·Clinical Research·

Comparison of the efficacies of patching and penalization therapies for the treatment of amblyopia patients

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Abstract

• AIM: To compare the efficacies of patching and penalization therapies for the treatment of amblyopia patients.

• METHODS: The records of 64 eyes of 50 patients 7 to 16y of age who had presented to our clinics with a diagnosis of amblyopia, were evaluated retrospectively. Forty eyes of 26 patients who had received patching therapy and 24 eyes of 24 patients who had received penalization therapy included in this study. The latencies and amplitudes of visual evoked potential (VEP) records and best corrected visual acuities (BCVA) of these two groups were compared before and six months after the treatment.

• RESULTS: In both patching and the penalization groups, the visual acuities increased significantly following the treatments (P <0.05). The latency measurements of the P100 wave obtained at 1.0°, 15 arc min. Patterns of both groups significantly decreased following the 6 -months -treatment. However, the amplitude measurements increased (P<0.05).

• CONCLUSION: The patching and the penalization methods, which are the main methods used in the treatment of amblyopia, were also effective over the age of 7y, which has been accepted as the critical age for the treatment of amblyopia.

• KEYWORDS: amblyopia; patching therapies; penalization therapies; visual evoked potential

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INTRODUCTION

Amblyopia is the unilateral or bilateral decrease of vision without the presence of an organic reason on the physical examination of the whole optic axis or the macula[1]. Amblyopia is caused by abnormal visual acuity early in life resulting from strabismus, anisometropia or stimulus deprivation [2]. Reduced vision in amblyopia is thought to result from abnormal neuronal network within the primary visual cortex. Cells of the primary visual cortex lose their innate ability to respond to stimulation of eyes. Abnormalities also occur in neurons in the lateral geniculate body[3]

Treating amblyopia involves making the patient use the weaker eye. The treatment options are correction of refractive errors, patching, penalization, pleoptic treatment and CAM[1,4]. Subsequently, the treatment is continued with one or multiple of the other methods according to the choices of the patient and the physician. There are two major ways to use the amblyopic eye involuntarily: patching or penalization. Patching treatment is based on the closure of the healthy eye in order to stimulate the amblyopic eye for vision[1]. Patching stimulates vision in the weaker eye and helps the part of the brain that manages vision develop more completely. The atropine penalization is applied to the sound eye to force fixation to the amblyopic eye for distant and near targets[5].

The Visual Evoked Potential (VEP) measurement is based on recording of the electrical outputs from the occipital region that are formed in the photoreceptors in response to visual stimuli. Pattern VEP has advantage of predicting the visual acuity objectively, also it particularly demonstrates the central retinal function and may be used in the follow-up of amblyopic patients[6,7].

Exposure to amblyogenic factors in the latent period, which is before the beginning of the critical period, does not lead to the development of amblyopia. This period is accepted as the proper time for elimination of congenital problems. The end of the critical period for humans has not been established definitely. It has been suggested between 6 and 12y of age. The most sensitive age in children regarding amblyopia is the first 2 or 3y of life. The sensitivity decreases until 6-7y of age gradually[8].

Table 1 Inclusion criteria

Amblyopia cases between 7 and 16y of age.
In the patching treatment group, more than 0.5 BCVA in the sound eye and 0.2-0.5 BCVA in the amblyopic eye according to the Snellen scale.
In the penalization treatment group, 1.0 (complete) BCVA in the sound eye and 0.2-0.5 BCVA in the amblyopic eye.
Patients with Snellen line vision acuity differences of more than two lines in both eyes.
Patients who had received patching or penalization treatments for at least 6mo.
Patients without myopia in either eye.
Patients with no previous history of eye surgery.
Patients with pattern VEP records.

BCVA: Best corrected visual acuity; VEP: Visual evoked potential.

