Amblyopia and amblyopia treatment study

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ABSTRACT

Amblyopia comes from the Greek word meaning dull sight or blunt sight. Amblyopia occurs to abnormal visual experience early in life. It can be both unilateral (U/L) and/or bilateral (B/L). Amblyopia itself produces no change in the appearance of ocular structures, but it nearly always develops in association with some other condition that is evident on physical examination, and which is responsible for abnormal visual experience. It is one of the most common causes of visual impairment in childhood. Unless it is successfully treated in early childhood, amblyopia usually persists into adulthood. In 1997, the pediatric eye disease investigator group (PEDIG) was formed to conduct clinical research in eye disorders affecting children. The studies were conducted through simple protocols with limited data collection and implemented by both university and community based pediatric eye care practitioners as part of their routine practice in USA. Hence PEDIG has laid emphasis on studies of treatment modalities of amblyopia, the Amblyopia Treatment Studies (ATS). The recent general guidelines for occlusion therapy are based on ongoing ATS. New concepts of management on amblyopia are practiced now- a-days based on ATS. This article is an update on amblyopia and its management.

Keywords: Amblyopia; Amblyopia Treatment Studies; Patching

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Background:

Amblyopia comes from the Greek word meaning dull sight or blunt sight. Amblyopia occurs to abnormal visual experience early in life. It can be both unilateral and/or bilateral. In amblyopia all the ocular structures are normal, but it nearly always develops in association with some other condition that is evident on ocular examination, and which is responsible for abnormal visual experience.[1]

Amblyopia is more complex than simply visual acuity loss and the better eye has sub-clinical deficits.[2] In addition to loss of Snellen and grating acuity, there may be loss of vernier acuity, [3] loss of sensitivity to the contrast in a stimulus[4], distortions in the shape of a stimulus [5], some uncertainty about the position of a stimulus[6], motion deficits[7] and an increase in the magnitude of the crowding effect or separation difficulty. [8]

Cause: Amblyopia results from disuse from inadequate foveal or peripheral retinal stimulation and/or abnormal

binocular interaction that causes different visual input from the foveae .[9]

Amblyopia is a visual impairment secondary to abnormal visual experience (e.g., strabismus, anisometropia, form deprivation) during early childhood. It is the most common cause of monocular blindness globally.[10]

Histological Findings: Atrophy of the cells of the of the lateral geniculate nucleus has been noted in monkeys with stimulation deprivation.[11]

Critical Period: Amblyopia is a neural disorder that results from abnormal stimulation of the brain during the critical periods of visual development. It is essential to understand the neural mechanisms of amblyopia in order to devise better treatment strategies. [10]

There are 3 periods in the development of visual acuity and development of ocular dominance. Evidence about acuity comes primarily from studies with humans. During the first 3 to 5 years of life, acuity develops from less than 20/200 to near 20/20, as measured by tests that exclude any crowding effects. During these years, acuity can be reduced by the various forms of deprivation leading to amblyopia. However, amblyopia is not confined to the first 3 to 5 years of life, but can result from strabismus or anisometropia at any age, from several months to 7 or 8 years of age. Recovery of acuity lost to amblyopia can occur in even older individuals.

Eye care professionals have obtained positive results after sustained treatment of teenagers, and in a few cases adults who are affected by amblyopia. Thus, one can talk about 3 periods for acuity: the period of development of visual acuity (birth to 3-5 years of age), the period during which deprivation is effective in causing amblyopia (a few months to 7 or 8 years of age), and the period during which recovery from amblyopia can be obtained (time of deprivation to the teenaged years or even into the adult years).[12] A similar distinction of periods is found in the study of ocular dominance in animals. The nerve fibers from the lateral geniculate that terminate in layer IV of the visual cortex segregates into left and right eye stripes between birth and 6 weeks of age in the macaque monkey, but this pattern of stripes can be altered by monocular deprivation until 10 weeks of age.[13]

Prevalence: In Nepal, there is no population based study on the prevalence of amblyopia. However there are few studies on school children which shows the prevalence of amblyopia to be 0.9 to 1.8%.[14, 15]

Types:

1. **Anisometropic Amblyopia:** Amblyopia can develop as a result of unilateral or bilateral refractive errors. Second in frequency to strabismic amblyopia, it develops when unequal refractive error in the two eyes causes the image on one retina to be chronically defocused. This condition is thought to result partly from the direct effect of image blur on the development of visual acuity in the involved eye and partly from interocular competition or inhibition similar (but not necessarily identical) to that responsible for strabismic amblyopia. Relatively mild degrees of hyperopic or astigmatic anisometropia (1.0 diopter [D] to 2.0 D) can induce mild amblyopia. Myopic anisometropia, less than -3.0 D, usually does not cause amblyopia, but unilateral high myopia (-6.0 D or greater) often results in severe amblyopic visual loss. [16, 17] Astigmatic anisometropia of >1.50 D may cause amblyopia.

