ABSTRACT

Intermittent exotropia (X(T)) is one of the most common form of strabismus with surgery being the mainstay of treatment. The main goal of surgery is to preserve binocular vision and stereopsis and to prevent its further loss. The decision to operate is mainly based on four aspects: increasing angle of exodeviation, deteriorating control of X(T), decrease in stereopsis for near or distance and quality of life. Bilateral lateral rectus muscle recession and unilateral lateral rectus recession with medial rectus resection, are the two most common surgical procedures performed and have been studied extensively in basic, divergence excess and convergence insufficiency types of X(T). However, there is no consensus over the relative efficacy of the two procedures in terms of postoperative alignment, residual or recurrent exotropia and consecutive esotropia with widely variable results, which can be attributed to poor understanding of the natural course of the disease. Multiple demographic, clinical and anatomic features that may influence the surgical outcomes have been studied to explain this variability. Moreover, most of the evidence regarding surgical outcomes of X(T) is from retrospective studies and the ongoing randomised prospective trials can shed light on long-term efficacy of these procedures. The goal of this review is to give a comprehensive overview of the outcomes of various surgical techniques in the management of different types of X(T), the preoperative and postoperative factors that may affect the surgical outcomes and to discuss the dilemmas faced by the treating surgeons including the effective management of overcorrection and undercorrection.

INTRODUCTION

Intermittent exotropia (X(T)) is one of the most common type of strabismus in children as well as adults, especially in the Asian and South Asian populations. In these populations, it has been estimated that the prevalence of exotropia can be up to 7–18.5 times higher than that of esotropia, out of which the most common type is X(T) accounting for about 63%. It is also one of the most common indications for strabismus surgery and its incidence is on the rise. This higher prevalence of exotropia in Asian population compared with West has been attributed to either ethnic differences or to the higher incidence of myopia in the Asian population. A wide variety of modalities have been described for the management of X(T) ranging from non-surgical to surgical. The goal of this review is to give a comprehensive overview of the relative outcomes of various surgical techniques in the management of different types of X(T), the preoperative and postoperative factors that may affect the surgical outcomes and to discuss the dilemmas faced by the treating surgeons.

SURGICAL MODALITIES

Spontaneous resolution of X(T) is rare and hence surgery has been the mainstay of the treatment of X(T).

Indications of surgery

The main goal of treatment in X(T) is to preserve the binocular vision and stereopsis and to prevent its further loss. The decision to operate is based on three major clinical aspects: increasing angle of exodeviation, deteriorating control of X(T) and decrease in stereopsis for near or distance. While the measurement of angle of deviation using alternate prism cover test and stereopsis using various modalities available is fairly reliable and objective, the measurement of control of X(T) is far more complex and subjective. Newcastle Control Score (NCS) is a simple tool devised to get reliable and easy to understand measurement of control by combining the assessment of control at home by guardians/parents and at office by the ophthalmologist to give a single numerical score with good interobserver and test–retest reliability. A similar office-only based scale by Mayo clinic measuring control for distance and near as a single numerical score has also shown good reliability, avoiding the recollection bias of home-based control assessment. Assigning a numerical value helps in serial monitoring of these patients for progression. Surgery is recommended if NCS ≥4 or if it worsens over time, if X(T) is seen for greater than 50% of the awake time at home or if X(T) manifests spontaneously or with any form of fusion disruption without recovery.

The most common non-clinical indication for surgery is to improve the quality of life. It has been shown that children are concerned...
about what others think of their appearance and strabismus can affect their ability to make friends, while parents worry more about the visual functions and the need for surgery. In such a situation, surgical correction may help in the psychosocial development of the individual, boosting their confidence and improving the way they interact with their peers and the society. It is important to understand that the decision of surgery cannot be taken based only on the above-mentioned parameters but is made depending on individual case. It is best to discuss with the individual and their parents/guardians about the management options available and encourage them to actively participate in choosing the right approach for them.

