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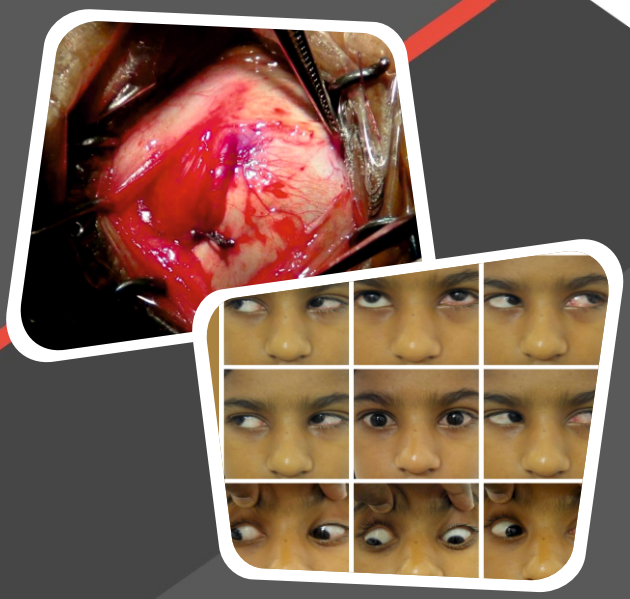

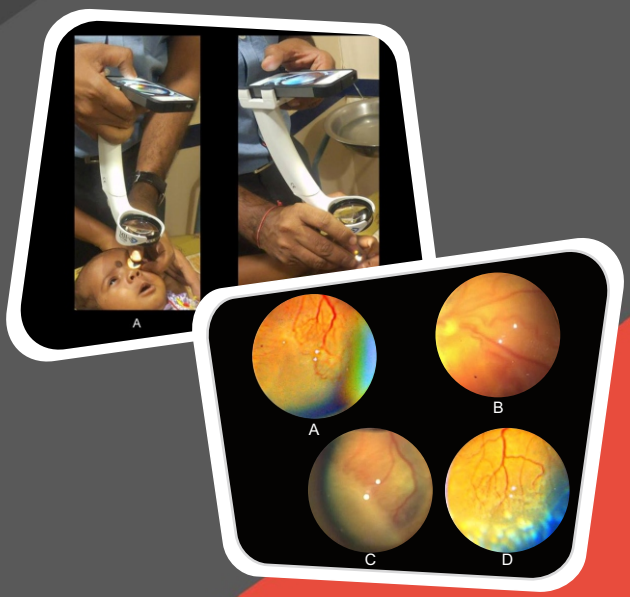

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CONTENTS

Original article

"HOW SUCCESSFUL IS FULL-TIME OCCLUSION THERAPY IN AMBLYOPIA ?"

Dr. Sameera Irfan

ABSTRACT:

A prospective, interventional study was conducted from Jan 2010 to Dec 2015, including 824 consecutive cases referred for either poor vision or a constant, unilateral strabismus. No upper age limit was fixed and all cases in whom BCVA could be assessed were included in the study, between 4 - 46 years. After wearing refractive correction for 8-12 weeks, full-time occlusion therapy of the good eye along with active use of amblyopic eye was started in all cases for a period of 12-24 weeks. For easy analysis of results, the 824 cases were divided into 3 subgroups according to age; Group A: age 4-7 years (279 cases), Group B: age 8-12 years (324 cases) and Group C: age 13-46 years (221 cases). They were followed up for a minimum period of 12 months after the completion of occlusion therapy. Statistical analysis regarding the improvement in visual acuity between the start and end of therapy was performed by a paired t-test for each group.

INTRODUCTION

Amblyopia, also known as a lazy eye,[1] is a disorder of the visual system characterised by reduced visual acuity in an eye that is otherwise physically normal. In other words, the visual loss is out of proportion to any associated structural abnormality in an eye. It is believed to result from disuse of an eye, either from an inadequate foveal or a peripheral retinal stimulation (where there is a lesser concentration of cones), or an abnormal binocular interaction due to different visual inputs from both the foveae.[2] The brain is designed to allow both eyes to function together to explore space, in both humans and animals. If signals from one eye are blurred or absent, brain blocks signals from the weaker eye to avoid confusion, created by an imbalance between the performance of both eyes, the image from one eye being much clearer than the other. This may occur due to a constant strabismus, a disproportionately high refractive error in one eye, a combination of both factors, or a blocked vision in an eye due to a droopy upper lid, media opacity like corneal or vitreous or a congenital cataract.[3]

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When that happens in the early developmental period of a child from age 1 to 5 years, called "the critical period",[4,5] brain compensates by shutting down the weaker eye and promoting a single, clear image from the good eye. Since visual pathway is a three neuronal pathway, the synapses in between these neurons are broken due to disuse of the amblyopic eye. Hence, amblyopia, in simple terms, is a wiring problem [6,7].

An amblyopic patient not only has a poor vision, but also suffers from poor spatial acuity, low contrast sensitivity, and a "higher-level" of visual deficit such as a reduced sensitivity to motion[8]. These deficits are usually specific to the amblyopic eye. In addition, the patient suffers from problems of binocular vision such as a reduced field of vision, limited depth perception and stereopsis, which interfere with estimation of depth and distances between objects and difficulty in seeing three-dimensional images (which can be detected by hidden stereoscopic displays such as autostereograms).[9]

An important question arises that why amblyopia should be treated? It has been estimated to affect 1–5% of the population. Its prevalence, worldwide, has not changed much over the years.[10,11] It is the number one cause of blindness in adults, which is treatable as well as preventable by organised screening programmes. It is a potential threat to loss of vision in the better eye.[12] An adult person with unilateral amblyopia is at three times greater risk and a child 17 times that of a normal person for losing vision in the better eye.[13] A spontaneous improvement of vision in an amblyopic eye after loss of vision in the good eye has been reported. This spontaneous improvement of visual acuity to a usable level (6/24 or better) is relatively low (<17%) unless a complete visual loss occurs in the better eye.[14]

It is generally believed that amblyopia becomes more difficult to treat in older children and may be untreatable in adults. This is because of mis-interpretation of studies by Wiesel and Hubel[15] regarding the "critical period" for visual development. Critical period means that during this period, an individual's retina and brain is most

sensitive to outside environment and stimuli than at other periods of life. Recent findings of neuroplasticity have replaced the formerly held opinion that brain is a physiologically static organ and have shown that it can modify throughout life.[16,17] Its development does not end beyond a certain age; it can adapt to environment by forming new connections between existing brain cells and strengthening the older ones. This ability is strong in early childhood when maximum brain growth occurs, slows down with age, but it never stops[18]. The molecule responsible for neuroplasticity - a protein receptor,[19] is held in an "OFF" mode in adults. It can be turned "ON" by continued, active brain stimulation.

