Title: The Effectiveness of Cervical Transforaminal Epidural Steroid Injection for the Treatment of Cervical Radicular Pain: A Prospective Cohort Study.

Primary Investigator: Zachary McCormick, MD
Co-Investigator: Aaron Conger, DO
Richard Kendall, DO

Objectives:

1. Determine the proportion of patients with an 80% or greater improvement in arm and neck numerical rating scale pain (NRS) score following an initial cervical transforaminal steroid injection (TFESI) at 4 weeks post-injection and the duration of response up to 12 months.
2. Determine the proportion of patients with a 50%-79% improvement in arm and neck NRS score following an initial cervical TFESI at 4 weeks post-injection and the duration of response up to 12 months.
3. Determine the proportion of patients with less than 50% improvement in arm and neck NRS score following an initial cervical TFESI at 4 weeks post-injection and the duration of response up to 12 months.
4. Determine the proportion of patients with an initial injection plus up to 3 additional injections that maintain 80% or greater, as well as 50-79%, improvement in arm and neck NRS score for up to 12 months.
5. Determine the proportion of patients with a clinically significant change in function defined by a minimally clinically significant change (MCIC) (≥10 point improvement) or 30% improvement in Neck Disability Index (NDI) score[13,14] following an initial cervical TFESI at 4 weeks post-injection and the duration of response up to 1-2 months.
6. Determine the proportion of patients with clinically significant improvement in the Medication Quantification Scale (MQS III) score[15] (≥6.8 point change, equivalent to 10 oral morphine equivalents) following an initial cervical TFESI at 4 weeks post-injection and the duration of response up to 12 months.
7. Determine the proportion of patients with clinically significant improvement in the categorical EuroQol 5 Dimensions tool (EQ-5D)[16] defined by ≥0.03 following an initial cervical TFESI at 4 weeks post-injection and the duration of response up to 12 months.
8. Compare patient demographic, clinical, and imaging characteristics between response groups and perform predictive modeling to better understand variables that increase the likelihood of a successful clinical outcome.
9. Report adverse effects.

Hypotheses:

1. At least 50% of patients with cervical radicular pain will experience 50% or greater relief of index pain at 1-month follow-up after cervical TFESI.
2. At least 50% of patients with cervical radicular pain will experience a clinically significant improvement in function at 1-month follow-up after cervical TFESI.
3. At least 50% of patients with cervical radicular pain will experience a clinically significant improvement in analgesic medication use at 1-month follow-up after cervical TFESI.
4. At least 50% of patients with cervical radicular pain will experience a clinically significant improvement in health-related quality of life at 1-month follow-up after cervical TFESI.

Introduction

Neck pain is now the fourth leading cause of years lost to disability, shortly after back pain, depression, and arthralgia.[17] Cervical radiculopathy, a common cause of neck and radiating arm pain, is estimated to afflict 83:100,000 individuals yearly.[1] Age-related cervical spondylosis and disc herniation are the most common causes, with the C6 and C7 nerve roots most frequently affected.[18] In general, patients who experience new onset radicular pain tend to improve within 4-6 months, with complete recovery in over 80% of patients by 24-36 months.[2] However, a significant proportion of patients experience severe pain and associated functional impairment despite conservative care, which often prompts physician directed interventions.

Cervical transforaminal epidural steroid injection (TFESI) is a target-specific treatment for refractory radicular pain. Analgesic mechanisms for epidural steroid administration include reducing inflammation at the nerve root, reducing nociceptive input from somatic nerves, stabilization of neural membranes, and blockade of C fiber activity in the dorsal root ganglion.[3–7] Previously, this procedure was associated with rare but catastrophic neurologic injury, thought to be related to inadvertent deposit of particulate steroid into the vertebral artery or radiculomedullary arteries, both of which traverse through or close to the cervical neuroforamina.[19,20] Since the physician community has adopted new guidelines that include the use of only non-particulate steroid during cervical TFESI[12], neurologic infarction has not been reported in the literature. When the Spine Intervention Society (SIS) clinical practice guidelines are employed, large cohort studies have demonstrated zero prevalence of serious complications associated with this procedure[21].

