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Review Article

The Effectiveness and Risks of Fluoroscopically Guided Cervical Transforaminal Injections of Steroids: A Systematic Review with Comprehensive Analysis of the Published Data

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Abstract

Objective. To determine the effectiveness and risks of fluoroscopically guided cervical transforaminal injection of corticosteroids in the treatment of radicular pain.

Design. Systematic review of the literature with comprehensive analysis of the published data.

Interventions. Three reviewers with formal training in evidence-based medicine searched the literature on fluoroscopically guided cervical transforaminal injection of steroids (CTFIS). Each reviewer independently assessed the methodology of studies found and appraised the quality of the evidence presented.

Outcome Measures. The primary outcome assessed was relief of radicular pain. Other outcomes such as reduction in surgery rate and complications were noted if reported. The evidence on each outcome was appraised in accordance with the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system of evaluating evidence.

Results. The searches yielded 16 primary publications on effectiveness. Available evidence, derived mainly from observational studies, suggests that approximately 50% of patients experience 50% relief of radicular pain for at least 4 weeks after CTFIS, and the intervention may have surgery-sparing effects. The literature also contains 21 articles with primary reports of serious complications, including 13 deaths and many catastrophic neurological injuries. The evidence of pain-relieving effects, of surgery-sparing effects, and of risks of CTFIS were all rated as of very low quality according to the GRADE system.

Conclusions. In patients with cervical radicular pain, fluoroscopically guided CTFIS may be effective in easing pain and reducing need for surgery. However, the evidence of effectiveness is of very low quality, and the benefits of the procedure are compromised by the risks of serious complications.

Key Words. Radicular Pain; Cervical; Transforaminal; Fluoroscopy; Injection; Steroids

Introduction

In 1933, Dogliotti described cervical epidural steroid injection, employing the interlaminar route, as a treatment for cervical radicular pain [1]. The procedure was found to be effective in some cases but the technique was hazardous

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because of the narrow width of the cervical epidural space between the ligamentum flavum and the dura mater covering the spinal cord. Transforaminal injection of corticosteroids was introduced as a treatment for sciatica in 1952 by Robecchi and Capra [2]. They described injection by a sacral, transforaminal route, passing a needle through the first dorsal sacral foramen to inject hydrocortisone around the first sacral nerve root. Later, the procedure was adapted to the lumbar spine, and transforaminal injection of steroids has been proven to be an effective treatment for many patients with lumbar and sacral radicular pain [3].

In 1988, Bard and Laredo described cervical epidural steroid injection via a transforaminal route for cervical radicular pain [4]. Cervical transforaminal injection of steroids (CTFIS) continues to be administered for this indication, although cervical interlaminar epidural steroid injection has remained in use. Both procedures have literature that suggests these injections could be effective, but both are also known to be associated with risks, including epidural hematoma, paralysis, and death.

The purported advantage of transforaminal injections over interlaminar injections is precise placement of steroid onto the spinal nerve that is assumed to be the source of radicular pain. Risks include injection into the vertebral artery or a radiculomedullary artery that supplies the spinal cord, and overpenetration of the needle through the foramen into the spinal cord. The use of real-time fluoroscopy enables the physician to visualize dispersal of contrast medium and the injectate around the target nerve.

The purpose of this project was to identify all publications on fluoroscopically guided CTFIS for the treatment of radicular pain and to assess the data on the effectiveness and risks of the procedure in preparation for the development of appropriate use criteria.

Those data should be considered in the light of the natural history of cervical radicular pain, its expected course in the absence of treatment. Natural history has a bearing on all such data produced over time; it provides a fundamental reference for prognosis and sets outcomes after treatment in perspective. Unfortunately, there are no rigorous epidemiological data on the natural history of cervical radicular pain so such comparisons are not possible. Studies of patients with neck pain who were treated conservatively do suggest that the long-term outcomes of cervical pain are favorable, but not all patients in these studies had radicular pain so it is not clear if they reflect the natural history of cervical radicular pain [5–7].

Methods

The three investigators, who all have formal training in evidence-based medicine and are members of the Standards Division of the International Spine Intervention Society (ISIS), searched the scientific literature independently for publications on the effectiveness and any unwanted effects of fluoroscopically guided cervical transforaminal injection of steroids (CTFIS). Initially, they each conducted digital searches using the search engine Ovid to explore the databases Embase, Medline, PubMed, and EBM Reviews, using the keywords transforaminal, cervical, injection, corticosteroids, steroids, nerve root sleeve, radicular pain, and radiculopathy. The searches encompassed all scientific articles published until June 2013. The only exclusions were non-English language articles, non-human studies, conference abstracts, and case reports, unless they were reports of complications. When suitable articles were retrieved, the references of each were perused for relevant citations that had not been identified by the database searches.

The articles retrieved by the searches were sorted by each of the investigators into two groups: primary publications (reports of studies that produced original data) and secondary publications (those not producing original data, such as literature reviews, editorials, and letters). The primary publications on the effectiveness of fluoroscopically guided CTFIS were then classified by each of the investigators into three types of study, termed observational studies, pragmatic studies, and explanatory studies. Observational studies were defined as those that simply described the outcomes observed after the use of an intervention; note was taken of whether the observational study design was prospective or retrospective. Pragmatic studies were defined as those in which the outcomes of one intervention were compared with those of another intervention expected to have a therapeutic effect. Explanatory studies were defined as those in which the outcomes of an intervention were compared with those of an intervention not expected to have a therapeutic effect. The three investigators then compared their individual classifications of articles, and any differences were discussed until they reached consensus about the class in which each primary study belonged.

The primary articles on effectiveness of fluoroscopically guided CTFIS were then appraised by each of the investigators independently, using an instrument developed by the ISIS Standards Division to facilitate reliable assessment of studies of therapeutic effectiveness. The instrument assesses study design and objective; the study population; the intervention under study and any other intervention used for comparison; the outcomes considered and the instruments used to evaluate them; the results reported and the times they were observed after the intervention; any methodological limitations apparent, including non-blinded observers; and losses to follow-up, etc. It also records the reviewer's assessment of the article and the data it reported, with specific attention to any apparent biases or inconsistencies, the precision of estimates of effect (including confidence intervals of data), and any confounding factors. Each reviewer then made a general comment led by the question: "Irrespective of what the authors may or may not have written, does the study provide valid data on the effectiveness of fluoroscopically-guided CTFIS, and if so, how compelling are those data?"

When the investigators had each completed their independent appraisals of the effectiveness articles, they

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shared the results of their assessments and discussed any differences of opinion on particular articles until they reached consensus on the value of each article's contribution to the published evidence of the effectiveness of CTFIS. The assessments were then appraised by other members of the ISIS Standards Division (all also trained in evidence-based medicine).

The results of studies that produced categorical data for individual patients were tabulated (see below). The data produced from all of the studies were appraised, and the resultant body of evidence was analyzed to determine whether it provided evidence of effectiveness of the procedure. That body of evidence was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system of appraisal to determine the quality of the evidence of the effectiveness of CTFIS.

The three investigators also searched the scientific literature independently for publications on the risks and any unwanted effects of fluoroscopically guided CTFIS. Again they conducted digital searches using the search engine Ovid to explore the databases Embase, Medline, PubMed, and EBM Reviews, using the same keywords and the terms safety, complications, and unwanted effects. As before, they perused the references of each article retrieved for relevant citations that had not been identified by the database searches.

The articles reporting complications and unwanted effects were also appraised by each of the investigators. The investigators then shared their findings and discussed any differences of opinion on particular articles until they reached consensus on the value of each article's contribution to the published body of evidence of the risks, complications, and unwanted effects of fluoroscopically guided CTFIS. The information provided in the reports of complications was collated, and the resultant body of evidence was evaluated using the GRADE system of appraisal to determine the quality of the evidence of the risks of CTFIS.

