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

O'Connell NE, Wand BM, Gibson W, Carr DB, Birklein F, Stanton TR

O'Connell NE, Wand BM, Gibson W, Carr DB, Birklein F, Stanton TR.
Local anaesthetic sympathetic blockade for complex regional pain syndrome.
Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD004598.
DOI: 10.1002/14651858.CD004598.pub4.

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[Intervention Review]

Local anaesthetic sympathetic blockade for complex regional pain syndrome

Neil E O'Connell[1], Benedict M Wand[2], William Gibson[2], Daniel B Carr[3], Frank Birklein[4], Tasha R Stanton[5,6]

[1]Department of Clinical Sciences/Health Economics Research Group, Institute of Environment, Health and Societies, Brunel University, Uxbridge, UK. [2]School of Physiotherapy, The University of Notre Dame Australia, Fremantle, Australia. [3]Pain Research, Education and Policy (PREP) Program, Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA. [4]University Medical Centre, Johannes Gutenberg University, Mainz, Germany. [5]Neuroscience Research Australia, Randwick, Australia. [6]The Sansom Institute for Health Research, School of Health Sciences, University of South Australia, Adelaide, Australia

Contact address: Tasha R Stanton, The Sansom Institute for Health Research, School of Health Sciences, University of South Australia, GPO Box 2471, Adelaide, South Australia, 5001, Australia. t.stanton@neura.edu.au. tasha.stanton@unisa.edu.au.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 7, 2016.
Review content assessed as up-to-date: 16 September 2015.

Citation: O'Connell NE, Wand BM, Gibson W, Carr DB, Birklein F, Stanton TR. Local anaesthetic sympathetic blockade for complex regional pain syndrome. *Cochrane Database of Systematic Reviews* 2016, Issue 7. Art. No.: CD004598. DOI: 10.1002/14651858.CD004598.pub4.

ABSTRACT

Background

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews, 2005, Issue 4 (and last updated in the Cochrane Database of Systematic Reviews, 2013 issue 8), on local anaesthetic blockade (LASB) of the sympathetic chain to treat people with 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

For this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 9), MEDLINE (Ovid), EMBASE (Ovid), LILACS (Birme), conference abstracts of the World Congresses of the International Association for the Study of Pain, and various clinical trial registers up to September 2015. We also searched bibliographies from retrieved articles for additional studies.

Selection criteria

We considered randomised controlled trials (RCTs) that evaluated the effect of sympathetic blockade with local anaesthetics in children or adults with CRPS compared to placebo, no treatment, or alternative treatments.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. The outcomes of interest were reduction in pain intensity, the proportion who achieved moderate or substantial pain relief, the duration of pain relief, and the presence of adverse effects in each treatment arm. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created a 'Summary of findings' table.

Main results

We included an additional four studies (N = 154) in this update. For this update, we excluded studies that did not follow up patients for more than 48 hours. As a result, we excluded four studies from the previous review in this update. Overall we included 12 studies (N = 461), all of which we judged to be at high or unclear risk of bias. Overall, the quality of evidence was low to very low, downgraded due to limitations, inconsistency, imprecision, indirectness, or a combination of these.

Two small studies compared LASB to placebo/sham (N = 32). They did not demonstrate significant short-term benefit for LASB for pain intensity (moderate quality evidence).

One small study (N = 36) at high risk of bias compared thoracic sympathetic block with corticosteroid and local anaesthetic versus injection of the same agents into the subcutaneous space, reporting statistically significant and clinically important differences in pain intensity at one-year follow-up but not at short term follow-up (very low quality evidence).

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 (very low quality evidence).

Eight small randomised studies compared sympathetic blockade to various other active interventions. Most studies found no difference in pain outcomes between sympathetic block versus other active treatments (low to very low quality evidence).

One small study compared ultrasound-guided LASB with non-guided LASB and found no clinically important difference in pain outcomes (very low quality evidence).

Six studies reported adverse events, all with minor effects reported.

Authors' conclusions

This update's results are similar to the previous versions of this systematic review, and the main conclusions are unchanged. There remains a scarcity of published evidence and a lack of high quality evidence to support or refute 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

Background

Local anaesthetic sympathetic blockade (LASB) is a common treatment for complex regional pain syndrome (CRPS). It involves blocking the activity of sympathetic nerves alongside the spine. The sympathetic nervous system mainly controls unconscious actions such as heart rate, blood flow, and perspiration. The injection of a local anaesthetic drug around the nerves temporarily blocks the function of the nerves. This updated review aimed to summarise 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.

Key results and quality of the evidence

In September 2015, we found a limited number of small trials, all of which had design flaws. 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. One small study found that injecting the thoracic (upper back) sympathetic nerves with local anaesthetic and steroid was better than injecting the same drugs just under the skin at one-year follow-up, but the study may have been prone to bias. Only six studies reported on the type and amount of side effects. These studies reported only minor side effects, but since some studies did not report this information we can draw no firm conclusions about the safety of LASB. The evidence was mostly of low or very low quality.

Overall, the evidence is limited, conflicting, and of low quality. While we cannot draw strong conclusions, the existing evidence is not encouraging.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Patient or population: adults with CRPS
Setting: secondary care
Intervention/comparison: LASB vs various comparisons
Outcome: pain intensity 0-10 (VAS or NRS)

Comparison	Studies	No of participants (studies)	Result (effect estimates reported where available from study report)	Quality of the evidence (GRADE)
LASB vs placebo	Aydemir 2006; Price 1998	23 (2)	No significant between-group difference	⊕⊕⊕◯ **Moderate**[a]
Thoracic LASB + steroid vs subcutaneous local anaesthetic+ steroid	Rocha 2014	36 (1)	Favours LASB Mean difference (0-10 scale) One month −1.25 (95% CI −3.2 to 0.7) One year −2.39 (95%CI −4.72 to −0.06)	⊕◯◯◯ **Very low**[b]
LASB vs ultrasound block	Aydemir 2006	18 (1)	No significant between-group difference	⊕⊕◯◯ **Low**[c]
LASB vs IVRB guanethidine	Bonelli 1983	19 (1)	No significant between-group difference	⊕◯◯◯ **Very low**[b]
LASB lumbar plexus vs pulsed radiofrequency lumbar plexus	Freitas 2013	40 (1)	No significant between-group difference	⊕◯◯◯ **Very low**[b]
LASB (lidocaine + clonidine) vs IVRB (lidocaine + clonidine)	Nascimento 2010	43 (1)	No significant between-group difference	⊕◯◯◯ **Very low**[b]
LASB + PT+ pharmacological vs PT + pharmacological	Rodriguez 2005	82 (1)	Favours SGB group	⊕◯◯◯ **Very low**[b]
LASB + PT vs PT	Zeng 2003	60 (1)	No significant between-group difference	⊕◯◯◯ **Very low**[b]
Continuous LASB vs continuous brachial plexus block	Toshniwal 2012	33 (1)	Favours brachial plexus block	⊕⊕◯◯ **Low**[c]

Image-guided LASB vs nonimage-guided LASB	Yoo 2012	42 (1)	Mean difference 2 weeks postinjection −0.58 (95% CI −1.51 to 0.35) 4 weeks postinjection −0.74 (95% CI −1.36 to −0.12)	◯◯◯◯ **Very low**[d]
Outcome: hand pain 0-3 scale				
LASB vs oral corticosteroids	Lim 2007	38 (1)	15 day follow-up, no significant between-group difference at 30 day follow-up 0.4 (95% CI −0.69 to −0.11), favours LASB with steroid	◯◯◯◯ **Very low**[d]
Outcome: duration of pain relief				
LASB bupivacaine + BTA vs LASB bupivacaine	Carroll 2009	9 (1)	Increased duration of relief with BTA Median time to analgesic failure (days): LASB bupivacaine + BTA 71 (95% CI 12 to 253) LASB bupivacaine 10 (95% CI 0 to 12)	⊕⊕◯◯ **Low**[c]

[a] Downgraded once for imprecision.
[b] Downgraded three times for limitations, inconsistency, and imprecision.
[c] Downgraded twice for inconsistency and imprecision.
[d] Downgraded four times for limitations, inconsistency, indirectness, and imprecision.

BACKGROUND

This review is an update of a previously published review in the Cochrane Database of Systematic Reviews, 2005, Issue 4 (and last updated in the Cochrane Database of Systematic Reviews, 2013 Issue 8), on local anaesthetic sympathetic blockade for complex regional pain syndrome.

