

Is intermittent exotropia a curable condition?

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Abstract

Surgical treatment of childhood intermittent exotropia (XT) is associated with high recurrence rates. In addition, the natural history of intermittent XT has not been rigorously studied and, anecdotally, some cases resolve without surgery. We compared long-term cure rates in children with surgically and non-surgically managed intermittent XT. Children undergoing surgery for intermittent XT who had 5 years follow-up were retrospectively identified. A non-surgical cohort of comparable children was selected by matching each surgical patient for age at onset and age at the 5-year examination. Cure was defined as no manifest tropia on examination or by history, no new monofixation (stereoacuity subnormal for age), and no additional surgery. Each group had 33 children (total follow-up from presentation 7.2 ± 2.6 years in the surgical group *vs* 6.8 ± 2.3 years). There were no significant differences between groups for age at onset, age at presentation, or distance or near angle of deviation at presentation (all $P \geq 0.4$). The cure rate at 5 years was 30% in the surgical group and 12% in the non-surgical group ($P = 0.1$; difference 18%, 95% CI -1 to 37%). Only a small proportion of surgical and non-surgical patients met our definition of cure, with the vast majority demonstrating a constant or intermittent manifest deviation after an average of 7 years follow-up. In childhood intermittent XT, long-term cure is difficult to achieve with surgical intervention, and in some patients managed non-surgically the intermittent XT will spontaneously resolve.

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Introduction

Intermittent exotropia (XT) is one of the most common types of childhood strabismus, occurring in ~1% of children.¹ Nevertheless, there is no

consensus regarding the optimum type of treatment and the optimum timing of treatment.^{2–4} Current management options include watchful waiting,⁵ part-time occlusion,^{4,6–8} over-minus spectacles,^{9–12} fusion exercises,¹³ and strabismus surgery.^{2–4} Much of the controversy is due to limited data on the natural history of intermittent XT and limited data on the long-term outcomes with each type of intervention. In the context of this uncertainty, it is not unreasonable to ask whether childhood intermittent XT can be ‘cured’. To try to shed light on this question, we designed a retrospective study to compare long-term outcomes with surgery *vs* conservative management in children with intermittent XT.

Materials and methods

Patients

We retrospectively identified all children with intermittent XT in our practice with at least 5 years of follow-up, by searching clinical and research databases. We included children with basic divergence excess, true divergence excess and pseudo divergence excess types of intermittent XT. We excluded patients with high AC/A ratio type and convergence insufficiency type intermittent XT (near angle > 10 prism diopters (PD) greater than distance) at the presenting exam. Subjects were required to be 12 years of age or younger at first presentation to allow for 5 years of follow-up while still considered a child. Children with previous eye muscle surgery and children with developmental delay were excluded.

Surgical cohort

From the entire cohort of children with intermittent XT, we identified those who had undergone surgery and had 5 years postoperative follow-up (5-year window: 3–9 years). For 5-year outcome data, we used the examination closest to 5 years following the

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initial surgery with a measure of near stereoacuity. For each patient, we recorded the estimated age at onset of the intermittent XT, based on the medical history.

Non-surgical cohort

We identified all children who had not undergone surgery and who had at least 5 years total follow-up (presentation to most recent examination). Any non-surgical treatment was recorded. To match the non-surgical cohort to the surgical cohort as closely as possible for age at onset of intermittent XT, and duration of the disease, we ordered both surgical and non-surgical cases first by estimated age at onset and then by age at the 5-year postoperative examination or most recent follow-up. For each surgical patient, we selected the first non-surgical patient from the ordered list with the same age at onset and with a follow-up examination at the same age (within 1 year) of the surgical patient's 5-year postoperative examination. For the non-surgical cohort, we then identified an interim examination (with a measure of near stereoacuity) that matched the age at the preoperative examination for the surgical patients as closely as possible.

Clinical data

Once examinations were identified, the following clinical data (if available) were collected for all included subjects at each visit: near stereoacuity (measured using either Preschool Randot, Frisby, or Titmus circles), angle of deviation in PD at distance (3 m) and near (1/3 m) measured using the prism and alternate cover test (PACT), distance and near exodeviation control score at distance and near (using the 0- to 5-point office control scale¹⁴ recognising that a single assessment of control may be inadequate¹⁵). At the 5-year outcome examination, we recorded the presence of a manifest deviation (yes/no) by parental history and by examination, as noted in the medical record.

