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[Intervention Protocol]

Surgical interventions for vertical strabismus in superior oblique palsy

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the relative effects of different surgical treatments for vertical strabismus in people with superior oblique palsy.

BACKGROUND

Description of the condition

Superior oblique palsy is considered the most common cyclovertical muscle palsy (Plager 1999). A recent epidemiological study found the annual incidence of adult-onset superior oblique palsy to be 6.3 cases per 100,000 people, but significantly higher in men than women (Martinez-Thompson 2014). In children younger than 19 years of age, the annual incidence was 3.4 cases per 100,000 (Tollefson 2006), with 31% of vertical strabismus in children attributed to superior oblique palsy, and represented equally by gender.

Superior oblique palsy may be congenital or acquired. Possible causes of congenital superior oblique palsy include hypoplasia of the trochlear nucleus or nerve and anatomical defects or absence of the superior oblique tendon or trochlea (Chan 1999; Helveston 1992; Mansour 1986). Acquired cases have been presumed to be most frequently secondary to trauma, although the association is in many cases tenuous. Other causes of acquired superior oblique palsy include inflammation, infection, vascular malformation, infarct, tumor, myasthenia gravis, or iatrogenic denervation of muscle complicating sinus, orbital, or neurologic surgery (Plager 1999; Tamhankar 2013).

Clinical characteristics

The main clinical feature of superior oblique palsy is vertical binocular misalignment (strabismus), which occurs when the vertical angular orientation of one eye is different from that of the other eye. In superior oblique palsy, there is ipsilesional hypertropia (upward deviation), which may present with diplopia (double vision) or be compensated by an abnormal head position. The head is usually tilted to the shoulder opposite direction the elevated eye, or the chin is lowered, because these positions minimize the vertical strabismus. There may also be excyclotorsion of the hypertropic eye, rotation of the eye about the line of sight so that the normally vertical meridian of the eye is tilted away from the midline of the face.

Diagnosis

Superior oblique palsy is typically considered to produce an incomitant strabismus in which the vertical misalignment varies in magnitude with different gaze positions relative to the head. However, there may be individual exceptions. The historical gold standard for diagnosis has been considered by many authors to be the Parks-Bielschowsky three-step test. The elements of the three-step test for acute, unilateral (one eye) superior oblique palsy consist of: 1) hypertropia of the eye ipsilateral to the palsied superior oblique muscle; 2) increased magnitude of hypertropia in lateral gaze contralateral to the affected eye; and 3) increased magnitude of hypertropia when the head is tilted towards the shoulder corresponding to the affected eye (Bielschowsky 1935). Investigators of more recent magnetic resonance imaging (MRI) studies of superior oblique structure and function have challenged the three-step test, demonstrating that is only about 70% sensitive, in Machandia 2014, and 50% specific, in Demer 2011, for deficient superior oblique function. Consequently, earlier studies reporting the clinical characteristics of superior oblique palsy as diagnosed by the three-step test probably included a substantial fraction of misdiagnosed alternative causes of vertical strabismus, and also systematically omitted many cases of actual superior oblique weakness.
It has been historically hypothesized that when longstanding, as in congenital superior oblique palsy presenting in adulthood, the vertical strabismus may be more comitant, or similar in magnitude in all gaze directions. In general, children are more likely to present with an anomalous head position rather than diplopia, because the developing brain suppresses central perception from one eye when the eyes are not aligned. Older children with acquired superior oblique palsy who see double may be unable to verbalize this symptom. Adults may present with an anomalous head position or diplopia from vertical misalignment or excyclotorsion.

Bilateral superior oblique palsy

Superior oblique palsy may be bilateral, involving both eyes. In this case, patients may have hypertropia that alternates with gaze position and head tilt, as well as crossing of the eyes (esotropia) increasing in down gaze with a V pattern. On right gaze, the left eye is hypertropic, while the right eye is hypertropic in left gaze. In addition, with the head tilted to the right, the right eye is hypertropic, while the left eye is hypertropic on left head tilt. The degree of excyclotorsion, twisting of the eye outwards around the line of sight, is typically larger in bilateral than in unilateral superior oblique palsy (Kushner 1988).

