Original Article

A Study On the Role of Omega Fatty Acids as an Adjuvant Therapy In Treatment of Amblyopia

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Abstract

Aim: *To study the role of omega fatty acids as an adjuvant therapy in treatment of amblyopia.*

Method: *This prospective, randomized, interventional study included thirty two patients aged 5-12 years of age with unilateral amblyopia or bilateral amblyopia. One group (A) of sixteen patients were prescribed occlusion therapy and the other group (B) received 1000 mg per day of omega fatty acids along with occlusion for a period of three months. Follow-up assessments included best corrected visual acuity (BCVA) (both distance and near) and stereoacuity measurements at 1 week and end of three months.*

Results: *The mean age of the patients was 8.68 ± 1.55 years. The mean baseline visual acuity for distance was 0.85 ± 0.071 Log MAR equivalent for Group A and 0.81 ± 0.073 Log MAR eq for Group B. At the end of therapy, the mean visual acuity was 0.48 ± 0.91 Log MAR eq and 0.40 ± 0.20 Log MAR equivalent for Group A and B respectively. There was statistically significant improvement in vision within Group A (p value-0.0008) and Group B (p value-0.0001). When both groups were compared, the results were insignificant (p value-0.373).*

Conclusion: *Omega fatty acids improve visual acuity in patients with amblyopia and maintain improved visual acuity but there is no additional benefit when compared to patching alone. This study encourages further research on this subject.*

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Keywords: *Amblyopia, Neuroplasticity, Omega fatty acids*

Introduction

Amblyopia can be considered the result of a lack of normal plasticity. By gaining some knowledge of neuroplasticity, the factors that modify the opening and closure of critical periods will lead to new therapeutic modifications which can lead to recovery of visual functions in both children and adults with amblyopia. Various treatment modalities such as refractive correction[1], occlusion therapy[2], penalization[3], drug therapy[4-5], home vision therapy[6], refractive surgery[7], pleoptics, CAM stimulator, red filter[8-9], acupuncture[10-11], transcranial magnetic brain stimulation[12], perpetual learning[13], near visual activities in the form of television games, Smart glasses and mobile games[14-15] have been tried, but none of them is fool proof. The ratio between excitation (glutamate receptors) and inhibition (GABA receptors) must be increased in order to recover from amblyopia by reducing intracortical inhibition and to restore plasticity which is a critical factor. Omega fatty acids act on hippocampal neurons by enhancing glutamatergic synaptic activities and inhibiting GABA receptor-mediated responses.[31-32] Omega fatty acids have been tried & found useful in treatment of dry eye, glaucoma & ARMD.[16-18] The belief that there are specific "brain foods" dates back quite a long way—or at least as far back as the lifetimes of our grandmothers who fed us cod liver oil to "cure all ills and make us smart." Today, we see an increasing abundance of research about the positive systemic and ocular effects of omega-3 fatty acids.[19-22] This study on omega fatty acids in treatment of amblyopia was based on antioxidant, anti-inflammatory, neuro protector, anti apoptotic, trophic stimulus and neuronal differentiation effects of omega fatty acids in treatment of amblyopia.

Methods

This prospective randomized controlled trial was conducted in 32 patients between 5-12 years with unilateral or bilateral amblyopia having visual acuity (on Snellen's chart) in the amblyopic eye between 6/60–6/12 (1-0.30 LogMAR equivalent) who were enrolled from Oct 2015 to February 2017. The study adhered to the Declaration of Helsinki and was duly approved by the institutional ethical committee. Informed consent was obtained from parents/guardians (as all study subjects were minors) prior to study initiation. A detailed history with onset, course, and treatment of amblyopia was taken. Ophthalmological evaluation included visual acuity, refraction using atropine, and fundus examination. Patients with previous surgery and with bleeding diathesis were excluded. Visual acuity was determined, first for the amblyopic eye and then for the better eye using the Snellen's chart at a distance of 6 meters. The visual acuity for near was recorded as 'N' notation (with Reduced Snellen type near vision chart at 40 cm). Stereoacuity (Titmus fly chart) and ocular deviation (measured with prism cover test) were recorded at all examination visits. All observations were recorded by the same examiner under similar conditions. During the course of the study, all the subjects wore their best optical correction. Patients were divided into 2 groups. Group A received 6 hours patching/day while Group B received 6 hours patching/day plus 30 to 40 mg/kg of body weight of omega 3 fatty acids in 5 to 12 yrs of age. Group B took the dosage in the form of capsules for five days a week for three months. Visual acuity was recorded before and during the follow up period at interval of 1 week and 3 months.

Patients were allocated into two groups by simple randomization using computer generated random number tables and numbered opaque envelopes were used for allocation concealment, without involving the investigator. The visual acuity measurements for distance were obtained by Snellen's charts, due to availability constraints, but were converted to LogMAR equivalents in order to get continuous scale data for statistical analysis.