The quality of the published evidence of effectiveness and the published evidence of risks were then both taken into account, and conclusions were drawn in accordance with the GRADE system about the strength of recommendations for use of CTFIS based on all published data on the procedure.

Results

The literature searches yielded 24 articles on the effectiveness of fluoroscopically guided CTFIS. Of these, 16 were primary studies producing original data on the effectiveness of the procedure, and the other eight articles were reviews or essays that discussed effectiveness but did not provide original data [8–15]. The literature searches also yielded 45 publications that discussed aspects of the safety of the procedure and its associated risks. Of these, 21 were articles reporting original data on significant complications.

Effectiveness

The 16 primary studies of effectiveness included 13 observational studies and 3 pragmatic studies. There were no explanatory studies. The 16 study reports were appraised using the standard instrument, and their data were assessed by 2 measures of outcome: relief of radicular pain and avoidance of surgery. The standard adopted in most studies for success in pain relief was at least 50% relief of radicular pain; that degree of relief for at least 4 weeks after CTFIS was considered by the reviewers a minimal standard of successful outcome in that regard. Data on the avoidance of surgery were extracted from studies that reported the outcomes of patients who were on waiting lists for surgery but after CTFIS did not go on to have the surgery that had been planned. The results of primary studies that yielded such data were then analyzed to determine what the whole body of published evidence shows about the effectiveness of fluoroscopically guided CTFIS for relieving radicular pain and reducing the need for surgery.

Observational Studies

The first article on the effectiveness of CTFIS was published in 1996; it was a prospective, observational study of 68 consecutive patients with cervical radicular pain treated with injections of lidocaine and triamcinolone by three different routes including CTFIS [16]. The outcomes were not stratified according to the types of injection administered, so the results were not able to be included in this review.

In 2000, the report of a retrospective, observational study showed the outcomes of 20 patients treated with therapeutic selective nerve root blocks (CTFIS) for atraumatic cervical spondylotic pain [17]. The symptomatic level was determined by reflex changes or myotomal weakness on physical examination, or in some cases by electrodiagnostic testing. If physical signs and electrodiagnosis did not identify the source of symptoms, a diagnostic selective nerve root block was done; if it produced 80% relief, the patient was offered CTFIS. Data were collected on average for 21 months after patients were discharged from treatment (range 12–45 months). Twenty patients were treated with CTFIS, and 12 of them were described as having good or excellent results for a set of outcomes measured by a questionnaire. With respect to pain scores, average visual analog scale (VAS) levels at initial presentation were provided, and good and excellent results were defined as verbal pain ratings of 3–4 and 0–2, respectively, but these group results were not suitable for inclusion in the tabulated data of this review.

In 2001, a prospective observational study was published of 32 patients with cervical radicular pain persisting after at least 2 months of conservative treatment [18]. Two patients had bilateral pain so the study involved 34 pain sources. Twenty-six patients had cervical spondylosis, five patients had disc herniations, and one patient had cervical spondylosis and a disc herniation. The patients had either

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one or two fluoroscopically guided CTFIS of 50 mg prednisolone, in conjunction with medical treatment which included wearing a cervical collar. After the injections, pain relief was assessed using a 100 mm VAS. The results showed radicular pain was relieved by at least 50% for up to 3 months in 18 of the 32 patients or 56% (CI_{95} 39–73%), and of those 18, 16 patients or 50% (CI_{95} 33–67%) reported sustained relief at 6 months. Patients who had no relief at 14 days did not experience any benefit later. Follow-up data 6 months after CTFIS showed the treatments were successful in 18 patients or 56% (CI_{95} 39–73%) who were able to resume their full lifestyles, and unsuccessful in 14 or 44% (CI_{95} 27–61%) who were unable to return to work or other activities. The authors stated that after eight of the 43 procedures, or 19% (CI_{95} 7–31%) of them, patients had "minor neurovegetative manifestations," which were not further defined. This article does not provide compelling data of the effectiveness of CTFIS for several reasons, including the possible effects of co-interventions.

In 2004, the same group who had published in 2000 reported a retrospective, observational study of the effectiveness of CTFIS for radicular pain induced by motor vehicle accidents, sporting injuries, falls, and other forms of trauma [19]. The subjects were 15 patients with cervical spondylosis and radicular pain diagnosed by clinical assessment, magnetic resonance imaging (MRI), electrodiagnostic criteria, and selective nerve root blocks with local anesthetic. All 15 had CTFIS using betamethasone; an average of 3.7 therapeutic injections was administered. Follow-up data collected at an average of 20.7 months after treatment claimed a good or excellent outcome for three patients, or 20% (CI_{95} 0–40%). Average verbal pain ratings were provided for all patients at initial presentation and at follow-up for patients who had avoided surgery, but because of the long times before follow-up, the results were not suitable for inclusion in the data of this review.

In 2005, an article was published reporting a prospective, observational study of outcomes after CTFIS in 21 patients with cervical radicular pain [20]. The patients had chronic, unilateral C6 or C7 radicular pain diagnosed by clinical assessment and corresponding imaging findings on MRI or myelography; 14 patients had cervical spondylosis, and seven had disc herniations. All patients had been deemed to need anterior cervical discectomy and fusion, and were on a waiting list for surgery. Each patient was treated with two CTFIs of triamcinolone, 2 weeks apart. Five patients registered relief of pain (as measured on a 100 mm VAS) almost immediately, and the positive effects were clearly measurable at the 6-week and 4-month follow-up evaluations. Of the 21 patients, five or 24% (CI_{95} 6–42%) had significant relief of radicular pain and no longer needed surgery, whereas the other 16 patients or 76% (CI_{95} 58–94%) proceeded to surgery. The outcomes were not stratified according to the original diagnosis of cervical spondylosis or disc herniation. These data provide some evidence of the effectiveness of CTFIS for relief of radicular pain and avoidance of surgery. It is noteworthy that this study was originally designed to follow 60 patients but it was stopped at 21 patients because other articles had been published reporting serious complications of the procedure.

In 2006, another retrospective, observational study reported the outcomes of 70 patients with cervical radicular pain treated by CTFIS [21]. The patients had cervical disc herniations causing nerve root compression, demonstrated on MRI, and all had failed to improve after conservative management including physical therapy and nonsteroidal anti-inflammatory medications. The patients had opted for surgical management and were offered a trial of CTFIS in attempts to delay or prevent surgery. The number of injections in the study group ranged from one to four (with a mean of 1.46); 48 patients had only one CTFIS, 13 patients had two injections, seven patients had three injections, and two patients had four CTFIS. Of the 70 patients followed for an average of 13 months, 44 or 63% (CI_{95} 52–74%) had substantial relief of their symptoms, as assessed by Odom's criteria, and were able to avoid surgery. Numerical pain scores were not provided so data for pain relief were not able to be included in this review.

In 2007, a retrospective, observational study was published of 24 consecutive patients with cervical radicular pain treated with CTFIS [22]. Five of the patients were lost to follow-up, so the outcomes reported were actually for 19 non-consecutive patients, 17 of whom were each treated with single CTFIS and two received two CTFIS, using triamcinolone. The results published showed that of the 24 patients, clinically significant sustained relief of radicular pain was reported by six or 25% (CI_{95} 8–42%), while two or 8% (CI_{95} 0–19%) had moderate (50%) relief. A successful outcome was defined as reduction of pain by greater than 40 points on a VAS for at least 6 months. The authors' conclusions that CTFIS may be effective for cervical radicular pain in some cases were qualified by their recognition of the limitations of the study.

