

## Role of Oral Citicoline in Treatment of Adolescent Amblyopia

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### ABSTRACT

**Aim-** To compare efficacy of Citicoline to occlusion and near activity exercise in amblyopia management in adolescent age group.

**Material and Methods-** We included 79 eligible patients of age group 10-19 years for study. Consent was taken from each of patients. All candidates underwent full ophthalmological examination and were prescribed the best corrected spectacles. They were divided in three groups(A, B, C) using randomization chart. Group A received full time occlusion, Group B received full time occlusion and near activity exercises and Group C received full time occlusion and oral Citicoline 500 mg BD for three months. They were followed up four weekly up to 24 weeks.

**Results:** During follow up 9 patients were lost to follow up. Out of 70 patients who completed study, 36 (51.43%) showed improvement in their vision for distance. We measured this improvement in lines on Snellen's Chart. No improvement was found in 14 patients (58%) in Group A, 15 patients (60%) in Group B and 5 patients (23.81%) in Group C. Of the respondents, groups A, B and C constituted 41.67%, 40% and 76.2% respectively. The difference among the three groups was statistically significant (p value-0.024 chi-square test).

**Conclusion-** Oral Citicoline is a new and effective modality for amblyopia management and chance of improvement in visual acuity is better than other treatment modalities.

**Keywords-** strabismus, amblyopia, occlusion.

### INTRODUCTION

Occlusion still remains the gold standard for the treatment of amblyopia. It was first advocated by Comet de Buffon<sup>1</sup> in 1743. It was abandoned and rejected for many years; but later on regained its popularity as the most effective treatment modality for amblyopia. Although the success rate of occlusion therapy is estimated somewhere between 30% to 92%, one of the major problems with it is compliance. This problem becomes specially evident in the case of children as their cooperation level is less than needed.

In spite of best efforts, like counselling and discussing the advantages of the apparently simple occlusion therapy, compliance rate could never improve and reach a satisfactory level. Even parents of patients with an urban background, besides those of rural patients, were found to be doubtful about the effectiveness of occlusion therapy. Most of the patients, specially children find it socially embarrassing to wear the patch owing to the cosmetic blemish associated with it for longer period of the day.

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Various studies have revealed that there is no demonstrable advantage to prescribing greater number of hours of patching, in either the rate or magnitude of improvement after fixed months of therapy. Thus, it is most logical to appreciate that pharmacological enhancement to occlusion therapy may overcome certain shortcomings such as problem of compliance and cosmetic blemish of the established occlusion therapy. However, the role of occlusion in older children and teenagers is still debatable. Thus, addition of some pharmacological agent potentiates the effect of occlusion in older children, and fear of compliance and cosmetic blemish is avoided in young children. It is well known to every Ophthalmologist that Levodopa and Carbidopa were instituted in amblyopia with significant visual improvement but were withdrawn due to their toxic effects. It is an established fact that Citicoline increases dopamine concentration.

Studies on rats have provided evidence that Citicoline potentiates dopamine release in the brain, presumably by stimulating release of acetylcholine. It is postulated that dopaminergic stimulation is a major mechanism for citicoline's effect on the retina.<sup>2</sup> This hypothesis is bolstered by a recent animal study showing citicoline raises the retinal dopamine concentration in rabbit.<sup>3</sup> Citicoline has demonstrated retinal ganglionic cell regeneration in tissue culture.<sup>4</sup> Citicoline (1,000 mg I.M. daily) was found to significantly improve visual acuity in patients with amblyopia.

Citicoline is routinely used by Neurologists in cases of stroke, Alzheimer's disease and bipolar disorders in much higher doses and for longer duration as compared to Ophthalmologists. Severe toxic effects are not reported in patients with neurological disorders being given Citicoline. However, very few studies are available in India to evaluate the effect of Citicoline in amblyopia as an adjuvant to occlusion therapy.

