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Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Is amblyopia of any severity fully treatable, irrespective of a patient's age?

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ARTICLE INFO

Article history:
Received 20-01-2024
Accepted 25-02-2024
Available online 30-03-2024

Keywords:
Amblyopia
Patching
Occlusion amblyopia
Anisometropic amblyopia
Eccentric fixation
Visual recovery

ABSTRACT

Primary Objectives: **1**: To find out the level of visual improvement and the time it takes in amblyopia of any severity. **2**: To find out whether the level of visual improvement is influenced by a patient's age at presentation.
Secondary Objectives: **1:** To note whether the level of visual recovery is influenced by previous amblyopia therapy. **2:** To note any regression of visual acuity with time after initial improvement by therapy. **3:** To note complications of full-time occlusion therapy, especially occlusion amblyopia.
Materials and Methods: In a prospective interventional study, 1701 consecutive cases with poor vision were included irrespective of a patient's age. After wearing refractive correction for 8-12 weeks and no further improvement in the BCVA, amblyopia therapy was started comprising of full-time patching of the good eye along with active use of the amblyopic eye by reading and writing at least 6 hours daily. Regular two weekly follow-ups were conducted. The endpoint of therapy was achieving a BCVA equal to that of the good eye. A regular post-patching follow-up was conducted for 1-3 years. Statistical analysis comparing the visual acuity at the start and the end of therapy was performed by a paired t-test for each group.
Results: There were 896 male and 805 female cases. 1383 cases (81.3%) had previously failed amblyopia therapy. 49 cases (2.9%) dropped out of the study due to poor compliance with therapy or an incomplete follow-up. For a simplified analysis of results, the 1701 cases were divided into three age groups: Group A: age 4-7 years (473 cases), Group B: age 8-12 years (618 cases) and Group C: age 13-46 years (610 cases). The overall success in Group A and B cases was 98% and 96.9% in Group C cases.
Conclusion: Full visual recovery is possible in amblyopia of any severity and age. The age of a patient at presentation should not preclude therapy.

1. Introduction

Amblyopia (lazy eye) is a disorder of the visual system that occurs in a physically normal eye, characterised by an unexplained reduction of visual acuity.[1] There is a rapid development of the whole visual system during the first 5-6 years of life, called "the critical period of visual development".[2,3] If the visual input is unequal from both eyes during this period, the brain shuts down (actively inhibits) the blurred signals from the weaker eye whilst promoting the clear image from the good eye. The neural connections of the amblyopic eye to the higher visual centers break due to its disuse. Hence, amblyopia has been considered a wiring problem that affects the brain globally.

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https://doi.org/10.18231/j.ijceo.2024.005

It is relatively easy to correct the visual loss during the critical period by improving the quality of visual input in an amblyopic eye.[4,5] The estimated prevalence of amblyopia worldwide is 1–5%.[6] In adults, it is considered the number one cause of unilateral blindness that can be prevented by organised screening programs in children. The potential risk to visual loss in the good eye increases to 17 times more in a child and 3 times more in an adult than in a normal person.[7]

Ophthalmologists generally believe that amblyopia is difficult to treat once the critical period of visual development has passed.[8] However, many cases of spontaneous improvement in the visual acuity of the amblyopic eye following visual loss in the good eye in elderly patients have been reported.[9–11] Studies on the neuroplasticity of brain have demonstrated that the brain is not a physiologically static organ; it can modify throughout life by forming new neural connections between existing brain cells and strengthening the older ones.[12,13] This ability is the strongest during the critical period when maximum brain growth occurs; it slows down with age but never stops.[14–16] This was explained based on GABA (Gamma Amino Butyric Acid) which is an excitatory neurotransmitter that stimulates neural receptors in immature, developing brains. The brain receptors are turned "Off" with age, but they could be turned "On" if GABA is released in response to a strong stimulus[17] that must be persistent to stabilise the newly formed neural connections. Dopamine is another neurotransmitter present in the retina that stimulates receptors but it does not cross the blood-brain barrier.[18] Therefore neural stem cells (progenitor cells) can be made to regenerate neurons in the brain.[19] That is how adults continue to learn throughout life due to continued neurogenesis in the memory area.[20]

An individual with an amblyopic eye not only has poor vision, but also a reduced field of clear vision, low contrast sensitivity, poor spatial acuity, and reduced sensitivity to motion in that eye.[21] Such an adult has a limited choice of professions due to reduced binocular functions like limited depth perception, stereopsis, and reduced field of vision.[22] This poses an important question to clinicians why amblyopia should not be treated in older children or adults? The findings on adult neurogenesis formed the basis of our study. We wanted to find out whether the neural connections of an amblyopic eye of any severity can be reactivated, irrespective of a patient's age, through strong and persistent stimulation.

2. Materials and Methods

A prospective, interventional study was conducted over 12 years, from January 2010 to December 202, at two tertiary care centres.

Literate cases presenting with unilateral mild, moderate, or severe amblyopia in whom the BCVA could be accurately assessed were included in this study. There was no upper age limit for inclusion in the study.

A complete history was taken regarding birth (prematurity, birth weight, asphyxia, cyanosis, jaundice, and oxygen therapy), developmental milestones, neonatal health problems, the onset of strabismus, visual problems, previous therapy with glasses, patching, atropine penalisation or strabismus surgery.