In 2008, another retrospective, observational study was published [23]. It reported the outcomes of 33 consecutive patients with cervical radicular pain persisting after conservative treatment with rest, analgesia, and physiotherapy for at least 2 months and corresponding findings of cervical disc disease and/or foraminal stenosis on MRI. The patients were treated with CTFIS using triamcinolone. Two patients were lost to follow-up and another three patients had surgery, which left 28 non-consecutive patients for follow-up. All 28 of these patients reported pain relief within 24–48 hours after CTFIS and that relief was sustained at 6 weeks and a year after the treatment. Only group data were presented: the mean pre-treatment VAS pain score was stated as 7.4 (range 5–10), which improved to 2.2 (range 0–7) at 6 weeks and 2.0 (range 0–4) at 1 year; the improvements were statistically significant. Twenty-one patients had cervical spondylosis, and 12 patients had disc herniations. There was no significant difference in outcome between these groups. These data provide some evidence of the effectiveness of CTFIS for

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radicular pain but are not compelling on their own because only group data were presented and the effect sizes were moderate. As categorical data were not provided, the results were not suitable for inclusion in the tabulated data of this review.

In 2009, a report was published of a retrospective, observational study of 159 consecutive patients treated for cervical radicular pain with CTFIS using either triamcinolone or dexamethasone [24]. Outcomes were assessed within a month of treatment, at an average of 15.8 days (range 4–31 days), using a 5-point scale of no pain, much improved, slightly improved, same as before, worse. For most patients, there was no long-term follow-up; that and the lack of numerical pain scores made the results unsuitable for inclusion in the review data.

In 2012, a prospective, observational study of 98 patients with cervical radicular pain was published [25]. All patients had pain persisting after 4 weeks of conservative treatment and corresponding imaging findings of cervical disc herniation and nerve root compression, so they were considered candidates for surgery. They were treated with up to three (mean 1.8) epidural injections of dexamethasone, by either an interlaminar or a transforaminal route, and in some cases both. The outcome data were not stratified according to the type of injection administered, so the results were not included in this review.

Also published in 2012 was another prospective, observational study of 145 consecutive patients treated with CTFIS for cervical radicular pain [26]. The patients all had chronic neck pain and arm pain of radicular type, MRI findings indicating cervical nerve root origin based on degenerative disease, and positive selective transforaminal diagnostic nerve root blocks with local anesthetics resulting in at least 50% temporary arm pain reduction. They were treated with CTFIS performed three times at intervals of 3 weeks, except for five patients who had one injection only. The authors of the original article only followed the 140 patients who completed the study; therefore, the five dropouts were considered failures in accordance with the convention of worst case analysis. The injectate was not specified. At follow-up 12–14 weeks after the first CTFIS, 69 of the original 145 patients or 48% (CI_{95} 40–56%) reported more than 50% relief of arm pain, and 38 or 26% (CI_{95} 19–33%) reported complete relief of arm pain. These data too provide evidence of the effectiveness of CTFIS for relief of radicular pain.

Another article published in 2012 was the report of a retrospective study of 28 consecutive patients treated with CTFIS for cervical radicular pain [27]. All patients had a single nerve root involved and imaging findings suggesting either spondylosis (19 patients or 68%) or disc herniation (nine patients or 32%), and all had failed to respond to at least 2 months of conservative treatment. CTFIS was performed using a mixture of triamcinolone and bupivacaine, and repeated at 2-week intervals up to a total of three injections; the mean number of injections per patient was 2.8. Only group data were reported. The mean pain score before treatment was 7.8; at follow-up after 1 week, the mean pain score was reduced to 3.6, and at 3 months, it was 2.9. After that, the mean pain scores rose again to 3.3 at 6 months and 4.6 at a year. These data add to the evidence of the effectiveness of CTFIS but as only group data were provided, the results are not suitable for inclusion in the tabulated data of this review.

In 2013, a retrospective observational study was published involving 441 patients with cervical radicular pain treated with CTFIS over a 5-year period [28]. The patients had either disc protrusions or foraminal stenosis demonstrated on MRI. The first 220 were treated with one to three CTFIS using triamcinolone and 1% lidocaine. The next 221 were treated with a similar number of injections using dexamethasone and 1% lidocaine. The main aim of the study was to compare the effects of the two steroids. Only group data were provided. In the triamcinolone group, the mean pain score before treatment was 6.61, and at follow-up 4 weeks after the last injection, it was reduced by a mean of 2.33. In the dexamethasone group, the pre-treatment mean pain score of 6.59 was reduced by a mean of 2.38. The differences were not statistically significant. There was no indication whether patients were consecutive, and no information provided about loss to follow-up. The procedure was described as a selective nerve root block but patients were injected with 0.5 mL of steroid, 2 mL of local anesthetic, and 2 mL of saline, a volume of injectate that would suggest the procedure was not selective. It is also noted that while reductions in mean VAS were reported, there were also increased requests for medication. For example, at 12 months, mean VAS decreased by 41%, but 46% of patients requested increased medication. As only group mean results were provided, the data for pain relief were not able to be included in the tabulated data of this review.

Pragmatic Studies

The three pragmatic studies were published between 2006 and 2011.

A pragmatic study published in 2006 compared outcomes after CTFIS using dexamethasone with those after CTFIS using triamcinolone for treatment of cervical radicular pain [29]. The subjects were 30 consecutive patients with cervical radicular pain, corresponding unilateral nerve root compression at a single segmental level as seen on computed tomography (CT) or MRI, and no litigation, worker's compensation, or disability remuneration. They were randomly allocated for treatment with a single CTFIS using either dexamethasone or triamcinolone and followed up 4 weeks later. Of 15 patients in the dexamethasone group, at least 50% relief of pain was reported by nine or 60% (CI_{95} 35–85%) and of 15 in the triamcinolone group, at least 50% relief of pain was reported by 10 or 67% (CI_{95} 43–91%); the overlap of confidence intervals shows there was no statistically significant difference between these results. Overall, significant pain relief was reported after CTFIS by 19 of the 30 patients or 63% (CI_{95} 46–80%).

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These data provide further evidence of the effectiveness of CTFIS for relief of cervical radicular pain but, as both arms of the study used CTFIS, the results were considered as those of an observational study for the purposes of this review.

In 2007, a pragmatic study of 40 consecutive patients with cervical radicular pain treated with either transforaminal injections of local anesthetic and steroid, or local anesthetic and saline was published [30]. All patients had unilateral cervical radicular pain associated with degenerative disease of the cervical spine, corresponding signs at one or two levels on MRI and a positive response, assessed as at least 50% pain relief, after a diagnostic transforaminal selective nerve root block at the level(s) identified by MRI. They were randomized into two equal groups for treatment with either CTFIS using methylprednisolone and mepivacaine or a transforaminal injection of a similar volume of saline and mepivacaine. At follow-up 3 weeks later, they were asked 10 questions about any changes in pain and other subjective effects at 1, 2, and 3 weeks after treatment. In both groups of 20 patients, at least short-term relief was reported by seven or 35% (CI_{95} 14–56%) but the degree to which pain reduced in intensity was not reported. Clearly, there was no statistically significant difference between the outcomes of the two groups. These data raise questions about the effectiveness of CTFIS for relief of cervical radicular pain but are of uncertain value because of the unvalidated outcome measure used and other limitations of the study design. The short-term follow-up made the results unsuitable for inclusion in the data of this review.

In 2011, a third pragmatic study was published, comparing outcomes of CTFIS guided by CT fluoroscopy and CTFIS guided by C-arm fluoroscopy [31]. The 116 patients all had intense cervical radicular pain, persisting for at least 3 months and not relieved by oral medications, along with corresponding MRI findings of cervical disc herniation at a single segmental level. They were allocated randomly for treatment with CTFIS using dexamethasone mixed with lidocaine, performed under either CT fluoroscopy or C-arm fluoroscopy. Eight weeks after treatment, the majority of patients in each group reported successful outcomes, defined as 50% or more reduction in Numeric Rating Scale and/or at least 40% reduction in Neck Disability Index scores. In the CT group of 51 patients, successful results for arm pain relief were obtained by 37 or 73% (CI_{95} 61–85%). In the C-arm group of 65 patients, successful results for arm pain were obtained by 36 or 55% (CI_{95} 43–67%). The differences between the group results were stated as statistically significant but the overlapping confidence intervals suggest otherwise. While questions can be raised (and were, by the journal editors) about the attribution of the claimed differences, the C-arm subgroup data do provide some evidence of the effectiveness of CTFIS for relief of cervical radicular pain. Effectively, the C-arm data were considered as those of an observational study for the purpose of this review.

