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Optimised minus lens overcorrection for paediatric intermittent exotropia: A randomised clinical trial

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Conflict of interest: None

Clinical Trial Registration

-Registration SITE: https://www.anzctr.org.au/trial/MyTrial.aspx

-Registration DATE: 03 March 2019

-Registration NUMBER: ACTRN12619000374167

ABSTRACT

Background: Aim of this study was to evaluate the efficacy of a novel algorithm to customise overminus lens (OML) therapy in intermittent exotropia (IXT) based on clinical factors associated with control of the deviation.

Methods: Clinical parameters in IXT vary among individuals. Based on individual's physiological factors, an algorithm was developed. Children aged between four and fifteen years with IXT were randomised into OML and observation groups. Participants in the observation group were corrected for any significant refractive error. IXT control score, angle of deviation, refraction, axial length and stereopsis were examined at baseline and follow up ranging between six and fifteen months and compared. Compliance and tolerance to OML was determined by a symptom survey.

Results: The OML power ranged between -1.00D and -6.25D. Of the total 141 participants (mean age 6.8 ± 2.5 year), 77 were in the OML and 66 were in observation group. IXT control score improved (mean difference -2.5 ± 1.1; $p<0.001$) and angle of deviation reduced (6.9 ± 7.2pd; $p < 0.001$) significantly in the OML group only. Compliance rate to OML wear was 80%; 90% never or rarely experienced asthenopia symptoms. Slightly greater myopic shift (-0.36 ± 0.53D vs -0.18 ± 0.55D) and change in axial length (0.17 mm vs 0.14 mm) were observed in the OML group, but these differences were not statistically significant

Conclusions: A customised overminus lens, calculated using this novel algorithm was effective in improving distance control, angle of deviation and stereopsis. Glasses wear was highly tolerable.

Key Words: Optimised minus lens, overminus lens therapy, intermittent exotropia, OML algorithm, Myopic Shift

1. INTRODUCTION

Minus lens overcorrection or overminus lens therapy, the use of additional minus power over the subject's refractive correction, is an established non-surgical treatment for intermittent exotropia (IXT).[1-4] Variable success rates in both frequency of manifest deviation and reduction in angle following the overminus lens therapy have been demonstrated. The therapy is effective in delaying the surgical treatment.[1, 5-8]

Overminus lenses have been suggested to promote motor control of exodeviation by stimulating accommodative convergence in response to induced hyperopic defocus.[7,9] An alternative mechanism proposes that the effort of convergence required to compensate for the exodeviation activates accommodation resulting in a convergence induced myopia, referred to as phoria myopia.[10,11] Additional minus lens corrects the phoria myopia induced blur allowing sustained fusional convergence thus aiding in controlling the exodeviation.[12]

There is, however, a lack of consistency in the methods used to determine the overminus lens power to be prescribed. Whilst some studies have used the lowest possible minus lens to produce objective orthophoria[8,13], others have used the maximum tolerable overcorrection.[6] Some prescribed the maximum minus possible without compromising best corrected visual acuity[14] and yet others have used a fixed overminus[3-5] depicting it as a 'reasonable' dose to induce fixed amount of accommodation.[4] Some published studies did not detail the basis of their overminus prescription.[1,7]

Both the sensory and motor status are highly variable amongst individuals with IXT. While some individuals with relatively large angles of deviation have good control, others with smaller angles have poor control. Similarly, AC/A ratio, fusional amplitude and refractive status may have direct or indirect effect on the control of deviation. Considering the wide range and variability of factors involved controlling the exodeviation, a fixed overminus approach may not be equally effective. Therefore, we hypothesised that a customised overminus correction determined by the individual patient's physiological factors associated with IXT would improve treatment outcomes. We developed an algorithm to customise the individual's

overminus requirement producing an 'optimised minus lens (OML)' power. To evaluate the efficacy of the OML in controlling distance IXT as the primary outcome, we conducted a randomised clinical trial. Secondary outcome measurements of the trial included the effect on angle of deviation and change in stereopsis. Changes in refraction and axial length and tolerability to OML over the study period were also evaluated. Outcomes of the OML treatment were compared against participants without OML therapy as the control group. We compared our results with the outcomes of methodically equivalent studies.

2. METHODS

This single site randomised clinical trial was approved by the Institutional Review Board (HREC Ref# HREC/19/QCHQ/48781) and followed ethical principles according to the tenets of the Declaration of Helsinki. Appropriate informed consent was obtained before enrolment. The trial was registered to Australia and New Zealand Clinical Trial Registry (ANZCTR 12619000374167). The report is in adherence to the CONSORT guideline (Figure 1).[15]

2.1 Subject Randomization and Enrolment

Inclusion/exclusion criteria of participants are given in Table 1. To ensure an equal probability of individuals with differing levels of IXT controls were evenly distributed in each treatment arm, eligible participants were stratified into three blocks based on their distance IXT control score obtained from a standardised office-based scoring system described in the next section: Block A = Control score 2 to ≤ 3 points; Block B = > 3 to 4 points; and Block C = > 4 points. Patients with IXT control score < 2 were excluded. Participants were then randomised within the block for allocation to one of the OML or the observation group.

Table 1: Inclusion and exclusion criteria

Inclusion Criteria	**Exclusion Criteria**
- Age between 4 and 15 years	- Constant strabismus/exotropia

- Patient with IXT measuring > 10Δ of distance IXT and mean distance control score of 2 points or worse - Best corrected visual acuity 6/9 or better in each eye - Near stereopsis of 100" arc or better - No ocular pathology that might affect ocular motility and visual acuity - Parents willing to and able to provide signed informed consent - Spherical equivalent of cycloplegic refraction between -6.0D and +3.0D.	- IXT treated with minus lens, prism or surgery within the last 6 months. - Any previous strabismus or intraocular surgery - Over 2 lines interocular difference in visual acuity - Inability to determine accurate visual acuity and strabismus assessment due to poor cooperation or intellectual impairment - Developmental delay or general debility interfering study purpose

2.2 Clinical Examination

A comprehensive ocular health assessment and cycloplegic refraction were performed at the initial visit. Cycloplegic refraction involved autorefraction (Retinomax, K-Plus 3, Tokyo, Japan) and objective retinoscopy. If discrepancy between the two varied by ± 0.5D or greater in spherical or cylindrical refraction, subjective refraction under cycloplegia was performed. Autorefraction or subjective refraction, if needed, was used in the calculation of OML and in analysis of refractive change.

