Systematic Review and Meta-Analysis

Medicine

OPEN

Binocular treatment for individual with amblyopia

A systematic review and meta-analysis

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Abstract

Objective: To assess the efficacy of binocular treatment for individual with amblyopia.

Methods: In this meta-analysis, a comprehensive search of literatures was performed from PubMed, Embase, Cochrane Library and Web of Science databases up to December 21, 2020. Sensitivity analysis was performed for all outcomes. The Begg's test was used to assess the publication bias. Heterogeneity test was conducted for each effect indicator. Indicators were analyzed by random-effects model when the heterogeneity statistic I2 ≥ 50%, on the contrary, indicators were analyzed by fixed-effect model. Standard mean difference (SMD) or weighted mean difference (WMD) was adopted as effect indicators, and the effect amount was expressed as 95% confidence intervals (CIs).

Results: A total of 13 literatures including 1146 participants were finally enrolled, with 595 in the intervention group and 551 in the control group. The results indicated that the improvement of amblyopic eye visual acuity [SMD: 0.882, 95%CI: (0.152, 1.613), $P = 0.018$] in binocular treatment group was better than that in control group. And binocular treatment could improve stereo acuity in individual with amblyopia [WMD: 0.138, 95%CI: (0.068, 0.208), $P < 0.001$].

Conclusion: Binocular treatment may be beneficial to visual acuity, stereo acuity and binocular function improvement for individual with amblyopia. In clinical practice, binocular treatment can be used as one of the treatments for individual with amblyopia.

Abbreviations: CIs = confidence intervals, NOS = Newcastle-Ottawa Scale, RCT = randomized controlled trial, SMD = standard mean difference, WMD = weighted mean difference.

Keywords: amblyopia, binocular treatment, meta-analysis, systematic review, visual acuity.

1. Introduction

Amblyopia is a neurodevelopmental disorder arising from abnormal visual experience during childhood, which refers to unilateral or, less commonly, bilateral reduction in best corrected visual acuity, with an overall prevalence of 2%–4%.[1–3] It has been reported that individual who have amblyopia in one eye are about twice as likely to have impaired vision in both eyes when reaching a certain age.[4] Moreover, untreated or undertreated unilateral amblyopia has been shown to result in reduced reading speed, abnormal fine-motor skills, and reduced stereo acuity.[3,5] Amblyopia severely affects development, academic work, and various aspects of social life in individual with amblyopia.[6] It is of great importance to find out proper treatment of amblyopia.

Current standard treatment for amblyopia involves refractive correction followed by patching or atropine penalization of the fellow eye.[2] Studies suggested that treatment of monocular deprivation amblyopia with intensive fellow eye patching rarely results in rehabilitation of binocular vision.[7,8] Atropine penalization is to instill tropine sulfate into the sound eye to blur the vision in the sound eye for near activities, hence forcing the amblyopic eye to be used preferentially for near vision tasks, so as to improve the vision of amblyopia.[9,10] But patients may suffer from drug allergies, photophobia, and the burden of increased drug costs.[10] In recent years, due to the development of image technology, a variety of amblyopia treatment devices that present the visual target to only the amblyopic eye under open binoculars have come out.[11–13] A number of studies demonstrated promising results of binocular therapy in visual acuity, binocular function and compliance improvement.[1,14–18] However, some studies revealed that binocular treatment may not improve visual outcomes more than other treatments.[2,19] Given the contradictory and inconsistent results, we conducted this meta-analysis to assess the efficacy of binocular treatment for individual with amblyopia.

2. Material and Methods

The data were obtained from openly available databases. There were thus no need to get the approval from Institutional Review Board of our hospital.

2.1. Search strategy

English literatures up to December 21, 2020 were searched in Pubmed, Embase, Cochrane Library, and Web of Science.

Conflicts of interest: The authors report no conflicts of interest in this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

How to cite this article: Jin L, Fang Y, Jin C. Binocular treatment for individual with amblyopia: a systematic review and meta-analysis. Medicine 2022;101:27(e28975).