Basic X(T)
Most commonly performed surgical procedures, unilateral lateral rectus recession and medial rectus resection (R&R) and bilateral lateral rectus recession (BLRc), have been successfully performed for the management of basic type X(T). Two randomised trials with one year follow-up have stated that R&R results in better alignment and lower chances of recurrence of exotropia compared with BLRc, especially in the presence of ocular dominance. However, R&R resulted in a higher incidence of overcorrection, which may induce diplopia or suppression and amblyopia. A recent meta-analysis concluded that R&R resulted in better alignment, lower recurrence and similar overcorrection as that of BLRc, possibly be due to the leash effect of the resected medial rectus. The follow-up period in most studies was short. However, R&R shows a greater exotropic drift after one year, with no significant difference between the two procedures over long term. Moreover, it is difficult to compare between different studies directly due to significant differences in the study populations, variable surgical doses used, different definitions of successful outcomes and varied duration of follow-up. Therefore, it has been advocated to standardise the reporting of outcomes in future studies with respect to four aspects, namely angle of deviation, stereopsis, control and the quality of life. Considering these four key features, a recent well-conducted randomised trial comparing BLRc and R&R, with 3 years postoperative follow-up, did not show any significant difference between the two types of surgeries. On the contrary, multiple studies with longer follow-up suggest that BLRc has better long-term outcomes compared with R&R, suggesting greater stability. Augmented surgical dosage for BLRc (aBLRc: augmenting the surgical dosage by 1–2.5 mm for each LR or increasing the target angle by 5 prism diptres (PD) and R&R (augmented R & R = aR&R: increasing the dosage of only MR resection by 1 mm) improved long-term results compared with the original dosage with no significant difference in overcorrection (table 1 shows various surgical approach to different types of X(T)).

### Table 1 Surgical approach to different types of intermittent exotropia

<table>
<thead>
<tr>
<th>Indication for surgery</th>
<th>Type of X(T)</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Poor/worsening of control</td>
<td>1. Basic or simulated divergence excess X(T)</td>
<td>1. BLRc</td>
</tr>
<tr>
<td>2. Increasing angle of deviation</td>
<td></td>
<td>2. U/L R&amp;R</td>
</tr>
<tr>
<td>3. Decrease in stereopsis for distance or near</td>
<td></td>
<td>3. U/L LRc</td>
</tr>
<tr>
<td>4. Double vision</td>
<td></td>
<td>4. Augmented BLRc</td>
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<tr>
<td>5. Parental demand</td>
<td></td>
<td></td>
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<tr>
<td>6. Quality of life</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Type of X(T)**
- 1. Basic or simulated divergence excess X(T)
  1. BLRc
  2. U/L R&R
  3. U/L LRc
  4. Augmented BLRc

**Resurgery†**

1. Residual/recurrent exotropia
   1. U/L or B/L MRs (post-BLRc)
   2. LR recession of other eye (post U/L surgery)
   3. LR recession (post small LR resection, but less predictable)

2. Consecutive esotropia
   1. U/L or B/L MRs
   2. LR advancement‡

†Preferably explore the previously operated muscle and look for stretched scar, slipped muscle, soft-tissue adhesions or other abnormalities in case of residual/recurrent exotropia or consecutive esotropia.
‡Dosage for LR advancement needs to be reduced due to greater effect per mm.
B/L, bilateral; BLRc, bilateral lateral rectus recession; LRc, lateral rectus recession; MRc, medial rectus recession; MRs, medial rectus recession; R&R, unilateral lateral rectus recession with medial rectus resection; U/L, unilateral; X(T), intermittent exotropia.
Small angle X(T) has been successfully managed by unilateral lateral rectus recession (ULRc), BLRc and R&R, but preoperative deviation of 20–25 PD X(T) has worse outcomes than <20 PD X(T). However, long-term results have been contradictory for ULRc with few studies showing good outcomes, while other showing poor outcomes compared with R&R. Direct evidence comparison of BLRc and R&R for small angle X(T) is scarce. Large angle X(T) of ≥40 PD showed significantly worse outcomes than moderate angle X(T) (20–30 PD), although no difference was found between BLRc and R&R in either of the groups. However, large dose R&R may result in abduction limitation, lateral incomitance and palpebral fissure height narrowing or enophthalmos.

The world is still divided over the choice of procedure for X(T) and is mostly based on individual surgeon’s experience. However, in view of better long-term results, lower incidence of overcorrection thus reducing the threat of suppression and amblyopia as well as decreased chances of inducing lateral incomitance, the authors believe that BLRc may produce better and more acceptable results than R&R for the management of basic type of X(T). Perhaps, long-term outcomes of the ongoing randomised trials may reveal the relative efficacy of the two procedures in the management of X(T).