According to recent studies,[20-23] GABA (Gamma Amino Butyric Acid), acts as an excitatory neurotransmitter in immature, developing brains and regulates proliferation of neural progenitor cells, proliferation and elongation of neuritis and formation of synapses by releasing of Brain-Derived-Neurotrophic Factor. This results in important brain functions like memory, learning, speech, motor control. It not only gradually decreases with age but in mature brains, it has an inhibitory affect by activating GABA-receptors and causing cell arrest in the S-phase (static phase). GABA given exogenously cannot cross the blood-brain barrier. Researchers obtained GABA secreting neurons from young mice while they were in their "critical period" and transplanted into the brains of adult, amblyopic mice. After some time, they found new neural connections forming in the visual pathway and restoration of normal eyesight in those adult, amblyopic recipient mice.[24,25] Similarly, in other studies, plasiticity of brain was shown to improve in specific regions by a specified stimulus. The brain receptors which were turned "Off" with age, could be turned "On" by GABA released in response to a stimulus. But in order to stabilise the newly formed neural connections, the stimulus had to be strong and persistent. An increase in the gray matter volume has been observed in professional typists due to long-term bimanual typing, suggesting that learning can affect not only function but brain structure as well in adults.[26] Dopamine is another neurotransmitter that stimulates receptors and turns them "On". It is present in retina and cerebral cortex but does not cross the blood-brain barrier. Its precursor, Levodopa, crosses that barrier and is converted to Dopamine in the brain. These studies prove that neural stem cells (progenitor cells) can be made to generate neurons in various brain areas of mammals[27]. Adults continue to learn throughout life and this is because of continued neurogenesis in the memory area.

Our study was conducted toknow whether neural connections in an amblyopic eye can be reactivated through persistent, active stimulation irrespective of a patient's age. The study was designed to find answers to the following queries regarding amblyopia therapy:

1: Is there an age limit for visual improvement ?

2: How long would it take to improve vision by full-time occlusion in an amblyopic eye of any severity ?

3: Would a previously attempted, failed amblyopia therapy had any affect on visual improvement if therapy was initiated at a later age?

4: Was the visual recovery following occlusion therapy permanent ? Can regression of amblyopia occur after therapy ? How can it be managed ? In which age group was it most likely to occur ?

5: Was there any risk of occlusion amblyopia in the good eye following full-time patching ? Which age group was more vulnerable? Was it reversible ?

6: Does visual improvement in a long standing amblyopic eye result in diplopia ?

8: Was there an improvement in stereopsis once equal visual acuity was restored in both eyes ?

9: How effective was full-time occlusion therapy than part-time patching ?

MATERIALS & METHODS:

This prospective, interventional study was conducted from Jan 2010 to Dec 2015. It included 824 consecutive cases, referred to a tertiary care centre, with either poor vision or a constant, unilateral strabismus. No upper age limit was fixed and all cases in whom BCVA could be assessed were included in the study, between 4 - 46 years.

A complete history was taken regarding birth (prematurity, birth weight, asphyxia, cyanosis, juandice, oxygen therapy), any health problems during the first few months after birth, developmental milestones, visual problems, onset of strabismus, past therapy with glasses, previous attempts at patching, atropine penalisation or strabismus surgery. A complete ophthalmological examination was performed by a single ophthalmologist as well as a complete assessment of strabismus and the presence or absence of eccentric fixation by a visuoscope. Visual acuity for both

distance and near vision with their present glasses or uncorrected (in cases not previously prescribed glasses) was assessed on ETDRS (as well as Snellen's at the beginning of the study and then at the end, while during follow-up, only on ETDRS Chart), Snellen's reading charts for near vision, color vision by Ishihara color plates, stereopsis by TNO plates was performed by a single optometrist. Cycloplegic refraction was carried out with atropine (prescribed for 3 times a day for 3 days) in cases of esophoria or an esotropia; cyclopentolate was used (3 - 4 times at 10 min intervals in the clinic) in cases which were either orthophoric or exotropic.

The diagnostic criteria for amblyopia was taken as a persistence of difference in the BCVA between the two eyes of 2 or more lines (tested on the ETDRS chart) subsequent to constantly wearing the refractive correction for 8-16 weeks; only cases with a reduced visual acuity in one eye and a BCVA of 0.8 on the ETDRS chart (equal to 6/6 Snellen's) in the good eye were selected for the study. For an easy analysis of results, the 824 cases were divided into subgroups according to age as Group A: age 4-7 years (279 cases), Group B: age 8-12 years (324 cases) and Group C: age 13-52 years (221 cases), Table 1

Group	Age	No	%
A	4-7 years	279	33.85%
B	8-12 years	324	39.32%
C	13-52 years	221	26.82%
Total		824	100%

Table 1: Demographics of Cases: Total No: 824

Type of Amblyopia	No of cases	% age	Moderate Amblyopia	Severe Amblyoia
Anisometropic	179	21.73%	Gp A=131 cases Gp B=125 cases Gp C=20 cases	Gp A= 148 Gp B= 199 Gp C= 201
Strabismic	156	18.93%		
Mixed	489	59.34%		
Total	824	100%	276=33.49%	548=66.50%

