Non-Interactive Amblyopia Treatment Modalities in Children: A Systematic Review and Meta-Analysis

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Abstract

Background: This review aimed to identify the most effective and safest amblyopia interventions in an integrative manner.

Methods: Eligible studies were identified from Cochrane library (CENTRAL), Pubmed central, Google Scholar, ScienceDirect and Scopus database up to 09/2018. Data pooling was performed for trials with a little heterogeneity (P>0.05, I^2 <50%) using the fixed-effect models. The mean difference (MD) and risk ratio (RR) at 95% confidence interval (CI) for visual acuity improvement, success of the treatment, reverse amblyopia and adherence rate were pooled.

Results: Eight trials consisting of 1253 participants were included. Regardless of child's age, cause and severity of amblyopia, six hours patching and full-time patching were equally effective (Pooled MD, 0.00; 95% CI, -0.54 to 0.55). Likewise, studies independently reported that two hours and six hours patching were equally effective for moderate amblyopia. The therapeutic outcome of patching was statistically comparable to atropine (pooled MD, 0.25 lines; 95% CI, 0.01 to 0.48). The weighted adherence rates for atropine was encouraging as compared to patching (pooled RR, 0.9; 95% CI, 0.84 to 0.96). However, significant reverse amblyopia and poor adherence was recognized in full-time patching and atropine. The risk of developing reverse amblyopia was lower by 19% for patching groups as compared to atropine (pooled RR, 0.19; 95% CI: 0.06 to 0.57).

Conclusion: Overall, considering six hours patching or atropine penalization as a first line treatment is a fair decision from effectiveness perspective but it should be under proactive monitoring to optimize the noted adherence and adverse effects issues.

Background

Amblyopia ('Lazy eye') is the second most common cause of functional low vision in children in

Low- and medium- income countries.[1] The prevalence of amblyopia in children is ranged from 0.74%-4.6%.[2–7] The condition is a unilateral or infrequently bilateral condition, which is caused by abnormal development of the visual system associated with strabismus, refractive error, and visual deprivation during the critical period of visual development (up to the age of 7 years).[5,8] Basically, the development of the visual system depends on the sensory input during the critical period when there is active neuroplasticity. If there is abnormal visual stimuli/input to the primary visual cortex from the two eyes, the normal binocular interaction and development of spatial processing can be disrupted. This results in loss of stereopsis, visual acuity and contrast sensitivity.[9] Some studies reported that morpho-physiological changes to the neural cells such as enlargement of receptive field size, disorganization of a topographical map, reduction of the complement of cortical cells and reduction of cortical magnification can be occurred.[10, 11] If the intervention is not given before the cessation of the critical period, the amblyopia will persist into adulthood. The lifetime risk of binocular visual impairment was 18% for amblyopic persons, whereas for non-amblyopic individuals, it was 10%.[12]

As diagnostic criteria, unilateral amblyopia is defined as a difference in best corrected visual acuity (BCVA) between the two eyes of 0.2 log MAR (logarithm of minimum angle of resolution with base ten) or 2 line difference. For children age less 3 years, asymmetric objection or failure to maintain fixation, an intraocular difference of ≥ 2 octaves in preferential looking of Teller acuity are indicators of unilateral amblyopia. Bilateral amblyopia is defined as a reduction of 0.2log MAR or more compared with the developmental norms for BCVA at a given age. [8, 13] Since the severity of amblyopia has its own implication on management protocol, amblyopia is classified as moderate (distance BCVA ≥ 6/24 or ≥ 0.60 logMAR) and severe (distance BCVA < 6/24 or < 0.60 logMAR). [14, 15]

The mechanism is to initiate the amblyopic eye by limiting the use of the sound eye. The neural basis of the treatment is associated with the phenomenon of neuroplasticity, which is mediated by the action of neuromodulators that promote long-term synaptic changes.[16] Patching of the fellow eye and providing visual stimuli to the amblyopic eye can remodel cortical functions [17] and morphologic changes in cells of the retina, lateral geniculate nucleus, and visual cortex as well.[18] The target of amblyopia treatments is to equalize the visual function of the two eyes, which is commenced after treating the underlying cause and the visual acuity is stabilized with optical correction for a minimum of 4months. A review article also recommended optical treatment of amblyopia should be considered prior to other treatment in those with refractive error.[19]

Recently, numerous clinical trials are being conducted on the effectiveness and safeness of passive amblyopia treatments, particularly PEDIG trials. Several original studies reported that the success of amblyopia treatment varies from 30% -92%.[20–23] Factors behind the success were patient compliance, high refractive error, magnitude of anisometropia, and severity of amblyopia, age, dose of treatment, eccentric fixation, binocularity and type of amblyopia.[20,24–26]

Moreover, some review articles were conducted on previous trials.[27,28] Li T[27] compared atropine with patching and recommended atropine penalization as a first line treatment. Yazdani et al[28] also compared Part-time with full-time patching and concluded that both are equally effective. Their conclusion was based on the therapeutic effect with little consideration of secondary outcomes such as reverse amblyopia and adherence rate. A case report study stated that the reverse amblyopia in atropine was refractory to treatment.[29] A study noted that compliance rates were higher in FTO as compared to PTO.[30] Similarly, atropine treatment had encouraging compliance over patching.[31] However, again these findings did not integrate the primary outcome streams. Basically, assuring overweighting of the benefit over the adverse effect is an essential step to choose a modality. Furthermore, both reviews included studies that did not consider visual acuity stabilization with optical correction.[31–33] Hence, this review was necessitated to fill the noted gaps through measuring the therapeutic effect of amblyopia interventions and their safeness in children simultaneously. The evidence elicited from this review would assist the clinicians in managing amblyopic patients.

Methods

Protocol

The study was compiled in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist format.[34]

Study Eligibility Criteria

For this review, articles with the characteristics of randomized controlled trials (RCTs), peer-reviewed publications were considered. The eligibility criteria were studies included children diagnosed with functional amblyopia that is associated with strabismus, Anisometropia, or mixed, no amblyopia treatment other than spectacles used within six months prior to enrollment, and children whose visual acuity was stabilized with spectacle correction for at least 18 weeks before enrollment. However, studies written in a language other than English, pilot studies, ongoing trials, retrospective record reviews, review articles and trials for residual amblyopia (have history of prior treatment of amblyopia other than spectacle) were excluded.