Description of the condition

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 (if any) and that is not restricted anatomically to the distribution of a specific peripheral nerve (Bruehl 2010). The International Association for the Study of Pain (IASP) introduced the diagnostic label of CRPS in the 1990s (Merskey 1994), and since then, others have updated it in an attempt to improve its specificity (Harden 2006; Harden 2010). We present these modified diagnostic criteria (the 'Budapest criteria') in Table 1. The term CRPS encompasses a variety of earlier diagnostic terms, including reflex sympathetic dys-

trophy (RSD), reflex neurovascular dystrophy, Sudeck's atrophy, causalgia, and algodystrophy/algoneurodystrophy (Stanton-Hicks 1995). CRPS can be classified into two subtypes: CRPS-I, in which there is no identified peripheral nerve injury, 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 sometimes spreading to other body regions (Stanton-Hicks 2002; Van Rijn 2011). Additionally CRPS presents with some or all of the following symptoms in the affected body parts: sensory disturbances; temperature changes; abnormal patterns of perspiration; 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 (Lewis 2007; Lotze 2007; Moseley 2006). CRPS occurs most commonly following wrist fracture and subsequent immobilisation. However, cases can potentially occur after 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. Research has identified abnormalities in the tissues of the affected area and the peripheral and central nervous systems (Jänig 2003; Marinus 2011). These include signs of increased neurogenic inflammation (Birklein 2001; Schinkel 2006; Schmelz 2001), an altered local immune response (Birklein 2014; Tan 2005), altered activity in the sympathetic nervous system (SNS) (Drummond 2004; Niehof 2006), increased sensitivity to normal SNS activity (Albrecht 2006; Ali 2000; Drummond 2001), and local tissue hypoxia (Birklein 2000; Koban 2003). Studies have also demonstrated changes 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 local function of the sympathetic nervous system. Usually an anaesthesiologist performs the procedure, injecting 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). Radiologic guidance such as fluoroscopy or computerised tomography (CT) scan often ensures the accuracy of needle tip placement, and successful blockade is often monitored by direct (e.g., galvanic skin response) or indirect (increase in blood flow to the extremity or increase in temperature) assessment (Breivik 2009). This approach is distinct from the injection of neurolytic agents in an effort to destroy sympathetic nerves. LASBs are also commonly called stellate ganglion blockades (SGB) or, when performed in the lower body, lumbar sympathetic blockades (LSB).

How the intervention might work

People with persistent pain following nerve injury have long been observed to have abnormalities of autonomic nervous system 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 (Campbell 1996). However, recent evidence regarding adrenaline content in venous effluents from affected limbs has not supported this hypothesis and suggests instead that any benefit of sympathetic blockade in CRPS may reflect transient reversal of a heightened local sensitivity to adrenaline (Binder 2009). 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, led to the incorporation of sympathetic block into current consensus treatment algorithms for CRPS (Carr 2011), 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 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). The value of blocking the sympathetic nervous system is also disputed (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, investigators obtained this estimate 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 safety of

sympathetic blockade with local anaesthetics to alleviate pain in people with 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.

METHODS

Criteria for considering studies for this review

Types of studies

We considered 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. We included studies that compared LASB with placebo interventions, no treatment, or alternative interventions. We also included studies that investigated the effect of adding LASB to other interventions.

Types of participants

We included studies that evaluated the effect of sympathetic blockade with local anaesthetics to treat CRPS in children or adults. We included studies 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. We excluded studies that reported the results of combined sympatholytic therapies, such as surgical sympathectomy or guanethidine intravenous regional block plus local anaesthetic blockade of the sympathetic chain. We also excluded studies of ganglionide local opioid analgesia (GLOA), a technique in which clinicians locally inject opioids such as buprenorphine into the stellate ganglion, because this procedure does not block sympathetic activity.

Types of outcome measures

The outcomes of interest were pain intensity levels, duration of pain relief. and adverse events. For this update, we excluded studies that had only immediate follow-up data ($\leq$ 48 h), because this information provides little clinically relevant information about the effectiveness of this treatment. We applied this new criterion to studies that had been included in previous updates of this review.

Search methods for identification of studies

For this update, we used identical search strategies to that of our 2013 review update. For the search strategies, see Appendix 1 for the Cochrane Central Register of Controlled Trials (CENTRAL), Appendix 2 for MEDLINE, Appendix 3 for EMBASE, and Appendix 4 for LILACS.

We performed the search for the original review from November 2003 to January 2004 updated it on 17 November 2011 and 22 November 2012 (2013 update). The present update encompasses searches run from 22 November 2012 to 16 September 2015.

We evaluated non-English language papers for inclusion.

For the 2016 update, we did not search the Cochrane Pain, Palliative and Supportive Care Group Specialised Register, as it is no longer updated.

Electronic searches

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

- CENTRAL (*The Cochrane Library* 2015, Issue 9).
- MEDLINE (Ovid) (1966 to September 2015).
- EMBASE (Ovid) (1974 to September 2015).
- LILACS (Birme) (1982 to September 2015).

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 2014. For this update, we expanded the search of the original review by also searching relevant clinical trial registers (from inception) for upcoming trials. We searched the following clinical trial registers:

the controlled trials register (15 October 2015; www.controlled-trials.com/), the United States National Institute of Health service ClinicalTrials.gov (15 October 2015; www.clinicaltrials.gov/); the Australian New Zealand Clinical trials register (15 October 2015; www.anzctr.org.au/), and the European Clinical Trials Register (7 December 2012; www.clinicaltrialsregister.eu/).

Personal contact

We attempted to communicate with authors if we needed additional information 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 review authors independently read each of the titles and abstracts of the reports identified by the search and discarded narrative reviews, case series, and case reports. If there was no abstract, we retrieved the full-text report. If there was disagreement, the authors met to reach consensus, consulting an independent third review author if necessary. We retrieved in full all abstracts and reports that made reference to a trial of sympathetic blockade with local anaesthetics . Two review authors then independently assessed the full-text articles. We did not anonymise the reports for the assessment.

Data extraction and management

Two review authors independently extracted the data. If there was disagreement, they met to reach consensus, consulting an independent third review author if necessary. 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, sex, number of participants recruited, number of study withdrawals or drop-outs, if any.
3. Participant clinical characteristics: duration of pain before sympathetic block, site of pain (arm, leg, mixed, or other such as facial).
4. Type of noxious initiating event (if known): 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 (including concentration and volume), 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 postprocedure analgesic requirements.
10. Information on conflicts of interest and statements of study support.

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

Assessment of risk of bias in included studies

We used a modified version of the Cochrane 'Risk of bias' tool with additional domains added in response to the recommendations of Moore 2010. On this basis we added two domains, 'size' and 'duration', using the thresholds for judgement suggested by Moore 2010. We have not added the 'outcome' domain as this is covered already by our choice of primary outcome measures. Thus in addition to the standard items in the 'Risk of bias' 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); and
- other sources of bias;

We also assessed the following domains as recommended by Moore 2010.

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

Two review authors completed the 'Risk of bias' assessment for each included study independently. If there was disagreement, the authors met to reach consensus, consulting an independent third review author if necessary.

Measures of treatment effect

We compared the post-treatment pain intensity scores between the trial arms. Where possible, we calculated the proportion of participants with a 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 planned to calculate the risk ratio (RR) as the measure of treatment effect and used this to calculate the number needed to treat for an additional beneficial outcome (NNTB) for 30% and 50% pain relief. We also collected data on the duration of pain relief postintervention where available.

For this update, we used the OMERACT 12 group's recommendations for minimally important difference for pain outcomes reported on a continuous scale (Busse 2015). They recommend 10 mm on a 0-100 mm visual analogue scale (VAS) as the threshold for minimal importance for average between-group change. They highlight that should be interpreted with caution as estimates that fall closely below this point may still reflect a treatment that benefits a considerable number of patients. We used this threshold but interpreted it cautiously.

Unit of analysis issues

No unit of analysis issues arose since we were unable to conduct a meta-analysis due to insufficient data.

Dealing with missing data

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

Assessment of heterogeneity

We planned to assess 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. However, no meta-analysis was possible.

Assessment of reporting biases

We considered the possible influence of publication/small study biases on review findings. For studies that utilised dichotomised outcomes, where possible, we planned to test 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.

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 (up 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 we identified adequate data.

Assessment of quality of available evidence

For this update we used the GRADE approach to assess the quality of evidence (Guyatt 2011a; Guyatt 2011b). Two reviewers independently applied the GRADE criteria to each key comparison. If there was disagreement, the authors met to reach consensus, consulting an independent third review if necessary. We present a summary of our judgements for each comparison in Appendix 5. To ensure consistency of GRADE judgements, we applied the following criteria to each domain equally for all key comparisons of the primary outcome.

- Limitations of studies: downgrade once if more than 25% of participants were from studies classified as being at a high risk of bias across any domain, excluding the 'study size' domain as this is accounted for in the assessment of imprecision.
- Inconsistency: downgrade once if heterogeneity is statistically significant and the I^2 value is more than 40%. When a meta-analysis was not performed we downgraded once if trials did not show effects in the same direction.
- Indirectness: downgrade once if more than 50% of the participants were outside the target group.
- Imprecision: downgrade once if fewer than 400 participants for continuous data and fewer than 300 events for dichotomous data.
- Publication bias: downgrade once where there is direct evidence of publication bias or if estimates of effect based on small scale, industry-sponsored studies raising a high index of suspicion of publication bias.

Two review authors (NEO, BMW) judged whether these factors were present. We considered single studies to be inconsistent and imprecise, unless more than 400 participants were randomised for continuous outcomes or more than 300 for dichotomous outcomes. We applied the following definitions of the quality of the evidence (Balshem 2011).

- High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate quality: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

- Low quality: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low quality: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

'Summary of findings' table

We included a 'Summary of findings' table to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcome pain intensity, hand pain, and duration of pain relief.

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 repeated versus single blocks.
Where possible we used the proportion of people with adverse side effects in each treatment group to calculate the number needed to treat for an additional harmful outcome (NNTH).