While high-quality outcome literature demonstrates both efficacy and effectiveness for analogous use of this intervention in the lumbar spine[22,23], far fewer studies have addressed clinical outcomes associated with cervical TFESI in which appropriate procedure technique[24], outcome measurement, data analysis, and results interpretation have been reported[25]. Outcome literature reporting on the use of cervical TFESI is limited by small sample size[9], retrospective design with loss of follow-up[26], lack of categorical data analysis[10], and a failure to stratify results by demographic and clinical variables that potentially influence pain and functional outcomes[10]. Further, outcome literature reports on the effect of particulate steroid injectate during cervical TFESI[9,27] are no longer relevant to appropriate clinical practice in the context of unequivocal guidelines.[12,28] Pragmatic studies with a cervical TFESI arm in which dexamethasone was used do allow for some insight regarding success rates associated with this procedure; studies report responder rates of 60% achieving >50% pain relief (CI_{95} 35-85%) at 4 weeks[9], 55% achieving >50% (CI_{95} 43-67%) at 8 weeks[10], and 65% achieving >50% at 12 weeks (CI_{95} 48-81%).[29] These responder rates are encouraging, but limited by wide 95% confidence intervals due to small sample size. Prior systematic review has concluded that the evidence for treatment benefit of radicular pain by cervical TFESI is of very low quality due to multiple limitations in study design introducing risk of bias, but does overall suggest approximately 50% patients experience 50% relief of radicular pain for at least 4 weeks after cervical TFESI.[8]

Image guidance is commonly studied, with some investigators suggesting the use of ultrasound [30,31](30, 31), or CT guidance[32] (3), however fluoroscopic guidance with use of digital subtraction

imaging (DSI) remains the gold standard imaging modality[33,34] (4,5). In terms of needle approach, a few new studies have been published to suggest possible alternative approaches. These include a modified parasagittal interlaminar approach under CT guidance[32] (3), parasagittal interlaminar approach under fluoroscopic guidance[35] (6), and standard interlaminar approach with threaded catheter[36] (7). None of these studies (including our own, ref. 36), has shown clinically significant benefit between approaches or significant safety differences. Further, multiple studies published prior to our original protocol submission have suggested that the route of delivery into the epidural space has little differential impact on the likelihood of clinically meaningful pain reduction and functional improvement[37-39] (8–10).

Several new studies have been published since 2018 which support the use of CTFESI for cervical radicular pain. In our own RCT we found clinically significant reductions in pain and improvement in function in those treated with cervical epidural steroid injections, with no significance between group differences depending on the route used (transforaminal versus interlaminar with catheter)[36] (7). Specifically, 49.1% (95% CI 36.4–62.0%), 46.4% (95% CI 33.8–59.6%), and 51.9% (95% CI 38.4–65.2%) of participants reported >50% pain relief at 1, 3, and 6 months after CTFESI. The majority of participants also reported feeling at least "much improved" at 6 months. There were no serious adverse effects or complications noted in this study. Another study published in 2020 showed a 60% responder rate at one month with similarly observed low levels of pain at 5 year follow up, likely evidencing the favorable natural history of cervical radicular pain[40] (11). Another report of outcomes after CTFESI showed significant reductions in pain and high patient satisfaction at two years[41] (12).

Additional clinical outcome literature is needed, particularly given recent policy decisions, such as that of Oregon State in relation to ending coverage of epidural steroid injections at any spinal level[12]. Without expansion of the evidence-basis for this important procedure, there is a risk that this treatment option may be taken away from patients suffering from cervical radicular pain by further policy change. A sham-controlled trial, similar to the Ghahreman study[23], would be ideal; however, due to cost considerations germane to a study designed and conducted in a manner that would prevent any possible criticism from the larger medical community, we instead propose a high-quality, large prospective cohort study as a significant contribution to the literature. Even the best designed trials, such as Dreyfuss' 2006 study, have been underpowered to definitively demonstrate effectiveness; notably, the lower bound of the 95% confidence interval of the proportion of treatment responders in this study was 35%. We aim to conduct a large enough cohort study narrow the 95% confidence interval of the proportion of responders substantially. Preliminary data from our center demonstrates a responder rate of 55% at 4-week follow-up (n=22), based on a definition of ≥50% improvement in index pain. These data represent analysis of consecutive patients who underwent cervical TFESI for unilateral radicular pain as a part of a different prospective outcome study at our center, nearing completion. This responder rate represents a conservative estimate of what might be expected in the proposed work, as the current study includes less stringent inclusion and exclusion criteria.

