Local anaesthetic sympathetic blockade for complex regional pain syndrome (Review)

Stanton TR, Wand BM, Carr DB, Birklein F, Wasner GL, O'Connell NE

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[Intervention Review]

Local anaesthetic sympathetic blockade for complex regional pain syndrome

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ABSTRACT

Background

This is an update of the original Cochrane review published in *The Cochrane Library*, 2005, Issue 4, on local anaesthetic blockade (LASB) of the sympathetic chain used to treat complex regional pain syndrome (CRPS).

Objectives

To assess the efficacy of LASB for the treatment of pain in CRPS and to evaluate the incidence of adverse effects of the procedure.

Search methods

We updated searches of the Cochrane Pain, Palliative and Supportive Care Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) on the Cochrane Library (Issue 11 of 12, 2012), MEDLINE (1966 to 22/11/12), EMBASE (1974 to 22/11/12), LILACS (1982 to 22/11/12), conference abstracts of the World Congresses of the International Association for the Study of Pain (1995 to 2010), and various clinical trial registers (inception to 2012). We also searched bibliographies from retrieved articles for additional studies.

Selection criteria

We considered for inclusion randomised controlled trials (RCTs) that evaluated the effect of sympathetic blockade with local anaesthetics in children or adults with CRPS.

Data collection and analysis

The outcomes of interest were reduction in pain intensity levels, the proportion who achieved moderate or substantial pain relief, the duration of pain relief, and the presence of adverse effects in each treatment arm.

Main results

We included an additional 10 studies (combined n = 363) in this update. Overall we include 12 studies (combined n = 386). All included studies were assessed to be at high or unclear risk of bias.

Three small studies compared LASB to placebo/sham. We were able to pool the results from two of these trials (intervention n = 23). Pooling did not demonstrate significant short-term benefit for LASB (in terms of the risk of a 50% reduction of pain scores).

Of two studies that investigated LASB as an addition to rehabilitation treatment, the only study that reported pain outcomes demonstrated no additional benefit from LASB.

Eight small randomised studies compared sympathetic blockade to another active intervention. Most studies found no difference in pain outcomes between sympathetic block and other active treatments.

Only five studies reported adverse effects, all with minor effects reported.

Authors' conclusions

This update has found similar results to the original systematic review. There remains a scarcity of published evidence to support the use of local anaesthetic sympathetic blockade for CRPS. From the existing evidence it is not possible to draw firm conclusions regarding the efficacy or safety of this intervention but the limited data available do not suggest that LASB is effective for reducing pain in CRPS.

PLAIN LANGUAGE SUMMARY

Local anaesthetic sympathetic blockade for complex regional pain syndrome

Local anaesthetic sympathetic blockade (LASB) is a common treatment for complex regional pain syndrome (CRPS). It involves blocking the activity of sympathetic nerves in the spine through the injection of a local anaesthetic drug. This updated review sought to identify the available evidence regarding whether LASB is effective at reducing pain in CRPS, how long any pain relief might last, and whether LASB is safe.

We found a small number of small trials, all of which may be at risk of bias. We did not find evidence that LASB was better than placebo in reducing pain, or that it provided additional pain relief when added to rehabilitation. While a number of small studies compared LASB to other treatments, most did not find that LASB was better than any other intervention. Only five studies reported on adverse events. These studies reported only minor side effects but since most studies did not report this information we can draw no firm conclusions about the safety of LASB.

Overall, while the evidence is very limited and precludes the drawing of strong conclusions, the existing evidence does not provide support for the efficacy of LASB in managing people with CRPS.

BACKGROUND

Description of the condition

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews, 2005, Issue 4 (and updated in the Cochrane Database of Systematic Reviews, 2010, Issue 1), on local anaesthetic sympathetic blockade for complex regional pain syndrome.

Complex regional pain syndrome (CRPS) is an umbrella term for a variety of clinical presentations characterised by chronic persistent pain that is disproportionate to any preceding injury and that is not restricted anatomically to the distribution of a specific peripheral nerve (Bruehl 2010). The diagnostic label of CRPS was introduced in the 1990s by the International Association for the Study of Pain (IASP) (Merskey 1994), and has since been updated in an attempt to improve its specificity (Harden 2006). These modified diagnostic criteria (the "Budapest criteria") can be seen

in Table 1. It encompasses a variety of earlier diagnostic terms including reflex sympathetic dystrophy (RSD), reflex neurovascular dystrophy, Sudeck's atrophy, causalgia and algodystrophy/algoneurodystrophy. CRPS can be classified into two subtypes: CRPS-I, in which no peripheral nerve injury can be identified, and CRPS-II where symptoms are associated with a definable nerve lesion (Harden 2006). This distinction is not always easily made (Harden 2006). Both subtypes of CRPS are characterised by severe pain that is disproportionate to the inciting event, most commonly affecting the hand or foot but which can spread to other body regions (Stanton-Hicks 2002). Additionally CRPS presents with some or all of the following symptoms in the affected body parts: sensory disturbances, temperature changes, abnormal patterns of sweating, swelling/oedema, reduced joint range of motion, movement abnormalities such as weakness, tremor or dystonia, trophic changes such as skin atrophy, altered hair and nail growth or localised osteoporotic changes (Bruehl 2010; De Mos 2009; Shipton 2009), and alterations in body perception/schema (Lewis 2007; Lotze 2007; Moseley 2006). CRPS occurs most commonly following wrist fracture and subsequent immobilisation. However cases can potentially occur after any, often relatively minor, trauma and may even occur spontaneously, albeit rarely (De Mos 2007; De Mos 2008; Sandroni 2003). The underlying pathophysiological mechanisms of CRPS are incompletely understood although there is growing consensus that it is primarily a disorder of the nervous system. Abnormalities in the tissues of the affected area and the peripheral and central nervous systems have been identified (for review see Jänig 2003; Marinus 2011). These include signs of increased neurogenic inflammation (Birklein 2001; Schinkel 2006; Schmelz 2001), an altered local immune response (Tan 2005), altered activity in the sympathetic nervous system (SNS) (Drummond 2004; Niehof 2006) or increased sensitivity to normal SNS activity (Albrecht 2006; Ali 2000; Drummond 2001), and local tissue hypoxia (Birklein 2000; Koban 2003). Changes have also been demonstrated in the brain in CRPS (Swart 2009), including alterations of the cortical (higher brain) representation of the affected body part (Maihöfner 2004; Pleger 2006), localised reductions in grey matter density and connectivity (Geha 2008), and altered inhibitory control (Schwenkreis 2003).

Description of the intervention

Sympathetic blockade includes procedures that aim to temporarily impede the function of the sympathetic nervous system. This involves the injection of local anaesthetic directly into sympathetic neural structures that serve the affected limb(s) such as the stellate ganglion or the lumbar sympathetic chain (Nelson 2006). Accuracy of needle location is often ensured using radiologic guidance such as fluoroscopy or computerised tomography (CT) scan and successful blockade is often monitored by direct (e.g., galvanic skin response) or indirect (increase in lower extremity blood flow or increase in temperature) assessment (Breivik 2009). This approach is distinct from the injection of neurolytic agents in an effort to destroy sympathetic nerves.

How the intervention might work

People with persistent pain following nerve injury have long been observed to have abnormalities of autonomic nervous function in the affected limb (temperature, blood flow, sweating) and abnormal skin texture or hair and nail growth attributed, at least in part, to local autonomic dysfunction (Bruehl 2010; De Mos 2009). Early uncontrolled observations of persistent improvement in signs and symptoms following local anaesthetic sympathetic blockade in people with what is now termed CRPS suggested that excessive sympathetic activity provoked or perpetuated this type of persistent pain. However, recent evidence regarding adrenaline content in venous effluent from affected limbs has not supported this hypothesis (Binder 2009) and suggests instead that any benefit of sympathetic blockade in CRPS may reflect transient reversal of a heightened local sensitivity to adrenaline.These clinical impressions of persistent benefit from transient local anaesthetic sympathetic blockade in CRPS, reinforced by similar longstanding impressions of prolonged benefit after temporary local anaesthetics blockade in peripheral neuralgias (Carr 2011) led to the incorporation of sympathetic block into current consensus treatment algorithms for CRPS, although doubt remains over the contribution of the sympathetic nervous system to pain and the concept of sympathetically maintained pain in CRPS (Harden 2013).

Why it is important to do this review

Despite preclinical evidence that suggests that the sympathetic nervous system is involved in the pathophysiology of CRPS, there is debate surrounding the contribution of the sympathetic nervous system to the clinical syndrome (Ochoa 1995; Schott 1995; Verdugo 1994a; Verdugo 1994b) and on the value of blocking the sympathetic nervous system (Fine 1994;, Hogan 1997; Jadad 1995; Verdugo 1994a). It is therefore important to evaluate the efficacy of sympathetic blockade with local anaesthetic in the treatment of CRPS. A meta-analysis of the effect of sympathetic blockade with local anaesthetics in people with CRPS reported that up to 44% of those subjected to sympathetic blockade would be expected to have no pain relief. Due to the lack of randomised controlled trials this estimate was obtained from pooling the results of observational studies (Cepeda 2002). Moreover, the review only evaluated English-language studies and it could have overlooked relevant RCTs. Hence, to overcome this limitation, we decided to perform a systematic review of the literature with no language restriction to determine both the efficacy and the effectiveness of sympathetic blockade with local anaesthetics to alleviate pain in people with CRPS.

OBJECTIVES

To determine:

1. If local anaesthetic sympathetic blockade (LASB) is effective for providing pain relief to people with complex regional pain syndrome (CRPS);

2. How long the pain relief persists;

3. The incidence of adverse effects of the procedure.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion randomised controlled trials (RCTs). As blinding of sympathetic block is not always possible, we included trials that were either double-blind, single-blind, or open.

Types of participants

We included studies that evaluated the effect of sympathetic blockade with local anaesthetics to treat CRPS in children or in adults. Studies were included even if the authors did not describe the constellation of symptoms necessary to diagnose CRPS and stated only that, "patients with RSD/CRPS were included". We took this approach to avoid excluding any of the relatively few RCTs of this intervention. We placed no restrictions regarding the number of participants recruited to trials.
We excluded trials that evaluated sympathetic blockade for other pain syndromes such as radiculopathy, herpes zoster, postherpetic neuralgia, fibromyalgia or phantom pain.

Types of interventions

We included studies that evaluated selective sympathetic blockade with local anaesthetics. We excluded studies that only evaluated somatic nerve blocks or studies that evaluated the effect of local anaesthetics or sympatholytic drugs administered orally, intravenously or epidurally. The following were also exclusion criteria, added for this updated review: we excluded studies that reported the results of combined sympatholytic therapies, such as surgical sympathectomy or guanethidine regional block plus local anaesthetic blockade of the sympathetic chain. For this update we also excluded studies of ganglionide local opioid analgesia (GLOA), a technique in which opioids such as buprenorphine are injected locally into the stellate ganglion, because this technique does not block sympathetic activity; we also excluded studies in which sympathetic blocks were performed in people with herpes zoster and people with postherpetic neuralgia and fibromyalgia.

Types of outcome measures

The outcomes of interest were reduction in pain intensity levels, pain relief, or duration of pain relief, and the presence of adverse effects in each treatment arm. We excluded studies that did not present quantitative outcome data.

Search methods for identification of studies

For this update we expanded the search strategy to capture all the search terms for CRPS that are commonly used and all the search terms for sympathetic injections. Specifically we have added numerous versions of block/blockades for the various names that are used for these injections. We have also added botulinum toxin as this has only recently been used to block sympathetic activity (2009). Due to the small number of studies identified in the previous review, the goal was to create a search strategy that was as sensitive as possible. For the updated search strategies, please see Appendix 1 for MEDLINE, Appendix 2 for the Cochrane Central Register of Controlled Trials (CENTRAL), Appendix 3 for EMBASE, and Appendix 4 for LILACS.
The search for the original review was run from November 2003 to January 2004. We ran our updated search for the original review on November 17, 2011 and subsequent searches were run on November 22, 2012.
We evaluated non-English papers for inclusion.

Electronic searches

We searched the following databases for the update of this review:

- Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 11, November)
- MEDLINE (1966 to November 2012)
- EMBASE (1974 to November 2012)
- LILACS (1982 to November 2012)

Searching other resources

Reference lists:
We searched the bibliographies of retrieved articles for additional studies.
Unpublished studies:
In order to minimise the impact of publication bias, we reviewed conference abstracts of the World Congresses of the International Association for the Study of Pain from 1995 up to 2011. For this update, we expanded the search of the original review by also searching relevant clinical trial registers (from inception) for upcoming trials. The following clinical trial registers were searched: the controlled trials register (November

30, 2012; www.controlled-trials.com/), the United States National Institute of Health service ClinicalTrials.gov (November 15, 2012; www.clinicaltrials.gov/); the Australian New Zealand Clinical trials register (November 15, 2012; www.anzctr.org.au/) and the European Clinical Trials Register (December 7, 2012; www.clinicaltrialsregister.eu/).

Personal contact:

We attempted to communicate with authors if additional information was needed that was not provided in the trial report. In addition, we provided the reference list of included studies to experts in the field to determine if any additional references were appropriate for the review.

Data collection and analysis

Selection of studies

Two independent review authors read each of the titles and abstracts of the reports identified by the search and discarded narrative reviews, case series, or case reports. If there was no abstract, the report was retrieved in full. If there was disagreement, the authors met to reach consensus and if consensus could not be reached an independent third review author was consulted. All abstracts and reports that made reference to a trial of sympathetic blockade with local anaesthetics were retrieved in full. Two review authors then independently assessed the full-text articles. The reports were not anonymised for the assessment.