Clinical procedures were conducted at the baseline visit while the child wore their habitual refractive correction, if any. Subjects who had significant refractive error during the screening visit but had no spectacles were corrected using wide-aperture trial lens.

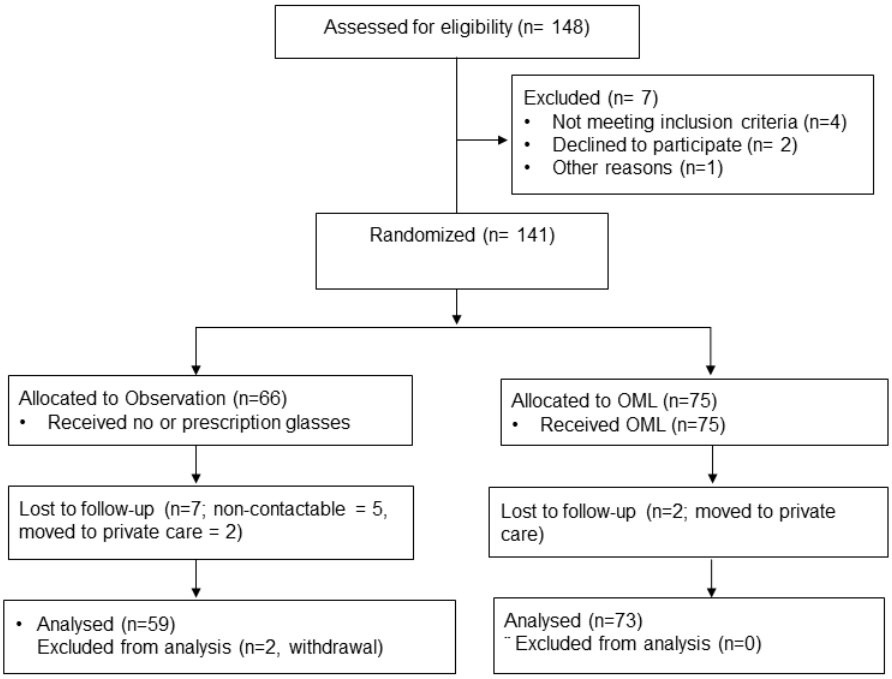

Figure 1: Consolidated Standards of Reporting Trials (CONSORT) of participants.

Control of IXT was assessed using an established and standardised office-based scoring system.[16] The score in this system ranges between 0 and 5, separately for distance (6 metres) and near (33 centimetres) fixation distance, based on the proportion of time the deviation is manifest over the 30 seconds observation period prior to dissociation and recovery of fusion after dissociation (Appendix 1). The IXT control scores were assessed three times, at least 5 minutes apart within the single visit with the average score being used for analysis.

The angle of deviation, in prism dioptre (PD) was measured using prism and alternate cover tests (PACT) at both distance and near fixation prior to and following 30 minutes of monocular occlusion without allowing fusion. Post-occlusion angle measurements were used in the analysis. AC/A ratio was determined using the gradient method; phoria measured first with +1.0D lens and re-measured with -1.0D lens using a high contrast accommodative fixation target (6/9 size letters) at 33 centimetres. An average of the AC/A ratio determined using plus and minus stimuli was used for the calculation. Both plus and minus lenses were used to reduce estimation error as AC/A ratio measured with individual plus or minus stimulus tends to produce differing values.[17] Binocular total accommodative amplitude (AA) was

measured using the minus lens method at near (33 centimetres) with a high resolution 6/9 size letters as fixation target.[18] Axial length was measured using IOL Master 700 (Carl Zeiss Meditec, AG).

Distance crossed stereoacuity was measured using the validated[19] Visotec Distance Stereo Test (Visotec Inc, NZ). Visotec is a polarised vectographic test measuring 60 to 320 arcsec stereoacuity administered at testing distance of six meters. Near stereoacuity was measured using vectographic Titmus circles (Stereo Optical Company, Inc, Chicago, IL, USA). Non-measurable stereopsis was recorded as 'Nil'. Order of the tests was: assessment of distance and near IXT control score (first), visual acuity measurement, distance and near stereopsis test, distance Worth-4-dot test, assessment of distance and near IXT control score (second), measurement of magnitude of angle of deviation, measurement of AA, biometry (axial length), assessment of IXT control score (third), monocular patching (30 minutes), post-patch measurement of a magnitude of angle of deviation and determination of AC/A ratio.

2.3 Development of Algorithm for OML Overcorrection

Magnitude and frequency of manifest deviation are major clinical factors used to describe and determine the clinical management of IXT patients. Factors such as accommodative convergence to accommodation (AC/A) ratio, fusional vergence and refraction have been proposed to influence severity of the condition.[20,21] AC/A ratio, defined as rate of change in angle of visual axes from per unit change in accommodation, was used to estimate the accommodation associated with the neutralisation of the deviation. Therefore, strength of OML overcorrection required can be given by:

$$OML = -\frac{\Delta A}{AC} \quad \text{..... (1)}$$

where, ΔA is the post occlusion distance angle of deviation in prism dioptre

AC is the Accommodative convergence per unit accommodation

In IXT, the frequency and control of the manifest deviation is assessed using an IXT control score. Whether an individual requires full or partial correction of their distance angle with overminus as determined using Equation 1 may be dependent on the level of control they exhibit: individuals with a good control may not need a full neutralisation of angle while others with poor control may benefit from full neutralisation. Therefore, we theorised that a child with a poorer control score would require more accommodative effort and hence a stronger overminus correction. The OML calculated using Equation (1) was therefore adjusted according to the individual's IXT control score, such that:

$$OML = -\left[\frac{\Delta A}{AC} - c\right] \quad \text{..... (2)}$$

where '*c*' is a constant based on an office-based distance IXT control score. Value of '*c*' was assigned between zero and three as follows:

IXT Control Score	Constant (*c*)
5	0
4 to <5	1
3 to <4	2
2 to < 3	3 (patients with IXT control score <2 were excluded)

For an optimum effect of overminus lens, adjustment of refractive error is essential to ensure desired accommodation is induced. Therefore, the OML deduced from the Equation (2) was further adjusted for cycloplegic refraction for the final prescription (OML^F) as:

$$OML^F = -[OML - R_X] \quad \text{..... (3)}$$

where, *Rx* is the spherical component of the cycloplegic refraction; superscript ^{F} represents final. Cylindrical component including the axis remain unchanged.

