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Botulinum toxin for the treatment of strabismus (Review)

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[Intervention Review]

Botulinum toxin for the treatment of strabismus

Fiona J Rowe[1], Carmel P Noonan[2]

[1]Department of Health Services Research, University of Liverpool, Liverpool, UK. [2]Department of Ophthalmology, Aintree University Hospitals NHS Foundation Trust, Liverpool, UK

Contact address: Fiona J Rowe, Department of Health Services Research, University of Liverpool, Waterhouse Building (B211), 1-3 Brownlow Street, Liverpool, L69 3GL, UK. rowef@liverpool.ac.uk.

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ABSTRACT

Background

The use of botulinum toxin as an investigative and treatment modality for strabismus is well reported in the medical literature. However, it is unclear how effective it is in comparison to other treatment options for strabismus.

Objectives

The primary objective was to examine the efficacy of botulinum toxin therapy in the treatment of strabismus compared with alternative conservative or surgical treatment options. This review sought to ascertain those types of strabismus that particularly benefit from the use of botulinum toxin as a treatment option (such as small angle strabismus or strabismus with binocular potential, i.e. the potential to use both eyes together as a pair). The secondary objectives were to investigate the dose effect and complication rates associated with botulinum toxin.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to July 2016), Embase (January 1980 to July 2016), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2016), 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 did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 11 July 2016. We handsearched the British and Irish Orthoptic Journal, Australian Orthoptic Journal, proceedings of the European Strabismological Association (ESA), International Strabismological Association (ISA) and International Orthoptic Association (IOA) (www.liv.ac.uk/orthoptics/research/search.htm) and American Academy of Paediatric Ophthalmology and Strabismus meetings (AAPOS). We contacted researchers who are active in this field for information about further published or unpublished studies.

Selection criteria

We included randomised controlled trials (RCTS) of any use of botulinum toxin treatment for strabismus.

Data collection and analysis

Two review authors independently selected studies and extracted data. We used standard methods expected by Cochrane and assessed the certainty of the evidence using GRADE. We defined ocular alignment as an angle of deviation of less than or equal to 10 prism dioptres.

Main results

Six RCTs were eligible for inclusion. We judged the included studies as at a mixture of low, unclear and high risk of bias. We did not consider any of the included studies as at low risk of bias for all domains.

Two trials conducted in Spain (102 people, number of eyes not specified) compared botulinum toxin with surgery in children that required retreatment for acquired or infantile esotropia. These two studies provided low-certainty evidence that children who received botulinum toxin may have a similar or slightly reduced chance of achieving ocular alignment (pooled risk ratio (RR) 0.91, 95% confidence interval (CI) 0.71 to 1.16), binocular single vision (RR 0.88, 95% CI 0.63 to 1.23), sensory fusion (RR 0.88, 95% CI 0.63 to 1.23) and stereopsis (RR 0.86, 95% CI 0.59 to 1.25) compared with children who received surgery. One trial from Canada compared botulinum toxin with surgery in 30 adults (30 eyes) with horizontal strabismus and reported a reduced chance of ocular alignment with botulinum toxin (RR 0.38, 95% CI 0.17 to 0.85; low-certainty evidence).

One trial in the UK suggested that botulinum toxin may result in a similar or slightly improved chance of ocular alignment in people with acute onset sixth nerve palsy compared with observation (RR 1.19, 95% CI 0.96 to 1.48; 47 participants, low-certainty evidence).

Very low-certainty evidence from one trial from Brazil suggested that adjuvant botulinum toxin in strabismus surgery may increase the chances of ocular alignment compared with strabismus surgery alone (RR 1.83, 95% CI 0.41 to 8.11; 23 participants).

One trial from China of 47 participants (94 eyes) suggested that people receiving botulinum toxin combined with sodium hyaluronate may have a similar or slightly reduced chance of achieving ocular alignment compared with botulinum toxin alone (RR 0.81, 95% CI 0.36 to 1.82; low-certainty evidence).

Reported complications in people given botulinum toxin in the included trials included ptosis (range 9% to 41.66%) and vertical deviation (range 8.3% to 18.51%). Ptosis occurred less frequently when treated with botulinum toxin combined with sodium hyaluronate compared to botulinum toxin alone.

Authors' conclusions

Most published literature on the use of botulinum toxin in the treatment of strabismus consists of retrospective studies, cohort studies or case reviews. Although these provide useful descriptive information, clarification is required as to the effective use of botulinum toxin as an independent treatment modality. Six RCTs on the therapeutic use of botulinum toxin in strabismus, graded as low and very low-certainty evidence, have shown varying responses. These include a lack of evidence for effect of botulinum toxin on reducing visual symptoms in acute sixth nerve palsy, poor response in people with horizontal strabismus without binocular vision, similar or slightly reduced achievement of successful ocular alignment in children with esotropia and potential increased achievement of successful ocular alignment where surgery and botulinum toxin are combined. Further high quality trials using robust methodologies are required to compare the clinical and cost effectiveness of various forms of botulinum toxin (e.g. Dysport, Xeomin, etc), to compare botulinum toxin with and without adjuvant solutions and to compare botulinum toxin to alternative surgical interventions in strabismus cases with and without potential for binocular vision.

PLAIN LANGUAGE SUMMARY

Botulinum toxin for the treatment of strabismus

What is the aim of this review?

The aim of this Cochrane Review was to find out how well botulinum toxin works as a treatment for strabismus. Cochrane researchers collected and analysed all relevant studies to answer this question and included six studies.

Key messages

The evidence as to the benefits and harms of using botulinum toxin for strabismus is uncertain.

What was studied in the review?

Strabismus occurs when the eyes are not aligned. Usually one eye turns inwards or outwards. Less frequently one eye turns upwards or downwards. It is commonly known as "squint".

Strabismus can lead to blurred vision or double vision. In children it can affect the long term development of vision in the affected eye. There are many causes of strabismus. In most cases, there are problems with the muscles or nerves around the eye.

Doctors can use botulinum toxin to stop individual muscles around the eye working for a while. This may help the eyes become more aligned and may lead to less blurred or double vision. One problem with using botulinum toxin is that it can result in a droopy eyelid (ptosis).

What are the main results of the review?

The review shows that:

• using botulinum toxin in children requiring primary treatment or retreatment for strabismus may make no difference, or slightly reduce the chances of recovering correct alignment of the eyes compared with surgery (low-certainty evidence);

• using botulinum toxin in adults with strabismus may decrease the chances of recovering correct alignment of the eyes compared with surgery (low-certainty evidence);

• people with sixth nerve palsy receiving botulinum toxin may have a similar or small increased chance of correct alignment of eyes compared with no treatment (low-certainty evidence);

• the evidence on using botulinum toxin with surgery, compared with surgery alone, was very uncertain (very low-certainty evidence);

• ptosis occurred commonly in people receiving botulinum toxin in these studies. The number of people affected ranged from 1 in 10 to 1 in 2 people. Everyone recovered when treatment stopped. Ptosis occurred less frequently when treated with botulinum toxin combined with sodium hyaluronate compared to botulinum toxin alone.

How up-to-date is this review?

The Cochrane researchers searched for studies that had been published up to 11 July 2016.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Botulinum toxin versus surgery in adults and children with strabismus

Patient or population: adults and children with strabismus
Setting: hospital
Intervention: botulinum toxin
Comparison: surgery

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery	Risk with botulinum toxin				
Primary outcome: improved ocular alignment ≤ 10 PD Follow-up: median 6 months	**Children**					
	750 per 1000	683 per 1000 (533 to 870)	RR 0.91, (0.71 to 1.16)	102 (2 RCTs)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
	Adults					
	750 per 1000	285 per 1000 (128 to 638)	RR 0.38 (0.17 to 0.85)	30 (1 RCT)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
Secondary outcome: achievement of binocular single vision	616 per 1000	542 per 1000 (388 to 758)	RR 0.88 (0.63 to 1.23)	102 (2 RCTs)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
Secondary outcome: achievement of 'sensory' fusion	616 per 1000	542 per 1000 (388 to 758)	RR 0.88 (0.63 to 1.23)	102 (2 RCTs)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.

Secondary outcome: achievement of stereopsis	557 per 1000	479 per 1000 (328 to 696)	RR 0.86 (0.59 to 1.25)	102 (2 RCTs)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
Adverse events with botulinum toxin Follow-up: median 6 months	Induced ptosis occurred in 20.8 to 41.66% across trials. Induced vertical deviation occurred in 2.2 to 8.3% across trials All adverse events recovered within the follow-up time period with no lasting adverse effect		-	102 (2 RCTs)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). We derived the relative risk from the standardised mean difference for continuous data related to measured change in angle of deviation, measured in prism dioptres (PD) or degrees. Relative risk for dichotomous data relating to achievement of binocular single vision as assessed by cover test, fusional vergence and stereoacuity.
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **PD:** prism dioptres; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[1]There was unclear sequence generation for 3 trials; the study investigators were aware of patient randomisation in the Tejedor 1998 and Tejedor 1999 trials.
[2]It was unclear from the results how many participants received unilateral or bilateral injections of botulinum toxin in the Tejedor 1998 and Tejedor 1999 trials. Bilateral injection would have a greater effect on the angle of deviation than unilateral injection.

BACKGROUND

Description of the condition

Strabismus is a deviation of the ocular alignment where one eye turns, which may be intermittent or constant. It is a common condition that occurs in up to 5% of the population and up to 50% in special populations such as those with cerebral palsy (Adams 2005; Donnelly 2005; Strömland 1993). In forms of strabismus that are intermittent, binocular function (using both eyes as a pair) is maintained with straight eyes for a variable proportion of the time. In other forms there is a manifest deviation usually with a variable degree of suppression of the deviating eye. Strabismus can be further divided into esotropia (inturning deviation), exotropia (outturning deviation) or, less commonly, hypertropia (upturning deviation), hypotropia (downturning deviation) and cyclotropia (rotatory deviation). Strabismus can be caused by a variety of insults such as abnormal anatomical development of extraocular muscles or the orbit, impaired neurological input to extraocular muscles, uncorrected refractive error or hereditary factors. Sequelae to strabismus can include blurring of vision, diplopia (double vision), impaired depth (3-D) perception, and in younger children, amblyopia. Amblyopia is impaired vision in the deviating eye due to the lack of correct stimulation of that eye and results in permanent loss of vision if left untreated at a young age.

Description of the intervention

There are various treatments associated with strabismus. Primarily treatment is directed at aligning the visual axes. Conservative options include prisms to realign the visual axes and orthoptic exercises to promote and establish binocular control of ocular alignment where both eyes can subsequently work as a pair. Invasive treatment options include surgery to permanently alter extraocular muscle function and thus permanently change ocular alignment, and botulinum toxin to individual extraocular muscles. Scott 1980 first described this latter option, which temporarily paralyses the extraocular muscle and results in a changed ocular alignment that resolves over time (usually a two to three month time interval). During this period of altered eye position, the visual axes may adopt an ocular alignment that permits binocular single vision. This is the ability to use both eyes as a pair so that both eyes contribute to seeing a single image. This may persist or regress necessitating further treatment. Botulinum toxin injection to extraocular muscles is an alternative option that has become established in the treatment of adults who have strabismus. Its use in children is less well studied. It is perceived to be difficult to use in children due to the need for sedation and complications following leakage of the toxin into the levator palpebral superioris muscle (the muscle responsible for elevating the eyelid) thus resulting in a droopy upper lid, known as ptosis (Rowe 2005).

Botulinum toxin has become recognised and accepted as both an adjunct and alternative to strabismus surgery in many types of strabismus (Bunting 2013; Campos 2000; Crouch 2006; Dawson 1999; Dawson 2004a; Dawson 2004b; Dawson 2005; Dawson 2012; Gardner 2013; Holmes 2001; Kerr 2001; Marsh 2003; McNeer 2003; Ozkan 2006; Rayner 1999; Rowe 2004; Sabetti 2003; Spencer 1997; Tejedor 2001). Diagnostic uses of botulinum toxin include investigation of postoperative diplopia (double vision), to detect whether fusion (which contributes to binocular vision) is present preoperatively, to differentially diagnose between a part and complete sixth nerve palsy, to aid in the prediction of surgical results for incomitant deviations and to help in the investigation of a possible slipped muscle following surgery. In terms of therapeutic uses botulinum toxin has been found useful in treating facial muscle spasm, strabismus, nystagmus, corneal ulceration and exposure keratitis to name a few. The therapeutic uses of botulinum toxin for strabismus are to restore fusion in those people with decompensating deviations, or those with a recovering sixth nerve palsy, to align the cosmetic form of strabismus, to aid surgical overcorrections and undercorrections and to aid in the improvement of visual acuity by relieving oscillopsia (perception of moving images) in cases of acquired nystagmus.