Stereoacuity data were categorized to enable classification of the patient's sensory status as either: bifixation, monofixation, or uncertain. Stereoacuity data were used in the following hierarchical order as available; Preschool Randot test (Stereo Optical, Chicago, IL, USA), Frisby test (Clement Clarke, Harlow, England), Titmus circles test (Stereo Optical). As described previously,¹⁶ children were classified as 'bifixation', if they achieved 40 or 60 arc seconds, 'monofixation' if worse than 60 arc seconds and also below normal for age, and 'uncertain' if worse than 60 arc seconds but not below normal for age.¹⁶

Analysis

For the purposes of the present study, given the limitations of the historical data, we defined 'cure' as

combined motor success and sensory success at the 5-year follow-up examination. Motor success was defined as no observed manifest deviation by clinic examination and by history. If an assessment of control using the office control score¹⁴ had been performed, a control score of 0 (pure phoria) or 1 (recovery 1–5 s after dissociation) was considered consistent with no manifest tropia but a control score of 2 (indicating recovery >5 s after dissociation) was not taken as success. A patient was also not considered a motor success if they had undergone an additional surgery prior to the 5-year follow-up examination.

Sensory success was defined as bifixation (40 or 60 arc seconds) or no evidence of induced monofixation (where the patient had bifixation at presentation, preoperative, or interim examinations, but had monofixation at the 5-year follow-up examination). Such a definition of sensory success did not preclude patients with monofixation being classified as sensory successes at their follow-up examination if they had monofixation on their presentation preoperative or interim examinations, which we felt was reasonable because a proportion of patients presenting with XT already have monofixation.^{16,17}

We compared the proportion of patients in the surgical and non-surgical cohorts classified as 'cure' at the 5-year follow-up examination, and also the proportion of patients with monofixation at presentation and at follow-up examination time points, using Fisher's exact tests. We also compared mean angle of deviation (by PACT) between groups using *t*-tests, and we compared median distance and near office control scores between groups using Wilcoxon tests.

Statement of ethics

We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Institutional Review Board approval was obtained from the Institutional Review Board at Mayo Clinic, Rochester, MN, USA and all procedures and data collection were conducted in a manner compliant with the Health Insurance Portability and Accountability Act. All research procedures adhered to the tenets of the Declaration of Helsinki.

Results

One hundred and thirty-four children with intermittent XT and at least 5 years of total follow-up were identified. Surgery had been performed in 47 (35%) of 134 children. Of the 47 undergoing surgery, 33 had 5 years postoperative follow-up with a measure of near

stereoacuity. These 33 children were therefore our surgical cohort and were matched as described above to 33 non-surgical patients.

Of the 33 matched non-surgical patients, 19 (58%) had no active treatment, 13 (39%) underwent some part-time occlusion therapy, and one of these was also treated with over-minus lenses for a short time. An additional patient was treated using convergence exercises.

Overall, the majority (58%) had an estimated age of onset in the first or second year of life. Mean age at presentation and mean total length of follow-up were comparable between surgical and non-surgical groups (Table 1).

Presentation and preoperative/interim examinations

Presentation and preoperative or interim characteristics were similar between surgical and non-surgical groups (Table 1), with the exception of preoperative *vs* interim angle of deviation, which was larger in the surgical group (distance: 28 ± 7 PD *vs* 24 ± 9 PD, *P* = 0.04; near 25 ± 9 PD *vs* 16 ± 11 PD, *P* = 0.002) and control score, which was worse in the surgical group (distance 3.5 (quartiles 2.0, 5.0) *vs* 2.0 (2.0, 3.0), *P* = 0.007; near 1.0 (1.0, 3.0) *vs* 1.0 (0.0, 1.0); *P* = 0.004) (Table 1).

Five-year follow-up examination

Ten (30%) of 33 patients in the surgical cohort had no manifest deviation recorded by history or by examination and no intervening surgical intervention (Table 1). For these 10 patients, the angle of exodeviation was <10 PD at distance and near for all but one patient, who interestingly was prescribed over-minus lenses at the 5-year postoperative examination for an exodeviation of 8 PD at distance and 12 PD at near. Three of 10 patients had monofixation at the 5-year examination, but 2 had documented monofixation at the preoperative examination and one had no measurement of stereoacuity preoperatively, so these patients were still considered 'cures'. Since no surgical patient failed for stereoacuity reasons alone (loss of bifixation), the study-defined 'cure' rate in the surgical cohort was therefore 30%.