Data extraction and management

Assessment of risk of bias in included studies

For this update we adopted a modified version of the Cochrane 'Risk of bias' (RoB) tool with additional criteria added in response to the recommendations of Moore 2010. On this basis we added two criteria, 'Size' and 'Duration', using the thresholds for judgement suggested by Moore 2010. We have not added the 'Outcome' criterion as this is covered already by our choice of primary outcome measures. Thus in addition to the standard items in the RoB tool:

- selection bias (random sequence generation, allocation concealment),
- performance bias (blinding of participants and personnel),
- detection bias (blinding of outcome assessment)
- attrition bias (incomplete outcome data; consideration of analysis methods, e.g., imputation method)
- reporting bias (selective reporting)
- other sources of bias.

We also assessed the following criteria as recommended by Moore 2010:

- Size (studies with fewer than 50 participants per arm were rated as being at high risk of bias, those with between 50 and 199 participants per arm at unclear risk of bias, and 200 or more participants per arm at low risk of bias)
- Duration (studies with follow-up of two weeks were rated as being at high risk of bias, two to seven weeks at unclear risk of bias and eight weeks or longer at low risk of bias).

Data extraction

Two independent review authors extracted the data. If there was disagreement, a meeting was held to reach consensus and if consensus could not be reached an independent third review author was consulted. We extracted the following data from each study:

1. Study details: Study design (parallel or cross-over), method of randomisation, presence or absence of blinding;
2. Demographic characteristics: age, gender, number of participants recruited, number of study withdrawals or drop-outs, if any;
3. Participant disease characteristics: duration of pain before sympathetic block, site of pain (arm, leg, mixed or other such as facial);
4. Type of noxious initiating event: surgery, fracture, crush injury, projectile, or stab injury;
5. Type of tissue injured: nerve, soft tissue, bone;
6. Presence of medico-legal factors (that may influence the experience of pain and the outcomes of therapeutic interventions);
7. Concomitant treatments that may affect outcome: antidepressants, physical therapy, etc;
8. Treatment characteristics: site of sympathetic block (cervical or lumbar), type of local anaesthetic used, evaluation of the technical adequacy of the block, duration of follow-up, duration of the pain relief, number of blocks performed, method of pain assessment, and presence of complications or adverse effects;
9. Information on post-procedure analgesic requirements.

If pain intensity was reported using a visual analogue scale or numeric rating scale, we extracted the mean and standard deviation of pain intensity in each study arm. If pain relief was reported, we extracted the proportion of participants in each category of pain relief.

Measures of treatment effect

For this update we compared the post-treatment pain intensity scores between the treatment arms. Where possible, we calculated the proportion of participants with specific degree of pain relief and converted it into dichotomous information to yield the number of participants who obtained a moderately important benefit (30% pain relief) or a substantially important benefit (50% or more pain relief) as defined by the IMMPACT recommendations (Dworkin 2008). We calculated the risk ratio (RR) as the measure of treatment effect and used this to calculate the number-needed-to-treat (NNT) for 30% and 50% pain relief.

Dealing with missing data

Where insufficient data were presented in the study report to enter a study into the meta-analysis, we contacted study authors to request access to the missing data.

Data synthesis

We pooled results where adequate data supported this, using Review Manager 5 software (RevMan 2012). Separate preplanned meta-analyses included sympathetic blockade versus sham/placebo procedure and sympathetic blockade versus no treatment or usual care. We used a random-effects model to combine the studies. We considered separate meta-analyses for short-term (0 to two weeks postintervention), mid-term (more than two to less than seven weeks postintervention) and long-term (seven weeks or longer postintervention) outcomes where adequate data were identified.

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity and its impact using the Chi^2 test and the I^2 test (Higgins 2003; Higgins 2011). Where significant heterogeneity ($P < 0.1$) was present we planned to conduct subgroup analyses. Preplanned comparisons included CRPS-I versus CRPS-II, children versus adults, and continuous versus single block.
Where possible we used the proportion of people with adverse side effects in each treatment group to calculate the number-needed-to-harm (NNH).

Assessment of reporting biases

We considered the possible influence of publication/small study biases on review findings. Where possible for studies that have utilised dichotomised outcomes we tested for the possible influence of publication bias on each outcome by estimating the number of participants in studies with zero effect required to change the NNTB to an unacceptably high level (defined as an NNTB of 10) as outlined by Moore 2008.

Sensitivity analysis

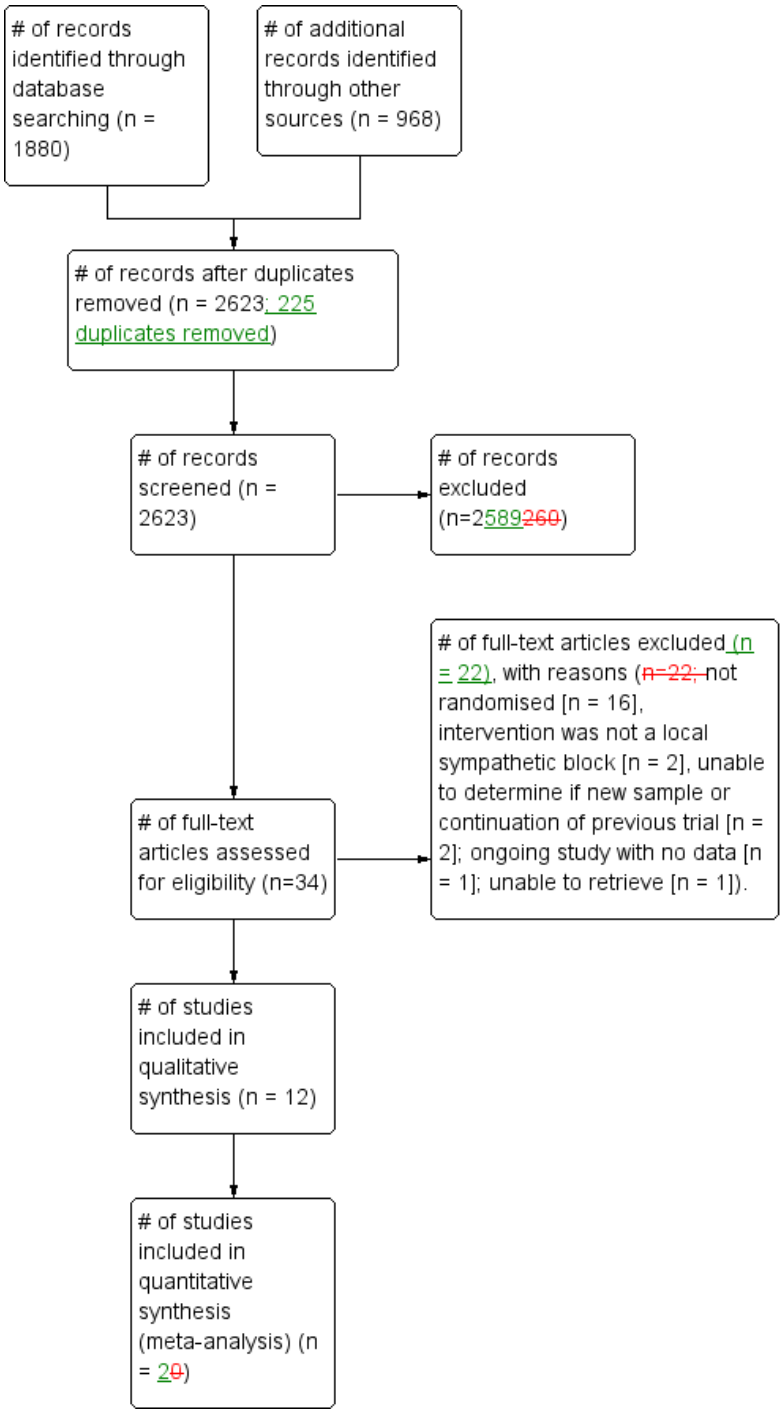
When sufficient data were available, we conducted sensitivity analyses on the following study factors: the effect of including/excluding studies classified as being at unclear or high risk of bias.

RESULTS

Description of studies

For this update we included an additional ten studies (Aydemir 2006; Bonelli 1983; Carroll 2009; Meier 2009; Nascimento 2010; Raja 1991; Rodriguez 2005; Toshniwal 2012; Wehnert 2002; Zeng 2003, combined n = 363). Overall we included 12 studies (n = 386).
Figure 1 presents a flowchart of the search screening process for the present update. A total of 1880 studies were identified by the database search strategy with an additional 968 studies identified through: hand-searching (n = 21); International Association for the Study of Pain (IASP) conference abstract searches (n = 356); clinical trial register searches (n = 591). After removal of duplicates and screening of titles and abstracts, we retrieved the full text for 34 studies. From these, we included 12 studies in the review. We excluded 16 studies as they did not use a randomised study design (Ackerman 2006; Arias 1989; Dellemijn 1994; Erickson 1993; Farcot 1990; Garrido 2005; Geurts 2006; Glynn 1993; Hartrick 2004; Linson 1983; Malmqvist 1992; Quevedo 2005; Schurmann 2001; Steinbrocker 1953; Wang 1985; Yucel 2009), two studies did not evaluate a local sympathetic blockade (Perrigot 1982; Tran 2000), two studies could not be confirmed as a new sample versus continuation of a previous study (Rodriguez 2006; Rodriguez 2008), and one study could not be retrieved (Salinas Cerda 1997). One additional study from a clinical trial registry met the inclusion criteria (Rocha 2012), but completion of data collection was estimated at November 2013. See the table Characteristics of excluded studies for summary details.

Figure 1. Study flow diagram for updated searches



The percentage agreement rate between the review authors (TS, BW) for screening of titles and abstracts was nearly perfect (99.9%) with only nine disagreements out of 2623 potential studies. The percentage agreement between the review authors for inclusion of studies was 88.2% with disagreements on 3 of 34 studies (Raja 1991; Wehnert 2002; Tran 2000). Two studies were included after discussion between the two review authors (Raja 1991; Wehnert 2002) and one was excluded (Tran 2000) after consultation with a third review author (NO).

We attempted to contact the authors of six papers; one for clarification of study population (Rodriguez 2005; two papers), two for retrieval of essential data (Nascimento 2010; Toshniwal 2012), one to determine if any data were present (Rocha 2012), and one to retrieve a manuscript that we were unable to source (Salinas Cerda 1997). Of these, we received correspondence and subsequent data from only two authors (Nascimento 2010; Toshniwal 2012). Two authors had been contacted in the original Cochrane review: Verdugo 1995 was contacted to determine if a paper in abstract form was published and the author reported that the trial had not been published in full (Verdugo 1995); Price 1998 was contacted to determine if a trial was randomised and the author confirmed that the trial was randomised.

Full details of the studies can be found in the Characteristics of included studies tables.

Study participants

Eleven studies (Aydemir 2006; Bonelli 1983; Carroll 2009; Nascimento 2010; Price 1998; Raja 1991; Rodriguez 2005; Toshniwal 2012; Verdugo 1995; Wehnert 2002; Zeng 2003) included only adults and one study specifically included only children with CRPS (Meier 2009).

Seven studies (Aydemir 2006; Bonelli 1983; Nascimento 2010; Rodriguez 2005; Toshniwal 2012; Verdugo 1995; Zeng 2003) included only people with upper limb CRPS (treated with stellate ganglion blockade), two studies (Carroll 2009; Meier 2009) included only people with lower limb CRPS (treated with lumbar sympathetic blockade), and three studies (Price 1998; Raja 1991; Wehnert 2002) included a mixed group with either upper or lower limb CRPS.

Study designs

Six studies used a cross-over design (Carroll 2009; Meier 2009; Price 1998; Raja 1991; Verdugo 1995; Wehnert 2002) and six a parallel design (Aydemir 2006; Bonelli 1983; Nascimento 2010; Rodriguez 2005; Toshniwal 2012; Zeng 2003). All included studies were small with total number of participants ranging from 7 to 82.

LASB versus placebo

We identified one new study comparing local anaesthetic sympathetic blockade (LASB) with placebo (Aydemir 2006) in addition to those identified for the previous update. Therefore only three studies (Aydemir 2006; Price 1998, Verdugo 1995) inform this comparison.

Price 1998 (n = 7) compared stellate ganglion block (four participants, 15 ml lidocaine 1%) or lumbar sympathetic block (three participants,10 ml bupivacaine 0.125%) with normal saline injection in people with CRPS of the upper or lower extremities based on the IASP diagnostic criteria. Verdugo 1995 (n = 16) compared a stellate ganglion block with bupivacaine (0.125%) to a normal saline injection in participants with CRPS of the upper extremity. Both studies investigated the proportion of participants who experienced 50% pain relief and Price 1998 also measured the duration of pain relief and the mean between-group difference in pain relief on a visual analogue scale (VAS). Aydemir 2006 compared stellate ganglion lidocaine block (10 ml lidocaine 1%) plus sham stellate ganglion ultrasound block (n = 9) to a double-sham condition (sham stellate ganglion lidocaine [10 ml saline] and ultrasound blocks; n = 7). Both groups received rehabilitation treatment. Spontaneous pain was measured post-treatment and at one-month follow-up.

LASB versus other interventions

In contrast to the previous version of this review we included studies which compared LASB to other interventions. Ten such trials were included (Aydemir 2006; Bonelli 1983; Carroll 2009; Meier 2009; Nascimento 2010; Raja 1991; Rodriguez 2005; Toshniwal 2012; Wehnert 2002; Zeng 2003).

Aydemir 2006 compared stellate ganglion lidocaine block (10 ml of 1%) plus sham stellate ganglion ultrasound block (n = 9) to stellate ganglion ultrasound 'block' (consisting of ultrasound delivered non-invasively over the stellate ganglion) plus sham stellate ganglion lidocaine block (10 ml of saline; n = 9). Both groups received rehabilitation treatment. The primary outcome of spontaneous pain was measured post-treatment and at one-month follow-up.