Similarly, for near visual acuity, "N" notation values were converted to LogMAR equivalents. All improvements in visual acuity were assessed from best corrected visual acuity, ie, visual acuity after 6 weeks of initial spectacle use and compared using unpaired t-test between groups and paired t-test within each group at various follow-ups. The qualitative variables were expressed as frequencies/percentages and compared using Chi-square test. A p-value < 0.05 was considered statistically significant. Statistical Package for Social sciences (SPSS) version 22 was used for statistical analysis.

Results

The mean age of patients in this study was 8.68 years ± 1.55 years. There was a significant improvement in mean visual acuity (both distance and near) in both groups after 6 weeks of spectacle use, and further improvements, for statistical analysis purposes, were noted from this BCVA. The mean BCVA in the amblyopic eye significantly improved on final follow-up to 0.48 ± 0.91LogMAReq (P= 0.0009) in Group A and 0.40 ± 0.20 LogMAReq (P = 0.0001) in Group B for distance. Among the groups, when compared, it was statistically insignificant (p value 0.373).

The improvement in visual acuity for near was 0.92±0.51 LogMAR equivalent (p = 0.029) for Group A & 0.96± 0.48 LogMAR equivalent (p = 0.16) for Group B. There was no statistical difference among the groups (p value = 0.56).

There was no improvement in near or distance in the better eye in Group A & Group B. The mean baseline stereopsis measured with Titmus fly test was 1969 (SD-1525) while in Group A and Group B, it was 2500 (SD-1425) and 1438 (SD-1260) respectively. When Group A was compared with Group B, it was not statistically significant (p value-0.17). In week 12, the mean baseline stereopsis measured with Titmus fly test was 1499 (SD-1321) while in Group A and Group B, it was 1587 (SD-1368) and 1412 (SD-1276) respectively. When compared with stereoacuity of Group A with Group B, it was not statistically significant (p value-0.71).

Suppression

Suppression was checked using Worth Four Dot Test. It was found that 25% of subjects in the study i.e. 3 subjects in Group A & 5 subjects in Group B had suppression in one eye. In the total study population, only 3 subjects from both groups improved after therapy.

Discussion

Omega fatty acid has proven effects for retinal maturation and visual acuity development through several randomized trials. Omega-3 fatty acids were provided to a group of students in a school in England and Australia, and showed improved school performance in the form of verbal intelligence, reading, learning and memory in comparison to students who didn't receive supplementation in the form of omega fatty acids.[19]

Neuroprotection is provided by Docosahexaenoic acid (DHA) due to their anti-oxidative and anti inflammatory actions. As a result of these properties, they reduce levels of reactive species (nitric oxide), and pro-inflammatory mediators and act by maintaining higher levels of GSH and anti-oxidant enzymes (i.e. glutathione peroxidase and glutathione reductase). These above mentioned effects of DHA leads to reduction in glutamate induced cytotoxicity. Omega fatty acids have been tried and found useful in treatment of dry eye, glaucoma & ARMD.

Drover et al conducted a study in which they provided different dietary concentrations of DHA during the first 12 months of life. They studied the effects of DHA on language development and school readiness. School readiness and receptive vocabulary was assessed at 2 and 3.5 years respectively. Dietary DHA during the first year of life did not enhance school readiness or language development.[23]

A study was conducted to determine whether the dietary supply of LCPs after weaning influenced the maturation of visual acuity (measured through Sweep VEP) and stereoacuity (randot stereoacuity). They studied effects of LCPs supplemented formulas at 6 weeks of age and that during 7-52 weeks. Infants who were provided with the formula that contained LCP's had significantly better visual acuity and stereoacuity at 17, 26, and 52 weeks of age, as compared to those who did not receive the formula. In their study, better acuity and stereoacuity at 17 weeks was correlated with higher concentrations of docosahexaenoic acid in plasma. Better acuity at 52 weeks was correlated with higher concentrations of docosahexaenoic acid in plasma and red blood cells.[24]

In another study, Birch et al tested the hypothesis that infant formula lacking LCPs during the first 17 weeks of life would result in visual acuity and IQ at 4 years of age that was significantly poorer than those who had dietary supply of LCPs during the first 17 weeks of life. HOTV testing was conducted for each eye using the Amblyopia Treatment Study (ATS) protocol and the Electronic Visual Acuity (EVA) system. It showed that the control formula diet group had poorer HOTV acuity in the right eye than the breast-fed group (tRE=2.96, p<0.004) as well as lower right eye acuity than the DHA group (tRE=2.24, p<0.03).[25]

Several randomized trials have been conducted and have found specific benefit of omega fatty acids supplementation for retinal maturation, visual acuity development, or cognitive development.