SUBJECTS AND METHODS

A total of 50 patients with the proper criteria (Table 1) treated with patching or penalization, who had presented to the Eye Clinics of Kartal Dr. Lütfi Kırdar Training and Research Hospital between 2009 and 2012, were evaluated retrospectively and included in our study.

A total of 64 eyes of 50 patients were selected according to the above criteria. The measured visual acuities were converted into their logMAR charts. The refraction errors of both eyes were converted to their spherical coequals by the following formula: (spherical value+cylindrical value/2).

Twenty four eyes of 24 patients in the penalization treatment group received 1 drop of 1% atropine (in 10 mL distilled water) 2 times a week (on Wednesdays and Sundays). These patients had been contacted for a measurement with an auto refractometer at the end of one week, and their visual acuities had been evaluated. The efficacy of atropine was evaluated according to the presence of at least two lines of a decrease in the sound eye, and if it were evaluated as insufficient, another 1% atropine was prepared for the patient. Forty eyes of 26 patients (14 bilateral cases) in the patching treatment group were recommended to close the sound eye for only 2h a day. In bilateral cases all eyes had 0.2-0.5 best corrected visual acuity (BCVA) and patching treatment was performed both eyes, alternatively.

The ocular electrophysiological test based on the recording of electroencephalographic signals derived from the brain response to visual stimuli. The visual evoked potential (VEP) recording has been defined by the International Society for Clinical Electrophysiology of Vision (ISCEV) in routine clinical applications.

There are two basic stimuli as flash and pattern forms. In pattern stimuli, there are checker board squares with equal sizes and numbers with black and white colors. There is a red plus at the center of this checker board pattern, which is the fixation point, and the patient is asked to look at this point continuously. A pattern stimulus is expressed as the "visual angle". The visual angle is measured by the division of the edge length of the pattern, by the distance between the tested eye and the center of the stimulus. The result expresses the tangent of the visual angle for each pattern element. Thus, the reverse tangent expresses the visual angle. The visual angle of pattern stimuli must be at least 15 degrees. The mean luminance should remain constant when the black and white squares of a pattern are flashing. However, the luminance should be constant at each element of the pattern. Making records of the responses at 15- and 60-arc minute sizes has been suggested. A large 60 arc min pattern stimulus forms a parafoveal response, whereas a small 15 arc min pattern stimulus forms a foveal response generally. The flashing rate of the black and white squares should be 1 per second[9].

ISCEV suggests three stimuli for the clinical VEP test, which are the pattern reversal VEP, the pattern onset-offset VEP and the Flash VEP (Figure 1). The VEP stimulus exchange in the transient (short-term) VEP response should be longer than the period the brain would exceed to the resting position without stimulation. The stimuli exchange rate in the steady-state (continuous) VEP examination should be fast as not to allow the brain to rest. Transient VEP can be obtained when the wave stimulus exchange rate is 5 Hz. The higher frequencies have steady-state VEP responses form.

The pattern VEP measurements of normal children between 8 and 19y of age obtained by the Roland-Consult Retiport instrument in Gülhane Medical Faculty were used as reference values, and these values were compared to the amblyopic eyes in our study [10] (Table 2). The reference values were: mean P100 wave latency for 1° pattern was accepted as 103 (94-113)ms, and for 15 arc min pattern, it was accepted as 115 (99-123)ms; the mean amplitude for 1.0° pattern was 23.8 (12.3-41.3) μV, and it was 23.8 (10.1-37.5) μV for the 15 arc min pattern.

The pattern VEP recordings were performed by the same person in the same environment using the Roland-Consult Retiport instrument in our study. The recordings were performed using two different dimensions of patterns (1st step: 1.0°, 2nd step: 15 arc min). The obtained latencies of P100 waves were recorded as milliseconds (ms) and the amplitudes were recorded as microvolts (μV). The measurements of P100 wave amplitudes and the latencies obtained in the records were compared.

