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Interventions for managing skeletal muscle spasticity following traumatic brain injury (Review)

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[Intervention Review]

Interventions for managing skeletal muscle spasticity following traumatic brain injury

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ABSTRACT

Background

Skeletal muscle spasticity is a major physical complication resulting from traumatic brain injury (TBI), which can lead to muscle contracture, joint stiffness, reduced range of movement, broken skin and pain. Treatments for spasticity include a range of pharmacological and non-pharmacological interventions, often used in combination. Management of spasticity following TBI varies from other clinical populations because of the added complexity of behavioural and cognitive issues associated with TBI.

Objectives

To assess the effects of interventions for managing skeletal muscle spasticity in people with TBI.

Search methods

In June 2017, we searched key databases including the Cochrane Injuries Group Specialised Register, CENTRAL, MEDLINE (Ovid), Embase (Ovid) and others, in addition to clinical trials registries and the reference lists of included studies.

Selection criteria

We included randomised controlled trials (RCTs) and cross-over RCTs evaluating any intervention for the management of spasticity in TBI. Only studies where at least 50% of participants had a TBI (or for whom separate data for participants with TBI were available) were included. The primary outcomes were spasticity and adverse effects. Secondary outcome measures were classified according to the World Health Organization International Classification of Functioning, Disability and Health including body functions (sensory, pain, neuromusculoskeletal and movement-related functions) and activities and participation (general tasks and demands; mobility; self-care; domestic life; major life areas; community, social and civic life).

Data collection and analysis

We used standard methodological procedures expected by Cochrane. Data were synthesised narratively; meta-analysis was precluded due to the paucity and heterogeneity of data.

Main results

We included nine studies in this review which involved 134 participants with TBI. Only five studies reported between-group differences, yielding outcome data for 105 participants with TBI. These five studies assessed the effects of a range of pharmacological (baclofen, botulinum toxin A) and non-pharmacological (casting, physiotherapy, splints, tilt table standing and electrical stimulation) interventions, often in combination. The studies which tested the effect of baclofen and tizanidine did not report their results adequately. Where outcome data were available, spasticity and adverse events were reported, in addition to some secondary outcome measures.

Of the five studies with results, three were funded by governments, charities or health services and two were funded by a pharmaceutical or medical technology company. The four studies without useable results were funded by pharmaceutical or medical technology companies.

It was difficult to draw conclusions about the effectiveness of these interventions due to poor reporting, small study size and the fact that participants with TBI were usually only a proportion of the overall total. Meta-analysis was not feasible due to the paucity of data and heterogeneity of interventions and comparator groups. Some studies concluded that the intervention they tested had beneficial effects on spasticity, and others found no difference between certain treatments. The most common adverse event was minor skin damage in people who received casting. We believe it would be misleading to provide any further description of study results given the quality of the evidence was very low for all outcomes.

Authors' conclusions

The very low quality and limited amount of evidence about the management of spasticity in people with TBI means that we are uncertain about the effectiveness or harms of these interventions. Well-designed and adequately powered studies using functional outcome measures to test the interventions used in clinical practice are needed.

PLAIN LANGUAGE SUMMARY

Treatments for spasticity (overactive muscle contractions) following brain injury

Review question

We reviewed the evidence about the effect of treatments (drug and non-drug) for spasticity following a brain injury caused by a blow to the head (traumatic brain injury (TBI)).

Background

Many people with TBI experience muscle spasticity, when their muscles contract or tighten involuntarily. This can impact on a person's ability to carry out daily activities causing pain, stiffness and broken skin. There are many treatments used to manage spasticity, including medicines, casting, splints and stretches. Often, these treatments are used in combination.

Study characteristics

We included nine studies in this review which involved 134 participants with TBI. Only five studies, including 105 people provided usable results. These studies tested the effects of a range of treatments, including medicines (baclofen or botulinum toxin A), casting, physiotherapy, splints, a table that moves people from the lying position to standing and electrical stimulation (where electrical impulses are delivered to the muscles). Studies inadequately reporting results had tested the effect of medicines (baclofen or tizanidine).

Study funding sources

Of the five studies with results, three were funded by governments, charities or health services and two were funded by a drug manufacturer and medical technology company. The other four studies without useable results were funded by drug manufacturer or medical technology companies.

Key results

This evidence is current to June 2017.

Interpreting the results of the studies was difficult because of a lack of information and concerns about the quality of the evidence. For spasticity, some studies concluded that the treatment they tested made an improvement, and others found no difference between treatments. The most common side effect was minor skin damage in people who received casting. We believe it would be misleading to provide any further description of study results given the quality of the evidence was very low for all measurements.

Quality of the evidence

The quality of this evidence was very low; we only had five studies with results and none of the studies were large or comparable with one another. We also had concerns about how they were conducted or analysed. Because of this, we cannot draw any firm conclusions about the benefits and harms of different treatments for spasticity in people with TBI.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Baclofen compared with placebo for spasticity in people with traumatic brain injury

Baclofen compared with placebo for spasticity in people with traumatic brain injury

Patient or population: adults with traumatic brain injury with spasticity in their arms and legs

Settings: outpatient rehabilitation clinic (US)

Intervention: intrathecal baclofen 50 µg (injected into the lumbar spine)

Comparison: saline placebo

Outcomes	Results and conclusions	No of participants (studies)	Quality of the evidence (GRADE)
Spasticity at up to 6 hours after treatment (measured by the Ashworth Scale, 0-, with a higher score indicating greater spasticity)	We are uncertain about the effect of baclofen on spasticity compared with placebo.[1]	11 (1)[2]	⊕⊖⊖⊖ **V ery low** [3]
Adverse events	We are uncertain about the effect of baclofen on adverse events compared with placebo.[4]	11 (1)[2]	⊕⊖⊖⊖ **V ery low** [5]
Sensory functions and pain	No study measured this outcome.		
Neuromusculoskeletal and movement-related functions up to 6 hours after treatment (Measured by spasm and deep tendon reflex scores, 0-5, with 0 being no reflexes and 5 being clonus, or repeated involuntary muscle contractions)	We are uncertain about the effect of baclofen on neuromusculoskeletal and movement-related functions compared with placebo.[6]	11 (1)[2]	⊕⊖⊖⊖ **V ery low** [7]
General tasks and demands	No study measured this outcome.		
Mobility	No study measured this outcome.		
Self-care	No study measured this outcome.		

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]One study of baclofen reported an improvement in spasticity in the upper and lower limbs, compared to placebo, several hours after the injections but it was unclear how meaningful this improvement was due to reporting of P values only (Meythaler 1996).
[2]Three additional studies, with 35 participants, measured this outcome but had no useable results (Meythaler 1997; Meythaler 1999a; Meythaler 1999b).
[3]Downgraded four times due to risk of bias limitations (this study provided insufficient information about random sequence generation or allocation concealment), our concerns about indirectness of the Ashworth Score, an inability to assess imprecision relating to an absence

of confidence intervals and a further downgrade for there only being one study for this outcome and the likelihood of publication bias in this area.
[4]No adverse events or changes in alertness level were observed in the baclofen or placebo group.
[5]Downgraded three times due to risk of bias limitations (no study provided sufficient information about random sequence generation or allocation concealment), the fact that there was only one study for this outcome and the likelihood of publication bias in this area.
[6]One study reported improvement in upper and lower limb spasm and reflexes compared to placebo several hours after treatment but it was unclear how meaningful this improvement was due to reporting of P values only (Meythaler 1996).
[7]Downgraded four times due to risk of bias limitations (no study provided sufficient information about random sequence generation or allocation concealment), an inability to assess imprecision relating to an absence of confidence intervals, the fact that there was only one study for this outcome and the likelihood of publication bias in this area.

Summary of findings 2. Botulinum toxin A (with and without casting) compared with placebo (with and without casting) for spasticity in people with traumatic brain injury

Botulinum toxin A (with and without casting) compared with placebo (with and without casting) for spasticity in people with traumatic brain injury

Patient or population: adults with traumatic brain injury with spasticity in their arms (1 study) or calves (1 study)

Settings: rehabilitation/neurology clinics or acute general hospital, in Europe or the UK

Intervention: botulinum toxin A × 1 dose (500/1000 U) or botulinum toxin A × 1 dose of 200 U + serial casting

Comparison: placebo (± casting)

Outcomes	Results and conclusions	No of participants (studies)	Quality of the evidence (GRADE)
Spasticity at 4-12 weeks (measured by both Modified Ashworth Scale, 0-5, at 12 weeks and Tardieu Scale, 0-5, at 4 weeks)	We are uncertain about the effect of botulinum toxin A (± casting) vs placebo (± casting) on spasticity.[1]	47 (2)[2]	⊕⊖⊖⊖ **Very low** [3]
Adverse events	We are uncertain about the effect of botulinum toxin A (± casting) vs placebo (± casting) on adverse events.[4]	47 (2)[2]	⊕⊖⊖⊖ **Very low** [5]
Sensory functions and pain	No study measured this outcome.		
Neuromusculoskeletal and movement-related functions at 12 weeks (measured by ankle dorsiflexion)	We are uncertain about the effect of botulinum toxin A (± casting) vs placebo (± casting) on adverse events.[6]	47 (2)[2]	⊕⊖⊖⊖ **Very low** [7]
General tasks and demands	No study measured this outcome.		
Mobility	No study measured this outcome.		
Self-care	No study measured this outcome.		

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Gracies 2015 reported that "with abobotulinumtoxinA, the angle of catch (XV3 of the Tardieu Scale) improved in finger (+35 degree), elbow (+22 degree) and wrist (+12 degree) flexors" but no further outcome data were provided. For Verplancke 2005, we calculated the between-group difference in spasticity (as measured by the Modified Ashworth Scale) as mean difference 0.30 (95% confidence interval -0.87 to 1.47).
[2]Included studies: Gracies 2015; Verplancke 2005.
[3]Downgraded four times due to: risk of bias concerns for both studies (downgraded twice, because either insufficient information about random sequence generation and allocation concealment, in one study, and potential selective outcome reporting in both studies), indirectness (one study included mixed traumatic brain injury and stroke populations, and measured spasticity using the Modified Ashworth Scale) and a high likelihood of publication bias in this area.
[4]In the main trial of Gracies 2015 (in which the traumatic brain injury population was a part (9.5%)) the most common botulinum toxin A-related adverse event was 'mild muscle weakness' and investigators reported that all adverse events were mild or moderate only. In Verplancke 2005, botulinum toxin A was reported to be well tolerated, with only one participant with 'flu-like' symptoms (i.e. shivering, sweating and fever). In groups who received casting (either alone, or in addition to botulinum toxin A), 41% to 50% developed 'minor' skin damage. Overall, 90.9% of those resolved spontaneously or with therapeutic dressing.
[5]Downgraded three times due to: risk of bias concerns for both studies (downgraded twice, because in one study there was insufficient information about random sequence generation and allocation concealment, and in both studies the adverse events data was reporting in percentages only) and a high likelihood of publication bias in this area.
[6] Verplancke 2005 reported between-group differences in ankle dorsiflexion, finding no differences between groups in a one-way ANOVA (casting + placebo versus casting + botulinum toxin A: P = 0.11). However, they did not report any summary statistics for this, or any baseline scores.
[7]Downgraded four times due to: risk of bias concerns for both studies (downgraded twice, because either insufficient information about random sequence generation and allocation concealment, in one study, and potential selective outcome reporting in both studies), indirectness (one study included mixed traumatic brain injury and stroke populations) and a high likelihood of publication bias in this area.

Summary of findings 3. Pseudoelastic orthosis versus traditional (static) splint for spasticity in people with traumatic brain injury

Pseudoelastic orthosis versus traditional (static) splint for spasticity in people with traumatic brain injury

Patient or population: children/young people aged 4-18 years with traumatic brain injury and with 'mild to severe spastic tetraparesis' (weakness) in all limbs

Settings: Istituro Eugenio Media (Italy)

Intervention: repositioning splints equipped with participant-specific pseudoelastic hinges

Comparison: traditional splints with fixed angle braces

Outcomes	Results and conclusions	No of participants (studies)	Quality of the evidence (GRADE)
Spasticity at up to 6 hours after treatment (measured by the Modified Ashworth Scale, 0-4, with a higher score indicating greater spasticity)	We are uncertain about the effect of pseudoelastic splints compared with traditional splints on spasticity.[1]	25 (1)	⊕⊖⊖⊖ **Very low[2]**
Adverse events	We are uncertain about the effect of pseudoelastic splints compared with traditional splints on adverse events.[3]	25 (1)	⊕⊖⊖⊖ **Very low[4]**
Sensory functions and pain	The included study did not report this outcome.		
Neuromusculoskeletal and movement-related functions post treatment (measured by range of movement)	We are uncertain about the effect of pseudoelastic splints compared with traditional splints on range of movement.[5]	25 (1)	⊕⊖⊖⊖ **Very low[6]**

General tasks and demands	The included study did not report this outcome.
Mobility	The included study did not report this outcome.
Self-care	The included study did not report this outcome.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]One study comparing novel pseudoelastic orthoses to traditional fixed angle splints reported no improvement in spasticity in the upper and lower limbs, over a period of one month of intervention. and that results of the two steps were not significantly different (Pittaccio 2013).

[2]Downgraded four times due to risk of bias limitations (study provided no information about sequence generation and allocation concealment; blinding was impossible for participants or personnel and not reported for outcome assessors; selective outcome reporting bias was high); our concerns about indirectness of the Ashworth Score and indirectness due to 36% of participants not having traumatic brain injury and one participant was of dubious eligibility; an inability to assess imprecision relating to an absence of meaningful outcome data (no numerical data were provided for spasticity; investigators reported only that there were no significant differences), and there was only one study for this comparison/outcome and that publication bias was possible in this area.

[3]No adverse events were reported for pseudoelastic orthoses neither did any require adjustments after fitting. Adjustments were required for 30% of traditional splints to reduce skin rash, haematomas and oedema.

[4]Downgraded four times due to risk of bias limitations (study provided insufficient information about sequence generation and allocation concealment, blinding was impossible for participants and personnel and not reported for outcome assessors, and selective reporting bias was high). We had concerns about indirectness given that 36% of participants did not have traumatic brain injury and one participant was of dubious eligibility. Furthermore, there was only one study for this comparison/outcome and publication bias was possible in this area.

[5]One study reported no improvement in range of movement in the upper and lower limbs, over a period of one month of intervention (Pittaccio 2013).

[6]Downgraded five times due to risk of bias limitations (this study provided insufficient information about sequence generation and allocation concealment, blinding was impossible for participants and personnel and not reported for outcome assessors, and selective reporting bias was high). We had concerns about indirectness due to 36% of participants not having traumatic brain injury and one participant was of dubious eligibility; our inability to assess imprecision given that means and standard deviations were only presented within a small box and whiskers plot, and a further downgrade for there only being one study for this comparison/outcome and the likelihood of publication bias in this area.

BACKGROUND

Traumatic brain injury (TBI) is the result of an external force to the head, that can lead to permanent damage to the brain. There are many causes of TBI including motor vehicle accidents, falls, violent assaults or blast injuries (Maas 2008). In 2005, The US Centre for Disease Control and Prevention estimated at least 3.17 million Americans, approximately 1.1% of the US population, are living with long-term disability as a result of TBI (Summers 2009). In Europe, the incidence of TBI in studies published between 1983 and 2013 has been estimated to be between 47.3 to 849 per 100,000 population per year (Brazinova 2016). There are limited data available for low- to middle-income countries. The impact of TBI to a person can be far-reaching and may result in ongoing physical, cognitive and behavioural issues (Khan 2003). Skeletal muscle spasticity is one of the major physical complications following TBI (Brashear 2016).

Description of the condition

Spasticity is defined as an ongoing contraction of a muscle caused by an increase in muscle tone and deep tendon reflexes that is partly due to a reduction of the skeletal stretch reflex threshold (Lance 1980). It is often described as muscle overactivity. Spasticity occurs due to damage of upper motor neurons (UMN) of the corticoreticular pathways in the brain cortex or internal capsule, or damage to the UMNs in the reticulospinal or vestibulospinal tracts in the spinal cord (Pandyan 2005). Spasticity may occur sporadically or continuously, for periods of short and long duration.

Spasticity tends to affect the antigravity muscle groups in the upper and lower limbs (Nair 2014). In the upper limbs, this can commonly include the shoulder adductors, elbow, wrist and finger flexors, forearm pronators and thumb adductors. In the lower limbs, spasticity often affects the hip adductors, knee flexors, ankle plantarflexors and invertors, and big toe extensors (Nair 2014). Spasticity can also affect muscles in the neck.

There are limited epidemiological data regarding the prevalence of spasticity following TBI (Martin 2014; McGuire 2016). In one systematic review of the epidemiology of lower limb spasticity, Martin 2014 identified only one study (Singer 2004), conducted in 105 people with TBI that found the prevalence of ankle spasticity was 13%. Similarly, McGuire 2016 was only able to find one study of spasticity prevalence following TBI (Wedekind 2005), which was a study of 32 people with TBI, in which the prevalence of spasticity (location unclear) was 32%. While both the definition and measurement of spasticity is inconsistent, and often poorly defined (Malhotra 2009), McGuire 2016 suggests that by extrapolating data from studies in other populations (including people with stroke, spinal cord injury and multiple sclerosis), 'problematic' spasticity may occur in between 30% and 50% of people with TBI.

Spasticity can lead to a range of musculoskeletal issues such as muscle contracture, involuntary and uncontrollable shaking, joint stiffness, reduced range of movement, broken skin and pain (Ada 2006a; Ada 2006b). The debilitating nature of the condition can directly impact a person's ability to carry out normal activities of daily living (ADL), such as self-care and household tasks, and is likely to lead to dependency on carers or family members for assistance. Participation in daily life and opportunities for community integration can prove difficult and may ultimately impact the person's quality of life (Kwakkel 1999). Management of spasticity in people with TBI varies from other clinical populations primarily due to behavioural and cognitive issues that affect their ability to participate in, or tolerate, treatment (e.g. their ability to follow instructions, monitor use of a spastic limb or tolerate a cast). These factors are likely to impact on whether or not a treatment is effective in this population and limit the applicability of findings from other populations where behavioural and cognitive issues are not a primary concern (Manchester 1997; Wood 1999). Furthermore, some studies have shown that mobility limitations can be improved over time and that the presence, distribution and severity of spasticity may not necessarily be the best determinant in recovery and mobility outcomes (Williams 2015a; Williams 2015b).

The measurement of spasticity in clinical practice, and in research, is challenging (Malhotra 2009). The most common scales to measure spasticity are the (Modified) Ashworth Scale (Pandyan 1999) and the (Modified) Tardieu Scale (Haugh 2006). The (Modified) Ashworth Scale is commonly used by clinicians as it is the easier scale to complete (Pandyan 1999), however it only measures the resistance in a muscle, which may or may not be caused by spasticity (Patrick 2006). This is in contrast to the (Modified) Tardieu Scale which measures spasticity by the spasticity catch angle as well as resistance in the muscle (Haugh 2006). The Tardieu has also demonstrated greater test-retest and inter-rater reliability compared with the Modified Ashworth Scale (Mehrholz 2005). The (Modified) Tardieu includes a continuous and nominal (or sometimes considered ordinal (Haugh 2006)) component, and the (Modified) Ashworth is ordinal, but both are commonly treated as continuous scales by trialists. While there does not appear to be a clear consensus about the most appropriate way to analyse these scales, we note that for another five-point ordinal scale used in TBI (the Glasgow Outcome Scale (Jennett 1975)), a sliding dichotomy or proportional odds methodology is recommended for analysis (Maas 2010).

Description of the intervention

Interventions for managing skeletal muscle spasticity can be broadly categorised as either pharmacological or non-pharmacological. Examples of pharmacological interventions include baclofen (Becker 1997), botulinum toxin A, clonidine, dantrolene sodium, tizanidine and phenol injection (Meythaler 2001a; Yelnik 2009). Examples of non-pharmacological interventions include casting, splinting, stretching, strengthening, transcutaneous electric nerve stimulation (TENS) (Aydin 2005), Bobath treatment, weight bearing gait training and seating. In practice, a combination of both pharmacological and non-pharmacological interventions is used to manage spasticity. Interventions can be either focal or systemic in their action. Focal interventions involve treatment of one or two muscle groups whereas systemic interventions are used to treat generalised spasticity.

How the intervention might work

Interventions used to manage spasticity all aim to reduce overactivity within the muscle so that it can be lengthened (Esquenazi 2006).