To maintain best corrected vision, an individual with a minus overcorrection requires to maintain sustained accommodation over a prolonged period. The total AA is an important predictor to determine tolerability of the overminus correction. On the basis of evidence that a pre-presbyopic individual can comfortably exert up to 75%

of their AA for sustained period[22]; the final overminus lens power used in this study consisted of the value resulting either from the Equation (2) or 75% of the AA, whichever was less.

Examples of OML calculation:

Example1: distance PACT (Δ) = 25PD; AC/A ratio = 5:1; IXT control score = 3 (*c*=2); refraction (Rx) = +1.25D; and AA = 8.0D

OML = -(25/5-2) = -3.00D.

Since the OML (-3.00D) is smaller than 75% of total AA (6.00D),

OML^F: - (3.0-1.25D) = -1.75D.

Example2: distance PACT (Δ) = 25PD; AC/A ratio = 4:1; IXT control score = 4 (*c* = 1); refraction = -1.25DS/-0.75Cyl x 90°; and AA = 8.0D

OML = -(25/4-1) = -6.25D.

Since the OML (-6.25) is greater than 75% of total AA (6.00D),

OML^F = -(6.00 – (-1.25)) = -7.25DS/-0.75DCyl x 90°.

2.4 Treatment Regimens

Participants in the OML group were prescribed glasses with the overminus correction for full time wear. Participants in the observation group were prescribed glasses only if their cycloplegic refraction exceeded by 1.00D hyperopia, -0.50D myopia and 0.50D astigmatism.

2.5 Follow-up visits

The original study protocol involved an interim three-month and final six-month follow up post randomization visits. Due to COVID-19 restrictions in the workplace, there was a protocol deviation, in which, the three-month visit was declared non-mandatory and the six month visit (henceforth referred as 'follow-up') was allowed to be extended out depending on individual circumstances. Study-related clinical examination procedures at the follow up visit followed the same protocol as conducted during the baseline examination. Measurement of angle of deviation and control assessment in the OML group were performed with and without the

overminus spectacles. To minimise examiner (JM) bias, baseline clinical data was not made available at the follow-up examination.

2.6 Compliance and Tolerability

Compliance and tolerability to OML wear was assessed at the follow-up visit using relevant questionnaires developed for the PEDIG IXT pilot study.[3] The compliance questions described frequency of wear and tendency for child to look over the glasses. The symptom questionnaire included hurting (nose and ear), headache, eyestrain and blurry vision. Responses were recorded as always (frequency >80%), often (50 to 80%), sometimes (30 to 50%), rarely (10 to 30%) and never (<10%).

2.7 Statistical Analysis

The data were analysed by intention to treat. Descriptive statistics were presented using means and standard deviation if normally distributed, or median and inter-quartile range (IQR) when data were not normally distributed. Categorical variables were presented using frequencies and proportions.

The primary analysis compared the mean difference of distance IXT control score from the baseline. Chi-squared test was used to test for differences between the treatment arms. Paired t-test was used to compare clinical variables between baseline and follow-up. Risk analysis was performed to evaluate if OML wear caused higher myopic shift (axial length and refraction). Stereoacuity was converted into log scale for homogeneity of data where 'Nil' stereopsis was assigned with a value of 500. Comparison of baseline and follow-up stereopsis between the two groups was made using the Wilcoxon Signed Rank Test. All statistical tests of significance are two-sided at the 5% level after Bonferroni correction, where applicable.

3. RESULTS

3.1 Demographics

Subject demographic and clinical characteristics at baseline are summarised in Table 2. One hundred and forty-one children with IXT aged four to fifteen years (mean 6.8 ± 2.5 years; 57% females) were consecutively enrolled between March 2019 and

December 2020; 47% (n = 66) of the participants were randomised to the OML group. There were 29% participants in block A and B each, 42% were allocated to Block C.

Overall completion rates for observation and OML groups were 93% and 89% respectively with a mean±SD follow-up duration of 8.6 ± 2.3 and 9.7 ± 2.9 months, respectively ranging between six and fifteen months in both groups. Nine subjects, two in the observation, and seven in the OML groups, were lost to follow up (Figure 1).

3.2 Profile of OML

The overall mean ± SD of the OML prescribed was -3.7 ± 1.2D ranging between -1.00 and -6.25D (median -3.8D). The proportion of subjects requiring > -2.0D, -2.0 to -3.0D, <-3.0 to -4.0D, < -4.0 to -5D and < -5.0D were 14%, 20%, 32% 18% and 17%, respectively. The OML did not exceed 75% of the total AA in any participant. The mean OML power prescribed to participants who were lost to follow up in the OML group (n = 7; -3.3 ± 0.8D) was not different to rest of the participants in this group.

Table 2: Baseline demographic and clinical characteristics of overall samples

	Randomisation (Groups)		*p*-value by group
	OML (n (%))	**Observation (n (%))**	
Demography: N (%)			
Overall Sample	**66 (100)**	**75 (100)**	
Age			
4-7 years	40 (61)	42 (56)	
8-11 years	21 (32)	27 (36)	
12-15 years	5 (8)	6 (8)	
Gender			
Female	40 (61)	40 (53)	
Male	26 (43)	35 (47)	
Stratification			
Block A	15 (23)	22 (29)	
Block B	20 (30)	22 (29)	
Block C	31 (47)	31 (41)	
IXT Type			
Basic	37 (56)	37 (49)	
	20 (30)	25 (33)	

Pseudo Divergence Excess	8 (12)	11 (15)	
Divergence Excess	1 (1.5)	2 (2.7)	
Convergence Insufficiency			
Clinical Characteristics: Mean±SD (Range)			
Age (years)	6.7 ± 2.7 (4 to 15)	7.0 ± 2.5 (4 to 14)	0.23
BCVA (logMAR)a	0.1 ± 0.1 (0.0 to 0.2)	0.08 ± 0.1 (0.0 to 0.2)	0.21
IXT Control Score - Distance	3.8 ± 0.8 (2.3 to 5.0)	3.5 ± 0.8 (2.0 to 4.8)	0.13
IXT Control Score - Near	1.6 ± 0.7 (0.0 to 3.3)	1.7 ± 0.80 (0.3 to 3.3)	0.46
PACT Distance (pd)	22.3 ± 5.9 (8.0 to 35.0)	22.2 ± 7.4 (12.0 to 50.0)	0.94
PACT Near (pd)	17.6 ± 7.2 (4.0 to 40.0)	16.7 ± 8.0 (6.0 to 45.0)	0.48
AC/A Ratio	5.2 ± 1.0 (2.5 to 8.0)	4.8 ± 1.1 (1.5 to 7.0)	0.07
Accommodative Amplitude (D)	9.6 ± 1.3 (5.5 to 11.0)	9.4 ± 1.2 (5.0 to 11.0)	0.82
Axial Length (mm)[a]	22.7 ± 0.8 (21.0 to 24.9)	22.7 ± 0.8 (21.0 to 24.8)	0.14
Refraction (SE)[a]	1.0 ± 0.8 (-1.5 to +2.5)	0.7 ± 1.0 (-2.5 to +3.0)	0.04*
Distance Stereopsis	270.1 ± 189.4 (60 to Nil)	269.7 ± 182.5 (60 to Nil)	0.99
Near Stereopsis	73.4 ± 43.2 (40 to Nil)	75.0 ± 59.9 (40 to Nil)	0.86

*[a]only the right eye data; SE – spherical equivalent refraction. Statistical significance *p<0.05; **p < 0.01, ***p < 0.001. IXT types are defined based on Burian's classification[22]*

In the observation group, 32% (n = 24) participants were prescribed glasses for their refractive error. Of these, 27% (n = 9) were myopic (-0.86 ± 0.61D; maximum -2.75D) and 32% (n = 11) were hyperopic (+0.80 ± 0.52D; maximum +2.0D) SE refraction. Among those requiring refractive correction, 50% (n = 12) had astigmatism of ≥ 0.5D.

3.3 Primary Outcome

3.3.1 Effect on Control Score

The mean distance IXT control scores at the baseline were 3.8±0.8 point in the OML group and 3.5 ± 0.8 point in the observation group. At the follow up, these were 1.6 ± 1.3 in the OML group compared to 3.7 ± 1.0 in the observation group (Table 3). Similarly, near control scores in the OML and the observation groups were 1.6 ± 0.7

and 1.7 ± 0.8, respectively at baseline and 0.6 ± 0.7 and 1.9 ± 1.0 respectively at follow up. Block-wise IXT controls scores at baseline and follow up are given in Appendix 2.

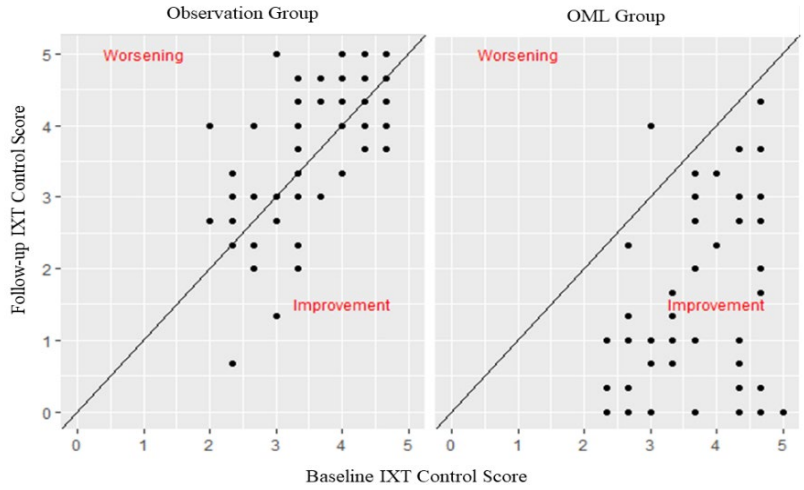

Figure 2: Scatterplot illustrating improvement or worsening of IXT control sore at follow-up

Mean difference in distance IXT control score between the groups at the follow up was -2.1 (95% CI: -2.8 to -2.2; p<0.001). The scatter plot (Figure 2) compares the distance IXT control score for each participant at baseline and follow-up. At the follow-up visit, 81% (n = 48) participants in the OML group had improvement of distance IXT control score by ≥ 1 point compared to 7% (n = 5) in observation group. Improvement in the control score by ≥ 2 points was observed in 61% (n = 36) in the OML group and none in the observation group. In the observation group, 16% (n = 12) participants showed deterioration in their distance IXT control score by 1 or more-point compared to one participant in the OML group.

When tested without the overminus glasses in the OML group at follow up, the mean±SD distance and near IXT control scores at the follow up were 3.3 ± 0.8 and 1.7 ± 0.8 points, respectively. These were not statistically different from the baseline measurement (p-value 0.08 for distance and 0.42 for near). Without glasses, the proportion of participants improving IXT control score by ≥ 1-point was 20% for distance and 12% for near.

3.4 Secondary Outcomes

3.4.1 Effect on Angle of Deviation

A significant improvement in both the distance and near angles were found in the OML group (Table 3) with a mean±SD reduction of 6.9 ± 7.2PD (95% CI: -8.7 to -4.9; $p < 0.001$) and 6.2 ± 8.6PD (95% CI: -8.2 to -3.8; $p < 0.001$), respectively compared to 0.0 ± 4.2PD (95% CI: -1.0 to 1.0; $p = 1$) and 0.2 ± 5.8PD (95% CI: -1.1 to 1.6; $p = 0.73$), respectively in the observation group. Distance and near angles of deviation at baseline and follow up for each block are given in Appendix 2. In the OML group, without their OML correction at follow up the mean±SD distance and near angles of deviation were 22.5 ± 6.3pd and 14.9 ± 6.8pd respectively. Both distance ($p = 0.82$) and near ($p = 0.82$) angles were not statistically different from the baseline measurement.