Search methods

The studies were identified through electronic databases searching from 'Cochrane Central Register of Controlled Trials (CENTRAL)', Pubmed Central, Google Scholar, ScienceDirect and Scopus from 08//2018 to 8/2019. Keywords such as 'amblyopia', 'patching', 'atropine', and "occlusion" were applied to look for the articles from the database. Additional trials were manually searched.

Selection of studies and data extraction

Initially, two authors independently assessed the titles and abstracts of the articles after duplicated records were ruled out. Disagreements between the two authors were alleviated through discussion in the presence of the third author. Each abstract was labeled as 'included' and 'excluded' after the abstract screening. Then full-text review was performed by all authors independently. For included studies, all relevant data were extracted using data extraction form, which was developed using Cochrane data collection form for intervention reviews(RCTs and non-RCTs) guideline.[35] The form consisted of the journal name, publication year, aim of the study, unit of allocation, study design, inclusion and exclusion, age, participants, sex, follow up duration, type of amblyopia, the severity of amblyopia, intervention type, type of comparison, outcome measures, the effect of the intervention, adverse effects, adherence and conclusion of the studies. The extracted data were compared between the authors and any discrepancy was resolved together.

Types of outcome measures and data item

The comparison that was considered in this review were patching with atropine, two hours patching with six hours patching, and part-time patching(Six hours) with full-time patching. The primary outcomes were the mean visual acuity improvement from the baseline in the amblyopic eye (in log MAR line) and improving visual acuity of amblyopic eyes by ≥ 2 log MAR lines from the baseline (Success rate). Since the improvement of 2 or more lines of visual acuity had good statistical power to detect treatment difference and minimize chance as compared to other dichotomous criteria (better than 20/25, better than 20/32, equal vision in both eyes, and improved 3 or more lines), it was considered as a criteria to measure success.[36] The secondary outcomes were adherence rate and significant reverse amblyopia (reduction of visual acuity in the sound eye by ≥ 2 Log MAR lines from the baseline in the sound eye).[13] So many studies defined treatment adherence rate as excellent (76%-100% of prescribed treatment completed), good (51%-75%), fair (26%-50%) and poor (≤ 25%) based on the author judgment.[37–39] Since the frequency was too small in this review, this classification was modified as good adherence (51%-100%) and Poor adherence (≤ 50%). Visual acuity reported in a number of letters was converted into a number of lines. A single letter of LogMAR chart is valued as 0.02. The numbers of letters per row of a log MAR chart are five letters. Thus, the value of a log MAR line is 0.1 log MAR unit (0.02 × 5 letters). Five log MAR letters improvement from the baseline is equivalent to one line improvement. The standard deviation of the mean improvement reported in letter form was changed into line through dividing the number of letters by five.

Assessment of risk of bias within and across studies

Three authors assessed the risk of bias using the validated Cochrane collaboration tool.[40] The parameters were random sequence generation; allocation concealment; masking (blinding) of outcome assessors; blinding of the participants; incomplete outcome data; selective outcome reporting; and other sources of bias. Finally, each trial was labeled as 'low risk of bias,' unclear risk' and 'high risk of bias 'with supporting evidence. Publication bias was also evaluated using funnel plots and statistically by Egger's regression intercepts method.

Data synthesis and Summary measures

The treatment effect was estimated using mean difference (MD) for visual acuity change from the baseline and Risk ratio (RR) for reverse amblyopia, visual acuity improvement in the amblyopic eye by ≥ 2 LogMAR lines and adherence at 95% confidence interval (CI). Data synthesis was considered for pooled results with low heterogeneity, where $p > 0.05$ and $I^2 < 50\%$. The individual studies were weighted using the fixed-effect models. The directions of effect were computed from two hours to six hours patching, part-time patching to full-time patching and from patching to atropine. Forest plots were constructed for each studies and pooled data (The squares and horizontal lines correspond to the study-specific risk ratio or mean difference at 95% confidence interval; the diamond represents the pooled risk ratio or mean difference at 95% Confidence interval; p-value indicates level of significance; I^2 indicates the percentage of total variation across studies). The qualitative synthesis was performed for trials with significant statistical heterogeneity. Furthermore, subgroup analysis for factors which influences visual acuity change was employed by Meta-regression analysis and moderator variables. The analysis was performed using review manager 5.3 and Comprehensive Meta-analysis version 2.

Results

Literature search

Altogether, 1892 records were retrieved from an electronic database and manual searching. After the removal of duplicated records, 1592 records were exposed for abstract screening, and 48 articles appeared to be relevant for full-text review. After full-text review, 40 articles were excluded due to various reasons. The remaining 8 articles passed the eligibility criteria, and all of them were included in the quantitative synthesis (Fig. 1).[15, 37–39, 41–44]

Characteristics of included studies

Eight randomized controlled trials with the total of 1253 participants were included. The mean age of the participants was ranged from 4.8 years to 13.6 years. Majority of the studies used a logMAR chart even if some of them presented the visual acuity in Snellen's decimal and fraction (Table 1).[39,41]

Quality assessment (Risk of bias and publication bias)

The risk of bias assessment was conducted based on the pre-specified criteria. The majority of the studies were free of allocation concealment bias (88%), random sequence generation (100%), attrition bias (88%), reporting bias (100%) and other potential bias (100%). However, a significant portion of the trials did not disclose blinding of participants (88%) and detection bias (38%) (Fig. 2 and Fig. 3). The supportive evidence for the author's judgment was documented (Table 2). Publication bias was evaluated for trials that compared patching with atropine. It indicated that nearly all studies appeared on the top of the funnel plot and they were symmetrically distributed with respect to the weighted mean, which was also supported by Egger's regression intercept (Bo= -0.5; 95% CI,-2.12 to 1.09; p-value = 0.3). Though publication bias is an unavoidable issue in a review article, it was not too foreboding for this review (Fig. 4)