Received: 17 June 2021 / Received in final form: 14 October 2021 / Accepted: 10 February 2022

http://dx.doi.org/10.1097/MD.0000000000028975

Search words were as follows: "Amblyopia" OR "Amblyopias" OR "Lazy Eye" OR "Eye, Lazy" OR "Eyes, Lazy" OR "Lazy Eyes" OR "Anisometropic Amblyopia" OR "Amblyopia, Anisometropic" OR "Amblyopias, Anisometropic" OR "Anisometropic Amblyopias" OR "Amblyopia, Developmental" OR "Amblyopias, Developmental" OR "Developmental Amblyopia" OR "Developmental Amblyopias" OR "Amblyopia, Suppression" OR "Amblyopias, Suppression" OR "Suppression Amblyopia" OR "Suppression Amblyopias" OR "Stimulus Deprivation-Induced Amblyopia" OR "Stimulus Deprivation Induced Amblyopia" OR "Amblyopia, Stimulus Deprivation-Induced" OR "Amblyopia, Stimulus Deprivation Induced" OR "Amblyopias, Stimulus Deprivation-Induced" OR "Deprivation-Induced Amblyopia, Stimulus" OR "Deprivation-Induced Amblyopias, Stimulus" OR "Stimulus Deprivation-Induced Amblyopias" And "binocular."

2.2. Inclusion and exclusion criteria

Inclusion criteria: (1) amblyopia patients; (2) patients treated with binocular treatment as experimental group and patients treated with other treatments as control group; (3) randomized controlled trials (RCTs) and Non-RCTs.

Exclusion criteria: (1) animal experiments; (2) patients suffering from developmental delay or systemic disease.

2.3. Quality assessment and data extraction

Two authors (Liwen J and Yiming F) were responsible for data extraction based on inclusion and exclusion criteria. The third author (Can J) would participate in coordination if disagreements occurred. For each study, the following information was extracted, including author, year of publication country, study, type of control group, training duration, gender, and age.

The revised Newcastle-Ottawa Scale (NOS) was used to evaluate the quality of the literature for Non-RCTs, with a total score of 10 scores, <5 being medium to low quality and ≥5 being high quality. The improved Jadad scale was used to evaluate the literature quality of RCTs. The total score of this scale is 7, which is divided into medium and low quality based on <4, and high quality based on ≥4.