Pharmacological interventions can act locally at the muscle or systemically through the central nervous system. For example, botulinum toxin A and phenol are both injected locally at the site of the spastic muscle whereas other interventions such as

tizanidine and clonidine are administered orally. Oral medications act systemically and can induce unwanted adverse effects, such as drowsiness. For those with severe spasticity in multiple areas, adverse effects associated with oral medications can sometimes outweigh the potential benefits of reduced spasticity. An alternative approach, as seen with baclofen, is to administer the treatment through a pump into the space around the spinal cord, thus reducing the impact of adverse effects whilst maintaining improved outcomes for spasticity (Becker 1997).

Non-pharmacological interventions involve the use of physical modalities such as stretching and strengthening to promote elongation and control of spastic muscles, or external devices such as casting or splinting to modify and maintain correct positioning of a spastic muscle. Table 1 provides a summary of the range of different interventions and their mode of action.

Table 1: Examples of the range of interventions to manage spasticity

Pharmacological intervention	Mode of action	Non-pharmacological intervention	Mode of action
Baclofen	Administered orally or via intrathecal pump to limit the release of excitatory neurotransmitters in the spinal cord.	**Casting**	Applied directly to the limb to maintain the muscle in an extended position.
Botulinum toxin A	A neurotoxin injected directly into the muscle to block the release of the neurotransmitter acetylcholine.	**Splinting**	Thermoplastic or fabric material that is customised to provide support to a person's limb and maintain the limb in the corrected position.
Clonidine	Administered orally or by transdermal patch to act on the central nervous system by reducing the excitability of alpha motor neurons.	**Seating**	Custom made seating for people to provide maximal support and reduce the impact of spasticity.
Dantrolene sodium	Administered orally to reduce the excitation-contraction coupling within the skeletal muscle and decrease the strength of muscle contraction.	**Stretching**	Promotes elongation of a muscle for varying lengths of time causing viscous deformation changes.
Phenol	Injected into specific nerves to induce neurolysis to permanently block nerve transmission.	**Transcutaneous electric nerve stimulation**	Portable electric stimulator placed on the skin over a spastic muscle to reduce pain.
Tizanidine	Administered orally to act on the central nervous system and reduce the excitability of alpha motor neurons.	**Surgery**	Surgical techniques primarily aim to alter the structure of a muscle or nerve or relocate a tendon to change its function.

Why it is important to do this review

A range of interventions are currently used to manage skeletal muscle spasticity for people with TBI. Clinical management often involves a combination of pharmacological and non-pharmacological interventions. Management of spasticity following TBI varies from other clinical populations because of the added complexity of behavioural and cognitive issues associated with TBI. Furthermore, the current management for spasticity in other conditions may not be applicable to TBI as a result of global UMN damage that can occur such as axonal shearing, haemorrhage and hypoxia. A comprehensive systematic review of interventions assessed in the TBI population is needed to identify those likely to have the greatest impact for managing spasticity as well as determining whether the severity of TBI or the timing of an intervention is relevant to the outcome.

Reviews of interventions for spasticity in people with TBI are focused solely on the effect of one intervention (botulinum toxin A), and include people with spasticity due to other conditions, predominantly stroke (Baker 2015; Dashtipour 2016; Dong 2017). None of these reviews allow conclusions to be drawn specific to people with TBI. Systematic reviews that consider the effects of a broader range of interventions for managing spasticity have done so in populations other than TBI such as stroke (Taricco 2000) and spinal cord injury (Demetrios 2013; Hsieh 2012). To our knowledge, there are no systematic reviews that consider all potential interventions used to manage skeletal muscle spasticity specifically for people with TBI.

OBJECTIVES

To assess the effects of interventions for managing skeletal muscle spasticity in people with TBI.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCT). Cross-over trials were included as long as the sequence of treatments was randomly allocated.

Types of participants

We included people with TBI of any age (i.e. children and adults), who had skeletal muscle spasticity experienced at any time after injury. We made a post-hoc decision to include only studies that either:

- included at least 50% of people with TBI amongst their participants;
- provided disaggregated data for participants with TBI if the proportion of participants within the trial was less than 50%.

This decision was made in response to the identification of a large number of studies with mixed populations (e.g. stroke and TBI) that were found during screening to ensure the evidence would be applicable to people with TBI.

Types of interventions

We included studies that compared any of the following: pharmacological or non-pharmacological intervention (or a combination of both) or placebo/no treatment.

Types of outcome measures

Primary outcomes

- Spasticity, measured using common tools such as the Tardieu or Modified Tardieu Scale (Haugh 2006), or the Ashworth Scale or Modified Ashworth (Pandyan 1999).
- Adverse events.

As a post-hoc decision, we took Tardieu or Modified Tardieu, in preference to the (Modified) Ashworth Scale, in the instance that an included study used both these measures. This decision was made given the (Modified) Ashworth poorly differentiates between spasticity and contracture (Patrick 2006), and as the Tardieu is considered to have greater test-retest and inter-rater reliability compared with the Modified Ashworth Scale (Mehrholz 2005).

Secondary outcomes

A range of secondary outcomes were included, classified according to the World Health Organization International Classification of Functioning, Disability and Health (WHO 2010) using the following domains.

Body functions

- Sensory functions and pain (e.g. pain intensity).
- Neuromusculoskeletal and movement-related functions (e.g. goniometric measurement).

Activities and participation

- General tasks and demands (e.g. Canadian Occupational Performance Measure (Law 2000)).
- Mobility (e.g. gait and balance measures).
- Self-care (e.g. Functional Independence Measure (Keith 1987)).
- Domestic life (e.g. Goal Attainment Scale (Kiresuk 1994)).
- Major life areas (e.g. Functional Assessment Measure (Hall 1993)).
- Community, social and civic life (e.g. quality of life measures).

Information size calculation

In line with Cochrane Injuries policy, we undertook a post-hoc information size calculation, to determine the sample size required in a meta-analysis for the primary outcome, spasticity. Determining the parameters for this calculation was difficult, as the most commonly used measure of spasticity (the Ashworth or Modified Ashworth Scale) was not necessarily the most clinically meaningful, or appropriate (Haugh 2006), and it is also an ordinal scale that is frequently treated as continuous. Considering we could be combining more than one spasticity scale, we applied the 'rule of thumb' for determining a 'small' difference between two groups as a standardised mean difference (SMD) of 0.2 standard deviations (Guyatt 2011). Assuming 90% power at the 5% significance level, this means that we require 526 participants in both the intervention and control groups within a meta-analysis to be able to detect a difference between groups, if such a difference exists.

Search methods for identification of studies

To reduce publication and retrieval bias, we did not restrict our search by language, date or publication status.

Electronic searches

The information in this review is current to June 2017. Studies were identified through searches run in 2013, 2016 and 2017.

In November 2013, we searched the following databases:

- Cochrane Injuries Group specialised register (1 November 2013);
- the Cochrane Library (2013, Issue 10);
- Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (1946 to 1 November 2013);
- Embase Classic + Embase (OvidSP) (1947 to 1 November 2013);
- PubMed (www.ncbi.nlm.nih.gov/pubmed/) (1 November 2013);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 01 November 2013);
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 1 November 2013);
- CINAHL Plus (1939 to 1 November 2013);
- PsycINFO (1806 to November 2013);
- PEDro (Physiotherapy Evidence Database) (1929 to November 2013);
- OTSeeker (Occupational Therapy Systematic Evaluation of Evidence) www.otseeker.com (1955 to November 2013);
- Database of Abstracts of Reviews of Effects (DARE) (November 2013).

In May 2016, the Cochrane Injuries Group Information Specialist developed and ran a new search. This was because of changes in the author team that meant we were unable to locate the exact search strategies used in the original search (beyond the MEDLINE strategy). The database list was reduced and included:

- Cochrane Injuries Group Specialised Register (16 May 2016);
- MEDLINE (OvidSP) (16 May 2016);
- Embase Classic and Embase (OvidSP) (16 May 2016).

The search strategies for the 2016 search are listed in Appendix 1.

The Cochrane Injuries Information Specialist conducted a final prepublication search in June 2017. Given these searches were revised again by the Cochrane Injuries Information Specialist, we have listed the databases below. Some of the original databases were not searched in 2017 as the databases did not yield any unique studies in earlier searches.

We searched the following databases in June 2017 (and deduplicated against earlier yields):

- Cochrane Injuries Group Specialised Register (SR-INJ) (22 June 2017);
- the Cochrane Library (2017, Issue 6);
- Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) (2013 to 22 June 2017);
- Ovid Embase (1974 to 22 June 2017);
- PubMed (not MEDLINE) (www.ncbi.nlm.nih.gov/pubmed/) (22 June 2017);
- ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to 22 June 2017);
- ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (1990 to 22 June 2017);
- ClinicalTrials.gov (www.clinicaltrials.gov) (22 June 2017);
- WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) (22 June 2017).

These search strategies are listed in Appendix 2 so they can be used in future updates.

Searching other resources

We screened the reference lists of all included articles and relevant reviews to identify additional studies for inclusion in the review.

Data collection and analysis

Selection of studies

Two review authors (KP, MC or AS) independently screened citations on abstract and title against the selection criteria. We obtained potentially eligible citations in full text and repeated the process. The two review authors discussed disagreements regarding study eligibility until consensus was reached or consulted a third review author for a final decision. For trials with mixed populations, we contacted study authors to obtain data or clarification (or both) to inform inclusion and exclusion decisions.

Data extraction and management

Two review authors (KP, MC or AS) independently extracted the data from included studies using a standardised data collection form, that was first piloted by two authors. One review author (KP) made a final check. We contacted the primary authors of included studies to provide data and clarification where adequate data were not reported.

Assessment of risk of bias in included studies

Two review authors (KP, MC or AS) independently assessed risk of bias of the included studies using the Cochrane 'Risk of bias' tool (Higgins 2011). We assessed sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; baseline imbalances and other bias issues. Additional domains for cross-over trials included appropriate study design and adequate washout period. Studies were rated as low, high or unclear risk of bias for each domain, according to the criteria used in the Cochrane 'Risk of bias' tool.

Measures of treatment effect

We extracted raw data (means and standard deviations for continuous outcomes and number of events for binary outcomes) for the primary and secondary outcomes. Where these were not provided, we extracted additional data such as sum scores and P values. We extracted postintervention scores over change scores.

Where possible, we calculated summary data as risk ratio (RR) with 95% confidence intervals (CI) (dichotomous outcomes) and mean difference (MD) with 95% CI (continuous data). Had we been able to pool continuous outcomes where the outcome was measured using different tools across studies, we would have used standardised mean difference (SMD) with 95% CI. We analysed data in Review Manager 5 (RevMan 2011).

Unit of analysis issues

We sought to explore unit of analysis issues in the cross-over trials, but were unable to do so due to insufficient reporting.

Dealing with missing data

We contacted the primary authors of potentially eligible studies to provide data and clarification, where required. While several authors provided additional information to inform eligibility decisions, we did not receive any additional outcome data (some authors did not respond to our contact and others no longer had access to study data). We describe missing data and dropouts/attrition for each included study in the 'Risk of bias' table, and discussed the extent to which the missing data could have altered the results and conclusions of the review.

Assessment of heterogeneity

We considered the clinical heterogeneity of studies, but statistical assessment of heterogeneity was not possible due to the absence of meta-analysis. If meta-analysis is possible in future updates, we will consider the magnitude and direction of effect and make a visual inspection of forest plots to assess the degree of overlap of CIs across separate studies and statistical heterogeneity quantified using the I^2 statistic (Higgins 2011).

Assessment of reporting biases

Due to insufficient studies, formal assessment of reporting bias (via funnel plots) could not be carried out. In future updates, if there are more than 10 studies assessing the same outcome(s), we will construct a funnel plot to investigate small study effects (Higgins 2011).

Data synthesis

We had planned to pool outcome data for studies that were considered sufficiently similar. The diversity of interventions and comparator groups as well as paucity of data available meant that a pooled analysis was not possible, therefore the results for each study are presented narratively. We grouped and assessed studies based on the type of intervention (pharmacological or non-pharmacological or a combination of both) and the comparison group (no treatment, placebo studies or an alternative intervention).

We assessed and reported the quality of the body of evidence contributing each outcome using the GRADE criteria (Schünemann 2011). These five criteria are: risk of bias, inconsistency, imprecision, indirectness and publication bias. Two review authors (AS, MC) independently assessed the quality of the evidence using the GRADE approach (Ryan 2016; Schünemann 2011).

Subgroup analysis and investigation of heterogeneity

We were unable to conduct planned subgroup analyses due to the lack of data. Should there be sufficient data in future updates, we will undertake subgroup analyses to investigate the effect of:

- timing of intervention post injury (i.e. early: within two years, versus late: at least two years' postinjury);
- severity of TBI defined by the Glasgow Coma Scale (Teasdale 1974);
- severity of spasticity as defined by the Ashworth Scale for muscle spasticity;
- single intervention versus combined interventions;
- mixed population studies versus studies with TBI participants only;
- adults versus children.

Sensitivity analysis

We were unable to conduct the planned sensitivity analysis due to the lack of available data. Should there be sufficient studies in future updates, we will investigate the effect of removing studies with inadequate or unclear allocation concealment from meta-analyses. This domain was selected as the allocation sequence can be concealed in all RCTs (unlike some domains, e.g. like blinding), and there is empirical evidence demonstrating the increased risk of selection bias that can be introduced by unconcealed allocation in studies with more subjective outcomes (such as spasticity and others assessed in this review) (Wood 2008).

'Summary of findings' tables

We made a post-hoc decision to prepare 'Summary of findings' tables to present the meta-analysed or narrative results along with the GRADE ratings of our main outcomes. These outcomes were selected on the basis of their clinical importance, rather than the study results. The outcomes included in the 'Summary of findings' table are: spasticity, adverse events, sensory functions and pain, neuromusculoskeletal and movement-related functions, general tasks and demands, mobility and self-care.

RESULTS

Description of studies

Results of the search

Combining the yields of all searches up to June 2017, we identified 1743 citations after deduplication, excluding 1527 of these on title and abstract (see Figure 1). This left 216 citations assessed in full text, of which 201 were excluded (see Figure 1; Excluded studies; Characteristics of excluded studies table and Table 1 for more information and reasons).

Figure 1. Study flow diagram for searches up until June 2017. TBA: traumatic brain injury.

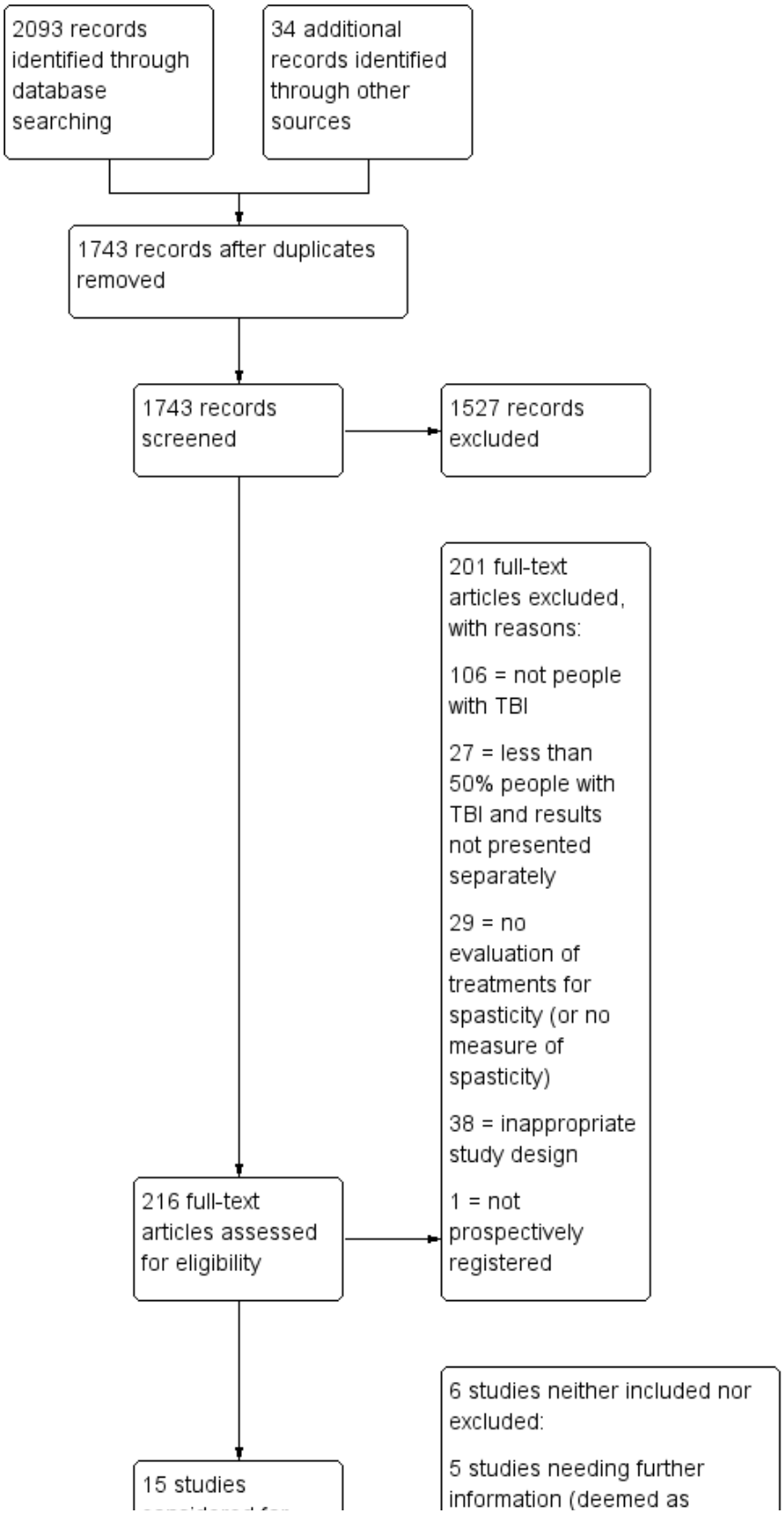
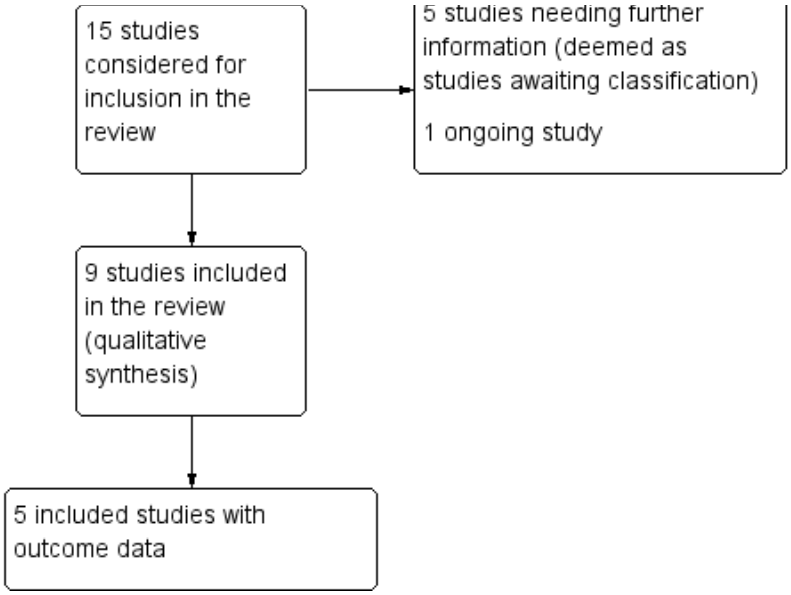


Figure 1. (Continued)



Of the remaining 15 studies that were considered for inclusion, we require further information about five studies (see the Characteristics of studies awaiting classification table) and one study is ongoing (see the Characteristics of ongoing studies table). The anticipated end date for the ongoing study investigating the combined effect of serial casting and botulinum toxin A on ankle contractures is September 2018 (ACTRN12615000821594).

We therefore included nine completed trials (Gracies 2015; Leung 2014; Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b; NCT00287157; Pittaccio 2013; Verplancke 2005).

Included studies

Design

We included nine studies involving data from 385 participants (134 with TBI) (Gracies 2015; Leung 2014; Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b; NCT00287157; Pittaccio 2013; Verplancke 2005; see Characteristics of included studies table). Of these, three were parallel group RCTs, with two (Leung 2014) or three comparator groups (Gracies 2015; Verplancke 2005). Six were randomised cross-over trials comparing treatment with placebo or standard care (Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b; NCT00287157; Pittaccio 2013).

Of the nine trials, three did not identify between-group differences in outcome data, neither did they report sufficient information about the results to allow us to calculate these differences (Meythaler 1997; Meythaler 1999a; Meythaler 1999b). Results from one trial remain unpublished and unavailable (NCT00287157). As such, only the data from five studies (combined 350 participants, of whom 105 had TBI) contributed outcome data to the results of this review (Gracies 2015; Leung 2014; Meythaler 1996; Pittaccio 2013; Verplancke 2005).

