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Meta-Analysis

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The Influence of Part-Time Occlusion Therapy on Control of Intermittent Exotropia: A Meta-Analysis of Randomized Controlled Trials

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Keywords
Intermittent exotropia · Part-time occlusion therapy · Meta-analysis

Abstract

Background: Intermittent exotropia is the most prevalent subtype of exotropia in children. Part-time occlusion (PTO) as an anti-suppression therapy was applied for nonsurgical management of intermittent exotropia. ***Objective:*** The aim of the study was to compare the effectiveness of PTO therapy and observation in the treatment of intermittent exotropia. ***Method:*** An exhaustive search of the literature from PubMed, Embase, Web of Science, and Cochrane Library databases was carried out until July 2022. No language restrictions were applied. The literature was rigorously screened against eligibility criteria. Weighted mean differences and 95% confidence interval (CI) were calculated. ***Results:*** A total of 4 articles with 617 participants were included in this meta-analysis. Our pooled results showed that PTO exhibited superior effects compared to observation, with greater decrease in exotropia control at distance and near (MD = −0.38, 95% CI: −0.57 to −0.20, $p < 0.001$; MD = −0.36, 95% CI: −0.54 to −0.18, $p < 0.001$); patients subjected to PTO therapy had greater decrease in distance deviations (MD = −1.95, 95% CI: −3.13 to −0.76, $p = 0.001$), and there was greater improvement in near stereoacuity among the PTO group in comparison with the observation group ($p < 0.001$). ***Conclusions:*** The present meta-analysis indicated that PTO therapy showed a better effect in improving control and near stereopsis and decreasing distance exodeviation angle of children with intermittent exotropia in comparison with observation.

Introduction

Intermittent exotropia (IXT) is a relatively common childhood strabismus worldwide, affecting 0.5–1% of the general population [1, 2]. Patients with this condition commonly present with an outward deviation of one or both eyes when fatigue, poor concentration, or fixating the far objects.

A whole range of treatment options is available, including watchful waiting, occlusion therapy, overminus lens therapy, orthoptic exercises, and surgery. However, surgery still carries risks, such as recurrence and overcorrection, especially overcorrection which may adversely

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affect stereopsis, and in addition, there is no consensus on the optimal timing of surgery [3].

Part-time occlusion (PTO) therapy is sometimes administered to prevent IXT from deteriorating, which has not been widely accepted by physicians because of the uncertainty of its therapeutic effects. For example, Brian G. Mohney found that deterioration over 6 months was uncommon in children aged 12–35 months with and without occlusion therapy for IXT that had not been previously treated with occlusion therapy [4]. Mohammad Reza Akbari noted that, compared with observations, PTO appeared to be effective in improving deviation control in 3- to 8-year-old children with IXT based on two common office-based control scales [5].

Recently, several randomized controlled trials (RCTs) have directly compared PTO with observation (watchful waiting), with mixed results [4–7]. A meta-analysis is necessary to better understand the effectiveness of occlusion therapy in the treatment of IXT.

This follow-up meta-analysis was aimed to assess the overall efficacy of PTO therapy in slowing the progression of IXT in children, and the change in deviation control at distance was chosen as the first outcome measure. To exclude the effect of confounding factors, only high-quality RCTs were included in this meta-analysis.

Materials and Methods

Search Strategy

This meta-analysis was based on Cochrane review methods. Two researchers (D.S.S. and J.Q.) independently searched the following electronic databases and screened relevant literature up to July 2022: Web of Science, MEDLINE, Embase, and the Cochrane Register of Controlled Trials databases. The searched keywords were as follows: "patch*, "occlu*," "therapy," "treatment outcome," "exotropia," "exodeviation," "divergent strabismus," "external strabismus," and "divergent squint." The search language was not limited to English, and for non-English articles, English abstracts were used. Furthermore, references to all searched articles were also manually searched for any additional relevant publications.

Study Inclusion and Exclusion Criteria

These controlled studies met the following inclusion criteria: (1) indicators of treatment outcome included exotropia control change at distance or at near; (2) subjects in the trials had IXT with no prior history of surgical or nonsurgical treatment other than refractive correction; (3) comparative studies of PTO therapy and observation; (4) studies with a follow-up period of at least 4 months; and (5) the type of study included was an RCT. Exclusion criteria were letters, correspondence, and reviews as well as unpublished articles (e.g., conference abstracts), case reports, or case series without a control group.

