Stability of Visual Acuity after the Cessation of Amblyopia Treatment: Review of the Literature

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ABSTRACT

Introduction and Purpose: The treatment of amblyopia in children is frequently discussed in the literature. Less attention, however, has been given to the durability of the visual acuity results attained with therapy. The objective of this review is to conduct an in-depth analysis of the existing literature, on the stability of visual acuity following cessation of amblyopia treatment, and to identify any gaps in the literature, which could guide future investigations.

Results: There did not appear to be any one consistent risk factor affecting the stability of vision after cessation of amblyopia treatment. Most of the reviewed studies varied with respect to lengths of follow-up visits, patient population, and method of visual acuity assessment. There was also a generalized lack of standardization of visual acuity measurements in these previous investigations. Only one of the studies analyzed was a prospective design.

Conclusion: The area of study in amblyopia is fraught with contradictions. It is obvious from this review that there exists uncertainty regarding the recurrence of amblyopia following treatment. Previous studies have failed to identify any common, predictive, influencing factors necessary for the maintenance of visual acuity after cessation of therapy. Also lacking is discussion on the potential role that therapy tapering plays in the recurrence of amblyopia following the cessation of treatment.
Stability of visual acuity in the amblyopic eye after treatment has been debated in the literature, although certainly few studies have dealt with this issue.\textsuperscript{1,2,4–14,17,21} In addition, only a small number of studies have addressed the longevity of the results of amblyopia treatment, and the majority of these studies were retrospective and therefore subject to the limitations that occur within this study design.\textsuperscript{2,5,7,8,14} The main concern regarding these retrospective studies is the overall lack of controls. Since the amblyopia management has already occurred, the data is generated from historical records. Unfortunately, there are few prospective studies on the recurrence of amblyopia following the cessation of treatment.\textsuperscript{1,2}

Data indicates that the recurrence rate of amblyopia varies widely, from as low as 6\%\textsuperscript{3} to as high as 75\%.\textsuperscript{4} Deterioration of visual acuity has been reported to occur following cessation of treatment in all of the studies found.\textsuperscript{1–14} There were differences in the type of treatment, the age when treatment was ceased, and the time period between cessation of treatment and the follow-up assessments. In most studies, it remains unclear as to what method of cessation of treatment was used: methods varied between tapering of occlusion or penalization, abrupt cessation of treatment, combination of tapering and abrupt, or the method was not specified. Also, the reports failed to offer guidelines for what constitutes deterioration of visual acuity. The criteria for deterioration of visual acuity varied from one to two lines, greater than two lines, and some did not state what represented regression.\textsuperscript{1–14}

It would be difficult to discuss stability of vision after treatment of amblyopia without a brief description of the critical periods of visual development, as well as the pathophysiology of amblyopia. Hubel and Wiesel\textsuperscript{15} received the Nobel Prize for their description of a sensitive period in the development of the visual system. Our current knowledge of this critical period has been summarized by Daw.\textsuperscript{16} He explains that visual functions processed at higher anatomical levels of the visual system will have a later critical period than those processed at lower levels. There are at least three periods for visual acuity: the period of visual acuity development (birth to 3–5 years), the period during which deprivation is effective in causing amblyopia (first few months to 7 or 8 years), and the period in which recovery from amblyopia is possible (from onset of deprivation to adulthood). The earliest is from birth to 3–5 years; visual acuity develops and is susceptible to stimulus deprivation causing amblyopia. It is also during this period, and potentially beyond, that amblyopia can effectively be treated. Even today the time frame for the development and treatment amblyopia is unclear.\textsuperscript{4,6,13,17,22–27} Therefore, the question of when is it safe to discontinue amblyopia treatment continues to haunt clinicians.

**EFFICACY AND DURABILITY**

A number of studies have addressed the efficacy of amblyopia treatment and the durability of the results. Chronologically, Sparrow and Flynn published one of the earlier studies in 1979.\textsuperscript{5} The authors investigated the effectiveness and stability of amblyopia treatment. In their report, data was evaluated retrospectively from 30 amblyopic patients with visual acuity of 6/60 or worse at the onset of treatment. All of the patients were followed for three years after the completion of their treatment. Only five of the 30 patients received their initial treatment before age six. Although retrospective, this study did verify that deep amblyopia can be successfully treated, and of the 56\% of patients who achieved a visual acuity of 20/40 or better, 40\% maintained this after three years of follow-up. The majority of the patients suf-
fered less than two lines of acuity regression. Patients with eccentric fixation were included in this particular investigation. It was noted that patients who did not achieve equal vision, in spite of treatment, and demonstrated eccentric fixation, had the more unfavorable (poor) prognosis. The authors failed to identify any relation between the presence of eccentric fixation and stability of visual acuity. Unfortunately, treatment modalities were not consistent in all thirty patients, therefore greatly limiting the value of the results.

Soon after, Scott and colleagues conducted two studies on the stability of vision in previously treated amblyopic patients. In the initial study, the effectiveness of full-time occlusion (24 hrs. / 7 days per week) therapy for amblyopia was also addressed. Although the authors did indicate that “full-time occlusion (24 hrs. / 7 days per week) is not a widely accepted practice,” they failed to identify what were the most accepted therapeutic modalities at the time of publication. Retrospective chart review was the design for both of these studies. In the first study, one hundred seventy-five subjects who had undergone full-time occlusion were included for data analysis. All types of amblyopia, including strabismic, anisometropic, organic, and deprivation, were included in the study. The authors determined that full-time occlusion was successful in the treatment of strabismic and anisometropic amblyopia with percentages ranging from 83% to 78%, respectively. Some patients did wear part-time maintenance occlusion; however, the specifics on the number and type of patients requiring this therapy was not outlined. It would appear it was determined on an “individual basis” and left up to the discretion of the clinician. The authors reported that 50–66% of the subjects maintained their visual acuity level following the cessation of occlusion treatment. They found that the level of visual acuity at the commencement of treatment seemed to have little effect on the final level of visual acuity. The amount of regression and the length of follow-up were not stated in this particular article. In a follow-up study, Scott and Dickey investigated patients who were at least nine years of age, as they were considered “visually mature,” to determine the stability of their vision. One hundred and thirty patients with strabismic amblyopia, who had undergone full-time occlusion therapy (FTO), were assessed to determine acuity stability after 9 years of age (visual maturity). Of the initial 130 subjects, 89 were included in this study. At the conclusion of the FTO therapy, 92% of the subjects had attained visual acuity of 20/40 or better. The final visual acuity was recorded from the most recent clinical evaluation at which time the mean age of the patients was 15.9 years (range 10–17 years). In 75% of the subjects there was no regression of visual acuity over time. Seventeen percent of patients lost a line of visual acuity and 8% lost two lines or more. Unfortunately, the time frame between the discontinuation of the occlusion therapy and the final acuity assessment was not clearly stated. The relationship with the density of amblyopia at the start of treatment and the regression rate was not statistically significant; however, a better vision at the completion of treatment increased the chance of maintaining that level of vision.

In 1986, Ching and colleagues examined the long-term visual acuity outcome in strabismic amblyopia patients. Data from 116 patients were analyzed. Although conventional occlusion of the sound eye was the only form of therapy, there was an inconsistency among the study population with respect to the amount of occlusion prescribed. This study reported that amblyopia did not recur in 48% of the patients at the cessation of therapy, but 52% of the patients required some maintenance therapy. The mean duration of maintenance occlusion was 31.3 months. Visual acuity
regression after the termination of all occlusion therapy was re-evaluated after subjects reached age nine. On the final acuity assessment the rate of regression was 8%, with the majority of the patients that suffered a loss of visual acuity belonging to the initial group requiring maintenance occlusion. It should be noted that none of the participants lost more than one line of vision. Unlike the study by Scott and Dickey, this paper concluded that the level of initial visual acuity was significant in the determination of the final stability of the vision. The deeper the amblyopia at the start of treatment, the more likely the patient would require maintenance patching. Of note, Ching’s study, like that of Scott and colleagues, indicates that age at the onset of treatment was not a predictive factor in determining vision stability.

CESSATION OF TREATMENT

When is it safe to stop patching? This question was the focus of a study initiated by Oster and associates in 1990. The authors conducted a retrospective study on 188 amblyopic patients treated and observed between 1981 and 1988. They included only patients who were compliant, or responsive, to the prescribed therapy. Two groups were compared: the clinically stable group (CSG) and the maintenance patching group (MPG). The CSG group consisted of patients who achieved equal or near equal visual acuity and did not require further occlusion. The MPG group needed further patching due to recurrence of ambylophia. They found that 53% of patients required some type of maintenance patching after primary occlusion was discontinued. This study determined that the recurrence of ambylophia was similar to the rates found in previous studies; however, the Oster study argued that age was an important factor in predicting the stability of vision. The relationship between age and stability of visual acuity was especially strong in the first four years of life. The CSG patients were significantly older at the onset and at the discontinuation of their therapy. The final conclusion of this study indicated that stability becomes evident between the third and fourth birthdays and, in general, patching could be safely discontinued after the third birthday. It was suggested that younger patients are more likely to require maintenance patching than older patients and thus should be followed more closely. The association between the stability of vision and using a recognition test needs to be considered when analyzing the results of the Oster study. Only the older patients were able to participate in recognition acuity assessment during the entire testing trial, undoubtedly making their results more reliable and comparable. The preverbal patients were initially assessed using the less sensitive fixation preference method. Therefore, when acuity was re-assessed using a recognition test, the results become less comparable. The diversity in the testing methodology may likely explain, in some situations, the variability noted in vision stability.

AMBYLOPIA AND AGE

The age beyond which treatment is ineffective is uncertain. In 1992, Rutstein and Fuhr looked at the efficacy and stability of ambylophia therapy in patients who were treated at 7 years of age or younger and patients treated after age 7. By including patients of various ages the authors recognized that maturation of the visual system might be a gradual process that is not complete at the same stage in all individuals. Supposedly, if the “amblyopiagenic” factors have not been completely eliminated, and the patient is still within the age of the sensitive period, continuation of the “amblyopiagenic” factors would result in acuity regression. Because ambylophia ceases to be a threat to the visual system after visual
maturity, its recurrence would be unexpected. It has yet to be determined to what extent the visual acuity improvement of the amblyopic eye within the older patient population remains improved long after therapy is discontinued. One of the main objectives of this particular study was to provide some insight into this uncertainty. The authors retrospectively reviewed the charts of 64 amblyopic patients who had undergone direct (conventional) occlusion of the sound eye. Multiple factors were investigated such as severity and type of amblyopia, duration of treatment, and level of stereopsis as they related to the efficacy and stability of treatment. For analysis purposes patients were divided into two groups: Group 1 consisted of patients aged 7 years or younger when treatment was initiated; Group 2 consisted of patients aged 8 years or older when treatment was initiated.

The earlier study by Oster reported that patients who were older at the beginning and at the end of treatment were less likely to regress than younger patients. Stability of vision for their patients existed only when treatment began after 3 years of age. In the study by Rutstein and Fuhr, regression was not correlated to the age of treatment. Seventy-five percent of the patients in this study who were treated at age 7 or less, and 67% of the patients regressed who were treated at age 8 or older. Patients in Group 1 were followed for an average period of 11.8 months (range 2 to 43 months) after the cessation of treatment, whereas the average follow-up period in Group 2 was slightly higher at 13.1 months (range 1 to 55 months). The average regression was 43% of the acuity gained. Although a number of patients in Group 2 did demonstrate some improvement in their visual acuity, it was below the level of improvement obtained in Group 1, which consisted of younger patients. The authors concluded that acuity improvement could be achieved in older patients; however, treatment was deemed more effective in the younger patients. The amount of occlusion was not consistent for all patients. The younger patients were required to wear the patch for all waking hours, whereas the older patients had been advised to wear the patch only during evenings and weekends. It is possible that the higher intensity of occlusion resulted in more substantial acuity gains rather than the patient’s age, as was implied by the results.

At least 67% of all amblyopic patients, in the Rutstein and Fuhr study, followed for approximately one year after the cessation of treatment, lost some visual acuity gain. This prevalence of visual acuity regression was higher than had been previously reported. This finding reflected what some previous authors had concluded. In concordance with the previous study conducted by Ching, this study did find that the severity of the amblyopia at the initiation of treatment did have an adverse effect on the stability of the visual acuity following the cessation of treatment. Regression of vision (0.3 log units or more) occurred in 36% of patients with moderate amblyopia at the onset of therapy and 27% with mild amblyopia at the onset of therapy. It was determined that regression of visual acuity is likely to occur within the first year after cessation of therapy. Therefore, it was recommended that all amblyopia patients, regardless of age, be followed at regular intervals. The regression rates in this study did not include the entire study population; therefore the rates may not reflect the population studied and results cannot be generalized to the broad field of amblyopia. Thirty-two of 39 from Group 1 and 18 of 26 from Group 2 were included in the long-term follow-up (approximately one year) regression rates. The authors did not specify the reason for the lack of long-term follow-up in the remaining subjects.

An initial paper by Oliver and associates in 1986 led to a series of articles on the
long-term results of successfully treated amblyopia. The efficacy of amblyopia treatment in the older patient population (8 years of age and over) was investigated. This paper addressed the question of whether or not treatment is justified in older patients, given the psychosocial implications of conventional occlusion. The authors hypothesized that these issues could be the cause of the lack of compliance in this age group, which in turn could explain the reported higher percentage of treatment failure in older patients. This study was a prospective study of 157 amblyopic patients divided into subgroups determined by their chronological ages. In agreement with results found later by Rutstein and Fuhr, older patients were noted to demonstrate improvement in visual acuity, although overall less improvement than the younger group. Treatment compliance appeared to be the key to improvement. The younger, more successful, patients were also the subjects who were compliant with their therapy. The authors theorized that the older patients could have obtained more improvement if they were compliant.

The study by Oliver and colleagues led to further follow-up articles conducted to evaluate and identify factors that affect the long-term results of successfully treated amblyopia. In the first of three articles, Levartovsky and associates (including Oliver), in 1992, looked specifically at the age at the beginning of treatment and the age at the cessation of treatment. This study was a cross-sectional study that consisted of reexamining the visual acuity of patients who had previously been successfully treated for amblyopia. A retrospective chart review of successfully treated amblyopic patients was conducted to identify potential subjects. One hundred and fifty-seven children were eligible for inclusion, with 104 (66%) returning for the final follow-up assessment. The patients ranged in age from 9–20 with reexamination between the fourth and eighth year after treatment was ceased. At the time of reexamination (average 6.4 years after treatment ceased), regression of vision was found in 55% of patients. The amount of regression was not stated. The authors concluded that the age at which treatment for amblyopia was initiated did not affect the final outcome following cessation of treatment.

PREDICTIVE FACTORS

A later study by the same authors, in 1995, looked at additional factors, such as the effect of the initial acuity level and type of amblyopia on the long-term stability of vision. The same patient population was used for this study as the previous investigation, again in a retrospective review. Of the 104 patients who were eligible, 94 children, who were monitored for visual acuity up to at least the age of 9 years, were evaluated in this study. In order to examine the influence of initial visual acuity, or the type of amblyopia, on the long-term vision results, the results were divided into subgroups. Two groups of amblyopic results were defined based on the initial visual acuity level. In Group 1 (45 patients), initial visual acuity was between 20/60 and 20/100. In Group 2 (49 patients), visual acuity was 20/200 or worse. The type of amblyopia was separated into three groups: strabismic, anisometropic, and strabismic anisometropic (mixed type). The results revealed that 44 (47%) of the patients maintained their visual acuity following cessation of treatment, although regression of vision (average 1–2 lines) occurred in 50 (53%) patients. Deterioration of vision was observed in both visual acuity groups. Patients with a lower initial visual acuity level were more likely to suffer deterioration of their visual acuity when compared to the group with the higher initial acuity (63% vs. 42%). Regression of visual acuity was noted to occur in all three types of am-
blyopia. Deterioration of visual acuity occurred in 46% of strabismic amblyopia patients, 36% of anisometropic amblyopia patients, and 79% of patients with strabismic anisometropic amblyopia. On average, visual acuity regressed one line of vision; however, patients with strabismic anisometropic amblyopia lost two lines of vision. Based on the results of this review, it was concluded that low initial visual acuity, and strabismic anisometropic amblyopia, are risk factors for deterioration of visual acuity.

LONG-TERM STABILITY

The third study, in 2001, by the same group of authors, was initiated to determine whether the results of occlusion therapy for amblyopia are maintained into adulthood. All subjects who were included in the previous study were invited to return for a visual acuity reassessment. Of the 94 original participants, 54 (59%) agreed to be reexamined. The average follow-up period was 21.5 years (range 17.2–25.1 years) after cessation of occlusion therapy. The results were quite impressive, as it was found that visual acuity was maintained or improved in two-thirds (66.7%) of the treated patients. Thirty-nine of the 54 patients reexamined (72%) who were treated for amblyopia achieved a final visual acuity of 20/40 or better in the amblyopic eye. Only compliant patients who attended all of their follow-up appointments, up to at least age nine, were included for data analysis. All of the patients were compliant with any additional therapy prescribed during the regular reassessments, which may account for the higher rate of visual acuity maintenance and improvement that was obtained by these authors. The authors concluded that amblyopia treatment is effective and the results can also be sustained into adulthood. This study did not analyze the relationship between the length of follow-up and the incidence of deterioration. Therefore, there was no evidence to determine at which point regression occurred.

A more recent study conducted by Ohlsson and associates, in 2002, attempted to evaluate the long-term visual outcome of treatment for amblyopia. Like the previous studies by Levartovsky and colleagues, this review was a cross-sectional design with subjects being invited for a final visual assessment after the discontinuation of their treatment. The authors included data from both strabismic and anisometropic amblyopic patients for analysis. Only 54% (24/44) out of the original sample was included in the data analysis. The authors acknowledged this limitation; however, the repercussion of this was not addressed. In the amblyopic eyes, 17% had a loss of visual acuity, 50% were stable, and 33% demonstrated an improvement. None of the subjects lost more than two lines of visual acuity, and only one subject lost two lines. The authors also evaluated the rate of acuity change in the nonamblyopic eyes of their subjects. They reported a statistically significant mean acuity gain of 0.06 logMAR in the nonamblyopic eyes. The percentage of regression (17%) in this study contrasted with the rates that have been reported in previous studies, which reported that in the majority of the amblyopic eyes visual acuity deteriorated after treatment was discontinued. The findings of this study were in agreement with those of Ching, Scott, and Leiba, who all noted that visual acuity is relatively stable in about half of the patients following the cessation of treatment. Unfortunately, these previous investigations did not clearly define what level of regression of vision constitutes a recurrence of amblyopia. The level of vision loss was also not clearly stated, therefore caution should be taken when attempting comparisons to these previous reports. Levartovsky found that strabismic amblyopia was a risk factor in the lack of stability of vision after
treatment. In this study, anisometropic amblyopia appeared to be more prone to regression. Similar studies noted difficulty capturing the original sample size and did make reference to this in their discussions. The incomplete sample size will make it difficult to formulate inferences with regards to the general population. It is unknown what the visual acuity results of those who did not return ultimately stabilized at. Those who did return do not represent a random sample of the entire study population.

RECURRENTE OF AMBLYOPIA

The need for a controlled, prospective study on the recurrence of amblyopia following the cessation of treatment led to the most recent study by the Pediatric Eye Disease Investigator Group (PEDIG). One hundred and five children from thirty clinical sites, with successfully treated anisometropic or strabismic amblyopia, who were younger than 8 years of age, and who received continuous amblyopia treatment for the previous three months, were enrolled in the study. Patients were included if they were receiving at least two hours of daily patching or prescribed at least one drop of atropine per week. Following the cessation of treatment, patients were followed for a period of 52 weeks to assess for regression of visual acuity. Recurrence occurred in 24% of the patients, and was similar in patients who had patching (25%) or atropine (21%) discontinued. The authors found that the higher the intensity of the therapy at the cessation of treatment the greater the chance of recurrence of amblyopia. Patients wearing higher levels of occlusion, (6 to 8 hours per day) at the time treatment was ceased, were more likely to suffer regression of vision when compared to subjects undergoing lower grades of therapy (2 hours of occlusion daily). The results of this study determined that 42% of patients who were wearing six or more hours of patching were likely to experience recurrence of amblyopia when patching was stopped abruptly, compared to lower levels of occlusion at the time of therapy discontinuation.

DISCUSSION

There did not appear to be any one consistent risk factor affecting the stability of vision after amblyopia treatment. Most of the studies did vary with respect to lengths of follow-up visits, patient population, and method of visual acuity assessment. There was also generalized lack of standardization of visual acuity measurement in these previous studies.

The majority of the studies mentioned have been based on retrospective study design. This is a hindrance, as they are limited to patients who already have been treated, and the various groups to be studied/compared will be defined by past therapeutic decisions. The variety and inconsistencies of the treatment modalities utilized result in conclusions that provide a clinician with little information that can assist them in their management of amblyopia. Careful definitions of the exclusion/inclusion criteria are necessary so that the study can be replicated. Practically, a study’s inclusion/exclusion criteria can permit a clinician to know whether or not the results of the study may be applicable to an individual patient. There have been past studies that have used the same sample population for consecutive reviews, altering the criteria for analysis in each report. This practice of retrospectively analyzing and then reanalyzing the same population may provide some insight into the clinical practices of the authors, but does not address shortcomings in the methodologies that can be addressed in a prospective study.

In medicine, prospective randomized tri-
als are seen as the gold standard for clinical investigations. They have unmatched capacity to avoid biases from sources both known and unknown. Only one of the studies analyzed, in this review of stability of vision following the cessation of treatment, was a prospective design. This was a multicenter study involving thirty clinical sites. The results of this study determined that 42% of patients who were patching 6 six or more hours, were likely to experience recurrence of amblyopia when patching was stopped abruptly, compared to lower levels of occlusion at the time of therapy discontinuation. Regression was defined as two or more logMAR levels. The actual amount of visual acuity regression, for each patient, was not stated. The data from this investigation suggest that the risk of recurrence is greater when patching is discontinued abruptly rather than when it is tapered. There is currently no previous research that has investigated whether or not there is any benefit to therapy tapering. It has been suggested in the past that the risk of recurrence is reduced when treatment is reduced in a titrated and gradual fashion.

The authors did acknowledge some of the limitations of their study. This study was an observational versus a randomized design. Patients were not randomized to the weaned and non-weaned groups rather they were prescribed a weaning regimen based on individual investigator discretion. The decision to wean certain subjects may be related to other factors that could potentially affect the amount of regression (i.e., age, type of amblyopia, prior history of regression). Obviously, it would be advantageous to have the group as homogeneous as possible prior to the initiation of any study variables. The treatment prior to enrollment was also not standardized, thus having a potential influence on the study’s outcome measures. The authors also recognized that the sample size in the atropinized group was small, making inferences difficult.

CONCLUSION

It is clear from the literature, that there exists uncertainty regarding the recurrence of amblyopia following treatment. The majority of our knowledge regarding stability of visual acuity following treatment cessation has been acquired through retrospective reviews, and therefore subject to the limitations that occur with this type of design. There is an obvious need for consistently controlled, prospective, randomized investigations that include long-term follow-up data. Previous studies have failed to identify a common predictive factor necessary of the maintenance of visual acuity after cessation of therapy. Studies have differed with regard to the therapeutic modality, patient population, and method of visual acuity testing and follow-up assessments. The criterion for regression was also variable making it difficult, if not impossible, to determine if there was truly a recurrence of amblyopia. The durability of the results is important in determining the true efficacy and cost-effectiveness of treatment.

Also lacking is discussions on the possible influence tapering therapy could have on the recurrence of amblyopia. Currently, there are no published studies designed to determine the most appropriate and effective method to end amblyopia treatment: slowly tapering therapy or ending it abruptly. In a recent article, the Pediatric Eye Disease Investigator Group did analyze the intensity of treatment, both patching and atropine penalization, to the amblyopia recurrence rate. Unfortunately, treatment prior to enrollment was also not standardized; rather it was left up to the investigators discretion. A prospective, randomized, controlled study comparing a standardized tapered regimen to abrupt
cessation is needed. This future study should attempt to control variables that were inconsistent in previous investigations such as age at cessation of treatment, intensity of occlusion at cessation, method of visual acuity assessment, length of time between follow-up appointments, and method of cessation.

REFERENCES


Key words: amblyopia, recurrence, stability