Other treatment options associated with strabismus include those that address the sequelae of strabismus, such as occlusion therapy for amblyopia which is a reduction in vision caused completely or in part by the strabismus.

How the intervention might work

Botulinum toxin is a drug that is an exotoxin of the bacterium *Clostridium botulinum*. Botulinum toxin type A is an injectable neurotoxin. In order for muscles to contract, acetylcholine is released at the nerve-muscle junction. Acetylcholine binds to muscle receptors causing a contraction. Botulinum toxin selectively blocks the release of acetylcholine from the cholinergic synapses found within a muscle, thereby blocking the nerve impulses and preventing contraction of the muscle cells. Paralysis (which is temporary) follows within days after injection of the toxin into the extraocular muscle, and the toxin becomes fully effective within three to seven days of the injection. The duration of paralysis is dependent on the individual, but generally lasts for three months. Once a muscle is paralysed, opposing muscles take on a greater movement force and the eye position changes allowing the visual axes to move into a straighter eye alignment.

Why it is important to do this review

Clear guidelines do not exist as to the recommended use of botulinum toxin for the treatment of strabismus particularly as so many types of strabismus exist. Much of the published literature

pertains to retrospective case series with varying treatment modalities using different types of botulinum toxin (e.g. Dysport™ or Botox™ or Prosign™) and different doses of the toxin.

OBJECTIVES

The primary objective was to examine the efficacy of botulinum toxin therapy in the treatment of strabismus compared with alternative conservative or surgical treatment options. This review sought to ascertain those types of strabismus that particularly benefit from the use of botulinum toxin as a treatment option (such as small angle strabismus or strabismus with binocular potential, i.e. the potential to use both eyes together as a pair). The secondary objectives were to investigate the dose effect of botulinum toxin and the complication rates associated with botulinum toxin.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) of treatment using botulinum toxin for strabismus.

Types of participants

Participants with strabismus suitable for treatment with botulinum toxin to align the angle of deviation. This included adults and children with no age limit.

Types of interventions

We considered trials in which botulinum toxin of all makes, e.g. Dysport™, Botox™, Prosign™ were compared to the following:

- strabismus surgery;
- botulinum toxin alternatives;
- conservative therapy; orthoptic exercises, prisms, lens therapy.

We made the following comparisons:

- single muscle versus multiple muscle injections of botulinum toxin;
- botulinum toxin in combination with conservative treatment versus conservative treatment alone;
- botulinum toxin versus other variant of botulinum toxin;
- botulinum toxin as an alternative to conservative treatment;
- botulinum toxin in combination with surgical treatment versus surgical treatment alone;
- botulinum toxin as an alternative to surgical treatment;
- botulinum toxin versus observation (no treatment);
- strabismus types with binocular potential versus those without binocular potential;
- small angle strabismus (less than 20 prism dioptres (PD)) versus large angle strabismus;
- level of dose of botulinum toxin and reported complications at each dose.

Types of outcome measures

Primary outcomes

- improved ocular alignment as measured by a reduction in the angle of deviation measured by prisms or the synoptophore.

We required a minimum of six months post-treatment follow up for assessment of primary outcomes.
We classed outcomes as:

- success: full control of angle of deviation within 10 PD of ortho (no deviation) with normal measures/ranges of binocular single vision (simultaneous perception, motor fusional vergence and stereopsis);
- satisfactory A: reduction in angle of deviation to within 20 PD of ortho with evidence of binocular single vision (simultaneous perception, motor fusional vergence or stereoacuity);
- satisfactory B: reduction in angle of deviation to within 20 PD of ortho without evidence of binocular single vision;
- fail: little or no change in angle of deviation and/or no improvement in binocular single vision measures.

We analysed separately the change in angle of deviation (continuous data) and the change in binocular single vision (categorical data) followed by a composite measure of the two (ordinal data).

Secondary outcomes

Secondary outcome measures included:

- achievement of binocular single vision as assessed by cover test, motor fusional vergences and stereoacuity.

Adverse outcomes

We considered the following adverse effects:

- induced ptosis;
- induced vertical deviation;
- subconjunctival haemorrhage;
- intolerable diplopia.

We categorized adverse effects as severe if they required further treatment, or minor if no further treatment was required.
Also we recorded the complications noted within two weeks of treatment in the included trials.

Economic data

We included details of the cost of any treatments where data were available.

Quality of life data

We considered any measure of participant or parent satisfaction relating to improvement in appearance or improvement to lifestyle.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (2016, Issue 6), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to July 2016), Embase (January 1980 to July 2016), Latin American and Caribbean Literature on Health Sciences (LILACS) (January 1982 to July 2016), 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 did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 11 July 2016.

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 WHO ICTRP (Appendix 7).

Searching other resources

We handsearched the British and Irish Orthoptic Journal, Australian Orthoptic Journal, proceedings of the European Strabismological Association (ESA), International Strabismological Association (ISA) and International Orthoptic Association (IOA) (www.liv.ac.uk/orthoptics/research/search.htm) and American Academy of Paediatric Ophthalmology and Strabismus meetings (AAPOS). These resources were searched from 1980 to 11 July 2016. We contacted researchers who are active in the field for information about further published or unpublished studies. We used the Pediatric Ophthalmology and Strabismus mailbase in the UK and USA. We screened the reference lists of publications.

Data collection and analysis

Selection of studies

Both review authors independently screened the titles and abstracts obtained by the searches to establish whether they met the criteria defined as include, exclude and unsure. Included papers encompassed RCTs. Excluded papers encompassed case reports. Unsure encompassed papers that comprised non-RCTs and case series and a decision to include followed discussion between the review authors. Arbitration from the Cochrane editorial base was not required. Following this process, we obtained the full copies of definitely or potentially relevant studies. Where information was unclear we contacted the study authors. We documented the details of excluded studies in the 'Characteristics of excluded studies' table. We constructed a PRISMA diagram to illustrate the study selection process.

Data extraction and management

The two review authors independently extracted information relating to outcomes using paper data collection forms developed by Cochrane Eyes and Vision. We resolved discrepancies by discussion and entered data into Review Manager 5 (RevMan 5) (RevMan 2014).

We extracted the following details from the included studies:

- methods: inclusion and exclusion criteria, follow-up period;
- participants: age, previous treatment, strabismus type;
- interventions: type of botulinum toxin used, dose measure, number of injections;
- outcomes: ocular alignment and binocular function after a minimum of six months;
- adverse events and quality of life measures.

We used the GRADE approach to interpret findings (Langendam 2013), and employed the GRADE profiler (GRADEpro) to import data from RevMan 5 to create 'Summary of findings' tables (GRADEpro 2014). These tables provide outcome-specific information concerning the overall certainty of evidence from studies included in the comparisons, primary and secondary outcomes.

Assessment of risk of bias in included studies

We assessed study quality according to the methods set out in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the Cochrane tool for assessing risk of bias. We assessed sequence generation, allocation concealment, masking (blinding) of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. We made judgements for each domain and graded each as either at low risk of bias, high risk of bias or unclear.

We used the GRADE approach to interpret findings and GRADEpro to import data from RevMan 5.3 to create 'Summary of findings' tables. These tables provide outcome-specific information concerning the overall certainty of evidence from RCTs included in the comparison, the magnitude of effect of the interventions

examined and the sum of available data on the outcomes we considered. For assessments of the overall certainty of evidence for each outcome, we downgraded the evidence from high-certainty by one level for each serious study limitation, e.g. risk of bias, imprecision.

Measures of treatment effect

We considered the relative risk for dichotomous data relating to binocular single vision and the standardized mean difference for continuous data relating to measured change in angle of deviation.

Unit of analysis issues

We expected that studies may have consisted of parallel group trials or cross-over trials. Where we found both in the search, we considered these separately as botulinum toxin is known to have a longer lasting effect than the average three months expected for extraocular muscle function to fully recover. When analysing secondary outcome measures, if possible we re-evaluated studies that reported results 'per person' to convert results to 'per injection' as a more realistic indicator of prevalence.

Dealing with missing data

We contacted primary investigators/authors to obtain missing data. We allowed a time period of three months for response. We recorded non-response as missing data.

Assessment of heterogeneity

We assessed studies initially for heterogeneity using the Chi^2 test. However, considering the expected heterogeneity, we considered the I^2 statistic value to quantify inconsistency. We deemed meta-analysis inappropriate on the basis of assessment of heterogeneity. Therefore, we provided a descriptive summary of results.

Assessment of reporting biases

There were insufficient trials to examine publication bias using a funnel plot.

Data synthesis

The results were heterogenous, hence we presented a descriptive summary of results.

Subgroup analysis and investigation of heterogeneity

We evaluated studies for clinical heterogeneity (variability in the participants or outcomes) and methodological heterogeneity (variability in trial design and quality).

Sensitivity analysis

We did not perform a sensitivity analysis to assess the sensitivity of the summary effect to the exclusion of trials assessed as inadequate in terms of concealment of randomisation or those with missing data or of questionable eligibility.

Methods for future updates

If trials become available in the future, we will include them in this review using the methods for the primary review.

RESULTS

Description of studies

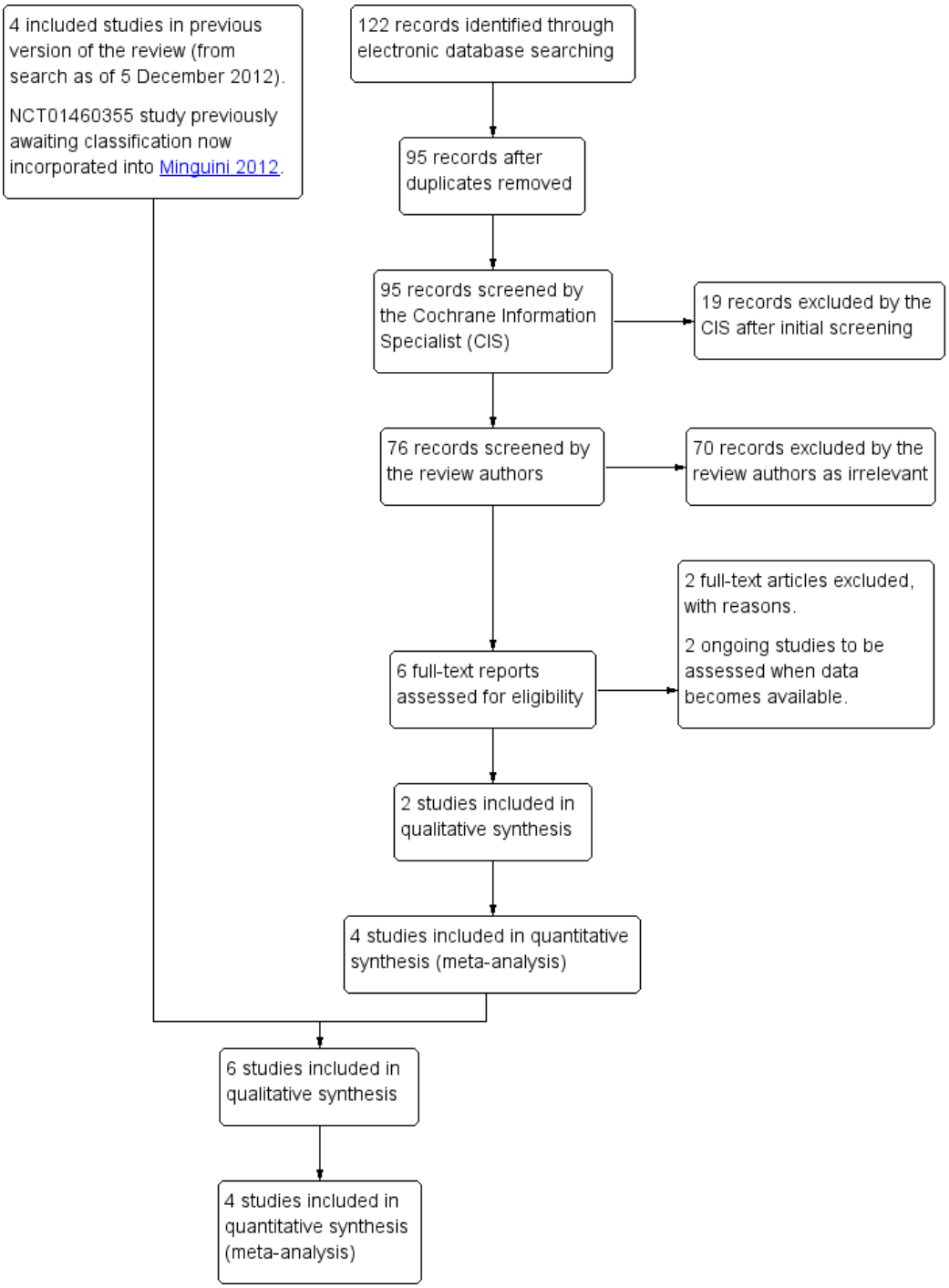
Results of the search

The electronic searches identified a total of 274 titles and abstracts. We requested the full text for a total of eight studies.