Congenital superior oblique palsy

Congenital superior oblique palsy may manifest in childhood or adulthood. Presentation may be precipitated by inability to sustain the effort required to compensate for the vertical misalignment. Clinical signs associated with a congenital superior oblique palsy include longstanding torticollis and facial asymmetry (Plager 1999), although the relationship between facial asymmetry and superior oblique palsy has been questioned (Velez 2000). People with congenital superior oblique palsy may also have a larger-than-normal vertical fusion amplitude. The vertical fusion amplitude refers to the greatest amount of vertical ocular misalignment that the brain can tolerate without the person experiencing diplopia. The normal vertical fusion amplitude is less than or equal to 3 prism diopters (Bharadwaj 2007; Parks 2005); people with a vertical fusion amplitude greater than this are suspected of having congenital superior oblique palsy.

Acquired superior oblique palsy

Superior oblique palsy may also be acquired in either childhood or adulthood. The trochlear nerve, which innervates the superior oblique muscle, may be compromised anywhere along its long course from the dorsal midbrain to the orbit, traversing intracranial structures including the tentorium cerebelli and cavernous sinus (Plager 1999). The superior oblique tendon itself may also suffer injury, particularly in the context of prior sinus or orbital surgery. People with acquired superior oblique palsy may present with an anomalous head position or vertical or torsional diplopia. Such patients generally have normal vertical fusion amplitudes and do not have facial asymmetry. Because the normal vertical fusion amplitude is less than or equal to 3 prism diopters, patients may be significantly disabled by small degrees of hypertropia caused by acquired superior oblique palsy.

Challenges to diagnosing superior oblique palsy

Although the Parks-Bielschowsky three-step test is considered the gold standard for diagnosing superior oblique palsy, 30% of people with superior oblique palsy confirmed by MRI may not fulfill all three of these criteria (Machandia 2014). More recent studies utilizing MRI have shown that many cases diagnosed clinically as superior oblique palsy may be related to connective tissue abnormalities rather than dysfunction of cranial nerves (Demer 2011). Specifically, heterotopic extraocular muscle pulleys can cause patterns of incomitant strabismus that may be attributed to oblique muscle dysfunction (Clark 1998; Suh 2016). Because neurogenic atrophy occurs rapidly and reliably after denervation of extraocular muscles (Demer 2010), superior oblique atrophy observed on MRI may be used to confirm the clinical diagnosis of superior oblique palsy (Demer 1995). In cases of head tilt-dependent hypertropia with absence of superior oblique atrophy, MRI demonstrates abnormal shifts of extraocular muscle pulleys during head tilt (Demer 2011). MRI studies have also shown that compartmental palsy of the superior oblique can occur, which may account for the heterogeneity of clinical presentation in this disorder (Shin 2015).

Description of the intervention

People with superior oblique palsy may seek treatment due to disabling vertical or torsional diplopia or the anomalous head posture adopted to minimize vertical ocular misalignment. Children with a constant head tilt can develop permanent contracture of the neck muscles, particularly the sternocleidomastoid muscle (Lau 2009). Various non-surgical and surgical treatment options exist. If patients are asymptomatic or minimally symptomatic, observation without treatment may be considered. In cases where the vertical deviation is small and comitant, prisms may be sufficient to improve symptoms. However, the majority of people treated for symptomatic superior oblique palsy undergo surgery (Plager 1999), the main goal of which is to reduce the vertical ocular misalignment such that the diplopia or anomalous head position, if present preoperatively, is improved or resolved.

Surgical options for hypertropia in superior oblique palsy include: ipsilateral superior oblique tendon plication ("tucking") (Bhola 2005; Durnian 2011); superior oblique tendon resection and advancement (Luton 1998; Wheeler 1934); procedures to weaken the ipsilateral inferior oblique, including recession (Hendler 2013; Parks 1972), myectomy (Bahl 2013; Lee 2015), myotomy (Lee 2015), marginal myotomy (Mellott 2002), disinsertion (Parks 1972; Yanyali 2001), anterior transposition (Elliott 1981; Farvardin 2002), anterior nasal transposition (Hussein 2007; Stager 2003), and orbital fixation (Ela-Dalman 2007); ipsilateral superior rectus recession (Ahn 2012); and contralateral inferior rectus recession (Mahmoud 2009).