Table 2: Types of Amblyopia

the cases were considered as having an *anisometropic amblyopia* (179 cases= 21.73%) if the difference between spherical equivalent of the two eyes was more than 1.5 D or an astigmatism of more than 1.0 D and they were orthophoric on the cover test. Cases which had a constant esotropia or an exotropia with none or a minimal refractive error were classified as having a *strabismic amblyopia (156 cases= 18.93%).* There was a *mixed variety* (489 cases= 59.34%) which had both a refractive error and an associated strabismus (a phoria, micro-tropia or a constant tropia). The fourth variety was *stimulus deprivation amblyopia* (18 cases) in which a previously blocked visual axis due to ptosis or congenital cataract had led to persistent amblyopia even though the cause had been removed. These cases also had either an exophoric or a constant exotropia hence *they were also included in the mixed variety,* Table 2. Out of the total 824 cases included in the study, 298 cases had a previously attempted part-time occlusion therapy, 53 cases had atropine penalisation and 84 cases had fogged glasses (Total= 435 cases= 52.79%) tried in the past elsewhere but had failed to produce any remarkable visual improvement.

The cases which were found to have an organic cause for amblyopia (central corneal scarring, macular scarring, optic atrophy, optic disc coloboma or hypoplasia), bilateral ammetropic amblyopia, nystagmus and in whom visual acuity improved after wearing the refractive correction for 8 - 16 weeks were excluded from the study. The study was approved by the ethics committee of the hospital. 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 as dropped out of the study.

A full refractive correction was prescribed to all cases with strabismus and anisometropic amblyopia under the age of 7 years while in older patients, subjective refraction was performed once the affect of cycloplegic drug had worn off (almost 1 week - 10 days after instillation of drops), and maximum correction was prescribed. They were called for follow-up after 8 weeks of constant spectacle wear and an improvement in BCVA was noted. Patients who showed an improvement in both eyes were asked to continue with their glasses for another 8 weeks. Cases which failed to show any further visual improvement after 16 weeks of constant spectacle wear were diagnosed as having amblyopia, and were

further divided into subsets of moderate amblyopia with an EDTRS score of 0.4-0.6 (n= 357= 42.32%) and severe amblyopia with an of ETDRS score of less than 0.2-0.3 (n= 467= 56.67%).

Those cases in whom the BCVA improved to 0.8-1.0 EDTRS in both eyes after 16 weeks of constant spectacle wear were not included in the study (as mentioned in the study exclusion criteria).

The patients along with their parents or caretakers were fully counselled regarding the rationale of full-time occlusion therapy and how it works in order to ensure full co-operation and compliance. A verbal consent was obtained from the parents/caretakers of all 824 amblyopic patients and was mentioned in the clinical notes. All cases were prescribed full-time occlusion of the good eye with commercially available, stick-on eye-patch to be worn over the good eye as soon as possible after waking up in the morning. They were strictly instructed not to take the patch off during the day but only when they were about to sleep at night. At the same time, they were instructed to wear the refractive correction and perform near visual activities with the amblyopic eye like reading (initially the font that was visible to them either on a newspaper, magazine or a computer screen and to gradually reduce the font size daily), colouring, drawing, writing and playing games on cell-phones for at least 4-5 hours/day. The moderately amblyopic patients were asked to continue with their normal activities like going to school, college or office, but those with severe amblyopia were issued a medical leave certificate for 3-4 weeks as they were unable to continue with their daily activities after occluding the good eye; they were instructed to stay home for a month and comply to the therapy.

Patients under the age of 7 years were followed up weekly while older ones were seen after every 2 weeks. At each visit, distance vision with ETDRS charts, both letters and E charts and near vision of the amblyopic eye were recorded first keeping the good eye patched; the eye patch was removed from the good eye and then its visual acuity was recorded. Any patch-associated skin problems or diplopia were noted. The full-time occlusion therapy was continued till a BCVA equal to that in the good eye was achieved (0.8 or 6/6). Stereopsis was assessed with TNO test plates with the patient wearing polarised glasses over the refractive correction and recorded in the clinical notes.

The weaning protocol for occlusion therapy was commenced once equal vision in both eyes was achieved or when the amblyopic eye failed to show any further improvement on repeat follow-up visits for 2 months. This consisted of one day off-patch in the first week and two days off in the second week. BCVA was checked after two weeks and if it remained stable, then further weaning was continued with 3 days off in the third week and 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 again commenced for a further 2 weeks and weaning re-started once full visual recovery was noted. Patients were regularly followed up after every two weeks for the next 12-24 months and their visual acuity for both distance and near vision, stereopsis and the angle of strabismus were measured and noted at each follow-up visit.

Cases in which a gross eccentric fixation (fixation far from the fovea) was detected, Inverse Occlusion was prescribed for two weeks during which the amblyopic eye was totally occluded by wearing 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 a dark tape applied over the correcting glasses. The cases with a mild degree of eccentric fixation (pera-foveal= 1.25mm from the foveal pit) Figure 1, 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 cut in tape over the glass of the amblyopic eye, Figure 2. Their visual progress was monitored similar to the other patients in the study.

Compliance to therapy was assessed by noting whether patients were strictly following the follow-up protocol (weekly in Group A cases and every 2 weeks for Group B & C cases), coming to the clinic wearing a patch over the amblyopic eye, performing near visual activities for 3-5 hours / day and by noting the presence of patch-related skin problems like mild skin redness or a few macules / papules noted after removing the eye-patch; a mild steroid cream was prescribed to be applied over the rash once eye-patch was taken off at night.