Table 1 Reported radicular pain-relieving effects of CTFIS

Study	Radicular Pain Relieved by at Least 50%	
Vallée et al. 2001 [18]	18/32	56% (CI_{95} 39–73%)
Kolstad et al. 2005 [20]	5/21	24% (CI_{95} 6–42%)
Dreyfuss et al. 2006 [29]	19/30	63% (CI_{95} 46–80%)
Razzaq et al. 2007 [22]	8/24	33% (CI_{95} 14–52%)
Lee JH et al. 2011 [31]	36/65	55% (CI_{95} 43–67%)
Persson and Anderberg 2012 [26]	69/145	48% (CI_{95} 40–56%)

The numbers of patients and their percentages (with confidence intervals) reported in six studies as having at least 50% relief of radicular pain for at least 4 weeks after CTFIS.

Evidence for Relief of Radicular Pain

Six primary studies reported patients having at least 50% relief of radicular pain for at least 4 weeks after CTFIS. The results are set out in Table 1.

Some data were reported for longer-term durations of pain relief. Outcomes at 4 months post-treatment were provided for six of the 21 patients involved in one study; five of the 21 patients or 24% (CI_{95} 6–42%) had at least 50% relief of radicular pain for that period [20]. In another study, the pain relief reported at 2 months was found to be maintained at 6 months in eight of the 24 patients, or 33% (CI_{95} 14–52%) [22]. Outcome data at 6 months were also available for 32 patients in another study; 18 or 56% (CI_{95} 39–73%) had at least 50% relief of radicular pain for that period [18]. Data were available at 12 months post-treatment for 32 patients in one study; 12 or 38% (CI_{95} 21–55%) had at least 50% relief of radicular pain for that period [18]. One study reported significant benefit that persisted for a year but the article did not provide categorical data; only group data were presented and the pre-operative mean VAS score was 7.4 (range 5–10), which improved to 2.2 (range 0–7) at 6 weeks and 2.0 (range 0–4) at 1 year after CTFIS [23].

The standard accepted as denoting success in these studies, at least 50% relief, is far from a truly satisfactory outcome for cervical radicular pain that is intense and disabling. Patients with such pain want complete relief if possible. Five studies reported patients achieving complete relief of radicular pain for at least 4 weeks after CTFIS and the success rates for that outcome are much lower, as shown in Table 2.

The patients in one of these studies were diagnosed with disc herniations [31] and patients in one study had cervical spondylosis [26]. Patients with either cervical spondylosis or disc herniations were treated in two studies, with the majority of patients in each of these studies diagnosed with cervical spondylosis [18,20]. The radiological diagnosis is not described in the remaining studies [22,29]. These

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Table 2 Reported radicular pain-relieving effects of CTFIS

Study	Radicular Pain Abolished	
Vallée et al. 2001 [18]	9/32	28% (CI_{95} 12–44%)
Kolstad et al. 2005 [20]	2/21	10% (CI_{95} 0–23%)
Dreyfuss et al. 2006 [29]	5/30	17% (CI_{95} 4–30%)
Razzaq et al. 2007 [22]	3/24	13% (CI_{95} 0–26%)
Persson and Anderberg 2012 [26]	38/145	26% (CI_{95} 19–33%)

The numbers of patients and their percentages (with confidence intervals) reported in five studies as having complete relief of radicular pain for at least 4 weeks after CTFIS.

studies do not suggest a trend of CTFIS being more effective for one diagnosis than the other.

Evidence of Surgery-Sparing Effects

Two primary studies reported patients on surgical waiting lists who did not go on to have surgery after CTFIS. Surgery was avoided in 24% (CI_{95} 6–42%) of patients in one study [20] and in 63% (CI_{95} 52–74%) in the other study [21]. It is of note that the 95% confidence intervals do not overlap (Table 3).

The patients in the study which reported a higher success rate with respect to surgery-saving had disc herniations [21], and the majority of the patients in the study which reported poorer outcomes had cervical spondylosis [20]. Further studies would be required to determine whether or not CTFIS is more likely to prevent surgery in patients with disc herniations than in patients with cervical spondylosis.

GRADE Evaluation of Evidence of Effectiveness

The effectiveness data were evaluated in accordance with the GRADE system of rating quality of evidence. The data for the two main outcomes were evaluated separately. The evidence of the reported radicular pain-relieving effects of CTFIS was found to be of very low quality. The evidence of the surgery-sparing effects of CTFIS was also found to be of very low quality.

Table 3 Reported surgery-sparing effects of CTFIS

Study	Surgery Avoided	
Kolstad et al. 2005 [20]	5/21	24% (CI_{95} 6–42%)
Lin et al. 2006 [21]	44/70	63% (CI_{95} 52–74%)

The numbers of patients and their percentages (with confidence intervals) reported in two studies as not going on to have surgery at various time periods after CTFIS.

The starting point in the GRADE system is the types of study from which data are produced to form the relevant body of evidence. That body of evidence is then rated as of lower quality if there are particular methodological problems in it, or as of higher quality if there are factors such as a large magnitude of effect.

The evidence for radicular pain-relieving effects comes from two pragmatic studies [29,31] and four observational studies [18,20,22,26] that reported successful outcomes for radicular pain after treatment with CTFIS. As there were no explanatory studies, the best evidence would be expected to come from the pragmatic studies. In both pragmatic studies the study design meant the results were effectively those of an observational study for the purposes of this review, as explained above [29,31]. When the data of the observational studies were added, the body of evidence for relief of radicular pain was downgraded further because of multiple limitations in the study designs introducing risks of bias. There was no reason to upgrade the body of evidence. Accordingly, the evidence for relief of radicular pain by CTFIS is of very low quality. The true effect is likely to be substantially different from the estimate of effect, and further research is likely to change the presented conclusions. Without explanatory studies, the degree to which any reported benefit of CTFIS is due to non-specific factors, including the natural history of the causative condition, is unknown.

Though not directly related to the quality of the literature, there is work that questions whether steroids are even necessary in CTFIS. There was one randomized controlled trial (RCT) that was excluded from this review because it used a non-validated outcome measure, and the follow-up did not reach 4 weeks, but that study's results suggested that the effectiveness of CTFIS was indistinguishable from that of placebo [30].

The evidence of reported surgery-sparing effects is also not compelling. The body of evidence came from two observational studies [20,21]. The evidence from the two studies produced evidence of a very low quality for the same reasons as stated above for the evidence for radicular pain relief. The authors have limited confidence in the estimate, and the true effect may be substantially different from the estimate of effect. A portent of this likelihood has appeared in abstract form [32]. Its authors found no surgery-sparing effect of CTFIS, though the full data could not be reviewed since only an abstract has been published. Further research is likely to change the presented conclusions significantly and help us understand better why some patients who have CTFIS go on to avoid surgery. The data currently available fall short of establishing CTFIS in terms of cause and effect in this regard. There are many reasons why patients do not have spinal surgery; not least is that most people try to avoid spinal surgery if they possibly can. Some use analgesic medications and other biomedical interventions to control the pain and some just adapt to life with the pain, perhaps with the aid of psychological interventions, hoping it will settle over time.