## MATERIAL AND METHODS

This prospective comparative study was conducted in patients with amblyopia in age group 10-19 years, presenting in outpatient department and/or squint and orthoptic clinic at Regional Institute of Ophthalmology, M.D. Eye Hospital, MLN Medical College, Allahabad, India during July 2013 to June 2014 after taking permission from the ethical committee of the institute.

Total 79 eligible amblyopes of age group 10-19 years were included in the study. Consent was taken from each patient's parents. Then they were randomly divided into three groups.

**Group A (28)** received only occlusion therapy along with full refractive correction.

**Group B (28)** received occlusion, near activity exercises along with full refractive correction.

**Group C (23)** received oral Citicoline 500mg BD for three months, occlusion along with full refractive correction.

## INCLUSION CRITERIA

- Strabismic amblyopia, anisometropic amblyopia, isometropic amblyopia, meridional amblyopia
- Patients between age 10-19 years,
- Visual acuity in amblyopic eye  $<6/12$ , visual acuity in sound eye  $>6/12$ , Inter eye acuity difference of 2 or more lines, refractive correction worn for four weeks.



## EXCLUSION CRITERIA

- Presence of anterior and posterior segment pathology as corneal opacity, cataract, pathological myopia, any fundal pathology, nystagmus, optic atrophy, any neurological pathology, refractory amblyopia, previous amblyopia therapy.

A detailed history was taken in each case regarding the chief complaints and reasons for visiting the hospital, whether it being deviation or decreased vision, age of onset of squint, type of deviation and any head posture if noted. History of previous treatment was recorded including any previous management such as occlusion therapy, spectacle correction, and use of miotic, orthoptic therapy or previous eye muscle surgery.

## EXAMINATION

- Visual acuity was determined, first for the amblyopic eye and then for better eye. A patch or occluder was used in front of left eye as the acuity of the right eye was checked, and vice-versa.
- Best corrected visual acuity for distance was tested using the Snellen's Chart at 6 metre distance. The same person made all measurements under similar physical conditions.

The visual acuity for near was recorded at 33 cm using near vision chart.

- Refraction under full cycloplegia was done.
- Maximum tolerated refractive correction was given.
- Angle of deviation was measured using the Prism Bar Cover Test (PBCT) at near (33cm) and distance (6 m), both with and without glasses. Whenever PBCT was not possible due to decreased visual acuity or in uncooperative patients, the deviation was measured using the Krimsky's Test (PBRT).
- Anterior segment and fundus assessment under full mydriasis was done to rule out any ocular causes of decrease in vision.
- Fixation pattern was assessed using Heine's Direct Ophthalmoscope by having the patient fixated in star with the eye, closing the other eye. Uniocular fixation pattern was measured and graded as follows as according to Bangerter classification:
  - a. Foveal
  - b. Parafoveal
  - c. Parafoveal
  - d. Peripheral / eccentric
- Test for Binocular function
  - Sterioacuity with TNO test
  - Worth Four Dot test –binocularity.
  - Synoptophore examination as required

## FOLLOW UP

All the patients were followed up at 1<sup>st</sup>, 4<sup>th</sup>, 8<sup>th</sup>, 12<sup>th</sup>, and 24<sup>th</sup> week.



Examination at follow up-

- Visual acuity including distance and near, under similar conditions all the time, as described.
- Refraction under full cycloplegia.
- Stereo acuity, side effects of patching- irritation, diplopia, occlusion amblyopia.
- Fixation pattern, side effects of drug- headache, GI disturbances. Speed of recovery- faster and sustained or non-responding, deterioration if any. Compliance and continuance of counselling.

## RESULTS

We conducted this study on 70 patients who completed the study (9 patients were lost to follow up, 4 in Group A, 3 in Group B and 2 in Group C) attending OPD and Squint clinic in Regional Institute Of Ophthalmology M. D. Eye Hospital, Allahabad.