### Divergence excess

Surgical outcomes in true divergence excess X(T) have been found to be better than basic X(T), with BLRc has been preferred over R&R for divergence excess type of X(T) due to greater chances of overcorrection following R&R. Distance deviation after prolonged occlusion test has been considered as the target angle for surgical correction. aBLRc has been reported to give better long-term outcomes in divergence excess type of X(T) with success rates close to 80% without any significant increase in overcorrection for distance as well as near, while stereopsis improved in half of these cases. These children have better near fusional capacity which may result in better fusional lock postoperatively leading to better stability of the angle.

In case of high AC/A ratio, bifocals for decreased near accommodation can be prescribed or faden procedure for medial rectus (MR) can be added to BLRc in order to prevent postoperative overcorrection for near. A new surgical procedure of posterior pulley fixation of MR along with BLRc has been described in similar cases with good outcomes, with theoretically lesser chances of scleral perforation. In summary, BLRc resulting in lesser overcorrection has been preferred over R&R with good surgical outcomes compared with basic X(T).

### Convergence insufficiency

A trial of non-surgical management like fusional and convergence exercises should be administered before surgical correction. It is common practice to add MR resection for treating convergence insufficiency and there is poor evidence for direct comparison of BLRc and R&R in these cases. Most authors have suggested an improved R & R (iR&R) higher dose of MR resection based on near deviation compared with a lower dose of LR recession based on distance deviation. Apart from the conventional R&R procedure, several methods like unilateral or bilateral medial rectus resection with or without slanting (greater resection

### Table 2 Surgical dosage for intermittent exotropia (as per authors’ experience)

<table>
<thead>
<tr>
<th>Exotropia angle in PD</th>
<th>Amount of recession/resection in mm</th>
</tr>
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<tbody>
<tr>
<td>Two muscles</td>
<td>BLRc</td>
</tr>
<tr>
<td>15</td>
<td>4.0</td>
</tr>
<tr>
<td>20</td>
<td>5.0</td>
</tr>
<tr>
<td>25</td>
<td>6.0</td>
</tr>
<tr>
<td>30</td>
<td>7.0</td>
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<tr>
<td>35</td>
<td>7.5</td>
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<tr>
<td>40</td>
<td>8.0</td>
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<tr>
<td>45</td>
<td>8.5</td>
</tr>
<tr>
<td>50</td>
<td>9.0</td>
</tr>
<tr>
<td>60</td>
<td>10.0</td>
</tr>
<tr>
<td>Three muscles</td>
<td>BLRc+U/L MRs</td>
</tr>
<tr>
<td>55</td>
<td>8.0+5.0</td>
</tr>
<tr>
<td>60</td>
<td>8.0+6.0</td>
</tr>
<tr>
<td>70</td>
<td>9.0+6.0</td>
</tr>
<tr>
<td>Four muscles</td>
<td>BLRc+BMRs</td>
</tr>
<tr>
<td>75</td>
<td>7.0+5.5</td>
</tr>
<tr>
<td>80</td>
<td>7.0+6.0</td>
</tr>
<tr>
<td>90</td>
<td>8.0+6.0</td>
</tr>
</tbody>
</table>

BLRc, bilateral lateral rectus muscle recession; BMRs, bilateral medial rectus resection; LRc, lateral rectus recession; MRs, medial rectus resection; PD, prism dioptres; R&R, unilateral lateral rectus recession with medial rectus resection; U/L, unilateral.
of lower fibres of MR for near deviation and lesser resection of superior fibres), improved R&R have been described for convergence insufficiency X(T) with variable success rates. Most patients have poor outcomes, which has led to the need to develop such diverse surgical procedures. iR&R showed better results compared with unilateral and bilateral MR resection. Various modifications of BLRc such as adjustable sutures, aBLRc and slanted BLRc (sBLRc) have shown satisfactory outcomes. sBLRc has shown better results compared with conventional BLRc and other procedures with 1 mm of slant reducing the near-distance disparity by 4.6–8.7 PD and lower rates of immediate postoperative overcorrection. However, long-term outcomes of this procedure are not available. A recent prospective study comparing three procedures iR&R (in non-dominant eye), sBLRc and aBLRc (in patients with no ocular dominance) showed a similar improvement for near deviation. However, sBLRc showed slightly better distance deviation outcomes compared with the other two procedures. aBLRc and sBLRc achieved better collapse of near-distance disparity compared with iR&R. Each procedure had their own set of adverse events. Overcorrection was reported in 27% of aBLRc cases at 1 year, especially for distance, iR&R had significantly higher undercorrection rate for distance compared with other groups while sBLRc induced asymptomatic pattern strabismus in approximately one in five cases. Although sBLRc achieved significantly better alignment compared with the other two groups with lowest rates of over or undercorrection, long-term outcomes of this procedure are yet to be reported. To conclude, management of convergence insufficiency is still challenging with no particular surgical procedure being superior to the other. However, most surgeons prefer to include at least one R&R in their surgical plan.