Study Selection and Data Extraction

The literaturestudies were independently retrieved and screened by two investigators, D.S. Song and J. Qian. The two researchers extracted the data provided in the articles using a literature data extraction table.

If any disagreement was encountered, the third author (Z.J. Chen) decided on the disagreement. Information from included literatures was extracted as follows: first author, publication year, length of follow-up, type of intervention, distance control at baseline, sample size, and OML power/occlusion strategy. Statistical analysis was carried out by using data from the last visit. This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Quality Assessment

The quality of the RCTs was evaluated using the Cochrane evidence-based medicine system [8]. The quality assessment for each trial included five domains: election bias (randomization order generation, allocation hiding); implementation bias (blind method); measurement bias (blind method in outcome evaluation); loss to follow-up bias (incompletely resolved data); publication bias (selective reporting of research results); and other biases.

Definitions and Data Processing

The control score in 6-point scale ranges between 0 and 5; the patient was observed for 30 s during fixation on an object. Constant deviation was scored 5, deviation remained more than 50% of this period was scored 4, and deviation remained less than 50% was scored 3. If deviation did not appear in 30 s of observation, the rest of classification was done according to how fast the fusion was reestablished after covering the eye for 10 s.

Stereopsis became a continuous variable by converting the seconds of arc scores to log arc/s values, for example, 40 (1.60), 50 (1.70), 60 (1.78), 80 (1.90), 100 (2.00), and 200 (2.30). Stereopsis threshold doubled (e.g., 100–200 arc/s) with 0.3 change in log-transformed value. The value of 1,600 (3.20) was considered for cases with undetectable stereoacuity.

Statistical Analysis

Statistical analysis was conducted using Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Weighted mean differences (WMDs) and 95% confidence interval were calculated. Heterogeneity between studies was assessed using I^2 and Q tests [9], and the fixed-effect model was performed when $p > 0.05$ or $I^2 < 50\%$; otherwise, the random-effect model was employed. Pooled results with a p value <0.05 were considered statistically significant.

Result

Search Results and Study Characteristics

The flow chart of our work is shown in Figure 1. Through an electronic literature search, it was found that three hundred and sixty studies were identified. After screening, four RCT studies met the inclusion criteria. A total of 617 patients were analyzed: 304 in the PTO group and 313 in the observation group. A summary of these included studies is