Number of participants

Within each study, the number of participants (TBI and non-TBI) ranged from six (Meythaler 1999a) to 243 (Gracies 2015). Most of these trials included mixed populations (TBI and non-TBI). Two studies solely recruited people with TBI (51 combined participants) (Meythaler 1999b; Leung 2014), while Gracies 2015 provided disaggregated data for their subgroup of 23 participants with TBI (in the form of a conference abstract; O'Dell 2015). In the remaining six studies with mixed populations, the number of participants with TBI ranged from three (Meythaler 1999a) to 20 (Verplancke 2005), and the proportions of participants with TBI ranged from 50% (Meythaler 1999a) to 91% (Meythaler 1996).

Setting

All the trials were conducted in high-income settings, including the US (four trials), Australia (one trial), the UK (one trial), Italy (one trial) and Israel (one trial). One trial drew data from sites in nine high-income countries (Belgium, Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia, USA) (Gracies 2015). Participants were recruited from either tertiary care (outpatient or inpatient, or both) rehabilitation clinics or acute general hospitals.

Of the five studies with results, three were funded by governments, charities or health services (Meythaler 1996; Leung 2014; Pittaccio 2013), and two were funded by pharmaceutical/medical technology companies (Gracies 2015; Verplancke 2005). The four studies without useable results were funded by pharmaceutical/medical technology companies (Meythaler 1997; Meythaler 1999a; Meythaler 1999b; NCT00287157).

Participants

Age and sex

With the exception of Gracies 2015, data for age and gender were not reported separately for TBI participants when they formed a proportion of 'mixed' populations. For this reason, the following information relates to the whole sample (including non-TBI participants) within trials except for Gracies 2015, along with Leung 2014 and Meythaler 1999b, which were the only trials in which all participants had a diagnosis of TBI.

Seven studies included adults, with a mean (or median) age of participants between 24 years (Meythaler 1996) and 41.5 years

(Verplancke 2005). Two studies included children (NCT00287157; Pittaccio 2013); only Pittaccio 2013 reported the mean age of participants, being 7.75 years. Where reported, all studies include more males than females, ranging from 60% (Meythaler 1999a) to 92% (Meythaler 1997).

Body part treated

Four studies treated spasticity anywhere in the lower limbs, but also treated upper limb spasticity, if present (Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b). Two studies treated spasticity in the calf muscles (gastrocnemius, or gastrocnemius and soleus) (Leung 2014; Verplancke 2005), while Gracies 2015 treated spasticity in the upper limbs only (specifically elbow flexors, wrist flexors or finger flexors) and Pittaccio 2013 treated spasticity in the ankle or elbow. One study did not report the location of the spasticity (NCT00287157).

Interventions and comparators

The nine studies tested a varied range of pharmacological and non-pharmacological interventions. Pharmacological interventions that were tested against saline/placebo included intrathecal baclofen (Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b) and tizanidine (NCT00287157). Two additional, three-armed trials tested botulinum toxin A; Gracies 2015 tested two different doses of botulinum toxin A against placebo, and Verplancke 2005 assessed botulinum toxin A plus casting against placebo plus casting and against physiotherapy.

Non-pharmacological interventions and comparisons tested include casting and physiotherapy (Verplancke 2005), pseudoelastic orthosis versus a traditional splint (Pittaccio 2013), and a combination of tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone (Leung 2014).

More details are provided about the interventions tested, grouped under different comparisons.

Baclofen versus placebo

Meythaler 1996 examined the effect of intrathecal baclofen for spastic hypertonia in the lower limbs. Eleven participants were allocated to receive a bolus intrathecal injection of either normal saline or baclofen 50 µg. Cross-over of participants occurred 48 hours after the initial administration. This study was in two parts: use of a bolus dose and then those participants with an adequate response were progressed to implantation of an intrathecal baclofen pump. This would be considered the usual method for evaluation for implantation of a baclofen pump.

The three other baclofen studies (Meythaler 1997; Meythaler 1999a; Meythaler 1999b) also assessed intrathecal baclofen infusion at the same dosage (50 µg), but provided no useable results.

Botulinum toxin A (with or without casting) versus placebo (with or without casting)

Gracies 2015 assessed the effect of botulinum toxin A versus placebo for upper limb spasticity in 23 participants with TBI. In the initial treatment cycle, 14 participants received either abobotulinumtoxinA (500 U or 1000 U) and nine received placebo. The mode of administration was intramuscular injection. However, for participants with TBI, results were given in a binary method (only intervention versus placebo, without regard to dosage of abobotulinumtoxinA).

Verplancke 2005 compared the effects of three different interventions in 25 adults with lower limb spasticity, which we split into three, two-arm comparisons. The comparison included here is botulinum toxin A injections plus casting (12 participants) (200 U/leg) versus placebo plus casting (12 participants) (total of 4 mL saline injections).

Physiotherapy versus placebo plus casting or botulinum toxin A plus casting

The remaining comparisons for Verplancke 2005 were physiotherapy alone (11 participants) compared with casting plus botulinum toxin A injections (12 participants) (200 U/leg) or casting with placebo (12 participants) (total of 4 mL saline injections) in adults with lower limb spasticity.

Tizanidine versus placebo

NCT00287157 assessed the effect of tizanidine versus placebo on spasticity, cognition and daily function. The results were unpublished and no data were available.

Pseudoelastic orthosis versus traditional splint

In Pittaccio 2013, 25 children with elbow or ankle spasticity wore a spring-loaded orthosis comprised of two parts that could rotate relative to one another around a common axis that was individually customised and worn for one month. A traditional static splint was fitted and worn for one month. These treatments were delivered in a randomised cross-over manner.

Tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone

Leung 2014 (36 participants) evaluated a multi-modal treatment including 30 minutes of tilt table standing with electrical stimulation to the ankle dorsiflexors five times a week, with 12 hours per day of ankle splinting, at least five days a week. This was compared to the control group, who received 30 minutes of tilt table standing, three times a week. The total programme duration for intervention and control groups was six weeks.

Outcomes

For the five studies in which outcome data were provided, results were available for the primary outcomes of spasticity (assessed using the Tardieu Scale (Gracies 2015; Leung 2014), the Ashworth Scale (Meythaler 1996), or the Modified Ashworth Scale (Gracies 2015; Pittaccio 2013; Verplancke 2005)) and adverse events. All authors treated their measures of spasticity as continuous and numerical data provided were often sparse. Secondary outcomes measured included neuromusculoskeletal and movement-related functions (i.e. deep tendon reflexes, ankle range of movement), mobility, major life areas and community, social and civic life. The remaining secondary outcomes of interest to this review (sensory function and pain, general tasks and demands, self-care and domestic life) were not measured. Detailed information about the domains and scores used for these outcomes and the timing of their measurement in the studies is described in Table 2 and Table 3.

Excluded studies

In total, we excluded 169 studies on reading the full text, for reasons including no TBI participants (96 studies), less than 50% of participants had TBI and results not presented separately (27 studies), no evaluation of treatments for spasticity (28 studies)

or ineligible study design (e.g. review article; 18 references; see Characteristics of excluded studies for a list of 58 key studies excluded on full text).

Given the relatively large number of studies (27) that were excluded as less than 50% of study participants had a TBI (and the data for these participants were not presented separately), we provided more information in Table 1. Across these studies, there were 1000 participants, of whom 142 (14%) had TBI. The percentage of people within each study who had TBI ranged from 2% to 47%.

Risk of bias in included studies

The risk of bias for all included studies varied as detailed in the Characteristics of included studies table, and presented in Figure 2 and Figure 3. Many items were scored as 'unclear' due to poor reporting.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. Nine studies are included in this review.

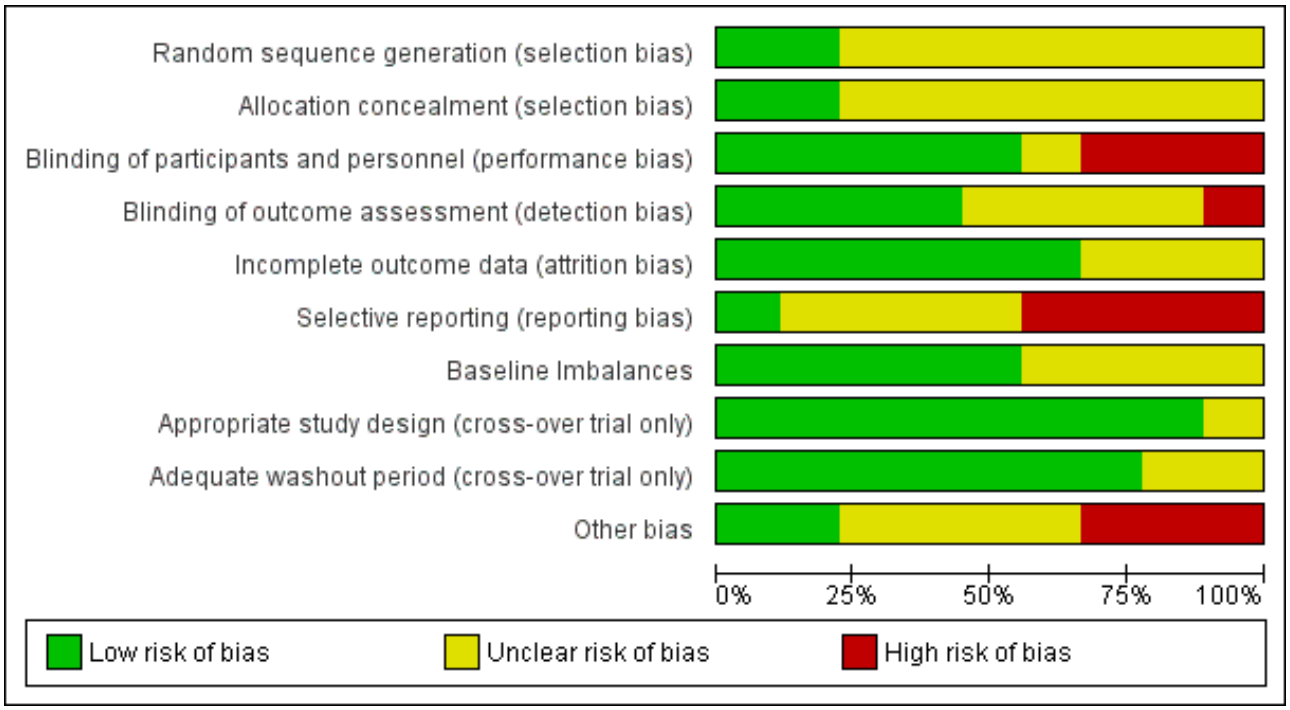
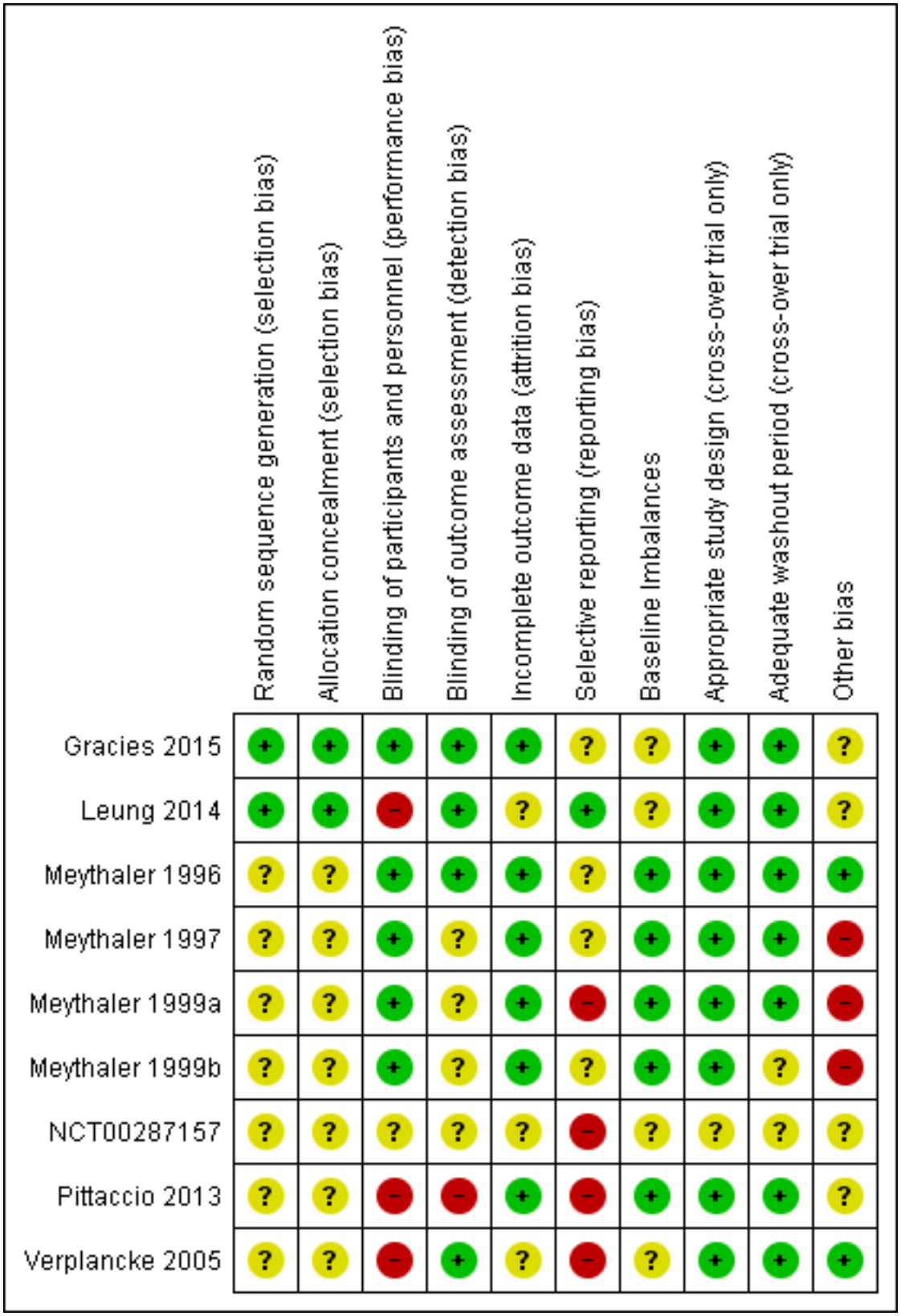


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study (note: only Meythaler 1996 and Verplancke 2005 contributed outcome data to the review).



Allocation

Of the nine included studies, investigators involved in only two studies clearly reported the methods of both randomisation and allocation concealment, and these were assessed at low risk of bias for these domains (Gracies 2015; Leung 2014). None of the other study authors provided details of either randomisation or allocation concealment methods, making it difficult to determine any associated risks of bias. Seven studies were thus rated at 'unclear' risk of bias for both these domains.

Blinding

Five studies reported adequate blinding of participants and personnel (Gracies 2015; Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b). In three studies neither participants nor personnel could be blinded due to the obvious differences between interventions and controls (e.g. serial casting, different orthoses/splints), leading to ratings of high risk (Leung 2014; Pittaccio 2013; Verplancke 2005). The registry entry for NCT00287157 provided insufficient information and as such this study was rated as unclear.

Four studies explicitly reported that outcome assessors were blinded (Gracies 2015; Leung 2014; Meythaler 1996; Verplancke 2005). It is noteworthy that these were amongst the only studies with outcome data included in the review. In four studies, it was unclear if outcome assessors were blinded (Meythaler 1997; Meythaler 1999a; Meythaler 1999b; NCT00287157), and in one study outcome assessors could not be blinded, hence it was rated at high risk (Pittaccio 2013).

Incomplete outcome data

Six studies reported no losses to follow-up and were at low risk of attrition bias (Gracies 2015; Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b; Pittaccio 2013). Verplancke 2005 reported four withdrawals and three deaths; however, their final measurements for these participants were those taken before withdrawal from the study (rated as unclear as they did not report which group they were randomised to). Leung 2014 reported four losses to follow-up, with reasons that were unrelated to the trial; however, they were not balanced between groups. Both studies were rated as unclear risk of bias. The rating for NCT00287157 was 'unclear' due to lack of information.

Selective reporting

One study was at low risk of bias given the availability of a published protocol, which aligned with the subsequently published trial (Leung 2014). Three studies were at unclear risk of bias for selective reporting, as there were no published protocols (Meythaler 1996; Meythaler 1997; Meythaler 1999b). One study was also rated at unclear risk of bias as, while it did have a published protocol for the main study, the TBI subset outcome data for different doses of the active intervention were conflated and results were given in the form of percentages only (Gracies 2015). Three studies did not reference published protocols (neither could we identify any) and were at high risk due to additional incomplete reporting of their results (Meythaler 1999a; Pittaccio 2013; Verplancke 2005). NCT00287157 was at high risk of bias as the authors advised that the trial data were "negative," and was subsequently not published.

Other potential sources of bias

Baseline imbalances

With regards to baseline imbalances, five studies were at low risk of bias (Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b; Pittaccio 2013). Four studies were judged as unclear for this domain (Gracies 2015; Leung 2014; NCT00287157; Verplancke 2005). NCT00287157 was judged as unclear due to lack of information, whereas the other two studies described their groups as being 'similar' at baseline, but subsequently outlined some differences between the groups.

Appropriate study design

For the six cross-over trials, five used an appropriate study design (Meythaler 1996; Meythaler 1997; Meythaler 1999a; Meythaler 1999b; Pittaccio 2013). The remaining trial was at unclear risk of bias.

Adequate washout period

Three cross-over trials provided enough information to be judged as having an adequate washout period (low risk of bias) (Meythaler 1996; Meythaler 1997; Meythaler 1999a). Investigators in one trial judged it unethical to have a washout period (Pittaccio 2013). Statistical tests were conducted and presented demonstrating that sequential order did not affect treatment response, so this trial was also assessed as having a low risk of bias. The remaining two cross-over trials were at unclear risk of bias for this domain (Meythaler 1999b; NCT00287157).

Other bias

With regards to 'other bias', three studies (Meythaler 1997; Meythaler 1999a; Meythaler 1999b) were at high risk of bias due to unit of analysis issues (outcomes were analysed by looking at upper versus lower extremities, rather than considering each muscle separately; scores for muscle tone, spasms and reflexes were averaged for the upper or lower extremities in each participant). Four studies were at unclear risk of bias due to insufficient information (NCT00287157); the close role of the funder (a pharmaceutical company) in the study design, conduct and analysis (Gracies 2015); the inclusion of a participant who did not meet the study inclusion criteria (Pittaccio 2013); and marked differences in the number of tilt table sessions between the intevention and control groups (Leung 2014). We did not identify any other bias concerns with the remaining two studies (Meythaler 1996; Verplancke 2005).

Effects of interventions

See: **Summary of findings for the main comparison** Baclofen compared with placebo for spasticity in people with traumatic brain injury; **Summary of findings 2** Botulinum toxin A (with and without casting) compared with placebo (with and without casting) for spasticity in people with traumatic brain injury; **Summary of findings 3** Pseudoelastic orthosis versus traditional (static) splint for spasticity in people with traumatic brain injury

Baclofen versus placebo

One study with usable results compared baclofen versus placebo (Meythaler 1996). (Three other studies compared baclofen to placebo but had no useable results; Meythaler 1997; Meythaler 1999a; Meythaler 1999b.) A summary of the results of the main

outcomes for this comparison is provided in Summary of findings for the main comparison.

Spasticity

Meythaler 1996 (11 participants, all included in the analysis) reported between-group differences in both the lower and upper extremity Ashworth scores using P values, but with no effect sizes or CIs. It was unclear which statistical tests were used. As the study authors did not report any raw data for the placebo group results, we could do no further analysis. The authors reported a 'significant' improvement with baclofen compared to placebo at four hours (P = 0.0084) and six hours (P = 0.0163) after administration. Baclofen was also associated with 'significant' improvements compared to placebo for upper extremity Ashworth score (P = 0.0097) at four hours after administration, however this effect was not sustained at six hours (P value not reported).

The quality of the evidence on the effect of baclofen versus placebo for spasticity was very low (downgraded four times). This was due to risk of bias limitations (no study provided sufficient information about the random sequence generation or allocation concealment), our concerns about indirectness of the Ashworth score, an inability to assess imprecision relating to an absence of CIs and a further downgrade for there only being a single study for this outcome and the likelihood of publication bias in this area. Considered together with the fact that we could not judge how clinically relevant the improvements were in this study, we were very uncertain about the effect of baclofen on spasticity and unable to draw any conclusions.