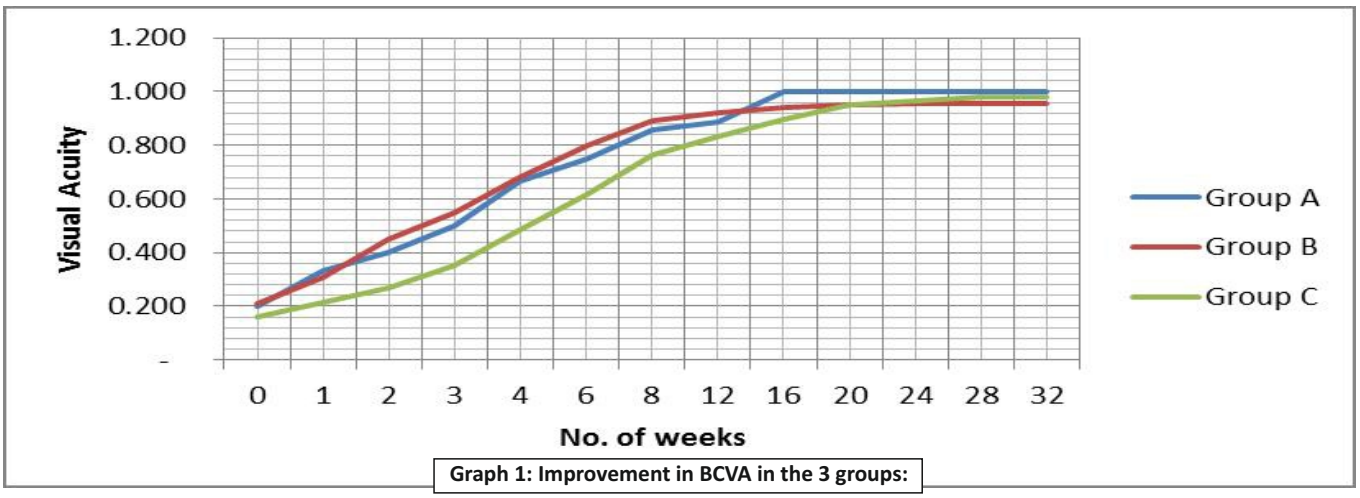
Statistical analysis for analysing the improvement in visual acuity between the start and end of full-time occlusion therapy in each group by performed by paired t-test.

RESULTS:

A successful outcome of occlusion therapy was considered when there was at least 4-5 lines counselled to comply to therapy after which the BCVA showed a gradual improvement to 0.8 ETDRS in a total of 14 - 18 weeks. 4 cases had a mild eccentric fixation and they showed a gradual improvement in the final BCVA. 9 cases (9.08%) were non-compliant to therapy and dropped out of

Group	Amblyopia Grade	No of Cases	Initial BCVA ETDRS	Final BCVA ETDRS	Therapy Duration	Dropped out	Lost to followup	Successful therapy	Overall Gp Success
A	Severe	148	0.1 - 0.3	0.8 - 0.9	12 ±4 wks	9 cases	12 cases	148-21= 127=85.8%	127+131= 258= 90.32%
	Moderate	131	0.4 - 0.6	0.8 - 0.9	8 ±2 wks	-	-	100%	p<0.001
B	Severe	199	0.1 - 0.3	0.8 - 0.9	12-24 wks	19 cases	13 cases	199-32= 167=83.9%	167+121= 288= 88.88%
	Moderate	125	0.4 - 0.6	0.8 - 0.9	12 ±4wks	-	4 cases	125-4=121=96.8%	p<0.001
C	Severe	201	0.1 - 0.3	0.7-0.8	22-24 wks	7 cases	3 cases	201-10= 191= 95%	191+14= 205=92.8 %
	Moderate	20	0.4 - 0.6	0.8 - 0.9	12 ±4wks		6 cases	20-6=14= 70.0%	p<0.001

Table 3: Improvement in BCVA in 824 cases



Graph 1: Improvement in BCVA in the 3 groups:

CF	6\60	6\36	6\24	6\18	6\12	6\9	6/7.5	6/6	6/5
0	0.1	0.166667	0.25	0.33333	0.5	0.666667	0.777	0.800	1.00

study while 12 (8.1%) were lost to follow-up. Hence out of the 148 severely amblyopic cases, 127 cases achieved a BCVA of 0.8-0.9 ETDRS (a success of 85.8%). All 131 moderately amblyopic cases in this group achieved a final BCVA of 0.9 within 8±2 weeks of therapy. The overall success in Group A was noted to be in 258 (127+131) out of 279 cases. This was considered as 90.32% success.

Complications (Table 4) *of this therapy like* Occlusion amblyopia of 1-2 lines in the patched, good eye was noted in 23 cases (8.9%) out of the total 258 cases who completed the study in this group. Instead of a regular weekly follow-up, they came for follow-up after 6-8 weeks and continued full-time, unsupervised patching. They were managed by taking the patch off for 1-2 days after which full visual recovery in the good eye was noted. Once this was achieved, the patching schedule for the amblyopic eye was resumed.

Regression of amblyopia, by 2 - 4 lines, was noted during the first 6-9 months follow-up in 28 cases (17.7%), out of 258 cases in this group who completed the minimum follow-up of 12 months. This was mainly because these children stopped wearing their refractive glasses for 1-2 months. It was managed by resuming the full-time patching protocol and near visual activities for 2-4 weeks after which full visual recovery was achieved. It was not noted again during the remaining follow-up period.

Eye Patch related complications like a mild skin rash in the form of a few papules was noted in 59 cases (22.86%) while a more severe periocular skin rash under the patch was noted in 5 cases (1.9%). This was treated with a mild steroid skin cream applied at night when the eye patch was taken off, and placing the eye patch on the spectacles for a few days till the rash cleared up. Eye irritation due to in-turning of eyelashes was noted in 57% of cases. This was managed by advising the patients to place a small roll of tissue-paper over the eyeball and then wear a patch over it. This prevented the eyelid from opening under the patch and in-turning of eye lashes. No other patch-related complication was noted during therapy.

Group B (8-12 years, mean age 10.38+/-2, median nine years) included 324 cases which were referred for either poor vision in one eye or strabismus. On examination, Table 2: moderate amblyopia (initial BCVA of 0.4-0.6 ETDRS) was noted in 125 cases while of a severe grade in the remaining 199 cases. All the moderately amblyopic cases (without an eccentric fixation) achieved 0.8-0.9 EDTRS vision in 12 ± 4 weeks.