Sensitivity analysis

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

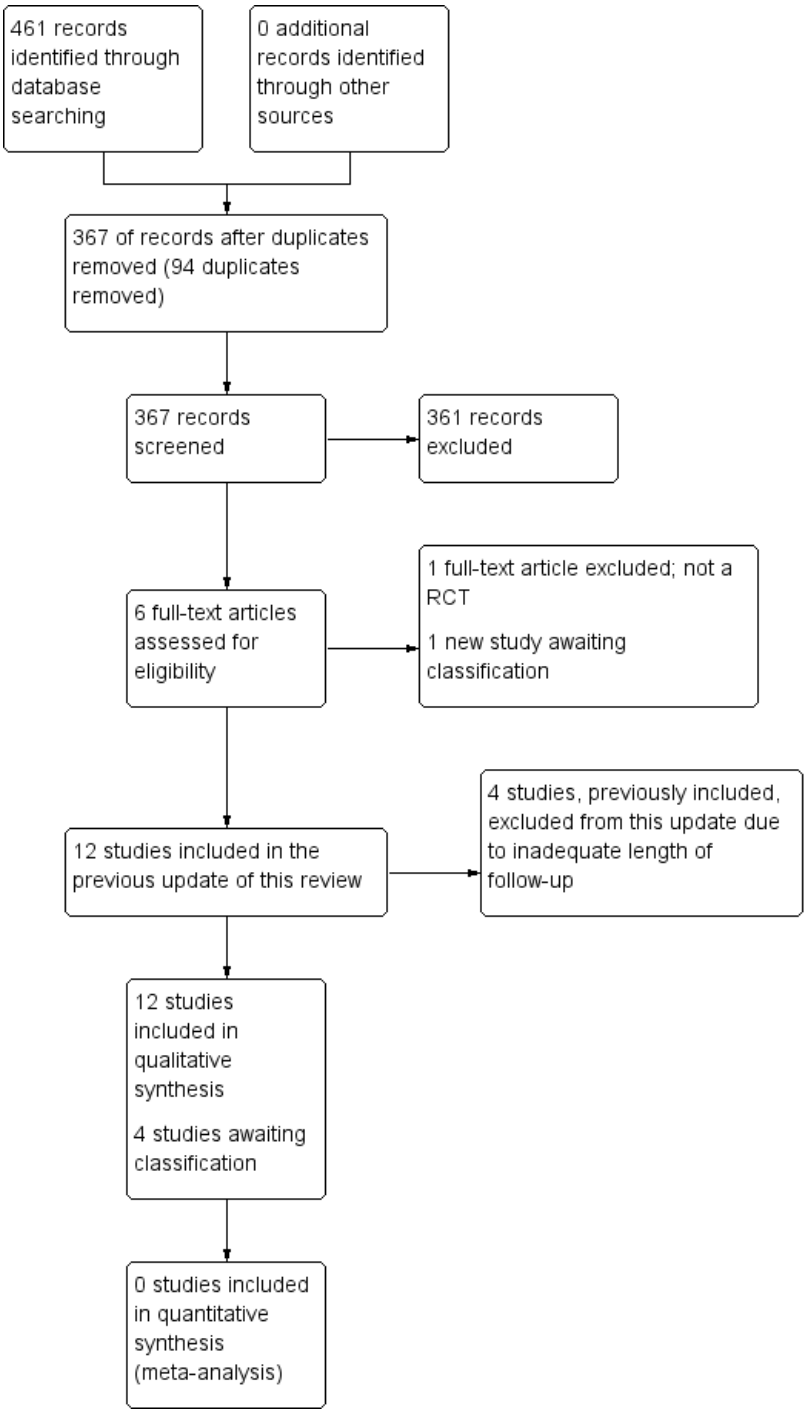
RESULTS

Description of studies

Results of the search

The previous update of this review included twelve studies (Aydemir 2006; Bonelli 1983; Carroll 2009; Meier 2009; Nascimento 2010; Price 1998, Raja 1991; Rodriguez 2005; Toshniwal 2012; Verdugo 1995, Wehnert 2002; Zeng 2003; combined N = 386). For this update, we included an additional four studies (Freitas 2013; Lim 2007; Rocha 2014; Yoo 2012; combined N = 154]). As our modified criteria excluded studies with follow-up of 48 hours or less, we excluded four studies from this update that had been included in previous versions of this review (Meier 2009; Raja 1991; Verdugo 1995; Wehnert 2002; combined N = 79). Overall, we included 12 studies with 461 participants in this update.
One new study is awaiting classification, as it was published as a protocol for a trial and in abstract format only, and it is unclear whether the trial was completed (Kostadinova 2012).
Figure 1 presents a flow chart of the search screening process for the present update. We identified 461 studies through the database search strategy and none from searching other sources. After removing duplicates and screening titles and abstracts, we retrieved the full text for five studies. Of these, we included four new studies in the review.

Figure 1. #Study flow diagram for updated searches



For this update we attempted to contact the authors of two studies: to retrieve essential data for Freitas 2013 and to check the status of the trial and request a report if available for Kostadinova 2012.

Included studies

We present full details of the studies in the Characteristics of included studies tables.

Study participants

All included studies evaluated only adult participants (Aydemir 2006; Bonelli 1983; Carroll 2009; Freitas 2013; Lim 2007; Nascimento 2010; Price 1998; Rocha 2014; Rodriguez 2005; Toshniwal 2012; Yoo 2012; Zeng 2003).

Nine studies included only people with upper limb CRPS treated with stellate ganglion blockade (Aydemir 2006; Bonelli 1983; Lim 2007; Nascimento 2010; Rocha 2014; Rodriguez 2005; Toshniwal 2012; Yoo 2012; Zeng 2003), and two studies included only people with lower limb CRPS treated with lumbar sympathetic blockade (Carroll 2009; Freitas 2013). The remaining study included a mix of upper and lower limb CRPS (Price 1998).

Study designs

Two studies used a cross-over design (Carroll 2009; Price 1998), and 10 employed a parallel design (Aydemir 2006; Bonelli 1983; Freitas 2013; Lim 2007; Nascimento 2010; Rocha 2014; Rodriguez 2005; Toshniwal 2012; Yoo 2012; Zeng 2003). All included studies were small, with total numbers of participants ranging from 7 to 82.

LASB versus placebo

Two studies compared LASB versus placebo (Aydemir 2006; Price 1998).

Price 1998 (N = 7) compared stellate ganglion block (n = 4, 15 ml lidocaine 1%) versus lumbar sympathetic block (n = 3, 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 and investigated the proportion of participants who experienced 50% pain relief. 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 (N = 25) 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). Both groups received rehabilitation treatment. Investigators measured spontaneous pain post-treatment and at one-month follow-up.

LASB versus other interventions

In contrast to the original version of this review, we included studies, totaling nine, that compared LASB to other interventions (Aydemir 2006; Bonelli 1983; Carroll 2009; Freitas 2013; Lim 2007; Nascimento 2010; Rocha 2014; Toshniwal 2012; Yoo 2012).

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. Investigators measured the primary outcome of spontaneous pain 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) versus 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 100 mm linear scale) measured post-treatment at 15 minutes, 60 minutes, 24 hours and 48 hours as well as at one and three 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%) versus bupivacaine alone (10 ml of 0.5%) in people with CRPS of the lower extremity. The primary outcome was the duration that pain (measured using a VAS) remained below baseline levels.

Freitas 2013 (N = 40) compared sympathetic block of the lumbar plexus with lidocaine and clonidine versus pulsed radiofrequency treatment of the same structure. Investigators measured pain intensity for up to six months follow-up.

Lim 2007 (N = 36) compared a course of five stellate ganglion blocks with lidocaine versus a two-week course of corticosteroids (prednisolone) in patients with CRPS following stroke. They used a self developed four-point scale (0 to 3) of hand pain with passive movement and followed patients up to 30 days from the start of treatment.

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

Rocha 2014 (N = 36) compared image-guided thoracic sympathetic block with ropivacaine and triamcinolone versus injection of the same agents into the subcutaneous space. Authors described this comparison condition as an "active control" as it might be predicted to induce physiological effects. This allowed blinding of

participants. Investigators followed up participants using the Brief Pain Inventory as an outcome measure at one month and one year. This study did not report a responder analysis.

Toshniwal 2012 compared continuous stellate ganglion block (SGB; n = 18; 280 ml, 0.125% bupivacaine at 2 ml/h for seven days) versus continuous infraclavicular brachial plexus block (n = 12; 400 ml, 0.125% bupivacaine at 5 ml/h for seven days) in people with CRPS-I of the upper extremity. Both groups received concurrent physiotherapy sessions. The primary outcome was the subscale scores on the neuropathic pain scale measured over a four-week period post-treatment.

Yoo 2012 (N = 42) compared stellate ganglion block with image guidance to the same block versus no image guidance in participants with CRPS following stroke. Of note, the group with image guidance received a higher dose of lidocaine (10 ml) than the non-guided group (5 ml). Investigators measured pain intensity with a VAS at two- and four-week follow-up.

LASB in addition to other therapies

Two studies evaluated the efficacy of LASB as an addition to other therapeutic management (Rodriguez 2005; Zeng 2003). Rodriguez 2005 evaluated physical therapy and 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, prerandomisation SGB). Investigators measured pain intensity, therapeutic efficacy (proportion with at least 50% pain reduction), and relapse rate at two months post-treatment. Zeng 2003 compared SGB (dose not reported) plus rehabilitation versus rehabilitation alone in a group (N = 60) with shoulder-hand syndrome following stroke. Pain (verbal rating scale) was measured at 10 and 20 days post-treatment.

Excluded studies

In total, we excluded 26 studies. For this update, we excluded one study at the full-text stage as it was not an RCT (Kastler 2013). In the last review we excluded two studies (Rodriguez 2006; Rodriguez 2008), as it was not clear whether they represented original trials in distinct cohorts or an expansion of the included trial by Rodriguez 2005, comprising many of the same participants' data. For this update we have reclassified these two studies to Studies awaiting classification and have again attempted to contact the study authors for clarification. See the table Characteristics of excluded studies for details of all studies excluded from all versions of this review.