Complete ophthalmological examination, assessment of strabismus, and foveal or extra-foveal fixation (by a visuoscope) were performed by two ophthalmologists.

Visual acuity was assessed by three optometrists who were unaware that these were study cases. First, the distance vision was checked on both the Snellen's & the ETDRS charts projected on a screen by electronic Visual Acuity Tester (ACP-8 chart projector) at a distance of 6 meter from the patient. The patients either wore the refractive glasses (prescribed elsewhere) or unaided in those cases who had not been prescribed glasses yet. It was recorded in the clinical notes in the British system (6/6,6/9-6/60), and its decimal fraction (6/6=1.0, 6/9=0.8) for easy understanding and plotting of the graphs. The near vision was checked by the Reduced Snellen's reading chart held at 14 inches with the patient wearing the refractive correction prescribed at the first visit by our optometrists. Color vision (tested by Ishihara color plates), evaluation of binocularity (by Bagolini's striated glasses and Worth four dot test), and stereopsis (Randot stereo test) were performed at the initial visit.

Cycloplegic refraction was carried out only in children between the age of 4-7 years. 1% atropine eyedrops were prescribed 3 times/day for 3 days (along with punctal occlusion by the parent) in cases with esophoria or esotropia. Cases that were either orthophoric or exotropic, had 1% cyclopentolate eye drops instilled 3 times at 15 min intervals in the clinic to confirm the refractive error. Subjective refraction was performed by the optometrists one week later after the effect of the cycloplegic drug had worn off and maximum correction was prescribed for constant wear. The cases that were older than 7 years were prescribed the refractive correction (without cycloplegia) that gave the Best Corrected Visual Acuity for both near and distant vision.

The diagnostic criteria for amblyopia was the persistence of difference in the BCVA of 2 or more lines between the two eyes after constant spectacle wear. The cases with a reduced visual acuity in only one eye and a BCVA of 0.8-1.0 on the ETDRS chart (equal to 6/6 Snellen's) in the good eye were selected for the study.

All cases were examined again after 8 weeks of constant spectacle wear and those with an improvement in the BCVA were asked to continue with their glasses for another 8 weeks. Cases which failed to demonstrate visual improvement after 12-16 weeks of constant spectacle wear were considered amblyopic and were enrolled in the study.

The cases with spontaneous improvement in the visual acuity after wearing refractive correction for 8-16 weeks (Refractive/optical Adaptation) were excluded from the study as they did not require occlusion therapy.

The cases with an organic ophthalmic cause for poor vision or bilateral ammetropic amblyopia were also excluded. They had central corneal scarring, maculopathy, optic disc hypoplasia or coloboma, optic atrophy, and nystagmus (as it gets worse by occluding an eye).

Definite amblyopia therapy: After having worn the refractive correction for 8-16 weeks, and achieving no further improvement in the visual acuity, amblyopia therapy was started that consisted of:

1. Full-time occlusion of the good eye by a commercially available adhesive eye patch worn over the closed eyelids during all waking hours (to be taken off only during sleep). .
2. An active use of the amblyopic eye by book-reading and writing (from their school, university syllabus) for minimum of 5-6 hours daily.

The patients were strictly instructed to wear the eye patch soon after waking up in the morning, with the refractive glasses worn over it. The eye patch must be worn during all waking hours and taken off only at bed time. They were instructed to start reading with the amblyopic eye initially, with an enlarged font that was visible to them with their glasses on (a newspaper, magazine, school book, or print-outs of their study syllabus taken from a computer). They should gradually reduce the font size daily or every second day. The younger children could also do colouring, drawing, and writing by connecting dots.

The cases with gross eccentric fixation (fixation far from the fovea) were advised Inverse Occlusion for two weeks. In this, the amblyopic eye was occluded by an eye patch. After two weeks, the study protocol was resumed and the good eye was occluded full-time while they were allowed to see with the amblyopic eye through a pinhole cut in the center of dark tape applied over the correcting glasses. The cases with a mild degree of eccentric fixation (para-foveal= 1.25 mm from the foveal pit), were allowed to follow the regular study protocol. Once they stopped showing further visual improvement on 2 consecutive follow-ups, they were instructed to use the amblyopic eye through the pinhole (explained above). Their visual progress was monitored similar to other patients in the study.

The mild to moderately amblyopic patients were allowed to continue their normal activities like going to school, college, or office. However, the cases with severe amblyopia were issued a medical leave certificate for 3-4 weeks as they were unable to follow the usual routine after occluding the good eye. They were instructed to stay at home and study with the amblyopic eye till its visual acuity had improved to at least 0.4-0.5 (6/18-6/12 Snellen's). Once this was achieved, they could safely go outdoors with the good eye occluded.

Cases that were of age 7 years or more were followed up regularly at two weekly intervals while those with age less than 7 years were followed up weekly. The duration of follow-up was a minimum of 12 months to a maximum of 3 years (median 24 months). The cases which failed to complete the minimum follow-up of 12 months were considered dropped out of the study.

At each visit, first, the distance vision with ETDRS and Snellen's charts (both letters and E charts) and then the near vision of the amblyopic eye was recorded whilst keeping the good eye patched. This was followed by removing the eye patch from the good eye and noting its visual acuity. Any patch-associated skin problems or diplopia were noted.