Table 1
Characteristics of included studies (the astrik * indicates that the data were obtained after pooling the mean of the groups)

Studies	Study Design, location	Age and sex	Cause of Amblyopia	Severity of amblyopia	Length of follow up	Comparison type: sample size	Baseline mean VA in the amblyopic eye	VA chart used	VA improv in the amblyo (Mean logMAI SD)
PEDIG 2003[a]	RCT,USA	5.2 yrs Male :106 Female: 83	MA	Moderate	4months	2hrs patching:92cases 6hrs patching:89cases	2hours: 0.48 log MAR 6hours: 0.48 log MAR	Electronic-ETDRS	2hours 1.34lin 6hours 1.6lines
PEDIG 2003[b]	RCT,USA	4.8yrs Male:94 Female: 81	MA	Severe	4months	PTO(6hrs):73cases FTO:84caes	PTO: 0.9log MAR FTO:0.89log MAR	Electronic-ETDRS	PTO(6h ± 2.3lin FTO:4.1 2.9lines
Stewart et al 2007	RCT,UK	5.6yrs Sex Not reported	MA	Moderate	> 3months	PTO(6hrs):40case FTO(12hrs):40case	PTO:0.45log MAR FTO:0.44logMAR	ETDRS chart(Log MAR)	PTO:2. 1.9lines FTO:2.4 2.4lines
Singh et al 2008	RCT,USA	9.43*Sex not reported	MA	Mixed	4.5months	2 hrs: 25case 4 hrs: 25 cases 6 hrs:25cases FTO:25cases	2hours:0.67logMAR units 4hours:0.80logMAR units 6hours:0.68logMAR units FTO: 0.76 log MAR	Carl Zeiss chart projector(SZP 350)Converted to Log MAR	2hours 1.1lines 4hours 1.7lines 6hours 1.6lines FTO: 3. 2.2lines
Menon et al 2008	RCT, India	13.6* Male:28 Female:29	AA	Mixed	6months	Atropine:28 cases FTO:29cases	Atropine:0.228(decimal) (0.642logMAR) Patching:0.22(decimal) (0.655logMAR)	ETDRS chart(Log MAR)	Atropin ± 1.14li FTO:2.3 1.19lin
PEDIG 2002	RCT,USA	5.3yrs Male:223 Female:196	MA	Moderate	6months	Atropine:194cases FTO:208cases	Atropine:0.53logMAR FTO:0.52 Log MAR	Electronic Log MAR chart	Atropin ± 1.6 li FTO:3.1 lines

Table 2
Supportive evidence for risk of bias assessment

Menon et al 2008		
Random sequence generation	Low risk	"Stratified randomization was used to place patients in these 2 groups depending on the visual acuity of patients at presentation."
Allocation concealment	Low risk	"Stratified randomization was used to place patients in these 2 groups depending on the visual acuity of patients at presentation."
Blinding of participants and personnel	Unclear risk	Not reported
Blinding of outcome assessment	Unclear risk	Not reported
Incomplete outcome data	Low risk	9% attrition. It was acceptable.
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Both groups were comparable at baseline.
PEDIG 2003a		
Random sequence generation	Low risk	"Randomization was accomplished on the studies web site's using a permuted block design of varying blocks size"
Allocation concealment	Low risk	It is not explicitly stated 'allocation was concealed' in PEDIG publications, but publications did state that participants were randomized using the PEDIG website, which means the allocations were concealed.
Blinding of participants	Unclear risk	Not reported
Blinding of outcome assessment	Low risk	"Visual acuity testing was conducted by a study-certified vision tester who was masked to the patient's treatment group."
Incomplete outcome data	Low risk	4% attrition, which was acceptable.
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Both groups were comparable at baseline and used large sample size.
PEDIG 2002		
Random sequence generation	Low risk	"Randomization was accomplished on the studies web site's using a permuted block design of varying blocks size"
Allocation concealment	Low risk	It is not explicitly stated 'allocation was concealed' in PEDIG publications, but publications do state that participants were randomized using the PEDIG website, which means the allocations were concealed.
Blinding of participants	Unclear risk	Not reported
Blinding of outcome assessment	Low risk	"Visual acuity testing was conducted by a study-certified vision tester who was masked to the patient's treatment group."
Incomplete outcome data	Low risk	4% attrition, which was acceptable.
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Both groups were comparable at baseline and used large sample size.
PEDIG 2003b		
Random sequence generation	Low risk	Randomization was accomplished on the study's website using a permuted-blocks design of varying block sizes."
Allocation concealment	Low risk	It is not explicitly stated 'allocation was concealed' in PEDIG publications, but publications do state that participants were randomized using the PEDIG website, which means the allocations were concealed.
Blinding of participants	Unclear risk	Not reported
Blinding of outcome assessment	Low risk	"At the 4-month outcome examination, visual acuity testing was conducted by a study-certified vision tester who was masked to the patient's treatment group."

Menon et al 2008		
Incomplete outcome data	Low risk	Attrition 10%
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Both groups were comparable.
PEDIG 2008		
Random sequence generation	Low risk	"Each subject were randomly assigned using a permuted blocks design."
Allocation concealment	Low risk	It is not explicitly stated 'allocation was concealed' in PEDIG publications, but publications do state that participants were randomized using the PEDIG website, which means the allocations were concealed
Blinding of participants	Unclear risk	Not reported
Blinding of outcome assessment	low risk	" The examiner was masked to treatment group"
Incomplete outcome data	Low risk	Attrition 11%
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Both groups were comparable.
PEDIG 2009		
Random sequence generation	Low risk	Probably done but not reported
Allocation concealment	Low risk	It is not explicitly stated 'allocation was concealed' in PEDIG publications, but publications do state that participants were randomized using the PEDIG website, which means the allocations were concealed
Blinding of participants	Unclear risk	Not reported
Blinding of outcome assessment	Low risk	Outcome assessor was masked.
Incomplete outcome data	High risk	Greater attrition 17%
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Both groups were comparable.
Singh et al 2008		
Random sequence generation	Low risk	They were randomized using computer-generated random numbers.”
Allocation concealment	Unclear risk	Not reported
Blinding of participants	Unclear risk	Not reported
Blinding of outcome assessment	Unclear risk	Not reported
Incomplete outcome data	Low risk	No attrition
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	had comparable groups
Stewart et al 2007		
Allocation concealment	Low risk	There was allocation concealment
Blinding of participants	Unclear risk	Neither investigator nor the parents were masked to group allocation