FACTORS AFFECTING SURGICAL OUTCOMES

Surgical outcomes in X(T) have been quite variable with various studies reporting quite different rates of success and this can be attributed to the poor understanding of the natural course of the disease. The influence of various demographic, clinical and anatomic features on these outcomes is still debatable. The association of the following factors with that of surgical outcomes in X(T) has been studied.

Age

It has long been debated over timing of surgery with some advocating an early surgery before 4 years of age but was associated with a higher incidence of amblyopia due to the mild overcorrection in the postoperative period in these children with immature visual system. Interestingly, binocular visual integration pathway in these cases is intact, unlike infantile esotropia which warrants early intervention. The exotropia being intermittent, allows for development of binocular fusion and stereopsis. Therefore, delaying the surgery should not influence the sensory and visual outcomes to a great extent, and many studies have advocated for a delayed approach as it may also allow for more accurate measurements and better results. However, multiple reports have suggested that best results are achieved if operated before the age of 7 years of age, due to a greater chance of postoperative bifoveal fusion with superior binocular vision and stereocuity. Other possible explanation could be the structural changes in the pericircular tissue due to longer duration of X(T) changing the elastic forces affecting the final postoperative correction. Age also affects the surgical dose-effect response, with postoperative change in deviation being highest in children <7 years age, followed by 7–12 age group and least in children >12 years age, in children undergoing BLRc. Reducing the surgical dose by 1 mm in children <7 years age did not change the overall surgical outcomes but decreased the chances of overcorrection, while increasing the surgical dosage by 1.5 mm for children>12 years age significantly improved the surgical outcomes. This could be due to narrower tendons in children <5 years age resulting in greater effect of recession and changes in the pericircular tissue in long-standing exotropia in older children, requiring augmented dosage to overcome their elastic forces.

In the authors’ opinion, best outcomes are obtained between 4 and 7 years of age allowing for more accurate preoperative evaluation, reducing the chances of postoperative suppression and amblyopia and good motor alignment (except in case of large angle of exotropia with poor or worsening control and stereopsis, in which case an early surgery is indicated).

Stereopsis, binocular vision, amblyopia

Distance stereopsis is affected earlier in X(T) compared with near stereopsis. Some investigators advocate the use of distance stereocuity to monitor the progression of distance, indication for surgery and as an outcome measure. It is intuitive to consider that better stereopsis must be associated with good control of X(T) and smaller angle of deviation. However, X(T) patients can have any possible combination of stereopsis, control and angle of deviation with weak or no correlation between these factors. Similarly, stereopsis or binocular vision has not been found to affect the surgical motor outcomes. Such poor correlation may result from variable measurements of stereopsis and angle of deviation in X(T) especially in younger children. Amblyopia is not common in these patients, if present is not severe but needs exploration.
for other causes like anisometropia and does not significantly affect the surgical outcomes.66 75

Refractive error
It has been recommended to overcorrect myopia slightly to induce convergence for better control of X(T) as a temporary measure. In case of significant myopia of ≥5D, it is advisable to reduce the surgical dosages accordingly.85–87 Although the effect of axial length on surgical outcomes is debatable, a recent study has shown negative correlation of axial length with mean dose response.88 Most studies have shown that refractive error or anisometropia does not affect the final surgical outcomes.58 63 67 Some studies have shown that myopia has less favourable response to surgery,77 while others have shown a favourable outcome.76 Anisometropia has also been reported to be associated with poor outcomes.89