All the analyses and examinations were evaluated using the SPSS 16.00 statistical program. Non-parametric tests (Mann-Whitney *U*, Wilcoxon Sign Test) were used for evaluation of the quantitative data, and the Chi-square test

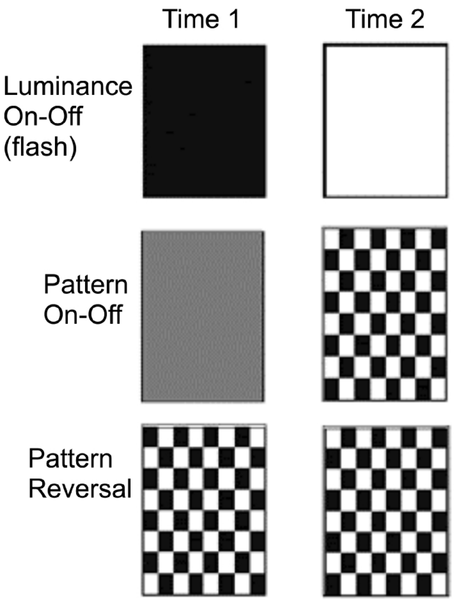

Figure 1 Three stimuli for the clinical VEP test 1) A flash stimulus comprising at least 20° visual field is suggested in the flash VEP; 2) The stimuli sizes are: large: 1.0° (60 arc minutes) and small: 0.25° (15 arc minutes) in the pattern onset/offset VEP; 3) The stimuli sizes are: large: 1.0° (1.0°: 60 arc minutes) and small: 0.25° (15 arc minutes) in the pattern reversal VEP.

was used for evaluation of the qualitative data such as gender. The assumption of equality of variance hypothesis tests was not achieved. For this reason non-parametric tests were preferred. Pearson and Spearman's Correlation analysis were also used to evaluate of correlation of visual acuity and VEP measurement.

The pattern VEP measurements and BCVA of these two groups were compared before and 6mo after the treatment.

All patients were adequately informed and signed a consent form. The study adhered to the tenets of the Declaration of Helsinki.

RESULTS

The mean age was 10.0±2.8 in the patching treatment group (n=26) and 11.6±3.0 in the penalization group (n=24). There was statistically difference between ages of two groups (P=0.024). In the patching treatment sub-group 17 patients were female (65.4%) and in the penalization sub-group 9 patients (36%) were female. There was statistically difference between sexes of two groups (P=0.024)

There was statistically difference between two groups in BCVA before the treatment [0.43±0.17 (0.41±0.16 logMAR) in the patching group; 0.25±0.05 (0.62±0.10 logMAR) in the penalization group] (P<0.05). Six months after treatment, the mean BCVA of patching group was 0.77±0.154 (0.13±0.08 logMAR) and 0.62±0.08 (0.21±0.04 logMAR) in the penalization group. In both groups, the BCVA following the treatment were found to be statistically significantly increased compared to the pre-treatment period, and parallel to that, the logMAR measurements were significantly decreased (P< 0.05) (Table 3).

Table 2 Reference values for 8 to 19 ages

VEP	N75 (ms)	P100 (ms)	N135 (ms)	P100 (μV)
2°	69 (60-77)	103 (91-114)	158 (133-211)	21.6 (11.8-43.2)
1°	72 (64-84)	103 (94-113)	149 (8129-179)	23.8 (12.3-41.3)
30'	77 (70-84)	107 (91-132)	149 (121-195)	22.0 (7.9-45.0)
15'	82 (68-89)	115 (99-123)	161 (136-202)	23.8 (10.1-37.5)

Table 3 Pre- and post-treatment visual acuities of the patching and penalization groups

VEP	Pre-treatment	Post-treatment	[1]Z	P
Patching	0.43±0.17 (0.41±0.16 logMAR)	0.77±0.15 (0.13±0.08 logMAR)	-5.40	0.000
Penalization	0.25±0.05 (0.62±0.10 logMAR)	0.62±0.08 (0.21±0.04 logMAR)	-4.31	0.000
[2]Z	-4.52	-3.87		
P	0.000	0.000		

[1]Wilcoxon Sign test; [2]Mann-Whitney U test.