Bonelli 1983 (n = 19) compared stellate ganglion block with bupivacaine (15 ml of 0.5%; n=10) to intravenous regional blockade (IVRB) with guanethidine (20 mg; n=9) in patients with reflex sympathetic dystrophy. The primary outcome was the intensity of pain (measured using a 100mm linear scale) measured post-treatment at 15 minutes, 60 minutes, 24 hours and 48 hours as well as at one and 3 months.

Carroll 2009 (n = 9, of whom seven completed the study) compared sympathetic block with botulinum toxin A (75 units) plus bupivacaine (10 ml of 0.5%) with just bupivacaine (10 ml of

0.5%) in people with complex regional pain syndrome (CRPS) of the lower extremity. The primary outcome was the duration that pain (measured using a VAS) remained below baseline levels.

Meier 2009 (n = 23) compared lidocaine delivered intravenously (1% lidocaine; 0.1 ml/kg, maximum 6 ml) with lidocaine sympathetic block (1% lidocaine; 0.1 ml/kg, maximum 6 ml) in children with lower limb CRPS-I or CRPS-II. In a cross-over trial participants received intravenous (IV) lidocaine and a placebo sympathetic block or a lidocaine sympathetic block and placebo IV. Pain intensity (global 4-point verbal scale and colour analogue scale) was measured 30 minutes post-treatment.

Nascimento 2010 (n = 43) compared sympathetic block with lidocaine (70 mg 1% lidocaine) with sympathetic block with lidocaine (70 mg 1% lidocaine) plus clonidine (30 μg) or with IVRB with lidocaine plus clonidine (7.0 ml solution, 1% lidocaine, 1.μg/kg clonidine). Intensity of pain (VAS) and duration of pain relief were measured post-treatment and at one-week follow-up.

Two studies (Raja 1991; Wehnert 2002) compared lidocaine LASB with IV phentolamine. The primary aim of these studies was to investigate the utility of phentolamine in diagnosing sympathetically maintained pain, but given the design (cross-over) and outcome used we considered that they present efficacy data for single doses of these interventions in CRPS. Raja 1991 used 0.25% bupivacaine hydrochloride (10 ml for stellate ganglion blockade (SGB) and 20 ml for lumbar block) versus phentolamine at three- to eight-minute intervals in increasing dose (from 1 - 10 mg to 25 - 35 mg). Pain intensity (VAS) was measured post-treatment (exact length of follow-up unclear). Wehnert 2002 used 0.1 ml per 0.25%/cm in height (plus 500 mL NaCl 0.9%) versus 0.5 mg phentolamine/kg (plus 500 mL NaCl 0.9%) for 15 minutes. Pain intensity (VAS) was measured hourly post-treatment for 8 hours.

Rodriguez 2005 evaluated physical therapy plus pharmacological treatment with or without SGB (n = 41 per group,10 cc, equal parts 2% lidocaine and 0.5% bupivacaine) in people with upper limb CRPS with a confirmed sympathetic component to their pain (50% pain reduction with screening, pre-randomisation SGB). Pain intensity, therapeutic efficacy (proportion with at least 50% pain reduction) and relapse rate were measured at two months post-treatment.

Toshniwal 2012 compared continuous SGB (n = 18; 280 ml, 0.125% bupivacaine at 2 mL/hour for seven days) to continuous infraclavicular brachial plexus block (n = 12; 400 ml, 0.125% bupivacaine at 5 mL/hour for seven days) in people with CRPS Type I of the upper extremity. Physiotherapy sessions were given concurrently in both groups. The primary outcome was the subscale scores on the Neuropathic pain scale measured over a 4 week period post-treatment.

Zeng 2003 compared SGB (dose not reported) plus rehabilitation to rehabilitation only in a group (n = 60) with shoulder-hand syndrome following stroke. Pain (verbal rating scale) was measured at 10 and 20 days post-treatment.

Risk of bias in included studies

The results of the 'Risk of bias' assessment can be found in Figure 2 and Figure 3. Percentage agreement between review authors (TS, BW) for risk of bias ratings was 90.9% for the items of adequate sequence generation, blinding of participants/assessors, and presence of other bias; 81.8% for the item of freedom from cross-over effects, and 63.6% for the items of selective reporting of results and incomplete outcome data adequately addressed. There was perfect agreement for the remaining items. The two review authors resolved disagreements through discussion. No studies were considered to be at low risk of bias across all criteria.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

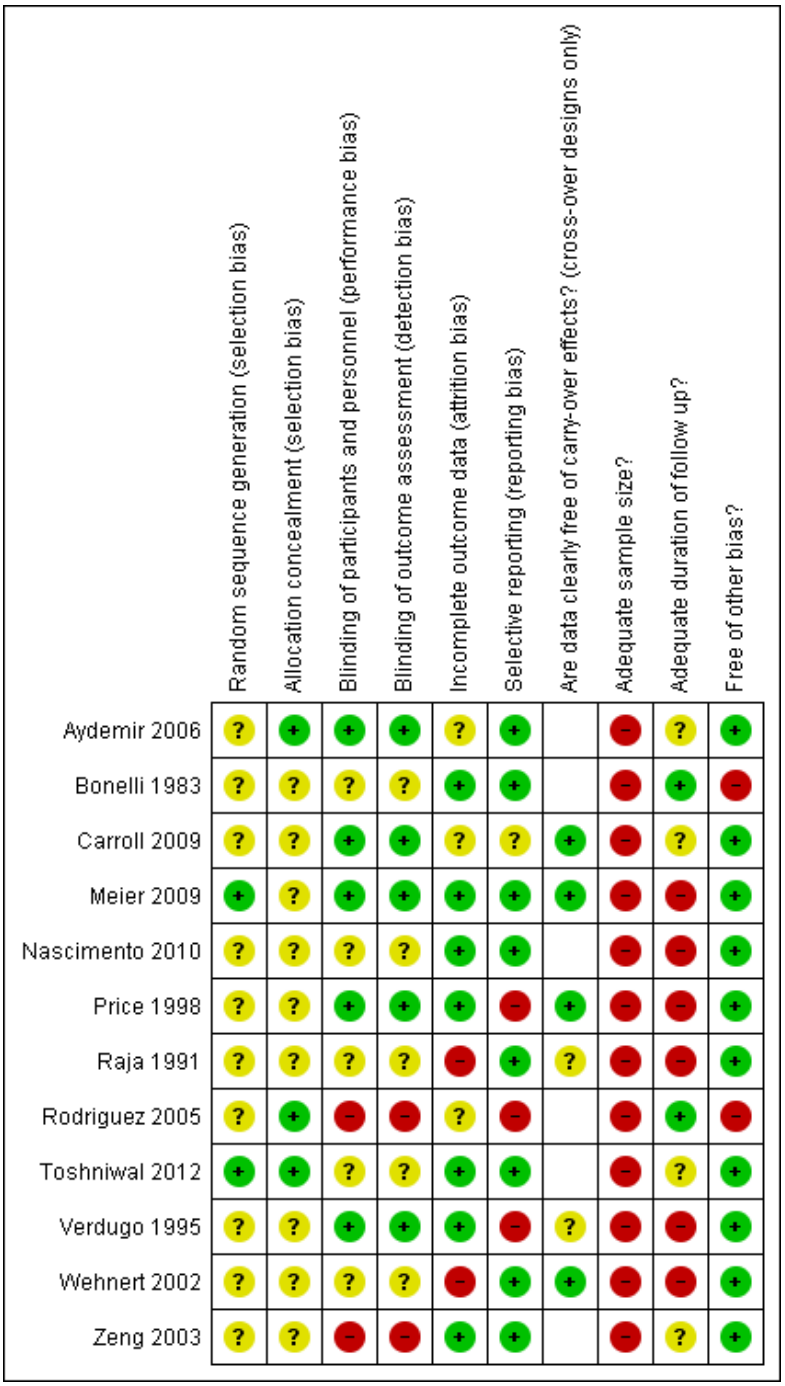
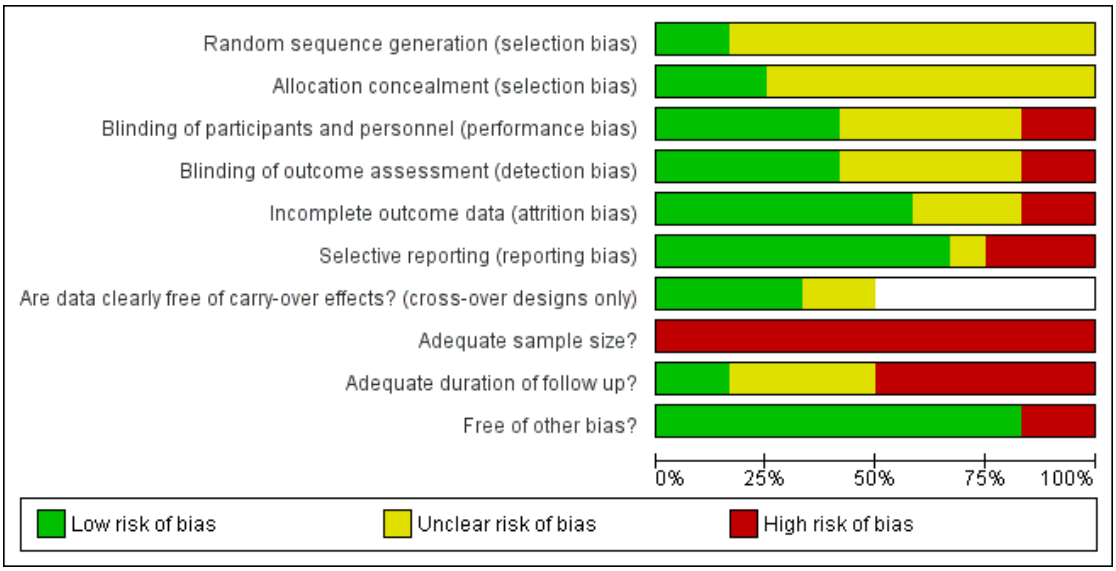


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Only two studies (Meier 2009; Toshniwal 2012) clearly described an adequate randomisation process; the other ten studies were judged to be at unclear risk of bias for this criterion. Three studies were rated as being at a low risk of bias for allocation concealment (Aydemir 2006; Rodriguez 2005; Toshniwal 2012), three studies were at an unclear risk of bias (Bonelli 1983; Nascimento 2010; Zeng 2003); the remaining studies used a cross-over study design (risk of bias for allocation concealment not applicable).

Blinding

Five studies were judged to have blinded participants and assessors adequately (Aydemir 2006; Carroll 2009; Meier 2009; Price 1998; Verdugo 1995). Five studies were judged to be at unclear risk of bias across these criteria (Bonelli 1983; Nascimento 2010; Raja 1991; Toshniwal 2012; Wehnert 2002) and in two studies blinding of the treatment conditions was not achievable, and were therefore judged to be at high risk of bias (Rodriguez 2005; Zeng 2003).

Incomplete outcome data

Two studies (Raja 1991; Wehnert 2002) were judged to be at high risk of bias for incomplete outcome data and three studies were judged to be at unclear risk (Aydemir 2006; Carroll 2009; Rodriguez 2005).

Selective reporting

Three studies were judged to be at high risk of bias for this criterion (Price 1998; Rodriguez 2005; Verdugo 1995) and one study to be at unclear risk of bias (Carroll 2009).

Data clearly free of carry-over effects?

Of the six included cross-over studies, two (Raja 1991; Verdugo 1995) were judged as being at unclear risk of bias for this criterion.

Adequate sample size?

All studies were judged to be at high risk of bias with regard to sample size.

Adequate duration of follow up?

All but two studies (Bonelli 1983; Rodriguez 2005) were at high or unclear risk of bias based on inadequate duration of follow-up.

Other potential sources of bias

Two studies were judged to be at high risk of bias for other reasons. In Bonelli 1983 the LASB group had a significantly shorter duration of symptoms than the IVRB guanethidine group and were significantly older. In Rodriguez 2005, no baseline data were provided on pain intensity.

Sources of funding and conflicts of interest

While not formally included within the 'Risk of bias' assessment, we extracted information regarding study funding and potential conflicts of interest. Six study reports offered no details regarding these issues (Aydemir 2006; Bonelli 1983; Nascimento 2010; Price 1998; Wehnert 2002; Zeng 2003).

Carroll 2009 declared that the authors had filed a patent for the inclusion of botulinum toxin in sympathetic blocks. Four studies (Meier 2009; Raja 1991; Rodriguez 2005; Verdugo 1995) all declared financial support from governmental or non-profit organisations. No study declared funding from industry sources.

Effects of interventions

LASB versus placebo

Short-term pain relief

The first aim of this systematic review was to determine the likelihood of pain alleviation after sympathetic blockade with local anaesthetics:

In Price 1998 there was no difference between lidocaine or normal saline; the same number of participants (6/7) achieved at least 50% pain relief. In Verdugo 1995 12 of 16 participants had at least 50% pain relief while receiving bupivacaine versus 8 participants of 16 while receiving normal saline. The combined effect of these two small randomised double-blind trials produced a risk ratio (RR) to achieve at least 50% of pain relief 30 minutes to two hours after the sympathetic blockade of 1.18 (95% confidence interval (CI) 0.76 to 1.84, p=0.46); Analysis 1.1). In Aydemir 2006: spontaneous pain scores were no different from baseline to post-treatment in either the group receiving lidocaine (plus sham ultrasound SGB; Z = -0.18, P = 0.86) or in the group receiving sham lidocaine and sham ultrasound (Z = -0.76, P = 0.45). No between-group comparisons were reported.

