European Journal of Ophthalmology / Vol. 17 no. 1, 2007 / pp. 11-19

Continuous full-time occlusion of the sound eye vs full-time occlusion of the sound eye periodically alternating with occlusion of the amblyopic eye in treatment of amblyopia: A prospective randomized study

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PURPOSE. *To compare continuous full-time (24 hours per day) occlusion of the sound eye with full-time occlusion (24 hours per day) of the sound eye 1 day more than the years of age periodically alternating with occlusion of the amblyopic eye for 1 day, as treatments for profound strabismic amblyopia in children older than 5 years.*

METHODS. *A total of 53 patients with visual acuity (VA) of 0.4 and less in the amblyopic eye (tested by crowded Landolt Cs) after previously being provided optimal optical correction were randomly assigned to receive either of the two patching regimens. VA and pattern reversal visual evoked potentials (PVEP) were recorded prospectively at 1-month intervals. Improvement in VA and the reduction in crowding difficulties (CD) were the main outcome measures of the treatment efficiency.*

RESULTS. *Both treatment modalities were equally effective. Of the 51 subjects who completed the study, 21 (41.2%) were cured whereas 32 (62.7%) attained satisfactory improvement. Recovery of VA was related to age, with cure being obtained in 23.5% (4/17) and satisfactory improvement in 52.9% (9/17) of patients older than 9 years. Larger gain in VA influenced the stability of the vision over time.*

CONCLUSIONS. *It can be concluded that in clinically monitored parameters both treatment modalities were equally effective without any statistical or clinical significance in the observed groups of patients. However, events like the "trade-off" effect, occurrence of occlusion amblyopia, or prolongation of PVEP latency of the sound eye indicate that full-time continuous occlusion possibly presents a more effective form of treatment. (Eur J Ophthalmol 2007; 17: 11-9)*

KEY WORDS. *Amblyopia, Full-time occlusion therapy, Strabismus, Visual acuity*

Accepted: July 17, 2006

INTRODUCTION

Full-time occlusion of the dominant eye has long been the mainstay of amblyopia therapy, its use dating back over 1000 years (1).

The work of the Nobel Prize winners Hubel and Wiesel demonstrated that the developing visual system is highly sensitive to deprivation, and this has had considerable impact on clinical practice, mainly with the recog-

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nition of the need for early diagnosis and intervention (2). But their experiments also contributed to a change of attitude toward occlusion therapy for patients with profound amblyopia. Because of concerns derived from animal studies about possible deleterious effects of occlusion on the immature visual system that could probably relate to human amblyopia having its onset in the first 12 to 18 months of life, many ophthalmologists started to abstain from longer periods of occlusion even when treating older children (3). This led to the concept of minimal occlusion in spite of the long-standing clear clinical percept that such therapy cannot be compared with full time occlusion (1, 4, 5).

Debate still continues regarding treatment and occlusion modalities. But the reality of amblyopia treatment is that the intensity of patching prescribed is not always the actual amount of patching that is received, even when special monitoring devices have been used (6). This is one of the reasons, aside from potentially better binocularity outcome, why recent studies have looked at the efficacy of atropine penalization rather than patching in the treatment of amblyopia. Regarding the efficacy of various protocols, there have been several reports with conflicting results (7-9). Treatment duration data have also been contradictory, ranging from no association with treatment effect to both direct and inverse relationships (10, 11).

It has long been known that the “white noise” of unilateral optical defocusing has both monocular and binocular detrimental consequences (12). Also, recent work has indicated that occlusion enhances binocularity more than penalization (13, 14), and that more intensive patching may be needed in children with better levels of vision in order to re-establish bifoveal fixation (15).

The conclusions indicating that lower intensities of patching are as effective as full time regimes (8) might be too optimistic (16) and have some limitations (17, 18). In some countries these studies have drawn much attention from the lay press to the point where this publicity appears to play an important role in influencing parent treatment preferences (19).

Should we change our practice and abandon full time occlusion so easily as a result of these studies? Since amblyopia in strabismic patients is more difficult to treat (20) it seems logical to treat those patients, particularly if older than 5 years, with the most efficient occlusion regimen.

The aim of this study was to prospectively compare continuous 24 hours per day full-time occlusion of the sound eye versus full-time occlusion 24 hours per day of the sound eye periodically alternating with occlusion of the amblyopic eye, with monthly reassessment, as treatments for profound strabismic amblyopia in children older than 5 years. To our knowledge, determining how each of these two most aggressive patching protocols contributes to treatment outcome has not been attempted in any previous study.

METHODS

Design: Prospective, randomized controlled trial.
Setting: Tertiary care university hospital.
Patients: 53 subjects, both sexes (25 male, 28 female), all older than 5 years.
Inclusion criteria: Patients with unilateral amblyopia associated with strabismus or microtropia where cover test is negative (angle of anomaly identical to the degree of eccentricity of monocular fixation), with or without anisometropia, age over 5 years, visual acuity (VA) of amblyopic eye (after full refractive adaptation where appropriate) 0.4 and less tested with crowded Landolt C (C-test) acuity chart 17.2 min of arc (21).
Exclusion criteria: Isolated anisometropic amblyopia and amblyopia associated with moderate and higher myopic refraction anomaly were not considered because of diminished retinal image (most frequently correcting spectacles are not placed at the anterior focal plane of the eye) and consequent presentation of lower VA not suitable for comparison, as well as associated structural ocular and systemic anomalies.

Intervention

All patients had a full ophthalmic examination including refraction under atropine or cyclopentolate cycloplegia. After the cessation of cycloplegia and 4 weeks of full-time spectacle correction where needed, complete orthoptic assessment was performed including single and linear VA (C-test charts, with constant space of more than 30-single, 2.6 and 17.2 min of arc between symbols for all acuity values, Haase and Hohmann, Oculus AG), Randot sup-

pression check test (Stereo Optical Co., Inc.), 4 PD test, and pattern reversal visual evoked potentials (PVEP) recordings. Patients who met the inclusion criteria of VA were then randomly allocated to one of two treatment groups and adhesive eye patching was initiated.

The experimental group (n=28) was treated with continuous full-time occlusion of the sound eye 24 hours per day, while the control group (n=25) was treated with alternating occlusion (the sound eye 1 day more than the years of age followed by patching of the ambylopic eye for 1 day) full-time 24 hours per day.

Monocular visual function was studied and PVEP recorded (monocular P100 latencies and amplitudes) at 1-month intervals regardless of age, until achieving maximal VA.

Treatment protocol was discontinued after equal VA has been obtained, or if after three consecutive, compliant episodes of treatment there was no further improvement of VA (17.2' test), if there was occurrence of diplopia, or if occlusion amblyopia appeared. For patients with microtropia, planned end of treatment was one line of acuity difference between eyes to avoid diplopia. Occlusion amblyopia was defined as increased crowding difficulties (CD) of the sound eye expressed by the fall of VA of two or more lines for C-test 2.6', with or without deterioration of parameters of PVEP, followed by the fall of VA of one or more lines on the next control for test with separation of symbols 17.2'. Some individuals have pronounced crowding difficulties even for healthy eyes for 2.6' test, as it enters the zone of critical separation for normal eyes from 1.8'-3.8' (22). For those patients who were identified before the treatment by increased CD for nonamblyopic eye, we did not use 2.6' chart for them subsequently. For the patients where 2.6' test was not applicable the same criteria were set for PVEP and fall of VA of one or more lines on the next control for 17.2' test.

Once treatment protocol had been discontinued, part-time occlusion of 6 to 4 hours/day combined with close work was instituted to maintain the level of VA attained in the amblyopic eye and gradually tapered with follow-up examinations every 3 months. If VA deteriorated by more than one line on the 17.2' test, part-time occlusion was intensified or re-initiated.

Great effort was made to ensure optimal compliance with the treatment protocol for both the child and family. The first period was the hardest to endure. The same ophthalmologist (B.S.) was responsible both for the examination and for information explained to the parents as to the methods of treatment.

Main outcome measures

The efficacy of treatment in terms of diminishing difference of VA and CD, final VA, time to achieve cure, and speed of initial improvement was evaluated in relation to age, initial VA, type and amount of deviation, fixation pattern, presence of anisometropia, compliance with occlusion, and previous treatment. Also the study tried to answer whether the presence of CD at the beginning of treatment influenced maximal VA obtained, whether absence of CD at the end of treatment influenced post treatment stability, and whether the changes in crowding phenomenon and PVEP could predict occurrence of occlusion amblyopia.

We analyzed acuity achievement in different ways. Statistical analysis was calculated from values recorded on a decimal scale (17.2' and 2.6' tests) and by transposing the decimal VA to the logarithm of the minimal angle of resolution (log MAR) VA. Logarithmic scale of VA has a more pronounced linearity, being able especially to differentiate fine distinctions at the lower range of VA. It was measured according to the method recommended by Epelbaum et al (23) as the reduction ratio of interocular acuity difference at the beginning and the end of treatment following the equation (A-B)/A where A is the initial difference in acuity and B the final difference, and calculated also using the same formula in logarithmic values.

Interocular acuity difference at the end of treatment has been presented in two ways: by subtracting values recorded on decimal scale, and calculating in decimal steps where the lowermost decimal expressed VA 0.06 was denoted by 1, and highest 1.25 by 15.

We also used a method of relative VA– by using the quotient between the performance of the amblyopic eye and the good eye before and at the end of treatment (24).

CD of the amblyopic eye was expressed by difference of VA decimal values as well as difference in decimal steps on single, 17.2', and 2.6' tests. Because the difference in VA for optotypes with different CD diminishes with age (25), to try to avoid possible influence of age in evaluation, we determined the mean diffrence in VA lines of sound eye for single and 2.6' test (where

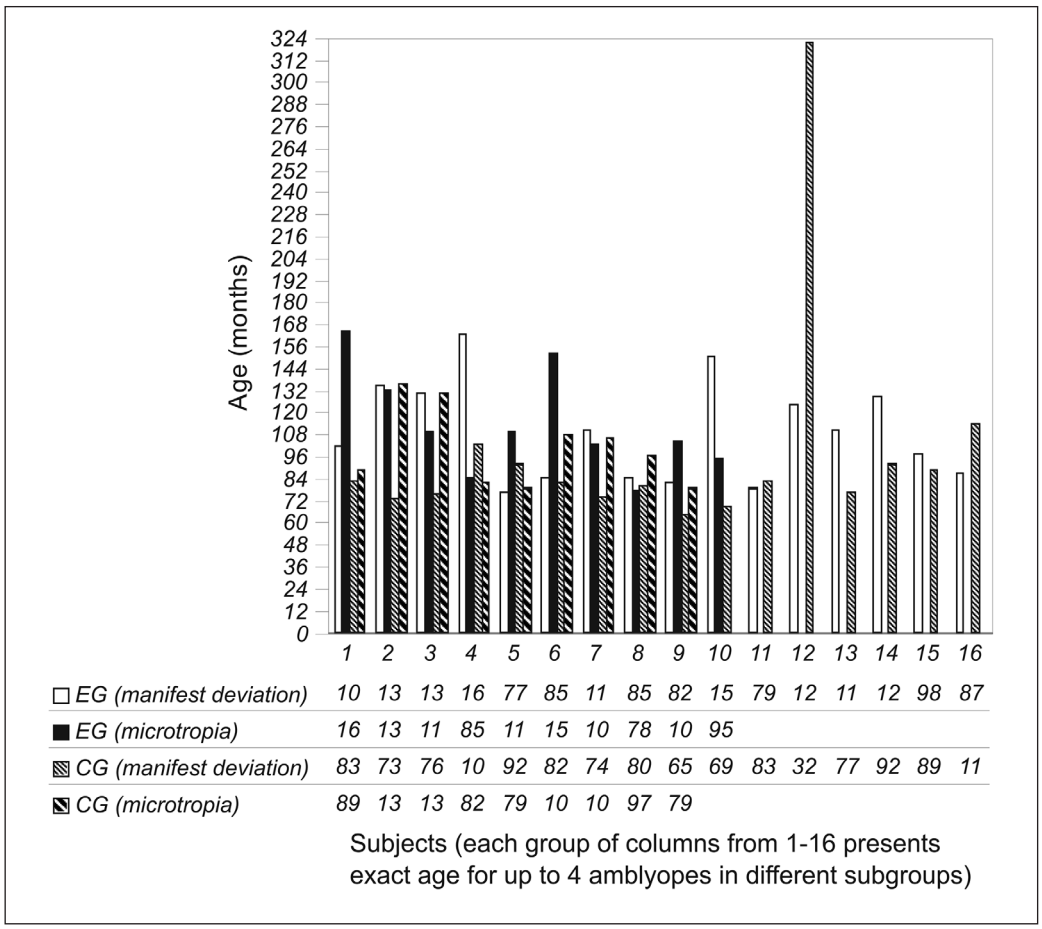

Fig. 1 - *Distribution of the subject's age at the initiation of treatment (treatment groups*, subgroups by the deviation type), p=0.29. *EG = experimental group; CG = control group.*

possible) or 17.2' at start of treatment and last control. A value equal to or higher than 3 was considered as the criterion for pronounced crowding difficulties. A value of 2 or less decimal steps for 17.2' and 4 or less for 2.6' test was defined as the criterion of CD normalization.

We defined the criterion for cure as an interocular difference of one step or less with diminishing separation difficulties 2 or fewer steps for the 17.2' test, while we defined a satisfactory result as achieving VA more than 0.5 with the same diminishing of separation difficulties.

In all cases the functional status was estimated prior to occlusion therapy, at the time of discontinuation of full time occlusion (point of achieving maximal VA), and at the most recent visit (point of achieving relative stability).

Statistical significance was determined using several tests including first and second Pearson's coefficient of shape, *t*-test for independent and dependent samples, Wilcoxon test, Mann-Whitney *U*-test, and Spearman's coefficient correlation of rank.

RESULTS

The mean follow-up was 16.34 months (range 13 to 19). Subject age ranged from 65 to 322 months (average 104.2, SD 39.4).

Two children, both younger than 7 years, initially in the experimental group (continuous full-time patching) developed occlusion amblyopia (one patient with manifest deviation and the other with microtropia). This was treated with inverse occlusion for 7 days, and then continuing with alternating occlusion. The 2.6' test (where applicable) detected occlusion amblyopia 1 month earlier than the 17.2' chart, as did prolongation of PVEP latency (>15 ms), which con-

TABLE I - CURED PATIENTS (visual acuity < 2 steps with crowding difficulties ≤ 2 steps for C-test 17.2')

Initial age, mo	Cured	Other	Total
<85	11 (64.7)	6 (35.3)	17 (100)
≥84 <109	6 (35.3)	11 (64.7)	17 (100)
≥109	4 (23.5)	13 (76.5)	17 (100)
Total	21 (41.2)	30 (58.8)	51 (100)

Values are n (%)

TABLE II - SATISFACTORY IMPROVEMENT ((visual acuity >0.5 with crowding difficulties ≤ 2 steps for C-Test 17.2')

Initial age, mo	Satisfactory	Other	Total
<85	12 (70.6)	5 (29.4)	17 (100)
≥84 <109	11 (64.7)	6 (35.5)	17 (100)
≥109	9 (52.9)	8 (47.1)	17 (100)
Total	32 (62.7)	19 (37.3)	51 (100)

Values are n (%)

TABLE III - LENGTH OF TREATMENT NECESSARY TO ACHIEVE BEST VISUAL ACUITY FOR C-TEST 17.2'

Initial age, mo	Length of treatment, mo			
	≤3	>3≤ 7	>7	Total
<85	2 (11.8)	9 (53)	6 (35.3)	17 (100)
≥84 <109	2 (11.8)	7 (41.1)	8 (47.1)	17 (100)
≥109	8 (47.1)	5 (29.4)	4 (23.5)	17 (100)
Total	12 (23.5)	21(41.2)	18 (35.3)	51 (100)

Values are n (%)

trary to testing of VA using charts, did not deteriorate further. The two patients who crossed over to the control group treatment could satisfy neither protocol and were excluded from further evaluation to avoid potential bias. *Z* test showed that occurrence of occlusion amblyopia was not statistically significant (Z=1.44016, level of significance 0.14982).

Twenty-six patients in experimental (continuous patching) and 25 in control group (alternate patching) completed our protocol (Fig. 1). Manifest deviation was present in 32, while microtropia was present in the remaining 19 subjects. Anisometropia was present in 36 of 51 patients.

Repeated comparison using different statistical tests of all potentially significant prognostic factors did not show any statistical difference between experimental and control groups, even when subgrouped according to type of deviation, except for the type of treatment received.

Both treatment modalities were equally effective. No statistically significant differences (p values ranged from 0.85 to 0.22) in clinically monitored parameters between treatment groups were detected (except PVEP interocular initial and final latencies difference).

The value for the mean initial interocular acuity difference value (using the 17.2' test) for the experimental group was 0.99 (10.3 decimal steps) in relation on difference at point of achieving maximal VA 0.57 (4.88 decimal steps), and this was highly statistically ($p<0.0001$) and clinically significant. The mean initial difference in the control group was 0.91 (9.56 decimal steps) and maximal 0.46 (3.84 decimal steps), and was also statistically ($p<0.0001$) and clinically significant. The difference between groups at the point of achieving maximal VA was 0.11 (1.04 decimal steps) and was not statistically nor clinically significant.

PVEP interocular initial and final latencies difference showed significant statistical improvement in experimental group (p=0.01).

In the experimental group the sound eye showed statistically significant lower VA after occlusion in relation to control group (p=0.01), but this difference disappeared quickly and at the most recent visit was not statistically nor clinically significant (p=0.14).

The mean value of initial compliance (a value of 5 denoted full complience, while 1 denoted that no occlusion was applied) was 4.38 for the experimental group and 4.32 for control group (p=0.75), and final 4.12 and 4.16 (p=0.85). The difference between initial and final compliance between groups was not statistically nor clinically significant (p=0.15, p=0.32).

CD at the beginning of treatment did not influence the final outcome, while its absence at the end of treatment indicated that attained VA would be stable.

Before treatment, all patients had suppression on Randot suppression test. A total of 30 subjects, consisting of 6 with manifest deviation and 7 with microtropia in the experimental group versus 9 and 7 in control group, overcame suppression at the end. Patients with manifest deviation had a negative correlation in overcoming suppression with the amount of deviation, and negative correlation with VA when the deviation was

less than 25 PD, whereas patients with microtropia had a positive correlation only with VA achievement. Satisfactory improvement was attained in 32 (62.7%) of the 51 patients, with 21 (41.2%) being cured according to our definition. VA recovery was related to age. Results showed cure in 23.5% (4/17) (Tab. I), and satisfactory improvement in 52.9% (9/17) patients older than 9 years (Tab. II).

The mean duration of occlusion necessary to achieve best VA was 5.38 months (range 2–8) and increased with the age of the patient (Tab. III). The larger number of patients in the age group more than 9 years of age with treatment ≤3 months reflected the fact that 5 (of 8) subjects had previous treatment. Previous attempts of treatment with poor compliance diminished the possibility of improvement, excluding those with previous successful treatment with relapse of amblyopia. The mean time from discontinuation of full time occlusion (point of achieving maximal VA) and the most recent visit (point of achieving relative stability) was 11.62 months (range 10–15). Larger gain in VA influenced the stability of vision over time and allowed earlier reduction and discontinuation of part-time occlusion. Any deterioration in VA could be regained with intensification or re-initiation of part-time occlusion during the course of follow-up.

There were two patients (129 and 322 months of age) who had a large recurrence of amblyopia several years after successful treatment, but after re-initiation of occlusion VA was restored close to earlier values, although the first patient had peripheral eccentric fixation, and in the latter, treatment was started again after 15 years, with minimal fall of acuity after cessation of occlusion.

Only three patients failed to gain improved VA in spite of good compliance. All were younger than 7 years old (79, 69, and 77 months), had peripheral eccentric fixation, and had manifest strabismus. The first was in the experimental group, while the others were in the control group.

In the control group, one patient required surgery to restore decompensated microtropia and one from the same subgroup (the only one who equalized VA) experienced diplopia. This diplopia quickly disappeared after changing to part-time occlusion. Equalization of VA occurred in three patients with manifest strabismus (two in experimental and one in control group), without any diplopia.

DISCUSSION

Recently it has been reemphasized that we should be more aggresive in treating amblyopia in younger children, as well as in older patients, despite the difficulties with compliance (26). Early detection and aggressive occlusion treatment are of paramount importance. Years ago Duke-Elder and Wybar pointed out that “occlusion should be total and continuous ... the use of intermittent form ... is an illusory and valueless procedure” (4), and von Noorden and Campos wrote that “the fixating eye should be occluded completely and constantly during all waking hours” (1), and also, “as there exists a direct relationship between the age at which amblyopic therapy is begun and its successfulness, no precious time should be wasted by occluding only part-time as a primary form of treatment” (27).

We compared two of the most aggressive patching protocols. Our results have shown equal outcome of applied treatment modalities.

The evaluation of amblyopia treatment outcome presents a serious challenge. Problems include the design of VA charts, which first of all because of their nonlinearity, do not allow correct mathematical analysis of acuity data. Since this nonlinearity problem of all acuity charts, both decimal and logarithmic, does not fulfill necessary conditions to be treated as proportional or interval, we tried to alleviate this by treating them as rank scales. Another problem is the enormous difference in symbols and unequal separation between them on most currently used test charts or projection slides (1, 28). We overcame this problem by using the C-test with Landolt ring, the physiologically most appropriate symbol, with equal CD for all acuity levels. There is also a problem in analyzing data of children with amblyopia that is not encountered in analyzing acuity data from adults. The VA of children, when tested by the same method, tends to improve with age. Several methods have been suggested to overcome this problem with the best being those calculated by reference to the acuity of the non-amblyopic eye (16). To avoid erroneous conclusions related to data interpretation, we analyzed VA achievement in several ways both in decimal and logarithmic values.

Our PVEP findings indicating better results in the experimental group could be challenged for two rea-

sons. First, the mean value of PVEP latencies of the sound eye in the experimental group showed growth trend, opposite to the control group. Arden and Barnard (29, 30) also reported the same changes in the visually evoked response after continuous occlusion. Although these tendencies did not show significant statistical difference in our study, in their absence interocular initial and final latencies difference would not show significant statistical improvement. Secondly, as we recorded PVEP at 1-month intervals, we noted that the trend of change in our patients was not always in the same direction, with periodical differences of even 20 ms, which could be attributed to the well-known influence of inadequate compliance.