Adverse events have also been further studied. A recent study of events after 1753 CTFESIs showed only 6 self–"limited" adverse events which included 2 vasovagal episodes, 1 instance of

localized urticaria, 1 episode of self-"limited" tachycardia, 1 episode of "light headedness" which resolved after 30 minutes, and one report of dysphagia that resolved after 30 minutes[42] (13). These rates are similar to that observed in very large (n= 52,935) prior studies of the safety of epidural steroid injections wherein serious procedure related complications occurred in only 0.011% of procedures performed[43] (14).

Further, we intend to use the results of this study as foundational data from which to propose a randomized controlled study through a large federal funding mechanism. It is imperative that such a trial be conducted by investigators who are experienced with this procedure and understand the appropriate standards for the design and interpretation of the results of a study of a treatment intervention for pain[25,44,45]. Our spine research group is well-positioned for this, and we absolutely welcome the input and mentorship of the Spine Intervention Society Research Division, Board of Directors, and other leadership towards this mutual goal.

Subjects

A total of 117 subjects, aged 18-80 on the day of enrollment, will be recruited for participation in this study. Participants who meet inclusion and exclusion criteria listed below will be enrolled into the study after consenting to and before receiving a first cervical TFESI.

De-identification

All subjects will be assigned a unique alphanumeric identifier. No personally identifiable information will be used in the final database. All data will be stored on a highly secure, password protected computer.

Participant Recruitment

Our intended subject demographic includes an active population between the ages of 18 and 80 years on the day of enrollment. Potential study participants will be identified from our research center's interventional and surgical clinics, as well as the interventional treatment room schedule. Additionally, we intend to recruit participants through word-of-mouth and physician referral. Further recruiting will take place through the distribution of flyers to the Health Sciences Education Building, University of Utah Student Life Center, University of Utah Orthopedic Center, University of Utah South Jordan Health Center, University of Utah Farmington Center, and the University of Utah hospital. Upon first contact with the potential participant, the study coordinator or research associate will provide a basic description of the study and review inclusion and exclusion criteria, general health status, and past medical history. Chart review at this point will consist of looking at their physician's diagnosis and MRI imaging results to make sure they meet inclusion and exclusion criteria. Interested volunteers who qualify will be asked to report to the University of Utah Orthopedic Center, University of Utah South Jordan Health Center, or University of Utah Farmington Center. Prior to screening procedures and after being informed of any potential risks involved in the study, volunteers will be asked to provide written, informed consent for study participation.

Inclusion Criteria:

1. Adult patients aged 18-80 capable of understanding and providing consent in English and capable of complying with the outcome instruments used.
2. Arm pain or shoulder girdle pain/periscapular pain with or without neck pain with duration less than or equal to 6 months.
3. 24 hour average numeric pain rating score (NRS) for arm pain or shoulder girdle/periscapular pain of at least 4/10 at baseline evaluation, with neck pain score not exceeding arm and/or shoulder girdle/periscapular pain score.
4. MRI (or CT if MRI not available) shows either a one level cervical disc herniation, disc osteophyte complex or degenerative foraminal stenosis, corresponding in side and location with predominately unilateral radicular pain, with or without neurological deficits. MRI may show degenerative changes at other levels.
5. Patient consents to treatment with epidural injection in a shared decision-making process with the treating physician.
6. Pain duration of at least 6 weeks or more.

Exclusion Criteria:

1. Those receiving remuneration for their pain treatment (e.g., disability, worker's compensation).
2. Those involved in active litigation relevant to their pain.
3. The patient is incarcerated.
4. Neck pain is greater than arm pain or shoulder girdle/periscapular pain.
5. Bilateral radicular signs/symptoms (< 90% laterality of pain intensity, or bilateral neurological signs).
6. BMI>35.
7. Prior epidural steroid injections for treatment of current episode.
8. Those unable to read English and complete the assessment instruments.
9. Spondylolisthesis at the involved or adjacent segments.
10. Systemic inflammatory arthritis (e.g., rheumatoid, lupus).
11. Addictive behavior, severe clinical depression, or psychotic features.
12. Possible pregnancy or other reason that precludes the use of fluoroscopy.
13. Treatment of infection with antibiotics within the past 7 days.
14. Progressive motor deficit and/or clinical signs of myelopathy.
15. History of prior cervical spine surgery.
16. Medical conditions causing significant functional disability (e.g., stroke, COPD)

Study design: Prospective cohort study

Participants who meet inclusion and exclusion criteria will be enrolled into the study after consenting to and before receiving a first cervical TFESI. The baseline examination and all baseline questionnaires will be completed within 2 weeks before the first cervical TFESI. Routine scheduled follow-up by clinic visit or telephone call will occur at 4 weeks(+/- 1 month),

3 months(+/- 1 month), 6 months(+/- 1 month), and 12 months(+/- 3 month), at which times all follow-up measures will be obtained.