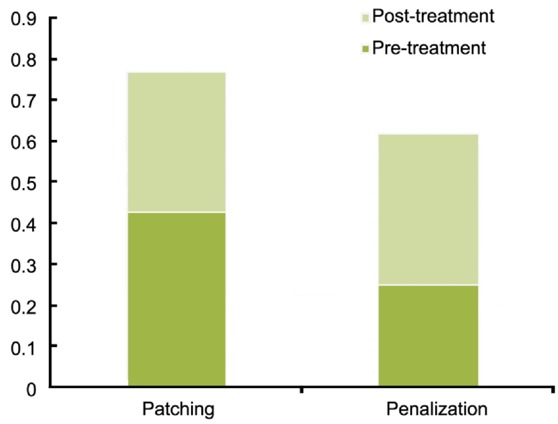

Figure 2 Pre- and post-treatment Snellen coequal graphics of the patching and penalization groups.

Table 3 and Figure 2 show the pre- and post-treatment visual acuities of the patching and penalization groups.

Reverse amblyopia was observed in one of our patients, who was 7 years old and had high hypermetropia, in the penalization group. Reverse amblyopia was defined as the visual acuity of sound eye worse than amblyopia eye 3 logMAR units after treatment. The visual acuity of this patient was improved by an alternate patching treatment after a 3wk resting period.

Comparison of improvements in both groups in terms of Snellen, latency and amplitude is presented in the Table 4. There was no difference (P>0.05) between patching and penalization groups as far as the average improvements of visual acuity, latency and amplitude. It can be concluded that the penalization therapy can be as effective as the patching therapy.

A significant difference was observed between the patching and the penalization groups with regard to spherical, cylindrical and spherical-equivalent values (P<0.05). The spherical and the spherical-equivalent values of the penalization group, and the cylindrical values of the patching group were determined to be significantly higher.

The evaluation of the pattern VEP records of 64 pre-treatment amblyopic eyes showed that the latency

Table 4 Comparison of improvements observed in the Patching and Penalization group in terms of snellen, latency and amplitude

Improvement in	Patching ($\bar{x} \pm s$)	Penalization ($\bar{x} \pm s$)	Test of equality of variances	Test	*P*
Snellen	0.3425±0.16	0.3750± 0.08	F-test, *P*=0.001; Levene, *P*=0.013	Mann-Whitney *U*	0.197
P100 Latency 1.0°	-7.60±6.32	-6.25±6.08	F-test, *P*=0.860; Levene, *P*=0.836	T=-0.84	0.405
P100 AMP 1.0°	7.55±4.30	8.21±3.45	F-test, *P*=0.267; Levene, *P*=0.209	T=-0.64	0.527

Table 5 Pre- and post-treatment latency and amplitude measurements of the P100 wave obtained in 1.0°, 15 arc min pattern according to the pattern VEP records

VEP	Groups	Pre-treatment	Post-treatment	Z[1], *P*
P100 Latency 1.0°	Patching	113±6.7ms	106±7.8ms	Z=- 5.22, *P*=0.00
	Penalization	113.4±7.3ms	107±4.9ms	Z= -3.61, *P*=0.00
	Z[1], *P*	Z=-0.378, *P*=0.706	Z=-0.85, *P*=0.390	
P100 Latency 15'	Patching	119±9.5ms	109±7.01ms	Z=-4.62, *P*=0.00
	Penalization	123.3±8.2ms	113±6.6ms	Z=-4.12, *P*=0.00
	Z[1], *P*	Z=-2.33, *P*=0.020	Z=-2.29, *P*=0.022	
P100 AMP 1.0°	Patching	4±3.7 μV	12±3.7 μV	Z=-5.38, *P*=0.00
	Penalization	2.8±1.5 μV	11±4.1 μV	Z=-4.32, *P*=0.00
	Z[1], *P*	Z=-1.24 *P*=0.214	Z=-1.20, *P*=0.229	
P100 AMP 15'	Patching	5±3.8 μV	12±4.3 μV	Z=-5.32, *P*=0.00
	Penalization	3.1±2.1 μV	12±4.9 μV	Z=-4.34, *P*=0.00
	Z[1], *P*	Z=-1.84, *P*=0.065	Z=-0.34, *P*=0.727	