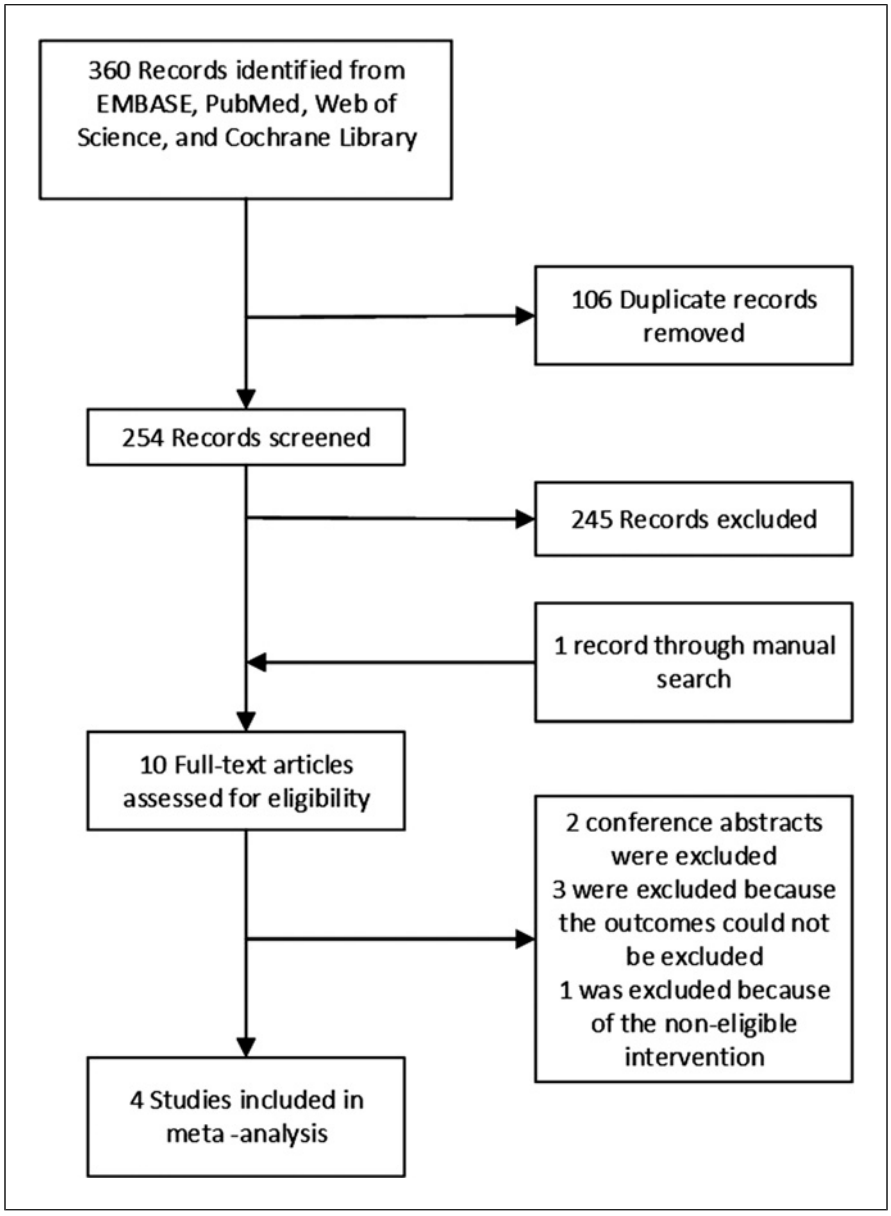

Fig. 1. Flow chart of the literature search and study selection. RCTs, randomized controlled trials.

shown in Table 1. Two authors independently assessed the risk of bias in each included study (Fig. 2).

A summary of the studies included is shown in Table 1. Akbari et al. [5] evaluated the effectiveness of PTO therapy on control of IXT in 76 children aged 3–8 years with a follow-up of 6 months. They revealed the efficiency of PTO therapy in improving deviation control in comparison with observation. Abdelfatah et al. carried out a study covering 60 children with IXT, from 2 to 10 years of age, which compared the PTO versus observation on short-term effectiveness in improving the control of IXT [7]. Significant improvement was revealed in distance exotropia control but not in near exotropia control and distance exodeviation after 4 months PTO therapy. Pediatric Eye Disease Investigator Group (2014) conducted this comparison in children with IXT aged from 3 to 10 years and concluded that although deterioration in the patch-prescribed group was slightly lower than in the observation group (difference = 5.4%, p value = 0.004), the rate of deterioration of untreated IXT regardless of use of patch therapy or simply observation was infrequent over 6 months [6]. Deviation control was not included in their deterioration criteria.

Table 1. Characteristics of the studies included in the meta-analysis

Study	Follow-up	Age, years	Intervention	Control score	Subjects	Occlusion strategy
Abdelfatah et al. [7] 2018	≥4 months	4.68±2.55	PTO	PTO 3.95±1.10 OBS 3.05±1.10	PTO 15 OBS 25	Alternately patched 4 h daily
Akbari et al. [5] 2020	6 months	PTO 5.34±1.26 OBS 4.68±1.33	PTO	PTO 2.8±1.1 OBS 2.6±1.1	PTO 35 OBS 41	Alternately patched 2 h daily, in the presence of significant dominancy, the dominant eye patched 5 days a week and other eye patched 2 days a week
PEDIG et al. [4] 2015	6 months	PTO 5.24.9 (6.8) OBS 24.2 (6.5)	PTO	PTO 2.3 (1.1) OBS 2.5 (1.2)	BMR 87 BTX 90	3 h daily for 5 months, with a 1-month washout period of no patching
PEDIG et al. [6] 2014	>6 months	PTO 5.9 (2.0) OBS 6.1 (2.0)	PTO	PTO 2.3 (1.2) OBS 2.4 (1.2)	PTO 159 OBS 165	3 h daily for 5 months, with a 1-month washout period of no patching

Control score, control score of IXT ranges between 0 and 5 based on the proportion of time the deviation is manifest over the 30-s observation period prior to dissociation and recovery of fusion after dissociation. PEDIG, Pediatric Eye Disease Investigator Group; PTO, part-time occlusion; OBS, observation.

