shown decreased contrast sensitivity function in the fellow eyes of amblyopic subjects. (Chatzistefanou et al. 2005; Leguire et al. 1990).

Table 6. Results from BCVA measurements, expressed as the median value (range) in logMAR

	Amblyopic eyes (n=24)	Fellow eyes (n=24)	Control eyes (n=25)
KM chart	0.1 (0.0-0.7)*	0.0 (-0.1-0.1)	0.0 (-0.1-0.0)
TriVA 50%	0.2 (0.0-0.4)*	0.0 (0.0-0.2)	0.0 (0.0-0.3)
TriVA 10%	0.4 (0.0-0.6)*	0.3 (0.0-0.5)	0.3 (0.2-0.5)

*Statistically different from control eyes ($p < 0.05$).

One child in the control group did not complete the RFT examination.

When foveal function was evaluated with the RFT, no significant difference between the amblyopic eyes and the fellow eyes was found. However, the RFT detected a significantly decreased foveal function in the previously treated amblyopic eyes and significantly lower values in the fellow eye compared to the control group ($p < 0.05$ for both comparisons) (Table 7). Our results agree with other studies that also have reported abnormalities in the fellow eye in previously treated patients with amblyopia. Johnson (Johnson 2006) detected a macular scotoma in the amblyopic and the fellow eye using microperimetry with scanning laser ophthalmoscope. Because a majority of cortical neurons are driven binocularly and many of these binocular cells are affected by amblyopia, it is reasonable to assume that the fellow eye is affected by the amblyopic eye (Hubel & Wiesel 1965a; Leguire et al. 1990).

Table 7. Results from RFT expressed as median (range)

	Amblyopic eyes (n=24)	Fellow eyes (n=24)	Control eyes (n=24)
Median MHR (%)	91.5 (38-100)*	94.5 (36-100)*	97 (73-100)
Reaction time (s)	0.58 (0.47-1.14)*	0.58 (0.46-1.02)*	0.54 (0.42-0.74)
Number of errors	2 (0-5)*	1 (0-5)	1 (0-4)

*Statistically different from control eyes ($p < 0.05$).

We found a significantly ($p < 0.05$) longer reaction time in the RFT examinations, both in the amblyopic and the fellow eyes compared to the controls (Table 7). Previous studies have reported a longer reaction time when visually stimulating the amblyopic eye compared to the fellow eye (Simons 2005).

The results in this study were based on psychophysical tests in children and, thus, will have some limitation in the accuracy. The results can also be expected to have higher variability due to the shorter attention span in this age group. In a previous study that evaluated RFT in adults (< 65 years), the median number of errors was 0 (range 0-2) (Malmer & Martin 2005). Our study showed a higher number of errors in the amblyopic eyes compared to the control eyes (Table 7). There may also be a learning effect associated with the RFT, which in the current study could be quantified as not significant in the control group. The median difference between the first and second examination was 1 percentage units, which agreed with the findings from Rarebit perimetry (Martin et al. 2008).

Another limitation in this study regarding the RFT might be unstable fixation. This is a well-known abnormality in amblyopic and fellow eyes (Simons 2005). Stable fixation during the RFT is facilitated by the use of a dynamic fixation target. In a recent study, fixation stability during the RFT was evaluated in healthy adults, including two subjects with amblyopia. The fixation remained stable in all subjects during the RFT examination (Nilsson et al. 2009).

In summary, when the foveal function was evaluated with optotype BCVA using the KM chart and the TriVA test at different contrast levels, the amblyopic eyes had significantly lower results compared to the fellow eyes and the control eyes. However, using the RFT, no significant difference was found when comparing the amblyopic eyes to the fellow eyes, although both the amblyopic eyes and the fellow eyes had significantly lower results compared to the control group. Our findings indicated that the RFT might provide different information about the foveal function compared to other methods, as recently reported in patients with diabetes with good BCVA (Nilsson et al. 2007).

5.3 TREATMENT OF ANISOMETROPIC AMBLYOPIA WITH SPECTACLES OR IN COMBINATION WITH TRANSLUCENT BANGERTER FILTERS (STUDY III), AND RANDOMIZED EVALUATION OF SPECTACLES PLUS ALTERNATE-DAY OCCLUSION TO TREAT AMBLYOPIA (STUDY IV)

Study III

A total of 14 children were lost to follow-up or excluded from the study.

