Original Article

Citicoline Treatment of Children with Visual Impairment; a Pilot Study

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Purpose: To determine the use of citicoline in children with visual impairment and its result in improvement of high and low contrast acuity, and to see, if citicoline effects were different in children with low vision due to retinal/optic nerve disease and central visual deprivation.

Material and Methods: The twenty-two children in this study were divided into a group of eleven with Visual Deprivation Amblyopia (VDA) and eleven with Peripheral Visual Impairment (PVI). Each child received 10 intramuscular injections containing 1 g of citicoline. Changes in visual acuity were assessed with high contrast and low contrast acuity tests applied at baseline (day 1), day 30 and day 90. Statistical analysis was done with an ANOVA model to analyze both the within and between group effects of the citicoline-treatment.

Results: Visual acuity increased in both groups of children but the changes were not statistically significant. Clinical assessment of acuity changes showed more rapid improvement in the VDA than in the PVI group. Decline of acuity 90 days after treatment was more often seen in the VDA than in the PVI group

Conclusions: Treatment with citicoline for a short period can improve contrast visual acuity in children with visual impairment. Further work is needed to determine the clinical relevance of citicoline treatment in visual impairment.

Citicoline has been used in treatment of neurological disease with minimal side effects, and it appears to improve functional outcome and reduce neurological deficit in acute stroke[1,2]. Citicoline is an intermediate metabolite in the major pathway for the synthesis of the membrane phospholipids, phosphatidylcholine, which is important for the maintenance of cell-membrane fluidity and cellular integrity. Citicoline can support cell-membrane repair, particularly neuronal cell membranes that have been damaged by trauma, ischemic events, toxins, infections or neural degeneration[3].

Patients in the studies of neurological impairment also have reported that colours were brighter and that visual contrast was enhanced, which have led to investigations of citicoline in various ophthalmic conditions. Studies in patients with glaucoma have suggested that citicoline repairs damage to the optic nerve and the retina[4]. Animal studies have shown that citicoline raised the retinal dopamine concentration in the retina[4].

Citicoline was found to significantly improve visual acuity in patients with amblyopia[5, 6]. Further investigations showed that both high and low contrast acuity was improved, mainly in the amblyopic eye, but some increase in contrast vision was reported in the better eye as well[7].

In view of the findings of citicoline effects on retinal and optic nerve function in glaucoma and visual cortical function in amblyopia, we have examined the effects of citicoline on visual acuity in children with severe visual handicap. Two different populations of visually impaired children were studied, one group with visual impairment mainly due to vision deprivation disease and the other group due to retinal or optic nerve disease. Both high and

low contrast visual acuity was assessed, using cardboard letter charts[8,9]. Previous studies in children with visual impairment had shown that visual function assessment with these tests corresponded quite well with assessment of the functional ability of the children[11].

The aim of the study was to see if contrast acuity could be improved by treatment with citicoline, if the effects were different for high and low contrast acuity, if there are differences in the effects related to the type of visual impairment, and if the response did vary with time after treatment.

MATERIAL AND METHODS

Visual Impairment according to WHO is defined as a presenting visual acuity of 6/18 to 3/60. "Severe Visual Impairment" is less than 6/60 and more than or equal to 3/60, and "moderate visual impairment" less than 6/18 and more than 6/60). In this study most of the visual impairment is in the category of severe visual impairment but we shall use the term visual impairment to describe all the children[10].

Twenty-two children with severe visual impairment at the Al Maktoom School for the Visually Impaired, Islamabad, Pakistan were included in the study. The research followed the tenets of the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. The children were divided into two groups of 11 children in each group. One group consisted of eleven children with visual impairment due to vision deprivation by bilateral congenital cataract, operated later than 1 year of age and other conditions blurring/opacifying the optical media (Table 1a). This group we hypothesized to have vision deprivation amblyopia (VDA). The other group consisted of eleven children with visual impairment due to retinal or optic nerve disease representing peripheral visual impairment (PVI) (Table 1a).

