A Randomized Controlled Trial for Combined Patching and Atropine versus Patching in the Treatment of Children with Severe Amblyopia

Protocol

Summary

Objectives:

To compare the effectiveness of atropine combined patching therapy and patching therapy in children with severe amblyopia (20/100 or worse) aged 3 to 12 years.

Design:

This is a single center, randomized controlled trial.

Participants:

Children with severe amblyopia (20/100 or worse) aged 3 to 12 years resulting from strabismus, anisometropia, or both.

Inclusion criteria:

1) Age 3 to 12 years old.
2) BCVA of 20/100 or poorer in the worse eye.
3) ≥ 2 lines interocular difference in BCVA.
4) No previous treatment for amblyopia except refractive correction.
5) Amblyopia associated with strabismus, anisometropia, or both.

Exclusion criteria:

1) Ocular causes for reduced visual acuity
2) Myopia
3) History of intraocular surgery
4) Allergic to atropine or other cycloplegics

Research procedure:

The participants are stratified by age (3 to 6 years and 7 to 12 years). Then participants of each stratification are randomly assigned to either atropine combined patching group (AP group) or patching group (P group).

AP group: 1 drop of atropine sulfate 1% eye gel once every two days, and patching for 6 hours per day.

P group: patching for 6 hours per day.

Primary and secondary outcomes:

The primary outcome measure was the change of VA in the amblyopic eye from baseline to 6 months.

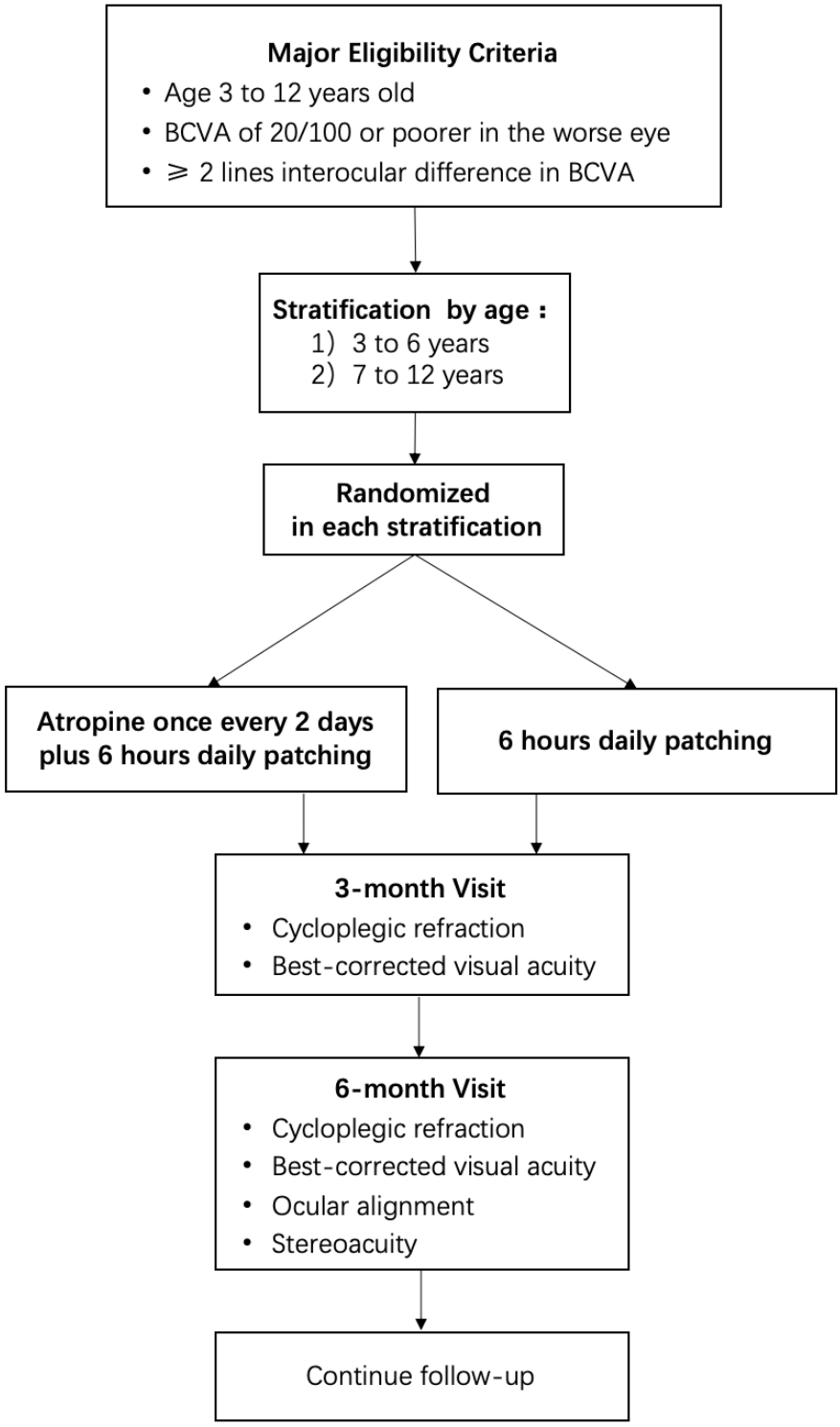
The secondary outcome measures were as follows:

1) the change of VA in the amblyopic eye from baseline to 3 months,
2) the proportions of patients with VA of 20/32 or better in the amblyopic eye at 6 months,
3) the proportions of patients with acuity decrease of 1 line or more in the fellow eye at 6 months.

Plan of follow-up:

	Baseline	3-month Visit	6-month Visit
	-2w~0w	3mon±1w	6mon±1w
Informed consent	√		
Inclusion criteria	√		
Cycloplegic refraction	√	√	√
BCVA	√	√	√
Ocular alignment	√		√
Stereoacuity	√		√

Study Summary Flow Chart



1. Background

Amblyopia is the most common cause of monocular vision impairment in children, young people, and even middle-aged people,[1, 2] with a prevalence rate of 2% to 3%.[2, 3] Without timely and effective treatment, the visual impairment caused by amblyopia will continue for life, not only for patients and their families, but also for the potential heavy burden on public health resources.

In the treatment of non-deprivation amblyopia, proper refractive correction is the first step. The second is to promote use of the amblyopic eye by occluding or blurring the fellow eye,[3] such as patching and atropine 1%. Patching therapy has been the standard treatment for amblyopia since it was proposed in the middle of the 18th century,[4] and it is currently the first choice of most ophthalmologists. [5]

The treatment of severe amblyopia has always been difficult in clinical work. Patients with severe amblyopia (20/100 to 20/400) have very low vision in the amblyopic eye, which is too low for patients to live normally after patching the fellow eye, so they have poor compliance. Therefore, patching therapy is often not effective enough for severe amblyopia.

In recent years, atropine therapy has been supported as an alternative to patching therapy for moderate amblyopia, and has gradually become one of the main methods of amblyopia treatment.[6] Previous studies have shown that the compliance of atropine therapy is better than that of patching therapy. [5, 7] However, although a randomized trial showed weekend atropine was effective to severe amblyopia aged 3 to 6 years old,[8] the blurring effect of atropine was considered to be insufficient to the sound fellow eye of severe amblyopia.[7, 9, 10]

So, could atropine combined with patching therapy improve compliance and promote use of the amblyopic eye, thereby improve the treatment efficiency of patients with severe amblyopia? A randomized study including children aged 7 to 12 years with severe amblyopia showed patients in the treatment group (prescribed patching combined optical correction plus daily atropine sulfate) improved more in VA than patients with optical correction alone.[11] And in our pioneer clinical work, it was found atropine combined patching therapy seemed to be more effective than patching alone in newly diagnosed patients with severe amblyopia.

2. Objectives:

To compare the effectiveness of atropine combined patching therapy and patching therapy in children with severe amblyopia (20/100 or worse) aged 3 to 12 years.

3. Design:

This is a single center, randomized controlled trial.

4. Participants Selection

4.1 Eligibility Assessment and Informed Consent

According to the routine diagnosis procedures, cycloplegic refraction using cyclopentolate hydrochloride 1% and the test of best-corrected visual acuity (BCVA) will be performed on the patients who come to the strabismus and amblyopia clinic of Eye & ENT Hospital of Fudan University, Shanghai, China.

The investigator will communicate with the patients who meet the eligibility criteria and their legal guardians, and the patients who give their informed consent will be included in the study.

4.2 Eligibility criteria

Inclusion criteria:

1) Age 3 to 12 years old.
2) BCVA of 20/100 or poorer in the worse eye.
3) ≥ 2 lines interocular difference in BCVA.
4) No previous treatment for amblyopia except refractive correction, and the correction is less than one month.
5) Amblyopia associated with strabismus, anisometropia, or both.
   a) Strabismic amblyopia：amblyopia in the presence of (1) strabismus at a distance and/or near fixation with/without spectacle correction, or a history of strabismus surgery and (2) refractive error below the criteria for anisometropic amblyopia.
   b) Anisometropic amblyopia：amblyopia in the presence of (1) ≥1.00 D difference in hyperopia or ≥1.50 D difference in astigmatism in any meridian and (2) without strabismus at a distance and near fixation.
   c) Mixed amblyopia: amblyopia in the presence of (1) strabismus at a distance and/or near fixation with/without spectacle correction, or a history of strabismus surgery and (2) anisometropia of ≥1.00 D difference in hyperopia or ≥1.50 D difference in astigmatism in any meridian.