Primary Outcomes:
The primary outcome is "treatment response" as defined by classification into one of the three following categories:

1. 80% or greater improvement in index pain following an initial cervical transforaminal injection of steroid (TFESI) at 4 weeks post-injection, 3 months post-injection and response at 12 months.
2. 50%-79% improvement in index pain following an initial cervical TFESI at 4 weeks post-injection, 3 months post-injection, and response 12 months.
3. Less than 50% improvement in index pain following an initial cervical TFESI at 4 weeks post-injection, 3 months post-injection, and response at 12 months.

Secondary Outcomes:

1. Disability (NDI)
2. Health-related quality of life (EQ-5D)
3. Surgery
4. Personal goal achievement
5. Work status
6. Analgesic use (MQS-III score[15])
7. Quantity and type of ancillary treatment
8. Number of repeat injections
9. Predictors of repeat injections from baseline physical and radiologic findings
10. Predictors of overall response with injection treatment from baseline exam and radiologic findings
11. Proportion of patients requiring more than one injection to reach the 80% improvement mark
12. Differences in long term outcome between the single injection group and the >1 injection group in
    a. Need for surgery
    b. Return to work
    c. Personal goal achievement (from COMBI)
    d. Quality of life (EQ-5D)

Power Analysis
Dreyfuss et al.[9] found that 60% of subjects who received a cervical TFESI with dexamethasone reported at least 50% improvement in NRS score (CI_{95} 35-85%) at 4 weeks. In order to distinguish the lower bound of a 95% confidence interval from a theoretical placebo/sham response rate of 30%, but also from less than a 50% responder rate (we suggest being the minimum acceptable to the medical community), a sample size of 105 subjects is necessary (95% CI 51-69%, assuming a 60% responder rate). In order to account for a conservative 10% attrition rate by the 4-week primary endpoint, we propose to enroll 117 patients.

Procedures

During the injection procedure, per standard clinical practice, the participant will be positioned on a fluoroscopy table. A pre-procedure time-out will be performed, as is protocol in the University practice. Using fluoroscopic guidance, cervical ESI will be performed (please note that the procedure specifications are provided as an example of the current clinical practice and minor variations in parameters are still considered standard of care and do not constitute protocol deviations):

Transforaminal epidural steroid injection (As performed as standard of care practice)
After injection of 1 to 2 mL of lidocaine to the skin and subcutaneous tissues, a 25-gauge spinal needle will be placed at the level and side of radicular pathology, based on clinical correlation of symptoms/signs and magnetic resonance imaging findings. Advancement to the appropriate target position in the neuroforamen will be performed under fluoroscopic guidance according to practice guidelines.[44] Once a satisfactory target position is achieved and confirmed in both anterior-posterior and oblique views, 0.5 to 3 mL of iodinated contrast medium will be injected under live fluoroscopic observation with or without digital subtraction angiography depending on suggestion of vascular uptake, as is standard practice and recommended by practice guidelines.[44] Upon confirmation of a satisfactory epidural contrast pattern without vascular uptake, 1mL (10mg/mL) of dexamethasone sodium phosphate mixed with lidocaine will be injected. After the injection procedure, participants will be observed and then discharged from the clinic with written discharge instructions (current standard practice).

Repeat injections
Participants who achieve 80% or more relief of their usual pain at the 4-week follow-up and who subsequently experience a recurrence of their usual index pain are offered a repeat procedure as per standard of care. "Usual pain" is defined as their cervical radicular pain (upper extremity pain or shoulder girdle/ periscapular pain) which is greater than axial neck pain. Participants with 50-79% relief will be offered a second injection (at 4-week follow-up) with the goal of achieving greater than 80% relief. Responders will be offered a repeat injection if pain returns to the extent that warrants consideration of an additional injection. Duration of relief will be considered the time from the provision of the TFESI procedure until the participant reports a worsening of pain to the extent that warrants consideration of an additional injection. This may occur during an unscheduled follow-up, by phone correspondence, or as reported during scheduled follow-up or when a repeat TFESI is requested and performed.

