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Binocular therapy as primary intervention in adults with anisometropic amblyopia

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Abstract:

PURPOSE: Refractive correction and patching is the timetested mainstay of treatment for anisometropic amblyopia within the critical period of visual development. Binocular therapies using dichoptic training which overcome suppression by balancing the contrast between two eyes has been increasingly gaining ground. We evaluated the efficacy of dichoptic training in the adult population with anisometropic amblyopia. This study aims to evaluate the effectiveness of dichopticbased active vision therapy, using “VisuoPrime” software as primary intervention, in adults with anisometropic amblyopes.

MATERIALS AND METHODS: A prospective interventional study in adults (18–40 years) with anisometropic amblyopia was conducted from August 2019 to March 2020. **METHODS:** Twenty-nine subjects with anisometropic amblyopia played binocular games through “VisuoPrime” software 30 min daily for 6 weeks. Bestcorrected visual acuity (BCVA) and binocularity was assessed at 1 and 3 months. Student’s paired ttest, Wilcoxon signedrank sum test and MannWhitney tests were used. Statistical package of SPSS version 20.0 was used for analysis, considering $P < 0.05$ as statistically significant.

RESULTS: BCVA of the amblyopic eye improved from 0.60 ± 0.40 logMAR to 0.45 ± 0.29 logMAR and 0.38 ± 0.23 logMAR at 1 and 3 months, respectively ($P = 0.0001$). Near acuity improved from 0.21 ± 0.14 to 0.14 ± 0.08 logMAR and 0.1 ± 0.04 logMAR at 1 and 3 months respectively ($P < 0.0001$). Improvement in stereopsis was observed in 24% of subjects which maintained at 3 month followup.

CONCLUSION: Dichopticbased active vision therapy using “VisuoPrime” software was effective as a primary modality in adults with anisometropic amblyopia.

Keywords:

Anisometropic amblyopia, best-corrected visual acuity, dichoptic therapy, stereoacuity, VisuoPrime

Introduction

Amblyopia with a worldwide prevalence of 1.44%^[1] and approximately 1.1%–6.6%^[2-6] in India, accounts for significant ocular morbidity. Patients with amblyopia not only face decreased visual acuity but also other functional deficits such as decreased contrast sensitivity, low accommodation, crowding, suppression, abnormal spatial localization, and abnormal interaction of spatial and temporal function.^[7,8]

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Conventional methods like patching are of limited use beyond the critical period of development, though levodopa^[9] and citicoline^[10] are tried. Recent data attributes the pathophysiology in anisometropic amblyopia to be due to difference in contrast signaling between the eyes, wherein the eye with higher refractive error carrying weaker contrast is suppressed by fellow normal eye with good contrast leading to amblyopia.^[11-13] Therefore, therapies are being directed to balance the contrast signaling between the eyes with resultant improvement in visual acuity as well as binocularity.^[14-17]

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Binocular therapy overcomes suppression by balancing the contrast from both the eyes using anaglyph glasses and performing binocular activities through active video game playing or passive watching of a 3D movie.^[18,19]

However, the effectiveness of binocular therapy as a primary intervention in adult subjects with anisometropic amblyopia subsets has not been studied so far. The objective of our study was to assess visual acuity and binocular outcomes with dichoptic therapy as primary modality of treatment in adults with anisometropic amblyopia.

Methods

A prospective interventional study design with subjects aged 18–40 years with anisometropic amblyopia, attending our outpatient department from August 2019 to March 2020 were evaluated.

Inclusion and exclusion criteria

Anisometropic amblyopia was defined as inter-ocular difference in visual acuity of >0.2 logMAR and anisometropia of $\geq 1.50D$ sphere or $\geq 1.00D$ spherical equivalent and latter being the cause for amblyopia. We included subjects in the age group of 18–40 years with anisometropic amblyopia willing to perform dichoptic training.