Possible Mechanisms

Neuroplasticity refers to the ability of the brain to reorganize the structure and function of its connections in response to the changing environment. It is considered that the brain is plastic and neural networks are initially shaped by experience during the sensitive period and subsequently stabilized during normal development. The experience-dependent maturation of GABAmediated inhibition during development establishes the beginning of the critical period for plasticity in the visual system. Therefore, a reduction of inhibitory transmission in early life halts the onset of the critical period for visual cortex plasticity. The limited plasticity in the adult visual cortex can be enhanced by previous visual deprivation, which is associated with a loss of GABA receptors, and reduced by GABAergic modulators. Other important players are the major modulatory systems in the brain, that is, adrenaline, noradrenaline, dopamine, acetylcholine, and serotonin. The adrenergic system has a significant impact on plasticity.[26-28]

Global dopaminergic activation has heterogeneous effects on plasticity. A certain amount of activity of the dopaminergic system is necessary for the induction of plasticity. Extension or movement of mitochondria into dendritic axons that are located far from the cell protrusions correlates with the development and morphological plasticity of dendritic spines. Molecular manipulations that reduce dendritic mitochondria lead to loss of synapses and dendritic spines. In contrast, increasing dendritic mitochondrial content or mitochondrial activity enhances the number and plasticity of synapses. This way, the dendritic distribution of mitochondria can be both essential and limiting for the support of synapses. Moreover, mitochondrial gene upregulation has been observed following synaptic and neuronal activity. First, following treatment for 24 and 48 hours, omega 3 fatty acids significantly induced PGC-1α, an essential precursor for mitochondrial biosynthesis. This finding is supported by the increase in total mitochondrial content observed by both flow cytometry and microscopy. This suggests that they are effective at increasing mitochondrial number, density and networking without influencing mitochondrial activity.[29-30]

Amblyopia can be considered the result of a lack of normal plasticity. Visual cortical dominance by the better eye leads to correspondent visual deprivation of the representations related to the eye with worse acuity. Knowledge of neuroplasticity and the factors that control the opening and closure of critical periods will lead to new therapeutic strategies which may allow for greater recovery of visual functions in both children and adults with amblyopia.

A direct demonstration that GABAergic signalling is a crucial brake limiting visual cortex plasticity was derived from the observation that a pharmacological decrease of inhibitory transmission effectively restores ocular dominance plasticity in adulthood. Indeed, intra cortical inhibitory circuitry has now emerged as a key factor in defining the limits of cortical plasticity. It has thus been hypothesized that a critical factor in restoring plasticity and inducting recovery from amblyopia is to increase the ratio between excitation (glutamate receptors) and inhibition (GABA receptors) by reducing intracortical inhibition.

DHA enhances glutamatergic synaptic activities with concomitant increases in synapsin and glutamate receptor subunit expression in hippocampal neurons. Spontaneous synaptic activity is significantly increased due to enhanced glutamatergic activity in DHA-supplemented neurons. On the other hand, lack of DHA results in inhibition of synaptogenesis, decreases in synapsins and glutamate receptor subunits, and impairment of long-term potentiation in hippocampal neurons.[31]

DHA inhibits GABA receptor-mediated responses in cultured neural cells in a concentration and time-dependent manner. It is shown that the γ subunit is essential for the potentiation of GABA induced Cl^- channel activity and effect on desensitization kinetics of the GABAA receptor. DHA accelerates desensitization after the peak of the GABA-induced current, potentiates the peak amplitude of GABA response, and gradually suppresses the peak amplitude of GABA response. It is suggested that the effect of DHA on GABA receptor is due to the effect on the lipid microenvironment for the GABA receptors.[32]

Chronic n-3 PUFA deficiency alters the internalization of dopamine (DA) in the storage pool of the frontal cortex . These observations suggest that alterations in synaptic membrane DHA have an impact on DA synaptic neurotransmission and plasticity.[33]

The Hensch lab in 2010 demonstrated that brain plasticity is modulated by cholinergic transmission, and that it may be possible to reactivate plasticity by manipulating cholinergic pathways, potentially reopening the window for effective amblyopia therapy after the “critical period” has passed. DHA deficiency produces a 10% decrease in muscarinic receptor binding, although acetylcholinesterase activity and the vesicular acetylcholine transporter are not affected.[34]

DHA supplementation elevates brain DHA content, normalizes levels of brain-derived neurotrophic factor (BDNF). BDNF is one of the main factors driving the onset of the sensitive period through spurring the development of inhibitory innervation. More recently, it was found that insulin growth factor-1 (IGF-1) has similar effects as BDNF, accelerating the development of inhibitory synapses, the onset of the sensitive period and the increase of visual acuity.[35]

DHA is an important component of neural membranes and is present in 30-40% of the phospholipids in the gray matter of cerebral cortex and photoreceptor cells in the retina. It mediates its molecular and cellular effects not only through regulation of physicochemical properties such as membrane fluidity, permeability and viscosity in synaptic membranes, but also via modulation of neurotransmission, gene expression, and activities of enzymes, receptors and ion channels. These processes are closely associated with activation of signaling pathways that sustain synaptic function and neuronal survival.[36-37]

Conclusion

The study did not find any beneficial effects of use of omega fatty acids in treatment of amblyopia in terms of distance visual acuity, near visual acuity and stereopsis. As more reports give an encouraging trend towards role of pharmacological therapy, it is an area that needs to be further explored. Further studies are recommended on the subject matter.

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