Data Collection:

An electronic data collection system (REDCap via computer) will be used to record all pre-procedure and follow-up data as listed above (See attached PDF for baseline survey):

- At initial visit
    - Patient's description of pain (characteristics of pain, e.g., burning, electric) and location of pain symptoms.
    - Demographics
    - Medical, surgical and psychiatric history

  - BMI (calculated from patient reported weight and height)
  - Radiologic details relating to location and morphology of the cervical disc herniation, disc osteophyte complex, or degenerative foraminal stenosis if present.
  - Categorical EQ-5D Health Related Quality of Life questionnaire (EQ-5D)
  - Neck Disability Index (NDI)
  - Personal goal achievement (from COMBI)
  - Work history and current status
  - Current medication(s) collected in REDCap survey
  - Ancillary treatment log, of any treatment related to the underlying condition other than analgesic use (e.g., physical therapy, chiropractic care, acupuncture, ice or heat, home cervical traction)
  - Physical examination
  - Neurological examination
  - NRS for arm pain or shoulder girdle/ periscapular pain and separately, NRS for neck pain (24 hour average) at baseline.
- Follow-up by clinic evaluation or standardized phone call survey
  - Date of initial injection (to be confirmed by EMR)
  - Number of repeat cervical TFESIs and dates (to be confirmed by EMR)
  - EQ-5D
  - Neck Disability Index (NDI)
  - Personal goal achievement (from COMBI)
  - Work history and current status
  - Current medication(s) collected in REDCap survey
  - Ancillary treatment log, of any treatment related to the underlying condition other than analgesic use (e.g., physical therapy, chiropractic care, acupuncture, ice or heat, home cervical traction)
  - Global perception of change
  - NRS for arm pain or shoulder girdle/ periscapular pain and separately, NRS for neck pain (24 hour average)

Immediately after injection the following will be obtained:

1) Fluoroscopy time
2) Post-injection NRS pain score
3) Adverse events, if they occurred

Data Storage:

Hard copy data will be collected and stored in a password-protected computer located in the Division of PM&R. Participants will each be assigned an ID number that will be used, along with their name, as the identifiers on any documents. Participant data will be compiled onto a single password protected file, where they will only be identified by their ID number. An enrollment log will be the only file where subject names are correlated with ID numbers. This will be kept in a separate, secure, password-protected file in the Division of PM&R.

Data Analysis Plan

The primary outcome will be the proportion of participants with 50% or greater reduction in neck and arm pain on the NRS pain score at the 1-month follow-up assessment. Secondary outcomes included reduction in median NRS pain score (both neck pain and arm pain), NDI-5, MQS III, opioid consumption in daily morphine equivalents, PGIC score, and satisfaction score. Secondary outcomes will also be defined based on categorical "responder analysis" definitions of important clinical change given the National Institutes of Health recommendation for responder analysis in the assessment of therapeutic spine pain interventions.[45] The responder analysis will include the proportion of patients with 30% or greater improvement on the NDI-5,[46,47] a PGIC score less than 3 (indicating "improved" or "very much improved"), a 6.8 or greater point reduction on the MQS III score (equivalent to approximately 10 daily morphine equivalents),[48] work status, number of repeat injections, and the proportion of participants who undergo surgical spine surgery.

Statistical analysis

Descriptive statistics (mean and SD for quantitative variables; frequency and proportion for categorical variables) will be calculated for patient demographics, along with the primary and secondary outcome variables listed above. A multilevel mixed-effects generalized linear model with ordinal family and logit link will be used to examine longitudinal changes in index pain following an initial cervical TFESI at 4 weeks, 3 months, and 12 months post-injection. Specifically, index pain will be categorized into three ordinal categories (≥ 80%, 50-79%, or < 50% improvement), and will be used as an ordinal outcome variable, while three time points described here will be used as a time variable. Potential covariates for the model will include: 1) age, 2) duration of pain, 3) baseline NDI score, 4) degree of nerve compression (grade 1, grade 2, grade 3, or grade 4), 5) work status (employed or unemployed), 6) DM2 (present or absent), 7) opioid use (yes or no), and 8) baseline NRS pain score separately for arm and neck.