Patients with strabismic and mixed amblyopia, previous ocular surgeries, media opacities, corneal irregularities, and past history of amblyopia therapy were excluded. In addition, those unable to comprehend and perform games, or co-operate for formal assessment of visual acuity and stereopsis, were also excluded from the study.

Informed consent was taken from all subjects. The study protocol was approved by Institutional Ethical Committee of our institute (approval number-ECR/705/Inst/KA/2015/RR-18).

Baseline examination

Baseline ophthalmological examination including best-corrected visual acuity (BCVA) using logMAR chart for distance and Jaegers chart for near was done. Near acuity was then converted from N notation to logMAR^[20] [Table 1]. Worth's four dot test, stereopsis using TNO test card, contrast sensitivity using Pelli-Robson chart, cover tests, anterior segment examination, cycloplegic refraction using cyclopentolate 1% ("Auropent" eye drops; Aurolab) and tropicamide 0.8% with phenylephrine 5% combination ("Tropicacyl plus" eye drops; Sunways) and posterior segment examination were performed.

Inter-ocular difference in visual acuity ≤ 0.3 logMAR acuity was graded as mild, of 0.3–0.6 logMAR as

Table 1: Conversion of N notation in near visual acuity to logMAR equivalents

N notation	LogMAR equivalent
N4	0.07
N5	0.1
N6	0.11
N8	0.14
N10	0.18
N12	0.22
N16	0.3
N20	0.35
N24	0.44
N30	0.52

moderate, and ≥ 0.6 logMAR difference severe amblyopia for the study.

About "VisuoPrime"

"VisuoPrime," (Visuoprime, Neurapy pvt. Ltd., Chennai, Tamilnadu, India) the software-based therapy system developed by one of the authors AG, has both diagnostic and therapeutic applications.

The diagnostics provide information about the size and depth of suppression scotoma, which would be extrapolated to therapeutic modules that utilize monocular, monocular fixation in binocular field (MFBF), anti-suppression, and binocular modes.

As amblyopia is manifested in the form of binocular competition, "VisuoPrime" works to improve fixation pattern, reduce the saccadic latency and improve eye-hand coordination. It also improves pursuit accuracy, accommodative amplitude, and spatial accuracy and reduces the crowding phenomenon with improvements in information processing speed.

Therapy and follow-up

In our study, we employed MFBF therapy using anaglyph glasses, wherein blue filter of glasses was worn in front of the amblyopic eye. Monocular fixation in binocular field involves amblyopic eye to perceive the target, while the normal fellow eye perceives the background. It includes games such as balloon pop circuit, smiley, catching the falling items, and matching the slanting lines.

For each type of game played, reward points were given by the software in the form of stars, with five stars being the maximum score and one being the least, to help in maintaining the interest. The type of exercise and difficulty level was titrated by the therapist based on the number of stars earned. Subjects were given an option to therapy either through home based or office-based platform to ensure that those with no access to computer and internet could also be treated with this modality.

The monitoring for progression and compliance was made using an in-built tracker, which kept a track record of daily activities, including duration of play.

The gaming duration was set to 30 min/day for 7 days a week for 6 weeks, with a total of 42 sittings. Subjects were instructed to maintain a distance of 50 cm from the display screen.

Subjects were followed up at 2 weekly intervals for 2 months and then after a month. At each visit, BCVA for distance and near, stereopsis, worth's four dot test, and contrast sensitivity were recorded. Subjects who played $\geq 80\%$ of therapy sessions were considered as compliant.

The therapy lasted for 6 weeks. BCVA recorded at 1 month to check for compliance and also to note any change in visual acuity from the baseline. The BCVA 3 months was compared to baseline and analyzed to study persistence of visual gain after therapy.

Impact of COVID-19 pandemic on follow-up

Due to the COVID-19 pandemic, 17 subjects were unable to come for their review at 3 months. Visual acuity testing for six of those subjects was done using "VisuoPrime" software itself, after its validation in 25 subjects which showed the readings to be correlating to that measured in person. The same was reported to the Institutional Ethics Committee. Further, 4 subjects were in a remote geography and had their visual acuity recorded by a qualified ophthalmologist. This data were included. Another 7 subjects were lost for follow-up. Although visual acuity assessment with different methods was a limitation was unavoidable owing to the COVID pandemic. Home-based therapy may have been a better option in view of compliance but other parameters needed patient to be assessed in office.