An update search was done in December 2011. After deduplication the search identified a total of 53 references. The Cochrane Information Specialist (CIS) (formerly known as Trials Search Co-ordinator) scanned the search results and removed 37 references which were irrelevant to the scope of the review. We assessed the remaining 16 references. Twelve references reported retrospective or case cohort studies and we excluded them. We obtained full-text copies of the remaining four references and extracted further details.

Updates searches ran in July 2016 yielded a further 122 references (Figure 1). After 27 we removed duplicates, the CIS screened the remaining 95 records and removed 19 references which were not relevant to the scope of the review. We screened the remaining 76 references and obtained the full-text reports of six references for further assessment. We included two new studies (Chen 2013; Minguini 2012), and excluded two studies (Etezad Razavi 2014: Gursoy 2012). We identified two ongoing studies (Jain 2015; PACTR201508001241218), and contacted the trial authors for further information. We received responses from both trial teams, who confirmed the ongoing recruitment to these studies.

Figure 1. Study flow diagram.



Included studies

We included six trials and provided details below. Additional details can be found in the 'Characteristics of included studies' table.
Tejedor 1999 randomised 55 strabismic children with infantile esotropia receiving retreatment to two different treatment procedures: reoperation or botulinum toxin (Botox™). This was a parallel RCT. The trial authors compared these groups to each other for percentage of successful motor outcome less than or equal to ($\leq$) 8 prism dioptres (PD) and percentage change in deviation. The latter was calculated as preoperative deviation - postoperative deviation/preoperative deviation x 100%. Inclusion and exclusion criteria were stipulated for the trial. Both groups were regarded as comparable as similarities were present for both groups regarding previous surgical procedures, mean age at initial surgery, average time lapse between first and second treatment, angle of deviation, refractive error and visual acuity measures. The trial achieved follow-up to a minimum of 36 months.
Tejedor 1998 randomised 47 strabismic children with acquired esotropia requiring retreatment to two different treatment procedures: reoperation or botulinum toxin (Botox™). This was a parallel RCT. These groups were compared to each other for percentage net change in distance deviation, the percentage of participants with successful motor outcome $\leq$ 8 PD and detectable fusion and stereopsis. Percentage net change was calculated as preoperative deviation - postoperative deviation/preoperative deviation x 100%. Inclusion and exclusion criteria were stipulated for the trial. Both groups were regarded as homogenous as similarities were present for both groups regarding previous surgical procedures, mean age at initial surgery, average time lapse between first and second treatment, angle of deviation, refractive error and follow-up. The trial achieved follow-up of 20 to 38 months.
Lee 1994 randomised 54 participants with acute unilateral sixth nerve palsy into two groups: those receiving botulinum toxin (Dysport™) to the isilateral medial rectus muscle and those observed for recovery with no invasive treatment. This was a parallel RCT. These groups were compared to each other for clinical diagnosis of recovery. A full recovery was defined as completely normal ocular rotations with full field of binocular single vision. Stable recovery was defined as normal binocular single vision with a minor asymptomatic abduction defect or a small asymptomatic vertical deviation. Non recovery was defined as a persisting esotropia in primary position with diplopia not controllable by normal amplitudes of fusional vergence. Two control participants were excluded and four were lost to follow-up. One botulinum toxin participant was lost to follow-up. Follow-up ranged from four to 42 months. Both groups were considered homogenous as gender, age range, aetiology of sixth nerve palsy, duration of symptoms and laterality of palsy were similar across both groups. The mean deviation of control participants was 17.8 PD and for botulinum toxin participants was 28.6 PD. The difference in deviation across both groups was significant (P = 0.02). Three of the 22 participants having botulinum toxin injection had one repeat injection.
Carruthers 1990 randomised 30 adult participants with esotropia or exotropia without binocular function requiring treatment by two different procedures: botulinum toxin (Botox™) or adjustable suture surgery. This RCT had a cross-over design. These groups were compared to each other for alignment of deviation $\leq$ 10 PD. In addition, percent net change was documented which was defined as preoperative deviation - postoperative deviation/preoperative deviation x 100%. Inclusion and exclusion criteria were stipulated for the trial. Both groups had similar angles of deviation and similar numbers of esotropia and exotropia angles. The trial authors stated that five participants required further treatment. However they did not provide any information as to whether this constituted a cross-over of treatment options. A statement was made that should cross-over occur, a minimum six month period of follow-up would occur between treatments to allow for treatment effect.
From the 2016 update, we included two trials. Minguini 2012 reported the results of the NCT01460355 trial previously found in the 2011 search. They randomised 23 adult participants with concomitant horizontal deviations (esotropia or exotropia) of less than 50 PD requiring surgery. This was a double-masked RCT. Group A received strabismus surgery plus botulinum toxin and group B received strabismus surgery with placebo (hyaline solution). The groups were compared for net percentage change in angle of deviation from pre-operative to 1 day through to six to 12 months postoperative in addition to numbers achieving alignment less than 8 PD. Inclusion and exclusion criteria were stipulated for the trial. Both groups were regarded as homogenous as similarities were present for age at surgery, angle of pre-operative deviation, surgery ratio, best corrected visual acuity of either eye and percentage of severe amblyopia. The trial achieved follow-up to six to 12 months.
Chen 2013 randomised 47 participants with infantile esotropia that required treatment with botulinum toxin as their first treatment option. This was a two-group randomised trial. Group A received botulinum toxin with sodium hyaluronate and group B received botulinum toxin only. The groups were compared for change in angle of deviation from pre-injection to 2 weeks, 3 months and 6 months post-injection in addition to numbers achieving less than 10 PD. Inclusion and exclusion criteria were stipulated for the trial. Both groups were regarded as homogenous as similarities were present for age at treatment, gender and pre-injection deviation. The trial achieved follow-up for 6 months.

Excluded studies

We excluded four studies in 2009 (Cooper 1991; Mills 2004; Sanjari 2008; Shallo-Hoffman 2006), three studies in 2011 (Li 2008; two reports by de Alba Campomanes 2010), and two studies in the 2016 update (Etezad Razavi 2014; Gursoy 2012).
For reasons of exclusion, see the 'Characteristics of excluded studies' table.

Risk of bias in included studies

We determined the risk of bias using the 'Risk of bias' assessment tool. This considers sequence generation, allocation concealment, masking of participants, personnel and outcome assessors, incomplete outcome date, selective outcome reporting and other potential threats to validity (Figure 2; Figure 3). Our 'Risk of bias' assessment deemed the included trials to be low risk for concealment of randomisation and we did not find incomplete data reporting.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

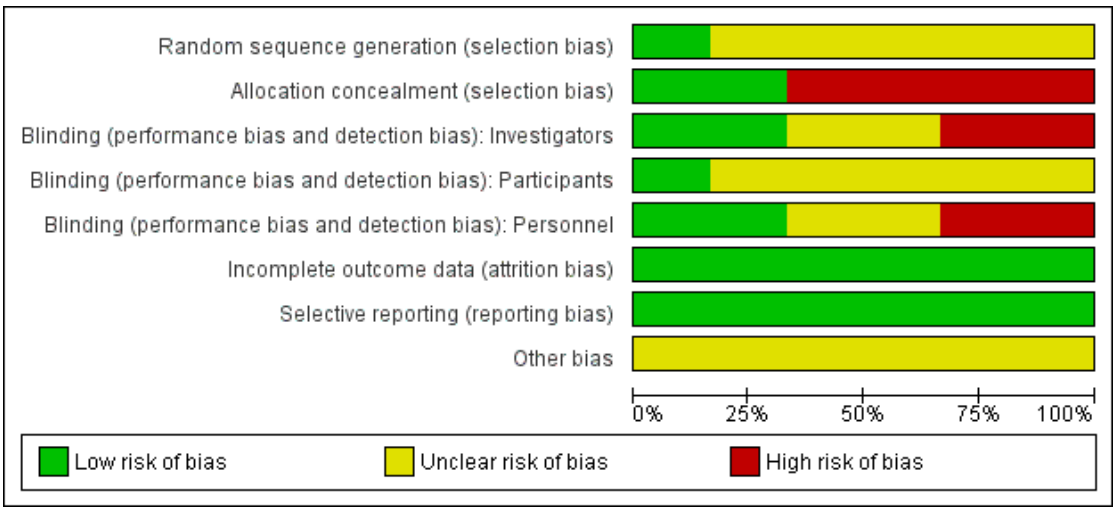
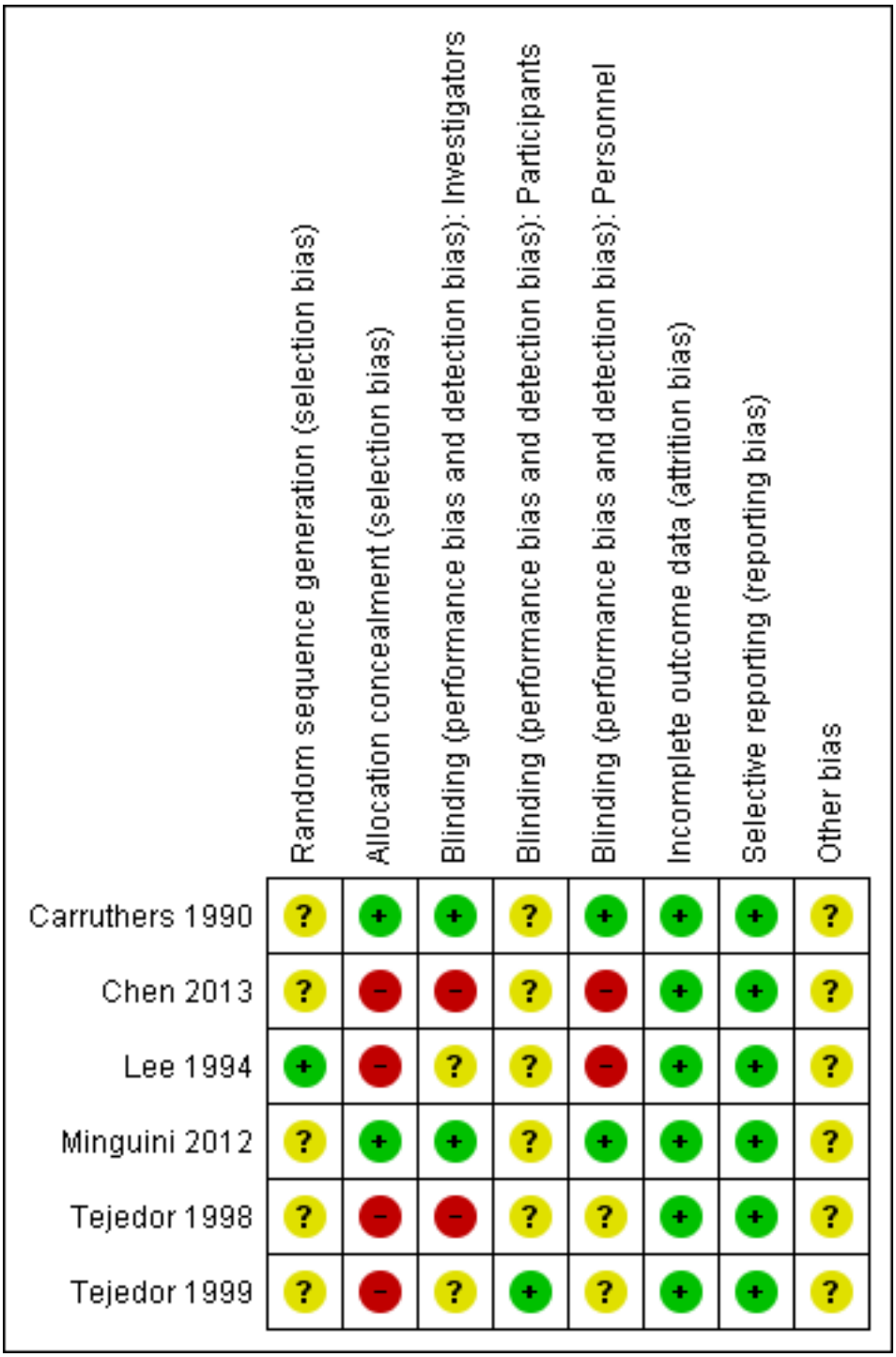


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation was unclear in five trials (Carruthers 1990; Chen 2013; Minguini 2012; Tejedor 1998; Tejedor 1999). It was evident that randomisation had occurred but the included trials did not state the method by which they did this. The latter four trials were reported as having homogenous groups following randomisation in terms of similarities for pre-treatment angle of deviation, age, gender, etc. Lee 1994 specified the use of a random number table for sequence generation and thus we considered this domain as at low risk of bias.