In patients symptomatic from excyclotorsion, surgical options include Harada Ito advancement of the anterior portion of the superior oblique tendon (Harada 1964; Nishimura 2002), inferior oblique weakening as listed above, and transposition of vertical recti (Nemoto 2000). We will not include surgical options to address excyclotorsion in this review, which will focus on surgical procedures to address symptomatic hypertropia.

How the intervention might work

Strabismus surgery works by changing the forces of the extraocular muscles and their associated orbital connective tissues (pulleys). A variety of surgical approaches are used to treat superior oblique palsy. Advancement, resection, or plication of the superior oblique tendon shorten a lax tendon, which may improve action of the superior oblique muscle. Weakening the superior oblique's opponent, the ipsilateral inferior oblique muscle, decreases the activity of the antagonist. Recession of the ipsilateral superior rectus muscle reduces the upward force elevating the hypertropic eye. Recession of the contralateral inferior rectus reduces the downward force of the contralateral eye, rotating it upward to match the position of the eye hypertropic due to the palsied superior oblique muscle.

Why it is important to do this review

Although many people with symptomatic superior oblique palsy undergo surgical treatment, there is no consensus as to which, if any, surgical procedure is most effective for remediating strabismus due to this condition, or whether different surgical approaches may be optimal for differing clinical presentations of superior oblique palsy. Moreover, although certain surgical procedures are subject to particular complications (for example iatrogenic Brown's syndrome in superior oblique tuck, or anti-elevation syndrome in inferior oblique anterior transposition), there is little data comparing the rates of complications between the various surgical procedures used to treat superior oblique palsy. A comprehensive review is needed to guide practitioners in choosing effective surgical interventions.

OBJECTIVES

To assess the relative effects of different surgical treatments for vertical strabismus in people with superior oblique palsy.

METHODS

Criteria for considering studies for this review

Types of studies

We will include only randomized controlled trials. We will not exclude studies on the basis of publication status or language of publication.

Types of participants

We will include studies of adults and children with acquired or congenital vertical strabismus considered compatible with the diagnosis of unilateral superior oblique palsy. We will not limit the studies based on the angle of deviation, as patients may be symptomatic at different degrees of hypertropia based on their vertical fusion amplitudes. We will exclude people who underwent surgical intervention for any strabismus before entering the trial. We will also exclude people undergoing surgical interventions primarily for torsion, as this review is focused on vertical strabismus. We will also exclude people who undergo concomitant horizontal rectus muscle surgery.

Types of interventions

We will include trials that compare any type of surgical procedure to another type. The types of surgical procedures to be compared may include:

- Superior oblique plication ("tuck")
- Superior oblique resection
- Superior oblique advancement
- Inferior oblique recession
- Inferior oblique myectomy
- Inferior oblique myotomy
- Inferior oblique marginal myotomy
- Inferior oblique disinsertion
- Inferior oblique anterior transposition temporal to the inferior rectus insertion
- Inferior oblique anterior transposition nasal to the inferior rectus insertion
- Inferior oblique orbital fixation
- Inferior oblique denervation and extirpation
- Superior rectus recession
- Inferior rectus recession
- Posterior fixation suture
- Combinations of any of the above

We will include studies that utilize unilateral or bilateral surgical procedures or both.

Additionally, we will include any studies that compare any surgical procedure to observation or non-surgical treatment.

Types of outcome measures

Primary outcomes

The primary outcome measure will be the proportion of participants with postoperative surgical success, defined as hypertropia at distance and near in primary position (with the head upright and looking straight ahead) of less than 3 prism diopters (PD), as measured by alternate cover testing with prism, without reversal of the direction of hypertropia, at one year postoperatively. If no one-year outcome data are available, then we will consider the proportion of surgical success at the longest postoperative follow-up time (minimum six weeks).

Secondary outcomes

We will evaluate all secondary outcomes at one year postoperatively, or at longest postoperative follow-up if no outcome data are available at one year.