The end point of therapy: The full-time occlusion therapy was continued till the BCVA in the amblyopic eye equalised to that of the good eye (0.8-1.0 or 6/7.5-6/6) or no further improvement was noted on two consecutive follow-ups. At that visit, binocular vision and stereopsis were re-assessed and recorded in the clinical notes.

The weaning protocol for occlusion therapy was commenced when no further improvement was noted in the amblyopic eye on 2-3 consecutive follow-up visits or when the BCVA equalised in both eyes.

Patients were instructed not to patch the good eye for one day in the first week and then two days in the second week while they would patch full-time in the remaining days of the week. BCVA was checked after two weeks and if it remained stable, then further weaning was continued with the patch off for 3 days in the third week, 4 days off in the 4th week, till patching was totally off after 7 weeks. If any regression of amblyopia was detected during the weaning period, full-time patching was resumed again for a further 2 weeks, and weaning re-started once full visual recovery was noted. Patients were regularly followed up at 2-3 week intervals for the next 12-24 months. At each visit, their visual acuity for both distance and near vision, the angle of strabismus, and stereopsis were measured.

Successful outcome of occlusion therapy was considered when there were a minimum of 4-5 lines improvement in the BCVA of the amblyopic eye.

Resolution of amblyopia was defined as an improvement in visual acuity of the amblyopic eye to within 1 line of the fellow eye i.e.6/9-6/6 (0.8-1.0).

Compliance with therapy was assessed by:

1. The patients came to clinic for regular follow-up visits (weekly in Group A cases and every 2 weeks for Group B & C cases).
2. They came to the clinic wearing patch over the amblyopic eye.
3. They were reading and writing regularly for 4-6 hours/day

4. Ophthalmologist noted patch-related skin discoloration, mild skin redness, or a rash (few macules/papules) after removing the eye patch. Cases with skin rash were instructed to apply a mild steroid cream over the rash once the eye patch was taken off at night.

The study was approved by the ethics committee of the hospital. The parents/care-takers and the patients were fully explained and counselled regarding the rationale of full-time occlusion therapy and how it works in order to ensure their full cooperation and compliance. Verbal consent was obtained from the parents/caretakers of all cases and mentioned in the clinical notes.

Statistical analysis for analysing the improvement in visual acuity in each age group, from the start and at the end of full-time occlusion therapy, was performed by the student's t-test and the p values were calculated for the given data.

3. Results

The total number of cases included in the study was 1701, with 896 male (52.7%) and 805 female cases (47.3%), as shown in Table 1.

Table 1: Demographics of total 1701 cases

Characteristics		**No. of cases**	**%**
Gender	Males	896	52.7%
	Females	805	47.3%
Previous Amblyopia Rx	Part-time patching	994	58.5%
	Atropine Penalisation	232	13.6%
	Fogged glasses	157	9.2%
	Total no with previous Rx	**1383**	**81.3%**
Age Groups			
	Group A: 4-7 yrs	473	27.8%
	Group B: 8-12 yrs	618	36.3%
	Group C: 13-56 yrs	610	35.9%

Cases with previously failed amblyopia therapy: 994 cases (58.5%) had previously attempted part-time occlusion therapy, 232 cases (13.6%) had atropine penalisation, and 157 cases (9.2%) had fogged glasses. Therefore a total of 1383 cases (81.3%) had previously failed amblyopia therapy (done elsewhere).

Cases that dropped out of the study: 49 cases (2.9%) *dropped out* of the study due to poor compliance with therapy or an incomplete follow-up.

For a simplified analysis of results, the 1701 cases were divided into three age groups: Group A: age 4-7 years (473 cases), Group B: age 8-12 years (618 cases), and Group C: age 13-46 years (610 cases) as demonstrated in Table 1.

They were further divided into subsets according to *the severity of amblyopia,* demonstrated in Table 2. The cases with *mild* amblyopia had an ETDRS score of 0.5-0.6 (Snellen's 6/12-6/9) in the bad eye while 0.8 to 1.0 (6/6) in the good eye, *moderate* amblyopia with an EDTRS score of 0.4-0.3 (6/18-6/24), and *severe* amblyopia with an ETDRS score of less than 0.2-0.1 (less than 6/36).

The underlying cause of amblyopia in our study is demonstrated in Table 2. 507 cases (29.8%) were orthophoric on the cover test and had anisometropic amblyopia(with the difference between the spherical equivalent of the two eyes was more than 1.5 D or an astigmatism of more than 1.0 D). 910 cases (53.5%) had constant strabismus along with refractive error and were classified as having (strabismus plus anisometropia). There were 268 cases (15.8%) of stimulus deprivation amblyopia due to a previously blocked visual axis (due to congenital ptosis or congenital cataract). Even though the cause had been removed surgically, elsewhere, the amblyopia persisted. Pure strabismic amblyopia was present in only 16 cases (0.9%); they had constant strabismus without a refractive error.

The initial presentation and outcome of therapy for each age group are discussed individually:

The 473 Group A cases (age 4-7 years, mean 5.37, median 5 years) presented with complaints of frequent blinking, rubbing the eyes, tilting the head to one side while writing, wandering of an eye inwards on waking up from sleep, or closing one eye outdoors. Mild amblyopia was noted in 57 cases, moderate in 191 cases, and severe in 225 cases in this group as demonstrated in Table 2. The severely amblyopic cases had a marked anisometropia of +7.50 ± +2.00, with astigmatism of +2.00 ± +1.00. Moderately amblyopic cases had a less severe anisometropia. The commonly noted refractive error was hypermetropia with astigmatism in 93.5% of cases while only 6.5% had myopia.