Fig. 2. Risk of bias assessment (green = low risk of bias, red = high risk of bias).

Nevertheless, their secondary outcome displayed the significant improvement in near exotropia control and distance exodeviation obtained in the PTO group compared to the observation group, while the treatment groups were not different with respect to 6-month control at distance, exodeviation at near, or stereoacuity at near. PEDIG (2015) conducted another randomized clinical trial to evaluate the effectiveness of PTO for treating IXT [4], in which participants aged from 12 to 35 months were randomly assigned to the PTO therapy group (3 h daily for 5 months, followed by 1 month of no patching) or to the observation group. After 6 months of treatment, deterioration occurred in 4.6% (4 of 87) of the participants in the observation group and 2.2% (2 of 90) of the participants in the patching group (difference, 2.4%; $p = 0.27$); deterioration rate did not differ between both groups. Their secondary outcome found that alternative occlusion therapy could improve exotropia control ability and reduce the angle of exodeviation at distance but not at near.

Change in Exotropia Control at Distance

All included studies reported changes in distance control of exotropia. The pooled data showed that the decrease of control score was significantly greater in the PTO group than in the observation group (MD = −0.38, 95% CI: −0.57

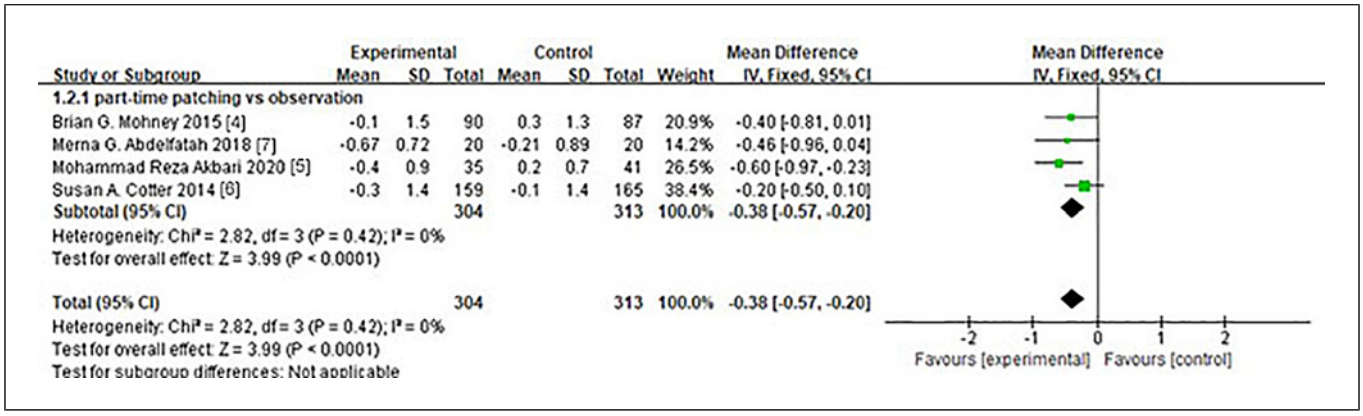

Fig. 3. Forest plot demonstrating the effect of PTO and observation on the change of exodeviation control at distance. CI, confidence interval.

to −0.20, $p < 0.001$). There was no significant heterogeneity among these studies ($p = 0.42$, $I^2 = 0\%$) (Fig. 3).

Change in Exotropia Control Near

Three studies reported changes in exotropia control at near between PTO and observation groups. The WMD in changes of exotropia control at near between the 2 groups was −0.36 (95% CI: −0.54 to −0.18, $p < 0.001$). The results of the test for heterogeneity showed no obvious between-study heterogeneity in the included trials ($p = 0.13$, $I^2 = 51\%$) (Fig. 4).

Change in Deviation Magnitude at Distance and Near

Three studies addressed changes in the magnitude of exodeviation angles at distance and near. Pooled results showed that for IXT, PTO was more effective in reducing distance and near angles compared with observation (MD = −1.95, 95% CI: −3.13 to −0.76, $p = 0.001$ at distance; MD = −1.30, 95% CI: −2.82 to 0.21, $p = 0.09$ at near), as shown in Figure 5. There was no significant between-study heterogeneity in deviation magnitude changes at distance and at near ($p = 0.78$, $I^2 = 0\%$; $p = 0.70$, $I^2 = 0\%$).