The amblyopia resolved in 94% of the children in both groups during the follow-up period, whereas in previous studies that evaluated treatment with spectacle correction alone the resolution of amblyopia ranged from 27% to 45% (Chen et al. 2007; Cotter et al. 2006; Stewart et al. 2004a). The average time to resolution of amblyopia was almost twice as long for the spectacles group (3.9 ± 3.2 months) compared to the filter group (2.2 ± 1.9 months), a difference that reached significance ($p < 0.05$). The resolution time of 3.9 months in our study agrees with several studies that evaluated treatment with refractive correction alone (Chen et al. 2007; Cotter et al. 2006; Stewart et al. 2004a); however, Steel et al. (Steele et al. 2006) reported a mean resolution time of 5.8 months.

The BCVA in the amblyopic eye improved significantly ($p < 0.001$ for both comparisons) in both groups. At the 3.5-month visit, the children treated with the Bangerter occlusion filters achieved a significantly ($p < 0.05$) better BCVA compared to those with spectacle correction alone (Figure 11). After 1 year, there were no significant differences in the visual outcomes between the groups (Table 8). Our results agree with other studies that reported similar or slightly lower outcomes when evaluating optotype VA or lines of improvement after treating anisometropic amblyopia with refractive correction alone (Chen et al. 2007; Cotter et al. 2006; Moseley et al. 2002; Steele et al. 2006; Stewart et al. 2004a). However, a complete comparison with other studies is difficult because of differences in defining treatment outcomes, patient selection, and follow-up periods. In addition, to our knowledge, only

one prospective study (Iacobucci et al. 2001) evaluated treatment with Bangerter occlusion filters as the primary therapy for amblyopia due to anisometropia and strabismus; that study was not comparable to ours because the children wore spectacles for 6 to 8 weeks before initiation of Bangerter occlusion filter treatment. However, the VA results in the study of Iacobucci et al. (Iacobucci et al. 2001) were similar to our results. The visual outcome after treating amblyopia depends on many factors, and it has been shown that the initial VA affects the treatment results (Clarke et al. 2003; Simons 2005; Stewart et al. 2005). In addition, the success of treatment of amblyopia is correlated with patient compliance (Lithander & Sjöstrand 1991; Loudon et al. 2003; Simons & Preslan 1999). However, as in most studies of amblyopia, compliance cannot be assessed accurately. Even though we asked parents to maintain a compliance calendar and the investigators assessed compliance at each visit, it is possible that the children occasionally looked over the spectacles and the Bangerter occlusion filter.

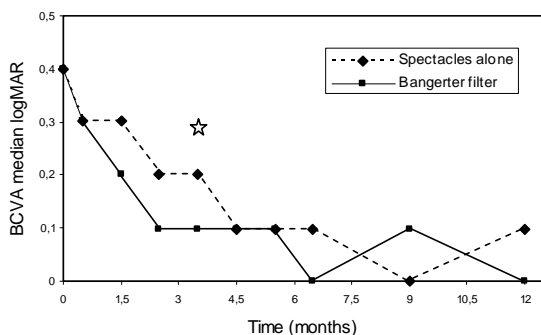


Figure 11. BCVA during the study period expressed as the median logMAR VA. The star indicates a significant difference in BCVA between the groups at 3.5 months.

Table 8. Visual outcome according to treatment group

	Spectacles	Spectacles + Bangerter Filter
BCVA amblyopic eye at 1 year		
Median logMAR (range)	0.1 (-0.1-0.2)	0.0 (-0.1-0.3)
BCVA fellow eye at 1 year		
Median logMAR (range)	0.0 (-0.2-0.1)	0.0 (-0.1-0.1)
Change in BCVA amblyopic eye (log units)		
Median (range)	0.4 (0.2-0.9)	0.4 (0.2-0.8)
Proportion of amblyopia deficit corrected [†]		
Median (range)	0.84 (0.55-1.00)	1.00 (0.39-1.00)
Time to resolution (months)		
Mean ± standard deviation (range)	3.9± 3.2 (0.5-13.3)*	2.2± 1.9 (0.4-9.7)*

[†] (Stewart et al. 2003).

*p<0.05.