Menon et al 2008		
Blinding of outcome assessment	Unclear risk	Not reported
Incomplete outcome data	Low risk	No attrition
Selective reporting	Low risk	No selective reporting
Other bias	Low risk	Enrolled comparable groups

Effect of interventions

Two hours versus 6 hours patching

Two studies with a total of 239 participants whose mean age of 7.3 years compared 2 hours patching with 6 hours patching.[15, 38] The length of the intervention for both was about 4 month. PEDIG 2003a[38] reported that the average visual acuity improvement from the baseline in amblyopic eye was 2.4 lines in each group (MD, 0.00; 95% CI, -0.45 to 0.45) and the study concluded both treatment modalities were equally effective. However, Singh et al [15] favored 6 hours patching over 2 hours patching, which was statistically significant(MD 1.3; 95% CI, -2.05 to -0.54). Since significant heterogeneity (I^2 = 88%) was evident, it was not pooled. Furthermore, PEDIG 2003a indicated that the incidence of reverse amblyopia was 6.5% (6/92 cases) in 2hours and 8.9% (8/89cases) in 6 hours patching. The rate of good treatment adherence judged by the investigator was 83% for 2 hours group and 74% for 6 hours patching group.

Part-time (6 hours) versus full-time patching

Three trials with a total of 287 participants compared part-time patching with full-time patching.[15, 42,44] PEDIG 2003[b] reported that the mean visual acuity after 4 month of follow up was 4.8 ± 2.3 lines in part-time patching (6 hours patching) and 4.7 ± 2.9 lines in full time patching (MD, 0.1; 95% CI,-0.71 to 0.91). Stewart et al [44] also found that the mean visual acuity improvement in the amblyopic eye after 3 months of follow up was 2.6 ± 1.9 lines part-time patching and 2.4 ± 2.4 lines in full-time patching, the difference was not significant (MD,0.2;95% CI,-0.75 to 1.15). Similarly, Singh et al[15] indicated that the visual acuity improved by 3 ± 1.6 lines in part-time patching and 3.5 ± 2.5 lines in full time patching (MD, -0.5 lines; 95% CI, -1.66 to 0.66), which was not statistically better in part-time patching. Hence, the three authors independently concluded that both 6hours patching and full-time patching can produce a similar outcome. This conclusion was supported by the pooled mean visual acuity difference in the amblyopic eye, which was nil (MD, 0.00; 95% CI, -0.54 to 0.55) (Fig. 5). Moreover, PEDIG 2003b[42] also showed that 93% of the participants from part-time patching and 84.5% of the participants from the full-time patching improved their visual acuity of the amblyopic eye by 2 ≥ log MAR lines from the baseline. Higher reverse amblyopia in the full-time group (11%) was also noted as compared to part-time groups (4%). Since Singh et al[15] and Stewart et al [44] did not report reverse amblyopia and VA response of 2 ≥ logMAR lines from the baseline, meta-analysis was not considered.

Patching (part-time or full-time) versus atropine

Four trials compared patching with atropine.[37, 39 41, 43] A total of 664 participants were enrolled. Two studies compared part-time with atropine.[39, 43] The remaining two trials were conducted on full-time patching and atropine. [37, 41] PEDIG 2002 [37], at 6 months, the mean visual acuity improvement in patching (3.16 ± 1.6 lines) and atropine group (2.84 ± 1.6 lines) was slightly favored for patching (MD 0.32; 95% CI; 0.01 to 0.63). However, the other three trials found that the mean visual acuity improvement in patching and atropine was similar. PEDIG 2008[39] reported that the mean visual acuity improvement in were 1.72 ± 1.56lines in patching and 1.52 ± 1.5 lines in atropine (MD, 0.2; 95% CI; -0.26 to 0.66). At 17th week of follow up, PEDIG 2009 [43] showed that the mean visual acuity improvement in the amblyopic eye in patching and atropine group was 1.8 ± 1.3 lines and 1.5 ± 2.1 lines, respectively. The difference was not significant (MD, 0.3, 95% CI;-0.86 to 1.46). Similarly, at 6 months of follow up, Menon et al [41] found that the mean visual acuity improvement in patching (2.38 ± 1.19lines) and in atropine group (2.34 ± 1.14lines) was not statistically different (MD, 0.04; 95% CI; -0.56 to 0.64). Hence, all authors agreed that patching was slightly better than atropine even if it was only statistically significant for PEDIG 2002[37]. The pooled estimate also indicated that patching was slightly favorable to atropine (MD, 0.25 lines; 95% CI, 0.01 to 0.48) (Fig. 6). Regarding the success rate, PEDIG 2002[37] reported that 87% of cases in patching group and 82.5% of the cases in atropine improved visual acuity of the amblyopic eye by 2 ≥ Log MAR lines from the baseline (RR, 1.06; 95% CI; 0.97 to 1.15). PEDIG 2008[39] also revealed that 45% of cases in patching group and 40% of the cases in atropine improved visual acuity of the amblyopic eye by 2 ≥ Log MAR lines from the baseline (RR,1.14; 95%CI; 0.8 to 1.61). PEDIG 2009[43] also indicated that 54% of cases in patching group and 40% of the cases in atropine improved visual acuity of the amblyopic eye by 2 ≥ log MAR lines from the baseline (RR,1.35; 95% CI; 0.61 to 2.81). Hence, all of them found that the probability of achieving a visual acuity of greater or equal 2 log MAR line was slightly higher for patching as compared to atropine but it was not significant. The weighted estimate (pooled RR) also indicated similar result, in which the pooled rate of improving visual acuity in the amblyopic eye by ≥ 2 log MAR lines was 74.1%% in patching groups and 67.2% in atropine groups (RR, 1.08; 95% CI, 0.98 to 1.18) (Fig. 7).