The secondary outcomes to be evaluated are as follows:

- Proportion of participants with an anomalous head position preoperatively who have a residual head tilt greater than 15 degrees in central gaze postoperatively
- Proportion of participants with postoperative hypertropia less than 3 PD, as measured by alternate cover testing with prism, in down gaze
- Proportion of participants with postoperative hypertropia less than 3 PD, as measured by alternate cover testing with prism, in contralateral gaze (adduction of affected eye)
- Proportion of participants with symptomatic cyclotorsion postoperatively
- Proportion of participants who received another strabismus surgery
- Scores from vision-specific quality of life instruments, such as the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) for adults, Adult Strabismus-20 Questionnaire (AS-20) for adults, and vision-specific pediatric quality of life instruments for children

Adverse effects

Adverse effects to be documented and compared are as follows:

- Orbital cellulitis
- Endophthalmitis
- Retinal perforation
- Iatrogenic Brown syndrome
- Anti-elevation syndrome
- Reversal of vertical deviation

We will report the following outcomes in the 'Summary of findings' table:

1. Proportion of participants with postoperative surgical success, as defined above
2. Proportion of participants with an anomalous head position preoperatively who have a residual head tilt greater than 15 degrees in central gaze postoperatively
3. Proportion of participants with postoperative hypertropia less than 3 PD, as measured by alternate cover testing with prism, in down gaze
4. Proportion of participants with postoperative hypertropia less than 3 PD, as measured by alternate cover testing with prism, in contralateral gaze (adduction of affected eye)
5. Proportion of participants who received additional strabismus surgery
6. Proportion of participants with reversal of the vertical deviation at distance or near postoperatively
7. Proportion of participants with the postoperative complication of orbital cellulitis

Search methods for identification of studies

Electronic searches

We will search the Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the Cochrane Eyes and Vision

Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to present), Embase (January 1980 to present), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to present), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We will not use any date or language restrictions in the electronic search for trials.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), Embase (Appendix 3), LILACS (Appendix 4), ISRCTN (Appendix 5), ClinicalTrials.gov (Appendix 6), and the ICTRP (Appendix 7).

Searching other resources

We will search the reference lists of identified trial reports to find additional trials. We will use the Science Citation Index to find studies that cited the identified trials. We will not conduct manual searches of conference proceedings or abstracts specifically for this review because proceedings and abstracts from major eye conferences are searched annually by Cochrane Eyes and Vision and trials identified are added to CENTRAL.

Data collection and analysis

Selection of studies

Two review authors will independently assess the titles and abstracts of all reports identified by the electronic and manual searches. We will classify the studies corresponding to the abstracts as (a) definitely relevant, (b) possibly relevant, or (c) definitely not relevant. For studies classified as (a) or (b) based on review of abstracts, we will obtain and assess the full-text reports. Using the full-text reports, we will classify each study as (1) include, (2) awaiting assessment, or (3) exclude. Any disagreements will be resolved by a third review author. We will assess studies identified as "included" for methodological quality. We will contact the primary investigators of studies classified as "awaiting assessment" for clarification and additional information. We will exclude studies identified by both review authors as "excluded." The review authors will be unmasked to the report authors, institutions, and trial results during this assessment.

Data extraction and management

Two review authors will independently extract data for study methods and characteristics, such as details of participants, interventions, outcomes, and other relevant information for all included studies, and quantitative outcome results onto data collection forms developed by Cochrane Eyes and Vision. The forms will be pilot tested on two trials, and the revised form will be used to extract data from the included trials. We will resolve discrepancies by discussion. We will contact primary investigators for missing or unclear data. Wherever possible, and for included trials for which we are unable to obtain data from the investigators, we will extract data from figures in the published papers using digital software (for example GetData 2013). One review author will enter data into RevMan 5, and a second review author will verify the data entry (RevMan 2014).

In addition to the outcome data described above, we will record study characteristics such as details of participants, interventions, outcomes, and other relevant information for all included studies.

Assessment of risk of bias in included studies

Two review authors will assess each included trial for risk of bias according to methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will consider the following domains: selection bias (sequence generation, allocation concealment before randomization), performance bias (masking (blinding) of participants and personnel), detection bias (masking of outcome assessors), attrition bias (incompletely reported outcome data), reporting bias (selective outcome reporting), and any other sources of bias. We will label each domain as high risk of bias, low risk of bias, or unclear risk of bias. A third review author will resolve any disagreements in bias assessment. For missing or unclearly reported information, we will seek to obtain further information from trial investigators. Whenever the investigators contacted do not respond within six weeks, we will use the available information to assess risk of bias. We will record our assessments in the Cochrane 'Risk of bias' table.