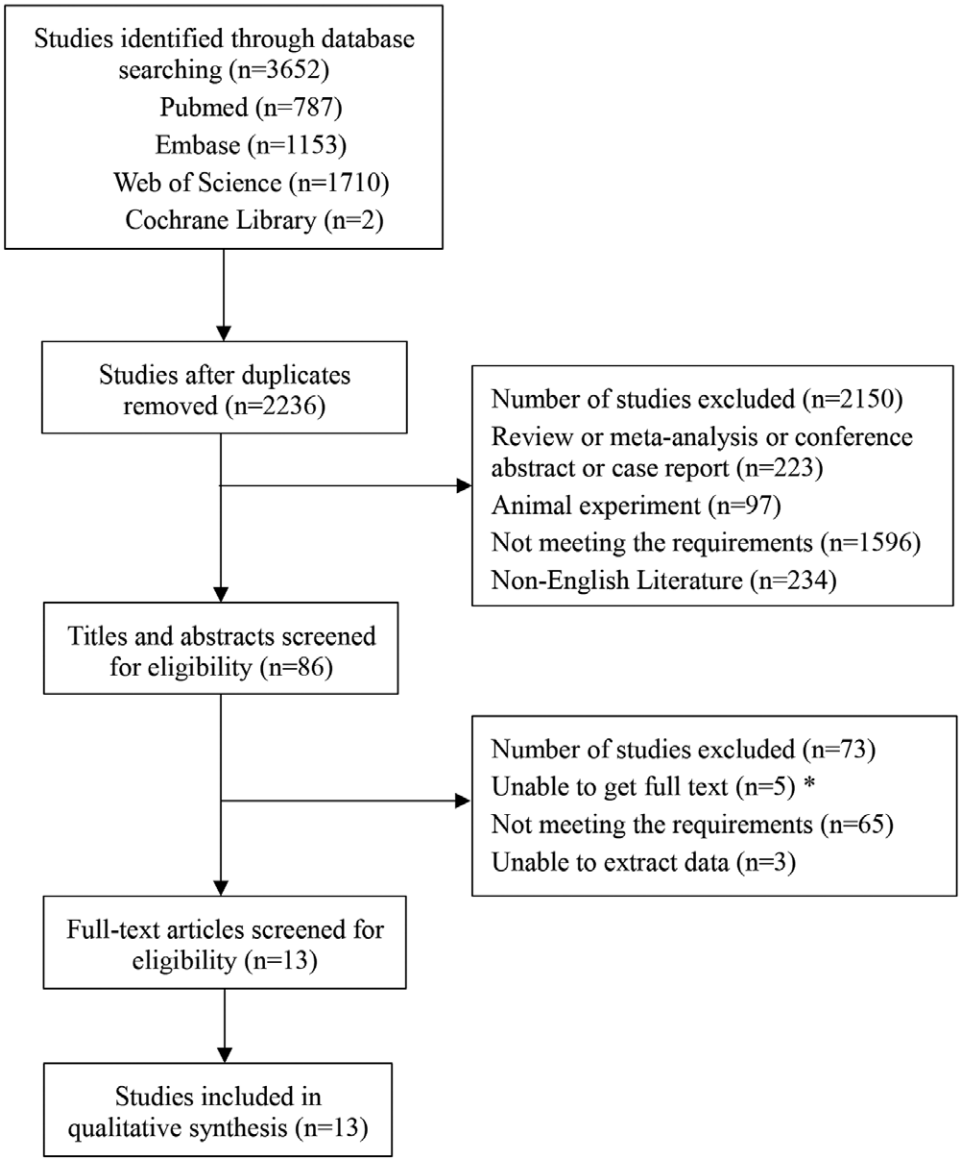

Figure 1. The flow chart depicting the study selection process.

2.4. Statistical analysis

Software Stata 15.1 (Stata Corporation, College Station, TX, USA) was used for statistical analysis. Heterogeneity test was conducted for each effect indicator. Indicators were analyzed by random-effects model when the heterogeneity statistic $I^2 \geq 50\%$, on the contrary, indicators were analyzed by fixed-effect model. Subgroup analysis was performed based on different types of researches. Sensitivity analysis was performed for all outcomes. The Begg's test was used to assess publication bias. The enumeration data used Standard Mean Difference (SMD) or Weighted Mean Difference (WMD) as effect indicators, and the effect size was expressed as 95% confidence intervals (CIs). $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Literature search and study characteristics

Initially 3652 studies were identified through a comprehensive search. After duplicates removed, 2236 studies were recognized, 86 articles were initially screened on title and abstract level for eligibility. Finally, 13 articles were finally enrolled based on inclusion and exclusion criteria in this meta-analysis.[2,6,15,20–29] The flow chart depicting the study selection process is shown in Figure 1. Totally 1146 patients were enrolled in this study, of which 595 patients underwent binocular treatment and 551 patients received other treatments. The characteristics of included studies are presented in the Table 1.

3.2. Amblyopic eye visual acuity

Amblyopic eye visual acuity improvement was analyzed in 10 studies including 16 sets of data (3 sets of data were from Vedamurthy 2015 based on different amblyopia types, the first "Vedamurthy 2015" is mixed amblyopia, the second "Vedamurthy 2015" is anisometropic amblyopia and the third is strabismic amblyopia; 6 groups of data were from Holmes 2016, Holmes 2018 and Pang 2020, which were included 2 times separately based on follow-up times) to assess the efficacy of binocular treatment for individual with amblyopia. The heterogeneity test results were statistically significant (I^2=89.4%), so the random-effect model was adopted. The result indicated that the improvement of amblyopic eye visual acuity in experimental group was better than control group [SMD: 0.473, 95%CI: (0.104, 0.841), $P < 0.001$]. Subgroup analysis was performed based on different types of researches. The result of 8 RCTs showed the improvement of amblyopic eye visual acuity in binocular treatment group was similar to control group [SMD: 0.169, 95%CI: (–0.183, 0.521), $P = 0.347$]. While the result of 7 Non-RCTs revealed that the improvement of eye visual acuity in binocular treatment group was better than that in control group [SMD: 0.882, 95%CI: (0.152, 1.613), $P = 0.018$] (Table 2, Fig. 2). The result was statistically significant.