An improvement in the BCVA in Group A (Figure 1): The mild to moderately amblyopic cases (57 + 191) achieved a final BCVA of 0.9 within 8-12 weeks of therapy. In the severely amblyopic 297 cases of this group, the BCVA improved from an initial 0.1 - 0.3 EDTRS (6/60 - 6/24 Snellen's) to 0.8-1.0 ETDRS (6/6 Snellen's) in 15 ± 3 weeks. 21 cases demonstrated progressive visual improvement initially but it became static on the 3-4th follow-up visit as they faltered in patching and book-reading only 1-2 hours with the amblyopic eye. After strong counselling, they started to comply with the therapy strictly and the BCVA showed a gradual improvement to 0.8 ETDRS as shown in Figure 1. 4 cases with mild eccentric fixation also had slow but gradual improvement in the final BCVA. 9 cases were non-compliant to therapy and dropped out of the study. The overall success in Group A cases was

Table 2: The severity & clinical types of amblyopia in 1701 cases

		Group A	Group B	Group C	Total No
Amblyopia Grade		Total 473 cases	Total 618 cases	Total 610 cases	
	Mild	57 cases	81 cases	37 cases	175 (10.1%)
	Moderate	191 cases	240 cases	174 cases	605 (35.6%)
	Severe	225 cases	297 cases	399 cases	921 (54.2%)
Type of Amblyopia					
	Anisometropic	81 cases	265 cases	161 cases	507 (29.8%)
	Stimulus Deprivation	99 cases	46 cases	123 cases	268 (15.8%)
	Mixed (anisometropia+strabismus)	288 cases	303 cases	319 cases	910 (53.5%)
	Pure Strabismic Amblyopia	5 cases	4 cases	7 cases	16 cases (0.9%)

98%.

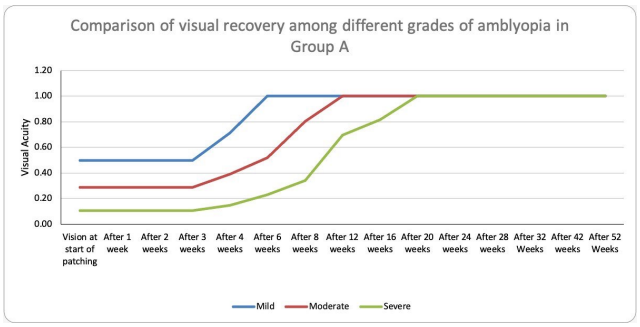

Figure 1: Improvement in visual acuity in different grades of amblyopic Group A cases with therapy

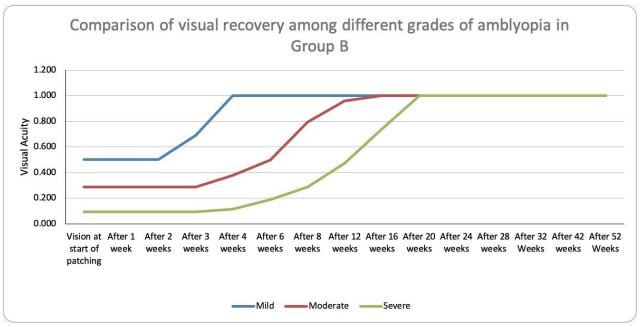

Figure 2: Improvement in visual acuity in different grades of amblyopic Group B cases with therapy

The 618 Group B cases (8-12 years, mean age 9.7, median 10 years were referred for either poor vision in one eye or strabismus. 81 cases were mildly amblyopic, 240 cases were moderately amblyopic, and 297 were severely amblyopic (Table 2). Their level of visual improvement is demonstrated in Figure 2. The mildly amblyopic cases achieved 1.0 ETDRS (6/6) within 4-6 weeks while the moderately amblyopic cases (without an eccentric fixation) achieved 0.8-0.9 EDTRS (6/6-6/9) in 12 ± 4 weeks.

Out of the severely amblyopic cases (BCVA of Counting Fingers or 0.1 ETDRS, 6/60 Snellen's), 91 cases had mild eccentric fixation (para foveal=1.25 mm from the foveal pit) with microtropia; their BCVA stopped improving beyond 0.4-0.5 ETDRS (6/18 Snellen's) after 9 weeks of occlusion therapy. But following the pinhole therapy, they gradually improved to 0.8 EDTRS (6/6 Snellen's). 16 had large angle strabismus (esotropia /exotropia) with gross eccentric fixation at presentation. 26 cases with microtropia and perifoveal eccentric fixation (2.75 mm from the fovea) improved only to 5-6 lines after 12-24 weeks of continued therapy including the pinhole. Their microtropia did not correct as well. 11 severely amblyopic cases could not comply with the therapy and dropped out of the study. An overall improvement in the BCVA in Group B was achieved in 98.2% of cases(Table 3).

In Group C, out of 610 cases (13-46 yrs, median 21 years, 99 cases (65%) had severe amblyopia, 174 cases had moderate amblyopia, and only 37 cases had mild visual loss. All mild-moderately amblyopic cases achieved BCVA of 0.8 EDTRS (6/6 Snellen's) within 10-16 weeks (Figure 3).