Risks/Benefits:

Risks of study participation include the potential loss of confidentiality.

Risks for standard of care procedure are the same as those for any standard fluoroscopically guided cervical ESI frequently performed in the PM&R Spine Clinic. These include: local infection, epidural hematoma or abscess, dural puncture and potential post-dural puncture headache, paresthesia during needle placement, pain at the injection side, failure of technique, allergy to latex or medications being used. Utilizing fluoroscopy, the risk of nerve damage, spinal cord injury or intravascular injection is less than 1:500,000. The length of stay and length of recovery is no longer than that of a standard ESI performed in the PM&R Spine Clinic at present.

There are no direct benefits to the individual by participating in this study. The patients will be presented with the same options of treatment whether they enroll in the study or decide not to. The information extracted from this study may provide the investigators a better understanding of patient's pain response following a cervical epidural steroid injection.

Study Termination Criteria

- Adverse events considered/identified by the medical staff during the procedure process
- The subject requests to be withdrawn from the study during the procedure.

Safety Monitoring Plan
Safety will be monitored by all members of the study team:

Zachary McCormick, MD
Richard Kendall, DO
Aaron Conger, DO

The Principal Investigator is an MD at the University of Utah. Members of the data and safety monitoring committee will be in close contact with all the subjects throughout the study, both in-person and via telephone. The members of the data and safety monitoring committee will review potential side effects and adverse reactions with each subject at the time of delivery of the study drug and at the time of each sample collection. All the committee members are located at the University of Utah clinical locations; all members have research experience.

References

1. Radhakrishnan K, Litchy WJ, O'Fallon WM, Kurland LT. Epidemiology of cervical radiculopathy. A population-based study from Rochester, Minnesota, 1976 through 1990. Brain. Apr 1994;117 (Pt 2):325-335.
2. Carette S, Fehlings MG. Clinical practice. Cervical radiculopathy. The New England journal of medicine. Jul 28 2005;353(4):392-399.
3. Heckmann JG, Lang CJ, Zobelein I, Laumer R, Druschky A, Neundorfer B. Herniated cervical intervertebral discs with radiculopathy: an outcome study of conservatively or surgically treated patients. Journal of spinal disorders. Oct 1999;12(5):396-401.
4. Johnston MM, Jordan SE, Charles AC. Pain referral patterns of the C1 to C3 nerves: Implications for headache disorders. Annals of neurology. Jul 2013;74(1):145-148.
5. Mizutamari M, Sei A, Tokiyoshi A, et al. Corresponding scapular pain with the nerve root involved in cervical radiculopathy. Journal of orthopaedic surgery. Dec 2010;18(3):356-360.
6. Ellenberg MR, Honet JC, Treanor WJ. Cervical radiculopathy. Archives of physical medicine and rehabilitation. Mar 1994;75(3):342-352.
7. Malanga GA. The diagnosis and treatment of cervical radiculopathy. Medicine and science in sports and exercise. Jul 1997;29(7 Suppl):S236-245.
8. Renfrew DL, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: fluoroscopic guidance and contrast administration. AJNR. American journal of neuroradiology. Sep-Oct 1991;12(5):1003-1007.
9. Mehta M, Salmon N. Extradural block. Confirmation of the injection site by X-ray monitoring. Anaesthesia. Oct 1985;40(10):1009-1012.
10. Stojanovic MP, Vu TN, Caneris O, Slezak J, Cohen SP, Sang CN. The role of fluoroscopy in cervical epidural steroid injections: an analysis of contrast dispersal patterns. Spine. Mar 1 2002;27(5):509-514.