Duration of pain relief

The second aim was to determine how long any pain relief persists: Studies evaluated different long-term outcomes, which precluded the combination of the results. Price 1998 evaluated the duration of pain relief and Verdugo 1995 evaluated the number of participants who had at least 50% of pain relief. Verdugo 1995 found that 5 out of 16 patients had at least 50% of pain relief receiving local anaesthetic versus 8 out of 16 receiving normal saline 48 hours after the blockade; Price 1998 found that when local anaesthetic was administered the mean duration of relief was longer (three days) versus 19.9 hours when saline was administered. Interestingly, this study found that short-term relief was similar in both groups. In Aydemir 2006, spontaneous pain scores were no different from baseline to one-month follow-up in either the group receiving lidocaine (plus sham ultrasound SGB; Z = -1.05, P = 0.29) or in the group receiving sham lidocaine and sham ultrasound (Z = -0.68, P = 0.50). No between-group comparisons were reported. None of the included studies reported postintervention analgesic requirements.

LASB versus other interventions

Most comparative studies demonstrated no significant difference in pain between groups (Bonelli 1983; Nascimento 2010; Raja 1991; Wehnert 2002; Zeng 2003). One study did not explicitly report between-group differences (Aydemir 2006) although no within-group differences in spontaneous pain scores were found between baseline and post-treatment nor at one-month follow-up in either the group receiving lidocaine SGB plus sham ultrasound SGB (Z-scores listed above) or in the group receiving ultrasound SGB plus sham lidocaine (Z = -0.59, P = 0.55; Z = -0.63, P = 0.53, respectively). Due to the variation in the interventions there were not adequate data to allow pooling of the results.

Carroll 2009 reported a significantly longer duration of analgesia in the botulinum toxin group (median time to analgesic failure 71 days (95% CI 12 to 253)) compared with bupivacaine alone (< 10 days, 95% CI 0 to 12; P < 0.02). However, while the authors reported that pain intensity declined significantly in the botulinum toxin group they did not provide numeric pain scores for either treatment group.

Meier 2009 compared lumbar sympathetic blockade (LSB; via lidocaine given through the lumbar catheter) and IV saline to IV lidocaine and saline given through the lumbar catheter. They reported a significant improvement in verbal pain scores in the LSB group; 11 participants reported greater improvement in pain scores with LSB compared with IV (P = 0.05, Wilcoxin signed-ranks test), three participants reported a trend towards greater improvement with IV than with LSB, and improvement in pain scores was no different between groups in nine participants. No significant between-group difference was observed in mean spontaneous pain scores (colour analogue scale, mean difference LSB - IV = -0.5, 95% CI -1.4 to 0.5). There were no significant differences between pre- and post intervention spontaneous pain scores for either group (LSB group: pre-intervention median (range) pain scores: 5.4 (1.5 - 10), postintervention: 4.8 (1.4 - 10); IV group: pre-intervention: 6.0 (1.8 - 9.8), postintervention: 5.8 (1.6 - 10)).

Rodriguez 2005 reported the treatment efficacy at the two-month follow-up to be 46% in favour of the SGB group, an absolute risk

reduction of 17% in favour of the SGB group with a number-needed-to-treat for an additional beneficial outcome (NNTB) of 6. The NNTB suggests that six people with CRPS would need to be treated with SGB (in addition to physical and pharmacological therapy) to prevent one relapse. There was a higher relapse rate in the control group (37%) versus the SGB group (20%); Hazard ratio: 2.7, 95% CI 1.1 to 6.7. The Kaplan-Meier estimates of the cumulative probability of not having a relapse at two months was 80% in the SGB group and 63% in the control group. However this study did not report the data for pain intensity, or the proportion who achieved meaningful pain relief.

Toshniwal 2012 reported significantly lower short-term pain scores in favour of the group receiving the continuous infraclavicular brachial plexus block versus the group receiving the continuous stellate ganglion block. Specifically,at 30 minutes, 2 hours and 12 hours, those receiving the continuous brachial plexus block had significantly lower intensity of pain (0.7, 0.5, 0.7, respectively) and unpleasantness of pain (0.7, 0.7, 0.8, respectively) scores compared with those receiving a continuous stellate ganglion block (intensity: 3.3, 2.7, 1.9; unpleasantness: 3, 2.7, 1.9; all $P < 0.05$). Dull pain scores were significantly reduced for the brachial plexus block group versus the stellate ganglion block group at 2 hours (0.1 versus 2.4), 12 hours (0.6 versus 1.9) and 24 hours (1.3 versus 2.6) with deep pain also significantly reduced at these time points (2 hours - 0.1 versus 2.3; 12 hours - 0.7 versus 1.6; 24 hours - 1.4 versus 2.4), as well as at 30 minutes post-cannulation (0.1 versus 2.3). There were no statistically significant differences between groups for short-term scores on any of the other Neuropathic Pain Scale components. Furthermore, there was no evidence of increased effectiveness of long-term pain relief for one group over the other, and no between-group differences were found at any other time points. Quality of pain score differences between groups were not statistically compared.

Reporting biases

There were insufficient data to support a formal statistical analysis of reporting/small study biases for any comparison.

Adverse events

Reporting of adverse events was generally limited or missing from study reports. Only five studies provided specific data regarding adverse events.

Carroll 2009 reported moderate side effects in one participant (14.2%) following the botulinum toxin type A LASB. This participant had significant nausea and emesis that began 5 hours after the injection and lasted 2 days, resolving spontaneously.

Meier 2009 found mild side effects for both groups. They reported a higher frequency of adverse effects in the IV lidocaine group (placebo sympathetic block) including headaches (17.4%; 4/23), lightheadedness (30.4%; 7/23), nausea (4.4%; 1/23), blurred vision (4.4%; 1/23), muffled sounds (4.4%; 1/23) and oral numbness (4.4%; 1/23). In the sympathetic block group (placebo IV), only lightheadedness was reported by 26.1% (6/23).

Nascimento 2010 also found mild side effects for all three groups. The SGB group receiving lidocaine and clonidine (Group 2) reported the highest frequency of side effects: 93.3% reported drowsiness (14/15), 13.3% dizziness (2/15), 13.3% hoarseness (2/15), 6.7% reported pain at the injection site (1/15), and 26.7% reported a feeling of dry mouth (4/15). The SGB group receiving only lidocaine (Group 1) reported the lowest frequency of side effects with nausea occurring in 6.5% (1/14), dizziness in 14.3% (2/14), hoarseness in 6.5% (1/14), and pain at the injection site in 6.5% (1/14). Lastly, the group receiving the IV regional block with lidocaine and clonidine (Group 3) reported drowsiness (46.1%; 6/13) and dizziness (7.7%;1/13).

Raja 1991 found mild side effects for the IV phentolamine group, with 55.6% (10/18) reporting nasal stuffiness, 16.7% (3/18) reporting headache and 11.1% (2/18) reporting dizziness. It is unclear whether adverse events were present for the lidocaine LASB group as this was not reported.

Toshniwal 2012 found side effects in both groups. In the continuous stellate ganglion block group, Horner's syndrome was most common (94.7%) while initial motor weakness was the most common side effect in the continuous infraclavicular brachial plexus group (100%). Positive catheter tip culture occurred in 61.1% (11/18) of the stellate ganglion block group and in 8.3% (1/12) in the brachial plexus group; no signs of infection at the catheter site were observed in either group. Catheter migration was found in 5.2% (1/19) of the stellate ganglion block group (versus 7.1% (1/14) of the brachial plexus group). Lastly, hoarseness of voice (for initial 12 hours) was found in 16.7% (3/18) of participants in the stellate ganglion block group.

DISCUSSION

Summary of main results

This systematic review had three objectives:

- To determine if local anaesthetic sympathetic blockade (LASB) is effective for providing pain relief to people with complex regional pain syndrome (CRPS);
- to assess how long pain relief persists;
- and to evaluate the incidence of adverse effects of the procedure.

Previous versions of this review revealed the scarcity of published evidence to support the use of LASB for CRPS and raised questions about its efficacy.

LASB versus placebo or no treatment

This update reveals little progress in developing high quality evidence to support this intervention since the last updates in 2005 and 2010. There are only three placebo-controlled randomised studies that met our inclusion criteria (Aydemir 2006; Price 1998; Verdugo 1995), all of which have very small sample sizes. No firm conclusions can be drawn from this evidence. It is notable that the results to date are not suggestive of a significant effect of LASB over placebo even in the very short term (30 minutes to two hours). We could not estimate the duration of pain relief, if any.

LASB versus other interventions

In a change from previous versions of this review we took the decision to include trials which compared LASB with alternative interventions, or that evaluated the effect of adding LASB to other treatments. We identified a number of such studies which investigated a range of comparisons, and the majority of these demonstrated no significant difference between the intervention and control groups. It is notable that in one small study (Bonelli 1983) LASB did not demonstrate superior effectiveness when compared to intravenous regional blockade (IVRB) with guanethidine, an intervention for which there is consistent evidence of inefficacy (Jadad 1995; McQuay 1997).

One small study provided limited evidence that, compared with LASB alone, sympathetic blockade with botulinum toxin A added to local anaesthetic (LA) may prolong analgesia (Carroll 2009). Another single study provided limited evidence to suggest that when added to usual physical therapy and pharmacological treatment LASB may reduce the risk of relapse (Rodriguez 2005) but this study was found to be at high risk of bias across multiple criteria, did not report data for pain relief, and the lack of a sham condition raises the possibility that the observed improvement may have resulted from non-specific effects. In contrast, Zeng 2003 found no benefit of adding cervical sympathetic blockade to usual comprehensive rehabilitative treatment for pain outcomes. In children with CRPS, Meier 2009 did not clearly demonstrate the superiority of LASB compared with IV lidocaine for our primary outcome of pain relief (termed 'spontaneous pain' by Meier 2009), although larger reductions in forms of evoked pain (outcomes not included in this review) were seen after LASB.

There is limited evidence that, compared with continuous infraclavicular brachial plexus blocks, continuous stellate ganglion LASB results in less relief in short-term pain intensity, pain unpleasantness, deep pain and dull pain (Toshniwal 2012). The same study also provides limited evidence of no difference in longer-term pain relief (up to four weeks) between groups (Toshniwal 2012).

Given the limited evidence available and the various sources of potential bias and uncertainty, we would conclude that there is little to no credible evidence to support the use of LASB for CRPS and that the majority of the limited evidence available suggests that LASB may be ineffective.

Adverse Events

The reporting of adverse events in the identified studies was inconsistent and limited. Only four studies provided complete data (Carroll 2009; Meier 2009; Nascimento 2010; Toshniwal 2012). Given this lack of reporting and the small size of all of the included studies we can draw no confident conclusions regarding the safety of LASB. While those adverse events that have been reported appear to be minor, the potential for rare but serious adverse events can not be ruled out. It is likely that to get a better estimate of the incidence and nature of adverse events we would need to review evidence from non-randomised observational study designs, but that was beyond the scope of this review.

Overall completeness and applicability of evidence

By undertaking a systematic search of unpublished and grey literature and consulting experts in the field we have limited the risk of excluding important and relevant evidence. Of the included studies, all were judged as being at unclear risk of bias on at least one criterion, reflecting a common lack of clarity in many study reports, and three were judged as being at high risk of bias specifically for the selective reporting of outcomes. This represents a significant challenge to a confident interpretation of an already limited evidence base. Two of the included studies (Raja 1991; Wehnert 2002) primarily aimed to investigate the comparative utility of LASB as a method of diagnosing sympathetically-maintained pain (SMP), rather than the efficacy of LASB as a treatment. We included these studies to provide evidence regarding the effectiveness of a single LASB.

We attempted to contact the authors of five studies, with mixed success. Two responded and provided necessary data (Nascimento 2010; Toshniwal 2012). However, as we were unable to source one study despite numerous efforts (Salinas Cerda 1997), and unable to include two studies (Rodriguez 2006; Rodriguez 2008) due to lack of clarity over the participant population (i.e., different from previously published studies?), it is possible that we are missing relevant data.

Quality of the evidence

None of the included studies was judged as being at low risk of bias across all criteria. Indeed, all but two studies were judged as being at unclear risk of bias for random sequence generation and for allocation concealment. These factors have been demonstrated to exaggerate the effects of studies, particularly those with subjective outcomes, such as pain (Schulz 1995; Wood 2008). All

studies were judged to be at high risk of bias for inadequate sample size and only two studies were judged as being at low risk of bias for adequate duration of follow-up. Small studies may well be underpowered to detect a clinical effect but conversely there is empirical evidence that small published clinical trials in pain have a tendency to exaggerate treatment effects (Moore 2010; Nüesch 2010).These numerous sources of potential bias might alone explain any observed positive effects in the included studies. As such, all of the evidence identified should be interpreted with caution.

Potential biases in the review process

While we have attempted to identify all eligible trials using a comprehensive search strategy, it remains possible that we may have missed some key literature. The inclusion of two studies (Raja 1991; Wehnert 2002) that primarily sought to investigate the utility of LASB as a diagnostic tool for sympathetically-maintained pain may be contentious. These studies recruited participants with CRPS in which sympathetic dysfunction had not been demonstrated. However the same can be said for the majority of included studies. Only three included studies used a positive response to a prior LASB to attempt to establish SMP as part of their inclusion criteria (Carroll 2009; Price 1998; Rodriguez 2005). This speaks to a wider issue concerning the use of LASB in CRPS. It is possible that LASB might only be effective in a subgroup of people with CRPS with sympathetic dysfunction, or perhaps characterised by other factors. However, to date evidence of predictors of a positive response to LASB are elusive (Sethna 2012).