Children in the VDA group were on an average older than children in the PVI group (11.9 years compared with 10.0 years) and they were also more likely to be female (64 % compared with 36 %). The groups were not significantly different with regard to age, but with regard to sex.

Each child received an intramuscular injection of 1 g of intramuscular citicoline for 10 consecutive days starting from day 1. Discomfort at injections was expressed by the children. Any other side effects were registered at the time of follow-ups.

Table 1a: Group 1 VDA (Vision Deprivation Amblyopia)

Sr. #	Sex	Age	Diagnosis
1.	M	8	Aphakia and nystagmus
2.	F	12	Aphakia and nystagmus
3.	M	8	Bilateral pseudoaphakia and nystagmus
4.	F	14	Corneal opacities + rejected grafts + dry eyes
5.	F	13	Congenital glaucoma and corneal opacities
6.	F	14	Buphthalmos + enucleated right eye
7.	F	14	Aphakia and nystagmus
8.	F	14	Congenital glaucoma and corneal opacities
9.	F	12	Aphakia and nystagmus
10.	M	10	Aphakia and nystagmus
11.	M	12	Aphakia and nystagmus

Table 1b: Group I1 PVI (Peripheral Visual Impairment)

Sr. #	Sex	Age	Diagnosis
1.	M	14	Road - cone dystrophy and nystagmus
2.	M	6	Macular hypoplasia and nystagmus
3.	F	10	Albinism and nystagmus
4.	F	6	Retinal degeneration and nystagmus
5.	M	10	Albinism and nystagmus
6.	M	8	Maculopathy and nystagmus
7.	M	10	Maculopathy and nystagmus
8.	M	14	Albinism and macular hypoplasia
9.	F	15	Albinism and high hyppermetropia
10.	M	9	Nystagmus, macular hypoplasia
11.	F	8	Optic atrophy

Visual acuity was determined with LEA symbol test charts of high contrast (>85%) and low contrast (2.5%) (Fig. 1). The instructions supplied with the test were followed. The high contrast visual acuity (HCA) and the low contrast visual acuity (LCA) was defined as the line of optotypes on which at least three of the five symbols were read correctly, and if the line was read twice, at least four of the symbols were required to be correct.[11] In this children population with visual impairment, the testing was done binocularly, at a viewing distance of one meter and the acuity values were re-calculated for the ordinary testing distance of three meters. Visual acuity was recorded using decimal notations, which was then converted into logMAR values. If the child could not see even the largest optotypes at one meter, this was marked as "no response" and given an arbitrary acuity value of 2.0 logMAR in the statistical analysis. The visual acuity was measured at baseline (day 1), on day 30 and on day 90. The examiner was not aware of the results of the previous assessments. (LH testing protocol)

The changes in visual function were also assessed with subjective methods. The children were asked the following two questions:

Do you notice any brightening or darkening of the light around you?

1. Do you think that the colours around you appear less or clearer and brighter?

In addition, an assessment was made of the degree of improvement or decline in HCA and LCA, using ordinary clinical measures. Improvement of visual acuity is generally estimated from the change in acuity level during or after treatment, and measured as the change in number of lines on the visual acuity chart. An increase in acuity of two or three lines on the chart was considered a relevant improvement, and was defined in this study as a moderate improvement of visual acuity. An increase of four lines or more was considered a marked improvement. A reduction of visual acuity was measured in the same manner and a decline of acuity of two to three lines was regarded as

Table 2a: Number of children showing improvement in visual acuity in the two groups of visually impaired children. Testing of HCA and LCA represented at different times after Citicoline treatment.

	VDA (n = 11)				PVI (n = 11)			
	Improvement				Improvement			
	Moderate		Marked		Moderate		Marked	
	HCA	LCA	HCA	LCA	HCA	LCA	HCA	LCA
0 - 30 d	5	3	1	1	2	1	1	-
0 - 90 d	2	-	2	1	3	3	1	-
30 - 90 d	-	-	1	1	1	1	-	2

Table 2b: Number of children showing reduction in visual acuity in the two groups of visually impaired children. Testing of HCA and LCA represented at different times after Citicoline treatment.