Measures of treatment effect

For primary and secondary dichotomous outcomes, we will calculate a risk ratio with 95% confidence intervals. Dichotomous outcomes will include the proportion of participants with postoperative surgical success, residual head tilt greater than 15 degrees in central gaze, hypertropia less than 3 PD in down gaze and contralateral gaze, and symptomatic cyclotorsion; the proportion of participants who received another strabismus surgery; and the proportion of participants with adverse effects.

We will calculate mean differences with 95% confidence intervals for continuous outcomes including quality of life scores.

Unit of analysis issues

The unit of analysis will be the individual participant.

Dealing with missing data

We will contact study investigators for any missing information or incompletely reported data. If the investigators do not respond within six weeks, we will use the data available.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by examining potential variations in participant characteristics, inclusion/exclusion criteria, and assessments of primary and secondary outcomes. When appropriate, we will combine study data in meta-analysis and test for statistical heterogeneity using the Chi^2 test and evaluate the I^2 value. We will interpret an I^2 value greater than 50% as the presence of substantial statistical heterogeneity. We will also examine the overlap of effect estimates and confidence intervals among studies, with poor overlap suggestive of heterogeneity.

Assessment of reporting biases

If we include 10 or more studies in a meta-analysis, we will examine funnel plots for asymmetry to identify any potential publication (reporting) bias. We will assess selective outcome reporting as part of the 'Risk of bias' assessment for individual trials.

Data synthesis

Data analysis will follow the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If we detect neither clinical nor methodological heterogeneity, we will combine the outcome data in a meta-analysis. We will use a fixed-effect model when there are fewer than three trials in a meta-analysis, and a random-effects model when there are three or more trials in an analysis. In cases of substantial statistical and clinical heterogeneity, we will not combine study results, but will present a narrative summary.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will perform subgroup analyses based on participant age (adults 18 years of age and older versus children); etiology of superior oblique palsy (congenital versus acquired); and clinical presentation (primarily symptomatic due to head tilt versus diplopia in various gaze positions). In the case of marked variability in data reporting, we will not perform subgroup analyses.

Sensitivity analysis

If we identify and include a sufficient number of studies, we will conduct sensitivity analyses to examine the impact of the exclusion of studies at high risk of bias, industry-funded studies, and unpublished studies.

Summary of findings

We will prepare a "Summary of findings" table which will include the assumed risk and corresponding risk for relevant outcomes specified above based on risk across control groups in the included studies. We will use the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) classification approach to grade the overall certainty of evidence for each outcome (www.gradeworkinggroup.org). We will assess the certainty of evidence for each outcome as "high," "moderate," "low," or "very low" according to the following criteria as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011).

- High risk of bias among included studies
- Indirectness of evidence
- Unexplained heterogeneity or inconsistency of results
- Imprecision of results (ie, wide confidence intervals)
- High probability of publication bias

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 [mh ^"Oculomotor Muscles"]
#2 [mh ^"Oculomotor Nerve"]
#3 [mh ^"Trochlear Nerve"]
#4 [mh ^"Trochlear Nerve Diseases"]
#5 superior near/2 nerve* near/2 pals*
#6 superior near/2 oblique near/2 pals*
#7 trochlear near/2 nerve* near/2 pals*
#8 fourth near/2 nerve* near/2 pals*
#9 IV near/2 nerve* near/2 pals*
#10 fourth near/2 cranial near/2 nerve*
#11 IV near/2 cranial near/2 nerve*
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 [mh ^"Ophthalmologic Surgical Procedures"]
#14 MeSH descriptor: [Strabismus] this term only and with qualifier(s): [Surgery - SU]
#15 oblique near/5 (insertion or disinsertion or resection or recession or transposition or myotomy or myectomy or plication or tuck or advancement)
#16 inferior near/4 (transposition or rectus or insertion or orbital or fixation or denervation or extirpation)
#17 Posterior near/2 fixation near/2 suture*
#18 superior near/4 rectus near/4 recession
#19 #13 or #14 or #15 or #16 or #17 or #18
#20 #12 and #19