Table 3: Follow-up clinical characteristics and comparison between the groups

	Mean±SD (Range)		*p*-value
	OML (n=59)	**Observation (n=73)**	
Follow-up (months)	9.7±2.9 (6.0 to 15.0)	8.6±2.3 (6.0 to 15.0)	0.03*
BCVA[a]	0.05±0.06 (0.0 to 0.30)	0.07±0.08 (0.0 to 0.30)	0.56
Control Score - Distance	1.6±1.3 (0.0 to 4.3)	3.7±1.0 (0.7 to 5.0)	<0.001***
Control Score - Near	0.6±0.7 (0.0 to 2.7)	1.9±1.0 (0.0 to 4.0)	<0.001***
PACT Distance	15.4±7.8 (-6.0 to 30.0)	22.2±6.9 (10.0 to 45.0)	<0.001***
PACT Near	11.4±7.7 (-6.0 to 30.0)	17.0±7.8 (4.0 to 40.0)	<0.001***
Axial Length[a]	22.9±0.8 (21.1 to 25.3)	22.9±0.8 (21.2 to 24.9)	0.98
Refraction (SE) [a]	0.7±0.9 (-2.0 to +2.3)	0.4±1.0 (-2.8 to +3.0)	0.29
Distance Stereopsis	157.0±135.4 (60 to Nil)	3.8.6±180.2 (60 to Nil)	<0.001***
Near Stereopsis	52.0±40.7 (20 to Nil)	72.3±116.0 (20 to Nil)	0.05*

[a] *right eye data; Statistical significance $^{*}p<0.05$; $^{**}p<0.01$, $^{***}p<0.001$. All results for OML group are with their OML spectacles in place.*

3.4.2 Stereoacuity and Suppression

Compared to baseline, stereoacuity at the follow up visit significantly improved in the OML group for both distance ($p < 0.001$) and near ($p = 0.001$). In the observation group, the overall change in stereoacuities were not significant (Table 4). Worth-4-dot test at baseline visit demonstrated intermittent or constant suppression of one eye in 54% (n = 32) in the OML and 51% (n = 37) in the observation groups. At follow up, no suppression was observed in 73% (n = 24) subjects in the OML group and 16% (n = 7) in the observation group.

3.4.3 Change in Refraction and Axial Length

Both groups had a myopic shift from baseline to follow up however there was a greater myopic shift in the OML group (mean -0.36 ± 0.53D (95% CI -0.46D to -0.22D; $p < 0.001$)) in comparison to the observation group (mean -0.18 ± 0.54D in 95% CI -0.33D to -0.07D; $p = 0.002$). The mean difference in myopic shift between the groups (-0.17D) however was not statistically significant ($p = 0.067$). Change in axial length did not differ between the groups (0.17mm vs 0.14mm; $p = 0.360$).

Table 4: Results of Paired Sample t-test showing for difference between baseline and follow-up measurement of clinical variables for each treatment arm

Difference	OML			Observation		
	Mean±SD	95%CI	*p*	Mean±SD	95% CI	*p-value*
BCVA[a]	0.0 ± 0.1	0.0, 0.0	0.032*	0.0 ± 0.1	-0.0, 0.0	0.97
CS_D	-2.5 ± 1.1	-2.8, 2.2	<0.001***	-0.3 ± 1.0	-0.5, -0.1	0.07
CS_N	-1.1 ± 0.8	-1.3, -0.9	<0.001***	0.0 ± 0.86	-0.2, 0.2	0.82
PACT_D	-6.9 ± 8.6	-8.4, -5.1	<0.001***	0.0 ± 4.16	-0.9, 0.9	0.99
PACT_N	-6.2 ± 8.6	-8.4, -3.9	<0.001***	0.2 ± 5.75	-1.1, 1.6	0.73
SE[a]	-0.36 ±0.53	-0.49, -0.22	<0.001***	-0.2 ± 0.54	-0.3, -0.1	0.002**
AL[a]	0.17 ± 0.18	-0.12, 0.21	<0.001***	0.1 ± 0.17	0.1, 0.18	<0.001***
D_Stereo	0.2 ± 0.4	0.1, 0.3	<0.001***	-0.1 ± 0.4	-0.1, 0.0	0.15
N_Stereo	0.2 ± 0.2	0.1, 0.2	<0.001***	0.1 ± 0.2	0.0, 0.1	0.01**

[a] *right eye data; CS_D –distance IXT control score; CS_N –near IXT control score, SE – spherical equivalent refraction, AmAcc - amplitude of accommodation, AL = axial length; D_&N_Stereo = Distance and near stereopsis (logscale); Statistical significance $^{*}p<0.05$; $^{**}p<0.01$, $^{***}p<0.001$*

Eleven participants in the OML group and six in the observation group were myopic at baseline (SE refraction < 0.00D). Of the myopic participants, 67% (n = 4) in the observation and 72% (n = 8) in the OML group had myopic shift of ≥ 1.0D. The risk ratio for such shift with OML wear was 2.5 (95% CI 0.8 to 7.8; p = 0.126).
The myopic shift was moderately correlated to baseline refraction both in the OML group (r = 0.38, p = 0.003) and the observation group (r = 0.27, p = 0.02). No significant correlations were found between the myopic shift with duration of OML wear (r = 0.05, p = 0.71) and strength of OML power (r = 0.04, p = 0.79).

3.5 Compliance and Symptoms

Parents of all 59 subjects in the OML group attending the follow-up visits completed the survey. Over 80% of the participants wore the glasses regularly (> 80% of times) and nearly 70% subjects never or rarely looked over the glasses (Appendix 3). Blurred vision, reported by 4% of participants, was the most significant asthenopia symptom associated with non-compliance to OML wear (r = 0.37, p = 0.004). Most of the participants (90%) rarely or never experienced asthenopia. Among the symptomatic subjects, 72% reported two or more and 23% experienced all five asthenopia symptoms at varying frequencies (rarely to always); 28% had only one of isolated symptom.