3.3. Best corrected visual acuity

The best corrected visual acuity improvement was identified in 3 studies involving 5 sets of data (2 groups of data were from Li 2014 based on control types, the first "Li 2014" is binocular games + patching VS. sham + patching, the second "Li 2014" is binocular games only VS. sham only; 2 sets of data were from Iwata 2018 according to follow-up times). The heterogeneity test results were statistically significant ($I^2 = 89.9\%$), so the random-effect model was adopted. The result revealed that binocular treatment cannot be considered superior to the control group for improvement in best corrected visual acuity [WMD: -0.006, 95%CI: (-0.092, 0.079), $P = 0.882$] (Table 2, Fig. 3).

3.4. Stereo acuity

A total of 4 studies including 8 sets of data (3 sets of data were form Vedamurthy 2015 based on different amblyopia types, the first "Vedamurthy 2015" is mixed amblyopia, the second "Vedamurthy 2015" is anisometropic amblyopia and the third is strabismic amblyopia; 2 groups of data were from Pang 2020 based on follow-up times) were enrolled to assess the stereo acuity. The result was statically significant [WMD: 0.138, 95%CI: (0.068, 0.208), $P < 0.001$], indicating binocular treatment could improve stereo acuity in individual with amblyopia. Subgroup analysis was preformed according to different study types. The result in RCT was statistically significant [WMD: 0.246, 95%CI: (0.133, 0.358), $P < 0.001$], suggesting that the binocular treatment group had better visual acuity improvement than

Table 1

Baseline characteristics of included studies.

						Intervention group			Control group			
Author	Year	Country	Study	Type of control group	Treat time	N	M/F	Age	N	M/F	Age	Quality
Li	2014	USA	Non-RCT	Sham games	4 h/w for 4 weeks	45	25/20	–	24	14/10	–	4
Birch	2015	USA	RCT	Sham iPad games	4 h/w for 4 weeks	45	–	–	5	–	–	5
Vedamurthy	2015	USA	Non-RCT	Watch movies	1.5–2 hours, for at least 2 and up to 5 times/ week, 40 hours	23	9/14	39.6 ± 16	15	7/8	40.1 ± 15	4
Holmes	2016	USA	Non-RCT	Patching	16 weeks, binocular group: 1 hour a day; patching group: 2 hours a day	190	92/98	8.4 ± 1.8	195	106/89	8.6 ± 2.0	5
Kelly	2016	USA	RCT	Patching	2 weeks	14	11/3	6.60 ± 1.39	14	10/4	6.95 ± 1.51	6
Gao	2018	Multicentre	RCT	Placebo	6 weeks	56	34/22	22.1 ± 13.9	59	31/28	21.0 ± 13.4	4
Iwata	2018	Japan	RCT	Glasses treatment	2 days a week, 30 minutes per day	23	–	4.9 ± 1.1	23	–	4.8 ± 1.2	5
Manh	2018	USA	RCT	Patching	16 weeks	40	24/16	14.3 ± 1.1	60	34/26	14.3 ± 1.1	5
Holmes	2018	Multicentre	RCT	Continued optical treatment	8 weeks, 1 hour a day 5 days per week	69	39/30	9.6 ± 1.6	69	34/30	9.6 ± 1.5	5
Sauvan	2019	France	Non-RCT	Patching	6 sessions of 1.5 hour	10	–	–	7	–	–	4
Birch	2020	Texas	RCT	Current treatment only	5 hours/week for 4 weeks	8	–	–	7	–	–	3
Pang	2020	China/Canada	RCT	Placebo	6 weeks	12	–	–	11	–	–	4
Yao	2020	China	RCT	Patching	3 months	36	20/16	6.50 ± 2.81	38	14/24	5.95 ± 2.28	3

RCT = randomized controlled trial; M/F = male/female.

Table 2

Overall and sensitivity meta-analysis results

Outcomes	SMD/WMD (95%CI)	*P*	I^2
Amblyopic eye visual acuity			
Overall	0.473 (0.104,0.841)	0.012	89.4
Sensitivity analysis	0.473 (0.104,0.841)		
Design			
RCT	0.169 (–0.183,0.521)	0.347	74
Non-RCT	0.882(0.152,1.613)	0.018	94.3
Best corrected visual acuity			
Overall	–0.006 (–0.092,0.079)	0.882	89.9
Sensitivity analysis	–0.006 (–0.092,0.079)		
Stereo acuity			
Overall	0.138 (0.068,0.208)	<0.001	65.4
Sensitivity analysis	0.138 (0.068,0.208)		
Design			
RCT	0.246 (0.133,0.358)	<0.001	0
Non-RCT	0.092 (0.023,0.160)	0.009	77.4

CI = confidence intervals, RCT = randomized controlled trial, SMD = standard mean difference, WMD = weighted mean difference.

the control group. Similarly, heterogeneous results of Non-RCT showed better visual acuity improvement in binocular treatment group [WMD: 0.092, 95%CI: (0.023, 0.160), P = 0.009] (Table 2, Figure 4).