We used a fixed-filter density of 0.3 in the current study, and, according to the manufacturer, this degrades normal vision to about logMAR 0.52. However, Odell et al. (Odell et al. 2008) studied the effect of Bangerter occlusion filters on optotype VA in 15 subjects and found that the visual degradation did not correspond to predicted levels; a 0.3 filter degraded the VA to mean 0.44 logMAR, although, Mitsuyu and Zimmer (Mitsuyu & Zimmer 1984) reported that Bangerter filters did degrade acuity to

predicted levels. To evaluate if Bangerter occlusion filters are more efficient than spectacles alone in children with mild-to-moderate amblyopia, we compared the final outcomes in both groups by evaluating the pre-treatment BCVA less than 0.6 logMAR and the BCVA less than 0.5 logMAR. No significant differences were found.

The baseline VA was based on the best VA with or without prescribed spectacles, since 42% of the 66 children had decreased VA with spectacles due to inability to relax accommodation. Nevertheless, most children (85%) had spectacles that were undercorrected by 0.5 dioptres. Three children (17%) from the subgroup with cylindrical refractive error and 25 children (52%) from the subgroup with spherical refractive error deteriorated VA with spectacles. These young children wore the spectacles for the first time at the baseline examination and had difficulties cooperating and determining whether a minus lens over the spectacles produced a better or worse VA. Therefore, we might have underestimated the BCVA in some children at baseline. Although at the follow-up visits when the children were more adapted to the spectacles and more confident with the examination, we placed a minus lens over the spectacles. However, excluding the children with a baseline BCVA determined without correction and with a resolution of amblyopia at 0.5 months did not alter the statistical results regarding the primary outcome measure.

The binocular function improved in both groups; at 1 year there was no significant difference between the groups. All 66 children had measurable stereopsis by the end of the study (Table 9). The responses to Bagolini glasses were positive at the final visit in all but one child who was treated with spectacles in combination with a Bangerter occlusion filter. Recovery of binocular function after treatment of amblyopia also was reported previously (Lee & Isenberg 2003).

Table 9. Binocular function according to number of children and treatment group

	Spectacles (n=33)	Spectacles + Bangerter filter (n=33)
Baseline visit/1 year		
Lang Stereo Test II	27/33	28/33
Bagolini Glasses Test	28/33	25/32

Our study showed a significant increase in the median spherical equivalent refractive error during the follow-up period in both groups in the amblyopic eyes ($p < 0.05$) and the fellow eyes ($p < 0.001$) (Table 10). One explanation for this might be that the cycloplegic drops did not relax accommodation fully at the first visit, but spectacle wear during the study relaxed the accommodation more (Bagheri et al. 2007). In addition, the degree of hyperopia usually increases until the age of 7 years (Brown 1938). However, there were less change in refraction in the amblyopic eyes than in the fellow eyes, and thus the magnitude of anisometropia decreased in both groups ($p < 0.001$ for both comparisons). A decrease in anisometropia with increasing age in anisometric amblyopes also was reported by Ohlsson et al. (Ohlsson et al. 2002) and in 70 % of the children in a study of Abrahamsson and Sjöstrand (Abrahamsson & Sjöstrand 1996).

The children were divided according to the type of anisometropic refractive error, that is, spherical or cylindrical anisometropia. We found a significant increase in the median spherical refractive error during the follow-up period in the amblyopic eyes and the fellow eyes. The median cylindrical refractive error decreased significantly or remained unchanged. Abrahamsson and Sjöstrand (Abrahamsson & Sjöstrand 1996) evaluated the natural history of children with anisometropia over a 10-year period and found that the astigmatism increased, decreased, or remained unchanged.

Table 10. Refractive error change in D, median (range)

	Amblyopic Eye		Fellow Eye	
	First Visit	1-Year Visit	First Visit	1-Year Visit
Spectacles only				
Spherical equivalent (n=33)	+3.50 (-1.25 to +6.75)	+4.00 (-1.50 to +7.50)*	+1.75 (-0.50 to +4.50)	+2.75 (-0.25 to +5.50)***
Spherical refractive error (n=22)	+4.50 (+2.75 to +6.75)	+4.75 (+3.50 to +7.50)***	+2.50 (+1.50 to +4.50)	+3.00 (+2.00 to +5.50)***
Cylindrical refractive error (n=11)	-2.50 (-4.00 to -1.50)	-2.50 (-4.00 to -1.50)	-0.50 (-1.00 to 0.00)	0.00 (-0.50 to 0.00)*
Spectacles + Bangert filter				
Spherical equivalent (n=33)	+3.75 (-2.00 to +6.50)	+4.00 (-2.75 to +7.00)*	+2.00 (-0.75 to +4.50)	+2.50 (-1.75 to +5.50)***
Spherical refractive error (n=26)	+4.00 (+3.00 to +6.50)	+4.50 (+3.00 to +7.00)***	+2.00 (+1.50 to +4.50)	+3.00 (+1.50 to +5.50)***
Cylindrical refractive error (n=7)	-3.00 (-4.00 to -2.00)	-2.75 (-3.50 to -2.00)*	-0.50 (-1.00 to 0.00)	-0.50 (-1.50 to 0.00)

*p<0.05.