4. DISCUSSION

By including clinically relevant parameters associated with IXT, we developed a practical algorithm to individually customise the overminus lens requirement for the treatment of IXT in paediatric population. This algorithm produced overminus strength requirements ranging between -1.00D and -6.3D. Kennedy, reported a similar range when subjectively determining the lowest possible overminus that resulted in orthophoria.[13] By way of comparison to a fixed overminus strategy of -2.50D, over 74% of our participants required stronger and 14% required weaker overminus by ≥ 0.50D. As we expected amongst the children of this age group, AA was not a restricting factor in determining the OML overcorrection in this study.

Definitions used to measure success of overminus lens therapy in earlier studies have been variable and consisted of measures such as cosmetically straight eyes[13], 'qualitative improvement'[1], exophoria at distance and near.[5,8] Results of these studies, being retrospective and observational in nature, are not readily comparable. More recent studies, such as the PEDIG randomised clinical trial[4], have focused on improvement in IXT control score.[2-4] Age of participants, study duration and inclusion/exclusion criteria in our study match closely to those in the recently reported PEDIG Trial; therefore, we suggest the results are comparable. The PEDIG study reported mean final distance office-based control score of 1.8 ± 1.3 points after wearing a fixed overminus correction (-2.50D). This compared to 1.6 ± 1.3 points in our OML group. The mean difference at follow up between the treatment arms in our study (-2.1 points; 95% CI: -2.5 to-1.9) was greater than that found in the PEDIG study (-0.8 points; 95%CI: -1.0 to -0.5). Improvement in distance IXT control score by ≥ 1-point was 85% and by ≥ 2-point was 58% in our OML group which compared to 61% and 34%, respectively in the PEDIG study at 12 months follow up.[4] These findings may, in part, be ascribed to a greater efficacy of customised OML in treating IXT than that with standard fixed overminus power. It should be noted however, that the distance IXT control score remained unchanged from baseline in our observation group whereas it improved by 0.4-points in PEDIG study. This may have contributed to the greater treatment effect observed in our study.

Angle of deviation and stereoacuity significantly improved amongst our participants wearing OML compared to the observation group. On average, the distance angle reduced by 6.9PD (95% CI -8.4 to -5.1) and the near angle by 6.2PD (95% CI -8.4 to -3.9) in the OML group at follow up. This result is consistent with previous report of a mean reduction in the distance angle by 7.0PD using -2.0 to -4.0D overminus correction.[14] The PEDIG study[4] found mean reduction of 5.0PD at 12 months follow up from baseline in their overminus participants.

In our OML group, proportion of subjects reporting 'hurting eyes' (10%), headache (6%), eyestrain (9%), and blurry vision (5%) with the frequency of 'always or sometimes' were lower than that reported in the PEDIG study[4] in which, the proportions were 38% 30%, 37% and 22% respectively. Similarly, only 18% of

participants in OML group always or often looked over the glasses compared to 43% in the PEDIG study. This may be suggestive of improved tolerance and compliance with customised overminus.

Although most previous studies reported that overminus lens therapy does not cause myopia[24,25], the recent PEDIG[4] study reported significantly higher myopic shift in their intervention group. The myopic shift in our OML group (-0.36D) was slightly higher than in the observation group (-0.18D) but smaller than that reported in the PEDIG study (-0.42D). Population studies have noted refractive changes of between -0.14D to -0.40D per year among aged 3 to 17 years children with +1.0D hyperopia to -2.0D myopia.[25] In children with untreated IXT, an annual myopia progression rate of -0.25D per year has been reported.[26] Although development of myopia may vary with various factors such as genetics, baseline refraction and individual environmental factors[27], the myopic shift in both of our groups could be regarded as being within the normally expected refractive growth. We also found a weak but significant correlation between myopic shift and baseline refraction in our both the OML ($r = 0.38$) and the observation ($r = 0.27$) groups which may suggest caution be required when prescribing overminus treatment in myopic individuals. This is consistent with previous reports of greater myopic shift among myopic individuals.[28,29] The relationships between the change in refraction and duration or strength of OML wear were not significant in our study. The PEDIG study population had significantly higher proportion of myopic participants compared to ours. Interestingly, they found essentially no change in refraction (-0.04D) in their observation group (compared to our 0.18D progression). Although our study duration was slightly shorter than the PEDIG (mean difference 2.4 months), this difference is unlikely to have significant impact on the results.

The possible mechanisms by which overminus lens correction might accelerate myopic shift are not clear. Sustained accommodation due to hyperopic defocus has been suggested as a precursor for eye elongation.[30] However, this hypothesis is not without controversies[31] with no clear evidence of their association.[32] Although the OML group in our study had slightly greater elongation of axial length compared to that of the observation group (0.17 mm vs 0.14 mm), the difference is clinically as well as statistically not significant ($p = 0.43$); the changes in both groups are within

the expected mean elongation rate in children of similar age (0.21 mm per year).[25,33] To our knowledge, this is the first clinical trial to provide change in axial length data associated with minus lens overcorrection in IXT.

It is known that unblinded randomised trials tend to yield a larger effect[34] and therefore, an important limitation of this study was that neither the families nor the examiner were masked. Overminus glasses, worn by participants in the OML group, could have been identified by the examiner (JM) potentially revealing the treatment allocation. To minimise bias, the examiner was kept naive to baseline clinical findings. Another limitation of the study could be that the algorithm does not include fusional amplitude however earlier studies have reported that fusional amplitude in IXT is similar to that in normal individual, hence we treated this as mathematically constant. Given the complex pathophysiological bases associated with IXT, further refinement of the algorithm may be needed. Further limitation is that we used relatively weak stimulating and relaxing lens powers in determining the AC/A ratio (± 1.0D). A higher strength lens could have been preferrable to minimise the effect of depth of focus on discriminating the accommodative target thereby improving the accuracy of measurement. Further research directly comparing efficacy of OML to other approaches of overminus treatment such as standard fixed overminus is worthwhile.