[1]Mann-Whitney *U* test.

measurements of the P100 wave obtained at 1.0°, 15 arc min pattern were longer than the reference values in 54 amblyopic eyes. However, the amplitude measurements were observed smaller. The post-treatment latency values of the P100 wave obtained at 1.0° , 15 arc min pattern were significantly decreased and the amplitudes were significantly increased in both the patching and the penalization groups (P<0.05).

Table 5 shows pre- and post-treatment latency and amplitude measurements of the P100 wave obtained in 1.0°, 15 arc min of the pattern VEP records.

The post-treatment latency values of the P100 wave obtained at 1.0° , 15 arc min pattern were within normal ranges compared to the reference values in all patients. However, the post-treatment amplitude measurements in 10 eyes treated *via* patching and 6 eyes treated *via* penalization were under normal ranges despite the increase of visual acuity.

Pearson and Spearman's correlation analysis was used to compare to determine the relationship of two continuous variables. In patching group, there was high correlation between visual acuity and latency or amplitude both pre and post- treatment (Figures 3, 4). In penalization group, there was no correlation between visual acuity and latency or amplitude neither pre nor post- treatment (Figures 5, 6).

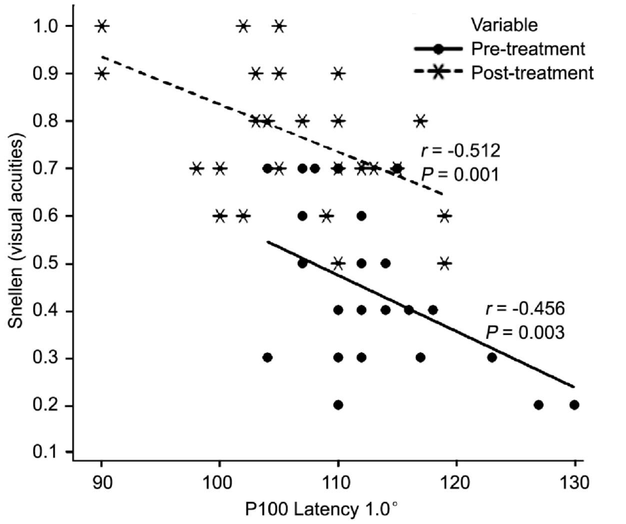

Figure 3 Pearson correaltion analysis of visual acuity and latency in patching group.

DISCUSSION

Amblyopia causes a higher extent of visual errors than all other eye disorders in the <45 age group [11]. This emphasizes the importance of the treatment in amblyopia. Patching and penalization therapies are widely used methods for the treatment of amblyopia, both in the past and at present. In our study we discussed the results of amplyopia patients between 7 to 16y after at least 6mo patching or penalization treatment. Increase of visual acuity and improvement in VEP test were observed in both groups. Therefore, it concluded that patching and penalization treatments were effective for amplyopia patients over critical age of 7y.