Preoperative angle of deviation
Few studies have suggested that preoperative deviation less than 40 PD does not affect the final surgical outcomes,58 63 while greater preoperative deviation especially if ≥40 PD is associated with poor outcomes.66 75 76 90 In authors’ opinion, preoperative exodeviations lying within the grey zone which pose the dilemma of whether to add an extra muscle like 20–25 PD (1 or 2 muscles), 45–55 PD (2 or 3 muscles) and 60–90 PD (3 or 4 muscles) have unpredictable outcomes, with most unpredictable outcomes in the first group of 20–25 PD.37 The surgical dosage for X(T) has been discussed in table 2. Variability in the measurement of exotropia (7.2 PD for distance and 12.8 for near for moderate angle deviation) may also affect the outcomes of surgery.89 Different surgical dosages are used for same amount of deviation which can potentially explain the wide variability of the outcomes reported in literature, however, no such relation was found in a study by Chia et al.27 Another potential cause for inconsistent surgical outcomes could be not operating for the maximum angle of deviation.91 Suggestions have been made to consider largest measured angle as the target angle for surgery for good outcomes, not necessarily the measurement of X(T) with a distant outdoor fixation target,92 without an increase in overcorrection.

Control
Preoperative control does not affect final surgical outcomes.22 The poor association of control, stereopsis and angle of deviation and their complex interactions in maintaining alignment, may be responsible for poor association between these factors and surgical outcomes. Most studies including the randomised trial have reported an improvement in control following surgery.25 93

Early postoperative angle
Postoperative exodrift is common, hence, a target angle of small esotropia (≤10 PD) is desirable in the immediate postoperative period,94–96 but it does not guarantee a successful outcome.97 98 Some studies suggest that initial overcorrection up to 17–20 PD is acceptable.60 94 99 but an overcorrection of ≥10 PD has higher chances of consecutive esotropia.96 Concerns have been raised regarding the development of consecutive esotropia and monofixation syndrome due to overcorrection, especially in young children.97 On the contrary, residual exotropia at immediate, one week and onemonth postoperative period is usually associated with higher recurrence rates.58 63 66

Follow-up period
It has been reported that the most important factor determining surgical outcomes based on alignment is the duration of follow-up, with half the surgeries failing after 5 years which increases to 76% at 10 years and 86% failing after 15 years.83 A total of 20%–60% patients require a second surgery at mean follow-up of 10 years, most of them for a recurrence of exotropia.83 89 Another study using more robust criteria for surgical success including motor alignment, stereopsis and control with at least 5-year follow-up, found successful cure in only 30% of patients undergoing surgery.93 Although surgery improved the distance and near deviation significantly compared with those who were observed conservatively, no significant difference was found in the final number of patients without tropia (considered as cured) and its control between the two groups after 5 years follow-up, raising the question ‘Is X(T) a curable condition?’.93 Although stereopsis improves following surgery, patients undergoing surgery had poorer final stereopsis compared with those managed conservatively,93 which may be due to the desired small target microtropia in the postoperative period or poorer preoperative stereopsis to begin with in this group. The natural course of X(T) does not show significant deterioration of angle of deviation, control or stereopsis in untreated cases.84 100 Considering the poor long-term surgical motor outcomes and the association of better stereopsis with conservative management, the advantage of reducing the angle of deviation and improving the quality of life in these patients by operating should be weighed cautiously in the presence good preoperative binocular vision and stereopsis especially in small angle X(T) cases.

Lateral incomitance
Few investigators found lateral incomitance to be a significant risk factor for development of consecutive esotropia,99 101 102 while others did not.24 Asymmetrical surgery may induce lateral incomitance postoperatively but it may also be indicated to reduce preoperative lateral incomitance if planned appropriately.32 35

Vertical strabismus
Primary oblique muscle overaction (7%–25%), disassociated vertical deviation (DVD) (5%–8%) and vertical
deviation (24%) although poorly studied are not uncommon in X(T). \textsuperscript{41,42} DVD in X(T) is smaller than in infantile esotropia and is associated with poorer stereopsis. \textsuperscript{103} If these anomalies are mild, horizontal muscle surgery may resolve vertical deviation and oblique muscle overaction. \textsuperscript{82,104,105} Vertical offset of horizontal muscles or vertical muscle surgery is indicated if the vertical deviation or DVD is ≥10–14 PD. DVD is manifest quite often, significant pattern deviation and oblique overaction of ≥2. \textsuperscript{82,106} DVD, vertical deviation and primary oblique muscle overaction did not significantly affect surgical outcomes. \textsuperscript{82,85}