The risk of developing reverse of amblyopia was 1.4% in patching and 8.7% in atropine groups, which was statistically significant (RR, 0.16; 95% CI; 0.05 to 0.55).[37] PEDIG 2009[43] reported one case of reverse amblyopia from atropine group but no cases from patching (RR, 0.5; 95% CI; 0.02 to 11.42).PEDIG 2008 stated that there was no incidence of reverse amblyopia in both groups[39]. The combined risk of developing reverse amblyopia was lower by 19% for patching groups as compared to atropine (RR, 0.19; 95% CI: 0.06, 0.57). With regard to adherence, good adherence was 83% in patching group and 96% in atropine

group, which was statistically favorable for atropine group (RR, 0.87, 95% CI;0.81 to 0.93). [37] PEDIG 2008, at 17 weeks, 80% of cases in patching group and 84% of cases in atropine group had good adherence, (RR 0.95, 95% CI; 0.82 to 1.09) [39]. At 6 month of follow up, Menon et al 2008 found that the good adherence was noted in 62% of the participants in patching group and 57% in atropine group, which was not statistically significantly different (RR, 1.09, 95% CI; 0.71 to 1.67)[41]. Even if there was disagreement between the authors, the pooled estimate favored for atropine, in which the adherence rate for patching was lower by 10% from atropine(RR, 0.9; 95% CI, 0.84 to 0.96) (Fig. 7).

Moderator variables and Subgroup analysis

In this review, the severity of amblyopia, the cause of amblyopia, a dose of patching and age of the participants were considered as moderator variables. The pooled mean visual acuity between part-time patching and atropine was 0.21 lines (95% CI,-0.21 to 0.64), which was not significantly different. Similarly, for trials that compared full time patching with atropine, the mean post-treatment visual acuity different was 0.26 lines (95% CI, -0.02 to 0.54), which was not also significant(Fig. 6).[37,41] Hence, the effectiveness difference between patching and atropine was not explained by the variation of the patching dose. The Meta-regression analysis showed that the effectiveness difference for patching and atropine did not associate with age (B0=-0.03; α = 0.5; p = 0.4) (Fig. 8). Regardless of the cause of amblyopia, Singh et al found that part-time patching and full-time patching can produce a similar visual outcome for mild to moderate amblyopia. However, in severe amblyopia, six hours and full-time occlusion treatment were significantly more effective than two hours occlusion[15]. It was also noted that there was no significant difference between 6hours and full time patching for severe amblyopia (p = 0.341). Furthermore, PEDIG 2003[a] indicated that the mean visual acuity improvement in strabismus, anisometropic, and mixed amblyopia was similar for both modalities.[40]

Discussion

This review suggests that two hours patching and six hours patching have similar effectiveness for moderate amblyopia irrespective of its cause.[15, 38] However, Singh et al., 2008 favored 6 hours patching over two hours patching for the mixed type of amblyopia (MD 1.3;95% CI,-2.05to-0.54)[15]. Since significant heterogeneity (I^2 = 88%) was evident, the studies were not pooled. The evidence concerning the event of reverse amblyopia and adherence is limited. Only a study reported that both two hours and six hours patching are equally tolerated and comparable adherence.[38]

This study also found that the pooled mean visual acuity difference in the amblyopic eye between six hours and full-time patching is nil (MD, 0.00; 95% CI, -0.54 to 0.55). This finding is supported by a meta-analysis study which concluded that part-time occlusion and full- time occlusion are equally effective.[28] Independently, three authors agreed that both six hours patching and full time patching are equally effective.[38, 42, 44] PEDIG 2003[b] also showed that the success rate of six hours (93%) and full-time patching are also comparable (84.5%). However, significant reverse amblyopia in the full-time group (11%) was also noted as compared to part-time groups (4%).[42] Regardless of the cause of amblyopia, Singh et al 2008 found that six hours and full-time patching can produce a similar visual outcome for mild to moderate amblyopia and severe amblyopia.[15]

Regarding atropine versus patching, majority of the trials concluded that both treatment modalities are equally effective. Similarly, previous review reported that both conventional occlusion and atropine produce comparable visual acuity improvement in the amblyopic eye and atropine penalization was implicated as first line treatment for amblyopia.[27] However, in this review patching is favorable over atropine (pooled MD, 0.25 lines; 95% CI, 0.01 to 0.48). In addition, the weighted probability of achieving a visual acuity of greater or equal 2 LogMAR line is slightly higher for patching as compared to atropine but it was not significant (RR, 1.08; 95% CI, 0.98 to 1.18). However, the pooled risk of developing reverse amblyopia was lower by 19% for patching groups as compared to atropine (RR, 0.19; 95% CI: 0.06, 0.57). On the other hand, the pooled RR estimate suggests that the adherence rate for patching is lower by 10% from atropine even if there was disagreement between the individual studies. As a subgroup analysis, it was found that effectiveness difference between patching and atropine was not explained by the variation of the patching dose and age participants at the time enrollment.

Several strengths can be recognized in the review, in which both primary and secondary outcomes are considered to choose the most effective and safe modality. Moreover, serious caution was taken while selecting the studies, particularly those conducted on residual amblyopia and visual acuity stabilization with optical correction. Though publication bias and risk of bias are an unavoidable issue in a review article, it was not too foreboding for this review. The majority of the studies were RCT trial, which is free of allocation concealment bias, random sequence generation, attrition bias and reporting bias. So the validity of the studies is fair.

Even if the majority of included trials free from the risk of bias, the blinding of the participants was not clearly disclosed. This review did not incorporate cost-effectiveness data which is important to choose economically efficient treatment modality. In addition, studies with variable length of follow up were synthesized. This review also did not include active amblyopia treatments which require the interaction patients with the treatment like a video game, vision therapy, and near activities. Since the number of studies that could be included is relatively small and heterogeneity was evident, meta-analysis was carried out for some of research questions. Moreover, this review did not aim to answer which intervention resolve faster.

Overall, this systematic review implicated that the choice of amblyopia treatment should rely on both primary and secondary outcomes. Regardless of the cause of amblyopia, selection of the modality depends on the severity of amblyopia. This review also indicates that atropine and full-time patching should be given under close follow up to prevent reverse amblyopia. Treatment adherence is compromised as the number of patching hours increase. Hence, strong physician-parents integration might be crucial for maximizing the adherence rate. Further research concerning the cost-effectiveness of the modalities, active amblyopia treatments and the optimal time (when maximum visual acuity is achieved) should be conducted.

Conclusions

Regardless of child's age, cause and severity of amblyopia, Six hours patching and full-time patching are equally effective despite significant reverse amblyopia and poor adherence in full-time patching. Similarly, two hours patching and six hours patching have similar effectiveness for moderate amblyopia

though six hours patching is preferable for severe amblyopia. Furthermore, the primary effect in patching and atropine are more acceptable even if there is significant reverse amblyopia in atropine. Hence, part-time patching, particularly six hours patching or atropine can be considered as a first-line treatment under proactive monitoring for atropine to minimize the risk of reverse amblyopia.

Abbreviations

BCVA,Best Corrected Visual Acuity; Log MAR, Logarithm of minimum angle of resolution; PEDIG, Pediatric Eye disease Investigative Group; FTO, Full time Occlusion; PTO, Part time Occlusion; RCT, Randomized controlled Trail; MD, Mean difference; CI confidence Interval; RR, Relative risk; I^2 describes the percentage of total variation across studies; SD, standard deviation; the US, United States; UK, United Kingdom; MA, Mixed amblyopia; AA, Anisometropia amblyopia; MAR, the minimum angle of resolution; hrs, hours; yrs, years; VA, visual; ETDRS, Early Treatment Diabetic Retinopathy Study

Declarations

Ethical approval and consent for participant: Since this manuscript is a review article, ethical approval and consent for participant is not applicable.

Consent for publication: Since this manuscript does not include individual data, consent for publication is deemed not required.

Availability of data and materials: The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request

Competing interests: None of the above authors have any proprietary interests or conflicts of interest related to this submission.

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Author's Contributions: All authors conceived, designed the study and analyzed the data. NF. and GT. retrieved the articles, screened the articles, extracted relevant data ,assessed the risk of bias for included articles . MS and AA wrote the first draft of the article. Finally, All authors read and approved the final manuscript.

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Figures

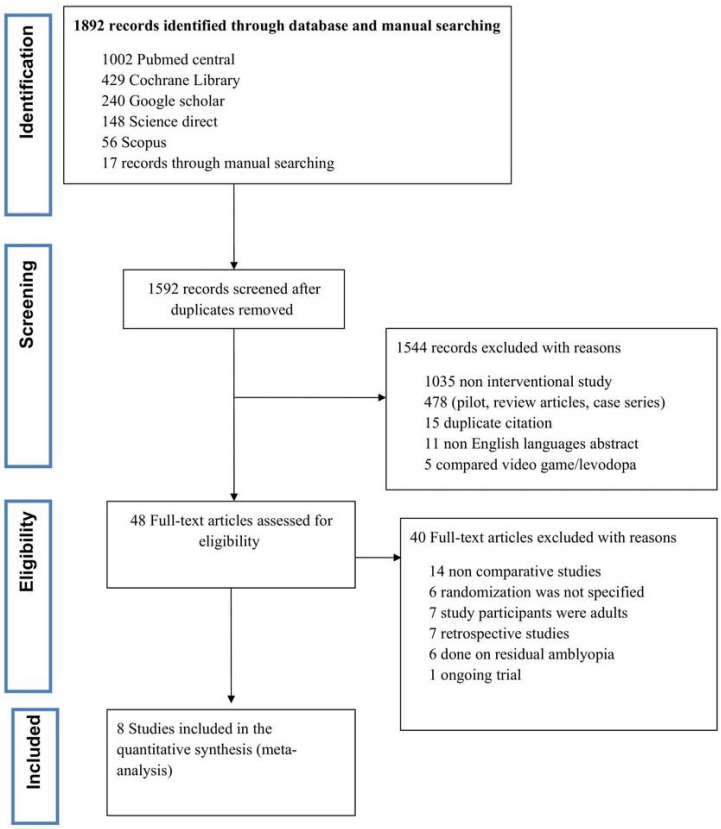

Figure 1

PRISMA flow diagram showing the literature searching and selection process

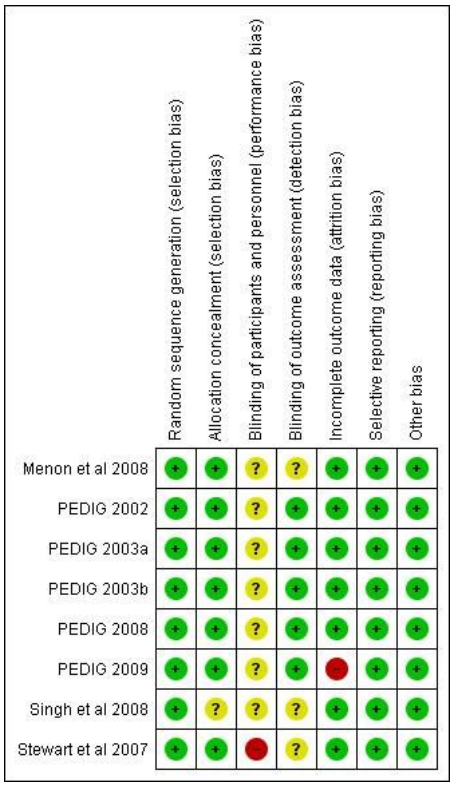

Figure 2

Assessment of risk of bias using Cochrane Collaboration Tool (The plus sign, indicates low risk; the red, indicates high risk; the question mark, indicates unclear risk)