The mean age of our study group was 14.67 years (SD-2.90). Our study population consisted of 60% male (42) and 40% female (28) patients. Most common presenting complaint in our patients was diminution of vision (75.71%), followed by deviation of eye (24.28%). Anisometropia was the most common cause of amblyopia in our study population affecting 74% of population, followed by combined anisometropia and strabismus affecting 17.14% patients, 4.48% isometropia and 4.48% strabismus. Most common type of refractive error found in our study population was hypermetropia (70% of patients) followed by myopia (17.14% of patients) and astigmatism (12.86%).

### BASELINE VISUAL ACUITY

Baseline visual acuity was FC-6/60 in 57.12% of total patients, 6/60-6/36 in 25.71%, 6/36-6/24 in 11.42% and 6/24-6/18 in 5.7% of patients in study population.

**Table 1: Baseline visual acuity in study groups.**

Visual acuity	Group A	Group B	Group C
FC – 6/60	13	15	12
6/60 – 6/36	6	7	5
6/36 – 6/24	3	3	2
6/24 – 6/18	2	0	2

### DEPTH/SEVERITY OF AMBLYOPIA

**Table:2 Depth of amblyopia in different groups**

Depth of Amblyopia	Group A	Group B	Group C
Mild (= 6/18)	2	0	2
Moderate (> 6/18 to = 6/36)	9	10	7
Severe (= 6/60)	13	15	12



## VISUAL IMPROVEMENT IN EACH GROUP

Table3: Visual improvement in each groups

Line of improvement	Group A	Group B	Group C
0	14	15	5
1	4	4	6
2	5	4	5
3	1	2	2
>3	0	0	3

## RESPONDERS / NONRESPONDERS

Out of total 70 patients who completed the study, 36 patients (51.43%) showed improvement in their vision for distance; remaining 34 patients (48.57%) were non responders.

Among groups, responders were 41.67%, 40% and 76.2% in group A, B and C respectively. The difference among three groups was statistically significant (p value-0.024 chi-square test).

Table 4: Responders/ Non responders

Groups	Responders	Non - Responder
Group A	10	14
Group B	10	15
Group C	16	5

Pvalue - 0.0243

## SIDE EFFECTS

Total 4 patients (5.71%) complained of rash due to occlusion given to them. One patient in Group C complained of mild headache which got relieved by medication after two days. Remaining 65 patients had no side effects.

## DISCUSSION

Treatment of amblyopia remains a therapeutic challenge for the ophthalmologists. It has perplexed clinicians over the centuries, both with regard to its diagnosis and treatment. This is further highlighted by the vastness and variety of treatment modalities tried and the research done in this field.

Occlusion remains the most popular treatment modality of amblyopia. By means of removing the suppression effect of brain cells driven by the sound eye over the brain cells which are involved in processing vision in the amblyopic eye, patching helps in improving the vision. However, the popularity it commands among the clinicians is not always shared by the patients and their relatives and their parents.



Major failure of the therapy is because of poor compliance due to cosmetic blemish associated with occlusion therapy. The other drawbacks like occlusion amblyopia, problems of fusion disruption and increase in angle of deviation, although rare, are at times disturbing both for the clinician and the child's family.

In our study Group C, we tried to find out the effectiveness of addition of Citicoline to conventional patching therapy for the treatment of amblyopia. Citicoline primarily acts by increasing the synthesis of phosphatidylecholine, the primary neuronal membrane phospholipid, thus enhancing the production of acetylcholine. It is proven that there is dopamine depletion from retinal amacrine cells leading to decreased contrast sensitivity, and dopamine supplemented from outside may reverse this depletion. Citicoline is similar to dopamine in action with comparatively very few side effects. Oral Citicoline administration increases the plasma levels of choline and cytidine, the building blocks used to restore neuronal membrane integrity. It is also postulated that Citicoline facilitates the preservation of sphingomyeline, which promotes signal transduction in nerve cells.

Citicoline may significantly impact the brain-remodelling activity. A study in rats has shown that citicoline treatment significantly increases the length and branch point of the dendrites, increasing the overall surface area occupied by neurons, which leads to an increased efficiency of sensory information processing. This mechanism of activity may potentially account for a significant portion of citicoline's neurorestorative functions.