Agreements and disagreements with other studies or reviews

Our results do not change the overall conclusions of earlier versions of this review. Similarly a number of earlier systematic reviews have included evaluations of the evidence for LASB (Forouzanfar 2002; Perez 2010; Tran 2010) and all have similarly agreed that the evidence is limited and that there is no clear evidence for the efficacy of LASB.

AUTHORS' CONCLUSIONS

Implications for practice

The limited data available, both in terms of size and quality, do not suggest that local anaesthetic sympathetic blockade (LASB) is superior to placebo in the treatment of complex regional pain syndrome (CRPS) or to a range of other interventions. Only one study, judged to be at high risk of bias, suggests that LASB may reduce the risk of recurrence of pain when added to rehabilitation and standard pharmacological care. However on the basis of such evidence it is not possible to make any clinical recommendations. There is currently little credIble evidence to support the use of LASB for CRPS.

Implications for research

If LASB is to continue to be offered to people with CRPS, there is a clear need for further, better quality research into its efficacy. It seems likely that the best chance of delivering high quality trials is through multi-centre, international collaborative research projects which might recruit from larger clinical populations. Future trials should use established diagnostic criteria and clearly report the type of CRPS under investigation. Trials should also consider the recent IMMPACT recommendations (Dworkin 2008; Dworkin 2009; Dworkin 2010; Turk 2008a; Turk 2008b) for the design of trials in pain to ensure that outcomes, thresholds for clinical importance and study designs are optimal. Furthermore, future trials should adhere to the CONSORT guidance (Altman 2012) on standards of reporting, and should clearly report all adverse events.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aydemir 2006

Methods	RCT, parallel design
Participants	n = 25; divided into 3 groups (Group 1: n = 9; Group 2: n = 9; Group 3: n = 7) Age mean (SD): Group 1: 21.9 years (1.05) Group 2: 21.4 years (0.73) Group 3: 21.1 years (0.38) Upper limb CRPS Type I (dominant arm: Group 1, n = 6; Group 2, n = 9; Group 3, n = 2); excluded if had SGB block in last month Diagnostic criteria: IASP (Bruehl 1999) Duration of symptoms: Group 1 (0 - 3 months, n = 5; 3 - 6 months, n = 2; > 6 months, n = 2) Group 2 (0 - 3 months, n = 6; 3 - 6 months, n = 2; > 6 months, n = 1) Group 3 (0 - 3 months, n = 5; 3 - 6 months, n = 0; > 6 months, n = 2) Type of initiating injury: Group 1 (Trauma, n = 7; Fracture, n = 2; Idiopathic, n = 0) Group 2 (Trauma, n = 2; Fracture, n = 5; Idiopathic, n = 2) Group 3 (Trauma, n = 3; Fracture, n = 4; Idiopathic, n = 0) Concomitant treatments: All groups received 21 sessions of physiotherapy which involved exercises, contrast baths, transcutaneous electrical nerve stimulation (TENS), pneumatic compression. If necessary, all groups had access to medical treatment which involved 500 mg oral paracetamol pill, 3 g/day Medicolegal factors: not reported Previous treatment: not reported
Interventions	Group 1: Stellate ganglion lidocaine block (real) plus sham stellate ganglion ultrasound block Group 2: Stellate ganglion ultrasound block (real) plus sham stellate ganglion lidocaine block Group 3: Sham stellate ganglion lidocaine block and sham stellate ganglion ultrasound block For the purpose of this review, we included comparisons between Group 1 and Group 3 as placebo-controlled and comparisons of Group 1 and Group 2 as comparison with another active intervention SGB lidocaine (real): Location: C6 level; 1.5 cm lateral to central line, 4 - 5 cm deep Dosage:10 ml of 1% lidocaine Number of blocks performed: 10 Eval. of technical adequacy of block: No. SGB (sham): Identical site, but injected 10 ml of saline. Number of blocks not reported. SGB ultrasound (real): Probe size of 1 cm^2; 5 minutes of intermittent US at 3 watt/cm^2 over the affected site

Aydemir 2006 (*Continued*)

	(over stellate ganglion) Number of treatments not reported. SGB ultrasound (sham): 5 minutes, no energy delivered. Number of treatments not reported.
Outcomes	Spontaneous pain: 0 - 10cm visual analogue scale Outcomes measured pretreatment, post-treatment, and at one-month follow-up Adverse events/side effects not reported.
Country of origin	Turkey
Study aim	To investigate the efficacies of stellate ganglion blockage (SGB) with lidocaine and ultrasound in CRPS
Notes	This study was translated and interpreted by a researcher fluent in Turkish. The study author, TS, worked with the researcher to fully interpret and score Conflict of interests not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: Method of randomisation not reported
Allocation concealment (selection bias)	Low risk	Envelope method used to conceal allocation; group assignment generated by an independent person
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind" Comment: Reported that participants and personnel blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Reported that outcome assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Drop-outs/withdrawals not reported.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were adequately reported on.
Adequate sample size?	High risk	Group 1, n = 9; Group 2, n = 9; Group 3, n = 7
Adequate duration of follow up?	Unclear risk	One month follow-up

Aydemir 2006 (*Continued*)

Free of other bias?	Low risk	Pain scores were not significantly different between groups at baseline; identical timing of outcome assessment between groups

Bonelli 1983

Methods	RCT, parallel design
Participants	n = 19 Age: mean(SD) 52.33 (5.04) Gender: not reported. Diagnosis of RSD following peripheral nerve injury. At least 3 of the following clinical signs: hyperpathia, allodynia, vasomotor disturbance, trophic signs, oedema, limited motion Mean (SD) duration of pain: Stellate ganglion block group: 6.55 (3.94) months IVRB guanethidine group: 17.55(14.9) months Previous treatment not reported. Concomitant treatment not reported 2 lost to follow-up at 3 months in SGB group Baseline pain (0 - 100 scale) mean (SD): Stellate ganglion block group: 70.5 (27.36) IVRB guanethidine group: 65 (25.46) Medico-legal factors: not reported
Interventions	SGB (n = 10) versus IVRB guanethidine block (n = 9); treatment period of 16 days SGB: Bupivacaine (0.5%) 15 ml No. of blocks: 8 (1 every other day for 16 days) Evaluation of adequacy of block? Skin temperature, plethysmographic wave IVRB guanethidine (20 ml), heparin (500 μl), isotonic saline (25 ml) No. of blocks: 4 (every 4 days)
Outcomes	Pain: 100 mm linear scale (specific details not reported) Pain measured at baseline and post-treatment at 15 minutes, 60 minutes, 24 hours, 48 hours, 1 month and 3 months Adverse events only mentioned in discussion (alludes to none in either group)
Country of origin	Italy
Study aim	To compare the effects of regional IVRB with guanethidine with stellate ganglion blocks in people with severe RSD following peripheral nerve injury of the upper limb
Notes	Conflicts of interest not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Bonelli 1983 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly allocated to two groups" Comment: Method of randomisation not reported.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participant blinding not reported. The interventions are likely to be distinguishable. Unsure if participants aware of study hypothesis
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessor blinding not reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data post-treatment and one-month follow-up. 3 months: 2/10 missing from SGB group, no missing data for IVRB group
Selective reporting (reporting bias)	Low risk	All outcomes listed in methods were reported in the results.
Adequate sample size?	High risk	n = 19; n = 10 stellate ganglion block group, n = 9 regional IV guanethidine
Adequate duration of follow up?	Low risk	Follow-up of 3 months
Free of other bias?	High risk	SGB group had a significantly shorter duration of symptoms than the IVRB guanethidine group (mean [SD]: 6.55 [3.94] months versus 17.55 [14.9] months; P < 0.05) and were significantly older (mean [SD]: 52.33 [5.04] years versus 42.77 [4.65] years; P < 0.01)

Carroll 2009

Methods	RCT cross-over
Participants	n = 9 Lower limb CRPS-I, with duration of pain of at least 6 months, spontaneous pain rating > 6/10, unsuccessful therapy with at least 2 non-opioid medications (for neuropathic pain), at least a 50% reduction in pain for > 5 hours but < 2 weeks from a previous lumbar sympathetic injection Inciting events: tarsal tunnel surgery n = 1, bunionectomy/cast n = 1, crush injury n = 1, plantar fasciectomy n = 1, foreign body removal n = 1, ankle arthroscopy n = 1, ankle fracture/cast n = 1, metatarsal fracture n = 1, back surgery n = 1 Diagnostic criteria: IASP (Merskey 1994) Medico-legal factors: not reported. Age mean (range) 49.4 (38 - 67) Gender: 1 man Duration of pain (years) mean (range) 3.8 (2 - 14)

	Baseline pain levels (whole group) mean (range) 7.2 (4.7 - 8.9) Concomitant treatments: Not reported but participants asked not to cease existing therapies, but not to start new therapies during study period
Interventions	Lumbar sympathetic blocks: Anterolateral border of L2 vertebral body, fluoroscopy guided Active: 10 ml of 0.5% bupivacaine with an added 75 units Botulinum toxin-A Control: 10 ml of 0.5% bupivacaine.
Outcomes	Primary outcome: time to analgesic failure (time for pain to return to baseline level) Daily pain intensity - 10 cm VAS, measured for 7 days prior to first injection and recorded daily until participants reported their pain returned to baseline or 1 month (whichever was longer) Adverse events reported.
Country of origin	USA
Study aim	To determine whether adding BTA to lumbar sympathetic blockade increases the duration of analgesia
Notes	Authors declared that they had filed a patent for BTA in sympathetic blocks

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Patients were randomly assigned to which injection they received first" Comment: Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All physicians and patients involved in the study were blinded to which injection contained botulinum toxin A. Data were not unblinded for any patient until the study was completed, and no interim analyses were performed"; "in the crossover injection, the patient received an identical injection" Comment: Injections were identical and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: as above. Comment: Self-reported outcomes and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2/9 participants did not complete the study (one due to technical issues related to the block - malpositioning of the needle - and one because outcome forms were not returned). Only 1 participant received Botox first and this participant dropped out Due to complete blinding and use of a cross-over study design, the effect that this drop-out has on the results is unclear

Selective reporting (reporting bias)	Unclear risk	Full data not presented for the secondary end point (VAS pain scores over time); comparison of within-injection group change over time provided, but comparison of between-injection group differences not provided
Are data clearly free of carry-over effects? (cross-over designs only)	Low risk	Quote: "patients were eligible for their crossover injection 1 month after they reported their pain had returned to baseline" Comment: 1 month washout period observed, after pain had returned to baseline levels
Adequate sample size?	High risk	n = 9
Adequate duration of follow up?	Unclear risk	Quote: "Patients continued to record daily VAS until they reported their pain had returned to baseline or 1 month, whichever was longer" Comment: Follow-up was observed until pain returned to baseline levels - for some this was only 4 weeks
Free of other bias?	Low risk	Cross-over study design ensured similarity between groups; participants allowed to continue current medications but could not start new medications

Meier 2009

Methods	RCT cross-over
Participants	n = 23 Children with unilateral lower limb CRPS (type I or II) Diagnostic criteria (Stanton-Hicks 1995) Gender: 3 boys Age: mean(SD) 14.4 (2.4) range 10 -18 Baseline pain levels: Slight: Group 1, n = 3; Group 2, n = 5 Moderate: Group 1, n = 6; Group 2, n = 10 Severe: Group 1 n = 14, Group 2, n = 10 Duration of pain: median (IQR) 9 months (4.5 - 23) Inciting events: sports injury n = 8, surgery n = 6, accidental trauma n = 8, unable to recall n = 1 Previous treatment: failed to respond to a 6-week trial of aggressive physical, bio-behavioural and pharmacological therapies Concomitant treatments: use of NSAIDs withheld for 2 days prior to trial intervention Medico-legal factors: not reported.
Interventions	IV lidocaine + placebo sympathetic block (Group 1) versus IV placebo + lidocaine sympathetic block (Group 2) Lumbar sympathetic block: percutaneous lateral paravertebral approach at anteromedial border of L 2/3 vertebral bodies. Fluoroscopy guided. Active: 1% lidocaine (0.1 ml/kg

	up to a maximum possible total of 6 ml) Placebo: saline 0.9% (0.1 ml/kg) IV lidocaine: 1% lidocaine (0.1 ml/kg up to a maximum possible total of 6 ml). Placebo: saline 0.9% (0.1 ml/kg) No. of blocks performed:1 for each condition Evaluation of adequacy of block: YES. Semi-objective measures of increased ipsilateral skin temperature and decreased evoked pain
Outcomes	Global 4-point verbal pain scale (none, slight, moderate, severe) Colour analogue scale for spontaneous pain. Both pain outcomes were measured pre- and 30 minutes post-intervention Adverse events measured.
Country of origin	USA
Study aim	To compare the efficacy of lidocaine administered by lumbar sympathetic or IV route
Notes	Grants and financial support reported but no clear statement relating to conflicts of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "We randomized the patients using a pseudo-random number generator" Comment: Probably done.
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "A single blinded researcher performed all bedside examinations and computerized quantitative sensory testing"; "Neither the investigator who performed and collected the pain assessment data in all patients nor the patients were aware of the nature of the solutions injected" Comment: Indistinguishable treatments and participants blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: as above Comment: Single assessor blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data; n = 23 in all tables.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes (in methods) adequately reported in the results
Are data clearly free of carry-over effects? (cross-over designs only)	Low risk	Quote: "two-paired injections were administered in two sessions 12 h apart to allow adequate systemic washout of lidocaine";

Meier 2009 (*Continued*)

		"The volume of lidocaine 1% was 0.1ml/kg and did not exceed a total of 6ml, which is minimally adequate to achieve satisfactory sympathetic ganglia blockade"; "No carryover effects were found for any variable of spontaneous and evoked pain assessment" Comment: 12-hour washout period, minimal required dose used, carry-over effects investigated and not found
Adequate sample size?	High risk	n = 23
Adequate duration of follow up?	High risk	Only 30 minutes post-injection follow-up
Free of other bias?	Low risk	Cross-over study design ensured similarity between groups. Outcome assessment timing identical between treatment

Nascimento 2010

Methods	RCT, parallel
Participants	n = 43 Gender: Group 1 (n = 14): 1 male Group 2 (n = 15): 1 male Group 3 (n = 14): 1 male Age mean (range): Group 1: 37.7 (27 - 54) Group 2: 38.6 (25 - 50) Group 3: 39 (27 - 50) Upper extremity CRPS Diagnostic criteria: IASP (Merskey 1994) Duration of pain (months) mean (range): Group 1: 24.2 (3 - 72) Group 2: 24.2 (8 - 72) Group 3: 22.3 (2 - 48) Baseline pain intensity (mean (SEM): Group 1: 8.7 (0.3) Group 2: 8.7 (0.3) Group 3: 8.3 (0.3) Inciting event: Repetitive strain injury n = 18, carpal tunnel syndrome n = 11, late post surgical pain n = 8, fracture and long lasting immobilisation n = 3, stab wound n = 2, unknown n = 1 Previous treatment for CRPS: unsuccessful use of tricyclic antidepressants, gabapentin, opioids or anti-convulsants At admission all free of drugs. Medico-legal factors: not reported
Interventions	Group 1: SGB, anterior paratracheal approach, fluoroscopy-guided, 70 mg 1% lidocaine Group 2: SGB, identical approach,70 mg 1% lidocaine + 30 μg clonidine Group 3: IVRB 7.0 ml solution 1% lidocaine with 1 μg/kg clonidine. Tourniquet

	pressure released 30 mins later Evaluation of adequacy of block?: YES, temperature checked No. of blocks: 5, x 1 weekly
Outcomes	Pain intensity 0 - 10 cm VAS (anchors "no pain" to "worst pain imaginable") Pain was measured immediately before and soon after the end of each procedure. Pain intensity scored daily. Pain measured one week after the last procedure Duration of analgesia calculated as the interval between the end of the procedure and the time at which VAS $\geq$ 3 was recorded Adverse events reported.
Country of origin	Brazil
Study aim	To compare the efficacy of IVRB produced by combining lidocaine with clonidine, to that of SGB produced by the injection of lidocaine, alone or combined with clonidine, into the stellate ganglion, for the management of pain in people with upper extremity CRPS-I
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned to one of three experimental groups" Comment: Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated that study was blinded nor whether participants were blind to the study hypotheses
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Side effects and effectiveness of treatment were recorded by another author who was unaware of the procedure" Comment: While side effects and effectiveness were recorded by a blinded assessor, the use of self-reported outcome in participants who may not have been blind to the study hypothesis is a possible risk of bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Excluded 2/45 with clear reasons and clear n reported for all graphs
Selective reporting (reporting bias)	Low risk	Adequately reported results for all prespecified outcomes (from methods section)
Adequate sample size?	High risk	n = 45; 15 participants per treatment group
Adequate duration of follow up?	High risk	1 week follow-up

Nascimento 2010 (*Continued*)

Free of other bias?	Low risk	No differences between groups for important prognostic factors, participants not taking any medication at inclusion, outcome assessment timing identical between groups

Price 1998

Methods	Quasi-randomised controlled trial (cross-over)
Participants	7 adults with CRPS I or II of upper or lower extremities (excluded if CRPS in multiple areas) Diagnostic criteria: IASP (Merskey 1994) n = 7 (3 lower extremity, 4 upper extremity pain) Age: mean 42 years (SD: 11; range: 32 - 52) Gender: 3 men Duration of symptoms: mean of 3 years (SD: 2 years; range 18 months to 7 years) Inciting event: trauma (n = 6), surgical (n = 1) Medico-legal factors: not reported Previous treatment: not reported Concomitant treatment: All participants continued concomitant physical therapy and medications
Interventions	Active condition: Stellate ganglion blockade with lidocaine (15 ml of lidocaine 1%) Lumbar sympathetic blockade with 15 ml 1% lidocaine (test solution) followed by 10 ml bupivacaine 0.125% Evaluation of technical adequacy of block? YES - evaluated Horner's syndrome and surface skin temperature for stellate ganglion blocks. Nothing reported for lumbar blocks Control condition: Stellate ganglion: 15 ml saline Lumbar: 15 ml saline +10 ml saline The blocks were separated by a period of 7 - 10 days. Number of blocks: 1 for each condition
Outcomes	Pain intensity and pain unpleasantness (0 - 10 VAS). Pain outcomes measured every 15 minutes for 1.5 hours prior to injection and every 15 minutes for 1 hour following injection. Pain outcomes then rated 4 times a day (morning, mid-day, afternoon, evening) for 7 days post-injection Time to peak analgesia measured as the VAS unit difference between pre-inujection baseline pain rating and the lowest VAS rating in the first hour Duration of pain relief measured as the time it took for pain intensity to return to 50% of the difference between baseline and peak analgesic effect
Country of origin	USA
Study aim	To evaluate the diagnostic and therapeutic value of local anaesthetic sympathetic blocks
Notes	Author confirmed the quasi-random allocation in correspondence

Price 1998 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "Four patients received S first with LA block second, and the order was reversed for the remaining 3 patients" Comment: Quasi-random process used, not truly random. Due to cross-over study design and successful blinding, we feel this presents an unclear risk of bias
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both the patient and the physician administering the sympathetic ganglia injections were blind with regard to the contents of the injecting syringe (S or LA) and with regard to whether skin surface temperature changes or Horner's syndrome occurred"; "The syringe was filled...by a third person who maintained the code for the contents of the syringes and the double-blind nature of the study"; "None of the 7 patients reported subjective differences between effects of S and LA blocks within the first hour after block. However, 2 patients correctly determined that they had received S injection because of the shorter duration of relief received." Comment: Blinding completed and blinding success was formally assessed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were self-rated and participants were blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/7 participants missed all pain unpleasantness data but pain intensity data complete
Selective reporting (reporting bias)	High risk	Group results for pain unpleasantness scores not reported
Are data clearly free of carry-over effects? (cross-over designs only)	Low risk	Procedures separated by 7 - 10 days. Figures illustrate pain returned to baseline levels prior to next block
Adequate sample size?	High risk	n = 7

Price 1998 (*Continued*)

Adequate duration of follow up?	High risk	7 days follow-up
Free of other bias?	Low risk	Quote: "Medication use and physical therapy were as similar as possible for the time periods following both saline and lidocaine blocks, and medications were not, as a rule, significantly adjusted during the study period." Comment: Also, cross-over study design ensured similarity between groups for important outcomes and outcome assessment at same time periods

Raja 1991

Methods	Randomised cross-over trial
Participants	n = 20, 10 upper limb, 10 lower limb Mean age: 40 (range 20 - 57) Gender not reported Diagnosis of sympathetically maintained pain was "under consideration" based on clinical criteria (chronic pain and hyperalgesia to pain and/or cooling stimuli) Mean duration of pain 37 months (range 6 - 120) All participants had a prior history of traumatic or surgical injury of which 10 had one or more peripheral nerve injuries Previous treatment not reported. Medico-legal factors not reported Concomitant treatment not reported
Interventions	Sympathetic blockade (stellate or lumbar) with bupivacaine versus IV phentolamine block Sympathetic block: Substance injected:0.25% bupivacaine hydrochloride (10 ml SGB, 20 ml lumbar) Site of block: Lumbar - anterolateral border of body of L2 or L3 vertebrae. Fluoroscopic guidance, single needle technique Cervical - anterior paratracheal approach to SGB No. of blocks: 1 Evaluation of technical adequacy of block?: YES - cutaneous temperature measures, sensory testing to exclude somatic nerve block Phentolamine block: IV catheter Substance injected: 300 - 400 ml lactated Ringers solution followed by basal infusion of 2 $ml.kgh^{-1}.h^{-1}$ 1 or more boluses of normal saline (3 - 5 ml) to establish the presence of significant placebo responses then phentolamine at 3 - 8 minute intervals in increasing dose ranging from 1 - 10 mg up to a total of 25 or 35 mg

Raja 1991 (*Continued*)

Outcomes	Intensity of ongoing pain (0 - 100 VAS, Anchors "no pain" to "most intense pain imaginable") Pain was rated every 5 minutes before, during, and after the interventions. Baseline pain measurements were made for at least 15 mins prior to the blocks. A subsample of patients was assessed at hourly intervals for several hours (sympathetic blockade, n=3; phentolamine, n=4) Maximum pain relief: difference between the control (average of two consecutive pain ratings immediately prior to intervention) and the lowest postblock rating (average of two consecutive lowest pain ratings), expressed as a percentage of the control pain rating Adverse events reported.
Country of origin	USA
Study aim	To determine if systematic α-adrenergic blockade with phentolamine can be used to diagnose SMP
Notes	Financial support from NIH & Canadian MRC stated 2 patients excluded from analysis after achieving substantial pain relief with infusion of normal saline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The sequence of the two sympathetic blocks was randomized such that half of the patients received the LASB first and the other half received the PhB first" Comment: Method of randomisation not reported, so unclear risk
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated whether participants/personnel were blind to the study hypothesis
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes were self-rated; not stated whether participants were blind to the study hypothesis
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "Two patients had nearly complete relief of pain and hyperalgesia during the saline injection period prior to the administration of propranolol. These two patients were excluded from further analysis"; "In four of the nine SMP patients, the duration of pain relief after PhB was followed for several hours"; "In three of the four above-mentioned SMP patients, the duration of pain relief after LASB also was followed for 4-8 h" Comment: 2/20 were excluded (10%), duration of pain

Raja 1991 (*Continued*)

		relief not followed up for the entire group
Selective reporting (reporting bias)	Low risk	Reported on all prespecified outcomes
Are data clearly free of carry-over effects? (cross-over designs only)	Unclear risk	Not reported; no clear washout period reported (range for 1 to 40 days)
Adequate sample size?	High risk	n = 20
Adequate duration of follow up?	High risk	Quote: "the duration of pain relief after PhB was followed for several hours...varied from 3 to 10 h"; "the duration of pain relief after LASB also was followed for 4-8 h" Comment: Maximum follow-up of 10 hours postintervention (ranged from 3 - 10 hours postintervention)
Free of other bias?	Low risk	Cross-over study design ensured similarity between groups and outcome assessment timing was identical

Rodriguez 2005

Methods	RCT, parallel design
Participants	82 participants with upper limb CRPS (Type I or Type II) with presence of pain mediated by the sympathetic nervous system (defined as a decrease in resting pain by 50% with a stellate ganglion block) Diagnostic criteria: IASP 1994 71.4% of CRPS cases were secondary to accidental or violent trauma and 18% occurred following surgical procedures 2 active intervention groups: 1. SBG group: n = 41, mean age: 44.1 years, gender: 36.6% men, 75.6% CRPS-1, 68.3% right hand affected, 14.6% had a compensation claim, duration of symptoms: 253.7 days 2. Control group: n = 41, mean age: 46.1 years, gender: 46.3% men, 70.7% CRPS-1, 46.3% right hand affected, 24.4% had a compensation claim, duration of symptoms: 213.4 days Previous treatment: participants were excluded if they had previous stellate ganglion blocks; no other previous treatment reported Concomitant treatment: those receiving stellate ganglion blockade also received physical therapy and pharmacological treatment
Interventions	SGB, physical therapy and pharmacological treatment vs physical therapy and pharmacological treatment SGB Group: Site of block: paratracheal at the height of the cricoid cartilage Number of blocks: 5 Type of substance injected: 10 cc of volume with equal parts of 2% lidocaine and 0.5% bupivacaine Evaluation of technical adequacy: Increase in temperature of at least 1°C of the hand

	and face (affected side) and the presence of Horner's syndrome (ptosis of the upper eye lid and conjunctivitis) Control group: Received physical therapy and pharmacological treatment.
Outcomes	1. Pain intensity (VAS). Measured at baseline, one month and two months. Exact follow-up time appears to be variable among participants (ie, followed for more than two months in some) 2. Therapeuctic efficacy: Number of participants with at least 50% reduction in the pain Measured at 2 months post-intervention 3. Efficacy: (incidence of pain in control group - incidence of pain in the SGB group)/ incidence of pain in the control group * 100 4. Absolute risk reduction (incidence of pain in control group - incidence of pain in the intervention group). Measured at 2 months post-intervention 5. NNTB = 1/ARR (calculated at 2 months post-intervention) 6. Relapse (return of pain to less than 50% reduction or return of pain to baseline levels or above); determined at 2 months post-intervention
Country of origin	Colombia
Study aim	To determine the analgesic efficacy of the stellate ganglion blockade (SGB) in the alleviation of pain mediated by the sympathetic nervous system in patients with Complex Regional Pain Syndrome
Notes	This is the first published study by Rodriguez. There are 2 other published studies and one IASP abstract that use an identical study design. It is unclear if all the studies represent the same base participant population. We attempted to contact the authors 3 times with no success This study was translated and interpreted by a researcher fluent in Spanish. The study author, TS, worked with the researcher to fully interpret and score Funded by Colciencias and the Universidad Libre Seccional Cali. No conflict of interest stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" Comment: Method of randomisation unclear
Allocation concealment (selection bias)	Low risk	Opaque envelopes used; randomly given to each participant.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "double blind" Comment: Probably not. Index and control groups are not indistinguishable and success of blinding was not tested
Blinding of outcome assessment (detection bias) All outcomes	High risk	The investigator was reported to be blinded; however, outcomes were self-reported and participants were likely not blinded