12 severely amblyopic cases had an eccentric fixation. Out of these, 7 highly motivated patients achieved BCVA of 0.8 EDTRS by first doing an inverse occlusion of the amblyopic eye 2 weeks, followed by 22-24 weeks of occlusion of the good eye and looking through a pinhole from the amblyopic eye. 5 cases had a persistent microtropia (4.1%), and refused pin-hole therapy. Their BCVA improved to 0.6-0.7 from the initial 0.1.

Out of the severely amblyopic cases, 12 cases dropped out of the study and 7 cases were lost to follow-up. The overall success of therapy was 591 cases out of 610 (96.9%).

The comparison of visual recovery between the three age groups is demonstrated in Figure 4 which shows that Group A cases had restoration of visual acuity much earlier than the older Group C cases.

Stereopsis: In *the severely amblyopic cases, the initial stereo acuity of 400* seconds of arc improved only to 200 seconds of an arc in 78% of cases. In the remaining, there was no improvement. In the mild-moderately amblyopic

Table 3: The results of amblyopia therapy on the BCVA

Group	Grade of Amblyopia	Initial BCVA	Final BCVA	Duration of Therapy in Wks	Overall Improvement in BCVA	p value
A	Mild	0.5-0.6 (6/12-6/9)	0.8-1.0 (6/6)	8 ± 2	100%	< 0.000
	Moderate	0.4-0.3 (6/18-6/24)	0.8-1.0 (6/9-6/6)	10 ± 2	100%	< 0.000
	Severe	0.2-0.1 (6/60-6/36)	0.8-1.0 (6/9-6/6)	15 ± 3	98%	< 0.000
B	Mild	0.5-0.6 (6/12-6/9)	0.8-1.0 (6/9-6/6)	6 ± 2	100%	< 0.000
	Moderate	0.4-0.3 (6/18-6/24)	0.8-1.0 (6/9-6/6)	12 ± 4	100%	< 0.000
	Severe	0.2-0.1 (6/60-6/36)	0.8-1.0 (6/9-6/6)	18 ± 4	98.2%	< 0.000
C	Mild	0.5-0.6 (6/12-6/9)	0.8-1.0 (6/9-6/6)	10 ± 2	100%	< 0.000
	Moderate	0.4-0.3 (6/18-6/24)	0.8-1.0 (6/9-6/6)	14 ± 2	100%	< 0.000
	Severe	0.2-0.1 (6/60-6/36)	0.8-1.0 (6/9-6/6)	20 ± 4	96.9%	< 0.000

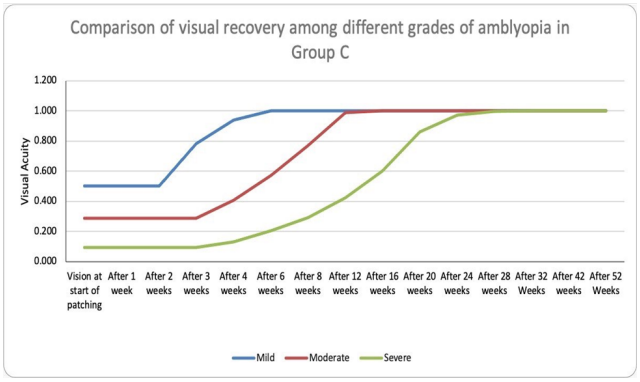

Figure 3: Improvement in visual acuity in different grades of amblyopic Group C cases with therapy

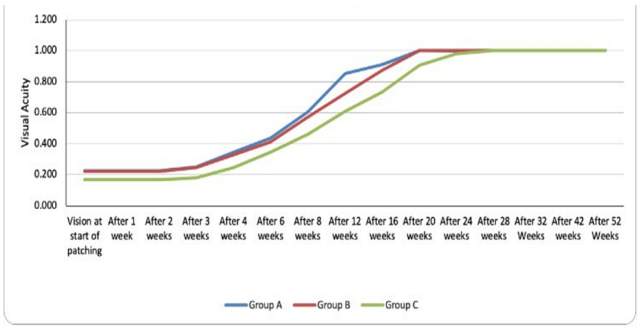

Figure 4: Comparison of visual recovery in the three age groups

cases, the initial stereo acuity of 400-200 seconds of an arc improved to 100 seconds only at the time of completion of therapy.

3.1. Complications of therapy (Table 4)

1. Occlusion amblyopia in the patched good eye of 1-2 lines occurred in 37 group A cases (7.8%) and 11 cases (1.8%) from group B. It was not noted in any group C case. In total, 48 cases (2.8%) out of 1701developed this complication. These patients continued full-time patching, unsupervised, for 8-10 weeks and missed the 1-2 weekly follow-up visits. They were managed by taking the patch off for 1-4 days after which full visual recovery in the good eye was noted. Once that was achieved, the patching schedule for the amblyopic eye was resumed.
2. Skin allergy: mild skin rash (few papules) was noted in a total of 891 cases (52.38%); more severe peri-ocular skin rash under the patch was noted in 41 cases (2.4%). This was treated with a mild steroid skin cream applied at night when the eye patch was taken off, and placing the eye patch over the spectacle-glass for a few days till the rash had cleared up.
3. Ocular irritation and watery eye*:* This was due to in-turned eyelashes in 633 cases (37.2%) out of 1701 cases. This was noted in younger patients of group A (411 cases=86.9%) and group B (222 cases=35.9%); none of the group C cases developed this problem. The parents were advised to place a folded tissue paper over the closed eyelids and then apply the eye patch over it. This prevented the eyelid from opening under the patch and in-turning of eyelashes. No other patch-related complication was noted during therapy.
4. Regression of amblyopia following a successful therapy, by 1-2 lines, occurred in a total of 129 cases out of 1701 (7.6%). 29 cases were from Group A, 33 cases from Group B, and 67 cases from Group C. These cases had stopped wearing their refractive correction for 2-3 months after a successful therapy. It was managed by resuming full-time patching for 2 weeks and gradual weaning.