Adverse events

There were no adverse events or changes in alertness level in the baclofen or placebo groups (see Table 4).

The quality of the evidence on the effect of baclofen versus placebo for spasticity was very low (downgraded three times). This was due to the same risk of bias concerns as for spasticity and that there was only one study for this outcome and the likelihood of publication bias in this area. As such, we were very uncertain about the effect of baclofen on adverse events compared to placebo and were unable to draw any conclusions.

Neuromusculoskeletal and movement-related functions

Meythaler 1996 (11 participants, all included in the analysis) reported that lower extremity spasm scores were significantly improved for baclofen versus placebo at four hours (P = 0.0073) and six hours (P = 0.0049) as were lower extremity reflex scores (P = 0.0086 at four hours and P = 0.0085 at six hours). This effect was also observed for the upper extremity spasm scores (P = 0.0117) and reflex scores (P = 0.0272) at four hours after administration when baclofen was compared to placebo. This effect was not sustained at six hours (P value not reported).

The quality of this evidence was very low (downgraded four times, for all the reasons outlined for spasticity) and we are very uncertain about the effect of baclofen on neuromusculoskeletal and movement-related functions.

Outcomes not measured

The study did not report: sensory functions and pain; general tasks and demands; mobility; self-care; domestic life; major life areas; and community, social and civic life.

Botulinum toxin A (with and without casting) versus placebo (with and without casting)

Two studies compared botulinum toxin A (with and without casting) versus placebo (with and without casting) (Gracies 2015; Verplancke 2005). A summary of the results of the main outcomes for this comparison is provided in Summary of findings 2.

Spasticity

Gracies 2015 (23 participants) report that four weeks after injection, "with abobotulinumtoxinA, the angle of catch (XV3 of the TS) improved in finger (+35 degree), elbow (+22 degree) and wrist (+12 degree) flexors, resulting in a gain in active muscle extension of at least 5 degrees active range of movement." No further outcome data were provided, and they did not comment on the 'statistical significance' of this result. We note that the dosage that produced this result (500 U or 1000 U) was unclear as data from both groups (total 14 participants) were pooled against placebo (nine participants).

Verplancke 2005 (35 participants) compared three different interventions, which we report as three two-arm comparisons (the authors analysed pre- and post-treatment differences in the Modified Ashworth Scale within groups, but not between groups). As such, we calculated the between-group difference in spasticity (as measured by the Modified Ashworth Scale at 12 weeks) for botulinum toxin A plus casting versus placebo plus casting as MD 0.30 points (95% CI -0.87 to 1.47; Analysis 1.1).

The quality of the evidence for this outcome was very low (downgraded four times). This was due to risk of bias concerns for both studies (downgraded twice, because either insufficient information about random sequence generation and allocation concealment, in one study, and potential selective outcome reporting in both studies), indirectness (one study measured spasticity using the Modified Ashworth Scale) and a high likelihood of publication bias in this area. As such, we were very uncertain about the effect of botulinum toxin A with and without casting versus placebo with and without casting on spasticity and were unable to draw any conclusions.

Adverse events

In Gracies 2015, the authors reported that "7 of 23 patients experienced a treatment emergent AE [adverse event]" and that of these, "none were unexpected." There was no further detail given in the short conference proceeding reporting results for the TBI population. In the main trial publication (of which people with TBI only made up 9%), the most common treatment-related adverse event was 'mild muscle weakness' and investigators reported that all adverse events were mild or moderate only (see Table 4).

In Verplancke 2005, botulinum toxin A was to be well tolerated, with only one participant with 'flu-like' symptoms (i.e. shivering, sweating and fever). For the casting group, 50% developed minor skin damage (66.6% of those was partial thickness skin loss involving epidermis). Finally, in the botulinum toxin A plus casting group, 41.7% of participants developed skin damage (60% of those

was discolouration, but skin still intact). Overall, 90.9% of those resolved spontaneously or with therapeutic dressing (see Table 4).

The quality of the evidence for adverse events was very low (downgraded three times). This was due to risk of bias concerns for both studies (downgraded twice, because in one study there was insufficient information about random sequence generation and allocation concealment, and in both studies the adverse events data were reporting in percentages only) and a high likelihood of publication bias in this area. As such, we were very uncertain about the effect of botulinum toxin A with and without casting versus placebo with and without casting on adverse events and were unable to draw any conclusions.

Neuromusculoskeletal and movement-related functions

Verplancke 2005 reported between-group differences in ankle dorsiflexion, and found no differences between groups in a one-way ANOVA (placebo plus casting versus botulinum toxin A plus casting: P = 0.11). However, they did not report any summary statistics for this, or any baseline scores.

The quality of the evidence for neuromusculoskeletal and movement-related functions was very low for the reasons outlined for spasticity (downgraded four times). As such, we were very uncertain about the effect of botulinum toxin A with and without casting versus placebo with and without casting on neuromusculoskeletal and movement-related functions and were unable to draw any conclusions.

Major life areas

Both Gracies 2015 and Verplancke 2005 measured outcomes we classified under major life area outcomes. Gracies 2015 reported an "improvement in subjective function for the treated group (>1 grade decrease from baseline for the principal target of treatment on the Disability Assessment Scale (DAS)): 71% versus 22% for placebo." They did not provide this in absolute numbers, or comment on the 'statistical significance' of the result. Verplancke 2005 reported Glasgow Outcome Scale (GOS) and Glasgow Coma Scale scores at follow-up in each of the three groups, but reported mean values and did not report between-group differences.

The quality of the evidence for major life areas was very low (downgraded three times). This was due to risk of bias concerns for both studies (downgraded twice, because in one study there was insufficient information about random sequence generation and allocation concealment, and in both studies the outcome data were inappropriately analysed or reported in percentages only) and a high likelihood of publication bias in this area. As such, we were uncertain about the effect of botulinum toxin A with and without casting versus placebo with and without casting on major life areas and were unable to draw any conclusions.

Community, social and civic life

In Gracies 2015, the authors reported two quality of life measures (subscores of the 36-item Short Form Health (SF-36) and the EuroQol (EQ-5D); however, these outcomes were not reported separately for the subset of participants with TBI.

Outcomes not measured

The studies did not report: sensory functions and pain, general tasks and demands, mobility, self-care and domestic life.

Physiotherapy versus placebo plus casting or botulinum toxin A plus casting

One study compared physiotherapy versus placebo plus casting or botulinum toxin A plus casting (Verplancke 2005).

Spasticity

Verplancke 2005 compared three treatment groups: physiotherapy, placebo plus casting and botulinum toxin A plus casting. The authors analysed pre- and post-treatment differences in the Modified Ashworth Scale within but not between groups. As such, we calculated the following between-group differences in spasticity (as measured by the Modified Ashworth Scale at 12 weeks): botulinum toxin A plus casting versus physiotherapy (MD -0.50 points, 95% CI -1.82 to 0.82; Analysis 2.1) and placebo plus casting versus physiotherapy (MD -0.80 points, 95% CI -2.00 to 0.40; Analysis 3.1).

The quality of the evidence for physiotherapy compared to casting or botulinum toxin A plus casting on spasticity was very low. This was due to concerns about risk of bias related to insufficient information provided about allocation concealment and blinding, concerns about indirectness of the Modified Ashworth Scale, an inability to assess imprecision relating to an absence of CIs and a further downgrade for there only being one study for this outcome and the likelihood of publication bias in this area. As such, we are very uncertain about the effect of casting versus botulinum toxin A plus casting versus physiotherapy on spasticity and were unable to draw any conclusions.

Adverse events

Verplancke 2005 withdrew two participants due to an adverse event (see Table 4). One was due to deep vein thrombosis (DVT) in the physiotherapy group and one was due to soft tissue contracture at the subtalar joint in the placebo plus casting group. For the adverse events related to botulinum toxin A, see the adverse events listed under the comparison above, botulinum toxin A with and without casting versus placebo with and without casting.

The quality of the evidence for physiotherapy versus placebo plus casting or botulinum toxin A plus casting on adverse events was very low. This was due to concerns about risk of bias related to insufficient information provided about allocation concealment and blinding, and a further downgrade for there only being one study for this outcome and the likelihood of publication bias in this area. As such, we were very uncertain about the effect of casting versus botulinum toxin A plus casting versus physiotherapy on adverse events and were unable to draw any conclusions.

Neuromusculoskeletal and movement-related functions

Verplancke 2005 reported between-group differences in ankle dorsiflexion and found no differences between groups in a one-way ANOVA (physiotherapy versus placebo plus casting: P value not significant, physiotherapy versus botulinum toxin A plus casting: P = 0.07). However, they did not report any summary statistics for this, or any baseline scores.

The quality of the evidence for physiotherapy versus placebo plus casting or botulinum toxin A plus casting on neuromuscular and movement-related outcomes was very low (downgraded three times). This was due to concerns about risk of bias (related to insufficient information provided about randomisation schedule

generation and allocation concealment, a lack of blinding and selective outcome reporting), an inability to assess imprecision relating to an absence of data and a further downgrade for there only being one study for this outcome and the likelihood of publication bias in this area. As such, we were very uncertain about the effect of casting versus botulinum toxin A plus casting on neuromuscular and movement-related functions and were unable to draw any conclusions.

Major life areas (e.g. Functional Assessment Measure)

Verplancke 2005 reported GOS and GCS scores at follow-up in each of the three groups, but reported mean values and did not report between-group differences.

Outcomes not measured

The study did not report: sensory functions and pain; general tasks and demands; mobility; self-care; domestic life; and community, social and civic life.

Pseudoelastic orthosis versus traditional (static) splint

One study compared pseudoelastic orthosis versus traditional (static) splint in children (Pittaccio 2013). A summary of the results of the main outcomes for this comparison is provided in Summary of findings 3.

Spasticity

Pittaccio 2013 measured spasticity using the Ashworth Scale, but reporting for clinical outcomes in this paper was scant. The authors provided no outcome data for spasticity but stated that, "there were no significant differences on means by paired 2-tailed Student's t test" between the two types of splint.

The quality of the evidence was very low. The rating was downgraded four times due to risk of bias limitations (the study provided no information about sequence generation and allocation concealment; blinding was impossible for participants or personnel and not reported for outcome assessors; selective outcome reporting bias was high); our concerns about indirectness of the Ashworth score and indirectness due to 36% of participants not having TBI and one participant was of dubious eligibility; an inability to assess imprecision relating to an absence of meaningful outcome data (no numerical data were provided for spasticity; investigators reported only that there were no significant differences), there was only one study for this comparison/outcome and publication bias was possible in this area. As such, we were very uncertain about the effect of pseudoelastic orthoses versus a traditional (static) splint on spasticity and were unable to draw any conclusions.

Adverse events

Pittaccio 2013 reported that both participants and families 'reacted positively' to the pseudoelastic orthoses, which were described as well-tolerated for several hours a day, and never caused problems familiar to those using more traditional devices including a skin rash, haematomas or pain (see Table 4). None of the pseudoelastic orthoses had to be modified to improve comfort, while some adjustments were required for approximately 30% of traditional splints, in order to reduce skin rash, haematomas and oedema. Tolerability was assessed by questionnaire. The investigators conceded that true knowledge of comfort/discomfort experienced by children in the trial was impossible to assess as most participants were unable to communicate; nevertheless, questionnaire data were reported to be encouraging and on average, the pseudoelastic devices were tolerated 40% longer than traditional splints.

The quality of the evidence was very low (downgraded four times). The quality was downgraded due to risk of bias limitations (this study provided insufficient information about sequence generation and allocation concealment, blinding was impossible for participants and personnel and not reported for outcome assessors, and selective reporting bias was high). We had concerns about indirectness given that 36% of participants did not have TBI and one participant was of dubious eligibility. Furthermore, there was only one study for this comparison/outcome and publication bias was possible in this area. As such, we were very uncertain about the effect of pseudoelastic orthoses versus a traditional (static) splint on adverse events and were unable to draw any conclusions.

Neuromusculoskeletal and movement-related functions

Pittaccio 2013 reported results for range of motion as non-significant ("no significant differences on means by paired 2-tailed Student's t tests") and no further numerical data were given.

The quality of the evidence was very low. The quality of the evidence was downgraded five times due to risk of bias limitations (this study provided insufficient information about sequence generation and allocation concealment, blinding was impossible for participants and personnel and not reported for outcome assessors, and selective reporting bias was high). We had concerns about indirectness due to 36% of participants not having TBI and one participant was of dubious eligibility; our inability to assess imprecision given that means and standard deviations were only presented within a small box and whiskers plot, and a further downgrade for there only being one study for this comparison/outcome and the likelihood of publication bias in this area. As such, we were very uncertain about the effect of pseudoelastic orthoses versus a traditional (static) splint on neuromusculoskeletal and movement-related functions and were unable to draw any conclusions.

Outcomes not measured

The study did not report: sensory functions and pain; general tasks and demands; mobility; self-care; domestic life; major life areas; and community, social and civic life.

Tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone

One study compared tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone (Leung 2014).

Spasticity

Leung 2014 measured spasticity at six weeks (end of programme) and 10 weeks (end of trial) using the 5-point 'reaction to passive stretch at high speed' component of the Tardieu Scale. Leung 2014 treated this as a continuous scale and reported the difference between groups using change scores, which we plotted using postintervention scores only (see Analysis 4.1). This resulted in an MD of -1.00 points (95% CI -1.66 to -0.34) at week six (in favour of tilt table standing, electrical stimulation and ankle splinting) and

an MD of 1.00 (95% CI 0.31 to 1.69) at week 10 (in favour of tilt table standing alone). This is broadly consistent with the conclusions of the authors that "there was a small mean reduction of 1 point in spasticity at Week 6 (95% CI 0.1 to 1.8) in favour of the experimental group, but this effect disappeared at Week 10."

The quality of the evidence for tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone on spasticity was very low (downgraded three times). This was due to concerns about indirectness (downgraded once for potentially inappropriate analysis of the Tardieu Scale as a continuous measure), imprecision (downgraded once as there was only one small study for this outcome) and the likelihood of publication bias in this area (downgraded once). As such, we were very uncertain about the effect of tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone on spasticity and were unable to draw any conclusions.

Adverse events

While Leung 2014 did not explicitly measure adverse events, they provided a description of a number of factors that influenced several participants' adherence to tilt table standing, including fainting, fatigue and storming (when someone with a head injury responds to a sensation with a tonic posture or sympathetic response). Additionally, two participants' adherence to splinting was affected by "skin problems" and "poor tolerance."

Neuromusculoskeletal and movement-related functions

Leung 2014 measured passive ankle dorsiflexion at 12 Nm at six weeks (end of programme) and 10 weeks (end of trial). Dorsiflexion was measured relative to a neutral ankle position (0 degrees), with a positive score indicating dorsiflexion (the desired direction of movement) and a negative score indicating plantarflexion. They explored the differential effects using change scores, but we recalculated this using postintervention scores (see Analysis 4.2). This yielded an MD of -2.00 degrees (95% CI -7.19 to 3.19) at six weeks and an MD of 1.00 degree (95% CI -3.31 to 5.31) at 10 weeks.

The quality of the evidence for tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone on neuromuscular and movement-related functions was very low (downgraded three times). This was due to imprecision (downgraded once) related to the CI including both a meaningful benefit and harm, using Leung 2014's prespecified 'minimum worthwhile treatment effect' of 5 degrees, there was only one study for this outcome (downgraded once) and the likelihood of publication bias in this area (downgraded once). As such, we were very uncertain about the effect of tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone on neuromusculoskeletal and movement-related functions and were unable to draw any conclusions.

Mobility

Leung 2014 measured mobility using walking speed (in metres/second) at six weeks (end of programme) and 10 weeks (end of trial). They assessed between-group differences using change scores, which we recalculated using postintervention scores (see Analysis 4.3). This yielded a MD of -0.10 m/second (95% CI -0.43 to 0.23) at six weeks and 0.00 (95% CI -0.38 to 0.38) at 10 weeks.

The quality of the evidence for tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone on mobility was very low. The quality of the evidence was downgraded four times due to risk of bias concerns (participants and personnel could not be blinded and there were some imbalances between groups in the length of time since injury and the number of tilt table sessions received), for imprecision (single study and the CI included a potential benefit and harm) and the likelihood of publication bias in this area. As such, we were uncertain about the effect of tilt table standing, electrical stimulation and ankle splinting versus tilt table standing alone on mobility and were unable to draw any conclusions.

The study did not report: sensory functions and pain; general tasks and demands; self-care; domestic life; major life areas; and community, social and civic life.

Tizanidine versus placebo

One study compared tizanidine versus placebo (NCT00287157) in children. However, we have no information regarding participants and no information about the effect of tizanidine versus placebo on spasticity or any other outcomes as the results of this study are unavailable and unpublished.

DISCUSSION

Summary of main results

We found nine RCTs, including 385 participants (of whom 134 had TBI), that assessed the effect of a wide range of pharmacological and non-pharmacological treatments for spasticity as a result of TBI. Only five of these studies reported results in sufficient detail to allow synthesis in the review. As such, we included data from studies with 350 participants (105 of whom had TBI) in which baclofen, botulinum toxin A, casting, physiotherapy, splints, tilt table standing and electrical stimulation were tested, either alone or in combination.

Given such heterogeneity of interventions, trials for any given intervention were few, and sample sizes were small. Added to this, reporting of methods and results for trials was patchy, we had concerns about indirectness given the number of studies in this review with mixed populations, and publication bias given the known (and potentially unknown) unpublished studies in this area. These factors combined to mean there was a paucity of evidence about the effect of interventions for the management of spasticity in people with TBI. The quality of the evidence for all outcomes was very low.

In the interests of completeness, we provided a rudimentary summary of the results for the primary outcomes of spasticity and adverse events. Results were mixed for spasticity, but we cautioned against drawing conclusion given the very low quality evidence. For pharmacological interventions, baclofen had a greater effect than placebo after six hours of treatment in the lower limbs but not upper limbs (Meythaler 1996), and botulinum toxin A had a greater effect than placebo at four weeks in the upper limbs (Gracies 2015), but when combined with casting it had no greater effect than casting alone in the lower limbs (Verplancke 2005). For non-pharmacological studies, physiotherapy compared with casting in the lower limbs (Verplancke 2005), and novel pseudoelastic splints with traditional splints at the ankle or elbow (Pittaccio 2013), demonstrated no differences between treatments.

For adverse events, the quality of the evidence was similarly very low, but the results were a little more consistent. For pharmacological treatments, there were no adverse events reported in the baclofen study (Meythaler 1996), or the group which received botulinum toxin A in Verplancke 2005, but 7/23 participants in the botulinum toxin A study by Gracies 2015 experienced a "treatment emergent adverse event" (no further information provided). Many of the non-pharmacological treatments were associated tolerability/adherence issues, including traditional splints (Leung 2014; Pittaccio 2013) and tilt table standing (Verplancke 2005). In Verplancke 2005, between 41.7% and 50% of participants who received casting developed minor skin damage, of which, 90% resolved spontaneously. In Verplancke 2005, two more serious adverse events developed in the physiotherapy group (DVT) and the casting plus placebo group (joint contracture).

Due to the very low quality of evidence, we were uncertain about the effects of any of these interventions for managing spasticity.

Overall completeness and applicability of evidence

This review indicated that the evidence for existing interventions for managing spasticity in TBI is limited. Given the paucity of well-designed and reported trials, the applicability of this review to the TBI population was limited as there were many factors that needed to be considered which none of the studies addressed.

Clinicians can find the management of TBI challenging due to the varying extent of the UMN damage causing spasticity affecting many muscles and joints, trunk, limbs, head and neck leading to complex physical disabilities and often coexisting cognitive and behavioural impairments. These confounding factors can impact on spasticity management as people with TBI may have a lower tolerance for treatments, as well as an inability to monitor or participate in the learning and practice required for rehabilitation. Consideration for a greater research base to be developed in this area is extremely important.

There are varying levels of evidence for the management of spasticity in other neurological populations (Ade-Hall 2000; Amatya 2013; Duarte 2016; Demetrios 2013; Lindsay 2013; RCP 2009; Shakespeare 2003; Taricco 2000). There is an assumption made that the effects of pharmacological and non-pharmacological interventions in other conditions (e.g. multiple sclerosis, stroke) are the same for TBI. While at an impairment level the outcome may potentially be comparable, there can be a difference at a functional level. There is little evidence for the effect of these interventions at a functional level (Francis 2004).

Quality of the evidence

The quality of the evidence for all outcomes was very low due to risk of bias concerns (a combination of poor reporting and poor conduct), indirectness related to mixed populations or the outcome measures used (or both), imprecision and the likelihood of publication/reporting biases in this area. We did not formally downgrade the quality of the evidence for the analysis approach taken in studies that measured spasticity (where all the authors treated the ordinal scales as continuous) given the lack of consensus about how best to analyse these data, but this may introduce a further flaw in the interpretation.