3.5. Other outcomes

Sauvan et al[22] reported the effects of interocular balance and stereo sensitivity in the training team. The interocular balance in the binocular treatment group was –22.67 ± 13.76 dB and –21.16 ± 15.44 dB in the patch group at baseline. After treatment, the interocular balance between the two groups was–21.61 ± 12.68 and –19.57 ± 19.12 dB. However, there was no significant difference in the improvement before and after treatment between the binocular treatment group and the patch group (P > 0.05).The stereo sensitivity of 4 subjects in the binocular treatment group increased from 165 ± 90 arcmin at baseline to 64 ± 43 arcmin at the end of training, and that of 2 subjects in the patch treatment group increased from 60 ± 0 arcmin to 38 ± 32 arcmin, but there was no significant improvement before and after treatment in both groups (P > 0.05). Kelly et al[25] found no difference in changes in stereo acuity, degree of inhibition, and depth of inhibition between binocular game and patch treatments during 2-week follow-up, with median (interquartile range) changes in stereo acuity is -0.00 (0.00–0.00) *vs.* 0.00 (0.00-0.00) and log angular seconds (U= 79.00, P= 0.56), respectively. The degree of inhibition was -2.21 (6.02) *vs.* 2.05 (6.52) degrees, respectively (mean difference 4.10 degrees; 95%CI, 0.71 to 8.91 degrees; T_{25} = –1.76, P= 0.09). Depth of inhibition was 1.58 (2.31) and 2.20 (2.42), respectively (mean difference 0.63; 95%CI, –1.25 to 2.51; t_{25} = 0.69, P = 0.50). Vedamurthy et al[21] measured the changes in visual acuity and reading speed in addition to the improvement of amblyopic vision and the improvement of stereo acuity. Visual acuity was measured by log CSF curve (AULCSF), and it was found that participants in the game group increased by 0.3 log units (from 2 ± 0.19 to 2.3 ± 0.13) on average, and participants in the film group only increased by 0.1 log units (from 1.8 ± 0.15 to 1.9 ± 0.16).

4. Discussion

In this meta-analysis, we performed a comprehensive search of literature from a variety of databases to assess the efficacy of binocular treatment for individual with amblyopia. A total of 13 literatures including 1146 participants were enrolled. Our study suggested that the improvement of eye visual acuity in binocular treatment group was better than that in control group. Moreover, binocular treatment group had better stereo acuity improvement than the control group.

Currently, treatment focuses on improving vision in the amblyopia eye, with the expectation that this will lead to improved binocular function.[30] However, it has been suggested that monocular treatment might impair binocular function.[31] The potential benefit of binocular therapies is to minimize suppression of the amblyopic eye, thereby improving not only amblyopic eye visual acuity but also binocular function.[1] Our result of 7 Non-RCTs revealed that the improvement of eye visual acuity in binocular treatment group was better. The improvements we report for the amblyopia are in agreement with prior treatment studies.[12,15,32] Similarly, in a study cohort,[33] visual acuity improved over 8 weeks in children with unilateral deprivation amblyopia who played a binocular contrast-rebalanced binocular iPad game. While Hamm et al[34] revealed a different finding that there was no significant improvement in visual acuity in 7 children who are 5–14 years of age and treated with a