2. **Isometropic Amblyopia:** It is a form of refractive amblyopia, where bilateral reduction in visual acuity is usually relatively mild and results from large, approximately equal, uncorrected refractive errors in both eyes of a young child. Its mechanism involves the effect of blurred retinal images alone. Hyperopia exceeding about 5.0 D and myopia in excess of 10.0 D carry a risk of inducing bilateral amblyopia.[16]

3. **Meridonial Amblyopia (MA):** Uncorrected astigmatism during early development can result in MA. In current clinical practice, astigmatism-related amblyopia in the absence of anisometropia, strabismus, and other ocular abnormalities is treated by providing the individual with clear visual input through optical correction of the astigmatism. Early retrospective studies suggest that the sensitive period for successful treatment of MA is prior to age seven years. [18]

4. **Strabismic Amblyopia:** It is associated with ocular misalignment and consequent abnormal binocular interactions. The patient favors fixation strongly with one eye and does not alternate fixation. Cortical suppression from the deviating eye results from inhibitory interactions of neurons carrying nonfusable images. This leads to inhibition of visual input to the retinocortical pathways. Incidence of amblyopia is greater in esotropic patients than in exotropic patients.

5. **Stimulation deprivation Amblyopia:** The old terms amblyopia *ex anopsia* and disuse amblyopia are

sometimes still used for visual deprivation amblyopia, which is caused by obstruction of the visual axis. Amblyopia results from disuse or under stimulation of the retina due to lack of pattern stimulation to the retina. Congenital ptosis, corneal opacities, congenital cataract, and congenital macular scars are the causes of the simulation deprivation amblyopia. [19] This is rare, accounting for less than 3% of amblyopic patients; however, it has the most potential to produce severe vision loss and difficult to treat.[20] Unilateral occlusion of the visual axis tends to be worse than that produced by B/L deprivation of similar degree because interocular effects add to the direct developmental impact of severe image degradation. Even in B/L cases, visual acuity can be 20/200 or worse. Newborns with U/L cataract have a better prognosis, if cataract surgery and optical correction is done by 3 months of age to minimize deprivation and maximize visual prognosis.[21, 22]

6. **Reverse Amblyopia:** Iatrogenic interference with vision in childhood (therapeutic occlusion or cycloplegia) can cause amblyopia. In the treatment of unilateral amblyopia, the initially amblyopic eye usually seems to achieve normal vision in the process, but occasionally bilateral amblyopia may result .[23] Severe amblyopia has been reported after as little as 1 week of unilateral patching in children under 2 years of age following minor eyelid surgery[24] However with the newer concept of part time occlusion, reverse amblyopia does not occur in the normal eye.

Visual acuity in amblyopia: Amblyopia is an example of abnormal visual development that is clinically defined as a reduction of best corrected Snellen acuity to less than 6/9 (20/30) in one eye or a two-line difference between the two eyes, with no visible signs of eye disease.[25]

Types of amblyopia according to severity as defined in ATS:

Mild to Moderate: visual acuity in the amblyopic eye between 20/80 or better

Severe: visual acuity in the amblyopic eye between 20/100 and 20/400.[16]

Spatial Interactions: Visual acuity is better when the patient is presented with single optotypes rather than a line of letters. This is the "crowding phenomenon" or "separation difficulty". In the normal fovea, contour interaction occurs when forms are separated by a distance of 1 to 3 minutes of arc (0.2 to 0.6 times the overall size of a 6 meter Snellen letter); in the normal periphery its extent is much greater. In the amblyopic fovea, contour interaction typically extends over an increased distance, to a degree that is roughly proportional to the reduction in acuity.[26]

Color vision: In amblyopia, color vision is not affected. However, when acuity is severely reduced errors are common.[1]

Pupillary Light Reactions: Pupillary reaction is normal in most amblyopic eyes. Pupillography shows subtle alterations of pupillary light reaction in amblyopic eyes. [27, 28] In about 10% of all amblyopic patients, afferent pupillary defect is detectable by swinging flashlight .[29]

Contrast sensitivity: Strabismic and anisometropic amblyopic eyes have marked losses of threshold contrast sensitivity, especially at higher spatial frequencies; this loss increases with the severity of amblyopia.

