Original Article

Looking beyond occlusion: A novel perspective for amblyopia treatment

KS Santhan Gopal, Chaitra Jayadev[1], Sherina Thomas[1], Sugandhi Gopal

Purpose: The aim of this study was to evaluate the efficacy of Orthoptek (Magnocellular Stimulator OMS; Carditek Pvt. Ltd., Bangalore) as a treatment modality for amblyopia and strabismus. **Methods:** Thirty-five patients with amblyopia of any type, reduced vision in one or both eyes with no binocular vision and or poor stereopsis were included in the study. All patients underwent a minimum of 10 sessions of therapy with each session lasting for a cumulative period of 60 min. At the end of the 10th session, patients were evaluated for improvement in visual acuity, stereopsis, Binocular single vision and amount of strabismus, if any. **Results:** The mean logMAR corrected distance visual acuity improved from 0.31 ± 0.34 and 0.32 ± 0.44 to 0.08 ± 0.12 and 0.07 ± 0.12 posttreatment in the right eye and left eye, respectively. Following therapy, 34 (97%) patients showed improvement in stereopsis, orthophoria was noticed in 28 (80%), and binocular single vision was noted in 33 (94%). All patients were followed up for 1 year with maintenance therapy and none showed any regression. **Conclusion:** We believe that top–down impulses and the role of the attention area in the parietal cortex have not been studied well enough in the treatment of amblyopia. Our device addresses these issues and corrects the visual deficits in amblyopia. However, the study needs validation of this pilot study from independent centers. The same will be done at some stage

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Amblyopia is a developmental disorder of the occipital cortical binocular cells, due to abnormal action potentials (in time or amplitude) reaching the binocular cortical cells from the retina of one or both eyes, during early development.[1] Occlusion therapy has been the most popular treatment option for amblyopia for many decades.[1-3] The results have been variable and inconsistent due to differences in age, etiology, and initiation and duration of treatment.[4] Moreover, monocular occlusion may not actively improve the binocular cooperation and stereopsis. Hence, the need for a more reliable and consistent treatment modality for amblyopia.

Vision is a complex process that starts in the retina and ends in the primary visual cortex V1, and processed beyond in the parietal and temporal cortices. The motor aspect of vision, which ensures bifoveal fixation during movement of the object or the body or both, is even more complex. It is likely to be near normal in many cases of amblyopia in the initial stages. The incident light is converted into neural impulse in the retinal ganglion cells, namely the parvocellular type (P cells), magnocellular type (M cells) and koniocellular (K cells).[5] The P cells are predominantly in the central retina and M cells in the periphery. There is a precise retinotopic fidelity both at the level of lateral geniculate body (LGB) and the cortical level, which is very important for many visual functions like object localization in space [Fig. 1].[6] The intricate connection between M-cell pathway and *P* cell pathway at various levels in the brain is well established and a considerable amount of information is exchanged between the two pathways.[7]

There are various types of eye movements like saccades, pursuit, optokinetic movements, and vestibular and vergence movements that work synergistically for visual orientation of both stationary or moving targets. Saccades are very short and fast eye movements lasting for 30-80 msec working through an internal feedback loop, based on the efferents of motor commands sent to the ocular motor neurons.[4] Sensory motor integration occurs in the posterior parietal cortex (PPC) also referred to as an "associative" cortical region, during the generation of a saccade.[6] The visual cortex V1 region shows a stronger activity during simple pro saccades/reflexive saccades than during more complex volitional/cognitive saccades.[7] The lateral occipital visual association cortex activation is present only during targeted saccadic condition, while internal cognitive saccades are not associated with lateral occipital cortical activity.[8] The retina between the fovea and the stimulated peripheral retinal point is suppressed during a saccade. The fovea is alerted about the peripheral retinal stimulus, a few miliseconds before the onset of saccade.[9,10]

Attention is the mechanism that directs the fovea of the retina to the salient stimulus, in the middle of an array of nonsalient stimuli being presented in the visual field. Its role

Kamala Nethralaya, [1]Vitreoretina Services, Narayana Nethralaya, Bangalore, Karnataka, India

Correspondence to: Dr. KS Santhan Gopal, Kamala Nethralaya, No 81, 1st Floor, 4th B Block, Behind BDA Complex, Koramangala, Bangalore - 560 034, Karnataka, India. E-mail: santhangopal@gmail.com

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in amblyopia is being recognized recently. Many studies have shown that shifting attention to a spatial location or to salient features of a target can enhance its discrimination ability and the attendant neural response.[11,12] Many studies have demonstrated that regions of the occipital, parietal and frontal cortex exhibit increased responses during endogenous and exogenous shift of spatial attention.[13] The hand area and the frontal eye field area (FEF) are closely located in the frontal lobe, get stimulated almost simultaneously and the FEF, in turn, is connected to the attention area in the posterior parietal cortex and it stimulates the V1, via top–down impulses.[14] The top–down impulses also originate in the prefrontal cortex and alter the attention mechanism and this in turn affects the striate cortex. When the peripheral stimulus makes the eye to move to, ensure foveal fixation, this is termed as overt attention. When the patient is fixating on central light and still can see the peripheral lights, it is called covert attention. Both covert attention and overt attention stimulate the lateral occipital cortex via the top–down impulses.