**Campos et al**<sup>5</sup> have also recorded that citicoline was effective in the treatment of amblyopia. They published the preliminary results of their study and stated that statistically significant improvement in visual acuity was found both for the amblyopic and sound eye in 46 of the 50 patients (92%). The improvement remained stable for at least four months.

Similarly **Porciatti et al**<sup>6</sup> recorded that visual acuity improved 1.4-1.5 lines in the amblyopic eyes and 0.4 in the normal eyes with citicoline. They also reported improvements in the contrast sensitivity and increase in the visually evoked potential. This study was conducted in adult with a mean age of 24.8 years.

**Ghosh S and Ghosh R**<sup>7</sup> in a study on amblyopic patients, in age group of 10-18 years reported that 71% of the patients had shown visual improvement with adding drug i.e. citicoline to occlusion and near activities. 58.68% overall showed response to therapy of varied level despite of the older age group. 2 line or more than 2 line improvement was seen in 26.76%. Our study is comparable to this study in terms of improvement as we also found 76% patients improved by adding citicoline, which was significantly better than remaining two groups (P value 0.02).

In our study, overall 51.43% patients had shown visual improvement with citicoline. 2 line or more than 2 line improvement was seen in 31.42% patients. Probably this remarkable concurrence of our study with the study of **Ghosh S and Ghosh R** is because age group and mode of institution of treatment modality in both the studies are almost similar. More or less amount of visual improvement in most of the patients is also approximately equal in both the studies.



**Prachee Vasant Pawar et al<sup>8</sup>**, also studied effectiveness of addition of citicoline to patching in the treatment of amblyopia in the age group of 4-13 years. They divided the study subjects into two subgroups, one of younger patients (age at start of phases 1  $\leq$  7 years) and the other group of older patients (age at start of phase 1  $\geq$  7 years). At the end of five months, in phase 2, the mean logMAR of the younger as well as older patients in group 1 was significantly less than that in group 2 showing significantly better improvement in younger and older patients with citicoline along with patching ( $p < 0.05$ ).

In contrast to above findings, **Michela Frenisa et al<sup>9</sup>**, have reported that addition of citicoline to patching therapy was not found to be more effective than patching alone after a 30 days treatment. In our opinion, he should have continued drug for a longer period as most of the studies had used the drug for longer time, realizing that it may take time for full effect of drug to come.

In our study, we found 41.67% patients to have improved in Group A, 40% in Group B and 76.2% in Group C. Difference among groups was statistically significant ( $p = 0.02$ ). Total 51.41% patients improved with treatment. This is encouraging that those patients who were older enough should also be given a chance to improve. We cannot comment on stability of vision improvement as this requires a longer follow up which we are doing at our Institute. Most of the patients in Groups A, B and C improved up to 2 line. In Group C, 3 line or more improvement was present in 5 patients (21.7%). It may be concluded that with drug therapy, early and greater visual improvement can be achieved.

Compliance remains the major challenge with occlusion therapy and near exercises and results with these modalities will depend upon compliance of patients. Due to poor compliance and acceptance, your anticipated full time occlusion may actually be part time occlusion only.

So compliance was given extra importance and carefully monitored

- Regular counselling of patients and parents.
- Regular maintenance of a diary by patients/ parents and its regular check up.
- All efforts were made to build up confidence towards otherwise simple looking occlusion method of therapy, thus making compliance and acceptance to achieve a much higher level.

Contrary to this, compliance was much better with the drug therapy. Patient /parents think they will be benefitted by medication. Along with this, the side effects associated with the drug are less, as seen in various studies. Therefore this drug is safe to use. So it may be concluded that use of citicoline can give better results in amblyopic patients, even in adolescent age group.

Limitations of our study were lesser number of patients and a need of longer follow up period to see whether the gain in vision remains stable or deteriorates in longer follow up period.



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