In summary, we have developed a simple algorithm to calculate an OML overcorrection based on a range of clinical factors associated with IXT. The results showed that the individually customised OML were very effective in controlling IXT. This effect, however, was not sustainable as the control score in overall subjects without the overminus glasses was not different from the baseline. Our results were not conclusive of increased risk of myopia associated with overminus but a correlation of progression of myopia with baseline refraction is suggestive of caution required in adopting the treatment method in an already myopic individual. Evaluation of biometric changes over a longer term may provide further guidance of this risk.

REFERENCES

1. Caltrider N, Jampolsky A. Overcorrecting minus lens therapy for treatment of intermittent exotropia. *Ophthalmol*. 1983; 90:160-1165.
2. Watts P, Tippings E, Al-Madfai H. Intermittent exotropia, overcorrecting minus lenses, and the Newcastle scoring system. *J AAPOS*. 2005; 9:460-464.
3. Chen AM, Holmes JM, Chandler DL, et al. A randomized trial evaluating short-term effectiveness of overminus lenses in children 3 to 6 years of age with intermittent exotropia. *Ophthalmol*. 2016; 123:2127-2136.
4. Chen AM, Erzurum SA, Chandler DL, et al., Overminus Lens Therapy for Children 3 to 10 Years of Age With Intermittent Exotropia: A Randomized Clinical Trial. *JAMA Ophthalmol.* 2021; 39:464-476.
5. Goodcare H. Minus overcorrection: Conservative treatment of intermittent exotropia in the young child – a comparative study. *Australian Orthop J*. 1985; 22:9-18.
6. Donaldson PJ, Kemp EG. An initial study of the treatment of intermittent exotropia by minus overcorrection. *Br Orthop J*. 1991; 48:41-43.
7. Reynolds JD, Wackerhagen M, Olitsky SE. Overminus lens therapy for intermittent exotropia. *Am Orthop J.* 1994; 44:86-91.
8. Rowe RJ, Noonan CP, Freeman G, DeBell J. Intervention for distance intermittent exotropia with overcorrecting minus lenses. *Eye*. 2009; 23:320-325.
9. Coffey B, Wick B, Cotter S, Scharre J, Horner D. Treatment options in intermittent exotropia: a critical appraisal. *Optom Vis Sci*. 1992; 69:386-404.
10. Firth AY, Davis H, Horwood AM. Binocular Visual Acuity in Intermittent Exotropia: Role of Accommodative Convergence. *Am J Ophthalmol*. 2013; 155:776-777.
11. Ha SG, jang SM, Cho YA, Kim SH, Song JS, Suh YW. Clinical exhibition of increased accommodative loads for binocular fusion in patients with basic intermittent exotropia. *BMC Ophthalmol*. 2016; 19:1-6.
12. Brodsky MC, Horwood AM, Riddell PM. Intermittent Exotropia - Are we underminusing by not overminusing? *J AAPOS*. 2015; 19:397-398.

13. Kennedy JR. The correction for divergent strabismus with concave lenses. *Am J Optom.* 1954; 31:605-614.
14. Bayramlar H, Gurturk AY, Sari U, Karadag R. Overcorrecting minus lens therapy in patients with intermittent exotropia: Should it be the first therapeutic choice? *Int J Ophthalmol.* 2017; 37:385-390.
15. The CONSORT 2010 Statement. CONSORT Transparent Reporting of Trials. Accessed March 2021. Available from http://www.consort-statement.org/.
16. Mohney BG, Holmes JM. An office-based scale for assessing control in intermittent exotropia. *Strabismus*, 2009; 14:147-150.
17. Amaechi O, Obiora I. A comparative study of the gradient accommodative convergence/accommodation ratios obtained through +1.00DS and -1.00DS in primary school children. *J Nig Optom Assoc*. 2004; 11:8-11.
18. Elliot DB. Chinical procedures in primary eye care. Butterworth-Heinemann 2007, 3rd ed:192-193.
19. Ale Magar JB, Shah SP, Sleep MG, Willett FA, Dai, SH. Validity and repeatibility of contour-based visotec distance stereoacuity test. Clin Exp optom 2022. (in press). Doi: 10.1080/08164622.2022.2033599
20. von Noordan GK, Cooper EC. Binocular Vision and Ocular Motility: Theory and management of Strabismus. Binocular Vision and Strabismus, 1993. 2002 6th Edition.
21. Superstein R, Dean TW, Holmes JM, et al. Relationship among clinical factors in childhood intermittent exotropia. *J AAPOS*. 2007; 21:268-273.
22. Wolffsohn JS, Sheppard AL, Vakani S, Davies LN. Accommodative amplitude required for sustained near work. *Ophthalmic Physiol Opt*. 2011; 31:480-486.
23. Burian HM and Spivey BE. The surgical management of exodeviations. *Trans Am ophthalmol Soc.* 1964; 62:276-306.
24. Kushner BJ. Does Overcorrecting Minus Lens Therapy for Intermittent Exotropia Cause Myopia? *JAMA Ophthalmol*. 1999; 117:638-642.
25. Matsumura H, Hirai H. Prevalence of myopia and refractive change in students from 3 to 17 years of age. *Surey Ophthalmol*. 1999; 44:S109-S115.

26. Ekdawi NS, Nusz KJ, Diehl NN, Mohney BG. The development of myopia among children with intermittent exotropia. *Am J Ophthalmol*. 2010; 149: 503-507
27. Cooper J and Tkathenko. A review of current concept of the etiology and treamtent of myopia. *Eye Contact Lens*. 2018; 44:231-247.
28. Goss D. Linearity of refractive change with age in childhood myopia progression. *Am J Optom Physiol Optics*. 1987; 64:775-780.
29. Rutstein RP, Marsh-Tootle W, London R. Changes in refractive error for exotropes treated with overminus lenses. *Optom Vis Sci*. 1989; 66:487-491.
30. Gwiazda JE, Hayman L, Norton TT, et al. Accommodation and related risk factors associated with myopia progression and their interaction with treatment in COMET children. *Invest Ophthalmol Vis Sci*. 2004; 45:2143-2151.
31. Mutti DO, Zadnik K. Has near work's star fallen? *Optom Vis Sci*. 2009; 86:76-78.
32. Chen Y, Drobe B, Zhang C, et al. Accommodation is unrelated to myopia progression in Chinese myopic children. *Sci Rep*. 2020; 10:12056.
33. Tideman JW, Polling JR, Vingerling JR, et al., Axial length growth and the risk of developing myopia in European children. *Acta Ophthalmol*. 2018; 96:301-309.
34. Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA Ophthalmol.* 1995; 273:408-412.