***p<0.001.

In summary, children with anisometropic amblyopia treated with Bangert filters had a faster increase in VA compared with children who used spectacles alone. The VA levels 1 year after treatment were not statistically significantly different between the 2 treatments. The hyperopia increased in both the amblyopic and the fellow eyes. In addition, the anisometropia decreased during the study period. We found improved binocular function in both groups.

Study IV

A total of 2 children dropped out of the study.

The median change in BCVA at 1 year favoured spectacles plus alternate-day patching with a change of 0.8 log units (the improvement was from 0.9 to 0.1 logMAR) compared to a change of 0.6 log units (with an improvement from 0.7 to 0.1 logMAR) for the children with spectacles plus daily occlusion, although no significant difference was found (p = 0.06) (Figure 12, Table 11).

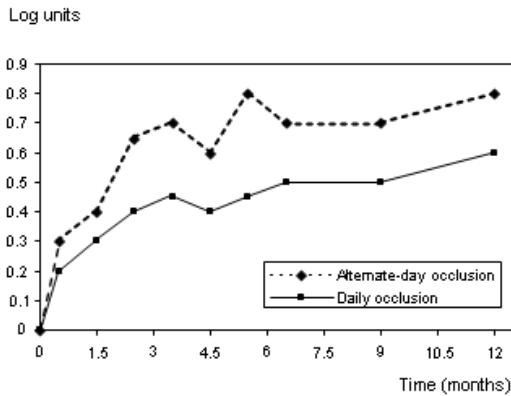


Figure 12. The median change in BCVA of the amblyopic eye over the study period expressed as log units.

Table 11. Visual outcome at 1 year according to treatment group

	Daily-Patching Group n=18	Alternate-Day Group n=20
BCVA amblyopic eye at 1 year		
Median logMAR (range)	0.1 (0.0-0.5)	0.1 (-0.1-0.4)
BCVA fellow eye at 1 year		
Median logMAR (range)	0.0 (-0.1-0.1)	0.0 (-0.1-0.1)
Change in BCVA amblyopic eye (log units)		
Median (range)	0.6 (0.2-1.1)	0.8 (0.2-1.2)
Change in BCVA fellow eye (log units)		
Median (range)	0.1 (0.0-0.2)	0.1 (0.0-0.2)
Proportion of amblyopic deficit corrected†		
Median (range)	0.92 (0.41-1.00)	0.96 (0.49-1.00)
Time to resolution (months)		
Median (range)	3.6 (2.0-12.9)	3.8 (0.6-12.7)

† (Stewart et al. 2003).

Several studies have reported that children who started with worse amblyopia showed a larger increase in VA (Awan et al. 2005; Clarke et al. 2003; Holmes et al. 2003); however, severe initial amblyopia is associated with a poor outcome (Flynn et al. 1998; Holmes et al. 2003; Stewart et al. 2005). In our study, severe amblyopia (BVCA ≥ 0.7 logMAR) was found in 56% of the children in the daily-patching group and in 80% of the children in the alternate-day patching group; the number of children was not significantly different between the groups. We found a substantial VA improvement from baseline to the 1-year control visit, with a final median BCVA of 0.1 logMAR in both groups ($p < 0.001$ for both comparisons). In addition, there were no significant differences in visual outcomes between the groups based on the BCVA at 1 year or the proportion of the amblyopia deficit corrected. Table 11 shows the visual outcomes at 1 year. There were no significant differences between the groups in the magnitude of change in BCVA or the median logMAR BCVA at all follow-up visits (Figure 12 and 13).