Cases requiring strabismus surgery following resolution of amblyopia? The ocular alignment of cases with mild-moderate amblyopia and small angle strabismus improved spontaneously from 5-20 PD following appropriate spectacle correction and the resolution of amblyopia (823 cases = 48.38%). However, in the cases with pure strabismic amblyopia (16 cases) and those with large angle strabismus due to mixed amblyopia =862), a total of 878 cases (51.6%)

Table 4: The complications of therapy

Type	Group A	Group B	Group C	Total
Occlusion Amblyopia	37 cases (7.8%)	11 cases (1.8%)	nil	48 cases (2.8%)
Regression Amblyopia	29 cases (6.1%)	33 cases (5.3%)	67cases (10.9%)	129 cases (7.6%)
Eye-patch related:				
i: Skin macule/papule	371 cases (78.4%)	319 cases (51.6%)	201 cases (32.9%)	891 cases (52.38%)
ii: Severe skin rash	15 cases (3.1%)	26 cases (4.2%)	nil	41 cases (2.4%)
iii: In-turned eyelashes	411 cases (86.9%	222 cases (35.9%	nil	633 cases (37.2%)
Diplopia following visual recovery	nil	nil	nil	nil
Diplopia following surgical alignment	nil	17 cases	91 cases	108 cases (6.4%)

needed strabismus surgery.

3.2. Statistical analysis

Post-treatment visual acuity in the amblyopic eye in each group was compared with pre-treatment visual acuity using a paired t-test. The results showed significant visual improvement in all three groups at the end of the study period ($P < 0.001$), as demonstrated in Figure 4.

4. Discussion

Our study provided answers to the following myths and queries regarding amblyopia therapy.

Q. 1: Is there an age limit to visual improvement in amblyopia?

A patient's age is considered a major factor that determines the response to therapy in various studies.[8,23] In this study, there was no upper age limit; the BCVA of even our oldest patient (age=56 years) with severe amblyopia improved to 6/9 (0.8). The median age in the 610 Group C cases (35.9% of the total 1701) was 21 years (range:13-56 yrs). Out of these, 399 cases (65.4%) had severe amblyopia. Resolution of amblyopia occurred in *96.9%* of cases of this group and in 98% of the younger children (less than 13 years of age) belonging to groups A & B.

To remove any bias on testing the BCVA, we included only literate patients in whom the visual acuity could be reliably assessed. It was done on both the ETDRS and Snellen's chart randomly at the beginning and at the end of amblyopia therapy. The chart projector displayed equal number of letters (five in each line) with a steady decrease in the font size per line. We found no difference between the results of testing on either chart. This was demonstrated in other studies too. Kaiser et al. found Snellen's acuities to be slightly worse than the equivalent "ETDRS" acuities in patients with poor vision while both charts were comparable at better visual acuities.[24] Kalpana et al. reported the magnitude of the advantage in terms of test-retest reliability was fairly small and it took more time to complete the ETDRS (1.86 times) than Snellen's chart.[25]

To the best of our knowledge, this level of visual improvement has not been demonstrated in any other study, especially in adult patients with severe amblyopia. In the Amblyopia Treatment Studies (ATS) by the Paediatric Eye Disease Investigator Group (PEDIG), 12 years was the upper age limit for therapy.[23,26] With part-time patching (2-6 hours) the resolution of amblyopia occurred in only 32% (41 cases) by 18 weeks. After increasing the duration of patching, ≥ 2 lines further improvement occurred in 75% of cases (97 children) and ≥ 3 lines in 54% (70 children). Its important to note that they initiated patching after 4 weeks of refractive correction. Thus, part of the visual acuity improvement in the PEDIG-ATS was likely to be due to continued refractive adaptation beyond 4 weeks.

Miranda Buckle et al., retrospectively studied the outcome following 6 hours of occlusion daily, using the PEDIG amblyopia protocols.[27] Only 40% of the severely amblyopic children (age 3-7 years) achieved BCVA better than 0.4 logMAR (6/15 Snellen's) at 32 weeks, increasing to 55% at 48 weeks; 71% of the moderately amblyopic eyes achieved BCVA 0.3 logMAR (6/12) at 32 weeks. The mean visual improvement was 4.2 lines in the severely amblyopic eyes and 2.1 lines in the moderately amblyopic eyes. In another PEDIG study,[28] with 2-6 hours daily patching and near visual activities, the BCVA improved by 2-4 lines in 53% of children aged 7-12 years and in *25% of cases* in the *13-17* year age group year age group.