Exclusion criteria:

1) Ocular causes for reduced visual acuity
2) Myopia
3) History of intraocular surgery
4) Allergic to atropine or other cycloplegics

4.3 Enrollment Examination Procedures

Ocular alignment, stereoacuity and ocular examination are examined. Ocular alignment is assessed using the simultaneous prism and cover test and the prism and alternate cover test; stereoacuity is assessed with the Titmus Stereo Test (Stereo Optical Co., Inc.). Ocular examination is performed to rule out any cause for reduced visual acuity other than amblyopia. All the examinations should be completed within 14 days before the randomization.

5. Randomization and Masking

The participants are stratified by age (3 to 6 years and 7 to 12 years). Then participants of each stratification are randomly assigned to either atropine combined patching group (AP group) or patching group (P group). The two randomization sequences will be generated in a 1:1 ratio by producing the unique random–number list using SPSS software (version 20).

Because the pupil of patients in the AP group will be dilated due to atropine, patients and their parents/guardians could not be masked to the treatment. In order to reduce the bias of outcome measurement as much as possible, the vision examiner will be masked to treatment group (see 7.2.1).

6. Treatment

6.1 Optical Correction

All of the participants are given optical correction (if needed). Patients can continue to wear the original spectacles if their spectacles meet the follow requirements. Otherwise, glasses need to be replaced.

• For patients with accommodative esotropia

1) hyperopia should be full corrected according to the cycloplegic refraction using atropine 1%.

2) astigmatism should be within 0.50 D of fully corrected.

3) anisometropia (spherical equivalent) should be within 0.50 D of fully corrected.

• For other patients

1) hyperopia should not be undercorrected by more than +2.0 D spherical equivalent.

2) astigmatism should be within 0.50 D of fully corrected.

3) anisometropia (spherical equivalent) should be within 0.50 D of fully corrected.

6.2 Patching and Atropine

• AP group: 1 drop of atropine sulfate 1% eye gel (Shenyang Xingqi Pharmaceutical Co.,Ltd.) once a day for the first 3 days and then once every two days, and patching for 6 hours per day.

The investigator decided to use atropine at this frequency based on our clinical experience. We had tried daily patching plus atropine 1% on two consecutive days per week for children with **severe amblyopia**, on the evidence that weekend atropine without patching was as effective as once daily atropine 1% for **moderate amblyopia**. But, based on a rough estimation, it seemed that patching plus weekend atropine was not more effective than patching alone for severe amblyopia. Therefore, we changed to use atropine 1% once a day for 3 days to achieve full cycloplegia and then once every 2 days to see whether it will work.

Parents were noted to wear sunglasses or hat for children outdoor to avoid the sunlight exposure.

• P group: patching for 6 hours per day.

For the patching regimen in both groups, we emphasized to parents that the patching time should be continuous and patching after kindergarten would be better since children might not like being different from others in kindergarten. If it is less than 6 hours of the after kindergarten time on workday, an alternative of patching for 4 hours on workday and 11 hours on weekend is provided.

The study will provide adhesive skin patches (Guangzhou Kanweila Heathcare Co.,Ltd). Children allergic to the eye patch will use a cloth patch mounted on the eyeglass frame.

If BCVA in the amblyopic eye improved to be equal to or only 1 line worse than that in the fellow eye at the 3-month visit, patching time would be decreased to 2 hours per day and atropine would be reduced to 2 times a week. If BCVA in the amblyopic eye became better than that in the fellow eye or reverse amblyopia occurred in the fellow eye, it would be judged by the investigator whether the treatment should be continued, reduced or stopped.

6.3 Near Activities

Patients in both groups are also instructed to do near-visual activities for at least 1 hour during the patching time, such as Written homework, reading, painting and video games.

6.4 Home Record of the treatment

Parents are asked to record the number of hours of patching in both groups and to record the day of using atropine in the AP group.

7. Follow-up Procedure

7.1 The plan of follow-up is listed in Table 1.

Table 1.

	Baseline	3-month Visit	6-month Visit
	-2w~0w	3mon±1w	6mon±1w
Informed consent	√		

Inclusion criteria	√		
Cycloplegic refraction	√	√	√
BCVA	√	√	√
Ocular alignment	√		√
Stereoacuity	√		√

7.2 Testing Procedures

7.2.1 Best-corrected Visual Acuity

At each visit, BCVA with a cycloplegic refraction was measured in both eyes using the Standard Logarithm Visual Acuity Chart (E optotype).