Penalization is based on blurring the sound eye in order to force the amblyopic eye to fixate. In randomized trials conducted by Pediatric Eye Disease Investigator Group (PEDIG) regarding the dosage of the atropine, one drop of 1% atropine daily was compared to its use only in the weekends in moderate amblyopia and similar benefits were observed in both groups [12]. Hainline *et al* [13] studied 133

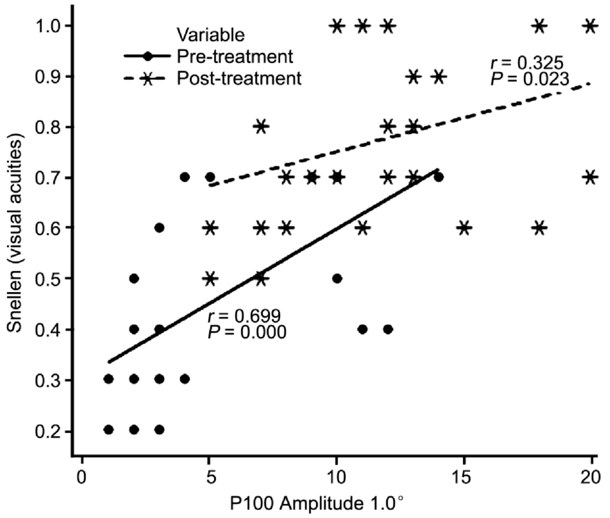

Figure 4 Pearson and Spearman´s correaltion analysis of visual acuity and amplitude in patching group *r* =0.325 Pearson correlation coefficient; *r* =0.699 Spearman's correlation coefficient.

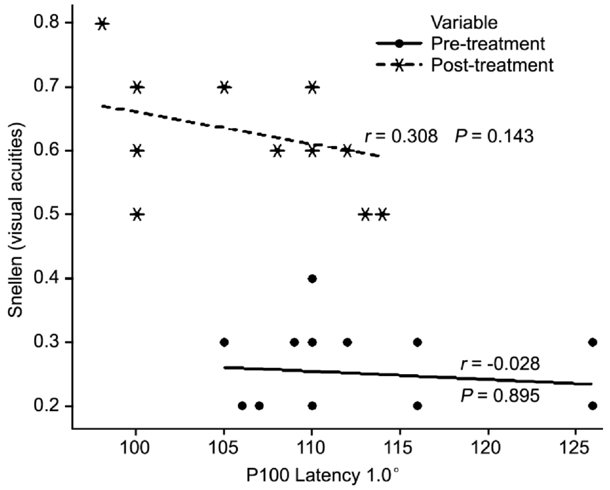

Figure 5 Spearman´s correaltion analysis of visual acuity and latency in penalization group.

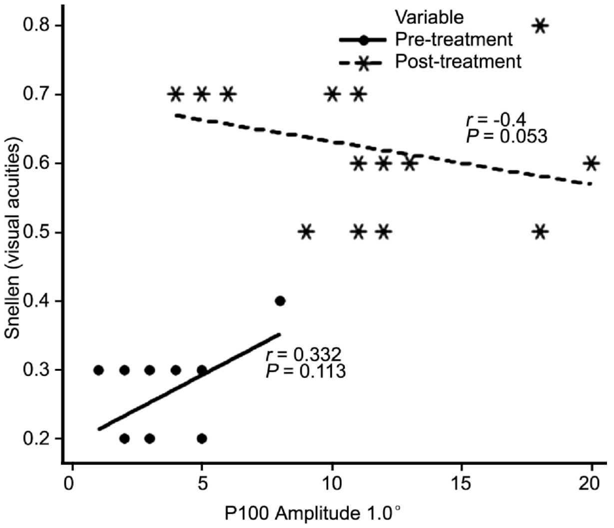

Figure 6 Spearman´ correaltion analysis of visual acuity and amplitude in penalization group.

patients with amblyopia who were treated with only atropine penalization or occlusion or a combination of penalization and occlusion. Of 133 patients, 8 developed reverse amblyopia. All of them were successfully treated, with six patients requiring only discontinuation of atropine and two requiring patching for the reverse amblyopia [13]. In the amblyopia treatment study showed that 47 of 204 patients who treated with atropine lost one or more lines of vision in the sound eye after 6mo follow-up. This was largely attributed to the cycloplegic effect of the atropine and incorrect spectacle correction. Follow-up examination was performed in 45 of these 47 patients. Visual acuity had returned to baseline in 40 patients while five patients had a residual decrease of one line. Only one patient required active treatment for decreased visual acuity[14]. It was reported in the study of PEDIG that reverse amblyopia was observed in only one of 372 eyes [15]. Reverse amblyopia was also observed in one of our patients in the penalization group. The visual acuity of this patient was improved by an alternate patching treatment after 3wk resting period.