The above motor and sensory aspects of vision are the principles used for the development of the Orthoptek Magnocellular Stimulator (OMS; Carditek Pvt. Ltd., Bangalore), a novel treatment modality for amblyopia. Stimulation of M cells, stimulates the fovea as well, and the foveal stimulation starts a few milliseconds before the saccadic movement has begun and lasts after the completion of the saccade. The farther away from the fovea the image is located on the retina, the greater the eye movement to bring the peripheral retinal image on to the fovea (for finer analysis), and greater is the retinomotor value of that receptor. Hence, the fovea has zero retinomotor value. This is an important principle used in the instrument design.

The calculation of the quantum and direction of movement the eyes have to make to fixate with the fovea is possible because the motor representation in the saccadic area in the posterior parietal cortex (PPC) from the two eyes is also arranged around the fovea. This motor accuracy of the two eyes is more critical, when the eyes move rapidly, like in saccadic movements. The M cell receptors in the peripheral retina are stimulated frequently and this in turn, compels the eye to move in such a way that the peripheral object is brought onto the fovea and the V1 area is stimulated repeatedly via the top–down impulses, by the attention area in the parietal cortex. If the amblyopic eye is made to execute the saccades repeatedly, in different directions, the vision is expected to improve by mitigation of the foveal suppression. Hence, the aim of this study was to assess the efficacy of OMS in the management of amblyopia using the above principles.

Methods

This is a prospective noninvasive, observational pilot study of 35 patients of amblyopia presenting between March 1, 2019 and March 6, 2020. The study was approved by the Institute Ethics Committee and the Institute Research Board and adheres to the tenets of the Declaration of Helsinki. All patients signed a written informed consent form prior to the therapy. A detailed history was recorded, including the duration of amblyopia and previous patching received, or surgical correction, if any. The corrected distance visual acuity (CDVA) and near visual acuity was recorded independently by two optometrists (logMAR) to avoid bias after full cycloplegic refraction and correction with glasses or contact lenses. Besides a complete ocular examination, binocular cooperation at distance was assessed using red-green goggles and stereopsis was recorded using Lang's acuity cards and Titmus fly cards (according to the age and vision of the patient). A spectral-domain optical coherence scan (SD-OCT; Spectralis HRA, Heidelberg Engineering, Heidelberg, Germany) was performed to rule out any structural abnormalities of the macula. If any abnormality was detected, they were not included in the study.

Treatment methodology: The OMS device has 3 rows of light-emitting diodes (LED) of which the central one is red and the others are white [Fig. 2]. The patient is made to sit at 1 m distance from the device wearing the correction with glasses or contact lenses, ensuring that the red light is at eye level with the patient's eye in primary position. The patient is instructed to quickly point at the light that switches on using a laser pointer, which also helps improve the hand eye coordination. The patient has to be quick and should not miss any of the lights that come up on the screen in a random sequence. Each time, the light is on for 300 to 500 milliseconds, which may be difficult for deeply amblyopic patients during the initial session or two. This procedure is first done for the amblyopic eye with the good eye patched for 20 min and repeated with the good eye open and amblyopic eye patched for 5 min. The process is then with both eyes open for 5 min. This stimulates the overt attention center in the brain which in turn stimulates the lateral occipital cortex. Following the above three, the patient is instructed to focus on the central red light, and without changing gaze count the peripheral lights that switch on for about 300 times. This part of the exercise stimulates the covert attention, which in turn stimulates the lateral occipital cortex. This constitutes one session of therapy. The patient is asked to repeat the session after 1 hour and then daily for 15 days or twice a day for a week. Maintenance therapy was one session a week later, 2 weeks later, and then every 2 months for 6 months and subsequently every 6 months, if needed.

All patients underwent a minimum of 10 sessions of therapy with each session lasting for a cumulative period of 60 min. At the end of the 10th session, patients were evaluated for improvement in visual acuity, stereopsis and amount of strabismus. Success was defined as improvement in stereopsis to at least 400 s of arc with binocular single vision with/without improvement in the amount of strabismus to orthotropia and a 0.1 logMAR improvement in Snellen visual acuity.