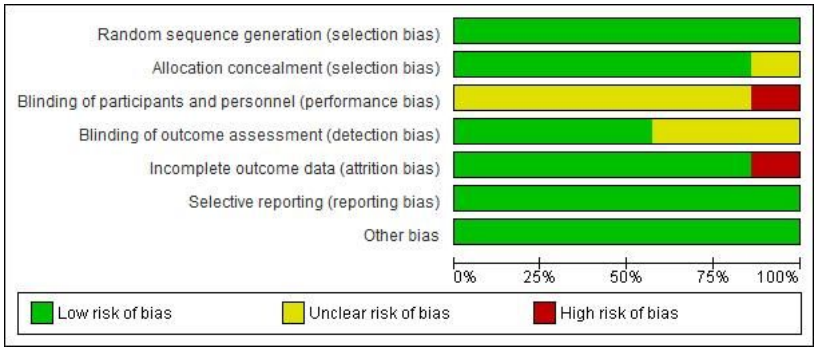

Figure 3

Summative assessment of the risk of bias (Number of studies=8)

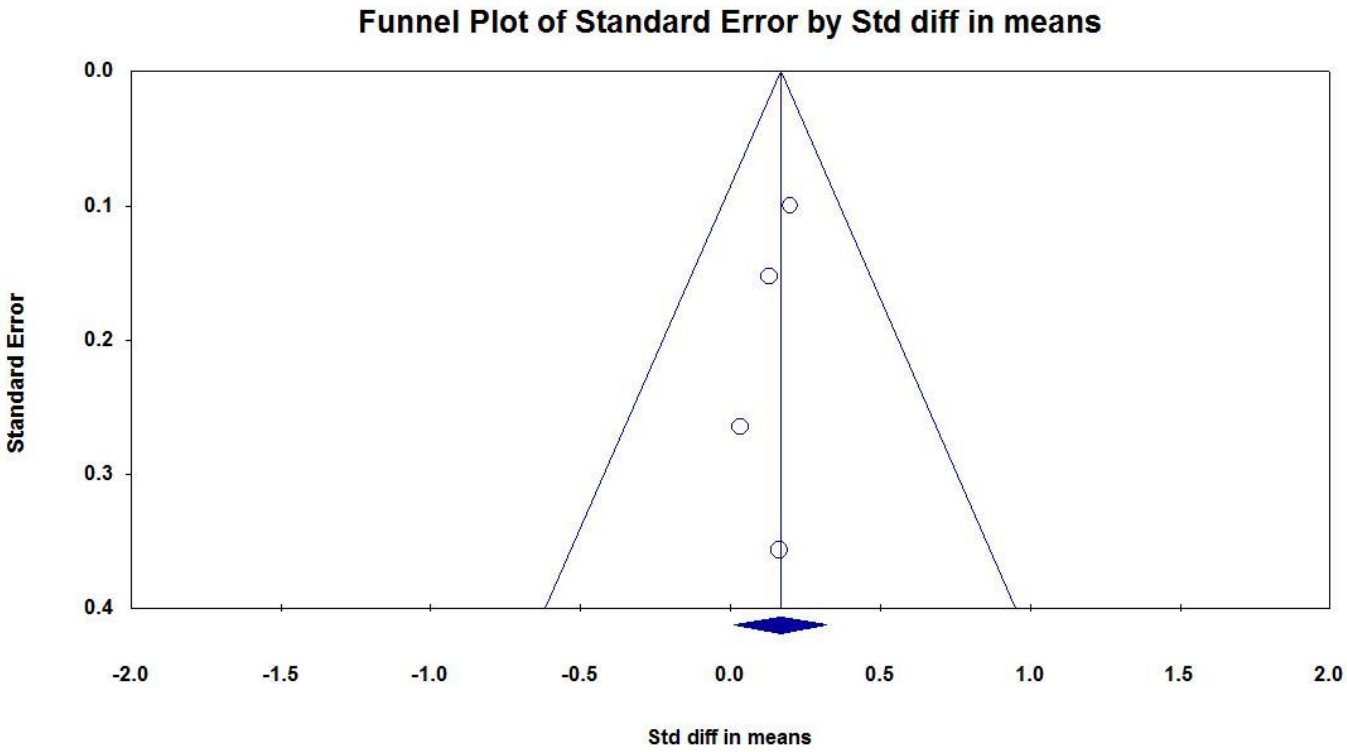

Figure 4

Funnel plot showing publication bias across the studies (The diamond indicates weighted mean difference value; the circles indicate the mean difference of each study)

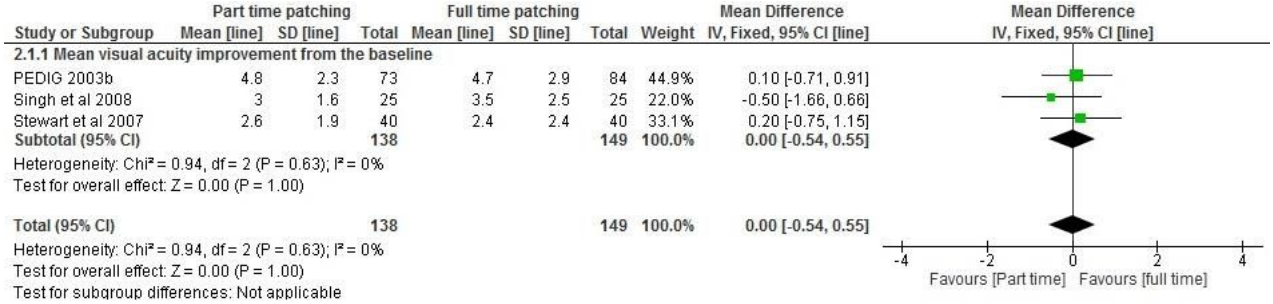

Figure 5

The visual acuity improvement in the amblyopic eye after part-time (6 hours) versus full-time patching (The squares and horizontal lines correspond to the study-specific mean difference and 95% confidence interval; the diamond represents the pooled mean difference; p-value indicates the level of significance; I2 indicates the percentage of total variation across studies)