Potential biases in the review process

The decision to limit inclusion of studies with a mixed clinical population to those with greater than 50% of participants with TBI had a major impact on the number of included studies in the review. Had we reduced or removed the threshold, we could have increased the number of included studies by a further 27. Had we increased the threshold to 100% (similar to the approach taken in one TBI trial overview (Bragge 2016)) we would have reduced the number of included studies to three. As such, the level of the threshold used in the review may have affected the results and conclusions. This threshold was set during the screening stages of the review (i.e. before extraction of results data) and was determined using clinical judgement.

Agreements and disagreements with other studies or reviews

As far as we are aware, this is the only systematic review evaluating any intervention for skeletal muscle spasticity, specifically in people with TBI. Three non-Cochrane systematic reviews of RCTs have each investigated the efficacy of botulinum toxin A for spasticity (due to TBI and other causes) in the upper limbs (Dong 2017), lower limbs (Dashtipour 2016), and upper and lower limbs (Baker 2015). Each review included a majority of studies in people with stroke, but all included some studies with mixed stroke and TBI populations. Dashtipour 2016 was the only review to include any study (Gracies 2015) that was common to our review. These reviews concluded that there was favourable evidence to support the use of botulinum toxin A in the upper limb (both Baker 2015 and Dong 2017 found improvements in global benefit or "ease of care" measures) and either an absence of evidence (Baker 2015) or 'the beginnings of an evidence base' showing spasticity reductions (Dashtipour 2016) in the lower limb. Given the included studies in each of these reviews included predominantly people with stroke, we would question the applicability of these results to people with TBI. One other non-Cochrane systematic review looked at the use of casting in people with brain injury, the majority of whom had TBI (Mortenson 2003). Only five out of the 13 included studies measured spasticity as an outcome and reported improvement to some extent following casting. However, it was noted by the author that the quality of this evidence was low and that none of these studies used a true randomised design.

There are several Cochrane Reviews that investigated a broader range of treatments for spasticity in other conditions such as stroke (Demetrios 2013), multiple sclerosis (Amatya 2013; Shakespeare 2003), amyotrophic lateral sclerosis/motor neuron disease (Ashworth 2012), cerebral palsy (Ade-Hall 2000; Hoare 2010), and spinal cord injury (Taricco 2000). Interventions ranged from multidisciplinary rehabilitation following botulinum toxin A (and other intramuscular treatment), pharmacological (e.g. botulinum toxin A, baclofen, tizanidine) and non-pharmacological interventions (e.g. physical activity), or a combination of interventions. It is notable that with the exception of one review (Hoare 2010), all reviews reported low or insufficient evidence for any of these interventions as a result of heterogeneity, high risk of bias and lack of information. Hoare 2010 found strong evidence to support botulinum toxin A as an adjunct to occupational therapy in managing upper limb spasticity in children with cerebral palsy.

AUTHORS' CONCLUSIONS

Implications for practice

This review identified a number of studies in which the authors evaluated the effectiveness of spasticity treatment in traumatic brain injury (TBI); however, there is insufficient evidence from clinical trials to guide clinical practice.

Implications for research

There is an urgent need for more high quality, adequately powered trials in this area; the lack of TBI participants in studies is of great concern. In addition, there is a need for further evaluation of the assessment tools to ensure that the outcomes for people with TBI and spasticity are reliable. Any future studies should include specific functional measures which focus on goal attainment for individual patients.

Data need to be made available from studies which remain unpublished.

Outcome assessment of spasticity treatment is complicated. Two assessment scales measuring the impairment caused by spasticity are generally used; the Modified Ashworth Scale (Pandyan 1999) and the Modified Tardieu Scale (Haugh 2006). Four studies included within this review used the (Modified) Ashworth Scale. This scale is considered to measure resistance to passive movement not spasticity, as it does not evaluate a muscle's response to movement at speed (Allison 1995; Pandyan 2005). Spasticity is an indication of abnormal neural mechanisms causing a velocity-dependent increase in tonic stretch reflexes (Lance 1980). Therefore, by this definition, it will only be seen when a muscle is moved at speed. Where spasticity may be present in a muscle, the muscle may have altered mechanical properties that have developed over time causing a resistance to passive movement. It is these properties which can affect the quantification of spasticity by the Modified Ashworth Scale (Morris 2002). In comparison, the Modified Tardieu Scale (Haugh 2006; Mehrholz 2005), used by two studies included within this review (Gracies 2015; Leung 2014), is considered by many to be more appropriate measure with similar characteristics as the Modified Ashworth Scale; however, the scale requires that movement be carried out at two different speeds recording a 'catch angle.' It is this component of the scale that is more appropriate for measuring spasticity (Haugh 2006; Morris 2002). However, it is also notable that there are reliability issues with both measures; the Modified Tardieu Scale has very good test-retest reliability, but both have reduced inter-rater reliability (Fleuren 2010; Haugh 2006; Mehrholz 2005; Morris 2002).

Any spasticity intervention needs to address specific functional limitations for a person such as drinking from a glass or fastening a button (Francis 2004; Mayer 2008; Parke 1989; Pierson 1996). An individualised goal directed functional assessment combined with an impairment assessment is recommended to evaluate the effect of an intervention for people with a TBI. Global measures of function are only valid where global treatments such as baclofen are used. It is important that specific measures are identified for specific functional deficits so that any intervention can be assessed by the functional gains made by a person. Potential harms also need to be considered for treatments with proven effectiveness. Spasticity interventions can be costly and painful for a person. Spasticity can be blamed for weakness, contracture and loss of function, and if not clearly identified interventions for spasticity can be used inappropriately, causing further discomfort for no measurable benefit, and a waste of time and money. With respect to impairments such as pain and broken skin, impairment measures alone can indicate an effective outcome.

It has been acknowledged that spasticity intervention should occur within the context of a rehabilitation team, and little evidence exists to demonstrate how or where this should occur (Demetrios 2013; Giovannelli 2007; Olver 2010; RCP 2009). It is recommended that "botox injection must be part of a rehabilitation program involving post-injection exercise, muscle stretch and/or splinting to achieve an optimal clinical effect" (RCP 2009, p.vii). The implementation of 'botox' clinics which have a multidisciplinary approach to allow for assessment, treatment and review can mirror some of the rehabilitation processes that occur in a rehabilitation programme. However, when people have returned to living in the community these processes may not occur so effectively due to lack of access or funding. It is not only the complexity of TBI with its associated behaviours and cognitive issues that complicate managing this population, but also where a person lives, their access to services and the type of support they have available to live their life.

A moderate to severe TBI can lead to long-term disability impacting on ADL and quality of life. Impairments such as spasticity can reduce independence, and cause pain and dysfunction in a person's life. It is important to identify interventions for this population which will maximise the functional gains required for a person with TBI to achieve their goals. We need to assess these outcomes utilising reliable and valid assessment scales and this needs to occur within management programmes which have structure and support for clinicians and people with TBI alike.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Gracies 2015

Methods	Randomised controlled trial (3 arms). Setting: 34 neurology or rehabilitation clinics in 9 countries (Belgium, Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia, USA). Funding: Ipsen (pharmaceutical company).
Participants	Total participants: 243 overall study, including 23 with TBI (65% male), for whom results were presented separately. Number of participants in each study arm: 9 (placebo), 8 (abobotulinumtoxinA 500 U) and 6 (abobotulinumtoxinA 1000 U). Adults: 23, children: 0. People with TBI: mean age 35 years (SD 13, range not reported). Inclusion criteria: • aged 18-80 years; • hemiparesis for at least 6 months post TBI (or stroke); • Modified Ashworth Scale score in the target muscle group ≥ 2 (if never had botulinum toxin injection) or ≥ 3 (if had botulinum toxin A injection before); • Disability Assessment Scale score ≥ 2 on the principal target of treatment; • spasticity angle of least 10° in the primary target muscle group and • mean Modified Frenchay Score of 1-8 (out of possible 10). Exclusion criteria: • major limitations of passive range of motion in the paretic limb; • intrathecal baclofen or physiotherapy initiated < 4 weeks prior to expected enrolment; • anticipated botulinum toxin A treatment during study period;

Gracies 2015 *(Continued)*

- administration of any alcohol or phenol in the study limb any time before the study;
- previous primary or secondary non-response to any botulinum toxin for the targeted condition;
- previous surgery to treat spasticity of the affected upper limb;
- any medical disorder increasing the risk of adverse events from botulinum toxin A administration;
- major additional neurological impairment that could affect functional performance;
- known disease of the neuromuscular junction;
- known sensitivity to botulinum toxin or any excipient of Dysport;
- infection at the injection site(s);
- any current or planned treatment that interferes with neuromuscular function;
- pregnant or women not willing to use contraception.

Location of spasticity:

- upper limb: elbow flexors, wrist flexors, finger flexors.

For each participant, the investigators selected the most hypertonic muscle group (defined by Modified Ashworth Scale score) out of elbow flexors, wrist flexors and finger flexors, and gave an additional injection to 2 other muscle groups (including these groups + shoulder extensors).

Interventions	AbobotulinumtoxinA 500 U: 2 vials (1 of placebo and 1 of abobotulinumtoxinA 500 U) were each diluted with 2.5 mL saline and combined into a single injection of 5 mL solution. This was injected into target muscle group and at least 2 other muscle groups (guided by electrical stimulation to identify the correct location). AbobotulinumtoxinA 1000 U: same as above (except 2 vials of active compound were used). Placebo: same as above (except 2 vials of placebo were used).
Outcomes	Outcome assessed at: baseline, and 1, 4 and 12 weeks. Primary outcomes: • spasticity/muscle tone: Tardieu Scale (at 4 weeks); • safety assessments (adverse events). Secondary outcomes: • upper limb function using the Disability Assessment Scale (4-point scale); • quality of life (subscores of the SF-36 and the EQ-5D). Length of follow-up: 12 weeks.
Notes	The full study (Gracies 2015) included more than just participants with TBI, but the results for participants with TBI were presented separately in the conference abstract by (O'Dell 2015). However, these results did not distinguish between different dosages and reported results as if for a 2-armed trial (abobotulinumtoxinA 550 U and abobotulinumtoxinA 1000 U vs placebo). This study also measured spasticity using the Modified Ashworth Scale, but we reported Tardieu Scale results given we prespecified this as our preferred measure. The authors also used the Physician Global Assessment scale for assessing the 'severity' of a condition. Given this is not a brain injury or rehabilitation-specific measure, neither is it clear which functional domain this outcome fitted within, this outcome was not included in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomly allocated in a ratio of 1:1:1.... Computer-generated randomisation lists were created by a sponsor statistician independent from the study..." Furthermore, "randomisation was stratified by botulinum-toxin-A treatment status at baseline only... irrespective of the centre of recruitment

Gracies 2015 *(Continued)*

		or of the cause of spastic paresis.... no rationale exists for stratification of patients by cause [stroke and traumatic brain injury]."
Allocation concealment (selection bias)	Low risk	"Computer-generated randomisation lists were created by a sponsor statistician independent from the study and treatment numbers were assigned when patients entered the study with a 24-h interactive response system from an external contract research organisation..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"A double-dummy technique was used to maintain masking of patients and investigators. A treatment pack contained two vials of abobotulinumtoxinA 500 U (1000 U group), one vial of abobotulinumtoxinA 500 U plus one vial of placebo (500 U group), or two vials of placebo (placebo group). The [treatment] packs were identical in appearance and the procedure for reconstitution in each group was identical."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The [treatment] packs were identical in appearance and the procedure for reconstitution in each group was identical."
Incomplete outcome data (attrition bias)	Low risk	In the main study (of which the TBI participants formed a subgroup of < 10%, i.e. 23 of 243 participants) reported that > 94% of those randomised completed the study to 12-week follow-up and that those lost were relatively evenly spread between groups. Reasons for discontinuation were provided, and ITT methods for missing data appeared appropriate. In the subgroup reported in a conference abstract, it would appear that all participants with TBI were retained within the study.
Selective reporting (reporting bias)	Unclear risk	Study protocol was registered on clinicaltrials.gov (NCT01313299). Outcome data reported appeared in line with those prospectively stated; however, for the TBI subset of participants included in this review, outcome data for different doses of the active intervention were conflated and results were given in the form of percentages only.
Baseline Imbalances	Unclear risk	Baseline characteristics were described as "similar" between the 3 groups, but no specific reference was made to the those in the TBI subgroup, wherein the differences in years since traumatic event were larger than for those with stroke. It is reported that "a majority" (74%) of the TBI group had previously received botulinum toxin treatment, but it was not reported whether this differed between intervention groups and placebo.
Appropriate study design (cross-over trial only)	Low risk	Not relevant, not a cross-over trial.
Adequate washout period (cross-over trial only)	Low risk	Not relevant, not a cross-over trial.
Other bias	Unclear risk	Authors reported that both the "funder and the corresponding author were jointly involved in the study design, data gathering, data management, and statistical analysis. With the exception of the four authors (FC, BBDF, CV, and PP) who were employees of the funder, the funder had no role in the interpretation of the data or in the decision to submit the manuscript for publication. The funder funded editorial assistance provided during the writing of the manuscript. All authors had full access to all the data in the study and final responsibility for the decision to submit the paper for publication."

Leung 2014

Methods	Randomised controlled trial. Setting: Sydney, Australia (Royal Rehabilitation Centre, Liverpool and Westmead Hospitals). Funding: Royal Rehabilitation Centre, Sydney and University of Sydney.
Participants	Total participants: 36. Number of participants in each study arm: intervention group 18, control group 18. Adults 36, children 0. People with TBI: 36, mean age: intervention 38 years (SD 14); control 38 years (SD 15). Inclusion criteria: • first TBI; • FIM Walking domain ≤ 4; • ankle contracture; • ability to participate in assessment and intervention; • no unstable medical conditions or ankle fracture; • no other neurological condition; • hospital stay > 6 weeks; • no botox injection to ankle joint in past 3 months. Exclusion criteria: not reported. Location of spasticity: gastrocnemius.
Interventions	Intervention: 30 minutes of tilt table standing with electrical stimulation to the ankle dorsiflexors 5 times a week, with 12 hours of ankle splinting a day, at least 5 days a week (total duration of intervention programme: 6 weeks). Control: tilt table standing for 30 minutes, 3 times a week (total duration of control programme: 6 weeks).
Outcomes	Outcome assessed at: baseline, and weeks 6 and 10 (follow-up). Primary outcomes: • passive ankle dorsiflexion measured at 12 Nm. Secondary outcomes: • passive dorsiflexion measured 3, 5, 7, 9 Nm; • FIM Walking domain; • walking speed; • spasticity (ankle plantarflexor muscle spasticity was rated based on reaction to passive stretch at high speed (not angle of catch) using the 5-point Tardieu Scale); • physiotherapist and participant global perceived effect of treatment and treatment credibility. Length of follow-up: 10 weeks.
Notes	Contacted author (J Leung) in April 2017 to confirm whether participants had spasticity, given spasticity was measured at baseline and as an outcome measure, but this was not mentioned as an inclusion criteria. The author confirmed that 35/36 participants had spasticity during the study, which we decided was sufficient to meet the inclusion criteria for this review. We selected the study's primary outcome of passive dorsiflexion (measured at 12 Nm of torque) as the measure to include under our review outcome, Neuromusculoskeletal and movement-related func-

Leung 2014 *(Continued)*

tions. The other dorsiflexion measures were not included in the review to avoid selective outcome reporting.

Similarly, we selected walking speed over the FIM Walking domain as the most appropriate measure of mobility in the review. The FIM Walking domain was not included.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"All participants were randomly allocated to one of two groups using a blocked randomisation schedule" and "The random allocation sequence was computer-generated."
Allocation concealment (selection bias)	Low risk	"The random allocation sequence was computer-generated by a person not involved in participant recruitment. Group allocation was concealed using consecutively numbered, sealed, opaque envelopes, which were kept off-site."
Blinding of participants and personnel (performance bias) All outcomes	High risk	"Assessors and medical staff were blinded to group allocation, but treating physiotherapists and participants were not."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The outcomes were measured by one of the five blinded and trained assessors who assessed participants of both groups" and "The blinding of the assessors was reasonably successful. Assessors were unblinded in two of the end-of-intervention assessments and one of the follow-up assessments. In two of these assessments, a third person, who was otherwise not involved in the study, was asked to take the readings from the dynamometer for the passive ankle range." While the blinding was broken in some assessments, all the outcomes included in this review were observer-reported/objective.
Incomplete outcome data (attrition bias)	Unclear risk	Participants lost to follow-up by week 10 (end of trial): 1/18 (6%) in intervention group, and 3/18 (17%) in control group. Reasons provided, and were unrelated to the trial. Authors reported conducting an ITT analysis, without imputing data. Given imbalance in loss to follow-up, and relatively large percentage in 1 group, rated as unclear.
Selective reporting (reporting bias)	Low risk	Protocol available, all planned outcomes reported.
Baseline Imbalances	Unclear risk	1/36 participants did not have spasticity during the study (unclear whether they belonged to intervention or control group) and the median time from injury to baseline assessment was longer in the intervention group (140 days) compared to control group (83 days).
Appropriate study design (cross-over trial only)	Low risk	Not relevant, not a cross-over trial.
Adequate washout period (cross-over trial only)	Low risk	Not relevant, not a cross-over trial.
Other bias	Unclear risk	The number of tilt table sessions was markedly different in the intervention group (30 sessions) compared to the control group (18 sessions).

Meythaler 1996

Methods	Randomised cross-over trial comparing bolus intrathecal baclofen and placebo. Setting: university tertiary care outpatient rehabilitation clinic. Funding: grant R49/CCR403641 from the US Department of Health and Human Services, Centers for Disease Control and Prevention - National Center for Injury Prevention and Control to the University of Alabama-Birmingham Injury Control Research Center.
Participants	Total participants 11 including 10 participants with TBI (90% male). Adults: 11, children: 0. People with TBI: mean age 24.0 years (SD 4.5, range 20-34). Inclusion criteria: • aged 18-65 years; • diagnosis of severe chronic spastic hypertonia in the lower extremities (although the upper extremities could also be involved) of at least 1 year' duration that was defined by a mean Ashworth Scale of ≥ 3 or a mean spasm score of ≥ 2, failure to respond satisfactorily to treatment with oral antispastic medications (including baclofen at 80-160 mg/day, and possibly diazepam, clonidine, dantrolene sodium, or a combination) or occurrence of unacceptable adverse effects at effective treatment dosages. Exclusion criteria: • pregnant or failure to use an adequate contraception (if not menopausal); • history of hypersensitivity to baclofen; • severely impaired renal function; • severe hepatic disease; • severe gastrointestinal disease. Location of spasticity: Upper limb: shoulder abduction, elbow extensions, elbow flexion and wrist extensions. Lower limb: hip abduction, hip flexion, knee flexion and ankle dorsiflexion. The authors did not report if the participants had bilateral or unilateral symptoms.
Interventions	Baclofen: intrathecal administration (Lioresal Intrathecal) supplied in single-use ampoules (10 mg/20 mL ampoules; 500 µg/mL) and diluted with preservative-free 0.9% normal saline to obtain a concentration of 50 µg/1 mL. All participants received baclofen 50 µg. A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 mL was injected. Placebo: preservative-free normal saline. Cross-over phase in administering the opposite treatment occurred at least 48 hours after the initial administration.
Outcomes	Outcome assessed at: baseline, and 1, 2, 4 and 6 hours. Primary outcomes: • spasticity: Ashworth Scale, Spasm score; • adverse effect: complications or adverse effects were noted. Secondary outcomes: • deep tendon reflexes. Length of follow-up: not reported.

Meythaler 1996 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to receive..." Insufficient information to determine whether adequate random sequence generation.
Allocation concealment (selection bias)	Unclear risk	Insufficient information to determine whether adequate allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patient nor the investigator know which substance was injected."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Before cross-over: "Neither the patient nor the investigator know which substance was injected. Data for the Ashworth scale, spasm score, deep tendon reflexes were then collected as described previously 1,2,4 and 6 hours post injection by the same investigator." After cross-over, "Again neither the patient nor the investigator knew which substance had been injected."
Incomplete outcome data (attrition bias)	Low risk	All outcome data presented for all participants.
Selective reporting (reporting bias)	Unclear risk	Reported all expected outcomes but no protocol referenced.
Baseline Imbalances	Low risk	Baseline data provided.
Appropriate study design (cross-over trial only)	Low risk	A cross-over study design was reasonable due to a small sample size.
Adequate washout period (cross-over trial only)	Low risk	"The crossover phase of the study occurred during a second outpatient clinic visit at least 48 hours after the initial administration." Appropriate washout period for baclofen.
Other bias	Low risk	No other bias noted.