Allocation sequence was adequately generated in Carruthers 1990, which constituted a low risk of bias as a research assistant allocated participants separately, and in Minguini 2012 who reported allocation as masked to surgeons. Allocation sequence was unclear or inadequately generated in the remaining trials.

Blinding

Carruthers 1990 achieved adequate prevention of knowledge of the allocated interventions in that the investigators and Orthoptist were masked to participant randomisation when undertaking the final evaluation of participants for outcome measures. Minguini 2012 achieved adequate masking as the trial authors reported masking of both surgeons providing the treatment and outcome assessors. The investigators were not masked to participant randomisation in the remaining trials. However it is unlikely that the absence of masking when evaluating final outcome of participants would be biased as the outcome measures related to actual measurements of eye position and responses to binocular assessments.

Incomplete outcome data

All studies adequately addressed incomplete outcome data, for which we determined a low risk of bias. The trial authors accounted for all participants throughout the trial and provided outcome data for participants that completed the trial and provided information on any participants that were lost to follow-up or excluded.

Selective reporting

We determined that all studies were free of suggestion of selective outcome reporting in that the trial authors addressed the outcomes specified in the methodology in the results of each study.

Other potential sources of bias

It was unclear whether any trial was completely free from potential sources of bias. Small numbers of participants were recruited in both adult trials of horizontal strabismus and additionally, the groups contained a mix of esotropic and exotropic participants which reduced numbers for direct comparison further (Carruthers 1990; Minguini 2012). It was unclear whether Lee 1994 was free from risk because of early discharge of some participants and lack of long-term follow-up across all participants for comparison. Three trials recruited low numbers of participants to the treatment groups, which could impact on direct comparisons of each trial group (Chen 2013; Tejedor 1998; Tejedor 1999).

Effects of interventions

See: **Summary of findings for the main comparison** Botulinum toxin versus surgery; **Summary of findings 2** Botulinum toxin versus observation; **Summary of findings 3** Surgery with botulinum toxin versus surgery without botulinum toxin; **Summary of findings 4** Botulinum toxin with sodium hyaluronate versus botulinum toxin without sodium hyaluronate

1. Botulinum toxin versus surgery

1.1 Primary outcome (improved ocular alignment $\leq$ 10 PD)

Tejedor 1999 defined a satisfactory outcome at one year follow-up as $\leq$ 8 PD. This was achieved in 75% of the reoperation group and 67.85% of the botulinum toxin group for treatment of infantile esotropia. Percentage net change was 82.02% for the reoperation group and 78.71% for the botulinum group. Tejedor 1998 defined a satisfactory outcome at one year follow-up as $\leq$ 8 PD. This was achieved in 75% of the reoperation group and 69.56% of the botulinum toxin group for treatment of childhood strabismus. Percentage net change was 81.31% for the reoperation group and 73.45% for the botulinum group. Carruthers 1990 reported percentage net change in deviation at six months follow-up. This was achieved in 92.7% in the surgery group and 50.59% in the botulinum toxin group for treatment of adult strabismus. A satisfactory outcome was defined as within 10 PD which was achieved in 76.9% of the surgery group and 29.4% of the botulinum toxin group. This difference was noted as significant (P = 0.027). 'Summary of findings' table 1 shows a risk ratio (RR) effect size of 0.79, 95% confidence interval (CI) 0.62 to 1.00; 132 participants; 3 studies; I^2 statistic = 55% (Summary of findings for the main comparison). We assessed the certainty of evidence as low. We downgraded certainty by one level for risk of bias and by one level for imprecision. Sequence generation was unclear; two trials were aware of participant randomisation and it was unclear for two trials how many had unilateral or bilateral injections of botulinum toxin.

1.2 Secondary outcomes (achievement of binocular single vision/sensory fusion/stereopsis)

Tejedor 1999 reported fusion (positive response with Worths four light test and Bagolini glasses test) and stereopsis (minimum of 480 seconds of arc) was present in 60.7% and 51.8% respectively of the reoperation group and 57.1% and 48.1% respectively of the botulinum toxin group. There were no statistically significant differences between these outcome measures across both groups. Tejedor 1998 reported fusion (positive response with Worths four light test) and stereopsis (minimum of 480 seconds of arc) was present in 62.5% and 54.16% respectively of the reoperation group and 56.52% and 47.82% respectively of the botulinum toxin group. There were no statistically significant differences between these outcome measures across both groups. Analysis for achievement of binocular single vision shows a RR effect size of 0.88, 95% CI 0.63 to 1.23; 102 participants; 2 studies; I^2 statistic = 0%. We assessed the certainty of evidence as low. We downgraded certainty by one level for risk of bias and by one level for imprecision. Sequence generation was unclear, two trials were aware of participant randomisation and it was unclear for two trials how many had unilateral or bilateral injections of botulinum toxin. Carruthers 1990 included participants with no binocular single vision. Thus secondary outcomes for achievement of binocular single vision and fusion are not reported for this trial.

2. Botulinum toxin versus observation

2.1 Primary outcome (improved ocular alignment $\leq$10PD)

Lee 1994 reported reduction in angle of deviation for acute onset sixth nerve palsy within 10 PD in 80% of control participants and 86% of botulinum toxin participants. The difference between both groups was not statistically significant. 'Summary of findings' table 2 shows a RR effect size of 1.19, 95% CI 0.96 to 1.48; 47 participants; 1 study (Summary of findings 2). We assessed the certainty of evidence as low. We downgraded certainty by one level for risk of bias. Investigators were aware of randomisation and it was not possible to mask investigators or participants to allocation.

2.2 Secondary outcomes (achievement of binocular single vision/sensory fusion/stereopsis)

Lee 1994 reported full recovery for sixth nerve palsy with achievement of binocular single vision in 80% of control participants and 95.5% of botulinum toxin participants (see Table 1). The difference between both groups was not statistically significant. Analysis gave a RR effect size of 1.19, 95% CI 0.96 to 1.48; 47 participants; 1 study; I^2 statistic = 0%. We assessed the certainty of evidence as low. We downgraded certainty by one level for risk of bias. Investigators were aware of randomisation and it was not possible to mask investigators or participants to allocation.

3. Surgery with botulinum toxin versus surgery without botulinum toxin

3.1 Primary outcome (improved ocular alignment $\leq$ 10PD)

Minguini 2012 reported net percentage change in deviation at six to 12 months. A satisfactory change (angle within 20 PD) was achieved in 79.4% of the surgery plus botulinum toxin group compared to 68% in the surgery with hyaline solution group in the treatment of adult large angle strabismus. Target alignment was defined as within 8 PD. This was achieved in 33% of group A and 18% in group B. 'Summary of findings' table 3 shows a RR effect size of 1.83, 95% CI 0.41 to 8.11; 23 participants; 1 study; I^2 statistic = 0% (Summary of findings 3). We assessed the certainty of evidence as low. We downgraded certainty by one level for imprecision. It was unclear how sequence generation was made.

4. Botulinum toxin with sodium hyaluronate versus botulinum toxin without sodium hyaluronate

4.1 Primary outcome (improved ocular alignment $\leq$ 10PD)

Chen 2013 reported change in angle of deviation from pre-injection to six months post-injection. Good alignment was defined as a deviation < 10 PD. This was achieved in 30.4% of group A receiving botulinum toxin with sodium hyaluronate and 37.5% of group B receiving botulinum toxin only for treatment of infantile esotropia, with no significant difference between groups. 'Summary of findings' table 4 shows a RR effect size of 0.81, 95% CI 0.36 to 1.82; 47 participants; 1 study; I^2 statistic = 0% (Summary of findings 4). We assessed the certainty of evidence as low. We downgraded certainty by one level for risk of bias in relation to allocation concealment, performance bias and detection bias. Sequence generation was not specified.

5. Adverse events with use of botulinum toxin

Tejedor 1999 reported transient ptosis in 37.03% of participants and transient vertical deviation in 18.51%. Tejedor 1998 reported transient ptosis in 34.78% of participants and transient vertical deviation in 17.39%. Carruthers 1990 did not report complications from use of botulinum toxin. Lee 1994 reported two cases with transient ptosis and four cases with transient vertical deviation with a total complication rate of 24% per injection and 27% per participant. Minguini 2012 reported ptosis in 41.6% and vertical deviation in 8.3% of group A with no complications described in group B. Chen 2013 reported complications of ptosis occurred in 2.2% of group A and 20.8% of group B which was significant (P = 0.008). Complications of vertical deviation occurred in 2.2% of group A and 2.1% of group B which was not significantly different. Analysis from five RCTs found transient ptosis occurring

in 9 to 41.66% of participants and vertical deviation occurring in 8.3 to 18.51% of participants (Table 2). We assessed the certainty of evidence as low. We downgraded certainty by one level for imprecision because of mixed populations reducing numbers for comparison. Sequence generation was unclear for all but one trial (Lee 1994).

ADDITIONAL SUMMARY OF FINDINGS [Explanation]

Botulinum toxin versus observation in adults with strabismus

Patient or population: adults with strabismus due to acute onset sixth nerve palsy
Setting: hospital
Intervention: botulinum toxin
Comparison: observation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery	Risk with botulinum toxin				
Primary outcome: improved ocular alignment ≤ 10 PD Follow-up: median 6 months	800 per 1000	952 per 1000 (768 to 1000)	RR 1.19 (0.96 to 1.48)	47 (1 RCT)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
Secondary outcome: achievement of binocular single vision	800 per 1000	952 per 1000 (768 to 1000)	RR 1.19 (0.96 to 1.48)	47 (1 RCT)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
Secondary outcome: achievement of 'sensory' fusion	-	-	-	0	-	-
Secondary outcome: achievement of stereopsis	-	-	-	0	-	-
Adverse events with botulinum toxin Follow-up: median 6 months[3]	Induced ptosis occurred in 9%. Induced vertical deviation occurred in 18%. All adverse events recovered within the follow-up time period with no lasting adverse effect		-	47 (1 RCT)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). Relative risk was derived from standardised mean difference for continuous data related to measured change in angle of deviation - measured in prism dioptres (PD) or degrees. Relative risk for dichotomous data relating to achievement of binocular single vision as assessed by cover test, fusional vergence and stereoacuity.

Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **RCT:** randomised controlled trial; **PD:** prism dioptres.

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[1]The study investigators were aware of randomisation.
[2]It was not possible to mask the study investigators or participants to treatment allocation.
[3]All participants in study had acute onset sixth nerve palsy.

Surgery with botulinum toxin versus surgery without botulinum toxin in adults with strabismus

Patient or population: adults with strabismus
Setting: hospital
Intervention: surgery with botulinum toxin
Comparison: surgery without botulinum toxin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery	Risk with botulinum toxin				
Primary outcome: improved ocular alignment $\leq$ 10 PD Follow-up: median 6 months	182 per 1000	333 per 1000 (75 to 1000)	RR 1.83 (0.41 to 8.11)	23 (1 RCT)	⊕⊕◯◯ very low[1,2,3]	Downgraded 1 level for risk of bias. Downgraded 2 levels for imprecision.
Secondary outcome: achievement of binocular single vision	-	-	-	-	-	-
Secondary outcome: achievement of 'sensory' fusion	-	-	-	-	-	-
Secondary outcome: achievement of stereopsis	-	-	-	-	-	-
Adverse events with botulinum toxin Follow-up: median 6 months	Induced ptosis occurred in 37.03%. Induced vertical deviation occurred in 18.51%. All adverse events recovered within the follow-up time period with no lasting adverse effect		-	23 (1 RCT)	⊕⊕◯◯ low[1,2,3]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). We derived the relative risk from the standardised mean difference for continuous data related to measured change in angle of deviation, measured in prism dioptres (PD) or degrees. Relative risk for dichotomous data relating to achievement of binocular single vision was assessed by cover test, fusional vergence and stereoacuity.
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **PD:** prism dioptres; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[1]Unclear if participants blinded to treatment allocation.
[2]Unclear how the sequence generation was made as it was unspecified.
[3]Mixed population of esotropia and exotropia participants, which reduced the numbers of participants for comparison.