11. Van Zundert J, Huntoon M, Patijn J, et al. 4. Cervical radicular pain. Pain practice : the official journal of World Institute of Pain. Jan-Feb 2010;10(1):1-17.
12. Johansson A, Hao J, Sjolund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. Acta anaesthesiologica Scandinavica. Jul 1990;34(5):335-338.
13. Benyamin RM, Singh V, Parr AT, Conn A, Diwan S, Abdi S. Systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain. Pain Physician. Jan-Feb 2009;12(1):137-157.
14. Stav A, Ovadia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. Acta anaesthesiologica Scandinavica. Aug 1993;37(6):562-566.
15. Castagnera L, Maurette P, Pointillart V, Vital JM, Erny P, Senegas J. Long-term results of cervical epidural steroid injection with and without morphine in chronic cervical radicular pain. Pain. Aug 1994;58(2):239-243.
16. Saal JS, Saal JA, Yurth EF. Nonoperative management of herniated cervical intervertebral disc with radiculopathy. Spine. Aug 15 1996;21(16):1877-1883.
17. Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. The Journal of bone and joint surgery. American volume. Nov 2000;82-A(11):1589-1593.
18. Buttermann GR. Treatment of lumbar disc herniation: epidural steroid injection compared with discectomy. A prospective, randomized study. The Journal of bone and joint surgery. American volume. Apr 2004;86-A(4):670-679.
19. Huntoon MA. Anatomy of the cervical intervertebral foramina: vulnerable arteries and ischemic neurologic injuries after transforaminal epidural injections. Pain. Sep 2005;117(1-2):104-111.
20. Abbasi A, Malhotra G, Malanga G, Elovic EP, Kahn S. Complications of interlaminar cervical epidural steroid injections: a review of the literature. Spine (Phila Pa 1976). Sep 1 2007;32(19):2144-2151.
21. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, RiewKD, Rosenquist RW, Aprill C, Rost NS, Buvanendran A, Kreiner DS, Bogduk N, Fourney DR, Fraifeld E, Horn S, Stone J, Vorenkamp K, Lawler G, Summers J, Kloth D, O'Brien D Jr, Tutton S. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. Anesthesiology. 2015 May;122(5):974-84.
22. Woodward JL HS, Wisdor RE, et al. Epidural procedures in spine pain management. Physiatric Procedures in Clinical Practice. 1995:260-280.
23. Woodward JL WS. Epidural injections for the diagnosis and management of axial and radicular pain syndromes. Physical Medicine and Rehabilitation Clinics of North America. 1995:691–714.
24. Costandi SJ, Azer G, Eshraghi Y, Zeyed Y, Atalla JE, Looka ME, Mekhail NA. Cervical Transforaminal Epidural Steroid Injections: Diagnostic and Therapeutic Value. Reg Anesth Pain Med. 2015 Nov-Dec;40(6):674-80.
25. Woo JH, Park HS. Cervical transforaminal epidural block using low-dose local anesthetic: a prospective, randomized, double-blind study. Pain Med. 2015 Jan;16(1):61-7.

26. McCormick ZL[1], Nelson A, Bhave M, Zhukalin M, Kendall M, McCarthy RJ, Khan D, Nagpal G, Walega DR. A Prospective Randomized Comparative Trial of Targeted Steroid Injection Via Epidural Catheter Versus Standard C7-T1 Interlaminar Approach for the Treatment of Unilateral Cervical Radicular Pain. Reg Anesth Pain Med. 2017 Jan/Feb;42(1):82-89.
27. Ackerman WE, 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. Anesth Analg. May 2007;104(5):1217-1222, tables of contents.
28. Gharibo CG, Varlotta GP, Rhame EE, Liu EC, Bendo JA, Perloff MD. Interlaminar versus transforaminal epidural steroids for the treatment of subacute lumbar radicular pain: a randomized, blinded, prospective outcome study. Pain physician. Nov-Dec 2011;14(6):499-511.
29. Schaufele MK, Hatch L, Jones W. Interlaminar versus transforaminal epidural injections for the treatment of symptomatic lumbar intervertebral disc herniations. Pain physician. Oct 2006;9(4):361-366.
30. Wu J, Xu Y, Pu S, Zhou J, Lv Y, Li C, et al. US-Guided Transforaminal Cervical Nerve Root Block: A Novel Lateral in-Plane Approach. Pain Med. 2021 Sep;22(9):1940–5.
31. Jang JH, Lee WY, Kim JW, Cho KR, Nam SH, Park Y. Ultrasound-Guided Selective Nerve Root Block versus Fluoroscopy-Guided Interlaminar Epidural Block versus Fluoroscopy-Guided Transforaminal Epidural Block for the Treatment of Radicular Pain in the Lower Cervical Spine: A Retrospective Comparative Study. Pain Res Manag. 2020;2020.
32. Hashizume K, Fujiwara A, Watanabe K, Kamihara M, Iwasaki S, Yamagami H. A prospective comparison of CT-Epidurogram between Th1-transforaminal epidural injection and Th1/2-Parasagittal interlaminar epidural injection for cervical upper limb pain. Pain Physician. 2019;22(2):165–76.
33. Binler D, House LM, Mattie R, Saltychev M, Nagao M, Pekmeczi M, et al. The Reliability of a Grading System for Digital Subtraction Imaging Quality During Cervical Transforaminal Epidural Steroid Injection. Pain Med. 2020;00(0):1–7.
34. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, et al. Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections. Anesthesiology. 2015 May 1;122(5):974–84.
35. Sim JH, Park H, Kim Y, Shin J-W, Leem J-G, Cho H-S, et al. Comparative Effectiveness of Parasagittal Interlaminar and Transforaminal Cervical Epidural Steroid Injection in Patients with Cervical Radicular Pain: A Randomized Clinical Trial. Pain Physician. 2021 Mar;24(2):117–25.
36. McCormick ZL, Conger A, Sperry BP, Teramoto M, Petersen R, Salazar F, et al. A Randomized Comparative Trial of Targeted Steroid Injection via Epidural Catheter vs Standard Transforaminal Epidural Injection for the Treatment of Unilateral Cervical Radicular Pain: Six-Month Results. Pain Med. 2020 Oct 1;21(10):2077–89.
37. McCormick ZL, Nelson A, Bhave M, Zhukalin M, Kendall M, McCarthy RJ, et al. A Prospective randomized comparative trial of targeted steroid injection via epidural catheter versus standard C7-T1 interlaminar approach for the treatment of unilateral cervical radicular pain. Reg Anesth Pain Med. 2017;42(1):82–9.
38. Smuck M, Rosenberg JM, Akuthota V. The Use of Epidural Corticosteroids for Cervical