Statistical analysis

Analysis of visual acuity, stereopsis, therapy, and compliance was done using the Student's paired *t*-test, Wilcoxon signed-rank test, and Mann-Whitney test using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

Results

Our study consisted of 29 adult subjects aged between 18 and 40 years, with anisometric amblyopia with near equal gender distribution. Anisohyperopia was the most common type of amblyopia, observed in 22 subjects, while anisomyopia in seven subjects. With regards to degree of amblyopia; moderate amblyopia was commonest in 17 subjects, while mild and severe amblyopia noted in three and nine subjects, respectively. Home-based therapy was

chosen by 24 subjects, while office-based therapy by five subjects. Fourteen subjects were compliant with therapy; however, 15 subjects were noncompliant, playing $< 80\%$ of therapy sessions [Table 2].

Distance visual acuity improved significantly from 0.60 ± 0.40 logMAR at baseline to 0.45 ± 0.29 logMAR ($P = 0.0001$) and 0.38 ± 0.23 logMAR ($P = 0.0001$) at 1 and 3 months respectively, while near acuity showed significant improvements from 0.21 ± 0.14 logMAR at baseline to 0.14 ± 0.08 logMAR ($P < 0.0001$) and 0.1 ± 0.04 ($P < 0.0001$) at 1 and 3 months, respectively [Figure 1].

Anisohyperopia subjects showed significant improvements in distance visual acuity from 0.6 ± 0.4 logMAR at baseline to 0.5 ± 0.27 ($P = 0.001$) and 0.37 ± 0.23 logMAR ($P = 0.0001$) at 1 and 3 months, respectively, while near acuity improved significantly from 0.2 ± 0.13 logMAR at baseline to 0.13 ± 0.05 ($P = 0.001$) and 0.11 ± 0.04 logMAR ($P = 0.001$) at 1 and 3 months. Anisomyopia subjects showed significant improvements in distance visual acuity from 0.6 ± 0.4 logMAR at baseline to 0.45 ± 0.25 logMAR ($P = 0.017$) and 0.44 ± 0.28 logMAR ($P = 0.03$) at 1 and 3 months, respectively, while near acuity improved significantly from 0.23 ± 0.19 logMAR at baseline to 0.18 ± 0.14 logMAR ($P = 0.041$) and 0.09 ± 0.03 logMAR ($P = 0.02$) at 1 and 3 months, respectively [Figure 2].

Visual acuity gain for both distance and near in mild amblyopia was statistically not significant and was significant in moderate and severe amblyopia subjects as described in Figure 3.

BCVA was significantly different between 1 and 3-month posttherapy. This needs to be viewed in the light of that therapy lasted for 6 weeks (that is beyond 1 month results) and so results at 1 month show interim improvement.

Home therapy subjects had a statistically significant visual acuity gain for both distance and near, while office-based therapy subjects had significant visual acuity

Table 2: Demographic details of subjects undergoing dichoptic therapy

Parameters	Number of subjects
Sex	
Male	15
Female	14
Type of amblyopia	
Anisomyopia	7
Anisohyperopia	22
Degree of amblyopia	
Mild	3
Moderate	17
Severe	9
Total number of subjects	29