We also identified one further study awaiting classification (Kostadinova 2012).

Risk of bias in included studies

We present the summary results of the 'Risk of bias' assessment in Figure 2 and Figure 3. We considered no studies to be at low risk of bias across all domains.

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

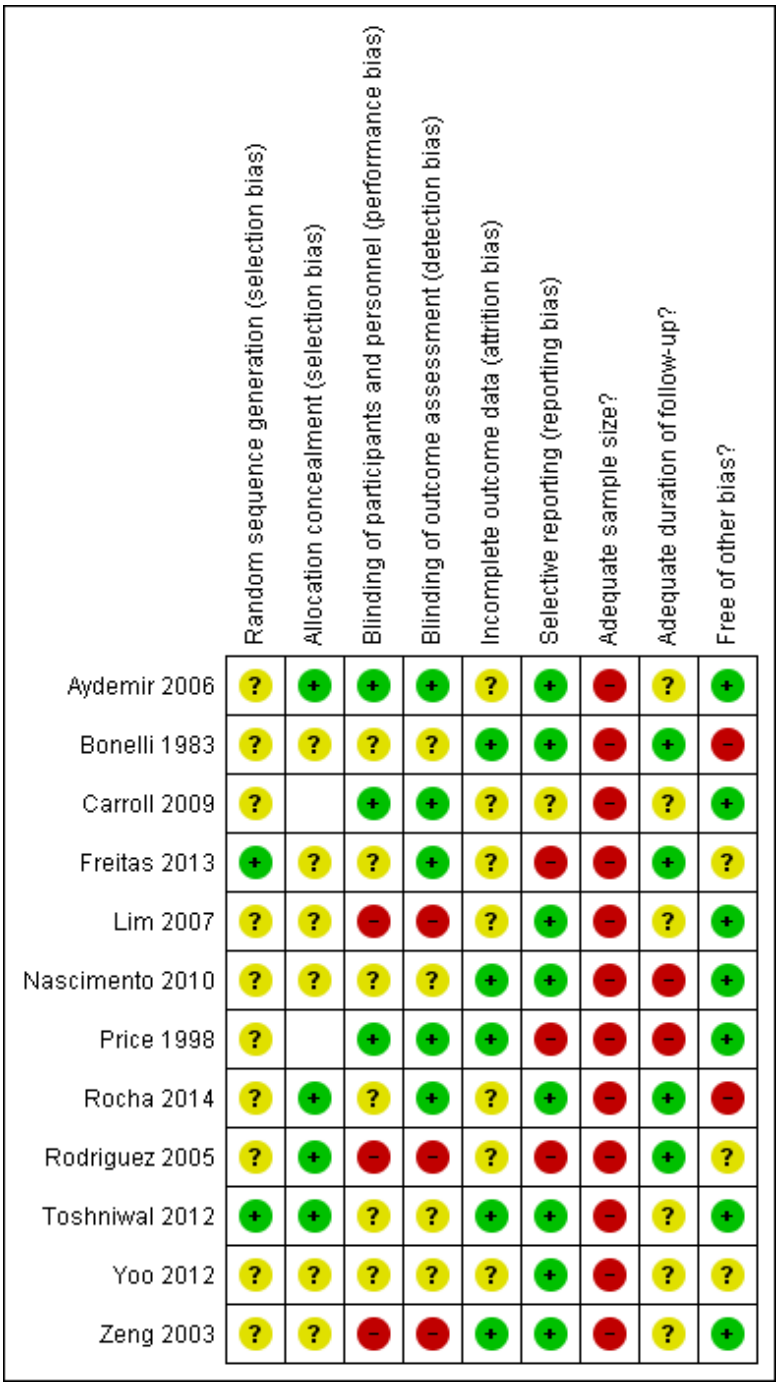
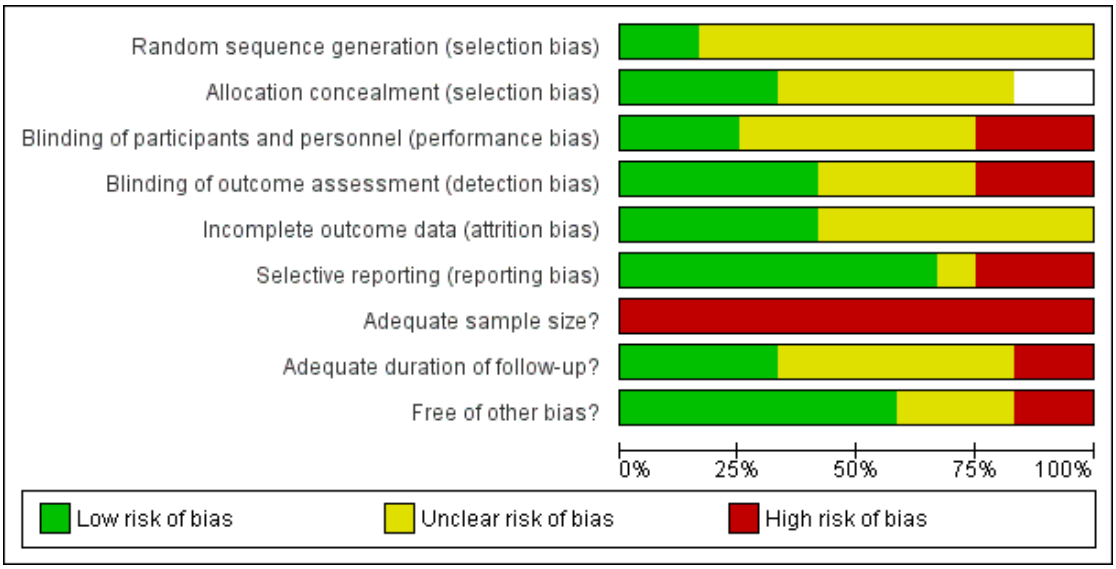


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Only two studies clearly described an adequate randomisation process (Freitas 2013; Toshniwal 2012); we considered the other ten studies to be at unclear risk of bias for this domain. We judged four studies as being at a low risk of bias for allocation concealment (Aydemir 2006; Rocha 2014; Rodriguez 2005; Toshniwal 2012), and we assessed six studies as being at unclear risk of bias (Bonelli 1983; Freitas 2013; Lim 2007; Nascimento 2010; Yoo 2012; Zeng 2003). The remaining studies used a cross-over study design (risk of bias for allocation concealment not applicable).

Blinding

We considered three studies to have blinded participants and personnel adequately (Aydemir 2006; Carroll 2009; Price 1998) (low risk of performance bias). We considered six studies to be at unclear risk of bias across this domain (Bonelli 1983; Freitas 2013; Nascimento 2010; Rocha 2014; Toshniwal 2012; Yoo 2012) as though the interventions were distinguishable, both were active invasive interventions. Three studies were at high risk of bias (Lim 2007; Rodriguez 2005; Zeng 2003;) as clinicians delivering the interventions were not blinded or the intervention conditions were clearly distinguishable. The outcome of interest for this review was self-reported pain. In this situation, the patient acts as the assessor; therefore risk of detection bias is primarily dependent on participant blinding. For blinding of outcome assessment, we judged five studies to be at low risk of detection bias as they clearly reported blinding of the participants (Aydemir 2006; Carroll 2009; Freitas 2013; Price 1998; Rocha 2014), four studies at unclear risk of bias as it was unclear whether patients were adequately blinded (Bonelli 1983; Nascimento 2010; Toshniwal 2012; Yoo 2012), and three studies were judged to have high risk of detection bias because patients were not adequately blinded (Lim 2007; Rodriguez 2005; Zeng 2003).

Incomplete outcome data

We considered seven studies to be at unclear risk of bias due to incomplete outcome data (Aydemir 2006; Carroll 2009; Freitas 2013; Lim 2007; Rocha 2014; Rodriguez 2005; Yoo 2012) as a result of the levels of drop-out reported or incomplete reporting of attrition.

Selective reporting

We judged three studies to be at high risk of bias for this domain due to incomplete reporting of pain scores (Freitas 2013; Price

1998; Rodriguez 2005). Carroll 2009 carried an unclear risk of bias for incomplete reporting of pain score at a secondary end point.

Adequate sample size?

We judged all studies to be at high risk of bias with regard to sample size as all had less than 50 participants per arm.

Adequate duration of follow-up?

We considered all but four studies to be at high or unclear risk of bias based on inadequate duration of follow-up (Bonelli 1983; Freitas 2013; Rocha 2014; Rodriguez 2005).

Other potential sources of bias

We judged two studies to be at high risk of bias for other reasons (Bonelli 1983; Rocha 2014). In Bonelli 1983, the LASB group had a significantly shorter duration of symptoms at baseline than the IVRB guanethidine group, and participants were significantly older. Rocha 2014 had average pain scores at baseline that differed by greater than one point between groups , but authors did not present tests for comparability at baseline. Three studies were at unclear risk of bias (Freitas 2013; Yoo 2012). Freitas 2013 and Rodriguez 2005 provided no baseline data, and neither Freitas 2013 nor Yoo 2012 gave details regarding concomitant treatments. We judged the two cross-over studies to be at low risk of bias for carry-over effects (Carroll 2009; Price 1998).

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

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. Seven study reports offered no details regarding these issues (Aydemir 2006; Bonelli 1983; Freitas 2013; Nascimento 2010; Price 1998; Yoo 2012; Zeng 2003).