Meythaler 1997

Methods	Randomised double-blind placebo controlled cross-over trial, initial stage of trial prior to baclofen pump insertion. Setting: outpatient rehabilitation clinic that was part of a single tertiary care university medical centre (10 participants) and inpatients from the same university medical centre (2 participants). Funding: Medtronic, Inc.
Participants	Total participants 12 including 9 participants with TBI (92% male). Adults: 12, children: 0, age range 17-39 years, mean 28 years. Inclusion criteria: • aged 10-75 years;

Meythaler 1997 *(Continued)*

	• diagnosis of severe chronic spastic hypertonia in lower extremities (although upper extremities could also be involved) of ≥ 6 months' duration that was defined by a mean Ashworth Scale score of ≥ 3 in the affected extremities (≥ 2 extremities) or a mean spasm score of ≥ 2 in the affected extremities; • did not respond satisfactorily to treatment with oral antispasmodic medications (including baclofen and possibly diazepam, clonidine, dantrolene sodium, or a combination of these); • experienced unacceptable adverse effects at effective treatment dosages of these drugs. Exclusion criteria: none reported. Location of spasticity: Lower extremities, upper extremities could be included, > 2 extremities affected.
Interventions	Baclofen: continuous intrathecal infusion of baclofen 50 µg. A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 mL bolus was injected. Participants also received intensive inpatient rehabilitation to benefit from the decreased motor tone or increased voluntary motor control (or both) they experience with the intrathecal baclofen. Placebo: preservative-free normal saline. Cross-over occurred during a second outpatient clinic at least 48 hours after the initial administration.
Outcomes	Outcomes assessed at 1, 2, 4 and 6 hours post injection. Primary outcome: • Ashworth Scale, spasm frequency, deep tendon reflexes; • adverse effects: not reported; stated "no untoward effects." Secondary outcomes: not reported. Length of follow-up: not reported.
Notes	No data for randomised component, prior to pump insertion. Author contacted and was attempting to locate the data; however, no further information received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reported as randomised but method not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patient nor the investigator knew which substance was injected until after the second trial phase was completed."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	While the authors reported that the 'investigator' was blinded, it was unclear if this investigator assessed outcomes.
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up (follow-up data for all 12 participants reported).
Selective reporting (reporting bias)	Unclear risk	Protocol not reported.

Meythaler 1997 *(Continued)*

Baseline Imbalances	Low risk	Baseline imbalances unclear but not relevant for a cross-over trial.
Appropriate study design (cross-over trial only)	Low risk	A cross-over study design was reasonable due to a small sample size.
Adequate washout period (cross-over trial only)	Low risk	"The crossover phase of the study occurred during a second outpatient clinic visit at least 48 hours after the initial administration." Appropriate washout period for baclofen.
Other bias	High risk	Unit of analysis issue. The outcomes were analysed by looking at upper vs lower extremities. "Rather than consider each muscle separately, scores for muscle tone, spasms, and reflexes were averaged for the upper or lower extremities in each patient."

Meythaler 1999a

Methods	Single-centre, randomised, double-blind, placebo-controlled cross-over trial. Setting: spasticity clinic in a tertiary care university-based outpatient physical medicine and rehabilitation clinic. Funding: Medtronic Inc.
Participants	Total participants 6 including 3 participants with TBI (60% male). Adults 6, children 0. Inclusion criteria: • aged 14-75 years; • diagnosis of severe chronic spastic hypertonia in lower limbs (although upper limbs could also be involved) for at least a 6-month duration that was defined by a mean Ashworth score ≥ 3 in the affected limbs (≥ 1 limbs) or a mean spasm score ≥ 2 in the affected limb; • either failure to respond satisfactorily to treatment with oral antispasticity medications (including baclofen and possibly diazepam, clonidine, dantrolene sodium, or a combination of these) or the occurrence of unacceptable adverse effects at effective treatment dosages. Exclusion criteria: not reported. Location of spasticity: lower extremities, upper extremities could be included, > 2 extremities affected.
Interventions	Baclofen: continuous intrathecal infusion of baclofen 50 µg. A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 mL was injected. Participants also received intensive inpatient rehabilitation to benefit from the decreased motor tone or increased voluntary motor control (or both) they experience with the intrathecal baclofen. Placebo: preservative-free normal saline. Cross-over occurred during a second outpatient clinic at least 48 hours after the initial administration.
Outcomes	Outcomes assessed at 1, 2, 4 and 6 hours' post injection. Primary outcome: • Ashworth Scale, spasm frequency, deep tendon reflexes; • adverse effects: not identified; stated "no untoward effects. Secondary outcomes: not reported.

Meythaler 1999a *(Continued)*

	Length of follow-up: not reported.
Notes	No data for randomised component, prior to pump insertion. Author contacted and was attempting to locate the data; however, no further information received.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reported as randomised but method not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patient nor the investigator knew which substance was injected until after the second trial phase was completed."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	While the authors reported that the 'investigator' was blinded, it was unclear if this investigator assessed outcomes.
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up (follow-up data for all 6 participants reported).
Selective reporting (reporting bias)	High risk	Protocol not published but authors reported they collected data at 2 time points but only 1 time point published.
Baseline Imbalances	Low risk	Baseline imbalances unclear but not relevant for a cross-over trial.
Appropriate study design (cross-over trial only)	Low risk	A cross-over study design was reasonable due to a small sample size.
Adequate washout period (cross-over trial only)	Low risk	"The crossover phase of the study occurred during a second outpatient clinic visit at least 48 hours after the initial administration." Appropriate washout period for baclofen.
Other bias	High risk	Unit of analysis issue. The outcomes were analysed by looking at upper vs lower extremities. "Rather than consider each muscle separately, scores for muscle tone, spasms, and reflexes were averaged for the upper or lower extremities in each patient."

Meythaler 1999b

Methods	Randomised, double-blind, placebo-controlled cross-over trial. Setting: outpatient rehabilitation clinic, tertiary care university medical centre. Funding: Medtronic, Inc.
Participants	Total participants: 17, all 17 participants with TBI (82% male). Adults: not reported, children: not reported; age range: 10-55 years. Inclusion criteria:

Meythaler 1999b *(Continued)*

- aged 14-75 years;
- diagnosis of severe chronic spastic hypertonia in the lower limbs (although the upper limbs could also be involved) for ≥ 6 months that was defined by a mean Ashworth score ≥ 3 in the affected limbs (≥ 1 limbs) or a mean spasm score ≥ 2 in the affected limb;
- either failure to respond satisfactorily to treatment with oral antispasticity medications (including baclofen and possibly diazepam, clonidine, dantrolene sodium, or a combination of these) or the occurrence of unacceptable adverse effects at effective treatment dosages.

Exclusion criteria: not reported.

Location of spasticity: lower extremities, upper extremities could be included, > 2 extremities affected.

Interventions	Baclofen: continuous intrathecal infusion of baclofen 50 µg. A lumbar puncture was performed at either the L3-L4 or the L2-L3 interspace, and 1 mL was injected. Participants also received intensive inpatient rehabilitation to benefit from the decreased motor tone or increased voluntary motor control (or both) they experience with the intrathecal baclofen. After implantation of the infusion device, all participants received intrathecal baclofen 100 µg/day continuously. Placebo: preservative-free normal saline. Cross-over occurred during a second outpatient clinic at least 48 hours after the initial administration.
Outcomes	Outcomes assessed at 1, 2, 4 and 6 hours post injection, 1, 3, 6, 9 months post pump placement. Primary outcome: • Ashworth Scale, spasm frequency, deep tendon reflexes; • adverse effects: not identified; stated "no untoward effects." Secondary outcomes: not reported. Length of follow-up: 1 year.
Notes	No data for randomised component, prior to pump insertion. Author contacted and was attempting to locate the data; however, no further information received. "Postoperatively all patients in this study received 24 to 36 hours of intravenous vancomycin and gentamicin for prophylaxis of infection." Inclusion criteria stated minimum age of 14 years, yet at least some participants as young as 10 years.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reported as randomised but method not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither the patient nor the investigator knew which substance was injected until after the second trial phase was completed."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	While the authors report that the 'investigator' was blinded, it was unclear if this investigator assessed outcomes.

Meythaler 1999b *(Continued)*

Incomplete outcome data (attrition bias)	Low risk	Outcome data for all participants reported.
Selective reporting (reporting bias)	Unclear risk	No published protocol.
Baseline Imbalances	Low risk	Baseline imbalances not clear but not relevant for a cross-over trial.
Appropriate study design (cross-over trial only)	Low risk	A cross-over study design was reasonable due to a small sample size.
Adequate washout period (cross-over trial only)	Unclear risk	Washout period not stated.
Other bias	High risk	Unit of analysis issue. Outcomes were analysed by looking at upper vs lower extremities. "Rather than consider each muscle separately, scores for muscle tone, spasms, and reflexes were averaged for the upper or lower extremities in each patient."

NCT00287157

Methods	Randomised, double-blind, cross-over trial (no information provided about randomisation method): Phase 1 study. Setting: not reported; assumed Jerusalem, Israel. Funding: Teva GTC.
Participants	Inclusion criteria: • children aged 8-18 years with TBI who had spasticity "that interferes with task performance;" • documented loss of consciousness for > 24 hours or initial GCS < 8; • able to co-operate and understand general explanations. Exclusion criteria: • history of allergy to tizanidine or any inactive component (including lactose intolerance); • use of other hypnotic medication within 3 days of baseline visit and during study; • botulinum toxin A therapy within 6 weeks of baseline, or use of baclofen pump during trial; • use of CYP1A2 inhibitors (e.g. ciprofloxacin or fluvoxamine) for duration of study; • girls taking oral contraceptives; • significant abnormalities in clinical screening laboratory parameters (alanine transaminase, aspartate aminotransferase, bilirubin > 2 x upper limit of normal; creatinine > 2 mg/dL; white blood cell count < 2300/mm^3, platelets < 80,000/mm^3); • taking other medications that may have adversely interfered with actions of study medication or outcome variables within 2 weeks or 5 half-lives of the baseline visit Location of spasticity: not reported.
Interventions	Intervention: tizanidine hydrochloride (administered sublingually). Comparison: placebo.
Outcomes	Primary outcomes: • improvement in spasticity, cognition and daily function at 4 weeks.

NCT00287157 *(Continued)*

	Secondary outcomes: • improvement in night-time sleep parameters as measured by actigraphy at 4 weeks.
Notes	Communication with authors: this was a pilot conducted in the Alyn Rehabilitation Hospital in Jerusalem. They reported the pilot yielded negative results, was not continued and that none of the results were published.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment method not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study described as "double blind" but whether both participants and personnel were blinded was unclear.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study described as "double blind" but whether outcome assessors were blinded was unclear.
Incomplete outcome data (attrition bias)	Unclear risk	Withdrawals and loss to follow-up not described.
Selective reporting (reporting bias)	High risk	Trial data "negative" as reported by authors, and no available data; unpublished.
Baseline Imbalances	Unclear risk	No information about participant demographics.
Appropriate study design (cross-over trial only)	Unclear risk	Not reported.
Adequate washout period (cross-over trial only)	Unclear risk	Not reported.
Other bias	Unclear risk	Inadequate information to make a judgement.

Pittaccio 2013

Methods	Randomised cross-over trial. Setting: Italy (at the Istituro Eugenio Media). Funding: Fondazione Cariplo (Philanthropic organisation).
Participants	Total participants: 25 overall study, including 16 with TBI (72% male in overall study). Overall participants (TBI not reported separately): age: 7.75 years (SD 5.40, range 4-19). However, the review author team calculated this (using the individual participant ages provided in the paper and, which resulted in a mean age of 9.08 years (SD 5.38)).

Pittaccio 2013 *(Continued)*

	Adults: 0, children: 16. Inclusion criteria: • acquired quadriplegia or hemiplegia; • aged 4-18 years; • Ashworth Score for the target limb > 1. Exclusion criteria: • pathologies of the target joint or skin affections in the target area. Location of spasticity: upper limb: elbow (flexors); lower limb: ankle (extensors).
Interventions	Pseudoelastic orthosis: spring-loaded orthosis comprised of 2 parts that could rotate relative to one another around a common axis. Each orthosis was individually customised and worn for 1 month. Traditional static splint: no further details provided about the splint, other than it was worn for 1 month. Washout period: no washout period as study authors considered it unethical to leave participants without any treatment.
Outcomes	Outcome assessed at: baseline, and 1 (at cross-over) and 2 months (end of second treatment). Unclear which were primary and secondary outcomes • range of motion; • spasticity: Modified Ashworth Scale. Length of follow-up: 2 months.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No detail on method of randomisation reported.
Allocation concealment (selection bias)	Unclear risk	No details on method of allocation concealment (if any).
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding within this study was impossible due to the nature of the 2 active treatments (traditional splints appear very different to the experimental 'pseudoelastic' ones).
Blinding of outcome assessment (detection bias) All outcomes	High risk	See above. In addition, no attempts to blind outcome assessors or data analysts to the treatment status of participants was reported.
Incomplete outcome data (attrition bias)	Low risk	Appeared that all participants completed treatment as intended and that there were no missing data.

Pittaccio 2013 *(Continued)*

Selective reporting (reporting bias)	High risk	No published protocol. Furthermore, there was a pronounced tendency in the paper to report perceived benefits in detail (e.g. data regarding rigidity outcomes for ankles in particular) whilst few details and no numerical data were provided for results wherein no difference between treated groups was apparent (e.g. for spasticity as measured by the Modified Ashworth Scale) despite these being collected after both treatment phases as well as at baseline. Whilst this does not indicate 'suppression' of data, it obviates meta-analyses (should comparable trials be identified).
Baseline Imbalances	Low risk	Baseline imbalances not clear but not relevant for a cross-over trial.
Appropriate study design (cross-over trial only)	Low risk	A cross-over study design was reasonable due to a small sample size.
Adequate washout period (cross-over trial only)	Low risk	Investigators considered it unethical to have a washout period; investigators also went to lengths to confirm that the sequential order of treatments did not make any difference to the final outcome (p = 0.30, T2-T0, TP vs PT, paired 2-tailed Student's t test, 23 participants).
Other bias	Unclear risk	Although the inclusion criteria stated that participants had to be aged 4-18 years and have a score > 1 on the Modified Ashworth Scale, 1 participant was 19 years of age and had a score of 0.

Verplancke 2005

Methods	Randomised controlled trial. Setting: acute general hospital in the UK. Funding: Allergan Inc. and 3M Health Care Ltd.
Participants	Total participants: 35, 71% male, including 20 participants with TBI. Adults: 35, children 0. Serial casting + botulinum toxin A 200 U: total 12 participants, median age 41.5 years; TBI 6 participants. Serial casting + placebo (saline): total 12 participants, median age 33.5 years; TBI 6 participants. Control (physiotherapy): total 11 participants, median age 40 years; TBI 8 participants. Inclusion criteria: • participants were screened twice weekly for 4 weeks and their passive range of ankle dorsiflexion was measured in a supine position by a goniometer attached to a multi-myometer and pressure strain gauge device (MIE Medical Research, Leeds, UK) at a force of 65 N and by the same person, who documented the higher of 2 joint range measurements; • unable to achieve 3 degrees of passive ankle dorsiflexion at 65 N of force. Exclusion criteria: • pregnant; • history of deep vein thrombosis within the previous 12 months; • severe lower limb injury or lower limb fracture; • previous exposure to continuous muscle relaxants; • hypersensitivity to botulinum toxin; • received botulinum toxin injections within the previous 3 months.

Verplancke 2005 *(Continued)*

	Location of spasticity: lower limb: gastrocnemius and soleus. The authors did not report if the participants had bilateral or unilateral symptoms.
Interventions	Physiotherapy (control): standard programme of physiotherapy, as currently practiced in the neurosciences unit, but were not supplied with sheepskin bootees. Casting and placebo: lower leg casting plus injections with saline into gastrocnemius and soleus muscles, those in casting and placebo were injected with 0.5 mL 0.9% normal saline into each of 4 standard points into gastrocnemius and soleus muscles, giving a total of 4 mL. They were additionally placed in a bespoke 'combicast' made up of Soft Cast and Scotchcast Plus (supplied by 3M Health Care Ltd, Loughborough, UK), which held the lower leg and foot in a neutral plantargrade position, but still allowed soft tissue functioning within the rest of the limb. Casting and botulinum toxin A: lower leg casting + injections with botulinum toxin A into gastrocnemius and soleus muscles. These participants were placed in casts in the same way as for casting and placebo participants, but were additionally given an injection of botulinum toxin A 200 U (Allergan Pharmaceuticals Inc., Irvine, CA, USA) per leg, equally divided into gastrocnemius and soleus muscles. Each 100-U vial of botulinum toxin A was diluted.
Outcomes	Outcome assessed at: baseline and 12 weeks. Primary outcomes: • spasticity: Modified Ashworth Scale; • adverse effect: not listed as an outcome measure, but was reported in the results section. Secondary outcomes: • range of movement (ankle); • Glasgow Outcome Scale; • Glasgow Coma Scale. Length of follow-up: not reported.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were enrolled in a strict numeric order, but the treatments were randomised in groups of three (i.e., block randomisation in groups of three)."
Allocation concealment (selection bias)	Unclear risk	No Information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	"This ensured that blinding of the active (casting +/- botulinum toxin A) treatments still occurred and that recruitment produced an even spread of patients within the groups. Blinding the assessor was not possible for control (physiotherapy) patients, as they were not cast. Those treating patients were also blinded." The authors attempted to blind the personnel; however, this was impossible due to some participants not receiving a cast.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The observer was blinded between the active groups, but the absence of a cast in control patients may have biased the findings. This is actually unlikely, as the primary outcome measure was a quantifiable number at a given force

Verplancke 2005 *(Continued)*

		and previous data were not available to the assessor for comparison until all the measurements were carried out."
Incomplete outcome data (attrition bias)	Unclear risk	4 participants were withdrawn from the study but it was not reported which groups they from. However, the final measure used in these participants was the 1 taken prior to their exclusion. "In order to prevent fixed contracture formation, patients were withdrawn from the study if they became unable to dorsiflex to > -10 degrees. At the time it was considered unethical to continue without using botulinum toxin A and/or casting, and rescue treatment was administered (botulinum toxin injections for groups controls and cast and saline and normal saline injections for cast and botulinum toxin patients). As the assessor continued to be blinded to treatment after rescue treatment was administered, assessment of patients' spasticity continued, but the final measurement prior to exclusion was used for statistical analysis."
Selective reporting (reporting bias)	High risk	All outcomes were reported but no published protocol. No baseline data for the primary outcome (ankle dorsiflexion). No between-group comparisons for the secondary outcomes.
Baseline Imbalances	Unclear risk	"...patients in the three groups were sufficiently uniform in their characteristics;" however, the authors later stated that, "The patients in all the groups were similar in most respects, but control patients had the smallest range of dorsiflexion at entry and exit."
Appropriate study design (cross-over trial only)	Low risk	Not relevant, not a cross-over trial.
Adequate washout period (cross-over trial only)	Low risk	Not relevant, not a cross-over trial.
Other bias	Low risk	No concerns noted.

EQ-5D: EuroQol; FIM: Functional Independence Measure; ITT: intention to treat; SD: standard deviation; SF-36: 36-item Short Form; TBI: traumatic brain injury.

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

Study	Reason for exclusion
Armstrong 1997	Number of TBI participants < 50% threshold. Total 19 participants, TBI 2 participants.
Ashby 1972	Number of TBI participants < 50% threshold. Total 15 participants, TBI 4 participants.
Baricich 2008	All participants had had a stroke.
Barnes 2010	Number of TBI participants < 50% threshold. Total 192 participants, TBI 11 participants.
Basmajian 1973	All participants had multiple sclerosis, spinal cord injury, dermoid cyst or meningioma.
Basmajian 1974	All participants had multiple sclerosis, spinal cord injury, demyelinating spinal cord disease or congenital quadriplegia.
Bensmail 2010	Control group not affected by spasticity and there was no randomisation.