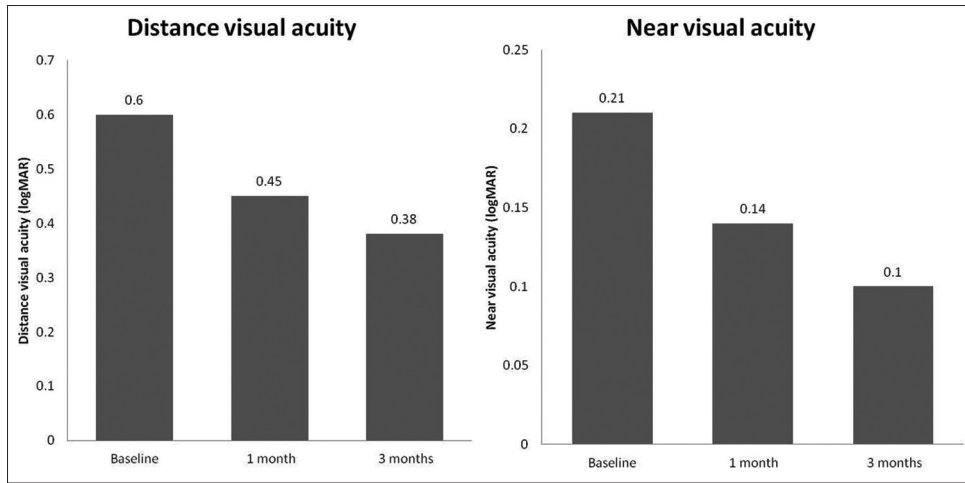


Figure 1: Graph representing change in distance and near visual acuity from baseline to 1 and 3 months

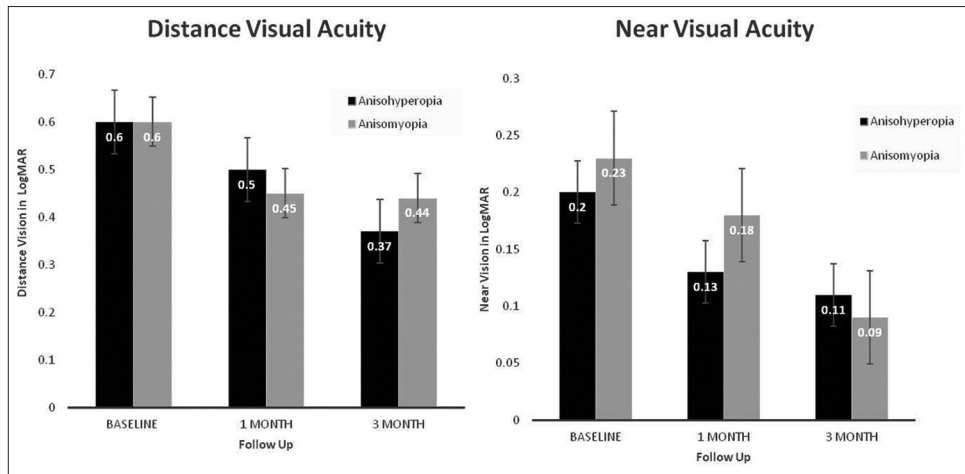


Figure 2: Graph representing change in distance and near visual acuity change from baseline to 1 and 3 months in anisohyperopic and anisomyopia amblyopia

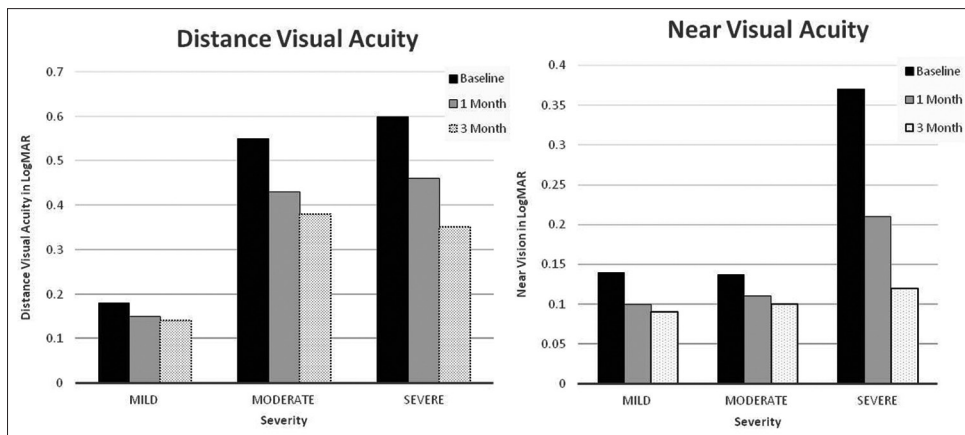


Figure 3: Graph representing change in distance and near visual acuity change from baseline to 1 and 3 months among mild, moderate and severe amblyopia

gain only for distance, and near acuity did not improve in them significantly as described in Table 3.