Botulinum toxin with sodium hyaluronate versus botulinum toxin without sodium hyaluronate in children with strabismus

Patient or population: children with strabismus
Setting: hospital
Intervention: botulinum toxin with sodium hyaluronate
Comparison: botulinum toxin without sodium hyaluronate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with surgery	Risk with botulinum toxin				
Primary outcome: improved ocular alignment ≤ 10 PD Follow-up: median 6 months	375 per 1000	304 per 1000 (135 to 683)	RR 0.81 (0.36 to 1.82)	47 (1 RCT)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.
Secondary outcome: achievement of binocular single vision	-	-	-	-	-	-
Secondary outcome: achievement of 'sensory' fusion	-	-	-	-	-	-
Secondary outcome: achievement of stereopsis	-	-	-	-	-	-
Adverse events with botulinum toxin Follow-up: median 6 months	Induced ptosis occurred in 23.4% overall; 2.2% in group A and 20.8% in group B Induced vertical deviation occurred in 17.39%. Ptosis occurred less frequently when treated with botulinum toxin combined with sodium hyaluronate compared to botulinum toxin alone		-	47 (1 RCT)	⊕⊕◯◯ low[1,2]	Downgraded 1 level for risk of bias. Downgraded 1 level for imprecision.

	All adverse events recovered within the follow-up time period with no lasting adverse effect	

*__The risk in the intervention group__ (and its 95% CI) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). We derived the relative risk from the standardised mean difference for continuous data related to measured change in angle of deviation, measured in prism dioptres (PD) or degrees. Relative risk for dichotomous data relating to achievement of binocular single vision was assessed by cover test, fusional vergence and stereoacuity.
Abbreviations: CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio; **PD:** prism dioptres; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate-certainty: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low-certainty: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low-certainty: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect

[1]Sequence generation was not specified for this trial; it was unclear how participants were randomised.
[2]The study investigators were aware of participation randomisation and were not masked to allocation.

DISCUSSION

We included six randomised controlled trials in this review which compared botulinum toxin (Dysport™ or Botox™ or Prosign™) to either strabismus surgery or conservative treatment or adjuvant solution. The strabismus conditions treated in five trials were unlikely to alter with time without treatment (Carruthers 1990; Chen 2013; Minguini 2012; Tejedor 1998; Tejedor 1999), whereas the ocular motility condition in the remaining trial was likely to change spontaneously with time (Lee 1994). Risk calculations in anticipated absolute effects across the different types of interventions in these trials varied greatly. This is reflective of the heterogenous groups that comprised different intervention comparisons and different types of ocular motility conditions.

From these trials we were able to make the following comparisons based on the information available in the trial papers: botulinum toxin as an alternative to conservative treatment; botulinum toxin as an alternative to surgical treatment; surgery with or without adjuvant botulinum toxin, botulinum toxin with or without an adjuvant solution; strabismus types with binocular potential versus those without binocular potential; and reported complications. Notably, for this last comparison, we were unable to evaluate occurrence of complications across a range of different doses due to insufficient data in the trial results.

We found the certainty of evidence for all outcomes to be of moderate- or low-certainty primarily due to risk of bias and imprecise results because of lack of clarity in reporting trial methodology. We were able to address the primary outcome of improved ocular alignment as measured by a reduction in angle of deviation in all six trials. However, the main limiting factor for analysis was that results were not comparable across the trials due to different conditions being targeted by each trial plus the different types and doses of botulinum toxin used in each trial. We were able to address the primary classification outcome (success, satisfactory A, satisfactory B or fail) in one trial only (Lee 1994), as two trials provided the information for change in angle of deviation and binocular outcome separately (Tejedor 1998; Tejedor 1999), and there was no binocular outcome for the participants in the remaining three trials (Carruthers 1990; Chen 2013; Minguini 2012).

Secondary outcomes included achievement of binocular single vision and documentation of adverse effects. We determined the former outcome in three trials (Lee 1994; Tejedor 1998; Tejedor 1999), but again the results were not comparable due to differences in target condition and use of botulinum toxin. Four trials used Botox™ (Carruthers 1990; Chen 2013; Tejedor 1998; Tejedor 1999), one trial used Dysport™ (Lee 1994), and one trial used Prosign™ (Minguini 2012), with varying doses utilised for each drug type. Hence the reported adverse effects were not comparable between trials. However, one trial compared the same type of botulinum toxin (Botox™) with one group receiving Botox™ plus sodium hyaluronate and the second group receiving Botox™ only (Chen 2013). This trial showed a significant increase in ptosis as an adverse event in the Botox™ only group.

We were not able to obtain information on the cost of treatment or on measures of participant or parent satisfaction relating to treatment options and effectiveness of botulinum toxin.

Summary of main results

There is a large body of literature on the subject of the use of botulinum toxin for the treatment of strabismus. Strabismus encompasses many types including esotropia, exotropia, vertical deviations, concomitant, acute onset and incomitant strabismus, plus strabismus with or without binocular vision. Therefore there are many variables that contribute to outcome after treatment. The literature on botulinum toxin consists predominantly of retrospective studies, cohort studies and case series, which are useful for describing the use of botulinum toxin in varying strabismus types but do not aid the establishment of reliable guidelines for the use of botulinum toxin as a treatment intervention or enable interpretation of treatment efficacy.

Improved ocular alignment

This was defined as measurement of a reduction in the angle of deviation by prisms or the synoptophore. All included trials achieved a reduction in angle of deviation using botulinum toxin to within 10 PD, ranging from 29.4% (Carruthers 1990), 30.4% (Chen 2013), 33.33% (Minguini 2012), 66.66% (Tejedor 1998), 69.56% (Tejedor 1999), to 95.5% (Lee 1994). The lowest percentage was achieved in a strabismus condition that did not have binocular potential and this was significantly different from the reduction in angle of deviation achieved by surgery in this trial. The highest percentage was achieved in an ocular motility condition in which all participants had binocular potential. The reduction in angle of deviation achieved using botulinum toxin in three trials where participants had binocular potential showed no significant difference to the reduction in angle of deviation achieved by strabismus surgery (Tejedor 1998; Tejedor 1999), or by observation/conservative treatment (Lee 1994).

Percentage net change in deviation was also calculated for five trials. For RCTs that compared botulinum toxin to reoperation, the percentage net change was not significant across both groups in which the strabismus type included presence of binocular vision as an outcome measure (Tejedor 1998; Tejedor 1999). For one trial where the strabismus type specifically excluded binocular vision, the percentage net change was significantly lower for the botulinum toxin group in comparison to the adjustable suture surgery group (Carruthers 1990). For a second trial in which the strabismus type had no demonstrable binocular vision, the net percentage change was greater for the surgery group combined with botulinum toxin compared to surgery alone (Minguini 2012). For the trial that compared botulinum toxin to observation for recent

onset sixth nerve palsy, the change in ocular alignment was similar for both groups (Lee 1994).
Effect size of risk ratio (RR) varied from 0.79 (botulinum toxin versus surgery) to 0.81 (botulinum toxin with versus without sodium hyaluronate) to 1.19 (botulinum toxin versus observation) to 1.83 (surgery with or without botulinum toxin).

Outcomes

A successful outcome was classed as full control of the ocular deviation with a measurement within 10 PD and with normal binocular single vision. This was achieved in 86% (botulinum toxin) and 80% (controls) respectively in participants from the trial of sixth nerve palsies (Lee 1994; Analysis 1.3). There was insufficient information provided in the trials by as outcomes for change in deviation and binocular vision were provided separately and not integrated (Tejedor 1998; Tejedor 1999; Analysis 2.1; Analysis 2.3). Carruthers 1990 and Minguini 2012 excluded participants with binocular vision potential and Chen 2013 did not report any information on binocular potential for their participants. Thus we could not apply our classification of successful outcome to these trials. Achievement of binocular vision was further classified in this review as satisfactory A (angle within 20 PD with binocular vision), satisfactory B (angle within 20 PD without binocular vision) and fail (little or no change in angle and without binocular vision). We were unable to use these classifications in Tejedor 1998 and Tejedor 1999 as measurements were not provided for the participants that failed to obtain a successful outcome plus outcomes for binocular vision were stated separately to outcomes for angle of deviation. Lee 1994 reported a successful outcome in 80% and 95.5%, satisfactory A outcome in 12% and 0% and a failed outcome for 8% and 4.5% for non treatment and botulinum toxin treatment groups respectively (Analysis 2.2). The participants recruited in Carruthers 1990, Minguini 2012 and Chen 2013 had no reported binocular function and thus would not fall in the satisfactory A classification. We were unable to classify participants from the trial by Carruthers 1990 to satisfactory B or fail categories with reliability as deviations were stated as greater than 10 PD but with no ranges provided for these unsuccessful participants. 23.1% of the surgery group and 70.6% of the botulinum toxin group were either satisfactory B or fail classifications. Five of 30 participants were unsatisfied with their exotropia deviation and required further treatment. The range of final responses for all participants having botulinum toxin spread from 0 to 100% change in deviation (0 would be classed as a fail) and for participants having surgery, the spread was 67% to 100% change. Minguini 2012 reported 5/12 participants in group A and 6/11 participants in group B as achieving satisfactory B with angles of deviation of less than 20 PD, and 2/12 participants in group A plus 3/11 participants in group B achieving a fail with angles of deviation greater than 20 PD. Chen 2013 reported no data on angles of deviation greater than 10 PD at follow-up.

Adverse outcomes

Such outcomes may include induced transient ptosis, vertical deviation, subconjunctival haemorrhage and intolerable diplopia. The included trials reported transient ptosis in 23.4%, 37.03%, 9%, 34.78%, 41.6% and 20.8% respectively and reported transient vertical deviation in 17.39%, 18.51%, 18%, 8.3% and 2.2% respectively for occurrence of adverse outcomes per participant (Chen 2013; Lee 1994; Minguini 2012; Tejedor 1998; Tejedor 1999). The overall complication rate ranged from 27% to 55.54% in these trials. Lee 1994 also reported the occurrence of adverse outcomes per injection as three participants underwent repeat botulinum toxin injection. The overall complication rate was 24% per injection. No other adverse outcomes were reported following the use of botulinum toxin in these trials. The duration of transient ptosis or vertical deviation was not stated in any of these trials. There were no adverse outcomes stated in any of the three trials relating to the strabismus surgery.

Overall completeness and applicability of evidence

Six RCTs of low-certainty evidence met the inclusion criteria of this review. Each trial related to a different type of strabismus or ocular motility condition; namely infantile esotropia, acute onset esotropia, sixth nerve palsy and horizontal strabismus without binocular vision. Hence this precluded a meta-analysis. It was not possible to ascertain information on dose effect as the six included trials used different types of botulinum toxin (Botox™ versus Dysport™ versus Prosign™) and different dosages. In addition, we were unable to obtain information on the cost of treatment or on measures of participant or parent satisfaction relating to treatment options and effectiveness. However, we described the outcome of treatment in each trial and ascertained the occurrence of adverse events in relation to the use of botulinum toxin.

Quality of the evidence

Downgrading of certainty of evidence was primarily related to risk of bias and/or imprecision. There was a lack of clarity on sequence generation or an inability to mask investigators and participants to allocation.

Potential biases in the review process

As far as we are aware we have minimised potential biases in the review process. We have followed the methods set out in the published protocol. The only amendment was to add in a summary of findings table and GRADE assessment as required by new Cochrane standards. To our knowledge, all potentially eligible studies were included - we implemeted an extensive search

strategy with independent checks by both authors of the search results. See Figure 2 and Figure 3.

We obtained mixed results when we evaluated the included trials for risk of bias. One study was at low risk of bias in relation to sequence generation (Lee 1994). This was unclear for the other included trials. Two trials had a low risk of bias in relation to allocation concealment (Carruthers 1990; Minguini 2012). This was not achieved by the other trials. We considered all trials as at low risk of bias for the domains of masking, incomplete outcome bias and selective outcome reporting. However, we judged all trials as unclear in relation to the potential risk of other sources of bias. This was due to small participant numbers in each trial group for five trials (Carruthers 1990; Chen 2013; Minguini 2012; Tejedor 1998; Tejedor 1999), and due to early discharge of participants who had shown recovery before a six-month follow up period with lack of long-term follow up comparison across both groups (Lee 1994).

Agreements and disagreements with other studies or reviews

Our results are in general agreement with published observation studies of the use of botulinum toxin for the treatment of strabismus. Notably, these observation studies consider a variety of strabismus or ocular motility conditions (Crouch 2006; Dawson 2004b; Dawson 2005; Marsh 2003; Rayner 1999; Scott 1980) and each trial in this review also addressed a different strabismus or ocular motility condition. In addition, the included trials used different types and doses of botulinum toxin - similar to other observation studies published in the literature (Crouch 2006; Rayner 1999). It was thus not possible to compare these studies for agreement or disagreement of results. Botulinum toxin shows no difference in response in comparison to surgery in participants who required retreatment for acquired esotropia or infantile esotropia and in whom there was potential for binocular vision. Botulinum enhanced the effect of strabismus surgery in participants with strabismus without binocular potential. Botulinum toxin had a poorer effect in comparison to surgery in participants with strabismus without binocular potential. It showed no difference compared to no treatment in acute sixth nerve palsy and thus was deemed to have no prophylactic effect in this condition. The occurrence of adverse effects was similar to those reported in previous observation studies, particularly ptosis and induced vertical deviations (Crouch 2006; Marsh 2003; Rayner 1999).