Krista Kelly et al. had only 1 line of visual improvement with binocular iPad games after 4 weeks of therapy in the moderately amblyopic children (initial BCVA 0.48 logMAR=20/63), between the ages of 4.6-9.5 years.[29] Holmes et al. achieved a 1.5 line improvement in the BCVA of 5-12-year-old children after 16 weeks with the Binocular iPad Games.[30] Cases have been reported in the scientific literature of spontaneous visual improvement in the severely amblyopic eyes in adults following visual loss in the good eye.[31–33] Therefore, no patient should be denied amblyopia therapy because of his/her age.

Q. 2: How long should the full-time occlusion therapy in amblyopia of any severity?

Our study demonstrated three major factors that determine the duration of therapy required for visual recovery:

1. The age at which the therapy was started: younger patients recovered the visual acuity much earlier (between ages of 4-12 years) than in the older Group C cases (ages of 13-56 years) (Table 3).
2. The severity of amblyopia: vision recovered earlier in mild-moderate amblyopia (6-10 weeks) than in severe amblyopia at any age (15-24 weeks).
3. Compliance with therapy: This is the main deciding factor for visual recovery. The patients who complied fully with both parts of therapy i.e. blocking the good eye from seeing and studying minimum of 6 hours daily with the amblyopic eye demonstrated one-line BCVA improvement at each two-weekly follow-up visit. On the other hand, patients who only did full-time patching but did not actively use the amblyopic eye by reading/writing, failed to demonstrate visual improvement on that follow-up visit. A good compliance with patching was gauged by noting patch-related mild dermatitis.

According to the PEDIG studies, a successful outcome was not related to the duration or type of occlusion therapy, but was determined by the age at which therapy was initiated, the depth of visual loss before treatment, and the type of amblyopia.[34] In these studies, part-time patching was continued for many months. In another PEDIG study, improvement in visual acuity by 2 or more lines occurred in 40% of cases with residual amblyopia when patching was increased to 6 hours daily versus 18% of those who patched for 2 hours.[35]

Q. 3: Why the visual acuity recovered much earlier in our study than the PEDIG studies?

Kleim et al. suggested that brain stimulation should be specific, intense, repetitive, and for longer periods of time.[36] It should be without any interference to get earlier improvement in the function and structure of the brain. In our study, this was achieved by book-reading for a minimum period of 6-7 hours daily by the amblyopic eye and then writing what the patient had read. This helped stimulate all parts of the brain and proved to be the strongest stimulus for visual improvement that was also cost-effective. Patients who studied for even longer hours improved earlier and demonstrated a constant improvement in the BCVA at each follow-up visit. Patients who did not study but watched TV or played computer games during a week or two failed to demonstrate visual improvement at that follow-up visit.

Morrone et al. demonstrated that monocular deprivation reduces the inhibitory influence of GABA in the primary visual cortex thus boosting the vision in the deprived eye.[37] It activates the homeostatic plasticity of neural connections related the amblyopic eye. The neural projection from the amblyopic eye has a topographic disorganization in all early visual areas.[38,39] Whilst the signals from the good eye are blocked by an eye-patch, the neural connections of the amblyopic eye are allowed to organise, grow, and stabilise. But when the patch is removed from the good eye (as in part-time therapy), the levels of inhibitory GABA rise to suppress neural connections of the amblyopic eye. Full-time patching was responsible for achieving full visual recovery in 97-98% of our cases within a short time period. This has not been demonstrated in other studies to date, but it required strong counselling of patients.

Q. 4: Did previously attempted (failed) amblyopia therapy affect visual improvement when therapy was initiated later in life?

In this study, we did not refuse therapy to any patient if they had received amblyopia treatment in the past. 81.3% of our cases (no=1383) had previously failed part-time patching, fogging, or atropine penalisation. The patients who had the good eye atropinised elsewhere, could still see better with that eye than the densely amblyopic eye. The resolution of amblyopia in 96-98% of cases in all age groups clearly proves that a previously failed amblyopia therapy does not preclude visual improvement later in life.

Q. 5*:* What was the risk of occlusion amblyopia following full-time patching of the good eye? Which age group was more vulnerable? Was it reversible?

Out of the total 1701cases, occlusion amblyopia occurred in only *2.8%* of our cases, (Group A=37 cases + B=11 cases. Total 48 cases). It was noted in 5-15 year age-group due to continued, unsupervised occlusion therapy for 6-8 weeks by the parents. These younger children were still in the critical period of visual development and needed close monitoring of occlusion therapy. However, it reversed readily within 1-2 days by taking the patch off the good eye.

It can be argued that in the vulnerable age group, why part-time occlusion therapy was not used? As demonstrated in our study,visual acuity recovered quickly (within 8-10 weeks) in 98% of Group A cases by the full-time occlusion therapy. It ensured better compliance from both parents and the patients as it was needed for a shorter period. In comparison, visual recovery occurred in only 32% of cases in the PEDIG study after part-time patching for 18-24 weeks.[27,28]

Q. 6: Was visual recovery permanent? Was recurrence of amblyopia noted after the cessation of therapy?

Regression of BCVA by 1-2 lines (Table 4) occurred in 129 cases (7.6%) during the 1-3 year follow-up. This occurred in the high anisometropic cases who had stopped wearing their refractive glasses for 2-3 months following a successful therapy. The visual loss was recovered by resuming the full-time patching for 2-3 weeks, followed by its gradual weaning. After this first incidence, the patients learnt the importance of constant spectacle wear. The gradual weaning of patching in our study resulted in

a lesser incidence of visual regression as it ensured the stabilisation of newly formed neural connections from the amblyopic eye to all parts of the brain.