Carroll 2009 declared that the authors had filed a patent for the inclusion of botulinum toxin A in sympathetic blocks. Rodriguez 2005 declared financial support from governmental and non-profit organisations. No study declared funding from industry sources. Toshniwal 2012 and Rocha 2014 declared no conflict of interest.

Effects of interventions

See: **Summary of findings for the main comparison** LASB for pain intensity and duration of pain relief in adults with CRPS

For a summary of all core findings, see Summary of findings for the main comparison.

LASB versus placebo

For the comparison of LASB versus placebo, we rated all evidence as being of moderate quality.

Pain intensity

In Price 1998, there was no difference between lidocaine and normal saline; the same number of participants (6/7) achieved at least 50% pain relief at two weeks. 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 plus sham ultrasound ($Z = -0.76$, $P = 0.45$). Authors did not report between-group comparisons.

Duration of pain relief

Price 1998 evaluated the duration of pain relief, finding that when local anaesthetic was administered, the mean duration of relief was longer (three days versus 19.9 hours in the saline group). However, 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 ($Z = -0.68$, $P = 0.50$). Authors reported no between-group comparisons. None of the included studies reported postintervention analgesic requirements.

Adverse Events

Price 1998 and Aydemir 2006 did not report adverse events.

LASB versus other interventions

Pain relief

Most comparative studies reported no significant difference in pain between groups (Bonelli 1983; Freitas 2013; Nascimento 2010; low to very low quality evidence). Aydemir 2006 did not explicitly report between-group differences, although they did not find any within-group differences in spontaneous pain scores 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; low quality evidence). Due to the variation in the interventions, there were not adequate data to allow pooling of the results.

Lim 2007 reported no significant difference in hand pain intensity (scale from 0 to 3) between LASB plus corticosteroid versus oral corticosteroids at 15-day follow-up (mean difference 0.00, 95%

confidence interval (CI) −0.35 to 0.35; very low quality evidence) and a statistically significant difference in favour of LASB with steroid at 30 days (mean difference 0.40, 95% CI −0.69 to −0.11; very low quality evidence).

Rocha 2014 reported that thoracic LASB with ropivacaine and steroid did not result in a statistically significant difference in average pain scores compared to injection of the same agents into the subcutaneous space (described as an "active placebo" at one month (0 to 10 scale mean difference −1.25, 95% CI −3.20 to 0.70; very low quality evidence), but there was a statistically significant difference at one-year follow-up in favour of thoracic LASB (mean difference −2.39, 95% CI −4.72 to −0.06; very low quality evidence). While not significant at one-month follow-up, the point estimate at both time points exceeds our threshold for clinical importance. However, it is worth noting that at one-year follow-up, attrition in the active group was 16% and in the control group 26%, introducing a possible risk of bias.

Toshniwal 2012 reported significantly lower short-term pain scores (on a 0 to 10 scale) 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, and 0.7, respectively) and unpleasantness of pain (0.7, 0.7, and 0.8, respectively) compared with those receiving a continuous stellate ganglion block (intensity: 3.3, 2.7, and 1.9; unpleasantness: 3.0, 2.7, and 1.9). Dull pain intensity 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 postcannulation (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 for long-term pain relief in one group over the other and no between-group differences at any other time points. There was no statistical comparison of quality of pain differences between groups. We rated this evidence as being of low quality.

Yoo 2012 found no statistically significant or clinically important difference between image-guided and non-guided stellate ganglion block at two weeks postinjection (0 to 10 pain VAS mean difference −0.58, 95% CI −1.51 to 0.35; very low quality evidence); there was a statistically significant but clinically unimportant difference at four weeks postinjection (mean difference −0.74, 95% CI −1.36 to −0.12; very low quality evidence) in participants with CRPS following stroke.

Duration of pain relief

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

Adverse events

Only six studies provided specific data regarding adverse events, and the level of detail of this reporting was mixed.

Carroll 2009 reported moderate adverse events in one participant (14.2%) following the botulinum toxin type A LASB. This participant had significant nausea and emesis that began five5 hours after the injection and lasted two days, resolving spontaneously.

Freitas 2013 reported that paraesthesia during needle positioning in "1 out of 10" in the LASB group and "2 out of 10" in the pulsed radiofrequency group. This is likely to be an error as it suggests that there were 20 participants in total while the trial reports 40 participants. The study reports that all participants in both groups reported soreness at the injection site lasting five to seven days.

Nascimento 2010 also found mild adverse events for all three groups. The SGB group receiving lidocaine and clonidine (gGroup 2) reported the highest frequency of adverse events: 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 (gGroup 1) reported the lowest frequency of adverse events, 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 IVintravenous (IV) regional block with lidocaine and clonidine (gGroup 3) reported drowsiness (46.1%; 6/13) and dizziness (7.7%; 1/13).

Rocha 2014 reported a similar overall rate of minor adverse events following thoracic blockade or subcutaneous injection with local anaesthetic and steroid and no major adverse events. Minor eventsThese included dizziness, blurred vision, puncture pain, increased pain, headache, nausea, vomiting, dysphagia, hoarseness, haematoma, dyspnoea, shivering, cold feeling, face swelling, and mouth numbness. Of note, 65% of participants in both groups reported "puncture pain";, 24% in the thoracic block group reported dyspnoea compared with 6% in the subcutaneous group. 35%Thirty-five per cent in the thoracic block group reported dizziness compared to 12% in the subcutaneous group. Twenty-four per cent in the thoracic block group reported dizziness compared to no participants in the subcutaneous group.

Toshniwal 2012 found adverse events 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 adverse event 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; investigators observed 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 reported hoarseness of voice (for initial 12 hours).

Yoo 2012 reported no adverse events in the group who received ultrasound guided blocks and two haematomas at the injection site for those who received unguided blocks.

LASB in addition to other interventions

Pain relief

Zeng 2003 and Rodriguez 2005 investigated the effectiveness of adding LASB to rehabilitation versus rehabilitation or medication alone. Zeng 2003 found no benefit of adding LASB at 10 days (0-10 Verbal Rating scale mean difference 0.2, 95% CI −1.3 to 1.7; very low quality evidence) or 20 days (mean difference 0.1, 95% CI −0.97 to 1.17; very low quality evidence). Rodriguez 2005 reported treatment efficacy (proportion with at least 50% pain reduction) 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 (HR) 2.7, 95% CI 1.1 to 6.7; very low quality evidence). 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 data for pain intensity or the proportion who achieved meaningful pain relief.

Duration of pain relief

No studies specifically presented data on the duration of pain relief for this comparison.

Adverse events

Zeng 2003 and Rodriguez 2005 did not report adverse events.

DISCUSSION

Summary of main results

The objective of this review was to assess the efficacy of LASB for the treatment of pain in CRPS 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 the use of LASB for CRPS since the last update in 2013. There are only two placebo-controlled randomised studies that met our modified inclusion criteria for this update (Aydemir 2006; Price 1998), both of which have very small sample sizes. We can draw no firm conclusions 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), the time frame that theory would suggest local anaesthetic is likely to have its maximum benefit. We could not estimate the duration of pain relief, if any.

LASB versus other interventions

In a change from the original version of this review, we took the decision to include trials that compared LASB with alternative interventions or that evaluated the effect of adding LASB to other treatments. We identified a number of such studies investigating 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 no effect (Jadad 1995; McQuay 1997; O'Connell 2013).

One small study (N = 36) at high risk of bias suggests a potentially clinically important effect for thoracic sympathetic blockade with bupivacaine and triamcinolone on average daily pain at one month and one year when compared to injection of the same agents into the subcutaneous space, though this difference was not statistically significant at one- month follow-up (Rocha 2014). The subcutaneous injection in this study was used as an active control condition, and might be expected to have systemic effects.

Carroll 2009 provided limited evidence that, compared with LASB alone, sympathetic blockade with botulinum toxin A added to local anaesthetic may prolong analgesia. Another single study, Rodriguez 2005, provided limited evidence to suggest that when added to usual physical therapy and pharmacological treatment, LASB may reduce the risk of relapse, but we found this study to be at high risk of bias across multiple domains; it 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.

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 conclude that there is little 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. Given this lack of reporting and the small size of all of the included studies, we cannot confidently draw conclusions regarding the safety of LASB. While those adverse events that have been reported appear to be minor, it is not currently possible to rule out the potential for rare but serious adverse events. To obtain a better estimate of the incidence and nature of adverse events, it might be necessary 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. We judged all of the included studies as being at unclear risk of bias in at least one domain, reflecting a common lack of clarity in many study reports. We deemed three 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.

We attempted to contact the authors of seven studies, with mixed success. Two responded and provided available data (Nascimento 2010; Toshniwal 2012). However, as we were unable to source two studies (Kostadinova 2012; Salinas Cerda 1997), did not receive a response from one to provide full data (Freitas 2013), and were unable to include two studies due to lack of clarity over whether the participant population overlapped with another included study (Rodriguez 2006; Rodriguez 2008), it is possible that we are missing relevant data.

Quality of the evidence

We did not judge any of the included studies to be at low risk of bias across all domains. Indeed, all but two studies carried an unclear risk of bias for random sequence generation and all but four 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). We assessed all studies to be at high risk of bias for inadequate sample size and only four studies to be 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. Thus, all of the evidence identified should be interpreted with caution.