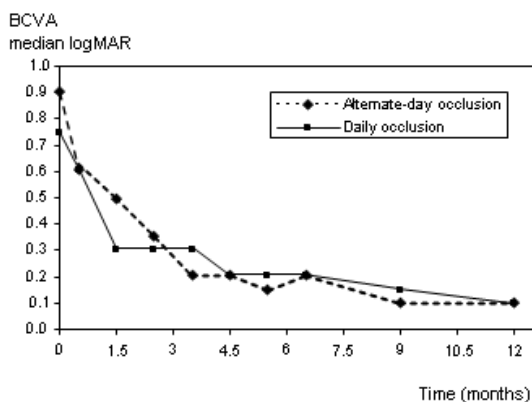


Figure 13. The BCVA over the study period expressed as the median logMAR.

The amblyopia resolved in 72% of the patients in the daily-patching group and in 75% of the patients in the alternate-day group. The median times to resolution of amblyopia (interocular difference, ≤ 1 line) were 3.6 months for the daily-occlusion group vs. 3.8 months for the alternate-day patching group, with no significant differences between the groups (Table 11). However, the study was dimensioned for the primary outcome measure, that is, the change in the BCVA, and any conclusions concerning the secondary outcome measures should be drawn with this in mind, since it is possible that these outcomes needed larger sample sizes to reveal clinically relevant differences.

Other studies have reported successful amblyopia treatment in 19% to 96% of patients (Flynn et al. 1998; Scott et al. 2005; Simons 2005; Stewart et al. 2004b), with the wide range probably due to differences in defining treatment outcomes, patient selection, treatment modalities and follow-up periods. Multicenter studies by the PEDIG reported a mean of 2.4 lines of improvement from baseline to 4 months and a mean VA of 0.24 logMAR at 4 months in both groups in children with moderate amblyopia treated with 2 hours vs. 6 hours of daily patching (Repka et al. 2003). Among children with severe amblyopia, improvements of a mean of 4.8 lines and a mean VA of 0.4 logMAR were found with 6 hours of daily patching, and with full-time patching the improvement averaged 4.7 lines from baseline to 4 months with a mean VA of 0.44 logMAR at 4 months (Holmes et al. 2003). The VA outcomes in the PEDIG studies are not comparable to the outcomes in the current study due to the lack of refractive adaptation before occlusion therapy in the current study and because VA testing was performed without reduced plus refraction on entry examination. In addition, there was a different duration of amblyopia treatment.

The baseline BCVA was based on the best VA with or without prescribed spectacles, since 34% of the children had decreased VA with spectacles due to the inability to relax accommodation. These young children wore spectacles for the first time at the baseline examination and had difficulties cooperating and determining the effect of a minus lens over the spectacles. Therefore, we might have underestimated the BCVA in some children at baseline; however, no child in either group had resolved amblyopia at 0.5 months. At the follow-up visits when the children were more adapted to the spectacles and more confident with the examination, we placed a minus lens over the spectacles.

Furthermore, since spectacles and patching were prescribed simultaneously without a period of refractive adaptation the improvement in VA in part may be secondary to wearing spectacles rather than patching therapy. Researchers have reported that VA can improve in strabismic amblyopia by refractive adaptation before occlusion therapy (Cotter et al. 2007; Moseley et al. 2002; Stewart et al. 2004a). However the studies evaluating treatment with spectacles alone in strabismic amblyopia have a small number of patients with no concurrent control group. Therefore it is possible that some of the improvement in these studies is due to learning effect, age effect, change in strabismus angle, regression to the mean, or chance account. Furthermore, Cleary reported that treatment with occlusion in combination with optical correction in strabismic amblyopia seems more effective than optical correction alone (Cleary 2000). In addition, researchers (Chen et al. 2007; Cotter et al. 2006) whom evaluated children with anisometropic amblyopia reported that severe amblyopia was unlikely to resolve with refractive correction alone, and that resolution of amblyopia was associated with lesser amounts of anisometropia. In the current study, anisometropia of 4 D or more was found in 7 (39%) of children in the daily-patching group and in 9 (45%) of children in the alternate-patching group.

Stewart et al., who objectively monitored occlusion, showed a positive, almost linear, dose response up to 400 hours (Stewart et al. 2004b; Stewart et al. 2007b) with most VA improvement occurring in the first 6 weeks of patching (Stewart et al. 2004b); they also found a plateau in the improvement at about 4 hours of patching a day (Stewart et al. 2007a). Nevertheless, we found no significant difference in the median change in BCVA or in the median time to resolution of amblyopia between the groups. Therefore, our study might indicate that not only the total number of hours of occlusion is important to VA recovery in amblyopia but also the total time from the initiation of amblyopia treatment. Since we did not use an objective method to measure occlusion, we cannot guarantee that the patients actually adhered to the patching regimen. However, compliance was estimated to be good in most children (72% of the children with daily occlusion and 80% of the children with alternate-day occlusion), with no significance difference between the groups. Compliance was determined by parental notations in a diary, direct questioning of the parents and the judgment of the investigator regarding good or reduced compliance. Children with good compliance had no reported compliance problems, whereas all children with reported compliance problems were judged as having reduced compliance. All parents were given the same information and support regarding therapy and outcome. Supplying parents with written information has been reported to change the parental attitudes and significantly increased compliance with treatment (Göransson et al. 1998; Newsham 2002).

We found improved binocular function in both groups, which agrees with other studies (Lee & Isenberg 2003). There were no significant differences between groups in the responses recorded at the final 1-year control for the Lang stereo test or the Bagolini glasses test (Table 12).

Table 12. Binocular function based on number of children and treatment group

	Daily-Patching Group (n=18)	Alternate-Day Group (n=20)
	Baseline visit/1 year	
Lang Stereo test II	0/4	0/7
Bagolini glasses test	5/15	8/18
Strabismus \geq 5 prism D with or without anisometropia	7/2	7/6
Strabismus $<$ 5 prism D with or without anisometropia, or anisometropia alone	11/16	13/14

The median spherical equivalent refractive error increased significantly during the study in the fellow eyes in both groups (daily occlusion, $p < 0.05$; alternate-day occlusion, $p < 0.001$) (Table 13). However, we found no significant change in the amblyopic eyes. Anisometropia was found in 12 (67%) children with daily occlusion and in 14 (70%) children with alternate-day occlusion (Table 14). Among these children, the anisometropia decreased significantly at the final visit in the daily-patching group ($p < 0.05$) and in the alternate-day group ($p < 0.001$). In study III, we also found an increase in the median spherical equivalent refractive error and a decrease in anisometropia in anisotropic amblyopes. One explanation for the increased hypermetropia might be that the cycloplegic drops did not relax accommodation fully at the first visit, but spectacle wear during the study relaxed the accommodation further (Bagheri et al. 2007). In addition, it previously was reported that hypermetropia increases during childhood until the age of 7 years (Brown 1938) and that anisometropia decreases with increasing age in amblyopes (Ohlsson et al. 2002).

Table 13. Change in median refractive error in D (range)

	Daily-Patching Group Spherical Equivalent (n=18)	Alternate-Day Group Spherical Equivalent (n=20)
Amblyopic eye		
First visit	+5.50 (+1.25 to +8.00)	+5.63 (+1.50 to +8.00)
1-Year visit	+5.50 (+1.25 to +8.75)	+5.75 (+1.50 to +8.50)
Fellow eye		
First visit	+2.00 (+1.50 to +7.00)	+2.50 (+1.00 to +4.00)
1-Year visit	+3.00 (+1.25 to +7.00)*	+2.88 (+1.00 to +5.25)***

* $p < 0.05$.

*** $p < 0.001$.

Table 14. Anisometropia change (D), median difference in refractive error between amblyopic eye and the better eye (range)

	Daily-Patching Group Spherical Equivalent (n=12)	Alternate-Day Group Spherical Equivalent (n=14)
First visit	+2.94 (+1.00 to +6.00)	+4.00 (+1.75 to +5.00)
1-Year visit	+2.38 (+1.75 to +5.25)*	+3.31 (+1.25 to +4.50)***

*p<0.05.

***p<0.001.

In summary, the magnitude of change in BCVA at 1 year after spectacles plus prescribed alternate-day patching did not significantly differ from that after spectacles plus prescribed daily patching for treating amblyopia in children aged 4 to 5 years. Therefore, alternate-day patching might be a way to adjust the occlusion treatment, especially in families in which daily occlusion may be problematic. The hyperopia increased in the fellow eyes and among the anisometropic children the anisometropia decreased during the study period. We found improved binocular function in both groups.

6 CONCLUSIONS

For the convenience of the readers, the aims (in italic type) are repeated with the conclusions.

1. To describe the refractive results and the visual outcome of paediatric cataract surgery in the Ukraine where postoperative correction with spectacles or occlusion therapy was not possible.