There was significant improvement in contrast sensitivity of the amblyopic eye from 1.45 ± 0.044 log units at baseline to 1.67 ± 0.30 log units ($P = 0.0001$) at 1 month

and 1.83 ± 0.14 log units ($P = 0.0009$) at 3-month follow-up.

Suppression, as recorded by worth's four dot testing for distance at baseline, showed suppression in ten subjects, which at 1 month was observed only in seven subjects

and at 3 months, it was seen in none. For intermediate distances at baseline, it was observed in eight subjects, while at 1 month seen in four subjects and none at 3 months. For near distances, at baseline seven subjects had suppression, which was seen in 1 subject at 1 month and none at 3 months.

The stereopsis was measurable in six subjects and not measurable in 23 subjects at baseline. Analyzing these two groups, significant improvement in visual acuity for distance was noted in both the groups, while near acuity improvement reached statistical significance only in non-measurable stereopsis group [Table 4].

Gain in stereopsis was noted in seven subjects, of whom four subjects had no baseline measurable stereoacuity.

Analyzing between compliant and noncompliant groups, a statistically significant visual acuity gain for both distance and near were noted in both the groups [Table 5].

Since “VisuoPrime” was home-based therapy software, subjects were able to play regularly at home during lockdown. Since most of the office-based subjects had their therapy sessions completed before the lockdown period, therapy remained unaffected in these subjects. However, the follow-up evaluation was troublesome in both the groups, which was dealt using “VisuoPrime” software evaluation platform in home-based subjects. We were able to record the visual acuity for distance and near; however,

other parameters like worth’s four dot test, contrast sensitivity, and stereopsis were not recorded. While office-based subjects had their visual acuity recorded from a nearby ophthalmic center, which was then converted to logMAR.

Discussion

It was widely believed that neuroplasticity ceases to exist after the age of 7 years, and restoration of visual acuity would not be possible beyond that critical period.^[21] However, recent studies have shown the restoration of visual acuity overcoming plasticity in later life with appropriate stimulation.^[12,22] It has been noted that pathogenesis of anisometropic amblyopia revolves around difference in contrast signal carried to visual cortex with weaker contrast from eye with higher refractive error, which is actively suppressed by the other eye resulting in amblyopia. Hence binocular therapies are aimed at reducing this contrast difference.^[14,22] Most of the studies were done in children, which show consistent results with binocular therapy.^[23-25] Our study focuses on its effectiveness in older amblyopes where none of other conventional modalities of therapy have been effective.^[26]

An improvement in distance visual acuity of 0.15 logMAR was noted in our series at 1 month and 0.22 logMAR at 3 months which was comparable to a study by Žiak *et al.* who found an improvement of 0.15 logMAR in anisometropic amblyopes aged 17–69 years after 8 sessions of training (40 min/session) for twice a week

Table 3: Improvement in visual acuity of home based versus office-based therapy

Visual acuity in logMAR	Home therapy (n=24)		Office based therapy (n=5)	
	Distance VA	Near VA	Distance VA	Near VA
Baseline	0.62±0.41	0.2±0.14	0.5±0.3	0.2±0.2
1 month	0.47±0.25 (P=0.001)*	0.13±0.07 (P=0.001)*	0.33±0.3 (P=0.042)*	0.17±0.15 (P=0.1)
3 months	0.4±0.21 (P=0.001)*	0.106±0.04 (P=0.001)*	0.32±0.32 (P=0.042)*	0.1 (P=0.31)