Change in Stereopsis Near

The stereopsis change at near was reported by 2 studies. The combined results revealed a WMD of −0.05, 95% CI (−0.07, −0.03, $p < 0.001$); the PTO group showed a greater improvement in stereopsis at near, as shown in Figure 6. No statistical heterogeneity was found between the 2 groups ($p = 0.75$, $I^2 = 0\%$) (Fig. 6).

Discussion

An analysis was conducted to examine the impact of PTO on IXT. Four published RCTs were included in this analysis. The pooled results showed that PTO treatment demonstrated higher outcomes compared to observation, with greater reductions in exotropia control scores at both distance and near, exodeviation angle at distance, and stereopsis at near.

Surgery is the most common treatment modality for IXT as it is directly effective in reducing the exotropia angle and promoting motor control; however, surgery still carries risks. The advantages of PTO treatments include no significant side effects and ease of performance. At the same time, there are some concerns with PTO therapy, such as a significant psychological burden on the family [8], skin irritation in patients with sensitive skin [6], and unsatisfactory treatment results. In addition, it does not result in a significant reduction in exotropia deviation. Therefore, the clinical application of PTO is indeed limited in this way. By control, it is meant the frequency of manifest deviations and the ease of readjustment. In the last few years, there have been many reports exploring the impact of PTO on control, with mixed results. In our meta-analysis, patients with IXT benefited more from PTO therapy.

PTO has been used as an anti-suppression treatment for the nonsurgical management of IXT with variable efficacy. Akbari et al. [5] found that patching therapy resulted in significant improvements in distance deviation control by using a 3-point system (the deviation control was classified as good, fair, and poor) and in near deviation control by using a 6-point system (the deviation control was classified into six grades according to the proportion of deviation time to total observation period and how fast the fusion was reestablished); no significant improvement was observed in near control according to the 3-point scale. They also observed a significant improvement in near stereopsis [10]. An RCT including 358 untreated patients aged 3–11 years with IXT showed that after 6 months, the patching therapy was slightly better than observed in terms

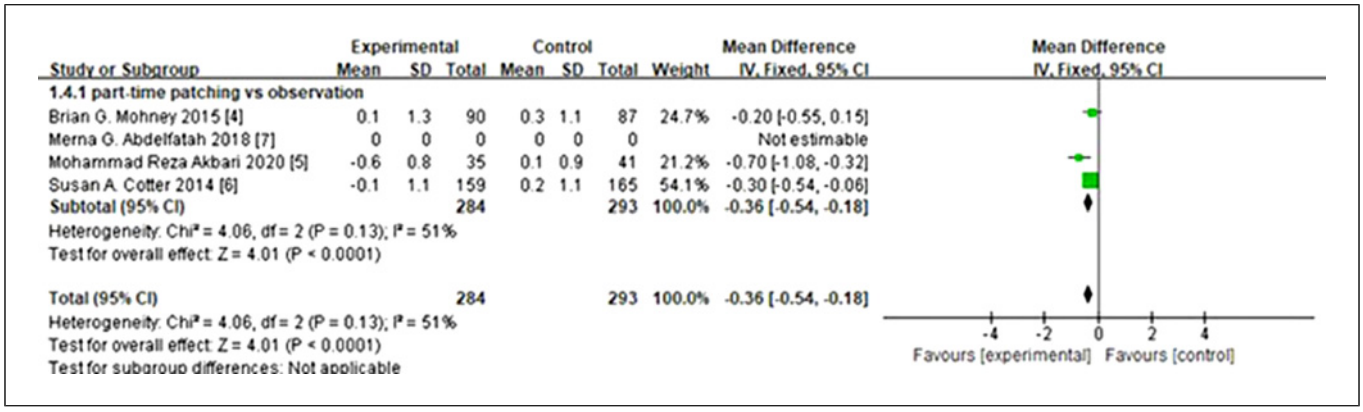

Fig. 4. Forest plot demonstrating the effect of PTO and observation on the change of exodeviation control at near. CI, confidence interval.