The immediate large postoperative astigmatism decreased substantially during the study period. The preoperative VA improved significantly to the postoperative 2-year control among the children with bilateral cataract and those with unilateral cataract despite no postoperative amblyopia treatment. This study showed that postponed surgery to treat bilateral or unilateral cataract of undetermined onset may be associated with visual improvement. Therefore, it is reasonable to recommend that almost all children with significant cataract, irrespective of age, should have cataract surgery if possible.

2. To evaluate foveal function in children treated for monocular amblyopia by conventional high contrast optotype BCVA testing, BCVA at two different contrast levels and the RFT.

When the foveal function was evaluated with optotype BCVA using the KM chart and with the TriVA test at different contrast levels, the amblyopic eyes showed significantly lower results compared to the fellow eyes and the control eyes. However, using the RFT, no significant difference was found when comparing the amblyopic eyes to the fellow eyes, although, both the amblyopic eyes and the fellow eyes had significantly lower results compared to the control group. The results agree with other studies that also reported abnormalities in the fellow eye in patients with anisometropia and/or strabismus. Our findings indicate that the RFT might provide different information about the foveal function compared to the other methods.

3. To conduct prospective and randomized clinical trials to evaluate different amblyopia treatments: such as translucent Bangerter filters or spectacles alone and different amount of prescribed patching regimens and to describe the refractive outcomes.

The anisometropia decreased and the hypermetropia increased in the fellow eyes during the follow-up period in both studies, in addition an increase in hypermetropia was found in the amblyopic eyes in study III.

We found improved binocular function in both studies.

Further, we found that children treated with Bangerter filters had a more rapid VA recovery than children treated with spectacles alone in eyes with anisometric amblyopia. However, the 1-year VA outcome did not differ significantly between the two treatments.

The median change in BCVA produced by spectacles plus alternate-day patching of 8 hours or more did not differ significantly compared with spectacles plus patching 8 hours or more daily 6 days a week for treating amblyopia in children 4 to 5 years old. Therefore, alternate-day patching might be a way to adjust the occlusion treatment, especially in families in which daily occlusion may be problematic.

7 SAMMANFATTNING PÅ SVENSKA

Avhandling för avläggande av medicine doktorsgrad vid Karolinska Institutet, Institutionen för Klinisk Neurovetenskap, Sektionen för Ögon och Syn, S:t Eriks Ögonsjukhus 2009.

AMBLYOPI

Synförmågan uppstår i ett finstämt samspel mellan ögonen och hjärnan. En bild når ögat och omvandlas i näthinnan till nervsignaler som skickas vidare via synnerven till hjärnan för bearbetning och tolkning. Amblyopi är den medicinska term som används för synnedsättning orsakad av ogynnsam synutveckling under barnaåren. Amblyopi är oftast ensidig. Ögat ser friskt ut, men används inte på ett normal sätt eftersom hjärnan favoriserar det andra ögat.

Amblyopi är den vanligaste orsaken till ensidig synnedsättning hos barn. Om amblyopin inte upptäcks och behandlas under barndomen riskerar barnet att få en bestående synnedsättning. I Sverige synprövas de flesta barn på barnavårdscentralerna första gången när de är 4 år gamla och då upptäcks vanligtvis amblyopin.

Det finns många olika orsaker till amblyopi, t.ex. skelning. Ibland uppkommer amblyopi när ena ögat har ett större brytningsfel än det andra ögat (anisotropi), vanligtvis översynthet eller astigmatism. Även andra synnedsättande tillstånd som t.ex. grumlad lins (grå starr) hos barn kan orsaka amblyopi.

Amblyopi behandlas genom att få barnet att använda sitt sämre öga, så att synutvecklingen stimuleras. Detta kan göras på olika sätt:

1. Skapa en klar bild i det amblyopa ögat med hjälp av operation vid synnedsättande tillstånd som t.ex. grå starr. Vid brytningsfel som orsakar amblyopi, kan glasögon förskrivas.
2. Synen i det amblyopa ögat kan stimuleras genom att täcka för det bättre ögat med en ogenomskinlig plåsterlapp på huden eller med ett halvgenomskinligt filter på glasögat. Att framkalla en oskarp bild med pupillvidgande ögondroppar i det bättre ögat är ytterligare en metod.

I avhandlingen studeras olika aspekter på amblyopi i 4 delarbeten.