**Anatomic factors**

Greater the LR insertion to limbus distance, greater is the surgical effect for a fixed amount of recession with twice the effect in BLRc compared with unilateral LR recession. \textsuperscript{107} Similarly, the effect of recession is larger in narrower LR tendon width. \textsuperscript{108} Although the role of anatomical factors in the natural history of X(T) and its surgical outcomes is poorly understood, multiple structural changes are seen in long-standing cases in the extraocular muscle including its myofilaments and sarcomeres, axonal supply, proprioception apparatus and the surrounding extracellular matrix and collagen. \textsuperscript{109–111} Early surgical intervention may prevent the progression of these changes. \textsuperscript{111}

**MANAGEMENT OF SURGICAL UNDER OR OVERCORRECTIONS**

(Table 1) A large overcorrection or undercorrection in immediate postoperative period with limitation of motility suggests a slipped muscle and should be operated immediately. If the motility is good, chances of spontaneous recovery are higher, \textsuperscript{97,112,113} and managed conservatively with monocular patching ±Fresnel prisms. If the esodeviation does not decrease for more than 9–12 months, chances of spontaneous resolution are slim, however, late spontaneous resolutions have been reported. \textsuperscript{112,113} Surgical correction may be considered in such cases based on ‘Cooper’s dictum’ which states that if there is no limitation of motility, surgery should be performed on unoperated muscles as if it was the initial operation, however, if there is motility limitation, surgery should be performed on previously operated muscles. \textsuperscript{114} In long term, residual exotropia is far more common than consecutive esotropia, since an exodrift is commonly seen in the postoperative period. \textsuperscript{83,89} Medial rectus resection (MRs) is recommended for residual exotropia after BLRc if motility is good. Unilateral MRs shows good outcomes for moderate exodeviations (≤25 PD) \textsuperscript{115–117} with one study suggesting similar outcomes while another reporting lower overcorrection compared with that of bilateral MRs. The amount of resection in case of bilateral MRs should be reduced as the lateral rectus has already been recessed. \textsuperscript{117,118} Residual/recurrent exotropia following unilateral R&R procedure can be managed with LR recession with or without MRs of the other eye. In case of consecutive esotropia with or without limited abduction following LR recession, surgical exploration for stretched scar and its repair, if present, is needed with or without MR recession or LR advancement. In case of normal motility MR recession with or without LR resection of the unoperated muscles is more predictable. LR advancement has been tried in patients with no motility limitation and produces a far greater effect per mm compared with the same dose of LR recession for treating exotropia. \textsuperscript{119} Hence, the dose of LR advancement should be reduced with Kim and Lee, suggesting to consider one fourth of the angle of esodeviation as the target angle and apply the doses of LR recession for same angle of exodeviation. \textsuperscript{120} This could be due to decreased elasticity of the previously recessed LR, hence its advancement may lead to a leash effect. \textsuperscript{120}

**SUMMARY**

Best success rates are achieved in divergence excess type of X(T) \textsuperscript{22} while convergence insufficiency results in worst outcomes. R&R produces better outcomes than BLRc at one year postoperatively, although most studies did not find any significant difference in long term. Since, most of the evidence regarding surgical outcomes of X(T) is from retrospective studies, ongoing randomised prospective trials comparing BLRc and R&R will shed light on the long-term stability of the two procedures. The debate over the preferred surgical procedure still continues and mainly depends on the surgeon’s experience. \textsuperscript{22} Surgical management of X(T) is far from perfect due to variable results. Various preoperative and postoperative factors that may influence the outcomes have been studied to explain this variability, although none has been found to have a strong association with the outcomes. Even the surgical dosages used by the surgeons across the world vary which may explain the variability of the reported success rates to some extent. Future studies should further examine these predictive factors to tailor the surgical choice and dosage for optimal results. In addition, there are lot of lacunae in understanding the aetiopathogenesis and natural course of the disease itself which needs further exploration.

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REFERENCES