Applying the GRADE approach, ratings across all comparisons were either low or very low quality except for the comparison of LASB versus placebo, which was of moderate quality. This rating is the result of the criteria we decided upon a priori when updating the searches. However, this moderate rating still merits some caution, since it is based on so few data. It is our view that for future updates, the rating of imprecision might be downgraded twice in the event that a comparison consists of fewer than 100 participants. Since each comparison consists of only one or two very small studies, and since all studies are at unclear or high risk of bias across various domains, it would be reasonable to characterise the entire body of included evidence as of low or very low quality.

Potential biases in the review process

While we have attempted to identify all eligible trials using a comprehensive search strategy, we may have still missed some key literature. Only three included studies used a positive response to a prior LASB to attempt to establish sympathetically maintained pain 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 in people with other characteristics. However, to date evidence of predictors of a positive response to LASB are elusive (Sethna 2012).

The decision to exclude studies with only very short term follow-up ($\leq$ 48 hours) has led to the exclusion of studies that had been included in previous updates of this review. We took this decision on the basis that such studies are of more value in terms of investigating the diagnostic potential of LASB, which was not the purpose of our review. These studies do not provide clinically useful information in terms of treatment effectiveness over a reasonable period of time. This review focused on pain as a primary outcome and did not consider outcomes such as function or other clinical

signs. However, LASB is commonly conducted with the primary goal of pain relief.

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, and all have similarly agreed that the evidence is limited and that there is no clear evidence for the efficacy of LASB (Forouzanfar 2002; Perez 2010; Tran 2010). Van Eijs 2011 recommended that LASB be considered for the treatment of CRPS if conservative multidisciplinary management has failed. However, they rated the evidence for the effectiveness of CRPS as level 2B+, characterised as "multiple RCTs, with methodologic weaknesses, yield contradictory results better or worse than the control treatment. Benefits closely balanced with risk and burdens, or uncertainty in the estimates of benefits, risk and burdens." This classification of the evidence seems consistent with our own conclusions, though we feel this level of evidence precludes clinical recommendations.

AUTHORS' CONCLUSIONS

Implications for practice

For people with CRPS

LASB is a treatment that may be offered for CRPS to help reduce pain and other symptoms. There is a scarcity of published evidence and a lack of high quality evidence to support or refute its effectiveness, though the available evidence is not encouraging. Due to the scarcity of evidence it is not possible to draw confident conclusions about the safety of LASB. People should consider this information when deciding whether to agree to receive the treatment.

For clinicians

There is a scarcity of published evidence and a lack of high quality evidence to support or refute its effectiveness, though the available evidence is not encouraging. One study, judged to be at high risk of bias, provides very low quality evidence that LASB may reduce the risk of recurrence of pain when added to rehabilitation and standard pharmacological care, and one study, also judged to be at high risk of bias, suggests that thoracic sympathetic block with local anaesthetic and corticosteroid may be effective. However, on the basis of such evidence it is not possible to make any clinical recommendations. Due to the scarcity of evidence it is not possible to draw confident conclusions about the safety of LASB.There is currently little credible evidence to support the use of LASB for CRPS.

For policy makers and funders

The available evidence relating to the effectiveness of LASB for CRPS is not compelling. While there is substantial uncertainty regarding the effectiveness of alternative therapeutic options (O'Connell 2013), it is not clear that investment in this procedure provides clinical value.

Implications for research

General

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 multicentre, collaborative research projects that can recruit from larger clinical populations. While many studies investigate the effect of adding therapeutic agents to LASB, there remains substantial uncertainty regarding the efficacy of simple local anaesthetic blockade for CRPS.

Design

Reducing this uncertainty requires adequately powered trials that utilise placebo controls, ensure adequate blinding and confirm the technical adequacy of the block. Future trials should use established diagnostic criteria and clearly report the type of CRPS under investigation. Trials should also consider the IMMPACT recommendations for the design of trials in pain to ensure that outcomes, thresholds for clinical importance and study designs are optimal (Dworkin 2008; Dworkin 2009; Dworkin 2010; Turk 2008a; Turk 2008b).

Measurement (endpoints)

Future trials should measure both immediate pain relief and long-term ($\geq$ 6 month) outcomes from LASB. Furthermore, future trials should adhere to the CONSORT guidance on standards of reporting and should clearly report all adverse events (Altman 2012).

ACKNOWLEDGEMENTS

We thank the Pain, Palliative and Supportive Care Review Group for running the searches and supporting the review process.

We would also like to thank Arturo Lawson, Murat Dalkilinc, Luciana Macedo, Ann Meulders, Eric Parent, Andrea Wand, Eva

Bosch and Ein-Soon Shin for their assistance in interpreting non-English language trials.

Cochrane Review Group funding acknowledgement: The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group. Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the NIHR, National Health Service (NHS) or the Department of Health.

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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) Mean age (SD): Group 1: 21.9 years (1.05) Group 2: 21.4 years (0.73) Group 3: 21.1 years (0.38) Sex: not reported. Upper limb CRPS-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), and pneumatic compression. If necessary, all groups had access to medical treatment, which involved 500 mg oral paracetamol pill, maximum of six tablets (3 g) per 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.

Aydemir 2006 (*Continued*)

	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 min of intermittent ultrasound at 3 watt/cm^2 over the affected site (over stellate ganglion) Number of treatments not reported SGB ultrasound (sham): 5 min, 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

Aydemir 2006 (*Continued*)

Adequate duration of follow-up?	Unclear risk	One-month follow-up
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 Mean age (SD): 52.33 years (5.04) Sex: 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 min, 60 min, 24 h, 48 h, 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	At baseline, 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 Age mean (range) 49.4 (38-67) Sex: 1 male 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 h 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 Mean duration of pain (range): 3.8 years (2-14)

	Baseline mean pain levels, 10 cm VAS (range): 7.2 cm (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
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 BTA 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

Carroll 2009 (*Continued*)

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
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 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

Freitas 2013

Methods	RCT parallel
Participants	N = 40 (though adverse event reporting implies 20 and no CONSORT flowchart presented). Presume 20 per group Age: not reported Sex: not reported Lower limb CRPS-I. Diagnostic criteria: IASP Bruehl 1999 Duration of pain prior to block: > 6 months Type of initiating injury: not reported Concomitant treatments: not reported Medico-legal factors: excluded if pending litigation Previous treatment: unresponsive to medication and physiotherapy (such as oral gabapentin 2400 mg/d, oral amitriptyline 100 mg/d, and oral carbamazepine 1000 mg/d and physiotherapy for more than 6 months
Interventions	Group 1: LASB lumbar plexus sympathetic block L2-3 and L3-4. 15 ml lidocaine and 100 mcg clonidine at each level Group 2. Pulsed radiofrequency (PRF) lumbar plexus L2-3 and L3-4, x3 120sec cycles at each level at 42º C. 1 ml of 2% lidocaine injected at each level Evaluation of technical adequacy of blocks: no Number of blocks: 1 per site, on 1 occasion Concomitant treatments: not reported

Freitas 2013 (*Continued*)

Outcomes	Pain intensity VAS, neuropathic pain scale. No numerical data provided SF-36. Means reported but no measures of variance Statistically significant difference seen in "hot pain" at "final score" but this time point is not clearly defined - likely 6 months Adverse events: "2 out of 10" had paraesthesia following PRF. "1 out of 10" had paraesthesia following LASB. Note; this implies 20 rather than 40 participants
Country of origin	Brazil
Study aim	To determine whether percutaneous PRF applied directly to the sympathetic lumbar plexus was more effective than lumbar sympathetic blocks, and, if so, whether this could be achieved without the risks associated with traditional ablative procedures
Notes	Conflicts of interest not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomized to either PRF or sympathetic lumbar block according to computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Comment: no information given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Personnel not blinded however, comparison is between two active invasive interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: Participants blinded to group assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant in pulsed radiofrequency group dropped out - reasons unclear and unclear whether data missing or excluded
Selective reporting (reporting bias)	High risk	Pain outcome data are not reported in numerical format
Adequate sample size?	High risk	N = 40 entered the study but reporting of adverse events suggests 20 participants
Adequate duration of follow-up?	Low risk	6-month follow-up
Free of other bias?	Unclear risk	No baseline data presented; no detail given regarding concomitant treatments

Lim 2007

Methods	Parallel RCT
Participants	N = 38 Mean age (SD): Group 1: 61.4 years (10.1) Group 2. 58.7 years (12.1) Sex: 21 female, 17 male Upper Limb CRPS poststroke Diagnostic criteria: unclear though described a "three phase bone scan test" Duration of symptoms: not reported Type of initiating injury: stroke. Concomitant treatment: conservative physical therapy including passive joint movements Medico-legal factors: not reported Previous treatment: not reported
Interventions	Group 1: LASB stellate ganglion, lidocaine Dosage: 10 ml 0.5% lidocaine Number of blocks: 5 blocks: 1 every 3 days for 15 days Evaluation of technical adequacy of block: not reported Group 2: oral corticosteroids for 14 days. 60 mg of oral prednisolone was administered in two 30mg doses depending on the hormone cortisol rhythm on days 1-3, and applied 40 mg on days 4-6, 30 mg on days 7-9, and 20 mg on days 10-12. Single dose of 10 mg was administered on days 13-14. Oral administration was stopped after 14 days
Outcomes	0-3 scale hand pain with passive movement or palpation. Measured at 15 and 30 days from start of treatment
Country of origin	Korea
Study aim	To compare the therapeutic effects between stellate ganglion block and steroid therapy in poststroke complex regional pain syndrome
Notes	Adverse events not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: no details reported
Allocation concealment (selection bias)	Unclear risk	Comment: no details reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Comment: Personnel not blinded. Non-invasive control qualitatively different to active intervention

Lim 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: Inadequate blinding of participants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: no information reported on attrition
Selective reporting (reporting bias)	Low risk	Comment: outcomes adequately reported
Adequate sample size?	High risk	Comment: N = 38
Adequate duration of follow-up?	Unclear risk	Comment: 30 days follow-up
Free of other bias?	Low risk	Comment: no other bias detected

Nascimento 2010

Methods	RCT, parallel
Participants	N = 43 Mean age (range): Group 1: 37.7 years (27-54) Group 2: 38.6 years (25-50) Group 3: 39.0 years (27-50) Sex: Group 1 (n = 14): 1 male Group 2 (n = 15): 1 male Group 3 (n = 14): 1 male Upper extremity CRPS-I Diagnostic criteria: IASP (Merskey 1994) Mean duration of pain (range): Group 1: 24.2 months (3-72) Group 2: 24.2 months (8-72) Group 3: 22.3 months (2-48) Mean baseline pain intensity (SE), 10 cm VAS scale: Group 1: 8.7 cm (0.3) Group 2: 8.7 cm (0.3) Group 3: 8.3 cm (0.3) Inciting event: Repetitive strain injury n = 18, carpal tunnel syndrome n = 11, late postsurgical 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

Nascimento 2010 (*Continued*)

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 min 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)

Nascimento 2010 (*Continued*)

Adequate sample size?	High risk	n = 45; 15 participants per treatment group
Adequate duration of follow-up?	High risk	1 week follow-up
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	N = 7 (3 lower extremity, 4 upper extremity pain) Mean age: 42 years (SD 11; range: 32-52) Sex: 3 male CRPS-I or -II of upper or lower extremities (excluded if CRPS in multiple areas) Diagnostic criteria: IASP (Merskey 1994) Mean duration of symptoms: 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: SGB 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 min for 1.5 h prior to injection and every 15 min for 1 h following injection. Pain outcomes then rated 4 times a day (morning, midday, afternoon, evening) for 7 days postinjection Time to peak analgesia measured as the VAS unit difference between pre-injection 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

Price 1998 (*Continued*)

Notes	Author confirmed the quasi-random allocation in correspondence; adverse events not reported

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
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
Adequate sample size?	High risk	N = 7
Adequate duration of follow-up?	High risk	7 days follow-up

Price 1998 (*Continued*)

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 Procedures separated by 7- - 10 days. Figures illustrate pain returned to baseline levels prior to next block

Rocha 2014

Methods	Parallel RCT
Participants	N = 36 Mean age (SD): Group 1 : 42 years (13.5) Group 2 : 44.4 years (8.9) Sex: 19 female, 17 male Upper limb CRPS Diagnostic criteria: IASP (Merskey 1994) then switched to IASP (Harden 2010). Participants screened under old criteria were then excluded Duration of symptoms (months): Group 1: 22.7 (26.3) Group 2: 21.0 (2.16) Type of initiating injury: mixed: fractures, contusions, surgery, work-related Concomitant treatments: unclear Previous treatment: 4 week standardised multimodal protocol including physical therapy, oral analgesic polytherapy: antidepressants, analgesics, opioids, gabapentin and psychological input Medico-legal factors: not reported
Interventions	Group 1: LASB T2 sympathetic ganglion (fluoroscopically guided) Group 2: subcutaneous space injection of same agents (fluoroscopy also used) Agents: 10 ml anaesthetic + steroid. 5 ml 75% ropivacaine, 5 ml triamcinolone Evaluation of technical adequacy of block: yes - measurement of arm temperature Number of blocks: 1
Outcomes	Average pain score from Brief Pain Inventory McGill Pain Questionnaire Adverse events 1 month and 1 year follow-up
Country of origin	Brazil

Rocha 2014 (*Continued*)

Study aim	To evaluate the efficacy of TSB for upper limb CRPS-I	
Notes	Authors declare no conflict of interest	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: no details reported
Allocation concealment (selection bias)	Low risk	Comment: participants asked to pick an unmarked opaque envelope containing allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Personnel not blinded however, comparison is between two active invasive interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: assessor blinded to intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 21% attrition at long-term follow-up and imbalanced across groups. No details provided regarding reasons for loss to follow-up
Selective reporting (reporting bias)	Low risk	Comment: outcomes reporting adequate
Adequate sample size?	High risk	Comment: N = 36
Adequate duration of follow-up?	Low risk	Comment: 1-year follow-up
Free of other bias?	High risk	Comment: average pain scores at baseline differ by more than 1 point

Rodriguez 2005

Methods	RCT, parallel design
Participants	N= 82 Mean age (no SDs provided): Group 1: 44.1 years Group 2: 46.1 years, Sex: Group 1: 36.6% male Group 2: 46.3% male 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 (Merskey 1994; Reinders 2002) Inciting event: 71.4% of CRPS cases were secondary to accidental or violent trauma and 18% occurred following surgical procedures Mean duration of symptoms (no SDs provided): Group 1: 253.7 days Group 2: 213.4 days Medico-legal factors: Group 1: 14.6% had a compensation claim Group 2: 24.4% had a compensation claim Previous treatment: participants were excluded if they had previous stellate ganglion blocks; no other previous treatment reported Concomitant treatment: Group 1 also received physical therapy and pharmacological treatment
Interventions	Group 1: SGB, physical therapy and pharmacological treatment 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) Group 2: Physical therapy and pharmacological treatment only(Control group): Received physical therapy and pharmacological treatment
Outcomes	Pain intensity (VAS). Measured at baseline, 1 month and 2 months. Exact follow-up time appears to be variable among participants (i.e. followed for more than 2 months in some) Therapeuctic efficacy: number of participants with at least 50% reduction in the pain. Measured at 2 months postintervention Efficacy: (incidence of pain in control group − incidence of pain in the SGB group)/ incidence of pain in the control group * 100 Absolute risk reduction (incidence of pain in control group − incidence of pain in the intervention group). Measured at 2 months postintervention NNTB = 1/ARR (calculated at 2 months postintervention) Relapse (return of pain to less than 50% reduction or return of pain to baseline levels or above); determined at 2 months postintervention
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

Rodriguez 2005 (*Continued*)

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 cohort. 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. No adverse events reported

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
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?	Unclear risk	No baseline data given on pain intensity; unsure if groups were similar at baseline

Toshniwal 2012

Methods	RCT, parallel design
Participants	N= 33 Mean age (SD): Group 1: 44.33 years (13.6) Group 2: mean age 42 years (16.6) Sex:

	Group 1 (n=19): 6 male Group 2 (n=14): 7 male CRPS-I of the upper extremity which had lasted at least 3 months and was refractory to medical management. People receiving any interventional procedure for the condition were excluded Diagnostic criteria: Bruehl 1999), Mean duration of pain (SD): Group 1: 8.8 months (4.4). Group 2: 9.3 months (SD 2.8) 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 Group 1: CSG block Site: stellate ganglion - 20 gauge 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/h) 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) Group 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: continuous 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/h 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 min); 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 min, 30 min, 2 h, 12 h, and 24 h, day 2, day 3, day 4, day 5, day 6, day 7, week 2, week 3, week 4

Toshniwal 2012 (*Continued*)

	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 allocation was concealed in sealed opaque envelopes that were not opened until patient consent had been obtained" Comment: likely done
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

Toshniwal 2012 (*Continued*)

Free of other bias?	Low risk	Groups were similar on important prognostic factors

Yoo 2012

Methods	Parallel RCT
Participants	N = 42 Mean age (SD): Group 1: 61.3 years (5.6) Group 2: 59.1 years (4.5) Sex: 25 males, 20 females (note: likely error as not consistent with overall N) CRPS poststroke, upper limb Type of initiating injury: stroke Diagnostic criteria: IASP Harden 2010 Duration of symptoms - "duration since stroke". Group 1: 2.8 months (1.1) Group 2: 2.3 months (0.9) Previous treatment: not reported Concomitant treatments: not reported Medico-legal factors: not reported
Interventions	Group 1: stellate ganglion block without ultrasound guidance. 10 ml lidocaine injection Group 2: stellate ganglion block with ultrasound guidance. 5 ml lidocaine injection Number of blocks: 2, 1 week apart Evaluation of technical adequacy of block: none
Outcomes	Pain intensity VAS, 0-10, anchors "no pain" and "the highest pain" 2- and 4-week follow-up Adverse events
Country of origin	Korea
Study aim	To evaluate the effectiveness of ultrasound-guided SGB by comparing with the blind SGB in poststroke CRPS patients in reducing pain and swelling of the affected limb
Notes	Conflict of interest not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Comment: allocation concealment not reported

Yoo 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: Participant blinding not reported. The interventions are likely to be distinguishable, however both were active invasive interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: blinding of participants is unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: there are anomalies between group numbers in the text and table 1
Selective reporting (reporting bias)	Low risk	Comment: outcome reporting adequate
Adequate sample size?	High risk	Comment: N = 42
Adequate duration of follow-up?	Unclear risk	Comment: follow-up stated at 4 weeks
Free of other bias?	Unclear risk	Comment: no information given on concomitant treatment