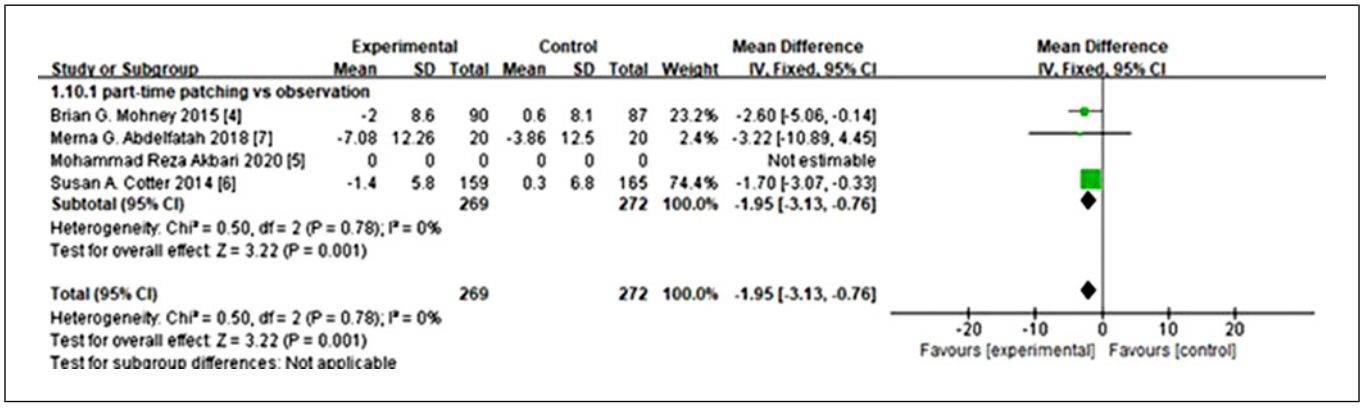

Fig. 5. Forest plot demonstrating the effect of PTO and observation on the change of exodeviation angle at distance. CI, confidence interval.

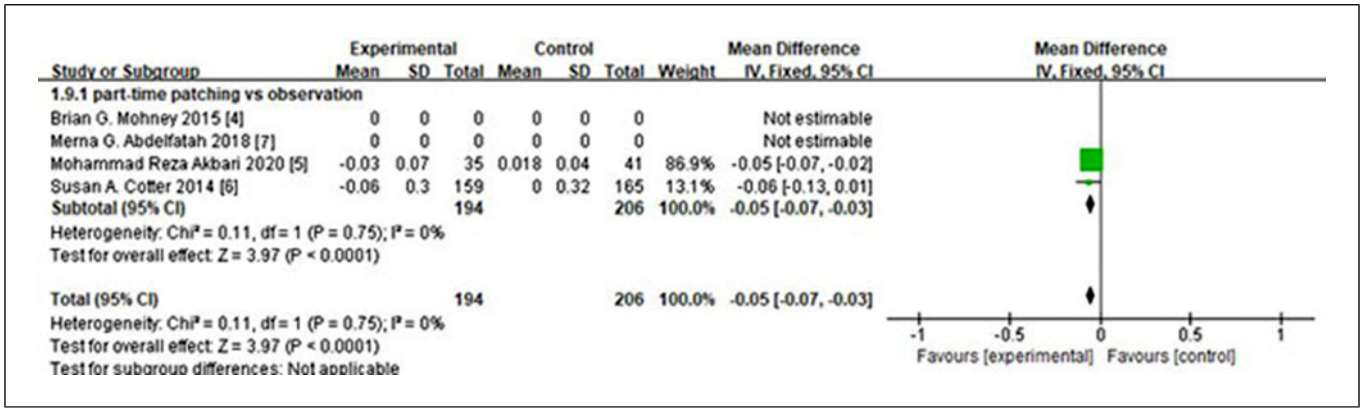

Fig. 6. Forest plot demonstrating the effect of PTO and observation on the change of stereopsis at near. CI, confidence interval.

of control scores in the near, and this difference was also found in terms of control in the distance; however, it did not reach statistical significance. In addition, they did not observe a significant improvement in near stereopsis [6]. Alkahmous et al. [11] evaluated the effect of occlusion treatment in 21 patients with IXT aged 4–10 years. Using a 6-point scale, they found that 77.7% of occlusion treatment cases were successful in distance deviation control and

100% were successful in near deviation control. However, the occlusion treatment did not significantly reduce exodeviation angle. On the other hand, Brian G. Mohney found that deterioration beyond 6 months was uncommon in children between 12 and 35 months of age, with or without occlusion treatment [4]. Our meta-analysis found that PTO was effective in reducing deviation control score at near and distance, reducing angle of exodeviation at distance, and improving stereoacuity at near, whereas PTO could not reduce angle of exodeviation at near.