Study	Reason for exclusion
Bes 1988	No valid measure for spasticity
Bovend'Eerdt 2009	Unable to identify if brain injured participants were due to trauma
Boyd 2001	All participants had cerebral palsy.
Burbaud 1996	Number of TBI participants < 50% threshold. Total 23 participants, TBI 4 participants.
Burke 1975	Number of TBI participants < 50% threshold. Total 9 participants, TBI 2 participants.
Chang 2009	Number of TBI participants < 50% threshold. Total 14 participants, TBI 3 participants.
Childers 1996	Number of TBI participants < 50% threshold. Total 17 participants, TBI 2 participants.
Cocchiarella 1967	All participants had cerebrovascular accident, cervical spondylosis or demyelinating disease.
Cohan 1980	All participants had multiple sclerosis, infarction of the anterior thoracic spinal cord, degeneration of the spinal cord, cerebral palsy, amyotrophic lateral sclerosis or cervical spondylosis.
Copley 2013	Number of TBI participants < 50% threshold. Total 10 participants, TBI 2 participants.
Corry 1998	All participants had cerebral palsy.
Fazekas 2007	Number of TBI participants < 50% threshold. Total 30 participants, TBI 8 participants.
Fietzek 2014	Number of TBI participants < 50% threshold. Total 52 participants, TBI 6 participants.
Francisco 2002	Number of TBI participants < 50% threshold. Total 13 participants, TBI 3 participants.
Gracies 2009	Number of TBI participants < 50% threshold. Total 21 participants, TBI 6 participants.
Grazko 1995	Number of TBI participants < 50% threshold. Total 20 participants, TBI 1 participants.
Guo 2006	Number of TBI participants < 50% threshold. Total 60 participants, TBI 17 participants.
Harvey 1974	No information could be obtained to clarify if any participants had a TBI.
Harvey 2006	Number of TBI participants < 50% threshold. Total 44 participants, TBI 7 participants.
Hill 1994	No valid measure for spasticity.
Imle 1986	No control/placebo comparison group.
Krewer 2014	Number of TBI participants < 50% threshold. Total 66 participants, TBI 3 participants.
Lannin 2003	Number of TBI participants < 50% threshold. Total 28 participants, TBI 2 participants.
Leung 2012	Majority of participants had stroke, not TBI.
Levine 1969	All participants had multiple sclerosis.
Levine 1977	All participants had multiple sclerosis or spinal cord injury.
Mancini 2005	All participants had stroke.

Study	Reason for exclusion
Martin 2014	Not an RCT (a systematic review).
Mayer 2008	Compared botulinum toxin A injection technique; motor point vs quadrant.
McPherson 1982	No valid measure for spasticity.
Meythaler 2001b	Number of TBI participants < 50% threshold. Total 17 participants, TBI 8 participants.
Middel 1997	All participants had multiple sclerosis or spinal cord injury.
Moseley 1997	Spasticity not an outcome measure.
Moseley 2008	Did not report whether the participants had spasticity.
Nakhostin 2009	Number of TBI participants < 50% threshold. Total 21 participants, TBI 1 participants.
NCT00776048	Observational study.
NCT00900666	Included < 50% people with TBI.
Pagano 1990	All participants had multiple sclerosis, myelopathy, cerebrovascular accident or perinatal encephalopathy.
Penn 1988	It is unclear if the study included people with TBI, but would appear that it solely included people with spinal cord injury or multiple sclerosis.
Richardson 2000	Unable to identify if the 12 brain-injured participants had experiences trauma.
Roussan 1985	All participants had multiple sclerosis, traumatic paraplegia or transverse myelopathy.
Sahuquillo 2000	Participants with cerebral vasospasms.
Simpson 1996	Participants had stroke.
Simpson 2009	Number of TBI participants < 50% threshold. Total 60 participants, TBI 11 participants.
Smith 2000	Number of TBI participants < 50% threshold. Total 21 participants, TBI 2 participants.
Snow 1990	All participants had multiple sclerosis.
Suputtitada 2005	All participants had stroke.
Thibaut 2015	Number of TBI participants < 50% threshold. Total 17 participants, TBI 7 participants.
Van Schaeybroeck 2000	Number of TBI participants < 50% threshold. Total 1 participant, TBI 1 participant.
Yelnik 2007	All participants had stroke.
Zhao 2015	Number of TBI participants < 50% threshold. Total 60 participants, TBI 1 participant.

RCT: randomised controlled trial; TBI: traumatic brain injury.

Characteristics of studies awaiting assessment *[ordered by study ID]*

2009-015868-34

Methods	Randomised controlled trial (completed). Setting: European sites (multiple), Russia, US. Funding: Ipsen Pharma SAS.
Participants	348 people with hemiparesis with lower limb spasticity due to stroke or TBI (unclear what percentage had a TBI).
Interventions	Intervention: Dysport (abobotulinumtoxinA) intramuscular injection 500 U/mL. Comparator: placebo (no further information provided).
Outcomes	Outcome assessed at: baseline, 4 weeks Primary outcomes: • spasticity (Modified Ashworth Scale) change from baseline in the gastrocnemius-soleus complex muscle tone (knee extended). Secondary outcomes: • mean Physician's Global Assessment Score; • mean change from baseline in comfortable barefoot walking speed without walking aids.
Notes	Results are unpublished and it states on the clinical trials registry site: "Results removed from public view." Contacted study sponsor in April 2017 seeking further information about results for participants with TBI but no further information received.

EUCTR2011-005375-16-SE

Methods	Randomised controlled trial (completed). Setting: Norway, Sweden, Denmark, Finland. Funding: Institut Produits Synthèse (IPSEN) AB.
Participants	88 participants, with upper limb spasticity due to stroke or TBI (unclear what percentage had a TBI).
Interventions	Intervention: low-concentration dilution (100 U/mL) Dysport (abobotulinumtoxinA) injected via the neuromuscular junction targeted technique. Comparison: high-concentration dilution (300 U/mL) Dysport (abobotulinumtoxinA) injected via "current clinical practice technique."
Outcomes	Outcomes measured as change from baseline at 4 and 12 weeks post-treatment. Primary outcomes: • spasticity (Modified Ashworth Scale); • adverse events. Secondary outcomes: • pain (spasticity related pain measured by visual analogue scale); • Global Attainment Scale.

EUCTR2011-005375-16-SE *(Continued)*

Notes	Results available on the EU Clinical Trials Register site but the results for people with TBI are not presented separately, and it is unclear what percentage of participants had a brain injury. The authors reported that "Due to slow recruitment rate it was clear that the study would not be completed in a reasonable time frame, therefore the study was stopped early." Contacted study sponsor in April 2017 but no further information received.

Gracies 2016

Methods	3-arm randomised controlled trial (completed). Setting: US, Australia, Belgium, Czech Republic, France, Hungary, Italy, Poland, Portugal, Russian Federation, Slovakia. Funding: Ipsen.
Participants	388 participants with stroke or TBI with lower limb spasticity. While the number of participants with TBI was not reported, a poster presented on the results of the follow-up open-label study (see Notes) reported 43/352 participants with TBI.
Interventions	Intervention: abobotulinumtoxinA 1000 U, 1 cycle. Intervention: abobotulinumtoxinA 1500 U, 1 cycle. Control: "placebo", 1 cycle.
Outcomes	Outcomes measured at 4 weeks. Primary outcomes: • spasticity in gastrocnemius/soleus muscles (Modified Ashworth Scale); • adverse event.
Notes	Found a protocol (see reference list) and a poster on ResearchGate, which describes the results for the follow-up open-label study. While the number of participants with TBI would appear to be below 50% the authors may subsequently publish, or be able to provide, the data for participants with TBI only.

IRCT2014041112777N

Methods	Randomised controlled trial (complete). Setting: Iran. Funding: Ahvaz Jundishapur University of Medical Sciences
Participants	40 participants with diffuse axonal injury without chronic hepatic or renal disease; aged 15-60 years.
Interventions	Intervention: oral cyproheptadine 2 mg/kg with oral baclofen 25 mg/kg every 8 hours for 15 days. Comparison: oral baclofen 25 mg/kg every 8 hours for 15 days.
Outcomes	Primary outcome: • spasticity (Modified Ashworth Scale) at days 1, 3, 6, 9, 12 and 15.

IRCT2014041112777N *(Continued)*

Notes	The clinical trial entry stated that, "patients will be randomly allocated into two groups according to table of random numbers" and that the trial is complete (recruitment was expected to end in December 2014). We found a published paper by the same investigators (Rasras 2014) also treating spasticity in people with TBI with considerable overlap (i.e. identical inclusion criteria) but with somewhat different interventions (baclofen, cyproheptadine + baclofen, baclofen + tizanidine + baclofen, and cyproheptadine + tizanidine). We noted that the randomisation procedure in this trial did not appear to be truly random. It was described as follows: "the first to third patients were randomly placed in the first to third groups. The next patients were distributed successfully within the groups with respect to their registration in the ward. This was continued until the sample size reached the required number." We contacted the trialists in August 2017 to clarify if the protocol and published paper were the same study but received no reply.

NCT02052024

Methods	Randomised controlled trial (complete; final data collection August 2015). Setting: US. Funding: Georgetown University (Solstice Neurosciences, a pharmaceutical company, listed as a collaborator).
Participants	People aged ≥ 18 years with spasticity due to a disorder or trauma (e.g. spinal cord injury, brain injury, tumour, stroke, multiple sclerosis or peripheral nerve injury).
Interventions	Intervention: botulinum toxin A (Botox), 100 U per injection, 1-3 injections per muscle at each visit. Comparator: botulinum toxin B (Myobloc), 5000 U per injection, 1-3 injections per muscle at each visit. Number of visits per week not reported but treatment administered for 36 weeks.
Outcomes	Primary outcomes: • adverse events (muscle atrophy, measured by volume and cross-sectional area of muscle) at 36 weeks; • spasticity (Modified Ashworth Scale), measured before, during and after treatment at every visit, up to 36 weeks.
Notes	We are unable to find any published results for this trial. As such, it was unclear what percentage of participants had TBI, or whether the results for this group is (or could be) presented separately.

TBI: traumatic brain injury.

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

ACTRN12615000821594

Trial name or title	Effectiveness of Combining Serial Casting and Botulinum Toxin for the Management of Ankle Contractures after Traumatic Brain Injury: a Randomised Controlled Study.
Methods	Randomised controlled trial (2 arms, with cross-over). Setting: Brain Injury Unit, Sydney, Australia. Funding: Royal Rehab Foundation (charitable).
Participants	Total participants: 10 (anticipated).

ACTRN12615000821594 *(Continued)*

	Age range: 18-85 years. Inclusion criteria: • diagnosed with first TBI; • presents with an ankle contracture of a severe degree; • able to receive botulinum toxin injections and serial casting; • unlikely to be discharged in 12 weeks; and • provides consent to participate in the study (the participants or the person legally responsible for them). Exclusion criteria: • unstable medical conditions or recent ankle fracture; • within 3 months after receiving botulinum toxin; • severe ankle varus or knee/hip flexion contractures (which affects the reliability of measuring ankle dorsiflexion). Location of spasticity: Calf muscles/ankle. Specific muscles that may be treated include soleus, gastrocnemius, flexor hallucis longer and flexor digitorium longus and tibialis posterior where necessary.
Interventions	Botulinum toxin and serial casting: ≥ 1 botulinum toxin injections into calf muscles (dose dependent on number of muscles needing injection, but not in excess of 400 mL). Serial casting with be commenced within a few days (duration of casting and number of cast applied may vary based on the participants' responses to casting), After completion of casting, a customised ankle splint will be used immediately. The splint will be worn 24 hours a day for the initial 2 weeks during which the splint will only be removed for hygiene reasons and therapy. Participants will receive usual care as well (see usual care). Usual care: placed on a wait list for 6 weeks during which they receive no botulinum toxin, splinting and passive stretch-based interventions for the ankle. Usual care includes multidisciplinary rehabilitation provided by the unit as appropriate. This consisted of physiotherapy, occupational therapy, speech therapy, recreational therapy and psychological therapy. Physiotherapy included an individualised motor training programme which might involve lower limb exercises, practice of sit to stand, standing and walking. Also involves positioning of participants' feet in dorsiflexion while seated and lying.
Outcomes	Primary outcome: • Passive dorsiflexion range at a standardised torque, measured within 3 days after completion of serial casting. Secondary outcomes: • Spasticity of ankle plantarflexors (Tardieu Scale score and Modified Ashworth Scale score), measured within 3 days after completion of serial casting; • FIM Walking score and 10-m walk test, measured within 3 days after completion of serial casting; • therapist questionnaire (perceived effectiveness, adverse events and treatment worth), designed specifically for study.
Starting date	1 July 2015 (date of first participant enrolment).
Contact information	Dr Joan Wai King Leung, Brain Injury Unit, Royal Rehab, Ryde, NSW. Email: joan.leung@royalrehab.com.au.
Notes	Anticipated end date (as per clinical trials entry last updated in 13 July 2016): 1 September 2018. Note that spasticity is not an inclusion criterion, but as per the other study by this investigator (Leung 2014), spasticity is being measured at baseline, and is an outcome. In future updates, the re-

ACTRN12615000821594 *(Continued)*	view author team will contact the lead investigator to determine how many of the participants had spasticity at baseline to therefore confirm it meets the inclusion criteria for the review.

FIM: Functional Independence Measure; TBI: traumatic brain injury.

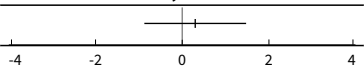
DATA AND ANALYSES

Comparison 1. Casting plus botulinum toxin A versus casting plus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spasticity at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Casting plus botulinum toxin A versus casting plus placebo, Outcome 1 Spasticity at 12 weeks.

Study or subgroup	Casting + botox		Casting + placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Verplancke 2005	12	1.3 (1.6)	12	1 (1.3)		0.3[-0.87,1.47]



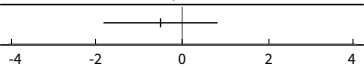
Favours casting + botox — Favours casting + placebo

Comparison 2. Casting plus botulinum toxin A versus physiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spasticity at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Casting plus botulinum toxin A versus physiotherapy, Outcome 1 Spasticity at 12 weeks.

Study or subgroup	Casting + botox		Physiotherapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Verplancke 2005	12	1.3 (1.6)	11	1.8 (1.6)		-0.5[-1.82,0.82]



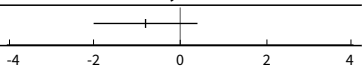
Favours casting + botox — Favours physiotherapy

Comparison 3. Casting plus placebo versus physiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spasticity at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Casting plus placebo versus physiotherapy, Outcome 1 Spasticity at 12 weeks.

Study or subgroup	Casting + placebo		Physiotherapy		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Verplancke 2005	12	1 (1.3)	11	1.8 (1.6)		-0.8[-2,0.4]



Comparison 4. Tilt table plus electrical stimulation plus splint versus tilt table

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Spasticity	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Passive ankle dorsiflexion	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3 Walking speed	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 4.1. Comparison 4 Tilt table plus electrical stimulation plus splint versus tilt table, Outcome 1 Spasticity.

Study or subgroup	Tilt table 'plus'		Tilt table		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Leung 2014	17	2 (1)	18	3 (1)		-1[-1.66,-0.34]
Leung 2014	17	3 (1)	15	2 (1)		1[0.31,1.69]

Analysis 4.2. Comparison 4 Tilt table plus electrical stimulation plus splint versus tilt table, Outcome 2 Passive ankle dorsiflexion.

Study or subgroup	Tilt table 'plus'		Title table		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Leung 2014	16	-2 (5)	15	-3 (7)		0%	1[-3.31,5.31]
Leung 2014	16	-5 (6)	17	-3 (9)		0%	-2[-7.19,3.19]

Analysis 4.3. Comparison 4 Tilt table plus electrical stimulation plus splint versus tilt table, Outcome 3 Walking speed.

Study or subgroup	Tilt table 'plus'		Tilt table		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Leung 2014	17	0.3 (0.5)	18	0.4 (0.5)		0%	-0.1[-0.43,0.23]
Leung 2014	17	0.4 (0.6)	15	0.4 (0.5)		0%	0[-0.38,0.38]

ADDITIONAL TABLES

Table 1. Excluded studies with less than 50% of participants with traumatic brain injury

Author (year)	n total	n TBI	% TBI	Intervention	Comparator	%TBI Intervention	%TBI comparator
Botulinum toxin A vs placebo							
NCT00900666	19	7	37	Botulinum toxin A	Placebo	NR	NR
Burbaud 1996	23	4	17	Botulinum toxin A	Placebo	NR	NR
Fietzek 2014	52	6	12	Botulinum toxin A	Placebo	12	12
Grazko 1995	20	1	5	Botulinum toxin A	Placebo	Cross-over trial	-
Simpson 2009	60	11	18	Botulinum toxin A	Tizanidine or placebo	15	14 and 26 placebo
Smith 2000	21	2	10	Botulinum toxin A	Placebo	10	16
Botulinum toxin A vs therapy							
Guo 2006	60	17	28	Botulinum toxin A with rehab	Rehab only	26	30
Botulinum toxin A vs botulinum toxin A (dosage)							
Gracies 2009	21	6	29	High dilution botulinum toxin A with endplate target	Low dilution botulinum toxin A with end plate target	NR	NR
Botulinum toxin A vs botulinum toxin A (volume)							
Francisco 2002	13	3	23	High volume botulinum toxin A	Low volume botulinum toxin A	16	28
Barnes 2010	192	11	6	High volume botulinum toxin A	Low volume botulinum toxin A	5	6
Botulinum toxin A vs botulinum toxin A (location)							

Table 1. Excluded studies with less than 50% of participants with traumatic brain injury *(Continued)*

Childers 1996	17	2	12	Botulinum toxin A injections towards mid belly	Botulinum toxin A injections away from mid belly	0	25
Gracies 2009	21	6	29	High dilution botulinum toxin A with endplate target	Low dilution botulinum toxin A with end plate target	NR	NR
Baclofen vs placebo							
Armstrong 1997	19	2	11	Intrathecal dose of baclofen	Saline	16	0
Van Schaeybroeck 2000	11	1	9	Intrathecal baclofen	Placebo	16	0
Cyclobenzaprine vs placebo							
Ashby 1972	15	4	27	Cyclobenzaprine	Placebo	Cross-over trial	-
Phenothiazine vs placebo							
Burke 1975	9	2	22	Phenothiazine	Placebo	Cross-over trial	-
Tizanidine vs placebo							
Meythaler 2001b	17	8	47	Tizanidine	Placebo	Cross-over trial	-
Tizanidine vs botulinum toxin A							
Simpson 2009	60	11	18	Botulinum toxin A	Tizanidine or placebo	15	14 and 26 placebo
Tizanidine vs diazepam							
Bes 1988	105	16	15	Tizanidine	Diazepam	10	20
Casting vs control							
Harvey 2006	44	7	16	Splint	No splint	13	21

Table 1. Excluded studies with less than 50% of participants with traumatic brain injury *(Continued)*

Casting vs therapy							
Harvey 2006	44	7	16	Splint	No splint	13	21
Splinting vs control							
Copley 2013	10	2	20	Individualised hand splint	No splint	33	0
Lannin 2003	28	2	7	Stretching and hand splint	Stretching only	NR	NR
Thibaut 2015	17	7	41	Soft splints	No treatment	NR	NR
Splinting vs therapy							
Lannin 2003	28	2	7	Stretching and hand splint	Stretching only	NR	NR
Thibaut 2015	17	7	41	Soft splints	Stretching	NR	NR
Functional electrical stimulation vs control							
Chang 2009	14	3	21	Upper limb botulinum toxin A injections for higher hand function	Upper limb botulinum toxin A injections for lower hand function	33	0
Electrical stimulation + splinting vs splinting							
Leung 2012	36	5	14	Electrical stimulation to the wrist and finger extensor muscles for 1 hour a day + wrist splint for 12 hours a day, over 4 weeks	Wrist splint for 12 hours a day, over 4 weeks	6	22
Repetitive peripheral magnetic stimulation vs sham							
Krewer 2014	66	3	5	Repetitive peripheral magnetic stimulation	Sham stimulation	10	0
Transcutaneous electrical acupoint stimulation vs another dose							
Zhao 2015	60	1	2	Transcutaneous electrical acupoint stimulation (100 Hz)	Transcutaneous electrical acupoint stimulation (2 Hz)	0	5

Table 1. Excluded studies with less than 50% of participants with traumatic brain injury *(Continued)*

Transcutaneous electrical acupoint stimulation vs sham							
Zhao 2015	60	1	2	Transcutaneous electrical acupoint stimulation (100 Hz)	Sham stimulation	0	0
Ultrasound vs infrared							
Nakhostin 2009	21	1	5	Infrared	Therapeutic ultrasound	NR	NR
Robot vs bobath							
Fazekas 2007	30	8	27	Robot-mediated therapy with bobath therapy	Bobath therapy	13	40

n: number of participants; NR: not reported; TBI: traumatic brain injury.
Some studies are listed in the table twice, given their multiple comparisons.