The data of 35 patients who underwent this treatment was analyzed with the GraphPad Prism software (version 8.3.0[538] for Windows, San Diego, California). The normal distribution of continuous variables was verified with the Kolmogorov-Smirnov test. Results of descriptive analysis for quantitative variables were expressed as mean with standard deviation while for categorical variables were expressed as number and percentage. Comparisons between pretreatment and posttreatment were done using the Fisher exact test for categorical variables like the presence of binocular single vision and presence of orthotropia. Comparisons between pretreatment and posttreatment were done using the Wilcoxon matched-pair rank sum test for quantitative variables like stereopsis and visual acuity. In all analyses, P values <0.05 were considered statistically significant.

Results

In this study, 35 patients with a mean age of 14.17 ± 10.52 years (range: 4–50 years) were included. There

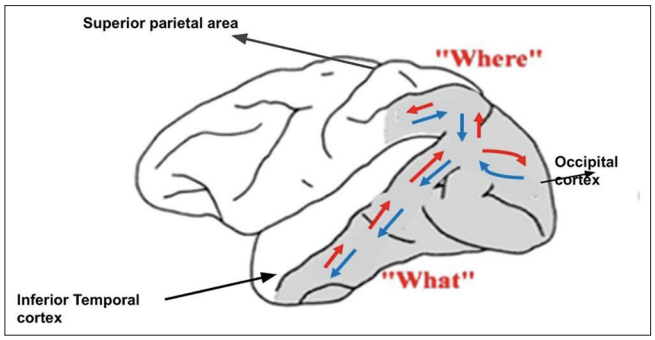

Figure 1: The parvocellular cells end in the primary visual cortex (V1) at level 4 C beta and magnocellular cells end in V1 at the level 4C alfa. The P cells are then further processed in the mid and inferior temporal cortex, concerned with " what " of vision and magnocellular cells discharge is further processed in the superior parietal cortex concerned with "where" of vision

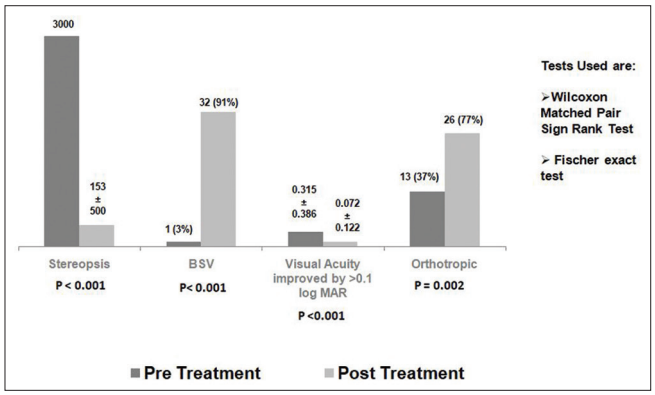

Figure 3: Comparative analysis of the Stereopsis, BSV (Binocular Single Vision), Monocular Vision, and Cover test results, before and after completion of treatment with Orthoptek

were 17 (49%) males and 18 (51%) females in the study. The mean presenting logMAR CDVA in the right eye and left eye was 0.31 ± 0.34 and 0.32 ± 0.44, respectively. The mean refractive error in spherical equivalent was -2.08 ± -2.94 and -2.87 ± -3.05 in the right and left eye respectively. All patients had poor stereopsis with a maximum of 3000 sec of arc. At presentation, binocular single vision was present in only one patient (3%). Of the remaining 34 patients with no binocular single vision, 1 (3%) patient had diplopia, 15 (44%) patients had right side suppression, 11 (32%) patients had left side suppression and 7 (21%) patients had alternate suppression. Anisometropic amblyopia was present in 13 of the 35 (37%) patients while the remaining 22 (63%) had strabismic amblyopia. Convergent squint was noted in 5 (23%) cases and divergent squint was noted in 16 (77%) cases. One patient had nystagmus with head nodding.

Following therapy, 34 (97%) patients showed improvement in stereopsis to at least 400 s of arc at the end of the 10th session. Of these, 18 (51%) patients recovered stereopsis up to 40 s of arc, 14 (40%) patients to 100 s of arc, and one patient to 400 s of arc. In one patient, there was no improvement in stereopsis. Prior to treatment, 14 (40%) patients had orthophoria which doubled to 28 (80%) following therapy. Binocular single vision was noted in 33 (94%) patients following treatment. The mean posttreatment visual acuity in the right eye and left eye was

Figure 2: Photograph of orthoptek instrument. It has three rows of LEDs of each each and central one is red