VA=Visual acuity, *p value being significant

Table 4: Improvement in visual acuity from baseline to 1 and 3 months in stereopsis present versus stereopsis absent group

Visual acuity in logMAR	Stereopsis present group (n=6)		Stereopsis absent group (n=23)	
	Distance VA	Near VA	Distance VA	Near VA
Baseline	0.4±0.14	0.22±0.13	0.65±0.42	0.22±0.15
1 month	0.29±0.17 (P=0.042)*	0.12±0.04 (P=0.06)	0.47±0.26 (P<0.0001)**	0.14±0.09 (P<0.0001)**
3 months	0.28±0.16 (P=0.027)*	0.11±0.04 (P=0.06)	0.38±0.23 (P<0.0001)**	0.10±0.04 (P=0.0017)**

VA=Visual acuity, *p value being significant, **Being highly significant

Table 5: Improvement in visual acuity from baseline to 1 and 3 months in compliant versus noncompliant groups

Visual acuity in logMAR	Compliant subjects (n=14)		Noncompliant subjects (n=15)	
	Distance VA	Near VA	Distance VA	Near VA
Baseline	0.6±0.42	0.23±0.15	0.6±0.37	0.18±0.13
1 month	0.46±0.25 (P=0.013)*	0.14±0.07 (P=0.005)*	0.43±0.27 (P=0.001)*	0.14±0.1 (P=0.005)*
3 months	0.4±0.2 (P=0.007)*	0.1±0.04 (P=0.003)*	0.37±0.26 (P=0.001)*	0.1±0.03 (P=0.026)*

VA=Visual acuity, *p value being significant

using oculus head-mounted display.^[27] A study by Hess *et al.* noted an improvement of 0.11 ± 0.08 logMAR in adult amblyopes aged 13–50 years using i-Pod with lenticular screen for 10–30 h.^[28]

Most of the studies on binocular therapy were done on children and including all forms of amblyopia, hence there were no studies describing the effect of binocular therapy in a particular type of amblyopia to compare our results with. Comparing distance visual acuity gain from our study on adults (0.15 logMAR) to the studies in children, a gain in visual acuity of 1.4 logMAR was noted at 1 month by Kelly *et al.*, in 6–10-year-old children.^[23] Similarly, an improvement of 0.17 logMAR units was noted in a study by Jayakumar *et al.* in south Indian children aged 9–14 years in the ambient group at 1 month.^[29] Study by Knox *et al.* and the Glasgow pilot study found an improvement in visual acuity in children with shorter therapy sessions of 1 week duration.^[17,30]

Near acuity gain in our study was 0.07 and 0.11 logMAR at 1 and 3 months, respectively ($P < 0.0001$), a parameter not studied in any prior studies.

Looking at subtypes further, distance visual acuity gain in anisohyperopic amblyopes was 0.1 and 0.23 logMAR at 1 and 3 months respectively, while anisomyopes had a visual acuity gain of 0.15 logMAR at 1 and 3 months. Although this is to be viewed under the lens of our sample having higher anisohyperopes. The visual gain for distance and near in adult amblyopes with respect to the type of amblyopia has not been reported so far, while studies in children by Jayakumar *et al.* found an improvement in distance visual acuity of 0.1 and 0.26 logMAR at 1 and 3 months, respectively in anisohyperopes, and an improvement of 0.12 and 0.29 logMAR at 1 and 3 months respectively in anisomyopes.^[29]

Moderate amblyopia subjects showed a significant gain in distance visual acuity of 0.1 and 0.15 logMAR at 1 and 3 months, respectively, and near visual acuity gain of 0.01 logMAR at both 1 and 3 months. Mild and severe amblyopes also showed gain in visual acuity for distance and near which failed to reach statistical significance in the former. Our study sample had unequal distribution of mild, moderate and severe amblyopes to compare the visual acuity gain difference between them.

Study by Jayakumar *et al.* showed an improvement of 0.08 and 0.18 logMAR at 1 and 3 months respectively in mild amblyopes, and no improvement in visual acuity noted for moderate and severe amblyopes in children.^[29] This was different than our results, may be explainable owing to different age of subjects dealt with.

There was a significant difference comparing 1 and 3 month results but the therapy lasted beyond 1 month results (till 6 weeks). BCVA does seem to show improvement after cessation of therapy. However, the optimum sessions needed and how long the improvement in visual acuity continues after therapy needs further studies.

Comparing the home-based therapy versus office-based therapy, it seemed that home-based therapy fared better. None of the prior studies have looked into this parameter so far. The number of sessions done by those on home therapy was the only variation noticed. With the population in both groups not being equal, we were unable to statistically analyze this parameter further

Comparing compliant versus noncompliant groups, we found that visual acuity improvement was noted even in patients not completely compliant as per the schedule. We found that visual acuity improvement was noted even in patients not completely compliant as per the schedule. Although the visual acuity improvement was comparable in compliant and non-compliant groups, it seems too quick to draw a conclusion that the number of treatment sessions could be reduced. A control group may be needed to exclude other biases such as learning effect. Owing to the absence of control group and small number of subjects, it is difficult to draw conclusions on the same from our study.

In a study by Li *et al.*, among 50 children with all forms of amblyopia in 4–10 years of age group, binocular therapy given up to 4 weeks and assessed at 1 month showed a visual acuity gain of 0.08 logMAR. Additional 4 weeks of therapy for children with no gain in visual acuity did not benefit further, suggesting no role of additional therapies.^[31]

Disinteresting games and work pressure made subjects to be noncompliant. Among office-based subjects, travel time for therapy was an added reason for noncompliance.

We found significant improvement in contrast sensitivity of the amblyopic eye of over 0.22 log units at 1 month and 0.38 log units over baseline, and no reported literature on this so far.

The suppression as noted by worth's four dot test showed improvement in suppression to fusion in all the subjects for distance, intermediate, and near distances at the end of 3 months. Transient mild diplopia was experienced by two subjects, which improved to fusion on continuation of therapy. None of the subjects experienced diplopia to an extent to disable their routine activities or to stop the therapy.

Gain in stereopsis was noted in seven subjects (24%) at the end of 3 months, among whom 4 subjects had

no measurable stereopsis at baseline. Comparing our results to the study in children by Kelly *et al.*, who noted a measurable stereopsis in 20% of the subjects.^[23]

Although the MFBF therapy in “VisuoPrime” was not intended to improve the stereopsis, the gain in stereopsis in a subgroup of subjects is not entirely explainable.

Most of the subjects enjoyed the therapy sessions, and no adverse events noted in any study subjects.

To the best of our knowledge, this is the first study looking at binocular vision therapy as a primary modality of therapy in anisometropic adults

Due to COVID-19 pandemic, few subjects were unable to come for follow-up, for whom “VisuoPrime” itself was used for evaluation, few subjects had their visual acuity tested at nearest centres, and another few were lost for follow-up. In this regard “VisuoPrime” was a great tool for evaluating the visual acuity, however, parameters like worth’s four dot test, stereopsis and contrast sensitivity were unable to assess through it.

Limitations of our study included loss of follow-up at 3 months owing to COVID pandemic, lack of control group and shorter follow-up. Although the visual acuity improvement was comparable in compliant and noncompliant groups, it seems too quick to draw a conclusion that the number of treatment sessions could be reduced. A control group may be needed to exclude other biases such as learning effect. Serial long-term follow-up of these subjects is necessary to know the stability of visual acuity gained. Further trials with large sample size are required to know long-term effects of therapy, effect of compliance on improvement as well as to ascertain the course of stereoacuity improvements due to therapy.

Conclusion

Our study shows the usefulness of dichoptic-based active vision therapy as an effective tool for the treatment of anisometropic amblyopia in adults as a primary modality. The long-term effectiveness and its use in strabismus or mixed amblyopia need to be studied further.

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Nil.

Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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