AUTHORS' CONCLUSIONS

Implications for practice

Due to the limited number of RCTs identified in this review, the low-certainty of evidence and the variations in the conditions being treated, it has not been possible to address fully the outcomes of this review.

Without considering the type of strabismus or ocular motility being treated, botulinum toxin has been shown to reduce the angle of deviation by amounts comparable to surgical intervention. However, the type of strabismus is important when considering the secondary outcome of binocular vision. In horizontal strabismus types without potential for binocular vision there was a poorer treatment effect reported with botulinum toxin treatment compared to strabismus surgery. However, for horizontal strabismus types without potential for binocular vision, there was an improved treatment effect reported with combined strabismus surgery and botulinum toxin in comparison to surgery alone. In those strabismus types where there is potential for binocular vision, such as acute onset esotropia, sixth nerve palsy and infantile esotropia, botulinum toxin has been shown to achieve little difference in levels of binocular vision compared to surgery. Therefore on the basis of these studies botulinum toxin can be considered as an independent treatment option.

In terms of adverse events there was difficulty in evaluating the studies because of the varying doses and types of botulinum toxin used. For trials using comparable types and/or doses of Botox™ the prevalence of reported adverse events were similar with approximately one third of cases developing transient ptosis and one fifth developing transient vertical deviation.

Implications for research

There is clearly a need for good quality trials to be conducted utilising botulinum toxin across the varying types of strabismus in order to improve the evidence base for the use of botulinum toxin as an independent management option. Standardisation is of utmost importance taking into consideration the types of botulinum toxin available and the dosages used as these aspects are not comparable. The presence or absence of binocular vision is also an important variable to consider in future trials.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Carruthers 1990

Methods	Surgery versus botulinum toxin in adult strabismus without binocular function Allocation: masked and randomised sequence Masking: achieved for provider and outcome Exclusions: 0 Losses: 0 Study design: RCT with cross-over of treatment if unsatisfactory result at 6 months
Participants	Country: Canada Randomised number: 30 participants (30 eyes) Recruitment dates: Fall 1985 to 1988 i.e. 2.5 years. Strabismus type: 20 exotropia (8 male and 12 female), 10 esotropia (4 male, 6 female) Botulinim toxin (BT); 12 exotropia, 5 esotropia Surgery; 8 exotropia, 5 esotropia Angle of deviation; 60 prism dioptres (PD) of exotropia to 50 PD of esotropia BT; 12 to 35 PD of esotropia (average 25.4 PD), 16 to 60 PD of exotropia (average 33. 7 PD) Surgery; 12 to 50 PD of esotropia (average 31.4 PD), 16 to 50 PD of exotropia (average 32.6 PD) Age > 16 years BT; mean 33 years (17 to 58 years) Surgery; mean 35 years (16 to 60 years) Sex: BT; 8 male, 9 female Surgery; 4 male, 9 female Inclusion criteria: angle greater than 10 PD, no binocular vision, > 16 years, attended follow-up appointments Exclusion criteria: evidence of binocular vision Repeat injections: undertaken in 9 participants
Interventions	Treatment: Surgery; Unilateral 2 muscle or surgery with adjustable on recessed muscle BT; 5 units Botox™. Participants offered repeat botulinum toxin (BT) injection if, at any time during 6 weeks following initial injection, the angle of deviation was not reduced below 10 PD. Re-injections provided twice for 5 participants, 3 times for 3 participants and four times for 1 participant Choice of eye for intervention: Side of intervention eye not specified Duration: minimum 6 months follow-up. Participants were followed up at 1 day, 6 weeks, 3 months and 6 months postoperatively
Outcomes	Reduction in angle to < 10 PD: Surgery; outcome achieved in 29.4% (5 participants) BT; outcome achieved in 76.9% (10 participants) % net change (preoperative deviation - postoperative deviation / preoperative deviation x 100%):

Carruthers 1990 (*Continued*)

	Surgery; 92.7% average change in deviation at 6 months BT; 50.59% average change in deviation at 6 months Choice of eye: Analysis of outcomes based on binocular measurement of change in angle of deviation and reported adverse events monocularly in the intervention eye
Notes	No complications reported No costs reported No quality of life indicators reported Funding: support from the British Columbia Health Care Research Foundation Declarations of interest: the Smith-Kettlewell Instititue of Vision Sciences supplied the needle for the trial. Alan Scott from the Smith-Kettlewell Institute supplied Oculinum Trial registration number: not specified.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomised but how this was done was not stated
Allocation concealment (selection bias)	Low risk	Participants were randomised by a research assistant
Blinding (performance bias and detection bias) Investigators	Low risk	Investigators were masked (blinded) to participant allocation for final outcome assessment
Blinding (performance bias and detection bias) Participants	Unclear risk	It was not possible to mask participants to the different treatment options. This was not judged to affect outcome measures
Blinding (performance bias and detection bias) Personnel	Low risk	Investigators and the orthoptist were masked to participant randomisation when undertaking the final evaluation of participants for outcome measures
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for in the results with provision of outcome data
Selective reporting (reporting bias)	Low risk	The specified outcomes in the methodology were reported in the results, i.e. percentage net change in deviation and success with final deviation < 10 PD
Other bias	Unclear risk	Small numbers of participants across each trial group. Mix of esotropia and exotropia participants further reduce numbers for comparison as these may respond differently to use of BT or surgery

Chen 2013

Methods	Botulinum toxin with sodium hyaluronate versus botulinum toxin alone for infantile esotropia Allocation: unknown Masking: unsure for outcome Exclusions: 0 Losses: 0 Study design: parallel RCT
Participants	Country: China Randomised number: 47 participants (94 eyes) = 23 in group A, 24 in group B Dates of recruitment: February 2008 to May 2011 Inclusion criteria: infantile esotropia with onset before 6 months of age. Botulinum toxin (BT) chosen as first line treatment Exclusion criteria: orthotropic after refractive correction, Previous strabismus surgery, Systemic diseases, Allergy to drugs Age: 12 to 81 months at time of injection. Group A = 38.0 ±17.5. Group B = 35.8 ±20.7 Sex: 22 male, 25 female. Group A = 43.5% male. Group B = 50% male Angle of deviation: Group A = 35.0 ±15.7 PD, group B = 33.9 ±16.7 PD Follow-up to 6 months.
Interventions	Group A: Bilateral injection of 0.05 mL Botox™ (2.5 to 3.75 units) with sodium hyaluronate (SH) in the absence of electromyography. Mix of BT solution with SH at volume ratio of 1:3 Group B: Bilateral injection of 0.03 mL Botox™ (2.5 to 3.75 units) without sodium hyaluronate in the absence of electromyography Doses of 2.5 units for deviations < 30 PD. Doses of 3.75 units for deviations > 30 PD Choice of eye for intervention: All received bilateral injections at 1 time point only
Outcomes	Change in angle of deviation: Group A = 30.4% achievement of angle < 10 PD. Group B = 37.5% achievement of angle < 10 PD. Presence of binocular vision not reported. Choice of eye: analysis of outcomes based on binocular measurement of change in angle of deviation and reported adverse events monocularly for each intervention eye
Notes	Ptosis: 2.2% in group A versus 20.8% in group B Vertical deviation: 2.2% in group A versus 2.1% in group B. No report of duration of transient adverse events. 10 with monocular amblyopia, 5 with primary inferior oblique overaction, 3 with dissociated vertical deviation (DVD), 1 with inferior oblique overaction and DVD No costs reported. No quality of life indicators reported. Funding: support from Guangdong Provincial Scientific Technological Research Fund Declaration of interests: the authors declared no interests. Trial registration number: not specified.

Chen 2013 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomised but how this was done was not stated. The two groups were evaluated as being homogenous
Allocation concealment (selection bias)	High risk	Investigators were aware of participant randomisation.
Blinding (performance bias and detection bias) Investigators	High risk	Investigators did not appear to be masked to the different treatment options
Blinding (performance bias and detection bias) Participants	Unclear risk	Patinets could be masked to the treatment allocation but it was not stated of they were informed of treatment group or not
Blinding (performance bias and detection bias) Personnel	High risk	All preparations for treatment were made by the same treating physician
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for in the results with provision of outcome data
Selective reporting (reporting bias)	Low risk	The specified outcomes in the methodology were reported in the results, i.e. change in angle of deviation and reporting of adverse events
Other bias	Unclear risk	Small number of participants across each trial group.

Lee 1994

Methods	Botulinum toxin versus observation for acute onset sixth cranial nerve palsy Allocation: random number table Masking: not achieved Exclusions: 2 due to change in diagnosis Losses: 5 lost to follow-up Study design: parallel RCT
Participants	Country: UK Randomised number: 54 participants (54 eyes) - 22 in botulinum toxin (BT) group and 25 in control group Dates of recruitment: August 1989 to August 1992 Age:

Lee 1994 (*Continued*)

	Controls; mean 61 years (24 to 86 years) BT; mean 63 years (24 to 83 years) Sex: Controls; 12 males, 13 females BT; 13 males, 9 females Inclusion criteria: Hospital emergency department walk-in Exclusion criteria: change in diagnosis Duration of symptoms: Controls; ≤ 1 week in 17, ≤ 2 weeks in 6, 3 weeks in 1 and 4 weeks in 1 BT; ≤ 1 week in 7, ≤ 2 weeks in 9, ≤ 3 weeks in 5 and 6 weeks in 1 Angle of deviation: Controls; primary position at distance fixation fixing with nonparetic eye; mean 17.8 PD (4 to 40 PD) BT; primary position at distance fixation fixing with nonparetic eye; mean 28.6 PD (6 to 70 PD) Repeat injections; undertaken in 3 participants
Interventions	Treatment: BT; 2.5 units Dysport™ to ipsilateral medial rectus muscle 3 participants had a second injection when first injection was inadequate Control: observation Duration: 4 to 42 months. Participants were followed up at 1 week, 6 weeks and 4 months as a minimum Discharged at 4 months if fully recovered Choice of eye for intervention: Ipsilateral eye to the cranial nerve palsy - conventional choice
Outcomes	Full recovery: normal range of eye movement and full field binocular single vision BT; 95.5% (20 participants) Controls; 80% (16 participants) Stable BSV: normal BSV with minor asymptomatic abduction deficit BT; 4.5% (1 participant) Controls; 16% (4 participants) No recovery: persistent esotropia in primary gaze with diplopia BT; 4.5% (1 participant) becoming 13.6% (3 participants) due to recurrence of the sixth nerve palsy over long term follow-up Controls; 20% (5 participants) Choice of eye: analysis of outcomes based on binocular measurement of change in angle of deviation and reported adverse events monocularly in the intervention eye
Notes	Overall complication rate of 24% per injection (6/25) and 27% per participant (6/22) 2 cases of ptosis 4 cases of vertical deviation No report of duration of transient adverse events No costs reported No quality of life indicators reported Funding: none specified. Declarations of interest: none specified. Trial registration number: none specified.