Cases which were found to have a severely amblyopic eye (BCVA of Counting Fingers or 0.1 ETDRS, 6/60 Snellen's) due to gross eccentric fixation at the initial presentation, an inverse occlusion of the amblyopic eye was advised for 2-3 weeks. After this period, the study protocol was started and the good eye was patched full-time. 91 cases had a mild eccentric fixation (pera foveal=1.25mm from the foveal pit) with microtropia, and the BCVA stopped improving beyond 0.4-0.5 ETDRS (6/18 Snellen's) after 9 weeks of occlusion therapy. At that time, they were instructed to continue near visual activities (reading, writing and computer games) by looking through a pinhole made by cutting a hole in a dense white tape applied on the refractive glasses over the amblyopic eye. After this technique, their BCVA showed a gradual improvement to 0.8 EDTRS (6/6 Snellen's) with continued therapy.

Group	Occlusion Amblyopia	Regression Amblyopia	Patch-related
A=279-21=258 cases	23cases (8.9%)	28 cases (17.7%)	mild rash= 59 (22.9%) severe rash= 5 (1.9%)
B: 324-36=288 cases	6 cases (2.0%)	19 cases (6.6%)	mild rash= 37 (12.84%) severe rash = 9 (3.1%)
C: 221-16=205 cases	——	4 cases (1.95%)	mild rash= 21 (10.24%)
TOTAL	29 cases = 3.86%	51cases = 6.7%	

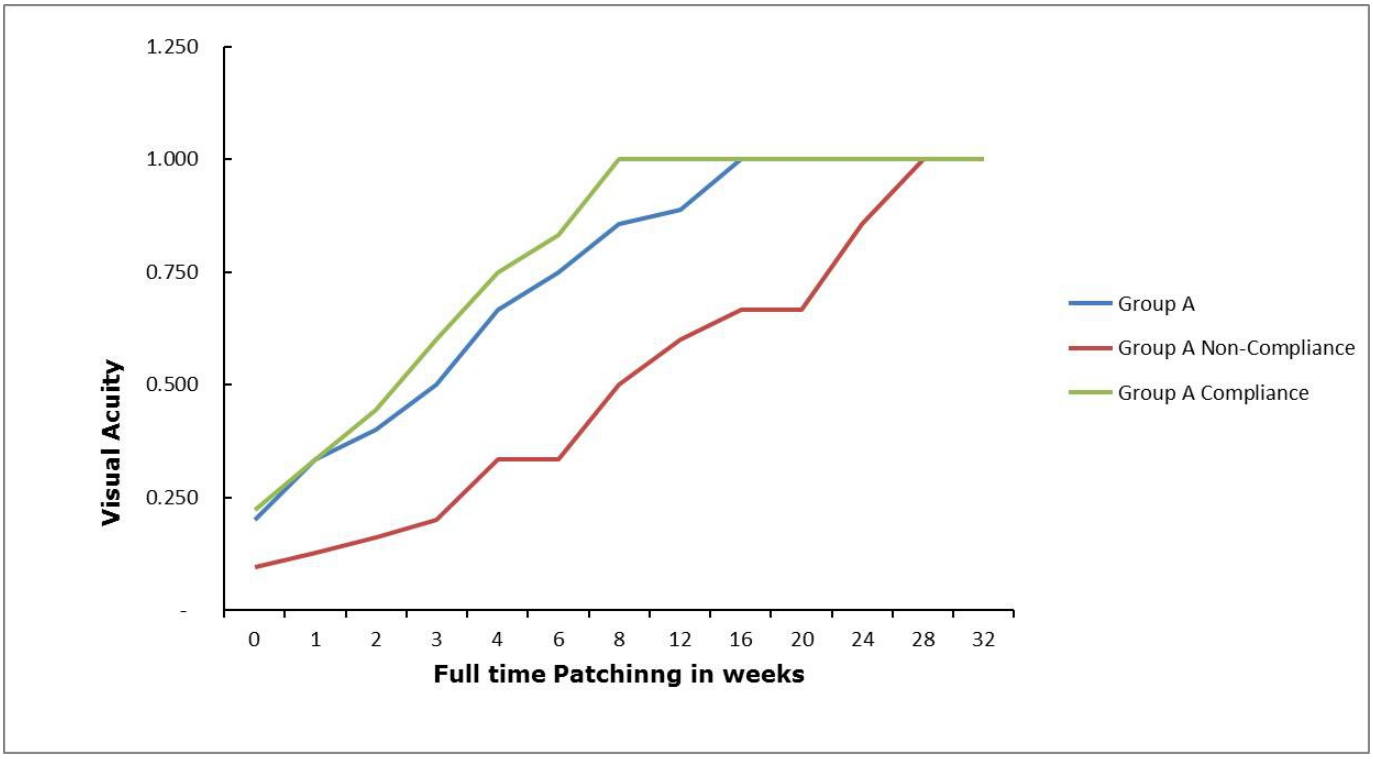
Table 4 : Complications noted in 751 cases who completed the study.

21 cases had a peripheral eccentric fixation (2.75

mm from the fovea) and showed only 5-6 lines improvement in VA after 12-24 weeks of continued therapy including the pinhole; their therapy was stopped when they failed to show further improvement for 4 more consecutive weeks and their microtropia did not correct as well.