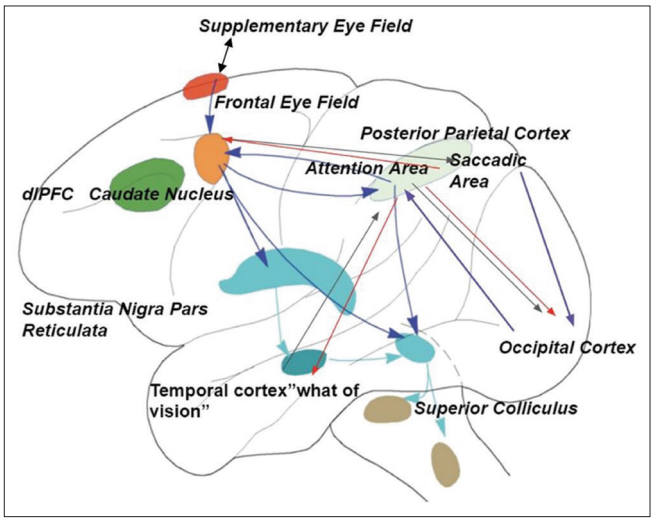

Figure 4: Sensory motor integration occurs in the posterior parietal cortex (PPC) also referred to as an "associative" cortical region, during the generation of a saccade.[6] The Occipital cortex receives top–down impulses from superoparietal cortex, attention area and saccadic area of the posterior parietal cortex, frontal eye field area (FEF) and also from the inferotemporal cortex via the attention area

0.08 ± 0.12 and 0.07 ± 0.12, respectively. Improvement in CDVA (≥0.1 logMAR) following therapy was noted in 45 (64%) eyes, no change in 25 (35%) eyes, and none of the eyes showed worsening. Following treatment, improvement in near visual acuity to N6 was noted in 69 (99%) eyes, while in the remaining one eye the near vision was N18. Improvement in strabismus to orthophoria was noted in 15 of the 22 (68%) patients at the end of the 10th session [Fig. 3]. Success as per the defined criteria was noted in 33 of the 35 (94%) patients. All patients were followed up for a 1-year period with maintenance therapy and none showed any regression.

Discussion

For many decades the most widely used treatment modality for amblyopia has been patching or optical or pharmaceutical penalization of the unaffected eye to stimulate visual development in the affected eye.[1,15] Of these, patching is the most popular, but is found to be successful in only 50%–75% of patients due to compliance issues and the inherent difficulties of patching the normal eye when the amblyopic eye has very poor vision. The recovery of stereopsis is also questionable with patching.[15] Two things assumed while patching the normal eye are that the patient will automatically use the fovea for fixation in the amblyopic, and that repeated stimulation from bottom–up impulses overcomes the suppression at the level of 4C beta in the visual cortex. The fixation by the fovea is secondary to the attention mechanism and we now know that amblyopia is associated with attention deficit.[16]

In our study using the OMS device, we noticed a rapid improvement in both vision and stereopsis in the amblyopic eye. This was true for all ages. This can be explained based on two processes which increase the top–down impulses from posterior parietal cortex (PPC) to the V1 area. One is magnocellular stimulation and the other is the stimulation of the attention mechanism.[14] Both the covert and overt attention mechanisms increase the lateral occipital activity.[15] When a patient detects and points out the light on the OMS board by altering the gaze, he or she is using the overt attention mechanism. When focusing on the central light and counting the peripheral lights, the covert attention mechanism is used. Both these mechanisms in turn stimulate the occipital cortex via the top–down impulses. The PPC is a critical center for the attention mechanism and saccadic eye movement node of the cerebral cortex, and exerts top–down control over activity in visual cortex V1. Three features usually seen in amblyopia are suppression of one or both eyes, reduced stereopsis and decreased vision in one or both eyes. All of these improved significantly with OMS therapy and sustained for months after cessation of treatment in contrast to other studies.[17,18]

Our study shows that the therapy with OMS was equally effective in both strabismic and anisometropic amblyopia.[19] The mean visual acuity in both groups was better at the end of treatment with improvement noted from 0.315 ± 0.386 at baseline to 0.061 ± 0.091 posttreatment ($P < 0.001$). Binocular single vision recovered in 91% and 80% turned orthotropic at the end of therapy. One study has reported a success rate of 74% compared to 92% in ours.[20] The higher success rate could be attributed to the repeated stimulation of the fovea by the saccadic movements alluded to earlier, which in turn stimulates the V1 via top–down impulses. The attention area activated by both the covert and overt mechanisms also stimulates the V1. Our device improves the spatial resolution, by increasing the V1 activity. Attention constricts the receptive field in the visual cortex and thereby increases resolution and visual acuity.

The management of amblyopia so far has ignored the role of the attention area in the parietal cortex [Fig. 4]. Our device is therefore unique as it stimulates the attention area, which in turn stimulates the V1 area, via top–down impulses. The deficits of amblyopia are corrected in a relatively short period of time, regardless of the age. The gain persists long after the cessation of treatment.

Conclusion

The OMS device can be a viable, noninvasive, and safe treatment option for patients with amblyopia. This pilot study needs further validation from different centers, and it is our belief, that this mode of treatment of amblyopia here to stay.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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