Delarbete I

Dubbelsidig medfödd grå starr är en vanlig orsak till behandlingsbar blindhet hos barn. Tidig operation följt av intensiv amblyopibehandling kan ge bra syn. I utvecklingsländer är oftast möjligheten att genomföra den efterföljande amblyopibehandlingen begränsad.

Sextiofem barn, 3 – 15 år, opererades i Ukraina för grå starr. Vid upprepade kontroller under 2 års tid utvärderades eventuella brytningsfel samt synskärpan. Ingen amblyopibehandling med glasögon/kontaktlinser eller lapp var möjlig pga. den svåra socioekonomiska situationen i Ukraina. Tidpunkten för uppkomst av grå starr var i de flesta fall okänd. Vi fann att den kraftiga astigmatismen (brytningsfel), som orsakas av

suturerna vid operationen, minskade signifikant under uppföljningstiden. Barnens synskärpa förbättrades trots avsaknad av amblyopibehandling efter operationen. Därför rekommenderar vi att de flesta barn med betydande grå starr, oavsett ålder, bör opereras om möjligt.

Delarbete II

Diagnos och uppföljning av amblyopi bygger på synundersökning med syntavla. Rarebit Fovea Test (RFT) är en ny metod att mäta gula fläckens (foveas) funktion och har utvecklats för att upptäcka små och/eller tidiga syndefekter.

I denna studie utvärderade vi gula fläckens funktion hos 24 barn med tidigare behandlad amblyopi samt 25 kontrollbarn. Barnens syn undersöktes på 3 sätt;

1/ synskärpebestämning vid hög kontrast (vanlig syntavla), 2/ synskärpemätning på olika kontrastnivåer (TriVA-test), 3/ med RFT. Med två av metoderna; vanlig syntavla och TriVA noterades att de amblyopa ögonens synskärpa var sämre än de icke-amblyopa "friska" ögonen samt även jämfört med kontrollbarnens ögon. När gula fläckens funktion utvärderades med RFT fann vi ingen skillnad i resultaten mellan det amblyopa ögat och det andra, "friska" ögat. Däremot kunde RFT påvisa ett sämre resultat när både de amblyopa ögonen och de "friska" ögonen jämfördes med kontrollbarnens ögon. Dessa fynd talar för att gula fläckens funktion i det "friska" ögat hos amblyopa barn kan vara nedsatt. Våra resultat överensstämmer med andra studier som också rapporterar försämrad funktion i det "friska" ögat hos barn med amblyopi. Fynden antyder även att RFT kan ge annan information om gula fläckens funktion jämfört med de andra metoderna i vår studie.

Delarbete III och IV

Lappbehandling är en vanlig metod för att behandla amblyopi. Behandling kan vara svår att genomföra då barnen inte vill bära lappen. Därför är det av värde att utvärdera andra metoder för amblyopibehandling samt att utvärdera effekten av olika lappbehandlingstider.

I **delarbete III** jämfördes amblyopibehandling med enbart glasögon mot behandling med glasögon + Bangerter filter (halvgenomskinligt filter). Åttio barn, 4-5 år, med amblyopi pga. anisotropi deltog i studien. Synskärpa, samsynsfunktion och brytningsfel kontrollerades regelbundet under 1 år. Vi noterade att översyntheten ökade i de amblyopa och i de icke-amblyopa ögonen i båda grupperna. Anisotropin minskade däremot i båda grupperna. Vi fann att synskärpan förbättrades snabbare med glasögon + Bangerter filter jämfört med enbart glasögon. Vid 1-års kontrollen noterades ingen skillnad i synskärpa mellan grupperna.

Delarbete IV utvärderar frågan om olika intensiv lappbehandling hos 4-5 åriga barn med amblyopi. Grupperna hade glasögon + lapp 8 timmar eller mer/dag, den ena gruppen 6 dagar/vecka, den andra varannan dag. Synskärpa, samsynsfunktion och brytningsfel mättes regelbundet under 1 år. Resultaten visade att anisotropin minskade i båda grupperna. Synskärpan ökade i båda grupperna till 0.1 logMAR (0.8 decimalsynskärpa). Vi fann ingen skillnad i förändringen av synskärpan under studietiden när grupperna jämfördes. Av detta skäl kan lapp varannan dag vara ett alternativt sätt att behandla barn som har svårigheter med daglig lappbehandling.

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