Radiculopathy: An Interlaminar Versus Transforaminal Approach. PM R. 2009 Feb;1(2):178–84.

39. Lee JH, Lee SH. Comparison of clinical efficacy between interlaminar and transforaminal epidural injection in patients with axial pain due to cervical disc herniation. Med (United States). 2016;95(4):1–6.

40. Jang SH, Boudier-Revéret M, Cho HK, Kwak SG, Chang MC. Follow-up of at Least 5 Years After Cervical Transforaminal Epidural Steroid Injection for Control of Cervical Radicular Pain. Vol. 21, Pain medicine (Malden, Mass.). England; 2020. p. 3240–2.

41. Hashemi M, Dadkhah P, Taheri M, Ghasemi M, Hosseinpour A, Farjam M. Patient-Reported Outcomes and Satisfaction after Cervical Epidural Steroid Injection for Cervical Radiculopathy. Galen Med J. 2019;8:e1478.

42. Bush K, Mandegaran R, Robinson E, Zavareh A. The safety and efficiency of performing cervical transforaminal epidural steroid injections under fluoroscopic control on an ambulatory/outpatient basis. Eur spine J Off Publ Eur Spine Soc Eur Spinal Deform Soc Eur Sect Cerv Spine Res Soc. 2020 May;29(5):994–1000.

43. Lee JW, Lee E, Lee GY, Kang Y, Ahn JM, Kang HS. Epidural steroid injection-related events requiring hospitalisation or emergency room visits among 52,935 procedures performed at a single centre. Eur Radiol. 2018;28(1):418–27.

44 Bogduk N (ed). Practice Guidelines for Spinal Diagnostic and Treatment Procedures, 2nd edn. International Spine Intervention Society, San Francisco, 2013.

45. Deyo RA, Dworkin SF, Amtmann D, et al. Report of the NIH task force on research standards for chronic low back pain. Pain Med. 2014;15:1249–1267.

46. Dworkin RH, Turk DC, McDermott MP, et al. Interpreting the clinical importance of group differences in chronic pain clinical trials: IMMPACT recommendations. Pain. 2009;146:238–244.

47. Kovacs FM, Abraira V, Royuela A, et al. Minimum detectable and minimal clinically important changes for pain in patients with nonspecific neck pain. BMC Musculoskelet Disord. 2008;9:43.

48. Gallizzi M, Gagnon C, Harden RN, Stanos S, Khan A. Medication Quantification Scale Version III: internal validation of detriment weights using a chronic pain population. Pain Pract. Mar 2008;8(1):1-4.