A transient fall in acuity of the sound eye after occlusion in the experimental group can be attributed to the well known "trade-off" effect (3), indirectly indicating more intensive effect of permanent occlusion. The explanation for equal efficiency of the two treatment modalities received by our patients could be due to the impossibility of obtaining "ideal" compliance. In spite of good and highly evaluated compliance in both groups, a small number of patients had compliance scored as excellent both in initial and final stage of treatment. Since scoring is subject to bias of parents and child as well as the examiner, we acknowledge the weakness in evaluations based on parental scoring. Objective electronic compliance monitoring, as that proposed by Fielder et al (6, 31) and Chopovska et al (32), could be the key to a more evidence-based treatment for amblyopia. It is clear that children do not like patching, and achieving compliance presents a serious challenge. Eggers (33) has stressed that everyone using continuous occlusion knows that even short failure in occlusion can jeopardize the treatment efficiency.

Although both treatments are very efficient, regardless of lack of ideal compliance, indirect results like "trade-off" effect, occurrence of occlusion amblyopia, and prolongation of PVEP latency of the sound eye indicate that continuous occlusion is a more aggressive but potentially more effective form of treatment. The question arises why the more aggressive patching regimen prescribed in our study did not show more efficacy in clinically monitored parameters. Besides the known heterogeneity in compliance, another reason for this may be the reflection of individual patient's underlying central nervous system potential (40). This could also be due to the artefact caused by the small number of patients older than 9 years, who until recently were considered too old for treatment, and in whom permanent occlusion potentially could have advantage.

Like most authors (1, 34), we found that recovery of acuity was related to age, and like Scott and Dickey (35), that larger gain in VA influenced the stability of vision over time. Our finding that absence of CD at the end influences post treatment stability is also in concordance with the literature (1, 20). Without normalization of CD we cannot consider that a patient with amblyopia has been cured, and future deterioration of VA is possible.

Binocularity was an index of treatment success in overcoming the suppression except for angles exceeding 25 PD. Achievement of binocularity could be simply a function of the level of VA achieved in the amblyopic eye. Such association has been reported in occlusion studies of amblyopes with anisometropia and/or small-angle or intermittent strabismus (36) but not in penalized patients with all forms of strabismus and amblyopia (37).

There is extensive literature debating concerns of weakening effect on suppression during prolonged, and even alternating, occlusion, and possible occurrence of diplopia, especially at later ages and in patients with microtropia (20, 38). This occurred in only one of our patients (in whom vision equalized even though we had aimed to achieve one line difference between the eyes in microtropia). It appears that diplopia happens exceptionally in those patients, and quickly disappears if detected early. Campos (20) stated that "Diplopia disappears by simply discontinuing treatment, if the problem is noted early". Fear of diplopia seems to be overemphasized, but still more frequent monitoring is needed for patients with microtropia.

The development of occlusion amblyopia, even though it did not reach statistical significance on analysis, could likely be a clinically significant complication of the continuous occlusion. For two of our patients development of occlusion amblyopia was a good prognostic sign, as they attained good acuity (1.25 and 1.0). Where the C-test 2.6' could be performed, it has been shown to be the most sensitive clinical test for detecting occlusion amblyopia, while PVEP prolongation could be considered only when associated with a fall in VA.

Acute strabismus occurring during occlusion therapy is a rare event and can develop even after part time occlusion (39). Our one case of decompensating microtropia in the less aggressive, alternating patching group could not therefore be considered as a significant complication.

Overall we conclude that a monitored period of full-time continuous occlusion could best and most quickly overcome profound amblyopia in strabismic patients older than 5 years of age, even in cases with useful binocular vision. Even when used beyond the usually accepted age limits, amblyopia can be cured, thus providing evidence of individual plasticity. While complications such as occlusion amblyopia or diplopia may occur, the risk is very small as compared to the potential benefit of constant occlusion, and we have found them to be rare and easily solvable with appropriate follow-up.

The authors have no proprietary interests in any of the commercial products, drugs, or instruments mentioned in this article.

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