Appendix 2. MEDLINE Ovid search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. Oculomotor Muscles/
14. Oculomotor Nerve/
15. Trochlear Nerve/
16. Trochlear Nerve Diseases/
17. (superior adj2 nerve$ adj2 pals$).tw.
18. (superior adj2 oblique adj2 pals$).tw.
19. (trochlear adj2 nerve$ adj2 pals$).tw.
20. (fourth adj2 nerve$ adj2 pals$).tw.
21. (IV adj2 nerve$ adj2 pals$).tw.
22. (fourth adj2 cranial adj2 nerve$).tw.
23. (IV adj2 cranial adj2 nerve$).tw.
24. or/13-23
25. Ophthalmologic Surgical Procedures/
26. Strabismus/su [Surgery]
27. (oblique adj5 (insertion or disinsertion or resection or recession or transposition or myotomy or myectomy or plication or tuck or advancement)).tw.
28. (inferior adj4 (transposition or rectus or insertion or orbital or fixation or denervation or extirpation)).tw.
29. (Posterior adj2 fixation adj2 suture$).tw.
30. (superior adj4 rectus adj4 recession).tw.
31. or/25-30
32. 12 and 24 and 31

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville 2006.

Appendix 3. Embase Ovid search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin$ adj3 trial$).tw.
14. ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.

15. exp placebo/
16. placebo$.tw.
17. random$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control$ or prospectiv$ or volunteer$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. Extraocular Muscle/
34. Oculomotor Nerve/
35. Trochlear Nerve/
36. Trochlear Nerve Disease/
37. (superior adj2 nerve$ adj2 pals$).tw.
38. (superior adj2 oblique adj2 pals$).tw.
39. (trochlear adj2 nerve$ adj2 pals$).tw.
40. (fourth adj2 nerve$ adj2 pals$).tw.
41. (IV adj2 nerve$ adj2 pals$).tw.
42. (fourth adj2 cranial adj2 nerve$).tw.
43. (IV adj2 cranial adj2 nerve$).tw.
44. or/33-43
45. Eye Surgery/
46. Strabismus/su [Surgery]
47. (oblique adj5 (insertion or disinsertion or resection or recession or transposition or myotomy or myectomy or plication or tuck or advancement)).tw.
48. (inferior adj4 (transposition or rectus or insertion or orbital or fixation or denervation or extirpation)).tw.
49. (Posterior adj2 fixation adj2 suture$).tw.
50. (superior adj4 rectus adj4 recession).tw.
51. or/45-50
52. 32 and 44 and 51

Appendix 4. LILACS search strategy

oculomotor nerve OR trochlear nerve OR superior oblique OR superior nerve OR fourth nerve OR IV nerve OR fourth cranial OR IV cranial and insertion OR disinsertion OR resection OR recession OR transposition OR myotomy OR myectomy OR plication OR tuck OR advancement OR rectus OR orbital OR fixation OR denervation OR extirpation

Appendix 5. ISRCTN search strategy

"(oculomotor nerve OR trochlear nerve OR superior oblique OR superior nerve OR fourth nerve OR IV nerve OR fourth cranial OR IV cranial) AND (insertion OR disinsertion OR resection OR recession OR transposition OR myotomy OR myectomy OR plication OR tuck OR advancement OR rectus OR orbital OR fixation OR denervation OR extirpation)"

Appendix 6. ClinicalTrials.gov search strategy

Interventional Studies | oculomotor nerve OR trochlear nerve OR superior oblique OR superior nerve OR fourth nerve OR "IV nerve" OR fourth cranial OR "IV cranial" | insertion OR disinsertion OR resection OR recession OR transposition OR myotomy OR myectomy OR plication OR tuck OR advancement OR rectus OR orbital OR fixation OR denervation OR extirpation

Appendix 7. ICTRP search strategy

oculomotor nerve OR trochlear nerve OR superior oblique OR superior nerve OR fourth nerve OR IV nerve OR fourth cranial OR IV cranial = Condition AND insertion OR disinsertion OR resection OR recession OR transposition OR myotomy OR myectomy OR plication OR tuck OR advancement OR rectus OR orbital OR fixation OR denervation OR extirpation = Intervention

CONTRIBUTIONS OF AUTHORS

- Conception and design of study: MYC, JLD
- Drafting the review or commenting on it critically for intellectual content: MYC, ALC, VLT, JLD
- Final approval of the document to be published: MYC, ALC, VLT, JLD

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MYC: none known

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