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Readers must be careful not to confuse "evidence of very low quality" with "evidence of very low effectiveness." What the GRADE rating signifies is not that the existing evidence shows the effectiveness to be poor but that the evidence itself is poor so better evidence is required before the issue of effectiveness can be determined.

Risks

The published evidence of severe risks of CTFIS is comprised of 23 original case reports of serious complications that occurred during or just after a CTFIS procedure and 25 other publications, including one survey report that detailed 63 other significant unwanted effects. The 23 original case reports and the survey report were appraised and are outlined below in the chronological order of their publication. Where the information was provided in the article, particular attention was given in the appraisals to injection technique; use of precautionary checks such as radiographic confirmation of position, aspiration, injection of contrast medium under digital subtraction angiography (DSA), neurography, and administration of a test dose of local anesthetic; and whether particulate or non-particulate steroids were injected.

The other 24 complication publications were not included in this review because they provided no new cases of major complications. These articles not included were four reviews [33–36], five letters [37–41], one survey [42], eight studies associated with vascular uptake [43–50], one cadaveric study [51], one device study [52], three observational studies [53–55], and one steroid study [56].

Primary Literature Reporting Complications

Spinal Cord Infarction Leading to Death

The first case report of a major complication of CTFIS was published in 2001 [57]. A 48-year-old man with intractable neck pain radiating into his right arm underwent CTFIS targeting the right C6 nerve root, using a 22 gauge (G) spinal needle. When the needle tip was in position, as seen on the fluoroscope, aspiration showed no sign of blood or cerebrospinal fluid. Contrast medium was injected and seen to flow along the nerve root. A mixture of bupivacaine and triamcinolone was then injected. Within a minute, the patient suffered flaccid paralysis; resuscitation was attempted but he went on to develop an anterior spinal cord syndrome and died in a hospital after a complicated stay. MRI post-injection showed extensive spinal cord infarction. It seems likely that particulate steroid was injected into a radiculomedullary artery.

Cerebral Injury and Cortical Blindness

In 2003, a 54-year-old male with right-sided radicular pain and past history of C3–C7 decompression and C6–7 fusion was treated with TFIS at C5–6 on the right, using a 22G spinal needle [58]. When the needle seemed in position, bright red blood was aspirated, suggesting arterial puncture. The needle was repositioned and aspiration was negative. Loss of resistance to 1 mL of injected air was followed by injection of 2 mL of nonionic contrast medium, which did not produce a satisfactory epidurogram. No other agents were injected but within seconds, the patient developed lateral nystagmus and within 45 minutes had total bilateral blindness. After a complicated hospital course, he was discharged a month later with mild short-term memory loss and persistent right homonymous hemianopia. Arterial air embolism was considered a likely cause.

Vertebral Artery Occlusion Leading to Death

Also reported in 2003 was another case of fatal complications after CTFIS [59]. A 44-year-old woman with intermittent left neck pain radiating into her left shoulder and arm had TFIS at C6–7 with a 25G needle. When its tip was judged to be in position, aspiration showed blood. The needle was repositioned until aspiration was negative. Contrast medium was injected, producing a C7 neurogram. Then 3 mL of a mixture of methylprednisolone and bupivacaine was injected. The patient became unconscious immediately. She was transferred to the hospital and treated intensively but died the following day. Autopsy showed massive cerebral edema due to dissection and thrombosis of the left vertebral artery.

Lateral Spinal Cord Infarction

Another article published in 2003 reported three cases of serious complications after CTFIS [9]. A 39-year-old woman with left neck and shoulder pain after a motor vehicle accident had an MRI showing a C6–7 disc bulge to the right without neural compression. Treatment was planned with alternating right and left C7 TFIS at weekly intervals. The first procedure, right C7 TFIS, was done without complication. A week later, left C7 TFIS was attempted using a 25G needle. During the procedure, the patient felt severe pain in the left arm so the C7 injection was aborted and left C6 TFIS was performed instead. Afterwards, the patient's left arm was numb and weak, consistent with C7 radiculopathy, which was persisting a year later when the report was published. MRI after the CTFIS showed signs of petechial hemorrhage in the lateral spinal cord.

Cerebral Ischemia and Hippocampal Atrophy

The second of the three cases reported in the 2003 article involved non-fatal brain injury [9]. A 65-year-old male had neck and left arm pain associated with cervical spondylosis. Left C5–6 TFIS was performed using a 25G needle. The needle position was checked on anteroposterior and lateral fluoroscopic views. Aspiration was not mentioned in the report. Contrast medium was injected and a C6 neurogram recorded. Then the treating physician began injecting 2.5 mL of a mixture of betamethasone and bupivacaine. During this injection, the patient became unconscious and had generalized seizures for 3–4 minutes, then went into a post-ictal state, which lasted for

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about 45 minutes. He recovered over time but was left with an organic brain syndrome, which prevented return to work. MRI undertaken within 24 hours of the TFIS showed normal findings. Follow-up MRI 6 and 12 months later demonstrated atrophy of the hippocampus.

Posterior Spinal Cord Infarction and Cerebellar Infarction

The third of the three cases reported in the 2003 article involved a 39-year-old male with left radicular pain and a left C5–6 disc bulge shown on MRI [9]. Left C6 TFIS was undertaken using a 22G needle placed in the left C5–6 foramen under fluoroscopic guidance. Aspiration was not mentioned in the report. A small amount of contrast medium was injected and "an appropriate pattern" was seen. Injection was then begun of 2.5 mL of a mixture of lidocaine and betamethasone solutions. When 1.5 mL had been delivered, the patient said he felt light-headed and became unconscious. The procedure was aborted and resuscitation commenced. The patient regained consciousness within 10 minutes but had dysarthria, left arm paralysis, and lower limb ataxia. His condition improved over a period of weeks but his left arm remained permanently weak and numb. Subsequent MRI showed signs of infarction of both the posterior spinal cord at the C1–C4 levels and the cerebellum.

Cerebellar and Cerebral Infarction Leading to Death

In 2004, another case of fatal complications after CTFIS was reported [60]. A 48-year-old woman had right C6 radiculopathy confirmed by electrophysiological testing and C5–6 disc herniation demonstrated on MRI. CTFIS was performed at C5–6 using a 25G needle. When fluoroscopy showed the needle tip in the required position, aspiration was negative for blood. Nonionic contrast medium was injected, and an appropriate epidurogram was produced with spread along the C6 nerve root. A mixture of bupivacaine and triamcinolone was injected with intermittent aspirations to check for blood, all negative. While being transferred from the C-arm table, the patient became unconscious and had respiratory arrest. She was resuscitated and regained consciousness, but had quadriparesis. She was taken to neurosurgical intensive care and underwent surgical decompression of the brain stem. She died the following day. Autopsy revealed cerebellar infarction and infarction of the left occipital cortex, suggesting vertebral artery injection.

Temporary Quadriplegia

Also published in 2004 was a case report of temporary paralysis after local anesthetic injection in what was planned as a CTFIS procedure [61]. A 55-year-old woman had cervical radicular pain that had been relieved previously by CTFIS. A right C6–7 TFIS procedure was initiated. The needle was positioned under fluoroscopic guidance and contrast medium injection demonstrated filling of the intervertebral foramen with no vascular uptake. A test dose of local anesthetic, 0.8 mL of 2% lidocaine, was then injected. After 60 seconds, the patient reported feeling unwell and the procedure was aborted. Over the next few minutes, she reported weakness and physical examination showed paralysis of all four limbs. Respiration was not affected. She was transferred to a recovery suite and monitored closely. After 20 minutes, all symptoms resolved and the patient had no lasting impairment due to the event. The authors of the case report believe there was inadvertent arterial uptake of local anesthetic.

Spinal Cord Infarction Leading to Quadriplegia

In 2005, a report was published of a 53-year-old man with a history of neck pain and left arm pain of radicular quality, and broad-based disc protrusions at multiple levels but no foraminal stenosis on MRI [62]. Left C6 TFIS was undertaken using a 25G needle positioned under fluoroscopic guidance. Injection of contrast medium under live fluoroscopy showed spread along the C6 nerve root and no sign of vascular uptake. Aspiration showed no blood. A mixture of bupivacaine and triamcinolone was then injected. The patient seemed well immediately afterwards but 10 minutes later reported weakness of his left arm and both legs. The weakness persisted and the patient's final outcome was classified as score C on the American Spinal Injury Association (ASIA) Impairment Scale—incomplete quadriplegia. MRI 24 hours after the CTFIS showed increased signal in the spinal cord from C2 to C5 and in the upper thoracic region, in the territories of both anterior and posterior spinal arteries.

Cerebellar Infarction and Brainstem Herniation

In 2006, the case was reported of a 31-year-old man with a 3-week history of pain in his neck and right arm, right hand paresthesia and weakness, and herniation of the C7–T1 disc to the right on MRI [63]. CTFIS was performed with a 25G needle placed in the right C7–T1 foramen under fluoroscopic guidance. Contrast medium was injected under continuous fluoroscopy in the postero-anterior view and seen to flow along the right C8 nerve root with no sign of vascular uptake. Aspiration was negative for blood. A mixture of methylprednisolone and lidocaine was then injected slowly, but during the injection, the patient complained of neck pain and headache so the injection was stopped. The patient was transferred to recovery, where he had continuing headache and nausea, and vomited when he sat up. Later he seemed to recover and was discharged. At home that night, his wife noticed his breathing was abnormal and he was taken to a hospital, where he had respiratory arrest. CT and MRI showed cerebellar infarction and hydrocephalus, and emergency surgery was undertaken to relieve cerebellar herniation into the foramen magnum. The patient recovered over time but had residual diplopia and persistent difficulties with concentration and short-term memory loss. The cause was suspected as inadvertent intra-arterial injection.

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Temporary Cortical Blindness and Paresis of Face and Upper Limbs

In 2007, a case was reported of a 41-year-old man who became profoundly confused and developed weakness of his face and left arm while undergoing left C5 TFIS under fluoroscopic guidance, without sedation, at an outpatient pain clinic [64]. No other details of the procedure were stated. The patient was transferred to the hospital where CT revealed subintimal contrast medium in the left vertebral artery extending from C3 to C6. He was admitted to a neurological intensive care unit for management. A left vertebral arteriogram obtained there showed dissection of the left vertebral artery consistent with the previous CT findings. After intensive treatment, the patient made a full recovery.

Spinal Cord Infarction Leading to Quadriplegia

Another article published in 2007 reported multilevel infarction of the spinal cord after CTFIS [65]. A 72-year-old woman with a long history of neck pain and left arm pain, of radicular type, had undergone anterior cervical discectomy and fusion at C4–5 and C5–6 with some effect, but radicular pain had recurred. TFIS was performed at C5–6 and C6–7 on the left, using 25 G needles. At each level, after the needle tip position was considered appropriate on fluoroscopic views, contrast medium was injected and its spread observed under live fluoroscopy. Aspiration was not mentioned in the report. After confirmation of contrast medium around the nerve root sleeve and no evidence of vascular uptake, a mixture of methylprednisolone and bupivacaine was injected at each level. The patient seemed well immediately after the procedure but about 30 minutes later, she complained of leg weakness. Her condition deteriorated and she developed persistent incomplete quadriplegia classified as ASIA-C. MRI demonstrated spinal cord infarction at multiple levels up to the cervicomedullary junction.

Temporary Paralysis of Right Leg

A third article published in 2007 reported temporary paralysis of one leg after CTFIS [66]. A 45-year-old male with chronic cervical pain after trauma underwent C6–7 TFIS using a 22G needle. It was inserted into the foramen under fluoroscopic guidance and its position was checked on biplanar views. Repeated aspirations throughout the procedure were negative for blood. Contrast medium injection under live fluoroscopic screening produced a C7 neurogram and showed no sign of vascular uptake. A mixture of triamcinolone and saline was injected. After about 30 seconds, the patient complained of numbness and paresthesia in his right leg, and within 2 minutes, his right leg was paralyzed. Treatment was instituted with nifedipine, heparin, and aspirin, and 3 hours later, the complications had resolved. MRI revealed no nerve damage or bleeding, but showed hypoplasia of the right vertebral artery (which is found in up to 40% of arteriograms).

Epidural Hematoma Causing Paraplegia

Also published in 2007 was the case of a 38-year-old woman who had radicular pain in her right arm after a motor vehicle accident and was treated with a series of three C7–T1 TFIS [67]. No details of the injections were reported. About 4 days after the third CTFIS, the patient awakened with severe upper thoracic back pain and she went on to develop progressive loss of sensation from the waist down and dense paralysis of both legs. MRI showed an epidural mass compressing the spinal cord from T1 to T5 levels. Surgical decompression was undertaken and a clot was removed. The patient's condition improved postoperatively, and after 6 months, she recovered fully.

Grand Mal Seizure

A fifth article published in 2007 was a case series of selective cervical nerve root block injections including a case with a major complication not published elsewhere [68]. A 45-year-old man had a therapeutic injection of betamethasone and lidocaine along a C6 nerve root. Within 10 seconds, the patient had a grand mal seizure lasting 3–4 minutes. He recovered completely within 30 minutes. No details were reported of the procedural technique used in this case, so it is not known what findings there might have been on aspiration or contrast medium injection.

Spinal Cord Injury Leading to Quadriparesis

In 2008, a case report was published involving a 55-year-old man with neck pain radiating into his left arm, considered to be in a C7 distribution [69]. TFIS was undertaken with a 23G needle introduced into the left C6–7 neural foramen under fluoroscopic guidance. On direction of the needle into what was thought to be the epidural space, the patient complained of sharp pain, which was considered due to irritation of the nerve root. The needle tip position was not verified by fluoroscopy: the reason given was that the patient was in an inappropriate posture due to severe pain. Rather, to determine the needle tip position, 0.5 mL of contrast medium was injected. During this injection, the patient reported a shock-like pain radiating to the left hand. The procedure was terminated. Over the next 2–3 minutes, the patient developed incomplete quadriplegia, classified as ASIA-C. CT demonstrated an air bubble and a hyperdense mass inside the spinal cord at C6–7. Apparently, the contrast medium had been injected directly into the cord. Treatment was instituted and the patient's condition improved somewhat, but 1 year later, he still had motor weakness in the left arm, weakness of the left hand, and a claw hand deformity. He also still had refractory pain in his left arm.

Transient Quadriplegia

In 2010, a report was published of a 43-year-old man with cerebral palsy and radicular pain in his left arm, associated with a cervical disc herniation [70]. He was treated surgically with laminectomy and C3–5 interbody fusion, but

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postoperatively had persistent left C5 radicular pain. TFIS was then performed, targeting the left C5 nerve root. A needle was placed in position under fluoroscopic guidance. Contrast medium was injected and seen to spread epidurally along the nerve root, with no sign of vascular uptake. During the injection, the patient complained of paresthesia, which was thought to be "caused by injection needles" (sic). On aspiration, no blood was seen. A mixture of triamcinolone and mepivacaine was infused. Within 3 minutes of the injection, the patient had total loss of sensation and motor function in all four limbs. He was transferred to intensive care and monitored, but did not require ventilation. He made a spontaneous and complete recovery over 2 hours.

Cerebral Edema and Cortical Blindness

In 2011, a article reported the case of a 54-year-old woman with recurrent neck pain radiating into her left arm [71]. She had one C5–6 TFIS and the pain settled but it recurred and another CTFIS was planned. A 23G spinal needle was directed into the C5–6 foramen under fluoroscopy. Contrast medium was injected twice, under real-time fluoroscopy in the anteroposterior view, to confirm the needle tip position. There was no evidence of intravascular injection, and on aspiration, no blood was seen. A mixture of triamcinolone and lidocaine was injected. Immediately after this the patient complained of headache, nausea, and dizziness, and 6 hours later, she had bilateral visual disturbance that worsened progressively until she could barely detect hand movements 30 cm in front of her eyes; the light reflex was prompt bilaterally, suggesting cortical blindness. MRI showed bilateral subcortical lesions in the occipital lobes. Over 48 hours the patient's vision returned to normal and at follow-up 6 months later, MRI was normal. The diagnosis was reversible posterior leukoencephalopathy syndrome.

Grand Mal Seizure after Local Anesthetic Test Dose

Also published in 2011 was the case of a 49-year-old woman with left C6 radicular pain associated with a C5–6 disc bulge [72]. The patient had obtained temporary relief from two previous CTFIS treatments and was scheduled for another. A 25G needle was introduced into the left C5–6 foramen under fluoroscopic guidance and adjusted until its tip seemed in the correct position. Contrast medium was injected, and its flow showed venous uptake. The needle tip was repositioned and more contrast medium was injected, producing what was considered a satisfactory proximal neurogram and outlining of the epidural space. A syringe was then connected directly to the needle hub, and 1% lidocaine was injected as a test dose. The patient was asked whether she felt dizzy or had any altered sensations but she did not answer even when the question was repeated several times. The drapes were taken down and the patient was found to be having a grand mal seizure. The procedure was aborted and resuscitation commenced. The patient recovered with no residual deficit. Retrospective review of the stored images revealed that what had been interpreted during the procedure as a satisfactory epidurogram was not; a dark wavy contrast medium line taken as the medial borders of the pedicles was actually the wall of the vertebral artery, which suggests the needle tip was in the vertebral artery when the lidocaine was injected.

Permanent Horner's Syndrome

Another case reported in 2011 involved a 31-year-old man with cervical degenerative disc disease who was treated with a right C7 TFIS [73]. No details of the technique were provided. Following the procedure, the patient had right ptosis and miosis, and pharmacologic testing confirmed a right Horner's syndrome, which persisted to become permanent. MRI and MRA showed no arterial dissection.

Temporary Flaccid Paralysis after Local Anesthetic Test Dose

In 2012, a article reported the case of a 40-year-old woman with severe right-sided cervical radicular pain who was booked for a CTFIS procedure [74]. A 23G spinal needle was introduced into the right C5–C6 intervertebral foramen and its placement checked in the anteroposterior view. A syringe filled with contrast medium was connected to the needle via an extension tube. Contrast medium was injected, and its spread along the nerve root was observed by right C6 neurography, although not with real-time fluoroscopy. The extension tube used for the radiculography was removed from the spinal needle and another extension tube with a syringe filled with lidocaine connected in its place. An aspiration test was negative for blood. The physician then injected 1.5 mL of 1.0% lidocaine slowly around the C6 nerve root. Immediately after the injection of local anesthetic, the patient developed flaccid paralysis, she became unresponsive, and her respiratory pattern was uncoordinated. Resuscitation was started, and after 20 minutes, she regained consciousness, and her sensation and limb muscle strength returned to normal.

Transient Causalgia

Also published in 2012 was an observational study of 28 patients of whom two suffered neurological complications [27]. One patient was reported as having causalgia for 5 months after the CTFIS treatment. No other details were provided.

Transient Horner's Syndrome

The other patient reported in the 2012 study as having neurological complications developed Horner's syndrome with ptosis after the CTFIS [27]. The condition lasted for a week but then resolved.

Other Reported Complications

In 2007, a article was published reporting the results of an anonymous survey of all U.S. physician members of the American Pain Society [75]. Overall response rate was

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21.4% (287 of 1,340). In all, 78 complications were reported, including 16 vertebrobasilar brain infarcts, 12 cervical spinal cord infarcts, and 2 combined brain/spinal cord infarcts. Brain infarcts invariably involved the cerebellum, brainstem, or posterior cerebral artery territory. Thirteen cases resulted in a fatal outcome: five with brain infarcts, one with combined brain/spinal cord infarcts, one following high spinal anesthesia, one associated with a seizure, and five with unspecified etiology. All four cases with corticosteroid alone involved methylprednisolone, resulting in three cerebellar infarcts and one posterior cerebral territory infarct. Of these, three had fatal outcomes, and two autopsies revealed no vertebral artery trauma. It is not known how many of the 24 case reports described above were included in the complications reported in this anonymous survey; if it is assumed that all 15 that occurred up until 2007 were included (so as to avoid exaggeration of the evidence), the results of the survey add another 10 fatal events and 53 other serious consequences to the complications reported specifically in the literature.

The reports of significant complications are summarized in Table 4.

Procedural Factors

The reports of serious and catastrophic complications raise questions about procedural factors that may help minimize such sequelae. Some proceduralists advise precautionary checks including radiographic confirmation of needle tip position, use of small-volume extension tubing, repeated aspiration, injection of contrast medium under live fluoroscopic screening, use of DSA, proximal neurography, and administration of a test dose of local anesthetic. The evidence shows that none of these precautions, or combinations of them, is entirely protective against the serious complications of CTFIS. Nonetheless, all are worthy of consideration.

Radiographic confirmation of needle tip position is mentioned in most of the case reports describing serious complications (although many reports do not state whether both antero-posterior and foraminal views were used); so, important as it is, radiographic confirmation does not seem to be of great value in preventing such events.

Fitting a small-volume extension tube to the hub of the spinal needle, rather than connecting syringes directly to

Table 4 Reported risks of CTFIS, expressed as complications described specifically in the literature

Report	Complications
Brouwers et al. 2001 [57]	Spinal cord infarction leading to death
McMillan and Crumpton 2003 [58]	Cerebral injury and cortical blindness *(persistent)*
Rozin et al. 2003 [59]	Vertebral artery occlusion leading to death
Windsor et al. 2003 [9]	Lateral spinal cord infarction *(persistent)*
Windsor et al. 2003 [9]	Cerebral ischemia and hippocampal atrophy *(persistent)*
Windsor et al. 2003 [9]	Posterior spinal cord and cerebellar infarction *(persistent)*
Tiso et al. 2004 [60]	Cerebellar and cerebral infarction leading to death
Karasek and Bogduk 2004 [61]	Quadriplegia *(transient)*
Ludwig and Burns 2005 [62]	Spinal cord infarction leading to quadriplegia *(persistent)*
Beckman et al. 2006 [63]	Cerebellar infarction and brainstem herniation *(persistent)*
Wallace et al. 2007 [64]	Cortical blindness, paresis of face, and upper limbs *(transient)*
Muro et al. 2007 [65]	Spinal cord infarction leading to quadriplegia *(persistent)*
Ruppen et al. 2008 [66]	Paralysis of right leg *(transient)*
Lee JY et al. 2007 [67]	Epidural hematoma causing paraplegia *(transient)*
Schellhas et al. 2007 [68]	Grand mal seizure *(transient)*
Lee JH et al. 2008 [69]	Spinal cord injury leading to quadriparesis *(persistent)*
Lee MH et al. 2010 [70]	Quadriplegia *(transient)*
Kim et al. 2011 [71]	Cerebral edema and cortical blindness *(transient)*
Chung SG 2011 [72]	Grand mal seizure *(transient)*
Kaplowitz and Lee AG 2011 [73]	Horner's syndrome *(persistent)*
Tofuku et al. 2012 [74]	Flaccid paralysis *(transient)*
Chung JY et al. 2012 [27]	Causalgia *(transient)*
Chung JY et al. 2012 [27]	Horner's syndrome *(transient)*
Scanlon et al. 2007 [75]	10 additional complications causing death
Scanlon et al. 2007 [75]	53 additional serious but non-fatal complications
Total	13 deaths 31 brain and spinal cord infarctions Numerous other serious and persistent CNS injuries

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it, in theory reduces the chance of the needle tip moving during or between injections.

Aspiration to check for blood is a traditional practice that has been assessed for validity: the evidence shows that blood seen on aspiration has 97.9% specificity but only 44.7% sensitivity for intravascular needle tip placement [66]; thus, there is no guarantee that the absence of blood on aspiration signifies extravascular injection. Intra-arterial injection stands out as a factor in many of the reports of serious complications and thus is one of the major risks. In this regard, it should be noted that a recent article has shown the vertebral artery to lie within 2 mm of ideal needle location in at least one posterior neural foramen in 29% of 198 consecutive patients whose CT angiograms were studied [76]. Severity of foraminal stenosis correlated with proximity of the vertebral artery to typical needle location. Ideal needle placement therefore does not guarantee protection from injury to, or injection into, the vertebral artery during CTFIS. The authors of that article recommended that physicians examine T2 axial MRI to check the location of the vertebral artery before performing CTFIS.

Visualization of the spread of injected contrast medium is supposed to aid in identifying correct needle tip placement but is of no help, and actually causes harm, if the needle is in a dangerous position such as inside the spinal cord as in the report of Lee JH et al. [69]. Visualization is better under live fluoroscopic screening and better still under DSA but identifying a problem more readily is no protection if it has already occurred; that said, there were no reports of major complications when DSA was used and there are many observational studies that demonstrate the value of DSA in preventing subsequent intravascular injection [42,43,45,46,50]. The production of a proximal neurogram (a fluoroscopic image of the target nerve root outlined by contrast medium injected into the epidural space) is another measure supposedly protective against injection at an inappropriate site. The theory is sound but the evidence shows that what is interpreted as a proximal neurogram may not be; for example, in the case reported by Chung SG [72], what was interpreted as outlining of the epidural space was actually contrast medium spreading up along the walls of the vertebral artery.

The injection of a local anesthetic test dose is another measure thought to protect against injection (of steroid) at an inappropriate site. Theoretical considerations suggest it may be worthwhile as a precautionary measure, on the grounds that the effects of local anesthetic are less enduring than those of steroid. The evidence includes three cases in which local anesthetic test doses produced effects that caused the procedures to be terminated before injection of steroids, which if injected at the same sites may have caused more serious complications [61,72,74]. There is no reported case of serious, long-term sequelae in which a local anesthetic test dose was used.

Another factor raised is whether particulate or soluble (non-particulate) steroids should be used for the therapeutic injectate. The evidence suggests that the risks of CTFIS may be increased if particulate steroids are injected. Certainly particulate steroids were used in most of the cases involving catastrophic complications, including all those that were fatal, but it is not clear that steroid particles were responsible for all the effects that occurred. On one hand, a complication like dissection of a vertebral artery would be serious whatever was injected into it, and on the other hand, there are several reports of serious complications after procedures in which particulate steroids were not used.

GRADE Assessment of Risks of CTFIS

When attempting to assess the quality of the evidence on the risks of CTFIS in accordance with the GRADE system, it is noted that the published evidence consists only of case reports. Accordingly, the body of evidence is of very low quality: we have very little confidence in the effect estimate and the true effect is likely to be substantially different from the estimate of effect. Readers must be careful not to confuse "evidence of very low quality" with "evidence of little significance" and perhaps go on to dismiss the risks of CTFIS as too rare to be of concern. The evidence of risks is of very low quality because few cases of serious complications have been published. This may reflect publication bias. There is a tendency for serious complications not to be publicized in articles; indeed in one of the descriptive articles, the authors mentioned an additional 15 cases they knew of that were not being published because they were *sub judice* [36]. Thus, the frequency of complications after CTFIS is uncertain but when they do occur they can be catastrophic and even fatal.

Discussion

This systematic review of the literature is comprehensive, including evidence from all studies published, not just from RCTs as do some "systematic reviews." The whole body of published, peer-reviewed evidence was appraised reliably in accordance with the GRADE system of evaluating evidence. In taking this approach, the authors have sought to honor the method advocated by Dr. Archie Cochrane, pioneer of evidence-based medicine. Cochrane advised consideration of all published evidence, giving weighting to the data included in it on the basis of the types and methodologies of studies from which they came, with those from RCTs weighted highest. In his book *Effectiveness and Efficiency*, 1977, he wrote: "In writing this section in praise of the RCT I do not want to give the impression that it is the only technique of any value in medical research" (p. 25) [77]. He wrote of the value of "observational evidence . . . (especially when efforts are made for) the exclusion of possible bias from the measurements" (p. 21). He also classified therapies as (*inter alia*) "Those therapies backed by RCTs and those where there is good experimental evidence of some effect, but no evidence from RCTs" (p. 30). The current authors feel that the systematic review of all published evidence,

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appraised reliably in accordance with the GRADE guidelines, is very close to what Cochrane tried to get medical science to adopt.

A literature review helps a physician determine if an intervention benefits patients but it does not necessarily show to which patients a physician should offer that intervention. That is the role of appropriate use criteria.

When an intervention is known to have catastrophic complications, there is no published resource that can determine if it should be offered to a particular patient. A patient's decision to have such an intervention should be based on an honest discussion between the patient and the treating physician of the potential benefits and risks. Only with all the information known about the intervention can a patient give properly informed consent to have it and decide if the attendant risks are worth taking.

The literature seems to indicate that CTFIS helps some patients with short-term relief of radicular pain and questionable long-term benefit. It shows that CTFIS relieves radicular pain in some cases and is associated with reduced rates of spinal surgery. When quantified, the benefit of CTFIS appears limited in the proportion of patients who benefit (approximately 40%), the extent to which they benefit (50% relief of radicular pain), and the duration of effect (4 weeks). Fewer patients, possibly 20%, achieve complete relief, but the confidence intervals approach and include zero. At 3, 6, and 12 months, the proportions of patients with any degree of benefit attenuate, as does the quality of the literature. It also shows clearly that CTFIS carries risks of serious and catastrophic complications, including permanent quadriplegia and death. The published evidence does not clearly identify the causes of those serious complications and does not show conclusively how they can be avoided.

The purposes of this review are to present all the data that have been published on CTFIS in all sorts of articles and to evaluate the resultant evidence of the intervention's effectiveness for relief of cervical radicular pain and its associated risks in accordance with the GRADE system of evaluating evidence. The authors have deliberately avoided giving any further interpretation of the procedure's potential benefits and risks so this review should not be interpreted in any way as a guide to criteria for its appropriate use. We leave that for others to determine.

Conclusions

CTFIS seems to help some patients with cervical radicular pain. The evidence of the effectiveness of CTFIS was rated according to the GRADE system as of very low quality for pain-relieving effects and as of very low quality for surgery-sparing effects. The authors are not confident of the estimates of effectiveness, and their true values may be substantially different. Further research is likely to change the presented conclusions significantly.

CTFIS is associated with serious complications which, although rarely reported, are catastrophic and even fatal in some cases. The evidence of the risks of CTFIS is rated according to the GRADE system as of very low quality: we can have very little confidence in what the evidence seems to show and the true effect is likely to be substantially different from the estimate of effect.

In accordance with the GRADE system, based on all published data on the procedure and taking into account the balance between desirable and undesirable effects, and the qualities of the evidence for each, the strength of recommendations for use of CTFIS is weak. That is an evidence-based appraisal of the procedure, limited by the available literature. If CTFIS is to be applied as an intervention for cervical radicular pain, its use would require the development of appropriate use criteria, which this article does not purport to address.

The evidence supporting these conclusions was revealed by systematic review and comprehensive analysis of all published data and found to be much more compelling than it would have been if the literature review had been of the limited scope of a "systematic review" of RCTs only.

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