Zeng 2003

Methods	RCT, parallel
Participants	N = 60 Age range: 38-71 Sex: 42 males Shoulder-hand syndrome following stroke Diagnostic criteria not reported Duration of symptoms; described as "in the early stages of SHS complicated with paralysis" Previous treatment not specified Mean baseline pain, 0-10 VRS (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 VAS (0 = no pain, 2 = little pain, 4 = frequent mild pain or occasional severe pain, 6 = severe pain but tolerable, 8 = continuous pain and intolerable, 10 = severe pain that couldn't be touched) Pain was measured before treatment, at 10 days and 20 days post-treatment

Zeng 2003 (*Continued*)

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; adverse events not reported	
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, rehabilitation kind" Comments: no difference between groups in age, sex, rehabilitation and duration of symptoms; outcome assessment timing identical

ARR: absolute risk reduction; **BTA**: botulinum toxin A; **CIBP**: continuous infraclavicular brachial plexus block; **CRPS**: complex regional pain syndrome; **CSG**: continuous stellate ganglion block; **IASP**: International Association for the Study of Pain;**IV**: intravenous; **IVRB**: intravenous regional blockade; **LASB**: local anaesthetic sympathetic blockade; **NNTB**: number needed to treat for an additional beneficial outcome; **PRF**: pulsed radiofrequency; **RCT**: randomised controlled trial; **RSD**: reflex sympathetic dystrophy; **SD**: standard deviation; **SE**: standard error; **SF-36**: 36-item short-form health survey; **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
Glynn 1993	Not randomised
Hartrick 2004	Not randomised
ISRCTN71968956	Not randomised
Kastler 2013	Not randomised
Linson 1983	Not randomised
Malmqvist 1992	Not randomised
Meier 2009	< 48 h follow-up postblock
Perrigot 1982	Not a local sympathetic block
Quevedo 2005	Not randomised
Raja 1991	< 48 h follow-up postblock
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
Verdugo 1995	<48 h follow-up postblock

(*Continued*)

Wang 1985	Not randomised
Wehnert 2002	<48 h follow-up postblock
Yucel 2009	Not randomised

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

Kostadinova 2012

Methods	Parallel RCT
Participants	N = 32
Interventions	Stellate ganglion block with bupivacaine vs bupivocaine plus neostigmine
Outcomes	Not reported
Notes	Abstract of protocol only available - authors contacted for further details

Rodriguez 2006

Methods	Parellel RCT
Participants	N = 71
Interventions	SGB, physical therapy and pharmacological treatment vs physical therapy and pharmacological treatment
Outcomes	Pain intensity VAS 10 cm. Proportion with 50% pain relief 1 month postblock
Notes	Not clear whether a distinct trial or an extension of Rodriguez 2005. Authors contacted for clarification.

Rodriguez 2008

Methods	Parellel RCT
Participants	N = 114
Interventions	SGB, physical therapy and pharmacological treatment vs physical therapy and pharmacological treatment
Outcomes	Pain intensity VAS 10 cm. Time to relapsing. 6-month follow-up
Notes	Conference abstract. Not clear whether a distinct trial or an extension of Rodriguez 2005. Authors contacted for clarification.

Salinas Cerda 1997

Methods	Study report not retrievable
Participants	-
Interventions	-
Outcomes	-
Notes	-

RCT: randomised controlled trial; **SGB**: stellate ganglion blockade; **VAS**: visual analogue scale.

DATA AND ANALYSES

This review has no analyses.

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: r**eports of hyperaesthesia, allodynia, or both. • **Vasomotor:** reports of temperature asymmetry, skin colour changes, skin colour asymmetry, or a combination of these. • **Sudomotor/oedema:** reports of oedema, sweating changes, sweating asymmetry, or a combination of these. • **Motor/trophic:** reports of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic change (hair, nail, skin), or a combination of these.
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), allodynia (to light touch, temperature sensation, deep somatic pressure, or joint movement), or both • **Vasomotor:** evidence of temperature asymmetry (> 1° C), skin colour changes, asymmetry, or a combination of these. • **Sudomotor/oedema:** evidence of oedema, sweating changes, sweating asymmetry, or a combination of these. • **Motor/t rophic:** evidence of decreased range of motion, motor dysfunction (weakness, tremor, dystonia), trophic changes (hair, nail, skin), or a combination of these.
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. 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 2. 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 3. EMBASE 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 or/1-15
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 or/17-27
29 16 and 28
30 random$.tw.
31 factorial$.tw.
32 crossover$.tw.
33 cross over$.tw.
34 cross-over$.tw.
35 placebo$.tw.
36 (doubl$ adj blind$).tw.
37 (singl$ adj blind$).tw.
38 assign$.tw.
39 allocat$.tw.
40 volunteer$.tw.
41 Crossover Procedure/
42 double-blind procedure.tw.
43 Randomized Controlled Trial/
44 Single Blind Procedure/
45 or/30-44
46 (animal/ or nonhuman/) not human/
47 45 not 46
48 29 and 47

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]

Appendix 5. GRADE judgements by comparison

Comparison	Studies	N for comparison	Result	GRADE CRITERIA					RATING
				LIMITATIONS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	
LASB vs placebo	Price 1998 Aydemir 2006	23	No difference	-	-	-	X	-	Moderate
Thoracic LASB + steroid vs subcutaneous	Rocha 2014	36	1 month - clinically important difference (not sig).	X	X	-	X	-	Very low

(*Continued*)

			1 year clinically important difference (sig)	X	X	-	X	-	
LASB vs ultrasound block	Aydemir 2006	18	No difference	-	X	-	X	-	Low
LASB vs IVRB guanethidine	Bonelli 1983	19	No difference	X	X	-	X	-	Very low
LASB vs BTA	Carroll 2009	9	Increased duration of relief with BTA		X	-	X	-	Low
LASB vs pulsed radiofrequency	Freitas 2013	40	No difference	X	X	-	X	-	Very low
LASB vs oral corticosteroids	Lim 2007	38	No difference	X	X	X	X	-	Very low
LASB vs IVRB (both lidocaine + clonidine)	Nascimento 2010	43	No difference	X	X	-	X	-	Low
LASB + PT + pharma vs PT + pharma	Rodriguez 2005	82	Favours SGB	X	X	-	X	-	Very low
LASB+ vs PT	Zeng 2003	60	No difference	X	X	-	X	-	Very low
Continuous LASB vs continuous brachial	Toshniwal 2012	33	Favours brachial plexus block	-	X	-	X	-	Low

(*Continued*)

plexus block									
Image-guided LASB vs nonim-age-guided	Yoo 2012	42	No differ-ence	X	X	X	X	-	Very low

X = downgrade on this criteria; **BTA**: botulinum toxin A; **IVRB**: intravenous regional blockade; **LASB**: local anaesthetic sympathetic blockade; **PT**: physical therapy; **SGB**: stellate ganglion blockades.

WHAT'S NEW

Last assessed as up-to-date: 16 September 2015.

Date	Event	Description
28 July 2016	Review declared as stable	See Published notes.

HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 4, 2005

Date	Event	Description
7 March 2016	New citation required but conclusions have not changed	The conclusions of the review remain unchanged.
16 October 2015	New search has been performed	This updated review used refined exclusion crite-ria (exclude studies with follow-up of <48hrs) (see Differences between protocol and review). This re-sulted in the exclusion of 4 studies from this update that had been included in previous versions of this re-view (Meier 2009; Raja 1991; Verdugo 1995; Wehnert 2002). We also updated the data analysis that included consideration of the minimally important difference (as per OMERACT 12 group recommendations) and evaluation of the quality of evidence using the GRADE approach

(*Continued*)

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 additional participants); two studies compared LASB to a placebo/inert treatment (Aydemir 2006; Price 1998), the remaining nine studies compared LASB with an active treatment [Bonelli 1983; Carroll 2009; Meier 2009; Nascimento 2010; Raja 1991; Toshniwal 2012; Wehnert 2002; Zeng 2003) or investigated the effect of adding LASB to an active treatment (Rodriguez 2005). 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 regional anesthesia)
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
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 block-

(*Continued*)

		ade 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
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	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	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	We have inserted a new Table (under other Tables) that provides the new Budapest criteria for diagnosing CRPS
21 September 2011	Amended	Addition of new criteria for considering studies for this review (Types of participants)
9 November 2009	Amended	Contact details updated.
30 October 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

NEO: informed the modification of the protocol; acted as the arbiter reviewer; 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.

WG: 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.

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

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

DECLARATIONS OF INTEREST

NEO: none known.

BMW: none known.

WG: none known.

DBC: none known; DBC practiced anesthesiology and pain medicine in busy academic medical centers from 1986-2005, directly treating patients with CRPS, but has not treated people with CRPS since 2005.

FB: none known; FB is a practicing neurologist and pain treatment specialist who treats patients with CRPS.

TRS: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Saltonstall Foundation, USA.
- Javeriana University School of Medicine, Colombia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This 2016 updated review used an expanded search strategy. In particular, we used additional search terms and also searched clinical trial registers for potentially relevant studies. For this update, we excluded studies that had only immediate follow-up data (≤ 48 h), because this information provides little clinically relevant information about the clinical effectiveness of this treatment.

Further, we used an updated version of the 'Risk of bias' assessment - specifically, we included 'size of treatment groups' and 'duration of follow-up' in the 'Risk of bias' evaluation. This updated review also included studies comparing local anaesthetic blockade (LASB) versus other active treatments (original review compared LASB with placebo/inert treatments only). Lastly, we updated the data analysis that included consideration of the minimally important difference (as per OMERACT 12 group recommendations) and evaluation of the level of evidence using the GRADE approach.

NOTES

A new search within two years is not likely to identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

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