Group	Pretreatment	Post-therapy, 1 week	post-therapy 1 month	post-therapy 3 months	post Rx 6 months	post RX 9 months	Post Rx 12 months
A: moderate Amb.	400sec	400sec	200sec	140sec	140sec	100sec	80sec
A: severe	800 sec	800 sec	400 sec	200 sec	200 sec	140 sec	140 sec
B: moderate	200 sec	200sec	140 sec	140 sec	100 sec	100 sec	100 sec
B: Severe	800 sec	800 sec	400 sec	400 sec	200 sec	140 sec	140 sec
C: moderate	400sec	400sec	200sec	200 sec	140 sec	140 sec	140 sec
C; severe	nil	800 sec	800sec	400 sec	400 sec	200 sec	200 sec

Table 5 : Improvement in Stereopsis : tested on TNO plates



CF	6\60	6\36	6\24	6\18	6\12	6\9	6\6
0	0.1	0.166667	0.25	0.33333	0.5	0.666667	1

Out of the severely amblyopic 199 cases in this group, 19 were non-compliant to therapy and dropped out of study while 13 cases were lost to follow-up. Amongst the moderately amblyopic 125 cases, only 4 were lost to follow up while the remaining completed the study. *So an overall improvement in BCVA in Group B was seen in (167+121=288) 288 cases (88.88%), Table 3.*

Occlusion amblyopia in this group was noted in 6 cases out of the 288 who completed the study (2.0%). They were between 7 - 10 years old and had continued with unsupervised occlusion therapy for 8-10 weeks. They were managed by taking the patch off the good eye for 2 days after which their vision recovered and the patching protocol was resumed.

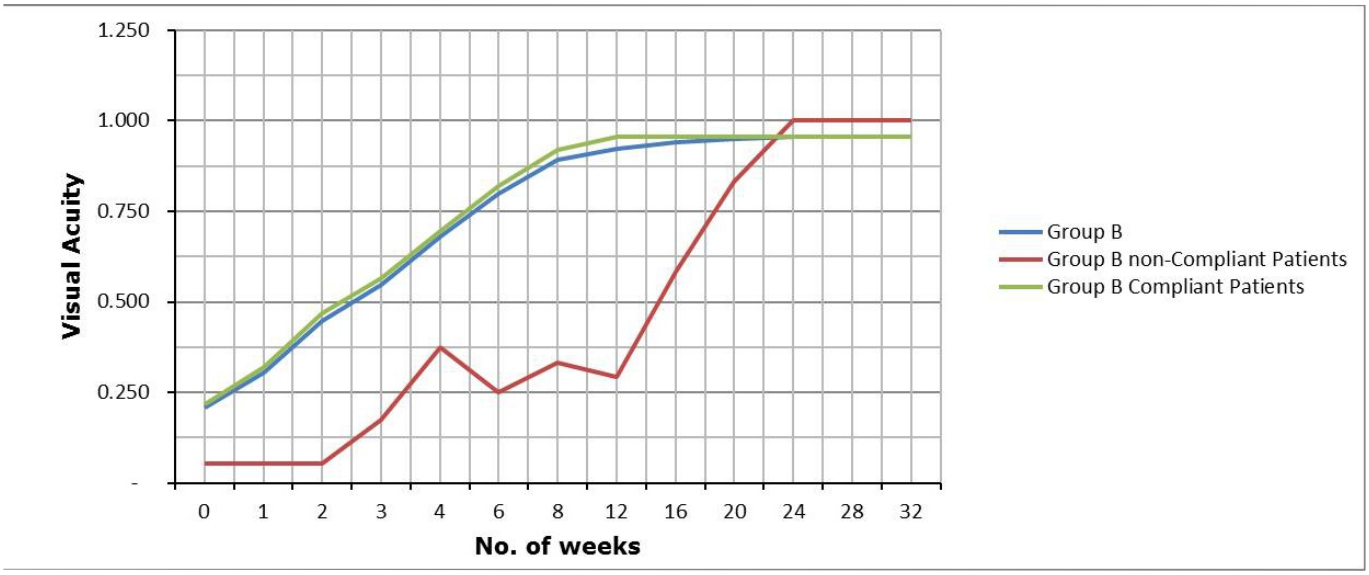
Regression of amblyopia by 1-3 lines during the follow-up period was noted in 19 cases (6.6%). This was again mainly due to not wearing the refractive correction for 1-3 months, or wearing a bad, loose frame. It was managed by full-time patching for 1-2 weeks after which full visual recovery occurred.

Eye patch related complications like a mild skin rash was seen in 37 cases (12.84%) while a more severe rash was noted in 9 cases (3.1%). It was managed as explained earlier. 32% cases in this group complained of eye irritation and watering due to in-turning of eyelashes by the eye patch which was managed as explained for group A cases. No allergic conjunctivitis was noted in any case.

In Group C (13-46 yrs, median 19 years) out of 221 cases, Table 2, 201 cases (90.95%) presented with strabismus and severe amblyopia while 20 cases (9.04%) presented with a moderate amblyopia in one eye (BCVA= 0.4, 6/18) and were found to be orthophoric. At the end of therapy, Table 3, all moderately amblyopic cases in this group achieved BCVA of 0.8 EDTRS (6/6 Snellen's) in 12 ± 4 weeks.

Out of the severely amblyopic cases with a large angle strabismus, 12 cases also had an eccentric fixation. Out of these, 7 patients were highly motivated and achieved a 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.

Figure 11 : Recovery of visual acuity on amblyopia therapy (Group A)



Out of the severely amblyopic cases, 7 cases dropped out of the study and 9 cases were lost to follow up. Hence an overall success of therapy was 205 cases out of 221 (92.8%).

Regression of amblyopia following a successful therapy, by 1-2 lines, occurred in 4 cases (1.95%) out of the 205 cases that completed the study. They were mainly 13-15 year old, who had stopped wearing their refractive correction. It was managed by resuming full-time patching for 2 weeks and gradual weaning. *Occlusion amblyopia* was not noted in any case in this group.

A mild skin rash was noted in 21 cases (10.24%) while a severe rash was not noted in any case in this group.

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 the visual acuity of the amblyopic eye became equal to that in the good eye, in all orthophoric cases the stereopsis also improved, slowly and gradually, as shown in Table 5. As noted in this Table, it was grossly present at the beginning of therapy in moderately amblyopic eyes in all groups, while it was absent in eyes with a dense amblyopia as well as strabismus. But as the visual acuity equalised to that of the good eye. stereopsis also gradually improving.This occurred earlier and continued to improve with time in group A and B cases as compared to Group C cases; also more improvement was noted in moderately amblyopic eyes as compared to the eyes which had a dense amblyopia.