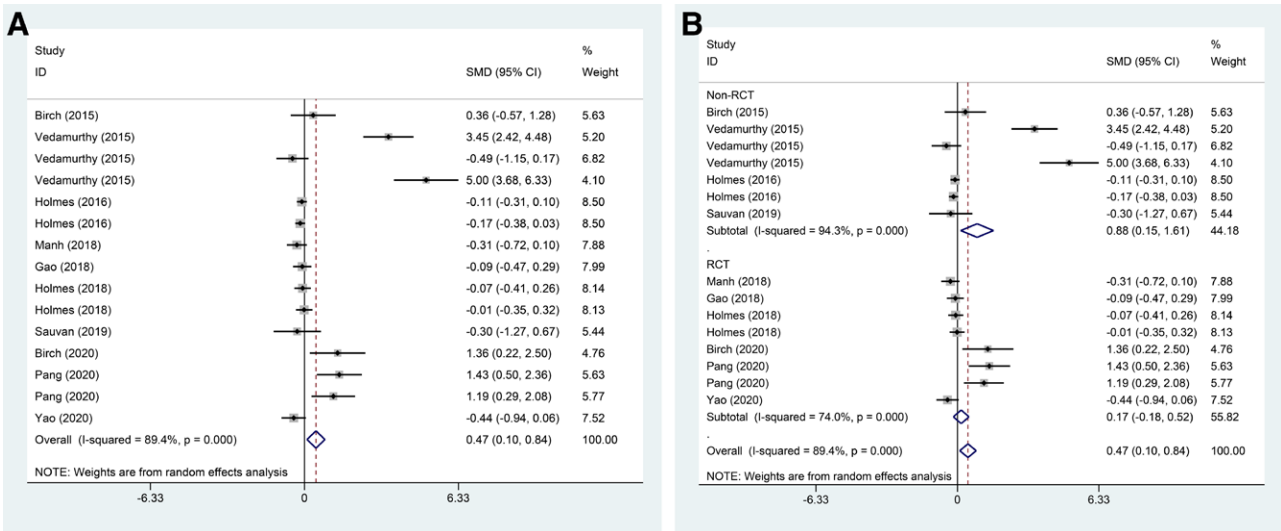

Figure 2. Forest plot of comparison on the amblyopic eye visual acuity in trial group and control group. (A) overall analysis; (B) subgroup analysis based on RCTs or Non-RCTs.

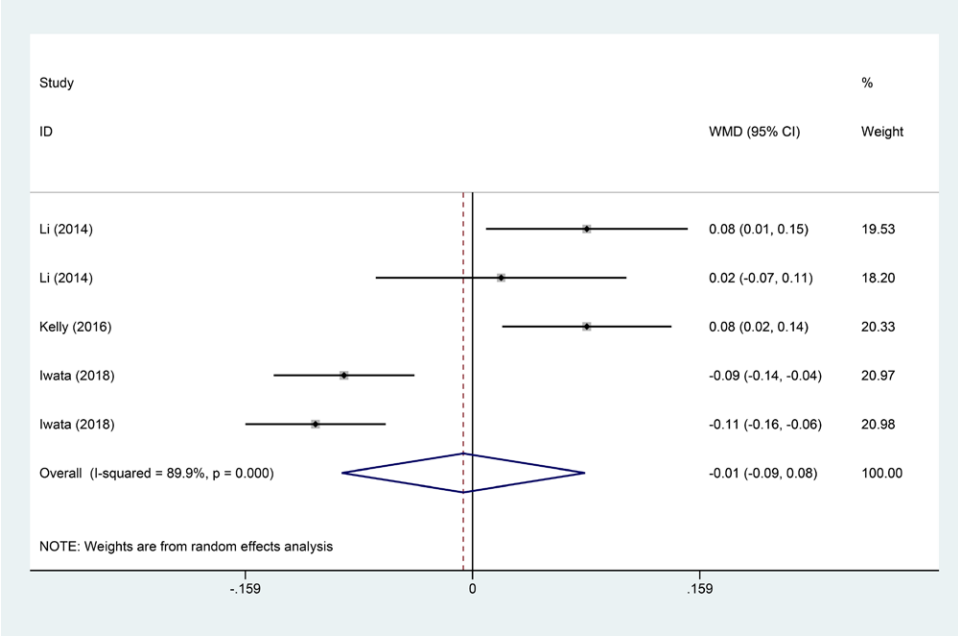

Figure 3. Forest plot of comparison on the best corrected visual acuity improvement in trial group and control group.

contrast-rebalanced binocular falling blocks game. We conjecture the reason of opposite result is likely to be complex and include confounding factors such as age, compliance, amblyopia classification, amblyopia type, etc.