Neutral density filters: Patients with strabismic amblyopia may have better visual acuity when tested with neutral density filters compared to the normal eye. This is not so in patients with anisometropic amblyopia.

Binocular function: Amblyopia usually is associated with changes in binocular function or stereopsis. Stereopsis will never be obtained unless amblyopia is treated, the eyes are aligned, and binocular fusion and function are achieved before the critical period for stereopsis ends. This occurs before 24 months of age. [26], [30] But the crucial pieces of basic science information are missing. It is not known when stereopsis develops. Stereoscopic acuity reaches 60 minutes of arc between 2 and 5 months of age, and then increases very rapidly over the next month .[31] There is a slower increase between 6 months and 3 years of age.[32, 33]

Treatment:

Treating amblyopia involves making the child use the eye with the reduced vision (weaker eye). Different modalities include:

1. Refractive correction
2. Patching/ occlusion therapy
3. Penalization
4. Surgery for stimulation deprivation amblyopia and strabismus

1. **Refractive correction:** The amblyopic eye must have the most accurate optical correction prior to any occlusion therapy. Glasses alone can improve

amblyopia in about one third of children especially in anisometropic amblyopia.[34] Full cycloplegic refraction should be given to patients with accommodative esotropia and amblyopia is treated successfully with spectacles alone.[34]

2. **Patching/Occlusion therapy:** has been the mainstay of treatment since the 18th century.[35] This forces the child to use the amblyopic eye. Patching stimulates vision in the weaker eye and helps the part of the brain that manages vision develop more completely.

   In 1997, the pediatric eye disease investigator group (PEDIG) was formed to conduct clinical research in eye disorders affecting children. Since amblyopia is the most common cause of monocular visual impairment in children and young and middle aged adults; PEDIG has laid emphasis on studies of treatment modalities of amblyopia, the Amblyopia Treatment Studies (ATS). The recent general guidelines for occlusion therapy are based on ongoing ATS.

   ATS1: The ATS 1 study was conducted to compare patching of the sound eye with atropine instillation. In this prospective randomized multicentric clinical trial, moderate amblyopes (20/40 to 20/100) in the age group 3 to 7 years were included. Improvement initially was faster in the patching group, but at 6 months difference in acuity between the 2 groups was clinically insignificant. The conclusions were both treatments were well tolerated, though atropine had more tolerability and patching works faster than atropine.[36]

3. **Penalization therapy:** In the past, penalization therapy was reserved for children who would not wear a patch or in whom compliance was an issue. ATS have also demonstrated that weekend atropine provided an improvement in visual acuity similar to that of daily atropine when treating moderate amblyopia in children aged 3-7 years.[37] Atropine drops or ointment is instilled in the non-amblyopic eye. This therapy is sometimes used in conjunction with patching or occlusion of the glasses.

   In the ATS that evaluated patching versus atropine penalization, atropine penalization and patching were used in conjunction with 1 hour of near visual activities. This technique may also be used for maintenance therapy, which is useful especially in patients with mild amblyopia.

Atropine has a very slow onset. It dilates the pupil, but that's not the major affect that is needed in the treatment of amblyopia. The major affect that is necessary is relaxation of accommodation. The drop last 24 hours, but its onset is very slow. The peak strength occurs if the medication is given at bedtime. If atropine is given in the morning, it may not be at its full strength until noon and part of the day is already over. Atropine works very well if the amblyopia is mild or moderate. It is easier than the patch. For, severe amblyopia, there is no substitute for a patch.

ATS 2A: ATS 2A compared 6 hours versus full time patching for severe amblyopia (20/100 to 20/400) in children 3 to 7 years old. This study formed the basis for a paradigm shift from full time daily patching routines to part time occlusion.[38]

ATS 2B: ATS 2B, compared 2 hours versus 6 hours of daily patching for moderate amblyopia in children aged 3 to 7 years old. It was noted that prescribing greater hours of patching did not seem to have a significant beneficial effect in the first 4 months of treatment. It was also noted that the hours of patching did not affect the rate of improvement.[38- 43]

ATS 2C: ATS 2C was undertaken to study the recurrence of amblyopia after discontinuation of treatment. Approximately one fourth of the children were noted to have a recurrence of amblyopia in the first year post treatment. This is similar in the patching and atropine group. In patients with intense patching (6-8 hours per day), recurrence was more common when the treatment was not reduced prior to cessation, than when treatment was reduced to 2 hours per day prior to cessation.[44] Thus, maintenance therapy or tapering of therapy should be strongly considered. This tapering is controversial, so individual physicians vary in their approaches.