DISCUSSION:

In this study, we tested visual acuity by the ETDRS charts (a modified Bailey Lovey chart) projected on a screen operated with a remote control. Various studies have found Snellen's visual acuity charts to have faults [28] like variable number and sizes of letters on each line, making visual acuity difficult to assess statistically [29]. Also, there is an irregular progression of letter sizes between lines resulting in an error when tested at variable distance from the chart. Lastly, Different manufacturers use different fonts, letters, spacing ratios, illumination as a "Snellen chart" has never been standardised.[30] The Bailey-Lovie chart [31] has equally spaced and sized 5 letters per row, exerting a controlled crowding phenomenon. It can easily be scored in logMAR units (logarithm of the mimimum angle of resolution) hence statistical analysis can easily be applied. The "ETDRS chart" (Early Treatment Diabetic Retinopathy Study) was introduced by Rick Ferris and has become the "gold standard" for visual acuity testing in clinical trials [32]. Some investigators mistakenly consider the ETDRS and Bailey-Lovie charts as "logMAR charts."[32] LogMAR is not a type of chart, but a term referring to a geometric notation which is used to express visual acuity. MAR refers to the width of one bar on a Snellen E. In logMAR notation, lower scores (0.1-0.3) correspond to a better visual acuity, while a higher score (0.8-1.0) means a poor acuity. However, in a study conducted by Kaiser [33], comparing Snellen versus ETDRS Protocol Visual Acuities, Snellen acuities were found to be slightly worse than equivalent "ETDRS" acuities especially in patients with poor vision while both charts were charts comparable at better visual acuities. Similarly, another study by Kalpana et al[34] found similar results. The magnitude of advantage in terms of test-retest reliability was fairly small but it took more time to complete the ETDRS (1.86 times) than the Snellen chart. In our study, we found similar results when patients were tested on either charts at the beginning of therapy and then at its end.

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

Q1: Is there an age limit to visual improvement in amblyopia?

Brar *et al.*,[35] reported a 90% improvement in visual acuity with full-time occlusion therapy for 18 weeks in 7-12 years old children. They observed an improvement in visual acuity in 98.7% of children younger than 12 years and only 46.2% children older than 12 years. All these cases had a mild to moderate amblyopia. They did not find a statistically significant difference in visual improvement with either full-time or part-time occlusion therapy (6 hours/day) in severe amblyopia and their follow-up post-therapy was very short (only 3 months).

While selecting cases for this study, we included all patients in whom visual acuity could be reliably checked i.e. not less than 4 years of age; no maximum age limit was set and all consecutive cases were added, the oldest being 46 years. For the analysis of results and to find out which age group was more prone to occlusion or regression of amblyopia, patients were divided into three different age groups. Since the age of 5-6 years is considered as the amblyogenic age because of "the critical period" for visual development, patients from age 4-7 years were included in Group A; they needed a close, weekly follow-up to detect and prevent occlusion amblyopia. Group B included cases between 8-12 years in whom clinicians believe that "some" visual improvement is possible. Group C included all patients older than 12 years who are generally refused any form of amblyopia therapy and are considered "untreatable". Group B and C cases were followed up every 2 weeks as they did not fall into the critical period of visual development.

The results of our study clearly demonstrate (Table 3) that in Group A, BCVA improved from an initial 0.2 ETDRS to 0.8 in 88% cases, in Group B in 90% cases and in Group C in 95.9%. This level of success has not been shown in any study conducted so far to the best of our knowledge. The visual recovery in Group A cases occurred earlier (almost within 12-14 weeks) and in almost 100% cases initially till the completion of occlusion therapy, as compared to

Group C cases, but 6.7% of Group A cases dropped out from the final follow-up at 12 months, hence could not be included in the final result; none of the Group C cases dropped out of the final follow-up, hence they fared better. All Group B & C patients were dependant on their parents for the final follow-up; the parents complied to the initial therapy but they had to move because of jobs etc. On the other hand, most of Group C patients were college-going students or adults, who were not dependant on parents to accompany them to hospital. Moreover, they clearly understood the importance of regular follow-ups. Therefore, they showed a better compliance and a better final outcome. But this did add a certain bias.

This study shows maximal visual recovery is possible at any age. This adds proof to other studies regarding neuroplasticity as mentioned in the introduction.

Q 2: ***How long does it take to improve visual acuity by full-time occlusion in amblyopia of any severity?***
Our study showed that visual recovery occurred earlier in Group A & B cases, mostly within 8-12 weeks as compared to the Group C cases, in 12-22 weeks. Visual improvement occurred earlier in moderately amblyopic eyes as compared to the severe ones, but in a much shorter time period (within weeks) as compared to that achieved in other studies by part-time occlusion. Similarly, Brar *et al.*[36], reported a 90% improvement in visual acuity after full-time occlusion for 18 weeks in children younger than 12 years and only 46.2% children older than 12 years. Flynn et al[36] achieved a success of 20/40 (6/9 Snellen's) 77.2% in strabismic amblyopia, 67.2% in anisometropic-strabismic amblyopia, and only 66.0% in anisometropic amblyopia after 1 year of patching.

The maximum visual improvement by full-time occlusion therapy done over a short time period of 8-12 weeks was a major factor that resulted in a better compliance in our study. It was due to strong motivation and inspiration of both the patients and parents. They were made to understand the fact that amblyopia is actually a wiring problem: when the good eye is patched, neural connections, connecting the bad eye to the brain, start forming. As long as the good eye is kept patched / blocked from seeing, these newly formed connections are favoured by the brain (as it has no choice) and strengthened. But as soon as the patch is taken off, even for a few minutes or hours during the day, the good eye takes over; brain starts favouring the good eye and neural connections / wiring of the amblyopic eye with the brain starts to break again, resulting in a poor net result for that day. They were stressed the need for a closer, regular follow-up to avoid occlusion amblyopia. At each visit, when the patient and parents witnessed a gradual visual improvement, their level of motivation to comply to therapy further increased. A good compliance to patching was gauged by one-line improvement in BCVA at every follow-up visit, as well as by noting patch-related mild dermatitis.