A meta-analysis of this issue was conducted by Pang et al. [3] who found that PTO achieved better treatment outcomes in terms of near and distant alignment compared to observation, with no evidence that PTO or observation was superior in terms of near stereoacuity. Several controversial aspects of this meta-analysis are worth noting, including the small number of studies (only 2 studies) and cases, the lack of assessment of bias control, and the comparison of only posttreatment distance alignment, near alignment, and near stereopsis, which may have been influenced by baseline values. Four RCTs were included in our meta-analysis. In addition, we systematically compared changes in deviation control at distance and near, changes in exodeviation angle at distance and near, and changes in near stereoacuity.

In our meta-analysis, change in control was selected as the primary measure of treatment outcome. Based on previous studies, PTO treatment appears to be less effective in reducing the exodeviation angle. Sometimes the amount of change in the angle of deviation reaches statistical significance, but its clinical importance remains unclear due to the relatively small amount of reduction. PTO treatment aims to stimulate motor fusion by eliminating or preventing suppression, and enhancing the amplitudes of fusional vergence helps reduce the frequency of exotropia. From this perspective, control is a more appropriate marker for predicting efficacy. On the other hand, if control scores, angle of exodeviation, and stereopsis at the last visit are chosen as the main comparators, results may be influenced by baseline values. For example, in Abdelfatah's study, baseline control scores were much lower in the observation group than in the PTO group, which directly led to lower posttreatment control scores in the observation group than in the PTO group; however, the latter was superior to the former in terms of the amount of change in control [7]. Ultimately, the change in deviation control at distance and near, the change in the angle of exodeviation at distance and near, and the change in stereoacuity at near were chosen as the main indicators of comparison in our meta-analysis.

Most previous studies about effects of patching on IXT were heterogeneous in patching regimen (varying from 2 h a day to all waking hours). In our meta-analysis, the occlusion dosage was 2 h daily in Akbari's study [5], 4 h daily in Abdelfatah's study [7], and 3 h daily in two other studies by PEDIG [4, 6]. Based on the forest plot, no clear differences in clinical effect were seen between the three occlusion strategies. It is possible that patching for more hours daily may have different results. Some authors have had a degree of success with 6 h daily [11]; it is incredibly difficult for us to identify whether a dose-response relationship exists for occlusion due to the limited number of literatures conforming to the inclusion criteria. More high-quality studies are required to explore the relationship between the patching time and the therapeutic effect gained in order to standardize treatment protocols.

In our current study, there are several flaws and shortcomings. First, even though the sample size here is the largest and the quality of the included literature is the highest, the limited number of subjects included in this meta-analysis may have contributed to some degree of selection bias and information bias. In addition, the different occlusion strategies in the included studies may have contributed to bias. Second, given the limited data from the included studies, our meta-analysis focused on clinical outcomes at the last follow-up rather than data collected at early, midterm, and long-term follow-ups, which may have had an impact on the current results. More detailed analyses (e.g., further subgroup analyses by follow-up period) would be required to address potential biases if sufficient clinical data were available. Finally, the included studies used different classes of deviation control scale, which may have contributed to clinical heterogeneity.

In conclusion, the results of this meta-analysis suggest that PTO treatment resulted in a greater decrease in near and distance exodeviation control and distance exodeviation angles in patients with IXT. Our findings also provide clear evidence that PTO therapy is superior to observation in improving stereopsis at near. Clearly, many issues require further research, for example, lack of a uniform occlusion strategy. In our meta-analysis, four studies focused on a comparison of PTO and observation, using three different occlusion strategies, which may increase clinical heterogeneity. Specifically, more studies should be conducted to explore whether the benefit of PTO treatment is stable after treatment termination, the relationship between compliance and treatment outcome, and the effect of increasing occlusion duration on outcomes.

Statement of Ethics

An ethics statement was not required for this study type as it is based exclusively on published literature.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Desheng Song and Zhijun Chen conceived the study. Jing Qian designed and performed the searches. Desheng Song and Jing Qian conducted data extraction, appraisal, and synthesis and wrote the manuscript. Qing Zhou contributed to revising and editing this manuscript. Juan Chen and Mengting Yang helped revise the manuscript. All authors participated in discussions about eligibility and quality of the included studies and critically reviewed and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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