Table 2. Primary outcome measures

Outcome measure	Domains with score	Studies referring to this outcome	Time point analysis
Ashworth Scale (0-4, lower score = better; Pandyan 1999)	0: no increase in muscle tone. 1: slight increase in muscle tone, manifested by a catch and release or by minimum resistance through remainder of range of motion 2: more marked increase in muscle tone through most of the range of motion; limb easily moved. 3: considerable increase in muscle tone; passive movement is difficult. 4: rigid limb.	Meythaler 1996;	Baseline, and 1, 2, 4, 6 hours
		Pittaccio 2013	Baseline, and 4, 8 weeks
Modified Ashworth Scale (0-5, lower score = better; Pandyan 1999)	0: no increase in muscle tone. 1: slight increase in muscle tone, manifested by a catch and release or is moved in flexion, extension/abduction, adduction, etc. 1+: slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of motion. 2: More marked increase in muscle tone through most of the range of motion, but the affected part is easily moved. 3: considerable increase in muscle tone, passive movement is difficult. 4: affected part is rigid flexion or extension/abduction or adduction.	Verplancke 2005	Baseline, 12 weeks
		Gracies 2015	Baseline, 4 weeks
Tardieu Scale (TS; 2 measurements: Quality of Muscle Reaction 0-4, lower score better, and Angle of muscle reaction, R2 - R1; Haugh 2006)	Quality of muscle reaction 0: no resistance throughout the course of the passive movement. 1: slight resistance throughout the course of the passive movement, with no clear catch at precise angle. 2: clear catch at precise angle, interrupting the passive movement, followed by release. 3: fatigable clonus (< 10 seconds when maintaining pressure) occurring at precise angle. 4: infatigable clonus (> 10 seconds when maintaining pressure) occurring at precise angle. Angle of muscle reaction (also referred to as R2 - R1) Measured relative to the position of minimal stretch of the muscle (corresponding to angle) where it is relative to the resting anatomic position. R2: first measure (the maximum passive range of movement of the muscle group).	Gracies 2015	Baseline, 4 weeks
		Leung 2014	Baseline, and 6 and 10 weeks

Table 2. Primary outcome measures *(Continued)*

	R1: second measure (the angle at which the initial 'catch' or muscle resistance is felt when the muscle is moved from its shortest to longest position using a 'rapid velocity stretch').

Table 3. Secondary outcome measures

Outcome measure	Domains with score	Studies referring to this outcome	ICF classification
Glasgow Coma Scale (Teasdale 1974) (3-15, higher score = better)	Eye opening (E) 4: spontaneous 3: to voice 2: to pain 1: none Verbal response (V) 5: normal conversation 4: disoriented conversation 3: words, but not coherent 2: no words, only sounds 1: none Motor response (M) 6: normal 5: localised to pain 4: withdraws to pain 3: decorticate posture (an abnormal posture that can include rigidity, clenched fists, legs held straight out, and arms bent inward towards the body with the wrists and fingers bend and held on the chest) 2: decerebrate (an abnormal posture that can include rigidity, arms and legs held straight out, toes pointed downward, head and neck arched backwards) 1: none The final GCS score or grade is the sum of these numbers. Severe: GCS 3-8 (minimum possible score is 3) Moderate: GCS 9-12 Mild: GCS 13-15	Verplancke 2005	b. Body functions b1-b8
Glasgow Outcome Scale (Jennett 1975)	To generalise and categorise the outcomes of people with TBI. 1: dead	Verplancke 2005	Body function b1-b8

Table 3. Secondary outcome measures *(Continued)*

(1-5, higher score = better)	2: vegetative state (meaning the person is unresponsive, but alive; a "vegetable" in lay language) 3: severely disabled (conscious but the person requires others for daily support due to disability) 4: moderately disabled (the person is independent but disabled) 5: good recovery (the person has resumed most normal activities but may have minor residual problems)		
Range of movement	The joint is taken through the total arc of movement from flexion to extension	Verplancke 2005 (ankle)	Body function b7
Deep tendon reflexes	0: reflexes absent 1: hyporeflexia 2: normal 3: mild hyperreflexia 4: 3 or 4 beats clonus only 5: clonus	Meythaler 1996	Body function b750
Disability Assessment Scale (DAS; Brashear 2002; 0-3, lower score better)	People are interviewed to determine the extent of functional impairment in: hygiene, dressing, limb position and pain, according to the following scale: 0: no disability 1: mild disability (noticeable but does not interfere significantly with normal activities) 2: moderate disability (normal activities require increased effort or assistance, or both) 3: severe disability (normal activities limited)	Gracies 2015	Activities and participation

ICF: International Classification of Functioning.

Table 4. Adverse effects

Adverse effect	Number of participants affected	Studies
Deep vein thrombosis	1 participants withdrawn from physiotherapy group.	Verplancke 2005
Contracture at subtalar joint	1 participants withdrawn from the casting + placebo group.	Verplancke 2005
No adverse events or changes in alertness level were observed in the baclofen group or placebo arm	Not applicable.	Meythaler 1996
Unspecified "treatment emergent AE [adverse ef-	7/23 participants, no other information given.	Gracies 2015 (O'Dell 2015)

Table 4. Adverse effects *(Continued)*

fects]": "none were unexpected"		
Skin rashes/oedema/tolerability issues	No pseudoelastic device required adjustment for comfort; 30% of traditional devices did. Families reported novel treatment tolerated for 40% longer than traditional (Pittaccio 2013). 2 participants adherence to splinting was affected by 'skin problems' and 'poor tolerance' (Leung 2014). 50% of participants in casting group and 41.7% of participants in casting + botulinum toxin A group developed 'minor skin damage'. Overall, 90% of those resolved spontaneously or with therapeutic dressing (Verplancke 2005).	Leung 2014; Pittaccio 2013; Verplancke 2005
Fainting, fatigue, storming[1]	Several participants' adherence to the tilt table was affected due to fainting, fatigue and storming.	Leung 2014

[1]When someone with a head injury responds to a sensation with a tonic posture or sympathetic response.

APPENDICES

Appendix 1. 2016 Search strategies

Cochrane Injuries Group Specialised Register
(spastic* or spasm*) or ((muscle* or muscular) and (spasm* or cramp* or clonus or hypertoni* or overact*))

MEDLINE (OvidSP)

1. exp Brain Injuries/
2. exp Craniocerebral Trauma/
3. exp Brain Edema/
4. exp Glasgow Coma Scale/
5. exp Glasgow Outcome Scale/
6. exp Unconsciousness/
7. exp Cerebrovascular Trauma/
8. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fractur* or contusion* or concus* or commotion* or pressur*)).ti,ab. (108776)
9. ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
10. (Glasgow adj3 scale).ti,ab.
11. "rancho los amigos scale".ti,ab.
12. ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
13. "persistent vegetative state".ti,ab.
14. ((unconscious* or coma* or concuss*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
15. or/1-14
16. Muscle Spasticity/
17. Spasm/
18. Muscle Hypertonia/
19. (spastic* or spasm*).ti,ab.
20. ((muscle* or muscular) adj3 (spasm* or cramp* or clonus or hypertoni* or overact*)).ti,ab.
21.16 or 17 or 18 or 19 or 20
22. randomised controlled trial.pt.
23. controlled clinical trial.pt.
24. randomized.ab.
25. placebo.ab.

26. drug therapy.fs.
27. randomly.ab.
28. trial.ab.
29. groups.ab.
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. exp animals/ not humans.sh.
32. 30 not 31
33. 15 and 21 and 32

Embase Classic + Embase (OvidSP)

1. exp Brain Injuries/
2. exp Brain Edema/
3. exp Craniocerebral Trauma/
4. exp Glasgow Coma Scale/
5. exp Glasgow Outcome Scale/
6. exp Unconsciousness/
7. exp Cerebrovascular Trauma/
8. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fractur* or contusion* or concus* or commotion* or pressur*)).ti,ab.
9. ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
10. (Glasgow adj3 scale).ti,ab.
11. "rancho los amigos scale".ti,ab.
12. ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
13. "persistent vegetative state".ti,ab.
14. ((unconscious* or coma* or concuss*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
15. 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 or 14
16. exp Muscle Spasticity/
17. exp Spasm/
18. exp Muscle Hypertonia/
19. (spastic* or spasm*).ti,ab.
20. ((muscle* or muscular) adj3 (spasm* or cramp* or clonus or hypertoni* or overact*)).ti,ab.
21. 16 or 17 or 18 or 19 or 20
22. 15 and 21
23. exp Randomized Controlled Trial/
24. exp controlled clinical trial/
25. exp controlled study/
26. comparative study/
27. randomi?ed.ab,ti.
28. placebo.ab.
29. *Clinical Trial/
30. exp major clinical study/
31. randomly.ab.
32. (trial or study).ti.
33. 23 or 24 or 25 or 27 or 28 or 29 or 30 or 31 or 32
34. exp animal/ not (exp human/ and exp animal/)
35. 33 not 34
36. 22 and 35

Appendix 2. 2017 prepublication search strategies

Cochrane Injuries Group Specialised Register (SR-INJ) (all years to 22-June-2017)
(spastic* or spasm*) or ((muscle* or muscular) and (cramp* or
clonus or contractur* or hypertoni* or overact*)) [all fields] IN REGISTER

Ovid MEDLINE Databases
(Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to 22-June-2017)
1. exp Brain Injuries/
2. exp Craniocerebral Trauma/
3. exp Brain Edema/
4. exp Glasgow Coma Scale/

5. exp Glasgow Outcome Scale/
6. exp Unconsciousness/
7. exp Cerebrovascular Trauma/
8. ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or inter-cran*) adj3 (injur* or trauma* or lesion* or damag* or wound* or destruction* or oedema* or edema* or fractur* or contusion* or concus* or commotion* or pressur*)).ti,ab. (108776)
9. ((head or crani* or cerebr* or brain* or intra-cran* or inter-cran*) adj3 (haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
10. (Glasgow adj3 scale).ti,ab.
11. "rancho los amigos scale".ti,ab.
12. ("diffuse axonal injury" or "diffuse axonal injuries").ti,ab.
13. "persistent vegetative state".ti,ab.
14. ((unconscious* or coma* or concuss*) adj3 (injur* or trauma* or damag* or wound* or fracture* or contusion* or haematoma* or hematoma* or haemorrhag* or hemorrhag* or bleed* or pressure)).ti,ab.
15. or/1-14
16. Muscle Spasticity/
17. Spasm/
18. Muscle Hypertonia/
19. (spastic* or spasm*).ti,ab.
20. ((muscle* or muscular) adj3 (spasm* or cramp* or clonus or hypertoni* or overact*)).ti,ab.
21.16 or 17 or 18 or 19 or 20
22. randomized controlled trial.pt.
23. controlled clinical trial.pt.
24. (RCT or randomised or randomized).ab.
25. placebo.ab.
26. drug therapy.fs.
27. randomly.ab.
28. trial.ti,ab.
29. groups.ab.
30. 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29
31. exp animals/ not humans.sh.
32. 30 not 31
33. 15 and 21 and 32

The Cochrane Library, Central Register of Controlled Trials (CENTRAL), Issue 6, June 2017
#1 MeSH descriptor: [Brain Injuries] explode all trees
#2 MeSH descriptor: [Brain Damage, Chronic] explode all trees
#3 MeSH descriptor: [Head Injuries, Closed] explode all trees
#4 (TBI or mTBI or sTBI):ti,ab,kw (Word variations have been searched)
#5 "diffuse axonal injury":ti,ab,kw (Word variations have been searched)
#6 ((head or brain or cerebr* or crani*) near (injur* or trauma*)):ti,ab,kw (Word variations have been searched)
#7 (#1 or #2 or #3 or #4 or #5 or #6)
#8 MeSH descriptor: [Muscle Hypertonia] explode all trees
#9 spastic* or spasm*:ti,ab,kw (Word variations have been searched)
#10 ((muscle* or muscular) near (spasm* or cramp* or clonus or contractur* or hypertoni* or overact*)):ti,ab,kw (Word variations have been searched)
#11 (#8 or #9 or #10)
#12 (#7 and #11)
#13 ((cerebral palsy or stroke or post stroke) not ((head or brain) and (injur* or trauma*))):ti (Word variations have been searched)
#14 (#12 not #13)

NLM PubMed (22 June 2017)
Precision maximising search: ((randomised[tiab] OR randomized[tiab] OR placebo[tiab] OR trial[ti] OR randomized controlled trial[pt]) AND ("Craniocerebral Trauma"[Mesh] OR TBI OR mTBI OR sTBI OR "brain injury" OR "brain injuries" OR "traumatic brain" OR "brain trauma") AND ("Muscle Spasticity"[MeSH] OR spastic[tiab] OR spasticity[tiab]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))

Ovid Embase <1974 to 2017 Week 25>
1 randomized controlled trial/
2 controlled clinical trial/
3 randomi#ed.ti,ab,kw.
4 randomization/

5 placebo.ti,ab,kw.
6 placebo/
7 *Clinical Trial/
8 ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask* or dummy)).ti,ab,kw.
9 double blind procedure/
10 (RCT or at random or (random* adj (assign* or allocat* or divid* or division or number))).ti,ab,kw.
11 trial.ti.
12 or/1-11
13 ((animal or nonhuman) not (human and (animal or nonhuman))).de.
14 12 not 13
15 head injury/
16 exp brain injury/
17 exp brain injury assessment/
18 ((head or crani* or cerebr* or capitis or brain* or forebrain* or skull* or hemispher* or intra-cran* or intracran* or intra-cereb* or intracereb*) adj3 (infarct* or injur* or trauma* or damag* or wound* or fracture* or contusion*)).ab,ti,kw.
19 (Glasgow adj3 (coma or outcome) adj3 (scale* or score*)).ab,ti,kw.
20 diffuse axonal injur*.ti,ab,kw.
21 ((midbrain or mid brain) adj syndrome).ti,ab,kw.
22 (TBI or mTBI or sTBI).ti,ab,kw.
23 or/15-22
24 muscle hypertonia/ or spastic paraplegia/ or spastic paresis/ or spasticity/
25 spasmolysis/
26 (spastic* or spasm*).ti,ab.
27 ((muscle* or muscular) adj3 (spasm* or cramp* or clonus or contractur* or hypertoni* or overact*)).ti,ab.
28 muscle contracture/ or muscle spasm/
29 or/24-28
30 14 and 23 and 29
31 remove duplicates from 30

Web of Science (WoS)
Indexes=SCI-EXPANDED, CPCI-S, ESCI Timespan=All years to 22-June-2017
Search 1. (TS=("head injur*" or "head trauma" or "brain injur*" or "brain trauma" or "traumatic brain" or TBI or mTBI or sTBI or "traumatic head" or "cerebr* injur*" or "cerebr* trauma*" or "crani* injur*" or "crani* trauma*") AND TS=(spastic*)) AND (TS=(RCT or randomized or randomised or "at random" or placebo) or TS=(random* same (allocat* or assign* or divi* or number)) OR TI=(efficacy or effectiveness))

Search 2 (22-June-2017), citation search. References in WoS citing included studies identified to July 2016. WoS records were downloaded into EndNote and filtered for RCTs by searching for: ((*RCT or randomised or randomized or randomly or placebo or double-blind) [all fields] or trial[title field]*)

Clinical Trial Registers
ClinicalTrials.gov
Basic search 1: (spastic OR spasticity OR spasm OR spasms OR contracture OR contractures OR muscle hypertonia | Interventional Studies | TBI OR sTBI OR mTBI or "brain injury" OR "brain injuries" OR "head injury" OR "head injuries" OR "traumatic brain" OR "brain trauma") OR Basic search 2: (Ipsen AND spasticity)
Trials for cerebral palsy or stroke patients (only) will be manually removed.

WHO International Clinical Trials Registry Platform (ICTRP)
Basic search: TBI AND spastic OR TBI AND spasticity OR TBI AND spasm OR TBI AND spasms OR TBI AND contracture OR TBI AND contractures OR TBI AND muscle hypertonia OR mTBI AND spastic OR mTBI AND spasticity OR mTBI AND spasm OR mTBI AND spasms OR mTBI AND contracture OR mTBI AND contractures OR mTBI AND muscle hypertonia OR sTBI AND spastic OR sTBI AND spasticity OR sTBI AND spasm OR sTBI AND spasms OR sTBI AND contracture OR sTBI AND contractures OR sTBI AND muscle hypertonia OR brain injury AND spastic OR brain injury AND spasticity OR brain injury AND spasm OR brain injury AND spasms OR brain injury AND contracture OR brain injury AND contractures OR brain injury AND muscle hypertonia OR
brain injuries AND spastic OR brain injuries AND spasticity OR brain injuries AND spasm OR brain injuries AND spasms OR brain injuries AND contracture OR brain injuries AND contractures OR brain injuries AND muscle hypertonia OR head injury AND spastic OR head injury AND spasticity OR head injury AND spasm OR head injury AND spasms OR head injury AND contracture OR head injury AND contractures OR head injury AND muscle hypertonia OR head injuries AND spastic OR head injuries AND spasticity OR head injuries AND spasm OR head injuries AND spasms OR head injuries AND contracture OR head injuries AND contractures OR head injuries AND muscle hypertonia

CONTRIBUTIONS OF AUTHORS

MC, KP and AS carried out study selection, data extraction and assessment of risk of bias.

OC, JW, KP, MC and AS completed analyses.

AS and KP led the writing of the manuscript, with input from MC and the coauthors.

DECLARATIONS OF INTEREST

Kate Phillips is the director of a private multidisciplinary community rehabilitation service and is a practising neurological physiotherapist, treating people who have had a TBI. Kate is a clinical consultant on the Clinical Panel of the Transport Accident Commission in Victoria, Australia. The Transport Accident Commission is a Victorian Government owned organisation, its role is to pay for treatment and benefits for people injured in transport accidents.

All authors were supported to complete this work by a grant received from the Transport Accident Commission, Victoria.

AS, MC, VP, DO, RG, JW, OC and LP declare no conflicts of interest.

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Internal sources

- From 2010 to 2012, Kate Phillips was supported by a PhD scholarship provided by Monash University, Victoria, Australia.

External sources

- Neurotrauma Evidence Translation Program, Australia.

  The Neurotrauma Evidence Translation program is funded by the Transport Accident Commission, Victoria, Australia
- National Institute for Health Research (NIHR), UK.

  This project was supported by the UK National Institute for Health Research, through Cochrane Infrastructure funding to the Cochrane Injuries Group. The views and opinions expressed are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol was published in 2010. Since that time the methodology of systematic reviews has evolved. To bring the protocol and subsequent review in line with the latest Cochrane methodology we made several necessary post-hoc adjustments to the assumptions and processes. These were separately highlighted throughout the text.

During screening, we found a number of studies with clinically diverse populations. As people with TBI were poorly represented (making up of only 26% of the participants), we therefore devised a threshold of 50% (meaning that the study needed to have at least 50% of participants with TBI to be included in the review) to ensure the evidence would be applicable to the TBI population. We also made a post-hoc decision to use the Tardieu or Modified Tardieu Scale as our preferred measure of spasticity, in preference to the Modified Ashworth Scale, in the instance that studies reported both these measures.

We added an information size calculation post-hoc, in line with updated Cochrane Injuries Group editorial policy, and 'Summary of findings' tables, in line with updated Cochrane standards.

Due to the paucity of data, a number of planned methods outlined in the protocol could not be implemented. These included the planned meta-analysis, investigation of statistical heterogeneity, subgroup analysis, sensitivity analysis and assessment of reporting biases. These methods will be retained for review updates pending sufficient studies.

The following authors joined the team since the publication of the protocol: AS, MC, OC, JW and LP.

NOTES

Since the publication of the protocol in 2010, network meta-analysis methods have been developed and adopted where necessary in Cochrane Reviews. We recognise that the most appropriate design for our review (which aims to assess the effectiveness of a number of interventions) would be that of a network meta-analysis.

However, in light of a number of issues identified while carrying out this review (such as the paucity of the data, number of available interventions, presence of heterogeneity, lack of 'pure' datasets for the condition of interest, etc.), we are aware that even if we were to alter the design of this review, a network meta-analysis would not be feasible. The current state of the available literature also indicates that in the short-term future updates of this review will encounter similar issues. We have hence retained the original protocol design and have presented our findings as a narrative.

The network meta-analysis design remains a viable future plan should adequate data become available.

INDEX TERMS

Medical Subject Headings (MeSH)

Baclofen [therapeutic use]; Botulinum Toxins, Type A [therapeutic use]; Brain Injuries, Traumatic [*complications]; Casts, Surgical; Electric Stimulation Therapy; Head-Down Tilt; Muscle Relaxants, Central [therapeutic use]; Muscle Spasticity [etiology] [*therapy]; Neuromuscular Agents [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans