To Compare the Efficacy of Standard Patching Therapy and Digital Smart Glasses in Treatment of Amblyopia

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ABSTRACT

BACKGROUND

Treatment of amblyopia by patching is the gold standard. However, it is associated with poor compliance, difficult to use, has risk of allergy, has social stigma and may cause cosmetic problems. We wanted to compare the efficacy of standard patching therapy and Digital Smart Glasses (Liquid Crystal Glasses) in the treatment of Amblyopia.

METHODS

In this comparative, prospective, interventional, safety/efficacy study with the primary purpose of treatment, 60 eyes of the children 3 - 8 years of age with previously untreated, moderate (visual acuity of 20/40 to 20/100 in the amblyopic eye), unilateral, anisometropic amblyopia were included. All subjects were using optimal refractive correction before start of occlusion therapy. Digital smart glasses group used a 6-hour intermittent occlusion therapy with liquid crystal glasses, set at 40-second opaque / 20 second transparent intervals (occluded 66% of wear time) which gives an effective 4 hours of occlusion and it is compared with 4 hours of continuous patching therapy. Occlusion was applied only to the good eye. All 60 children were followed up regularly for 36 weeks. Best corrected visual acuity for distance was measured. Visual acuity for distance was measured with the help of Snellen's chart.

RESULTS

There is a statically significant gain in visual acuity in both groups from baseline in each visit. Difference in mean gain in visual acuity was statically significant between both groups at 4 weeks , 8 weeks, 12 weeks, 24 weeks of therapy ($p<0.05$) with lower LogMAR value in Digital Smart Glasses group on each visit.

CONCLUSIONS

This pilot study suggests that intermittent occlusion therapy (IO-Therapy), with Digital Smart Glasses with 6 hours daily wear time (set at 40 sec occlusion and 20 sec transparent time, 66% occlusion time) is not inferior to 4-hours of daily continuous patching when treating children in the 3 - 8 years age group with moderate, unilateral amblyopia. This promising device provides an alternative form of amblyopia treatment for children and their frequently frustrated families.

KEYWORDS

Digital Smart Glasses, Liquid Crystal Glasses, IO therapy, Amblyopia, Digital Patch

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BACKGROUND

Amblyopia is a developmental defect of spatial visual processing that occurs in the central visual pathways of the eye.[1] Amblyopia is the most common vision deficit in children, affecting 2-5% of children worldwide.[2,3] and the second most common cause of functional low vision in children in low-income countries.[4] These defects may be explained by the mechanism of lack of use of an eye because of media opacity or extreme refractive errors that cause a chronically blurred image to form on the fovea of that eye; however, the cause of amblyopia in an eye that has strabismus is not as straightforward and is the result of abnormal binocular interaction. There are different types of amblyopia depending on the cause, strabismus amblyopia, stimulus deprivation or amblyopia of disuse, anisometric amblyopia, meridional amblyopia, and ametropic, amblyopia secondary to nystagmus, idiopathic amblyopia and organic amblyopia.[5] Clinically, unilateral amblyopia is conventionally defined as a difference in best-corrected visual acuity (BCVA) between the two eyes of 0.20 LogMAR (2 lines on an acuity chart,[6] similarly, bilateral amblyopia is defined as a reduction of 0.20 LogMAR or more compared with the developmental norms for BCVA at a given age. Amblyopia is graded into three grades, Mild amblyopia (BCVA>20/40, Moderate amblyopia (BCVA 20/60- 20/80) and Severe amblyopia (BCVA=20/120).[7] Anisometric Amblyopia develops when unequal refractive errors in the two eyes cause the images on one retina to be chronically defocused. There are different treatment options available, and patching is the gold standard therapy.[5] A new treatment modality which has come-up in the form of occluding the eye intermittently by wearable glasses whose screen is made-up of liquid crystal glasses (digital patch).[8,9] In this treatment modality the dominant eye is occluded intermittently. This new treatment approach is a good alternative to conventional patch therapy, as it has several advantages over conventional patch therapy e.g. better compliance, lower chances of suppression of better eye, easy to operate, and the duration of occlusion of eye can be adjusted, no social stigma, and no allergic reactions, cosmetically accepted. Its efficacy in the form of visual acuity improvement of two Snellen's line is comparable to standard patch therapy after 3 months of therapy.[8,9] Therefore, in this study, we investigated to compare the efficacy of standard patching therapy and digital smart glasses (liquid crystal glasses) in treatment of amblyopia.

METHODS

This comparative, prospective, interventional, safety/efficacy study with primary purpose of treatment was conducted at the Eye Out-Patient Department of Base Hospital, Delhi Cantt, which is a tertiary eye care center; from Mar 2016 to Mar 2017. Institutional ethical clearance was taken for conduct of study and informed consent was also taken from patient's custodian. Sixty (60) eyes of the Children, aged 3-8 years with previously untreated, moderate (visual acuity of 20/40 to 20/100 in the amblyopic eye), unilateral, anisometropic amblyopia were included in study.

Sample Size Calculation

Sample size was calculated keeping in view at the most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence level). However, the past data, which gives idea of variation in the variables, plays an important role in calculating the sample size. A sample size of 12 subjects per group has been shown to be effective for estimating within-group means and variances when little prior data is available. This study was pilot study a number of 12 would work for a pilot study,[10] we overestimated the sample size to 30 in each group to account for Lost in follow-up and cost constraints involved in the study. Based on collected data from 60 subjects and effective size difference of 0.1, we re-estimated this study as a non-inferiority trial with continuous outcome and power is calculated as approximately 80%.

Total sixty (60) was taken in study which was maximum number which can be included in study considering monetary constrains involved. They were divided into two groups as follows-

Group 1:
Included 30 eyes of the children 3-8 years of age with previously untreated, moderate, unilateral anisometropic amblyopia (visual acuity of 20/40 to 20/100 in the amblyopic eye). All subjects were using optimal refractive correction. This group used a 6-hour intermittent occlusion therapy with Liquid Crystal Glasses (Vidi glasses, manufactured by BNM Fabrika Biyo Nano Mikro Teknoloji San. Ve Tic. Ltd)), set at 40-second opaque/ 20 second transparent intervals (occluded 66% of wear time).

Group 2:
included 30 eyes of the patient with Children 3-8 years of age with previously untreated, moderate, unilateral amblyopia (visual acuity of 20/40 to 20/100 in the amblyopic eye). All subjects were using optimal refractive correction. This group used a 4-hour continuous patching (occluded 100% of wear time).

For each patient, visual acuity was measured using Snellen's vision chart at enrolment, 1 week, 4 weeks, 8 weeks, 12 weeks, 24 weeks and at 36 weeks of treatment. For the ease of calculation and standardizing analysis the Snellen's visual acuity was converted into LogMAR. Data was analysed by using SPSS software version 18.

Inclusion Criteria

1. Children 3-8 years old.
2. Untreated, moderate, unilateral amblyopia.

3. Anisometropic amblyopia.
4. Amblyopic eye vision 20/40 to 20/100.

Exclusion Criteria

1. Patients unwilling to give consent and take part in long term follow-up/lost to follow-up**.**
2. Patients already on treatment for amblyopia.
3. Patients having associated ocular diseases.
4. Severe amblyopia with vision <20/100.

The primary outcome was the visual acuity change in the amblyopic eye, in LogMAR units, at the 36-week outcome visit. A paired t-test was applied to analyse visual acuities before and after treatment for each group; an independent t-test was applied to analyse visual acuity improvement between the two groups. Confidence intervals of visual acuity improvement were reported in a non-inferiority manner, after intervention type was considered, correlation coefficients were calculated for the treatment response (improved visual acuity in the amblyopic eye) to the variable, baseline visual acuity. The level P <0.05 was considered as the cut-off value or significance.

Statistical Analysis

Statistical methods used in the study were t-test for comparing mean values in two groups. Paired t-test was used to see the relative change in the variable with respect to time. Pearson's Chi-square test was used for qualitative data comparisons between two groups. Data was analysed by using SPSS software version 18.

RESULTS

Following the intent-to-treat strategy, the 36-week primary outcome examination was completed by 30 of the patients in the IO-Therapy Group and 30 patients in the Patching Group. Between April 2016 and March 2017, a total of 85 patients of amblyopia were examined, out of which 72 were found eligible for the study trial based on inclusion and exclusion criteria. Of these, a total of 60 patients (83.3%), 30 patients in each group were followed up through the entire duration (36 weeks) of this study. There were total 42 male patients (71%) and 18 female patients (29%) (Table 1 and chart 1). The mean age of all the patients was 6.63 years. Baseline demographics of the two treatment groups were similar, particularly in terms of the mean age, and baseline visual acuity. There were more male subjects in the IO therapy by Liquid Crystal Glass (Vidi glasses) Group than in the Patching group. The mean baseline visual acuity was 0.51 ± 0.12 LogMAR in group 1 and 0.52 ± 0.09 LogMAR in group 2. There were no statistically significant differences in characteristics between the treatment groups. (Table-4) (p<0.05).

		Group		Total	Pearson Chi-Square	p-value
		Vidi	Patch			
Gender	Male	23	19	42	1.27	0.26
	Female	7	11	18		
Total		30	30	60		

Table 1. Gender Distribution of Study Groups

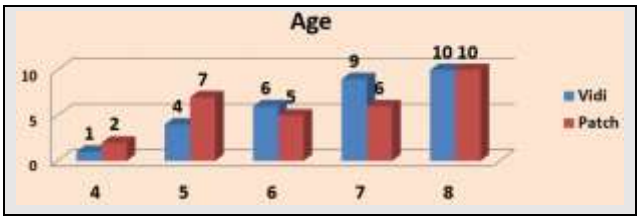

Chart 1. Age Distribution of Study Group

This chart compares the age distribution among Vidi group and the Patch group. The difference of means in both the groups at baseline were statistically insignificant (P=0.270).

Primary Outcome Measure

For primary efficacy analysis, mean gain in visual equity between baseline and last follow-up was used. The mean gain in visual acuity was from 0.51 LogMAR (N=30, S.D.= 0.12) to 0.07 LogMAR (N=30, S.D.= 0.11) in Vidi group. The mean gain in visual acuity was from 0.52 LogMAR (N=30, S.D.= 0.09) to 0.15 LogMAR (N=30, S.D.= 0.13) in Patching group. There is statically significant gain in visual acuity of treatment group from baseline in each visit (Table-2).

		Mean	N	S.D.	Mean Difference	t-value	p-value
Pair 1	Baseline LogMAR	0.51	30	0.124	0.050	3.746	0.001
	LogMAR 4 week	0.46	30	0.130			
Pair 2	LogMAR 4 week	0.46	30	0.130	0.090	4.791	<0.001
	LogMAR 8 week	0.37	30	0.151			
Pair 3	LogMAR 8 week	0.37	30	0.151	0.133	5.525	<0.001
	LogMAR 12 week	0.237	30	0.145			
Pair 4	LogMAR 12 week	0.237	30	0.145	0.127	7.648	<0.001
	LogMAR 24 week	0.11	30	0.154			
Pair 5	LogMAR 24 week	0.11	30	0.154	0.037	2.796	<0.009
	LogMAR 36 week	0.07	30	0.108			
Pair 6	Baseline LogMAR	0.51	30	0.124	0.437	20.633	<0.001
	LogMAR 36 week	0.07	30	0.108			

Table 2. Comparison of Visual Acuity Gain from Baseline on Each Visit in Smart Glasses Group (Vidi Group) (Unpaired t-Test)

	Mean BCVA (LogMAR ± SD)	
	Smart Glass (Vidi Group)	Patch Group
Baseline	0.51 ±0.12	0.52 ±0.09
4 week follow-up	0.46±0.01	0.51 ±0.08
8 week follow-up	0.37 ±0.15	0.39 ±0.11
12 week follow-up	0.24 ±0.14	0.34 ±0.10
24 week follow-up	0.11 ±0.15	0.20 ±0.08
36 week follow-up	0.07 ±0.11	0.15 ±0.13

Table 3. Mean Best Corrected Visual Acuity at Baseline and During Follow-Up in Both Treatment Groups

Table showing comparison of visual acuity gain on each visit in Smart Glasses group (Vidi group). There is statically significant gain in visual acuity in Vidi group at 4 week, 8 week, 12 week, 24 week and 36 weeks of treatment ($p < 0.05$).

There is statically significant gain is visual acuity of treatment group from baseline in each visit (table-3). Mean gain is visual acuity were statically significant between both group at 4-weeks, 8-weeks, 12-weeks, 24-weeks of therapy (table-6) ($p<0.05$) with lower LogMAR value in Vidi group on each visit.

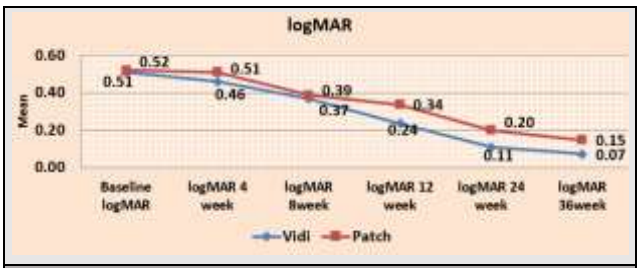

Chart 2. Comparison Of Mean LogMAR at Baseline and at Each Follow Up in Both Treatment Groups

This chart compares the mean best corrected visual acuity in LogMAR at baseline and each follow up among Vidi group and the Patching group.

Secondary Outcome

Patient compliance to the prescribed treatment was calculated as the self-reported wearing hours versus the prescribed hours daily (patient should wear 100% of prescribed time). At 36-weeks, compliance was reported by 30 (100%) patients in the IO-Therapy Group and 22 patients (73%) in the Patching Group. This difference is statistically significant ($p<0.05$) in Smart Glasses group (Vidi group), no patient reported skin rash, and in Patch group 3 (10%) patients reported skin rash which is not statistically significant ($p>0.05$). No patients in Smart Glasses group (Vidi group) reported itching and 22 patients (73%) in Patch group reported itching, which is statistically significant ($P<0.05$). No patient in both treatment group developed inverse Amblyopia (defined as 2 or more line drop of visual acuity from baseline).