Miranda Buckle et al. had recurrence of amblyopia in 19%–50% of cases. In the PEDIG study, the cumulative probability of worsening visual acuity was 7% by 2 or more lines during the first year following cessation of therapy.[28,40] In contrast, Rohit Saxena et al. reported the risk of amblyopia recurrence increased with increasing age of the patient.[41] Repka et al. reported 59.9% of children (less than 7 years age) treated for moderate amblyopia had good visual acuity of 20/25 when followed up for 10-15 years.[42]

Recurrence of amblyopia is possible in every case after cessation of therapy, irrespective of the age of a patient. The most sensitive period for visual regression is the first 12 months as noted in our study since the neural connections are still strengthening and stabilising. Therefore the need for good counselling of patients and their parents regarding regular spectacle wear and follow-ups post-amblyopia therapy cannot be over-stressed.

Q. 7: Was there an improvement in ocular alignment following amblyopia therapy? How many cases needed surgery for strabismus?

Ocular alignment improved spontaneously in 823 cases (48.38%) with strabismus of 5-20 PD (strabismic or mixed amblyopia) once the visual acuity was equalised in both eyes. Strabismus surgery was needed in cases with large angle strabismus (878 cases, 51.6%). This has been demonstrated in other studies.[43,44]

Q. 8: Did diplopia occur in any case following visual improvement?

Diplopia occurred in patients who had strabismus surgery for large angle exotropia (strabismic and mixed amblyopia) following equalisation of vision by amblyopia therapy. This was due to the over-correction of exotropia by 5-10 PD and it gradually disappeared post-operatively within 2-8 weeks. It was not noted in the orthophoric cases. This highlights the fact that once ocular alignment and equal vision are restored in both eyes, binocular single vision develops by the sensory fusion mechanism. Hou et al. suggested that amblyopia is associated with a form of attentional neglect; the visual system prioritises input from one eye over the other.[45] The equalisation of visual acuity and restoration of ocular alignment gradually reduces suppression and diplopia disappears. However, this needs to be studied more.

Q. 9: Was there an improvement in stereopsis following amblyopia therapy?

This occurred earlier and continued to improve with time in Group A and B cases as compared to Group C cases. More improvement was noted in moderately amblyopic eyes as compared to the eyes that had dense amblyopia. In our orthophoric cases, as the visual acuity of the amblyopic eye equalized to that of the good eye, stereopsis also improved, slowly and gradually.

The visual system is designed to use both eyes simultaneously to explore visual space. Stereoacuity is the most advanced binocular function, and its loss or decrease has a diverse impact on the daily activities of amblyopic patients. Therefore, it is important to demonstrate the association between the severity of amblyopia and stereoacuity. Awaden et al. found that only 35.9–54% of patients achieved a stereoacuity of 60 arc seconds or better despite an improvement in the VA in amblyopic eyes.[46] According to them, better initial visual acuity and better final visual acuity were associated with better binocular function as demonstrated in our study.

According to them, better initial visual acuity and better final visual acuity were associated with better binocular function as demonstrated in our study.[47] However, we did not use any binocular therapy to further enhance the stereo acuity in our cases due to lack of funding. This was a shortcoming in our study. Clavagnier et al. suggested that the cortical deficit in amblyopia was due to an immature cerebral cortical system; there was a normal complement of cells whose spatial resolution was reduced and the topographical map was disordered.[48] This bears upon a number of competing theories for the psychophysical defect and affects future treatment therapies.

5. The Strengths of Our Study

1. A large number (1701) of consecutive cases
2. 81.3% of our cases had previously failed amblyopia therapy.
3. A long follow-up (minimum of 12 months) post-therapy.
4. 72.2% of our cases were above the age of 7 years when amblyopia is considered untreatable by general ophthalmologists globally.
5. 54.2% of our cases had severe visual deficits, while 35.6% had moderate amblyopia. 98% of these cases recovered their BCVA to 6/6 and maintained it during repeated follow-ups. Only 7.6% had a regression by 1-2 lines which was easily recovered by repeated patching.
6. Only those cases were considered amblyopic and were included in the study which failed to show improvement in the BCVA with spectacle correction (Refractive Adaptation). Interestingly, in the PEDIG studies, patients were labelled amblyopic before prescribing refractive correction.[24] We propose this point should be clarified in all future studies regarding amblyopia therapy.

6. Conclusion

Our study highlighted the following points:

1. Full visual recovery is possible in amblyopia of any severity and at any age. Therefore, amblyopia therapy should not be denied to any patient.
2. Quick resolution of amblyopia depends upon three important factors:
   (a) To completely remove the inhibitory influence of good eye over the amblyopic eye during therapy by full-time patching.
   (b) To stimulate the brain strongly and actively: book-reading and writing for 5-6 hours daily offers a practical, the most economical, and the easiest option.
   (c) The proper counselling of patients and the parents at each follow-up visit ensures good compliance with the therapy.

7. Source of Funding

None.

8. Conflict of Interest

None.

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Cite this article: Irfan S, Aadil N, Maurya RP, Saqib M. Is amblyopia of any severity fully treatable, irrespective of a patient's age?. *Indian J Clin Exp Ophthalmol* 2024;10(1):26-36.