Amblyopia is defined as the reduction of best corrected visual acuity of one or both eyes caused by conditions that affect normal visual development,[35] which determine the importance of best corrected visual acuity. Minjuan Zhu et al[36] found that after short-term binocular visual perception network training, best corrected visual acuity value of amblyopia patients was improved, and the smaller the best corrected visual acuity value was before training, the larger the best corrected visual acuity value was after training. Similar results were observed by multiple studies.[13,15,37] However, for patients with different degrees of amblyopia, the efficacy of binocular visual training needs to be further studied.[37]

Stereo acuity refers to the minimum depth difference that can be perceived in human depth vision.[38] Some investigators have examined the relationship between stereo acuity and amblyopic eye visual acuity, who found that better baseline stereo acuity is predictive of improvement in amblyopic eye acuity.[39–41] Our study indicated that binocular treatment has improved the stereo acuity of the amblyopia eye. A recent study which was to analyze the consolidation effect of binocular visual function training on amblyopia treatment has found that the normal rate of stereo acuity in the experimental group was significantly improved, higher than that in the conventional group.[42] However, a randomized trial of a binocular iPad game[43] showed change in stereo acuity did not differ significantly between treatment groups for the overall cohort.

The superiority of the present study was that it was the first meta-analysis to evaluate the efficacy of binocular treatment for individual with amblyopia. What's more, we provided an update for the management of amblyopia to provide better visual outcomes. However, some limitations of our study must be acknowledged. Firstly, there were few literatures that can be enrolled in this meta-analysis, which may influence the credibility of our study. Secondly, we failed to consider the factors influencing severity of and recovery of amblyopia, such as age,

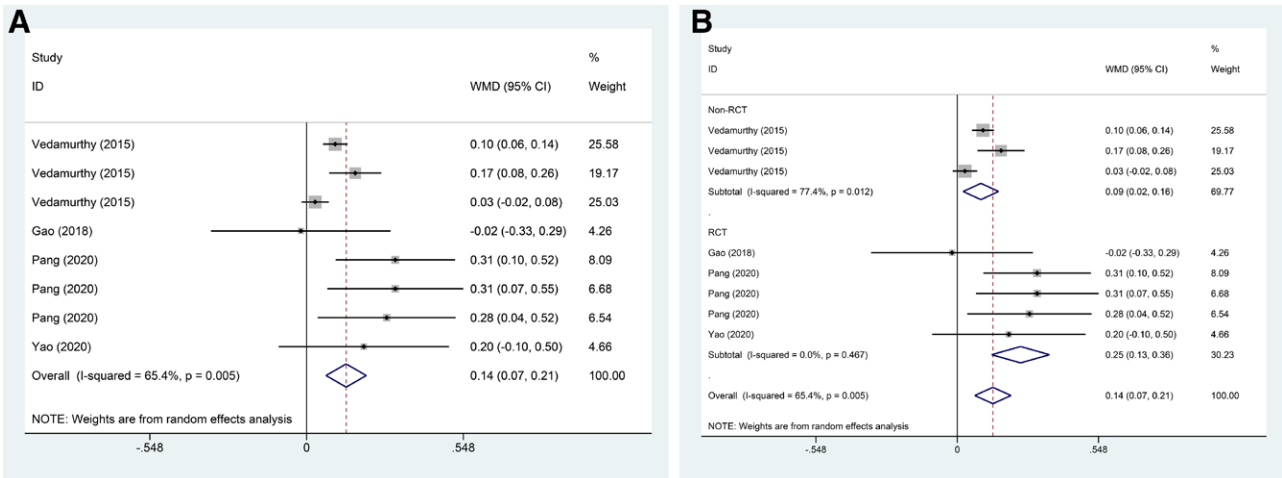

Figure 4. Forest plot of comparison on the stereo acuity in trial group and control group. (A) overall analysis; (B) subgroup analysis based on RCTs or Non-RCTs.

amblyopia classification, treatment type, and adverse outcomes. In the future, we plan to do more analysis to further investigate the effect of binocular therapy on amblyopia.

The results of this meta-analysis indicated that binocular treatment is beneficial to visual acuity, stereo acuity and binocular function improvement. Nevertheless, further pursue in research context for amblyopia is likely needed.

Author contributions

Liwen Jin and Yiming Fang designed the study. Liwen Jin wrote the manuscript. Liwen Jin and Can Jin collected, analyzed and interpreted the data. Liwen Jin critically reviewed, edited and approved the manuscript. All authors read and approved the final manuscript.

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