The vision examiner will be masked to treatment group, for the children are mydriatic when they meet the examiner.

• For children in the AP group, the fellow eye will be tested with full cycloplegic correction in the use of atropine. The amblyopic eye will be tested with full cycloplegic correction using cyclopentolate hydrochloride 1%.

• For children in the P group, both eyes will be full cycloplegic correction using cyclopentolate hydrochloride 1%.

7.2.2 Ocular Alignment and Stereoacuity

At the 6-month visit, ocular alignment and stereoacuity are measured in the P group and at a second visit after discontinuance of atropine for 2 weeks in the AP group.

7.3 Follow-up after 6 months

Since severe amblyopia often cannot be cured for 6 months, the plan of treatment and follow-up depend on the 6-month VA of each patient.

• For patients whose VA becomes equal in both eyes, amblyopia treatment will be stopped and the refraction correction is continued. We advise a visit after 3 months to check whether there is any decrease in the amblyopic-eye VA.

• For patients who are not cured, the hours of patching time and the frequency of atropine will be decided by the investigator according to the 6-month VA. The treatment will last until VA becomes equal in both eyes or the VA in the amblyopic eye does not improve for 6 months.

8. Adverse Events and Side Effects

8.1 Adverse Events

Comparing to amblyopic patients who do not participate in this study, there was no additional risk.

8.2 Side Effects of Atropine

Atropine 1% could cause photosensitivity and conjunctival irritation. Adverse systemic effects include dryness of the mouth and skin, fever, fever, flushing, and tachycardia.

To minimize the risks, parents are advised as follows:

• Applying direct digital pressure over the lacrimal sac and puncta for 20 to 30 seconds to reduce systemic absorption and toxicity.

• Wear sunglasses and/or a hat for the children.

If atropine should be discontinued due to serious side effects, the patient can use homatropine 5% instead.

8.3 Side Effects of Patching

Patching could cause skin irritation. Children allergic to the eye patch would switch to use a cloth patch mounted on the eyeglass frame.

8.4 Reverse Amblyopia

It has been reported transient reduction of visual acuity in the fellow eye due to patching or atropine. The investigator will pay attention to VA in the fellow eye of participants. For the participant whose VA in the fellow eye decreased 1 line or more from the baseline, the VA would be tested again, and whether to continue, reduce or stop the treatment was at senior investigator discretion. The subsequent follow-up data of VA in the fellow eye were used to evaluate whether the reduction was permanent or not.

8.5 Development of Strabismus or Diplopia

Parent/guardian is advised to have their child see the investigator if the child develops an ocular deviation or the preexisting squint angle increases obviously. If the deviation is confirmed, whether to continue or discontinue the treatment will base on the opinions of investigator and parent.

According to our clinical experience, there are few cases of diplopia developed during the amblyopia treatment in children younger than 12 years old, and the diplopia usually disappear soon.

9. Primary and Secondary Outcomes

The primary outcome measure was the change of VA in the amblyopic eye from baseline to 6 months.

The secondary outcome measures were as follows:

1) the change of VA in the amblyopic eye from baseline to 3 months,

2) the proportions of patients with VA of 20/32 or better in the amblyopic eye at 6 months,

3) the proportions of patients with acuity decrease of 1 line or more in the fellow eye at 6 months.

10. Sample Size Estimation and Statistical Analysis

10.1 Sample Size

On the basis of a prior study,[12] a sample size of 100 participants was estimated and would have 80% power and a type I error of 5% to detect a difference between groups of 0.15 logMAR in 6-month mean VA change, under the assumption of a standard deviation (SD) of 0.25 logMAR in VA change and 10% loss to follow-up. The sample size was calculated using G*Power software (version 3.1).

10.2 Data analysis

An intention-to-treat analysis are performed to evaluate the effect of two treatments on VA. The mean difference and relative risk (RR) with a 2-sided 95% confidence interval (CI) are estimated for primary and secondary outcomes using the univariate linear regression and univariate logistic regression.

The outcomes based on per-protocol analysis are adjusted for age, sex, and cause of amblyopia using multivariate linear regression and multivariate logistic regression.

Comparison between groups was performed using the independent sample t test, Wilcoxon rank-sum test, Pearson chi-square test or Fisher exact test as appropriate. A change of 0.1 logMAR values was equivalent to a change of 1 line in VA.

All analyses are performed using the open source R statistical software (R Foundation, Vienna, Austria). Statistical significance is defined as $P < 0.05$ with 2-sided testing.

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