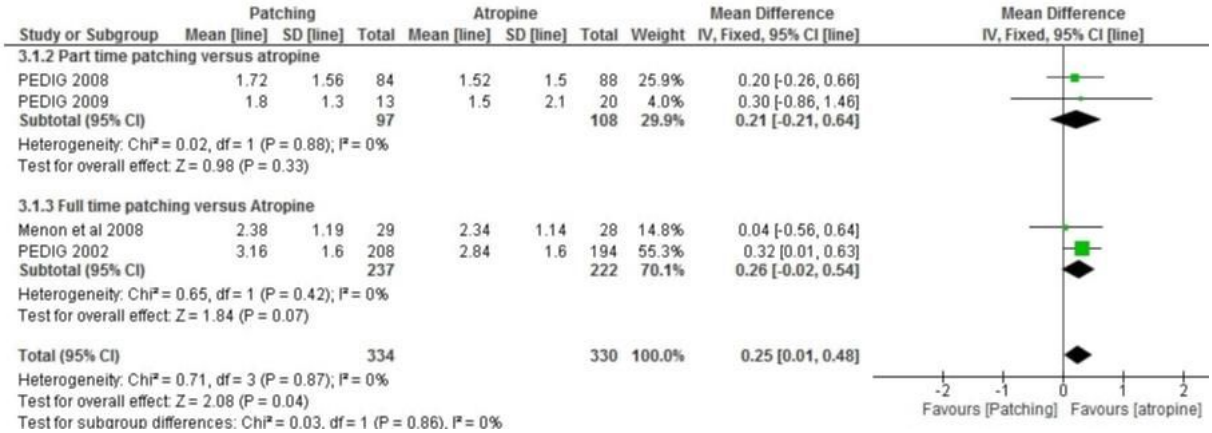

Figure 6

The visual acuity improvement in the amblyopic eye after patching versus atropine

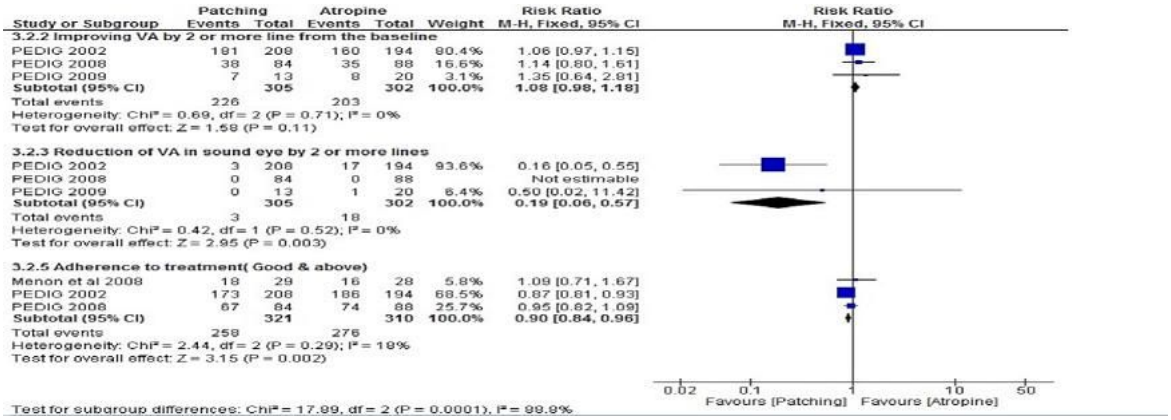

Figure 7

The success, adherence and incidence rate of reverse amblyopia in patching versus atropine

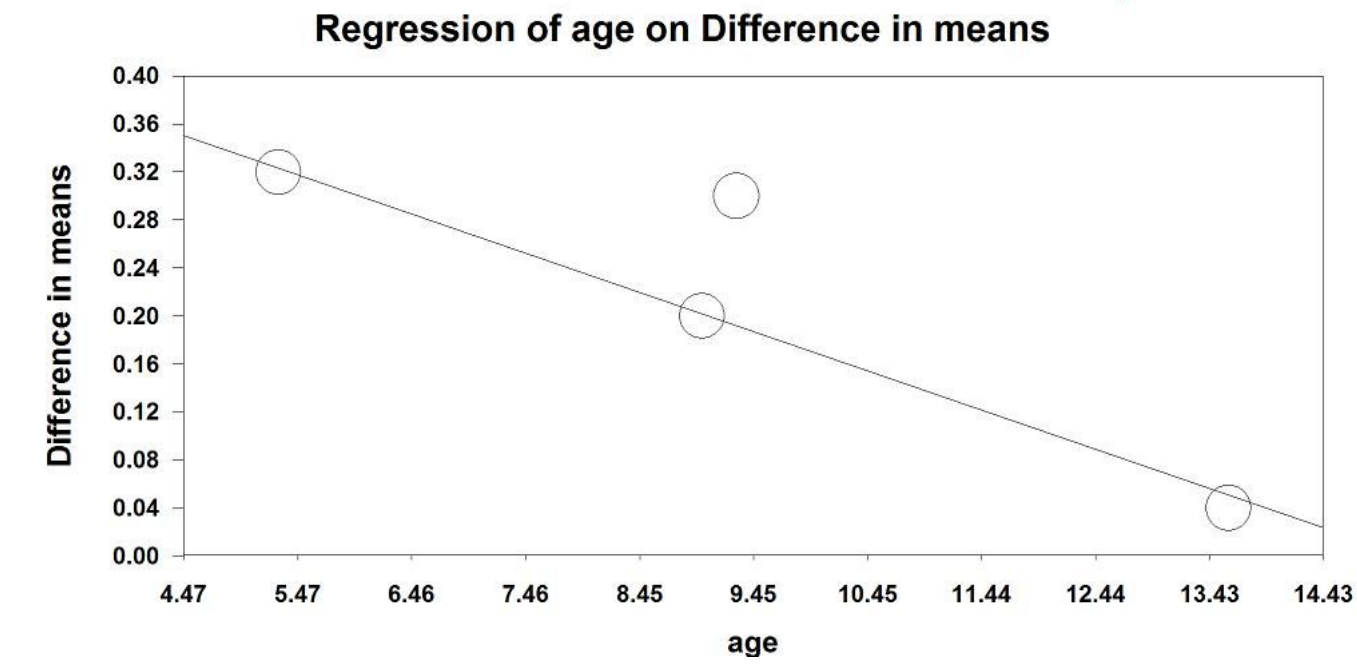

Figure 8

Meta-regression analysis showing the effect of age on the effectiveness of patching and atropine