Interestingly, for the total surgical cohort of 33 patients, 7 patients had a second surgery prior to the 5-year examination, 4 for consecutive esotropia, 2 for recurrent exotropia, and 1 treated with botox for consecutive esotropia. Two patients still had an esodeviation at distance or near at the 5-year examination. All these patients were motor failures at 5 years because they had a manifest tropia, except one patient who failed for

Table 1 Characteristics of 33 surgical and 33 non-surgical cohorts at presentation, preoperative, and interim examinations, and after ~5 years of follow-up

	Surgical cohort	n ^a	Non-surgical cohort	n ^a	Comparison between groups
<i>Presentation examination</i>					
Estimated age at onset: mean ± SD years	2.0 ± 2.4	33	2.0 ± 2.4	33	<i>P</i> > 0.99
Age at presentation: mean ± SD years	3.8 ± 3.2	33	3.6 ± 2.5	33	<i>P</i> = 0.7
Total length of follow-up: mean ± SD years	7.2 ± 2.6	33	6.8 ± 2.3	33	<i>P</i> = 0.5
Distance PACT: mean ± SD (range), PD	23XT ± 8 (10XT to 40XT)	30	24XT ± 6 (10XT to 35XT)	31	<i>P</i> = 0.5
Near PACT: mean ± SD (range), PD	17XT ± 11 (0 to 40XT)	30	15XT ± 13 (0 to 40XT)	24	<i>P</i> = 0.5
<i>Preoperative/interim examination</i>					
Age: mean ± SD years	6.4 ± 2.8	33	6.6 ± 2.9	33	<i>P</i> = 0.8
Distance PACT: mean ± SD (range), PD	28XT ± 7 (14XT to 45XT)	33	24XT ± 9 (4XT to 40XT)	30	<i>P</i> = 0.04
Near PACT: mean ± SD (range), PD	25XT ± 9 (4XT to 45XT)	32	16XT ± 11 (0 to 40XT)	28	<i>P</i> = 0.002
Stereoacuity: <i>n</i> (%) monofixation	9 (36%)	25	3 (13%)	24	<i>P</i> = 0.2
Distance control score: median (quartiles) ^b	3.5 (2.0, 5.0)	20	2.0 (2.0, 3.0)	26	<i>P</i> = 0.007
Near control score: median (quartiles) ^b	1.0 (1.0, 3.0)	19	1.0 (0.0, 1.0)	25	<i>P</i> = 0.004
<i>5-year examination</i>					
Age: mean ± SD years	11.0 ± 3.1	33	10.4 ± 2.7	33	<i>P</i> = 0.4
Distance PACT: mean ± SD (range), PD	8XT ± 9 (12 ET to 25XT) ^c	33	21XT ± 8 (0 to 40XT)	33	<i>P</i> < 0.0001
Near PACT: mean ± SD (range), PD	9XT ± 9 (8 ET to 30XT) ^c	32	14XT ± 11 (2 ET to 45XT) ^d	30	<i>P</i> = 0.03
Stereoacuity: <i>n</i> (%) monofixation	18 (55%)	33	7 (21%)	33	<i>P</i> = 0.01
Distance control score: median (quartiles) ^b	2.0 (1.0, 3.0)	13	2.0 (1.0, 2.0)	30	<i>P</i> = 0.8
Near control score: median (quartiles) ^b	1.0 (1.0, 4.0)	9	1.0 (1.0, 1.0)	30	<i>P</i> = 0.4
No tropia by history or exam (equivalent to 'cure' rate) <i>n</i> (%)	10 (30%)	33	4 (12%)	33	<i>P</i> = 0.1

Abbreviations: ET = esotropia; PACT = prism and alternate cover test; PD = prism diopter; XT = exotropia.

^a *n* = number of patients with data.

^b Control was assessed using the 0- to 5-point office control scale.¹⁴

^c Four surgical patients had an esodeviation at distance (range 1–12 PD) and five had an esodeviation at near (range 1–8 PD). Four patients were orthotropic at distance and two at near. Twenty-five had a recurrent exodeviation at distance (range 2–25 PD) and 25 at near (range 2–30 PD).