DISCUSSION

This study is the first large sample size pilot randomized clinical trial comparing the effectiveness of Digital smart glasses and adhesive occlusion patches when treating children 3-8 years of age with moderate unilateral amblyopia. This is the hypothesis-based study to compare intermittent occlusion with continuous occlusion. The results suggest that 6-hours of intermittent occlusion (occluded 66% of wear time) is not inferior to 4-hours of continuous occlusion.

Table-4 demonstrates how our study differs from three previous IO-Therapy studies with liquid crystal glasses,[11,12] primarily in the following aspects: (1) we studied only moderate amblyopia, which is similar to Spierer et all, (we have large sample size from all previous studies) and Neely et all while Erbagci et all included both severe and moderate amblyopia in their 14 patients. Visual acuity improvement in our study is greater than all previous studies. (2) The occlusion time is more in our study and result is analyzed at longer duration (36 weeks of study). In both previous studies, (except Neely et all study) IO-Therapy hours were not fixed and prescribed amounts were left to the individual physicians' preference, which varied from 4 to 12 hours.[13,14] But in our study we keep occlusion time fixed at 6 hrs. of occlusion at 66% of time occluded. (3) in study conducted by Neely et all sample size was 17 were taken and occlusion time was four hours with 50% occlusion time, in our study sample is 30 and occlusion time is 6 hrs. with 66% occlusion time. Mean gain in visual acuity is more in our study from all previous studies (0.07 ± 0.11 at 36 weeks).

Power Calculation of This Study

Given that hospital where we enrolled patients is a tertiary referral center serving a state-wide population, several patients in both groups did not keep the scheduled follow-up visit. Therefore, the sample size of this study decreased from 72 to 60. However, based on available data from the sample size obtained, the power of this study as a non-inferiority trial is calculated as approximately 80%. Thus, this study has enough power to confidently reach conclusions from the 36-week outcome.

	Spierer et al[13] (2010)	Erbagci et al[14] (2015)	Neely et al (2016)	Our Study
Study Design	No Control Group	No Control Group	Clinical Trial with Patching Control Group	Clinical Trial with Patching Control Group
Sample size	24	14	19 IO vs 15 Patch	30 IO vs 30 Patch
Age at treatment (years)	4-7.8	4.5-10	3-8	3-8
Patients characteristics	Moderate amblyopia, previously treated or untreated	Moderate and severe amblyopia, previously untreated, no optical correction adaptation period	Moderate amblyopia, previously untreated, optical correction adapted,	Moderate, unilateral an-isometropic amblyopia, previously untreated, no optical correction adaptation(sample size 30 in IO group)
IO-Therapy glasses occlusion setting	40 seconds on and 20 seconds off	30 seconds on and 30 seconds off	30 seconds on and 30 seconds off	40 sec on and 20 sec off
Daily IO-Therapy hours	At least 8 hours	4-12 hours	4 hours	6 hours
Reported follow-up period (months)	1.5, 3, 4.5, 6, 9	3 to 7 (mean 4.0±1.2)	3	1, 2, 3, 6, 8
Visual acuity improvement (LogMAR)	0.16±0.3 (at 3-months)	0.3±0.2	0.15±0.12	0.07±0.11 (at 36 weeks)

Table 4. Comparison of Three Previous IO-Therapy Studies with Liquid Crystal Glasses

Clinical Meaning and Insight of This Study

In 2014, the FDA approved Amblyz™ IO-Therapy glasses as a medical device (but not as a specific therapy for amblyopia), (it was a prototype of device and today its production has been stopped and new product with additional feature is manufactured as brand name Vidi). However, clinicians did not previously have an evidence-based guideline for prescribing these glasses. Our study will further suggest such evidence. The promising results at 36-weeks clearly warrant further investigation with a larger number of patients at multiple study centers and with longer follow-up. Moreover, this study does not simply provide evidence that 6-hours of daily IO-Therapy glasses are equally effective as compared to 4-hours of patching but, perhaps more importantly, this study suggests that it may be the cumulative time of occlusion that is important rather than what time increment it is delivered in.

CONCLUSIONS

This pilot study suggests that IO-Therapy, with liquid crystal occlusion glasses with 6 hours daily wear time (set at 40 sec occlusion and 20 sec transparent time, 66% occlusion time) is not inferior to 4-hours of daily continuous patching when treating children 3 - 8 years old with moderate, unilateral amblyopia. This promising device provides an alternative form of amblyopia treatment for children and helps their frequently frustrated families.

Limitations

The limitation of the study is the small number of subjects in each study arm. However, this is a pilot study. It is suggested that an RCT based on a similar protocol on a larger study population with a longer follow-up to compare the efficacy of Vidi glasses versus conventional patching would help in further validating the results and provide conclusive evidence to the efficacy of Digital Smart Glasses in treatment of amblyopia.

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