Rodriguez 2005 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants that dropped out or underwent surgery were excluded from the analysis. The number of excluded participants per group is not reported
Selective reporting (reporting bias)	High risk	No pain scores were given and time to relapse was unclear
Adequate sample size?	High risk	n = 82 (41 in each group)
Adequate duration of follow up?	Low risk	Follow-up of 2 months
Free of other bias?	High risk	No baseline data given on pain intensity; unsure if groups were similar at baseline

Toshniwal 2012

Methods	RCT, parallel design
Participants	33 people diagnosed with CRPS type I of the upper extremity (diagnostic criteria IASP 1999), which had lasted at least 3 months and was refractory to medical management. People receiving any interventional procedure for the condition were excluded Participants were randomised to one of two active intervention groups: 1. Continuous stellate ganglion block (CSG) n = 19 (1 excluded due to catheter dislodgement), mean age 44.33 years (SD: 13.6), 6 men, mean duration of pain: 8.8 months (SD 4.4) 2. Continuous infraclavicular brachial plexus block (CIBP) n = 14 (1 excluded due to catheter dislodgement and 1 due to failure to follow-up after 2 weeks), mean age 42 years (SD 16.6), 7 men, mean duration of pain: 9.3 months (SD 2.8) Both groups: Inciting event: not reported. Medico-legal factors: not reported Previous treatment: not reported Concomitant treatment: Physiotherapy (4 weeks), no change in medication
Interventions	Continuous stellate ganglion block (CSG) versus continuous infraclavicular brachial plexus block (CIBP). Both groups received physiotherapy (as per recommendations from same physiotherapist) for 4 weeks. No change in regular medications in either group 1. CSG block Site: Stellate ganglion - 20 G IV cannula was inserted anterolaterally into the neck, lateral to the cricoid cartilage. Cannula inserted until the C6 tubercle was hit at which time the stylet was removed and the cannula vertically sutured to the skin. Cannula position confirmed via injection of 2 mL of radio-opaque dye under fluoroscopy Number of blocks: Continuous block for 7 days Type/amount of anaesthetic: bolus of 10 mL (5 + 5 mL) 0.25% bupivacaine was injected. An elastomeric pump (solution of 0.125% bupivacaine 280 mL, delivering at 2 mL/hour) was attached to the catheter. Pump was changed on day 5 Evaluation of technical adequacy: Measured temperature difference between arms (> 1. 5°C temperature increase in the affected arm considered adequate sympatholysis) and

	degree of vasodilatation using plethysmography scores (where an increase in the waveform reading score by 2 was considered improved circulation secondary to sympatholysis/ vasodilatation) 2. CIBP block Site: Brachial plexus - identified using nerve stimulation by vertical approach and inserting a Contiplex D needle with catheter. Position was confirmed via injection of 3 cc of radio-opaque dye under fluoroscopy Number of block: Continuoue block for 7 days Type/amount of anaesthetic: Bolus of 30 mL 0.25% bupivacaine was injected through the catheter. An elastomeric pump containing 0.125% bupivacaine 400 mL delivering at 5 mL/hour was connected to the catheter. Pump was changed on days 3 and 6 Evaluation of technical adequacy: As above. Both groups had an increase in temperature of the blocked arm (vs contralateral hand) and improvement in circulation (at 30 mins) ; no difference between groups
Outcomes	Neuropathic pain scale - components analysed separately (intensity, sharp, hot, dull, cold, sensitive, itchy, unpleasant, deep pain, surface pain, and quality of pain). Scale was 0 (i.e., intensity, 0 = no pain) to 10 (i.e., intensity, 10 = most intense pain sensation imaginable) Measured at 6 minutes, 30 minutes, 2 hours, 12 hours, and 24 hours, day 2, day 3, day 4, day 5, day 6, day 7, week 2, week 3, week 4 Adverse events reported.
Country of origin	USA
Study aim	To compare the efficacy of continuous stellate ganglion (CSG) block with that of continuous infraclavicular brachial plexus (CIBP) block in management of CRPS type I of upper extremity
Notes	The authors acknowledged editorial support from 2 doctors from Wayne State University, Detroit. The authors declared that they have nothing to disclose and no conflict of interest

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients...were randomly assigned to receive CSG block or CIBP block using a computer-generated table of random numbers (50 numbers in two columns)" Comment: Likely done.
Allocation concealment (selection bias)	Low risk	Quote: "Group allocations was concealed in sealed opaque envelopes that were not opened until patient consent had been obtained" Comment: Likely done.

Toshniwal 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Both active interventions but does not mention blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes are self-rated, thus unclear risk due to uncertainty whether participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Three patients were dropped from the study. One patient from each group was excluded from the study as their catheters became dislodged during the follow-up period, and one patient in the CIBP group was excluded because he failed to follow up after 2 weeks" Comment: Drop-out rates < 20% (1 group had 1/19 drop out [5.3%] and 1 had 2/14 drop out [14.3%]). Similar reasons for drop-out
Selective reporting (reporting bias)	Low risk	Reports all outcomes and all between-group differences
Adequate sample size?	High risk	n = 18 (CSG), n = 12 (CIBP)
Adequate duration of follow up?	Unclear risk	4 weeks of follow-up
Free of other bias?	Low risk	Groups were similar on important prognostic factors.

Verdugo 1995

Methods	Randomized double blind cross-over study
Participants	16 adults with CRPS of upper extremity. Symptoms of < 3 months duration Age, gender, previous treatments not reported. CRPS diagnosis method not reported. Inciting event: not reported Concomitant treatments: not reported Medico-legal issues: not reported
Interventions	Stellate ganglion blockade with normal saline or with bupivacaine 0.125%
Outcomes	Intensity of spontaneous pain (0-10 VAS) measured pre-block, 2 hours post-block and 48 hours post-block Significant response considered a reduction in pain by 50%.
Country of origin	Chile
Study aim	There are no placebo-controlled studies showing a specific effect of this method (stellate ganglion blockade)

Verdugo 1995 (*Continued*)

Notes	The abstract was published in the proceedings of a scientific meeting. The author has not published the final results. Financial support from Fondecyt Project No. 1940309 stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "The patients were randomly assigned" Comment: Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "double blind"; "the patient was wearing sunglasses to prevent observation of Horner's syndrome"; "the anesthetist, who was not aware of which substance had been given" Comment: Participants/personnel blinded to the nature of the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Self-report outcomes and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	High risk	Results for pain with movement outcome were not provided
Are data clearly free of carry-over effects? (cross-over designs only)	Unclear risk	Interventions were separated by a 1-week period, but long-lasting effect on pain was not measured, so it is unclear if participants returned to baseline levels of pain
Adequate sample size?	High risk	n = 16
Adequate duration of follow up?	High risk	Follow-up of 48 hours
Free of other bias?	Low risk	Cross-over study design ensured similarity between treatment groups, outcome assessment timing identical

Wehnert 2002

Methods	Randomised, cross-over study
Participants	29 participants with "persistent pain in the area of the upper or lower extremities". Used inclusion criteria of Campbell 1996: resting pain + 3/11 symptoms (e.g., changes to skin temperature) Gender: 8 men Age: 43 years (range of 23 - 64) Based on a lack of temperature change in the affected limb with a local sympathetic blockade (n = 9) or a placebo response to saline (n = 1), only 19 participants were considered to have had a correctly performed sympathetic block and pain results were only presented for these 19 participants 12 upper limb, 17 lower limb. Mean duration of pain 21.3 months (minimum of 2 months, maximum of 15 years) Previous treatment not specified No difference in pain scores prior to the 2 interventions (Z = -0.540, P = 0.589) Inciting event: post-surgical or post-traumatic (numbers not reported) Previous treatment: Not reported Medico-legal issues: Not reported Concomitant treatment: Not reported.
Interventions	Stellate ganglion blockade (cervical stellate ganglion in upper limb participants, sympathetic chain of lumbar spine for lower limb participants) versus IV phentolamine infusion Stellate ganglion blockade: Substance injected: 0.1 mL bupivacaine 0.25%/cm plus 500 mL NaCl 0.9% Site of block: Number of blocks: 1 Evaluation of technical adequacy of block?: YES - cutaneous temperature measures Control intervention: Intravenous phentolamine infusion Substance injected:0.5 mg phentolamine/kg for 15 minutes plus 500 mL NaCl 0.9% Site of intervention: provided to a non-affected limb. Number of interventions: 1
Outcomes	VAS pain intensity (0 - 100), measured at baseline and then hourly for 8 hours A significant improvement was defined as reduction of pain of at least 50%
Country of origin	Germany
Study aim	To determine whether the phentolamine test is as suitable as sympathetic blockade in diagnosing cases of sympathetically maintained pain
Notes	While the aim of the study was to diagnose SMP, the data available also provide us with pain outcomes for a local stellate ganglion blockade versus IV phentolamine infusion in participants with SMP, allowing for inclusion in the present review This study was translated and interpreted by a researcher fluent in German. The study author, TS, worked with the researcher to fully interpret and score No statement of financial support or conflict of interest.
Risk of bias	

Wehnert 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized study" Comment: method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported as to whether participants were blinded to the study aims
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported as to whether outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomisation was completed prior to exclusion of 10 participants, therefore 34% drop-out rate
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported
Are data clearly free of carry-over effects? (cross-over designs only)	Low risk	Pain scores prior to the interventions were not significantly different
Adequate sample size?	High risk	n = 19
Adequate duration of follow up?	High risk	Follow-up of 8 hours
Free of other bias?	Low risk	Cross-over study design ensured similarity between participant groups, pre-intervention pain scores similar, outcome assessment timing identical

Zeng 2003

Methods	RCT, parallel
Participants	Shoulder-hand syndrome following stroke. Diagnostic criteria not reported. Duration of symptoms; described as "in the early stages of SHS complicated with paralysis" n = 60 Gender: 42 men Age range: 38 - 71 Previous treatment not specified Baseline pain mean (SD): SGB + rehab group: 6.95 (3.24) Rehab-only group: 6.85 (3.24) Medico-legal factors not reported.

	Concomitant treatments: not reported.
Interventions	Stellate ganglion block + rehabilitation versus rehabilitation only SGB: anterior entry, transverse process of C7, agent, dose not reported Rehabiliation details: reports "comprehensive treatment" eliminating causes of oedema, avoid weight loading of limb, avoid limb trauma, remove factors causing shoulder pain, movement exercises, joint mobilisations, ice therapy, physical therapy
Outcomes	Pain VRS (0 = no pain, 2 = little pain, 4 = often pain but mild or occasional but severe (sic), 6 = severe pain but tolerable, 8 = continuous pain and intolerable, 10 = severe pain that couldn't be touched) Pain was measured before treatment and at 10 days and 20 days post-treatment
Country of origin	China
Study aim	Effect of stellate ganglion is observed on base of comprehensive rehabilitation treatment (sic)
Notes	No statement of financial support or conflict of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided into two groups" Comment: method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Index and control groups are not indistinguishable and success of blinding was not tested
Blinding of outcome assessment (detection bias) All outcomes	High risk	Participant-rated outcomes; participants not blinded (as above)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs.
Selective reporting (reporting bias)	Low risk	All prespecified outcomes adequately reported on.
Adequate sample size?	High risk	n = 60 (30 in each group)
Adequate duration of follow up?	Unclear risk	20 days follow-up
Free of other bias?	Low risk	Quote: "All patients were in early stage of SHS complicated with paralysis"; "there weren't statistical differences at age, sex,

Zeng 2003 (*Continued*)

		rehabilitation kind" Comments: No difference between groups in age, gender, rehabilitation and duration of symptoms; outcome assessment timing identical

BTA: botulinum toxin A; CRPS: complex regional pain syndrome; IASP: International Association for the Study of Pain; IVRB: intravenous regional blockade; LASB: local anaesthetic sympathetic blockade; NNTB: number-needed-to-treat for one additional beneficial outcome; NPS: neuropathic pain scale; NSAID: non-steroidal anti-inflammatory drug; RCT: randomised controlled trial; RSD: Reflex sympathetic dystrophy; SD: standard deviation; SEM: standard error of the mean; SGB: stellate ganglion blockade; SMP: sympathetically maintained pain; VAS: visual analogue scale; VRS: verbal report scale

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

Study	Reason for exclusion
Ackerman 2006	Not randomised.
Arias 1989	Not randomised.
Catala 1994	Sympathetic blockade versus intravenous lidocaine for postherpetic neuralgia
Dellemijn 1994	Sympathetic blockade versus phentolamine infusion.
Erickson 1993	Not randomised.
Farcot 1990	Not randomised.
Fukusaki 1995	Nerve blocks (including sympathetic blocks) for cervical radiculopathy
Garrido 2005	Not randomised.
Geurts 2006	Not randomised.
Glynn 1993	Not randomised
Hartrick 2004	Not randomised.
Linson 1983	Not randomised.
Malmqvist 1992	Not randomised.
Perrigot 1982	Not a local sympathetic block.
Quevedo 2005	Not randomised.

(*Continued*)

Rodriguez 2006	Identical study design to Rodriguez 2005 (included) and recruited from the same sources and time period therefore it seems that this study may have recruited the same population (participant demographics are also very similar). Unable to contact authors to confirm whether these were different populations of participants
Rodriguez 2008	Identical study design to Rodriguez 2005 and Rodriguez 2006, just a larger sample of participants (n=114). Therefore it seems that this study may be using the data from the original studies. Unable to contact authors to confirm whether these were different populations of participants
Salinas Cerda 1997	Could not retrieve this study.
Schurmann 2001	Not randomised.
Steinbrocker 1953	Not randomised.
Tran 2000	Sympathetic blockade plus iohexol versus sympathetic blockade plus saline; evaluating the effect of the contrast agent iohexol
Wang 1985	Not randomised.
Yucel 2009	Not randomised.