Lee 1994 (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table was used
Allocation concealment (selection bias)	High risk	Investigators were aware of participant randomisation
Blinding (performance bias and detection bias) Investigators	Unclear risk	Investigators did not appear to be masked to the different treatment options
Blinding (performance bias and detection bias) Participants	Unclear risk	It was not possible to mask participants to the different treatment options. This plus investigator knowledge of participant allocation to treatment group was not judged to affect outcome measures
Blinding (performance bias and detection bias) Personnel	High risk	Investigators appeared aware of the different treatment options
Incomplete outcome data (attrition bias) All outcomes	Low risk	Participants lost to follow-up or excluded were accounted for along with participants followed to designated follow-up periods. Despite loss of participants, a similar number of participants existed for each group in the trial
Selective reporting (reporting bias)	Low risk	The specified outcomes in the methodology were reported in the results, i.e. full recovery, stable BSV and non recovery of palsy
Other bias	Unclear risk	Follow-up varied upwards from 4 months post onset of palsy

Minguini 2012

Methods	Surgery with botulinum toxin versus surgery alone for large angle adult strabismus Allocation: unknown Masking: achieved for provider and outcome Exclusions: 0 Losses: 2 from group A did not attend final follow-up visit Study design: parallel RCT with double-masked assessment
Participants	Country: Brazil Randomised number: 23 participants (23 eyes) = 12 in group A, 114 in group B Inclusion criteria: adults > 18 years of age with large angle (>50 PD) concomitant horizontal strabismus (esotropia or exotropia) Exclusion criteria: previous strabismus surgery, neurological or systemic disease, oblique extraocular muscle over or under action, vertical deviation, dissociated vertical deviation (DVD), paretic or restrictive strabismus Age: Group A = 34.3 ± 6.4. Group B = 28.8 ± 9.8 Sex: Group A = 6 females and 6 males. Group B = 6 females and 5 males Angle of deviation: Group A = 65.8 ±14.9 PD with 6 exotropia and 6 esotropia, group B = 60.0 ±16.9 PD with 7 exotropia and 4 esotropia Follow-up to 6 months.
Interventions	Group A: Strabismus surgery plus injection of 5 units of botulinum toxin (Prosign™) in 0.1 mL of hyaline solution Group B: Strabismus surgery plus injection of 0.1 mL of hyaline solution Choice of eye for intervention: non-fixing eye - conventional choice
Outcomes	Percent net change in angle of deviation from pre-operative to 6 to 12 months postoperative: Group A = 33.33% achievement of angle < 10 PD. Group B = 18.1% achievement of angle < 10 PD. Presence of binocular vision not reported. Choice of eye: analysis of outcomes based on binocular measurement of change in angle of deviation and reported adverse events monocularly in the intervention eye
Notes	Ptosis: 41.6% in group A versus 0% in group B Vertical deviation: 8.3% in group A versus 0% in group B. No report of duration of transient adverse events. No costs reported. No quality of life indicators reported. Funding: none specified. Declarations of interest: the authors declared no commercial or proprietary interests Trial registration number: none specified

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Minguini 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Participants were randomised but how this was done was not stated
Allocation concealment (selection bias)	Low risk	Surgeons were masked to treatment allocation.
Blinding (performance bias and detection bias) Investigators	Low risk	Double-masked assessment with surgeons and assessors masked to allocation
Blinding (performance bias and detection bias) Participants	Unclear risk	Possible to mask participants to treatment allocation but not specified as to whether this was done
Blinding (performance bias and detection bias) Personnel	Low risk	Double-masked assessment with surgeons and assessors masked to allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for in the results with provision of outcome date
Selective reporting (reporting bias)	Low risk	The specified outcomes in the methodology were reported in the results, i.e. percentage net change in deviation and adverse events
Other bias	Unclear risk	Small numbers of participants across each trial group. Mix of esotropia and exotropia participants which may further reduce numbers for comparison as these may respond differently to use of surgery with/without botulinum toxin

Tejedor 1998

Methods	Surgery versus botulinum toxin for childhood strabismus Allocation: unknown Masking: unsure for outcome Exclusions: 0 Losses: 0 Study design: parallel RCT
Participants	Country: Spain Randomised number: 47 participants - 24 in surgery group (38 eyes) and 23 in botulinum toxin (BT) group (number of eyes unclear) Dates of recruitment: 1989 to 1994 Age at treatment in RCT: not specified Age at initial surgery:

	Surgery; mean 3.56 years (SD 1.53) BT; mean 3.29 years (SD 1.28) Time between initial and secondary treatment: Surgery; mean 1.5 years (SD 0.98) BT; mean 0.99 years (0.84) Sex: not specified Inclusion criteria: adequate; < 11 years old, 1 previous operation, 10 PD angle Exclusion criteria: adequate; Near/Distance disparity, Vertical deviation > 4 PD, nystagmus, A/V pattern, amblyopia > 4 lines Pretreatment angle of deviation: Surgery; mean 21.32 PD (SD 18.84) at near fixation and mean 18.58 PD (SD 18.52) at distance fixation BT; mean 22.16 PD (SD 16.83) at near fixation and mean 18.69 PD (SD 16.56) at distance fixation
Interventions	Treatment: Sx for esotropia; recession/resection or re-recession or bilateral resection Sx for exotropia; bilateral recession BT: 3 to 10 units Botox™ Follow-up after treatment: Surgery; mean 2.9 years (SD 0.81) BT; mean 2.7 years (SD 0.42) Minimum 1 year follow-up Repeat BT injections; none reported Choice of eye for intervention: Surgery; unilateral surgery if previous surgery was unilateral (10 participants), bilateral surgery if previous surgery was bilateral (14 participants) BT; unilateral injection if dose required < 5 units, bilateral injection if dose required > 5 units
Outcomes	Reduction in angle to < 8 PD: Surgery; outcome achieved in 75% (18 participants) BT; outcome achieved in 69.56% (16 participants) Presence of binocular vision: Surgery; outcome achieved in 62.5% (15 participants) BT; outcome achieved in 56.52% (13 participants) Reduction in angle of deviation and presence of binocular vision were considered separately Net % change (preoperative deviation - postoperative deviation / preoperative deviation x 100%): Surgery; mean 81.31% change in deviation at 1 year BT; mean 73.45% change in deviation at 1 year Choice of eye: Analysis of outcomes based on binocular measurement of change in angle of deviation and reported adverse events monocularly in each intervention eye
Notes	Overall complication rate of 52.17% (12/23) per participant Ptosis; 34.78% (8/23) Vertical; 17.39% (4/23) No report of duration of transient adverse events No costs reported

Tejedor 1998 (*Continued*)

	No quality of life indicators reported Funding: none specified Declarations of interest: none specified Trial registration number: none specified

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomised but how this was done was not stated. The two groups were evaluated as being homogenous
Allocation concealment (selection bias)	High risk	Investigators were aware of participant randomisation
Blinding (performance bias and detection bias) Investigators	High risk	Investigators did not appear to be masked to the different treatment options
Blinding (performance bias and detection bias) Participants	Unclear risk	It was not possible to mask participants to the different treatment options. This plus investigator knowledge of participant allocation to treatment group was not judged to affect outcome measures
Blinding (performance bias and detection bias) Personnel	Unclear risk	This was not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for in the results with provision of outcome data
Selective reporting (reporting bias)	Low risk	The specified outcomes in the methodology were reported in the results, i.e. percentage mean change in deviation, successful motor outcome with final deviation < 8 PD and successful sensory outcome with positive fusion and stereo response
Other bias	Unclear risk	Small numbers of participants across each trial group

Tejedor 1999

Methods	Allocation: unclear Masking: unsure for outcome Exclusions: 0 Losses: 0 Study design: parallel RCT
Participants	Country: Spain Randomised number: 55 participants - 28 in surgery group (56 eyes) and 27 in BT group (number of eyes unclear) Dates of recruitment: 1990 to 1994 Age at retreatment in RCT; not specified Age at initial surgery: Surgery; mean 15.33 months (SD 3.31) BT; mean 14.25 months (SD 3.12) Time between initial and secondary treatment: Surgery; mean 6.25 months (SD 1.60) BT; mean 5.50 months (1.23) Sex: Surgery; 13 females, 15 males BT; 12 females, 15 males Inclusion criteria: adequate; esotropia < 6 months, no accommodative element, retreated within 12 months Exclusion criteria: adequate; accom element present, vertical > 4 PD, medical or neuro disease Pretreatment angle of deviation: Surgery; mean 28.87 PD (SD 12.41) at near fixation and mean 25.40 PD (SD 11.35) at distance fixation BT; mean 24.12 PD (SD 16.02) at near fixation and mean 20.27 PD (SD 15.15) at distance fixation
Interventions	Treatment: Surgery for esotropia; bilateral LR resection ± bilateral MR recession Surgery for exotropia; bilateral LR recession or MR advancement BT: 3 to 12.5 units Botox™ Follow-up after retreatment: Surgery; mean 3.75 years (SD 0.12) BT; mean 3.5 years (SD 0.21) Minimum 6 month follow-up Repeat BT injections: none reported Choice of eye for intervention: Surgery; all had bilateral surgery as previous surgery was bilateral (28 participants, 56 eyes) BT; unilateral injection if dose required < 5 units, bilateral injection if dose required > 5 units
Outcomes	Reduction in angle to < 8 PD: Surgery; outcome achieved in 75% (21 participants) BT; outcome achieved in 66.66% (18 participants) Presence of binocular vision: Surgery; outcome achieved in 60.71% (17 participants)

Tejedor 1999 (*Continued*)

	BT; outcome achieved in 51.85% (14 participants) Reduction in angle of deviation and presence of binocular vision were considered separately Net % change (preoperative deviation - postoperative deviation / preoperative deviation x 100%): Surgery; mean 82.02% change in deviation at 6 months BT; mean 78.71% change in deviation at 6 months Choice of eye: analysis of outcomes based on binocular measurement of change in angle of deviation and reported adverse events monocularly in each intervention eye
Notes	Overall complication rate of 55.54% (15/27) per participant Ptosis; 37.03% (10/27) Vertical; 18.51% (5/27) No report of duration of transient adverse events No costs reported No quality of life indicators reported Funding: none specified Declarations of interest: the authors declare no conflicts of interest Trial registration number: none specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Participants were randomised but how this was done was not stated. The two groups were evaluated as being homogenous
Allocation concealment (selection bias)	High risk	Investigators were aware of participant randomisation
Blinding (performance bias and detection bias) Investigators	Unclear risk	Investigators did not appear to be masked to the different treatment options
Blinding (performance bias and detection bias) Participants	Low risk	It was not possible to mask participants to the different treatment options. This plus investigator knowledge of participant allocation to treatment group was not judged to affect outcome measures
Blinding (performance bias and detection bias) Personnel	Unclear risk	This was not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were accounted for in the results with provision of outcome data

Tejedor 1999 (*Continued*)

Selective reporting (reporting bias)	Low risk	The specified outcomes in the methodology were reported in the results, i.e. percentage mean change in deviation, successful motor outcome with final deviation < 8 PD and successful sensory outcome with positive fusion and stereo response
Other bias	Unclear risk	Small numbers of participants across each trial group

Abbreviations: A&E: accident and emergency department; AV: A or V pattern; Accom: accommodation; BSV: binocular single vision; BT: botulinum toxin; BV: binocular vision; F: female; F/U: follow-up; LR: lateral rectus muscle; M: male; MR: medial rectus muscle; N/D: near/distance; PD: prism dioptres; RCT: randomised controlled trial; Sx: surgery.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cooper 1991	The paper consisted of the preliminary findings for the paper by Lee 1994 documented in the 'Included studies'
de Alba Campomanes 2010	Prospective, non-randomised comparative study and not a randomised controlled trial (RCT)
Etezad Razavi 2014	Prospective, non-randomised comparative study and not a RCT
Gursoy 2012	Retrospective review of botulinum toxin versus strabismus surgery outcomes for treatment of esotropia
Li 2008	Prospective, non-randomised clinical study and not a RCT
Mills 2004	Review article and not a RCT in itself
Sanjari 2008	Case series and not a RCT
Shallo-Hoffman 2006	Study of the influence of adaptation in people with chronic sixth nerve palsy having botulinum toxin. Results not applicable to the objectives of this review

Abbreviations: RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

Jain 2015

Trial name or title	Intraoperative botulinum toxin in large angle strabismus
Methods	Prospective randomised case control study
Participants	Large angle strabismus
Interventions	Surgery alone versus surgery with botulinum toxin
Outcomes	Postoperative reduction in angle of deviation plus adverse events from botulinum toxin
Starting date	August 2012
Contact information	Chief investigator: Mr S Jain, Royal Free Hospital, London
Notes	-

PACTR201508001241218

Trial name or title	Botulinum toxin in childhood strabismus
Methods	Prospective randomised parallel arm controlled trial
Participants	Children aged 6 months to 6 years with esotropia
Interventions	Botulinum toxin versus bilateral medial rectus muscle recession surgery
Outcomes	Degree of alignment; cost effectiveness comparison; adverse events
Starting date	February 2015
Contact information	Chief investigator: Mr I Mayet, St John Eye Hospital, Soweto, Johannesburg
Notes	-

DATA AND ANALYSES

Comparison 1. Botulinum toxin versus surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome - improved ocular alignment ≤ 10 PD	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Children	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.71, 1.16]
1.2 Adults	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.17, 0.85]
2 Secondary outcome - achievement of binocular single vision	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.63, 1.23]
3 Secondary outcome - achievement of 'sensory' fusion	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.63, 1.23]
4 Secondary outcome - achievement of stereopsis	2	102	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.59, 1.25]

Comparison 2. Botulinum toxin versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome - improvement of ocular alignment ≤ 10 PD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Secondary outcome - classification			Other data	No numeric data
3 Secondary outcome - achievement of binocular single vision	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Surgery with botulinum toxin versus surgery without botulinum toxin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome - improved ocular alignment ≤ 10 PD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 4. Botulinum toxin with sodium hyaluronate versus botulinum toxin without sodium hyaluronate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Primary outcome - improved ocular alignment ≤ 10 PD	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Botulinum toxin versus surgery, Outcome 1 Primary outcome - improved ocular alignment ≤ 10 PD.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 1 Botulinum toxin versus surgery