However, it was noted that reading for at least 4-5 hours per day was the strongest stimulus for visual improvement; patients improved earlier who studied for long hours and showed a constant improvement in BCVA on every follow-up visit. Patients, who did not study at all but watched TV etc during a week or two, failed to demonstrate any visual improvement at that follow-up. This has been shown in other studies too.[37] A study by Kleim et al[38] suggested that brain stimulation should be specific, repetitive, intense, for longer periods of time, should involve a patient's full concentration and without any interference to get earlier improvement in brain structure and function.

Q 3: Does a previously attempted and failed amblyopia therapy has any affect on visual improvement if therapy is initiated at a later age?

It is generally believed that if part-time occlusion therapy, atropine penalisation or any other form of amblyopia therapy has failed in the past, then no visual improvement is possible by treating it again as the child grows older. To find out any truth in this myth, we did not refuse any patient in whom any form of amblyopia therapy had been tried in the past. 298 cases out of the total 824 had an unsuccessful part-time occlusion therapy for 2-6 hours/day for a period of 1-2 years. It had improved their visual acuity by only 2-3 lines so the patients and their parents got frustrated, stopped wearing the refractive correction and amblyopia regressed. 53 cases had atropine penalisation. They came for the initial clinical examination with good eye atropinised but could still see better with that eye than the amblyopic eye. 84 cases had previously tried wearing a frosted glass over the good eye. That failed to improve vision in the amblyopic eye as the child would cheat by lowering the glasses and see mainly with the good eye. Hence out of the total 824 cases in our study, 435 cases (52.79%) had a previously failed amblyopia therapy. The success of 88-92% in our study clearly proves that a previously failed amblyopia therapy does not preclude visual improvement by further

therapy.

Q 4: ***Is there any risk of occlusion amblyopia following full-time patching of a good eye ? Which age group is more vulnerable? Is it reversible ?***

Out of the total 824 cases included in the study, only 29 cases developed an occlusion amblyopia in the patched good eye. It was mainly noted in the Group A patients (23 cases, 8.9%) and in Group B, only 6 cases (2%) but not in any of the Group C cases. It occurred due to continued, unsupervised occlusion therapy for 4-6 weeks by the parents though they had beed warned. This clearly demonstrates that younger patients need a close follow-up as they are in the critical period of visual development. It can be argued that in this vulnerable age group, why not switch over to part-time occlusion therapy? As demonstrated in our study, full-time occlusion therapy resulted in quick and better visual improvement (almost within 8 weeks) and 100% equal to the good eye i.e. 0.8 ETDRS or 6/6 Snellen's, as compared to part-time patching. This ensured a much better compliance by both parents and the patients. Moreover, the occlusion amblyopia was readily reversible within 1-2 days by taking the patch off the good eye.

Q5: Is the visual recovery following occlusion therapy permanent? Is there a possibility that amblyopia might regress?

Our cases were followed up for a minimum of 12 months to a maximum of 3 years. Out of the total 824 cases included in the study, 35 cases (4.8%) dropped out of the study and 38 cases did not complete the minimum follow-up of 12 months. In those who completed the follow-up (751 cases), a regression of amblyopia by 1-2 lines (Table 4) was noted in a total of 51 cases (6.79%) which was due to not wearing the refractive glasses for 2-3 months during the first one year after the therapy. This visual loss was readily recovered by starting full-time patching again for 2-3 weeks and its gradual weaning. After this first incidence, the patients learned the importance of wearing glasses constantly so no further episodes were noted during the remaining follow-up period. This showed that the most sensitive period for regression of amblyopia was the first 12 months after a successful therapy, as the neural connections are still stabilising and strengthening during that period. This clearly establishes the need for good counselling of both the patients and their parents.

Q 6: Does visual improvement in a long standing amblyopic eye result in diplopia ? There were 98 cases in Group B & C, who had a large angle strabismus which needed surgical correction once equal visual acuity was restored in both eyes. All these cases complained of diplopia post-operatively for a period of 2-4 weeks. They were reassured and it gradually disappeared. No other treatment was needed in any case. This shows that once ocular alignment and equal vision is restored in both eyes, binocular single vision is gradually restored due to sensory fusion mechanism in the brain.

Q 8: Is there an improvement in stereopsis once equal visual acuity is restored in both eyes ?

The visual system is designed to use both eyes simultaneously to explore visual space. An amblyopic eye looses this important visual function. It has been shown in previous studies that vision therapy retrains the brain to use both eyes together.[39] This visual improvement occurs by an active, intense and persistent stimulation of GABA secreting neurons and up-grading of receptors. This was achieved in our study by full-time occlusion of the good eye so that its inhibitory influence over the newly forming neural synapses was totally avoided. The active intense stimulus was provided by near visual activities like reading and writing with full concentration for at least 4-5 hours per day, playing computer games on cell-phones. Finally, the neural connections were given adequate time to stabilise as patching was weaned gradually. The visual improvement was permanent and regression was seen only in those few cases (51 =6.7%) who stopped wearing their refractive correction for 2-3 months. They improved after resuming patching for a few weeks.

CONCLUSION:

Our study offers a clinical proof, supporting previous researches on Neuro-plasticity. As the visual acuity in the amblyopic eye becomes equal to the good eye, in all orthophoric cases, the stereopsis also improved, slowly and gradually. This occurred earlier and continued to improve with time in moderately amblyopic eyes as compared to the eyes with a dense amblyopia. This also fully supports the concept of Neuro-plasticity at all levels in the brain. Not only did the visual acuity improved in our cases but higher visual functions like stereopsis too. This further stresses the need that all amblyopic patients should be offered help by all ophthalmologists; no special gadgets are needed to restore sight in such a

huge number of patients but a belief that its treatment is possible, and a persistent, whole-hearted effort by the treating ophthalmologist, the patient and the parents, to achieve it.

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