	VDA (n = 11)				PVI (n = 11)			
	Reduction				Reduction			
	Moderate		Marked		Moderate		Marked	
	HCA	LCA		HCA	LCA		HCA	LCA
0 - 30 d	2	2	0 - 30 d	2	2	0 - 30 d	2	2
0 - 90 d	1	-	0 - 90 d	1	-	0 - 90 d	1	-
30 - 90 d	1	-	30 - 90 d	1	-	30 - 90 d	1	-

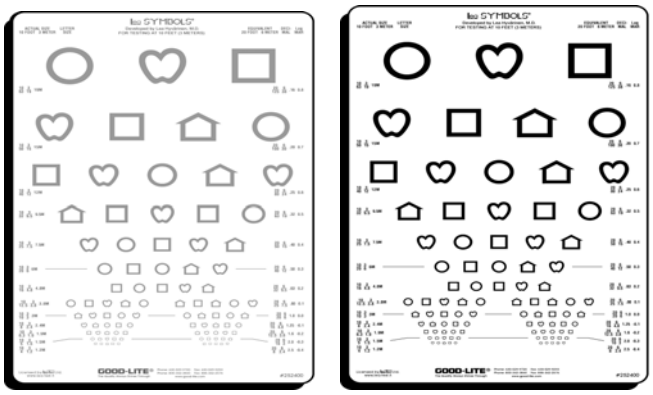

Fig. 1. Lea's symbol
(a) High contrast tests. (b) Low contrast tests

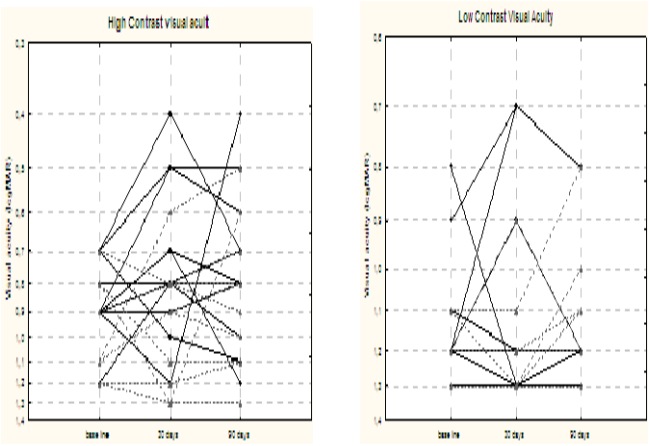

Fig. 2a&b: Visual acuity testing in individual children of the two groups and at different times are shown in figure 2*a* and *b* for HCA and LCA respectively. Solid line indicate VDA group and interrupted line PVI group.

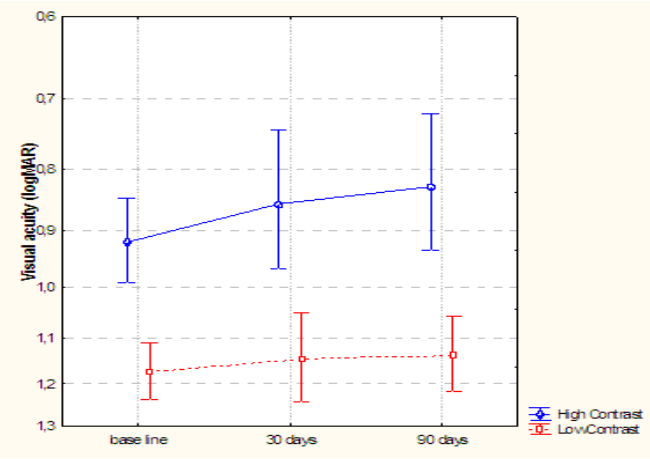

Fig. 3: Mean values of HCA and LCA in all children.

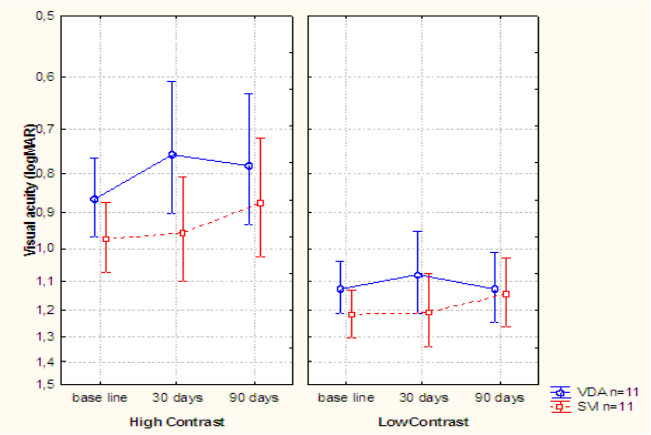

Fig. 4: Mean values in visual acuity for the HCA (fig. A) and for LCA (fig. B).

moderate and four lines or more as marked. The number of children with moderate and marked increase and decrease in visual acuity were recorded for the different groups of visual handicap, and for the high and low contrast testing levels.

An ANOVA for repeated measures analysis was performed on the visual acuity data. The within-effect of contrast (high contrast and low contrast) and the effect of time during treatment (base line, 30 days and 90 days) as well as the between-effect of the groups VDA and PVI was assessed in the ANOVA model. The data were further analyzed for trends with a linear contrast analysis, which is a planned comparison (post test) to evaluate if there is a trend in the measured response. The variables were analyzed by Mauchley's test of Sphericity for compound symmetry and the results were adjusted by the Huynh-Feldt correction paradigm. All analyses were done with the STATISTICA (data analysis software system), version 7. StatSoft, Inc. A p-value of ≤ 0.05 was regarded as statistically significant.

RESULTS

Subjective visual assessment

The first signs of improvement in the visual functions after citicoline treatment were observed in the subjective assessments. All children except two, both in the PVI group, reported that the surroundings looked brighter and colour clearer during in the treatment with intramuscular injections of citicoline while they were receiving the injections and till almost 30 days from start of treatment.

Visual acuity assessment

The results of visual acuity testing in individual children of the two groups and at different times are shown in figure 2*a* and *b* for HCA and LCA respectively. There were no significant differences between the two groups at baseline with respect to either HCA (t-test, p=0.12) or LCA (t-test, p=0.62). In many children of the VDA group the visual acuity had increased at the 30 day testing and stayed at the same level or declined during the following period. In the PVI group the changes were more irregular, but often an increase was seen in the LCA testing. The mean values of HCA and LCA in all children are shown in figure 3.

It is seen that treatment with citicoline had a positive effect on visual acuity when considering all children over time but the effect was not statistically significant [F(2,40)=1.74, p=0.188)]. A linear contrast analysis revealed a close to significant increase in visual acuity in the PVI group (p=0.09) and a less significant effect for the VDA group (p=0.41).

The mean values for the two groups are shown in figure 4a for HCA and in figure 4b for LCA. The values for the VDA group was higher than the values for the PVI group but no significant difference could be found when analyzing the acuity-change to treatment between the groups [F(1,20)=0.69, p=0.41]. In the VDA group the increase in HCA and LCA occurred at 30 days and declined slightly at 90 days. In the PVI group the increase was more marked at 90 than at 30 days. However, these differences were not statistically significant between groups.

Clinical visual assessment

The improvement or decline in visual acuity after citicoline treatment was recorded as the change in the number of lines that could be recorded on the visual acuity chart. The number of children with improvement in HCA and LCA at different periods of measurement is shown in table 2a for the VDA and the PVI groups, and the number of children with decline in table 2b.

As seen in Table 2a moderate and marked increase of HCA was seen in 6/11 of subjects in the VDA group and in 3/11 in the PVI group, and moderate or marked increase of LCA was seen in 4/11 subjects of the VDA group but in only one subject of the PVI group. The improvement in VDA patients seemed to occur mainly during the early phases (0 – 30 days), while the PVI patients often showed improvement over a longer period, up to 90 days.

As seen in Table 2 b, a moderate or marked decline of HCA was noted in 2/11 children with VDA and in 3/11 children with PVI, and a decline in LCA in 2/11 children with VDA and 2/11 children with PVI.

DISCUSSION

We found that children with visual impairment experienced subjective improvement of visual function and often also showed improvement of visual acuity after treatment with citicoline administered intramuscularly for 10 days. No side effects were noted which is in agreement with previous studies in children[5-7]. Most of the children of course noticed there arm being sore for the duration of the treatment especially at the injection site. However, there was no mention of nausea, vomiting or feeling of unwell being.

Testing of visual acuity using charts containing both high and low contrast optotypes is possible in children with visual impairment as shown by Siddiqui, Rydberg & Lennerstrand[11]. A strong positive correlation between contrast acuity and a functional assessment of visual ability was reported[11]. In the present study we have used the LEA symbol test charts with high and low contrast optotypes. These charts gave reliable results and were well accepted by the children.

In this study of the effect of citicoline on visual function of visually impaired children, the subjects were divided into two groups with respect to the cause of the impairment.

We hypothesized that:

Visual Impairment due to congenital cataract or other opacities of the optical media, and treated with surgery later than one year of age would represent amblyopia related to vision deprivation, the VDA group of children[12, 13].

Visual impairment due to congenital diseases of the retina and the optic nerve would be connected with defects in the peripheral visual elements of the retina / macula and optic nerve, the PVI group of children.

Assuming that the site of the damage to the visual system was different, it would be possible that the effects on visual function by treatment with citicoline would vary in the two groups both with regard to level and time course of change.

An increase of visual acuity was seen in many of

the children after citicoline treatment. The changes were most prominent for the high contrast acuity, but were noted also for low contrast testing. In a small number of children a reduction of acuity was recorded. Statistical analysis showed that the changes were not significant when values for the two groups were compared at the different testing times.

In clinical practice the improvement and reduction of visual acuity by different treatment modalities has been estimated as the change in the number of lines recorded with the visual acuity chart. Such an approach has acceptance in the clinical literature on for example amblyopia treatment.5, 6 Modern acuity charts are arranged with a logarithmic scale and each step on the chart represents the same change in visual resolution independent of the level of visual acuity. We have defined a moderate improvement in visual acuity after treatment as a difference of two to three lines and a change of more than three lines as a marked improvement. Estimated in this way, improvement of acuity after citicoline treatment occurred more often in children with VDA than in children with PVI. Further the improvement was seen mainly during the first 30 days in the VDA children, whereas in the PVI group the improvement appeared more often in the later part of the follow-up period, i.e. from day 30 to day 90. However, the effect of citicoline did not seem to last more that about 1 month, and a decline of visual acuity was often noted at the end of the observation period of 3 months. This corresponds to the findings in studies of citicoline effects in amblyopia where a reversion of visual acuity levels has been observed after about 4 months[5,6].

Citicoline has been found to improve visual performance in amblyopia when measured by visual acuity, contrast sensitivity and visual evoked potential[7]. The effect of citicoline could in amblyopia conditions be attributed to modifications of neuronal mechanisms in the geniculate body and the visual cortex where the functional and morphological changes in amblyopia are known to occur[12-14]. This may also be the basis for improvement of HCA and LCA in the VDA group.

In glaucoma, the improvement of vision by citicoline has been suggested to be due to repair of retinal and optic nerve elements[4, 15]. In the PVI group citicoline might have affected the function of the retina and the optic nerve as well as the higher levels of the visual pathways.

It is also possible that the increase in visual acuity may have been related to improvement of accommodative ability or parts of the oculomotor system involved in fixation, since testing was done at the distance of 1m, which requires a slight accommodative effort in addition to control of fixation.

The change in visual acuity induced by citicoline would probably lead to improvement in the visual performance of the children, since visual acuity measured with high and low contrast charts have been shown to correspond with measures of functional capabilities of the children.[12] Treatment with citicoline in children with visual impairment could be useful in improving their visual capacity, but this study is only a preliminary one and extended investigations are needed in order to establish the dosage, the length of treatment and other parts of the protocol of treatment with citicoline in visual dysfunction. Oral medication has recently been reported useful in children with amblyopia,[16] and might also be tried in a group of children with visual impairment.

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