Outcome: 1 Primary outcome - improved ocular alignment ≤ 10 PD

Study or subgroup	Botulinum toxin n/N	Surgery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Children					
Tejedor 1998	16/23	18/24		46.1 %	0.93 [0.65, 1.32]
Tejedor 1999	18/27	21/28		53.9 %	0.89 [0.63, 1.25]
Subtotal (95% CI)	**50**	**52**		**100.0 %**	**0.91 [0.71, 1.16]**
Total events: 34 (Botulinum toxin), 39 (Surgery)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.78 (P = 0.44)					
2 Adults					
Carruthers 1990	5/17	10/13		100.0 %	0.38 [0.17, 0.85]
Subtotal (95% CI)	**17**	**13**		**100.0 %**	**0.38 [0.17, 0.85]**
Total events: 5 (Botulinum toxin), 10 (Surgery)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.37 (P = 0.018)					
Test for subgroup differences: Chi^2 = 4.14, df = 1 (P = 0.04), I^2 =76%					

Analysis 1.2. Comparison 1 Botulinum toxin versus surgery, Outcome 2 Secondary outcome - achievement of binocular single vision.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 1 Botulinum toxin versus surgery

Outcome: 2 Secondary outcome - achievement of binocular single vision

Study or subgroup	Botulinum toxin n/N	Surgery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tejedor 1998	13/23	15/24		46.8 %	0.90 [0.56, 1.45]
Tejedor 1999	14/27	17/28		53.2 %	0.85 [0.53, 1.37]
Total (95% CI)	**50**	**52**		**100.0 %**	**0.88 [0.63, 1.23]**
Total events: 27 (Botulinum toxin), 32 (Surgery)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Not applicable					

Analysis 1.3. Comparison 1 Botulinum toxin versus surgery, Outcome 3 Secondary outcome - achievement of 'sensory' fusion.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 1 Botulinum toxin versus surgery

Outcome: 3 Secondary outcome - achievement of 'sensory' fusion

Study or subgroup	Botulinum toxin n/N	Surgery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tejedor 1998	13/23	15/24		46.8 %	0.90 [0.56, 1.45]
Tejedor 1999	14/27	17/28		53.2 %	0.85 [0.53, 1.37]
Total (95% CI)	**50**	**52**		**100.0 %**	**0.88 [0.63, 1.23]**
Total events: 27 (Botulinum toxin), 32 (Surgery)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.77 (P = 0.44)					
Test for subgroup differences: Not applicable					

Analysis 1.4. Comparison 1 Botulinum toxin versus surgery, Outcome 4 Secondary outcome - achievement of stereopsis.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 1 Botulinum toxin versus surgery

Outcome: 4 Secondary outcome - achievement of stereopsis

Study or subgroup	Botulinum toxin n/N	Surgery n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tejedor 1998	11/23	13/24		44.7 %	0.88 [0.50, 1.55]
Tejedor 1999	13/27	16/28		55.3 %	0.84 [0.51, 1.40]
Total (95% CI)	**50**	**52**		**100.0 %**	**0.86 [0.59, 1.25]**

Total events: 24 (Botulinum toxin), 29 (Surgery)

Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 0.78 (P = 0.43)

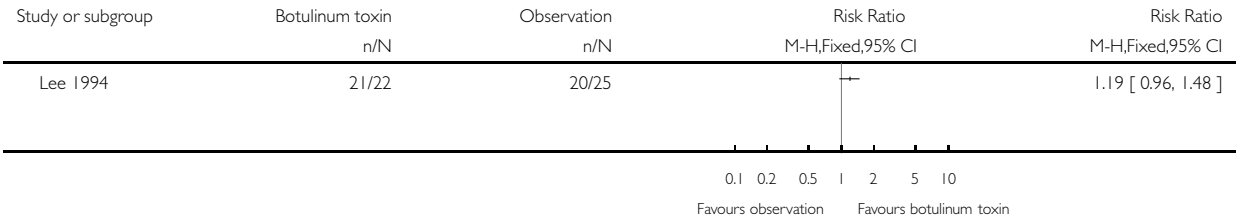
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Botulinum toxin versus observation, Outcome 1 Primary outcome - improvement of ocular alignment ≤ 10 PD.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 2 Botulinum toxin versus observation

Outcome: 1 Primary outcome - improvement of ocular alignment ≤ 10 PD



Analysis 2.2. Comparison 2 Botulinum toxin versus observation, Outcome 2 Secondary outcome - classification.

Secondary outcome - classification

Study	**Total participants**	**Success**	**Satisfactory A**	**Satisfactory B**	**Fail**	**Data**
Lee 1994	47 22 (Botulinum toxin) 25 (Observation/ Conservative)	21 (95.5%) 20 (80%)	3 (12%)		1 (4.5%) 2 (8%)	Ordinal

Analysis 2.3. Comparison 2 Botulinum toxin versus observation, Outcome 3 Secondary outcome - achievement of binocular single vision.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 2 Botulinum toxin versus observation

Outcome: 3 Secondary outcome - achievement of binocular single vision

Study or subgroup	Botulinum toxin n/N	Observation n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Lee 1994	21/22	20/25		1.19 [0.96, 1.48]

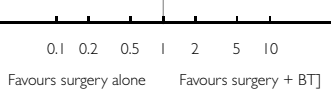
Analysis 3.1. Comparison 3 Surgery with botulinum toxin versus surgery without botulinum toxin, Outcome 1 Primary outcome - improved ocular alignment ≤ 10 PD.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 3 Surgery with botulinum toxin versus surgery without botulinum toxin

Outcome: 1 Primary outcome - improved ocular alignment ≤ 10 PD

Study or subgroup	Surgery with BT n/N	Surgery without BT n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Minguini 2012	4/12	2/11		1.83 [0.41, 8.11]

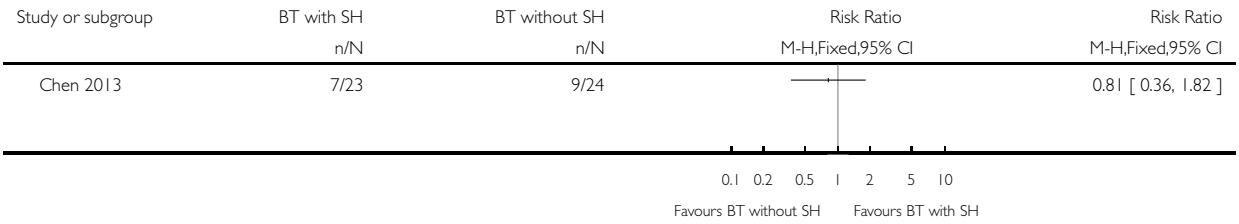


Analysis 4.1. Comparison 4 Botulinum toxin with sodium hyaluronate versus botulinum toxin without sodium hyaluronate, Outcome 1 Primary outcome - improved ocular alignment ≤ 10 PD.

Review: Botulinum toxin for the treatment of strabismus

Comparison: 4 Botulinum toxin with sodium hyaluronate versus botulinum toxin without sodium hyaluronate

Outcome: 1 Primary outcome - improved ocular alignment ≤ 10 PD



ADDITIONAL TABLES

Table 1. Botulinum toxin versus observation

Study ID	Total participants	Success	Satisfactory A	Satisfactory B	Fail	Data
Lee 1994	22 botulinum toxin 25 observation/ conservative 47 in total	21 (95.5%) 20 (80%)	3 (12%)	-	1 (4.5%) 2 (8%)	Ordinal

Table 2. Adverse events with botulinum toxin

Study ID	Total participants (Botox)	Total participants (Dysport)	Total participants (Prosign)	Ptosis (per patient)	Vertical deviation (per patient)	Ptosis (per injection)	Vertical deviation (per injection)
Chen 2013	47	-	-	23.4% (11/47)	4.25% (2/47)	-	-
Lee 1994	-	22	-	9% (2/22)	18% (4/22)	8% (2/25)	16% (4/25)
Minguini 2012	-	-	12	41.66% (5/12)	8.3% (1/12)	-	-
Tejedor 1998	23	-	-	34.78% (8/23)	17.39% (4/23)	-	-

Table 2. Adverse events with botulinum toxin (*Continued*)

Tejedor 1999	27	-	-	37.03% (10/27)	18.51% (5/27)	-	-

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Strabismus
#2 strabism* or squint*
#3 esotropi*
#4 exotropi*
#5 hypertropi*
#6 hypotropi*
#7 cyclotropi*
#8 heterophori*
#9 esophori*
#10 exophori*
#11 hyperphori*
#12 hypophori*
#13 cyclophori*
#14 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 MeSH descriptor Botulinum Toxins
#16 botulin* toxin*
#17 botox*
#18 dysport*
#19 MeSH descriptor Clostridium botulinum
#20 clostridium botulin*
#21 (#15 OR #16 OR #17 OR #18 OR #19 OR #20)
#22 (#14 AND #21)

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomized).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. exp strabismus/
14. (strabism$ or squint$).tw.
15. esotropi$.tw.
16. exotropi$.tw.
17. hypertropi$.tw.
18. hypotropi$.tw.
19. cyclotropi$.tw.
20. heterophori$.tw.
21. esophori$.tw.
22. exophori$.tw.
23. hyperphori$.tw.
24. hypophori$.tw.
25. cyclophor$.tw.
26. or/13-25
27. exp botulinum toxins/
28. botulin$ toxin$.tw.
29. botox$.tw.
30. dysport$.tw.
31. exp clostridium botulinum/
32. clostridium botulin$.tw.
33. or/27-32
34. 26 and 33
35. 12 and 34

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$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. exp strabismus/
34. (strabism$ or squint$).tw.
35. esotropi$.tw.
36. exotropi$.tw.
37. hypertropi$.tw.
38. hypotropi$.tw.
39. cyclotropi$.tw.
40. heterophori$.tw.
41. esophori$.tw.
42. exophori$.tw.
43. hyperphori$.tw.
44. hypophori$.tw.
45. cyclophor$.tw.
46. or/33-45
47. botulinum toxin/
48. botulin$ toxin$.tw.
49. botox$.tw.
50. dysport$.tw.
51. Botulinum toxin A/
52. exp clostridium botulinum/
53. clostridium botulin$.tw.
54. or/47-53
55. 46 and 54
56. 32 and 55

Appendix 4. LILACS search strategy

botulin$ or botox$ and strabism$

Appendix 5. ISRCTN search strategy

botulinum and strabismus

Appendix 6. ClinicalTrials.gov search strategy

Strabismus AND (Botox OR Botulinum)

Appendix 7. WHO ICTRP search strategy

(Condition) Strabismus AND (Intervention) Botox OR Botulinum

WHAT'S NEW

Last assessed as up-to-date: 11 July 2016.

Date	Event	Description
11 July 2016	New search has been performed	Issue 3, 2017: electronic searches were updated
11 July 2016	New citation required but conclusions have not changed	Issue 3, 2017: two new trials were included in the review (Chen 2013; Minguini 2012). Inclusion of GRADE

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 2, 2009

Date	Event	Description
7 December 2011	New citation required but conclusions have not changed	Issue 2, 2012: electronic searches were updated but no new trials were identified
7 December 2011	New search has been performed	Issue 2, 2012: the 'Risk of bias' assessments were updated according to new Cochrane methodology
14 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

FR proposed the review question and co-ordinated the review, organised retrieval of papers and wrote to study authors for additional information.

FR and CN screened search results, screened retrieved papers against inclusion criteria, appraised quality of papers, extracted data from papers, provided additional data about papers, obtained and screened data on unpublished studies, entered data into RevMan 5 (RevMan 2014), provided a methodological, clinical, policy and consumer perspective and wrote the review.

FR and CN updated the review.

DECLARATIONS OF INTEREST

FR has no known conflicts of interest.

CN has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- University of Liverpool, UK.
- Aintree University Hospital NHS Foundation Trust, UK.

External sources

- National Institute for Health Research (NIHR), UK.
- Richard Wormald, Co-ordinating Editor for the Cochrane Eyes and Vision (CEV) acknowledges financial support for his CEV research sessions from the Department of Health through the award made by the NIHR to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
- The NIHR also funds the CEV editorial base in London.

The views expressed in this publication are those of the review authors and not necessarily those of the NIHR, the NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We used the 'Risk of bias' tool to assess the risk of bias of the included studies and the GRADE approach to assess the certainty of the evidence for each outcome. Given the developments in the production and use of botulinum toxin since the original protocol, for interventions in the current review, we added comparisons for the following:

- comparison of botulinum toxin alternatives, i.e. different brands of botulinum toxin compared to each other;
- comparison of botulinum toxin with and without added substances, e.g. sodium hyaluronate, saline.

INDEX TERMS

Medical Subject Headings (MeSH)

Abducens Nerve Diseases [*drug therapy]; Botulinum Toxins, Type A [*therapeutic use]; Neuromuscular Agents [*therapeutic use]; Randomized Controlled Trials as Topic; Strabismus [*drug therapy; surgery]

MeSH check words

Adult; Child; Humans