Recurrence was usually detectable within the first 13 weeks after discontinuation of therapy. When the decision is made to discontinue amblyopia treatment, weaning may decrease the rate of regression and patients should have close follow-up, especially during the first 3 months after therapy has been discontinued.

ATS 3: ATS 3 evaluated the effectiveness of treatment in children aged 7 to 17 years.[45,46] For patients aged 7 to 12 years, 2 to 6 hours of patching with near visual activities and atropine improves the visual acuity even if the amblyopia has been previously treated. For

patients aged 13 to 17 years, 2 to 6 hours of patching per day with near visual activities may improve when amblyopia has not been previously treated, but is of little benefit if amblyopia was previously treated with patching.

Additional follow-up is being conducted to determine if improvement in visual acuity will be sustained once treatment is discontinued. It is not yet known whether visual acuity improvement will be sustained once treatment is discontinued; therefore, conclusions regarding the long-term benefit of treatment and the development of treatment recommendations for amblyopia in children 7 years and older await the results of a follow-up study that are being conducted on the patients who responded to treatment. Long-term results from these studies are still pending.

Optical correction: PEDIG study in 2006 conducted to evaluate the results of 2 hours of daily patching for amblyopia in children aged 3 to 7 years old. There were 2 phases (1) spectacle phases in which maximum improvement with spectacles was noted and the (2) randomized trial comparing a group using patching treatment and spectacles with a control group using spectacle correction alone. Following treatment with spectacles, 2 hours of daily patching combined with 1 hour of near visual activities modestly improves moderate to severe amblyopia in children 3 to 7 years old.[7,48]

Role of near activities PEDIG study 2005 was designed to determine whether children randomized to near or non-near activities would perform prescribed activities and to obtain a preliminary estimate of the effect of near versus non near activities on amblyopic eye visual acuity when combined with 2 hours of daily patching. Performing near activities while patching may be beneficial in treating amblyopia.[45]

How much treatment is enough?

In answer to this question, Repka in 2008 has mentioned that the target is the spontaneous alternation of fixation or equal visual acuity in both eyes.[49]

Conclusions from the PEDIG studies

These studies conducted by PEDIG put forth new ideas and concepts in the management of amblyopia based on prospective trials.[35] The conclusions of the various studies have been summarized below.[35]

- In moderate amblyopes, patching works faster than atropine; however at 6 months the improvement is the same with patching and atropine.
- In severe amblyopes, improvement with full time and 6 hours patching is similar.
- In moderate amblyopes, 2 hours patching gives similar results to 6 hours of patching.
- About 25 % of the children have a recurrence of amblyopia in the first year post treatment.
- Recurrence is less common when patching was tapered to 2 hours per day before stopping.
- In patients 7 to 12 years of age, visual acuity improves with treatment even if amblyopia has been previously treated; in the 13 to 17 year age group, there may be little benefit if the amblyopia has been previously treated.
- Glasses improve visual acuity in anisometropic amblyopia and B/L MA.
- Most cases of moderate amblyopia (20/40 to 20/100) resolve.
- Patching with near activities is beneficial in treating amblyopia.
- Maximum improvement with therapy occurs in the first 6 weeks.
- Outcome is better in younger child.

Surgical Management

For the strabismic amblyopia, strabismus surgery is performed according to the type of strabismus. Similarly, for the stimulation deprivation, pediatric cataract surgery, or the ptosis surgery should be done according to the aetiology of the stimulation deprivation. However, glasses should be used and patching should be done even after the surgery as per visual and refractive status of the patient.

Conclusion:

Amblyopia occurs to abnormal visual experience early in life. It is one of the most common causes of visual impairment in childhood. As per the ATS studies, the treatment of amblyopia is part time patching of the better eye. For severe and moderate amblyopia, six hours and two hours of patching is advised respectively. Atropine is also used in children with poor compliance. Trial of patching can be given in patients as old as 17 years of age.

Conflicts of Interest: None

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