Appendix 1: An Office-based Distance IXT Control Scoring System[18]

0 = No exotropia unless dissociated, recovers in <1 second (phoria)

1 = No exotropia unless dissociated, recovers in 1 to 5 seconds

2 = No exotropia unless dissociated, recovers in > 5 seconds

3 = Exotropia <50% of the times during 30 seconds observation before dissociation

4 = Exotropia >50% of the times during 30 seconds observation before dissociation

5 = Constant Exotropia

Appendix 2: IXT control scores and angle of deviation (Median [IQR] or Mean±SD (Range)) in each block at baseline and follow up visits

		Baseline		**OM Group**		
		OML (n=66)	*Observation (n=75)*	*OML Group (n=59)*	*Observation (n=73)*	*p*
IXT Control Distance	Block A	2.7 [2.3, 2.8]	2.3 [2.3, 2.6]	0.5 [0.0, 1.0]	2.3 [2.3, 3.0]	<0.001***
	Block B	3.3 [3.3, 3.7]	3.3 [3.3, 3.5]	1.3 [1.0, 2.3]	3.3 [3.0, 4.3]	<0.001***
	Block C	4.7 [4.3, 4.7]	4.3 [4.3, 4.7]	2.2 [0.4, 3.0]	4.5 [4.0, 5.0]	<0.001***
	Overall	**3.8±0.8 (2.3 – 5.0)**	**3.5±0.8 (2.0 – 4.8)**	**1.6±1.3 (0.0 – 4.3)**	**3.7±1.0 (0.7 – 5.0)**	**<0.001****
IXT Control Near	Block A	0.8 [0.6, 0.8]	1.0 [0.7, 1.3]	0.0 [0.0, 0.3]	0.5 [0.0, 1.0]	<0.001***
	Block B	1.3 [1.2, 1.5]	1.7 [1.2, 1.7]	0.7 [0.0, 1.0]	2.0 [1.0, 2.7]	<0.001***
	Block C	2.3 [2.0, 2.3]	2.3 [2.0, 2.7]	0.5 [0.0, 1.3]	2.3 [2.0, 3.0]	<0.001***
	Overall	**1.6±0.7 (0.0 – 3.3)**	**1.7±0.80 (0.3-3.3)**	**0.6±0.7 (0.0 – 2.7)**	**1.9±1.0 (0.0 – 4.0)**	**<0.001****
PACT Distance	Block A	17.2±5.2 (8.0 – 25.0)	17.5±5.2 (12.0 – 30.0)	13.0±8.1 (8.3 – 17.7)	18.4±5.9 (15.8 – 21.0)	0.027*
	Block B	21.6±3.8 (15.0 – 30.0)	21.0±5.0 (12.0 – 30.0)	17.4±4.3 (14.2 – 23.6)	22.0±5.4 (19.6 – 24.5)	0.031*
	Block C	25.3±5.4 (10.0 – 35.0)	26.6±7.8 (14.0 – 50.0)	16.2±9.1 (-6.0 – 19.7)	25.4±7.3 (22.7 – 28.1)	<0.001***
	Overall	**22.3±5.9 (8.0 – 35.0)**	**22.2±7.4 (12.0-50.0)**	**15.4±7.8 (-6.0 – 30.0)**	**22.2±6.9 (10.0 – 45.0)**	**<0.001****
PACT Near	Block A	14.6±6.6 (4.0 – 26.0)	11.6±3.9 (6.0 – 24.0)	11.4±8.2 (6.7 – 16.2)	12.5±6.0 (9.9 – 15.1)	0.65
	Block B	14.7±4.2 (8.0 – 25.0)	15.4±6.3 (6.0 – 30.0)	12.9±5.5 (10.1 – 15.7)	16.4±5.3 (14.0 – 18.8)	0.05
	Block C	21.0±7.6 (8.0 – 40.0)	21.2±8.9 (7.0 – 45.0)	12.2±8.6 (-6.0 – 15.5)	19.5±9.2 (16.1 – 23.0)	0.003**
	Overall	**17.6±7.2 (4.0 – 40.0)**	**16.7±8.0 (6.0 – 45.0)**	**11.4±7.7 (-6.0 – 30.0)**	**17.0±7.8 (4.0 – 40.0)**	**<0.001****

IXT – Intermittent Exotropia; PACT – Prism and alternate cover test

*Statistical significance (two-sided) *p<0.05; **p<0.01, ***p<0.001*

Appendix 3: Summary of Survey Responses

Compliance & Symptom Questions: n (%)	**Always**	**Often**	**Sometimes**	**Rarely**	**Never**
How often does your child wear glasses?	24 (41)	23 (39)	8 (14)	4 (7)	0 (0.0)
Does your child look over glasses?	3 (1)	10 (17)	5 (9)	22 (37)	19 (32)
How often does your child take his/her glasses off?	0 (0.0)	8 (14)	13 (22)	24 (41)	14 (24)
Does your child complain of hurting ear/nose?	0 (0.0)	1 (2)	9 (15)	13 (22)	36 (61)
Does your child complain of headache that is likely related to	0 (0.0)	1 (2)	5 (9)	10 (17)	43 (73)
glasses?	0 (0.0)	0 (0.0)	9 (15)	20 (34)	30 (51)
How often does your child complain of eye strain (tired, sore)?	0 (0.0)	2 (3)	8 (14)	9 (15)	40 (68)
Does your child avoid reading close-up?	1 (2)	1 (2)	3 (5)	16 (27)	38 (64)
Does your child report blurry vision with the glasses?					