^d One non-surgical patient had a 2 PD esodeviation at near.

undergoing surgery for recurrent intermittent XT 10 months before the 5-year outcome examination. None of the surgical patients were categorized as failure for having a control score of 2; all surgical failures had a manifest tropia by history or examination or an additional surgery.

For the non-surgical cohort, 4 (12%) of 33 patients had no manifest deviation recorded by history or by examination at the 5-year follow-up examination. All these four patients also had bifixation at the 5-year examination, and therefore all four met the study definition of 'cure'. Two of the four patients designated 'cure' received no intervention, one underwent part-time patching and one was treated using exercises.

The difference between 'cure' rate for surgical and non-surgical cohorts was not significantly different (30 *vs* 12%; $P = 0.1$, difference 18%, 95% CI -1 to 37%).

Monofixation status

For the surgical cohort, 26 of 33 were assessed at the 5-year examination using the Preschool Randot and seven using Titmus circles. Monofixation was present in 18 (55%) of 33 patients (Table 1) and 15 (45%) had bifixation. Six patients who had monofixation at the 5-year follow-up also had monofixation at the preoperative exam, indicating that their monofixation did not develop following surgery, but three patients appeared to develop monofixation following surgery, based on documented bifixation at the preoperative examination. Nevertheless, these three surgical patients with a new monofixation also had a manifest tropia at the 5-year examination, so did not fail for sensory reasons alone.

For the non-surgical cohort, 29 of 33 were assessed at the 5-year examination using the Preschool Randot and four using Titmus circles. Monofixation was present in 7 (21%) of 33 patients (Table 1), 25 (76%) had bifixation, and one (3%) was categorized as uncertain. Two of the non-surgical group who had monofixation at the 5-year follow-up also had monofixation at the interim examination, but one patient appeared to develop monofixation based on documented bifixation at the interim examination. Nevertheless, all non-surgical patients with monofixation at the 5-year examination also had a manifest tropia, so none failed for sensory reasons alone.

The prevalence of monofixation at the 5-year follow-up examination was significantly higher in the surgical cohort compared with the non-surgical cohort (55 *vs* 21%; $P = 0.01$, Table 1).

Discussion

In this retrospective study evaluating long-term outcomes in children with intermittent XT, surprisingly,

we found a low cure rate with surgery, which was somewhat similar to the cure rate in conservatively managed patients (30 *vs* 12%; $P = 0.1$, difference 18%, 95% CI -1 to 37%). Our data suggest that surgical intervention in intermittent XT is far from a panacea and that conservative management, including watchful waiting, can sometimes result in an excellent outcome.

Long-term surgical outcomes have been reported in previous studies of children with intermittent XT, by evaluating motor alignment alone. Nevertheless, most previous studies report motor outcomes in terms of angle of deviation, rather than by presence/absence of tropia. Ekdawi *et al*¹⁸ defined success as < 10 PD of misalignment and found a motor success rate of 55% at an average of 10 years follow-up (range 0–26 years). Richard and Parks¹⁹ defined success as a distance exodeviation of 10 PD or less and reported an overall success rate of 57% at least 2 years following surgery. Maruo *et al*²⁰ defined success as within 10 PD of orthotropia and found a 53% success rate after 4 years of follow-up, and Dadeya and Kamlesh²¹ defined success as within 5 PD of orthophoria and found a success rate of 78% at 3 years postoperatively. More recently, Kim *et al*²² defined success as alignment within 10 PD and reported a 62% success rate at 2 years postoperatively. On re-examining our 5-year data on angle of misalignment, with success defined as alignment within 10 PD at distance and near, our cure rate would be 54% (18 of 33 patients), which is comparable with these previous studies. Nevertheless, in this present study we elected to use absence of tropia as our motor success criterion since it is possible that a manifest deviation may occur even in the context of a small angle deviation, and conversely a larger deviation may in fact be very well controlled.

In other studies, a successful outcome or cure has been defined using more comprehensive criteria than purely angle of deviation. Pratt-Johnson *et al*²³ used a rigorous definition of cure, including no manifest tropia at any distance, 40 arc seconds stereoacuity, excellent divergence and convergence amplitudes, recognition of diplopia, and absence of monocular eye closure. Applying these strict criteria Pratt-Johnson *et al*²³ reported a cure rate of 41% at least 1 year (up to 8 years) postoperatively. Buck *et al*²⁴ reported surgical outcomes an average of 21 (range 6–46) months postoperatively and found 35% achieved an excellent outcome defined as 0–8 PD of exodeviation at distance and stable near stereoacuity. At 2 years,²⁵ the proportion with no detectable strabismus (Newcastle Control Score of zero) was 30% in the surgical group and 10.5% in the non-surgical group (observation only, non-surgical treatment or treatment for reduced visual acuity), strikingly similar to the reported cure rates in our present study (30 *vs* 12%).

We included the assessment of stereoacuity as the indicator of sensory status, defining monofixation as subnormal stereoacuity for age. For conservatively managed patients, we found the rate of monofixation ranged from 13% (interim examination) to 21% (5-year follow-up), which is similar to the prevalence of monofixation in unselected children presenting with intermittent XT reported in previous studies.^{16,17} Although we have previously reported the risk of misclassifying monofixation due to test-retest variability,¹⁶ we would expect any misclassification to be similar between non-surgical and surgical groups. We found the rate of monofixation was significantly higher at the 5-year outcome for surgically managed patients than for conservatively managed patients, suggesting that either monofixation was induced by surgical intervention, or that patients who underwent surgery already had, or were at higher risk for developing monofixation. Previous authors have suggested that evidence of monofixation postoperatively is attributable to monofixation being present preoperatively.^{17,26} Nevertheless, it appears that monofixation can be induced through surgical intervention, as highlighted in the study by Pratt-Johnson *et al*.²³ Although it has been proposed that a postoperative microtropia with monofixation is a good result that lends itself to long-term motor stability,²⁷ our data suggest few if any of these patients did in fact have good long-term alignment. The now uncertain potential 'benefit' of long-term stable monofixation with a microtropia should be weighed against the potential 'harm' of inducing subnormal stereoacuity in patients where it was previously normal.

An alternative explanation for the increased rate of monofixation is deterioration over time as a function of the natural history of the condition, maybe particularly in those with more severe or progressive disease. There are currently few data on the natural history of intermittent XT, but in a previous study of the course of stereoacuity in children with untreated intermittent XT, we found a very low deterioration rate over a 2-year period.²⁸ Further data on stereoacuity in the context of the natural history of intermittent XT, as well as following surgery, will be available at the completion of ongoing randomized clinical trials currently being conducted by the Pediatric Eye Disease Investigator Group (clinical trial identifiers: NCT01032330 and NCT01032603). We also need better methods of categorizing children with intermittent XT as having either monofixation or bifixation, and the new Pediatric Vision Scanner may prove useful in this endeavor.^{29,30}

Our finding of low cure rates with both surgical and conservative management of intermittent XT has important implications for clinical practice and for future research. It seems clear that surgical management often

falls short when aiming to 'cure' intermittent XT, consistent with previous studies reporting a high recurrence rate.¹⁸ Such poor outcomes indicate a pressing need to better understand the pathophysiology of intermittent XT, and to then develop more effective treatments. It is important to note that in this present study, 4 of 33 conservatively managed patients were classified as cured at ~7 years of follow-up, highlighting the reasonableness of active monitoring or non-surgical treatment, unless clear deterioration occurs.

Our study is not without limitations. Owing to its retrospective nature and the young age at presentation, we had some missing data, especially for stereoacuity at younger ages. In addition, we found that the surgical patients on average showed a larger angle of deviation and worse control preoperatively compared with non-surgical patients, which may indicate more severe or more progressive disease in the surgical patients, making the groups less comparable. Also, we allowed 3 years of follow-up as the lower limit on the 5-year window and it is possible that the cure rate would be lower if we restricted to a minimum of 5 years. Conversely, we did not study whether the cure rate would have been greater if multiple surgeries were performed.

In this retrospective study of long-term outcomes with surgical and non-surgical management of childhood intermittent XT, only a small proportion of patients in each group met our definition of cure. The majority of surgical and non-surgical patients demonstrated a constant or intermittent manifest deviation after an average of 7 years follow-up, and some patients who were followed without treatment met cure criteria. Long-term cure appears difficult to achieve, highlighting the need for further research into the pathophysiology of the disease and more effective treatments. In the meantime, while cure is elusive, surgery to reduce the magnitude and/or frequency of exodeviation may be reasonable to address psychosocial concerns and symptoms in older children.

Conflict of interest

The authors declare no conflict of interest.

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