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

Rocha 2012

Trial name or title	Thoracic sympathetic block for the treatment of complex regional pain syndrome I of the upper limb
Methods	RCT parallel
Participants	Estimated n = 60 CRPS (IASP 1994 criteria) Age 18 years or older Pain scores > 5 on 0 - 10 VAS Poor outcome to (?prior) treatment (< 50% improvement in pain VAS scores)
Interventions	Active: Thoracic sympathetic blockade with ropivacaine (5 ml, 0.75%) and triamcinolone (2%) Control: Dorsal subcutaneous delivery of the same active agent
Outcomes	Analgesia after block at 1 month (McGill pain questionnaire, Brief pain inventory, DN4 questionnaire, VAS)
Starting date	January 2010
Contact information	Roberto O Rocha MD email: contato@drrobertorocha.com.br
Notes	Attempted to contact author, but email address no longer works

IASP: International Association for the Study of Pain

DATA AND ANALYSES

Comparison 1. Local anaesthetic block versus normal saline

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of patients who achieved at least 50% of pain relief	2	46	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.76, 1.84]

Analysis 1.1. Comparison 1 Local anaesthetic block versus normal saline, Outcome 1 Number of patients who achieved at least 50% of pain relief.

Review: Local anaesthetic sympathetic blockade for complex regional pain syndrome

Comparison: 1 Local anaesthetic block versus normal saline

Outcome: 1 Number of patients who achieved at least 50% of pain relief

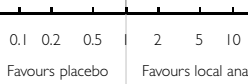
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Price 1998	6/7	6/7		58.5 %	1.00 [0.65, 1.53]
Verdugo 1995	12/16	8/16		41.5 %	1.50 [0.85, 2.64]
Total (95% CI)	**23**	**23**		**100.0 %**	**1.18 [0.76, 1.84]**

Total events: 18 (Treatment), 14 (Control)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 1.61$, df = 1 (P = 0.20); $I^2 = 38\%$

Test for overall effect: Z = 0.74 (P = 0.46)

Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Budapest criteria: diagnostic criteria for Complex Regional Pain Syndrome

To make the *clinical diagnosis, the following criteria must be met:*
1. Continuing pain, which is disproportionate to any inciting event
2. Must report at least one symptom in *three of the four* following categories: · **Sensory:** Reports of hyperaesthesia and/or allodynia · **Vasomotor:** Reports of temperature asymmetry and/or skin colour changes and/or skin colour asymmetry · **Sudomotor/Oedema:** Reports of oedema and/or sweating changes and/or sweating asymmetry · **Motor/Trophic:** Reports of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
3. Must display at least one sign **at time of evaluation** in *two or more* of the following categories: · **Sensory:** Evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch and/or temperature sensation and/or deep somatic pressure and/or joint movement) · **Vasomotor:** Evidence of temperature asymmetry (> 1°C) and/or skin colour changes and/or asymmetry · **Sudomotor/Oedema:** Evidence of oedema and/or sweating changes and/or sweating asymmetry · **Motor/ Trophic:** Evidence of decreased range of motion and/or motor dysfunction (weakness, tremor, dystonia) and/or trophic changes (hair, nail, skin)
4. There is no other diagnosis that better explains the signs and symptoms

For research purposes, diagnostic decision rule should be at least one symptom in all four symptom categories and at least one sign (observed at evaluation) in two or more sign categories. A sign is counted only if it is observed at time of diagnosis.

APPENDICES

Appendix 1. MEDLINE search strategy

1 exp Complex Regional Pain Syndromes/
2 complex regional pain syndrome.mp.
3 CRPS.mp.
4 reflex sympathetic dystrophy.mp.
5 reflex neurovascular dystrophy.mp.
6 (RSD or RND).mp.
7 shoulder hand syndrome.mp.
8 algoneurodystrophy.mp.
9 algodystrophy.mp.
10 sudeck*.mp.
11 causalgia.mp.
12 (sympathetic* adj3 pain*).mp.
13 SMP.mp.
14 ((posttraumatic or post-traumatic) adj dystrophy).mp.
15 neuralgia.mp. or exp Neuralgia/
16 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 or 15
17 exp Sympatholytics/
18 exp Nerve Block/
19 exp Anesthetics, Local/
20 bupivacaine.mp.
21 lidocaine.mp.
22 guanethidine.mp.
23 (nerve* adj5 block*).mp.
24 (stellate adj5 block*).mp.
25 (sympathetic* adj5 block*).mp.
26 sympatholytic*.mp.
27 (local adj5 (anaesthetic* or anesthetic*)).mp.
28 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29 16 and 28
30 randomized controlled trial.pt.
31 controlled clinical trial.pt.
32 randomized.ab.
33 placebo.ab.
34 drug therapy.fs.
35 randomly.ab.
36 trial.ab.
37 groups.ab.
38 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39 29 and 38

Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Complex Regional Pain Syndromes] explode all trees
#2 complex regional pain syndrome
#3 reflex sympathetic dystrophy
#4 reflex neurovascular dystrophy
#5 (RSD or RND)
#6 shoulder hand syndrome
#7 algoneurodystrophy
#8 algodystrophy
#9 sudeck*
#10 causalgia
#11 (sympathetic* near/3 pain*)
#12 SMP
#13 ((posttraumatic or post-traumatic) next dystrophy)
#14 neuralgia
#15 MeSH descriptor: [Neuralgia] explode all trees
#16 #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 or #15
#17 MeSH descriptor: [Sympatholytics] explode all trees
#18 MeSH descriptor: [Nerve Block] explode all trees
#19 MeSH descriptor: [Anesthetics, Local] explode all trees
#20 bupivacaine
#21 lidocaine
#22 guanethidine
#23 (nerve* near/5 block*)
#24 (stellate near/5 block*)
#25 (sympathetic* near/5 block*)
#26 sympatholytic*
#27 (local near/5 (anaesthetic* or anesthetic*))
#28 #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#29 #16 and #28

Appendix 3. EMBASE search strategy

1 exp Complex Regional Pain Syndromes/ (6878)
2 complex regional pain syndrome.mp. (4608)
3 CRPS.mp. (1726)
4 reflex sympathetic dystrophy.mp. (2181)
5 reflex neurovascular dystrophy.mp. (22)
6 (RSD or RND).mp. (13575)
7 shoulder hand syndrome.mp. (522)
8 algoneurodystrophy.mp. (77)
9 algodystrophy.mp. (1014)
10 sudeck*.mp. (691)
11 causalgia.mp. (1077)
12 (sympathetic* adj3 pain*).mp. (1851)
13 SMP.mp. (1349)
14 ((posttraumatic or post-traumatic) adj dystrophy).mp. (39)
15 neuralgia.mp. or exp Neuralgia/ (67140)
16 or/1-15 (83936)
17 exp Sympatholytics/ (323887)
18 exp Nerve Block/ (23581)
19 exp Anesthetics, Local/ (176914)

20 bupivacaine.mp. (28226)
21 lidocaine.mp. (60809)
22 guanethidine.mp. (9806)
23 (nerve* adj5 block*).mp. (26239)
24 (stellate adj5 block*).mp. (1455)
25 (sympathetic* adj5 block*).mp. (4992)
26 sympatholytic*.mp. (1986)
27 (local adj5 (anaesthetic* or anesthetic*)).mp. (40074)
28 or/17-27 (514951)
29 16 and 28 (9126)
30 random$.tw. (778937)
31 factorial$.tw. (20300)
32 crossover$.tw. (45775)
33 cross over$.tw. (20846)
34 cross-over$.tw. (20846)
35 placebo$.tw. (187218)
36 (doubl$ adj blind$).tw. (138732)
37 (singl$ adj blind$).tw. (13056)
38 assign$.tw. (216590)
39 allocat$.tw. (73290)
40 volunteer$.tw. (168077)
41 Crossover Procedure/ (35530)
42 double-blind procedure.tw. (224)
43 Randomized Controlled Trial/ (334989)
44 Single Blind Procedure/ (16651)
45 or/30-44 (1279784)
46 (animal/ or nonhuman/) not human/ (4530619)
47 45 not 46 (1128169)
48 29 and 47 (1039)
49 (201111* or 201112* or 2012*).dd. (1342582)
50 48 and 49 (133)

Appendix 4. LILACS search strategy

"complex regional pain syndrome" or CRPS or "reflex sympathetic dystrophy" or "reflex neurovascular dystrophy" or RSD or RND or "shoulder hand syndrome" or algoneurodystrophy or algodystrophy or sudeck$ or causalgia or sympathetic pain$ or SMP [Words] and bupivacaine or lidocaine or guanethidine or (nerve$ block$) or (stellate block$) or (sympathetic$ block$) or sympatholytic$ or (local anaesthetic$) or (local anesthetic$) [Words]

WHAT'S NEW

Last assessed as up-to-date: 31 July 2013.

Date	Event	Description
26 June 2013	New search has been performed	This updated review used an expanded search strategy, updated Risk of Bias assessment, and updated inclusion criteria. These changes resulted in inclusion of 10 additional studies compared with the initial review (n = 363

(*Continued*)

		additional participants; one study compared LASB to a placebo/inert treatment [Aydemir 2006], the remaining nine studies compared LASB with an active treatment [Bonelli 1983; Carroll 2009; Meier 2009; Nascimento 2010; Raja 1991; Rodriguez 2005; Toshniwal 2012; Wehnert 2002; Zeng 2003]). Despite these methodological updates and inclusion of new studies, the conclusions of the review remain unchanged; there is a dearth of published evidence for LASB and the available evidence suggests lack of efficacy. Readers of the original review would benefit from reading this update as new evidence is provided for treatment comparisons between LASB and other active interventions (for example, intravenous nerve blocks)
26 June 2013	New citation required but conclusions have not changed	Despite methodological updates and inclusion of new studies, the conclusions of the review remain unchanged; there is a dearth of published evidence for LASB and the available evidence suggests lack of efficacy

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2005

Date	Event	Description
3 October 2011	Amended	The following changes have been made to the methodology of the protocol. We have made them all to bring the protocol up to date with the current PaPaS author guidelines: We have chosen to adopt a modified version of the Cochrane ROB tool with additional criteria added in response to the recommendations of Moore et al. (2010). As such we have added 2 additional criteria "Size" and "Duration" using the thresholds for judgement suggested by Moore 2010. We have not added the "Outcome" criteria as this is covered already by our choice of primary outcome measures We have rewritten the data synthesis/ analysis sections to fit the current RevMan headings. We now specify that we will calculate Risk Ratio for achieving a moderately important benefit (30% or more) or a substantially important benefit (50% or more) and have specified time windows for short, medium and long term follow up. We suggest the following preplanned subgroup analyses where adequate data allow: CRPS I vs II, Adults vs children and single vs continuous blockade We have added a planned sensitivity analyses, where data are sufficient, to allow testing of the effect of including/ excluding studies whose risk of bias is unclear or high
3 October 2011	Amended	The Background section has been substantively rewritten to fit the headings now suggested in RevMan

(*Continued*)

22 September 2011	Amended	Searching other resources - unpublished studies: We have expanded this search strategy to also include clinical and controlled trial registers, such as http://www.controlledtrials.com/, the Australian New Zealand Clinical Trials Register (http://www.anzctr.org.au/), and a European Clinical Trials Register (https://www.clinicaltrialsregister.eu/).
21 September 2011	Amended	Methods: selection of studies. Two independent reviewers will screen the titles and abstracts of the search results in order to determine which full text articles to retrieve. This is changed from one reviewer
21 September 2011	Amended	Addition of new criteria for considering studies for this review (Types of interventions)
21 September 2011	Amended	Addition of new criteria for considering studies for this review (Types of participants)
21 September 2011	Amended	We have added new search terms to the search strategy that will make it more sensitive and conforms to updates in treatment (for example, Botox now being used for sympathetic chain blockades). Also attached is an updated search strategy for Medline, created in collaboration with Jane Hayes from PaPaS
21 September 2011	Amended	We have inserted a new Table (under other Tables) that provides the new Budapest criteria for diagnosing CRPS
9 November 2009	Amended	Contact details updated.
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

TRS: Led the modification and writing of the protocol; performed the literature search; screened, identified and evaluated studies; extracted data; led the data synthesis and the writing of the manuscript.

BMW: Informed the modification of the protocol; screened, identified and evaluated studies; extracted data and contributed to the writing of the manuscript.

DBC: Designed the original protocol and consulted on the modifications; contributed to the writing of the manuscript.

GW: Informed the modification of the protocol and contributed to the writing of the manuscript.

FB: Informed the modification of the protocol; assisted in the clinical trial register searches and contributed to the writing of the manuscript.

NEO: Informed the modification of the protocol; acted as the arbiter reviewer; informed the data synthesis and contributed to the writing of the manuscript.

DECLARATIONS OF INTEREST

None known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This updated review used an expanded search strategy. In particular, additional search terms were utilized and we also searched clinical trial registers for potentially relevant studies. Further, an updated version of the Risk of Bias (ROB) assessment was used - specifically, 'size of treatment groups' and 'duration of follow-up' of the studies were included in the ROB evaluation. Last, this updated review also included studies in which local anaesthetic blockade (LASB) was compared with other active treatments (original review compared LASB with placebo/inert treatments only).

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthetics, Local; Autonomic Nerve Block [*methods]; Causalgia [drug therapy]; Complex Regional Pain Syndromes [*drug therapy]; Randomized Controlled Trials as Topic; Reflex Sympathetic Dystrophy [drug therapy]

MeSH check words

Adult; Child; Humans