Similar to other studies, the patching period was determined as 2h daily and atropine was administered once on weekdays and once during the weekend (a total of two doses weekly) in our study [16-18]. The maximum period for the response to the patching therapy has been reported as 6mo in many studies [15,19]. Therefore, we included the patients who had received treatment for an average of 6mo in our study.

In the study of PEDIG, 419 children aged between 3 and 5y, the efficacy of atropine drop administration once daily was compared to 6h/d patching treatment, and 6mo later, an improvement of an average of 3 lines was observed in the visual acuity of both groups with a faster improvement in the patching group [15]. It had been considered in profound amblyopia that the vision of the sound eye may not be reduced under the level of the amblyopic eye by the atropine drop; thus, it was not considered as a treatment option. However, according to the results of 2 randomized studies conducted by PEDIG, it was reported that atropine could improve the vision in profound amblyopia as well as patching [19]. In one of the studies of Cochrane Eyes and Vision Group including 525 amblyopic eyes, the improvement of vision acuities was observed by 3.16 lines in the patching group and 2.84 lines in the penalization group at the 6th month and in the second study, the improvement was 1.8 lines for the patching group and 3.4 lines for the penalization group according to the Snellen coequal. It was concluded that the penalization method should be the first option in the treatment of amblyopic patients [20]. In the study of Simons *et al* [21], 75 eyes underwent penalization mono-therapy, 87 eyes underwent patching therapy and subsequent penalization therapy, and 30 eyes underwent part-time patching therapy. No significant difference was observed between the groups with regard to the efficacy of the treatments. In our study, six months after treatment an increase of 3.4 lines was observed in the patching group according to the Snellen coequal, whereas an increase of 3.7

lines was observed in the penalization group (P<0.05). In both groups improvement in visual acuity was observed whereas pre-treatment condition was significantly different in two groups, it could not conclude that visual acuity increased more in one of them.

The pattern VEP is the mostly used VEP in clinical practice. In many studies, it was showed that P100 wave amplitude was increased and latency of P100 was decreased with the increase in visual acuity. VEP may be useful in the follow-up of the visual acuity in cases with amblyopia and in the prediction of the visual acuity that may probably be achieved following the amblyopia treatment[7,22,23]. Similarly, the pattern VEP records of 64 pre-treatment amblyopic eyes were evaluated retrospectively and it was observed that the latency measurements of the P100 wave obtained by 1.0°, 15 arc min pattern stimulus in 54 amblyopic eyes were longer than the reference values and the amplitude values were lower in our study. Following the treatment of amblyopia, the latency of P100 was decreased and the amplitudes were increased. In Pearson correlation analysis, correlation between Pattern VEP records and visual acuity could be showed in patching group although not in penalization group, however improvement in visual acuity and pattern VEP records could be showed in both groups.

In our study we concluded that the patching and the penalization methods, which are the main methods used in the treatment of amblyopia, were also effective in those over 7y of age, which has been accepted as the critical age for the treatment of amblyopia. In both of the treatment methods the latency values were decreased and the amplitude values were increased in the pattern VEP records and improvement in visual acuity could be showed in both groups. In conclusion, there was no difference (P>0.05) between patching and penalization groups as far as the average improvements of visual acuity, latency and amplitude are concerned. It can be concluded that the penalization therapy can be as effective as the patching therapy in the treatment of amblyopia in patients incompliant to patching therapy.

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Conflicts of Interest: Cabi C, None; **Sayman Muslubas IB,** None; **Aydin Oral AY,** None; **Dastan M,** None.

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