Title: Do Cervical Interlaminar Epidural Steroid Injections with Low-dose Lidocaine Cause Transient Objective Upper Extremity Weakness? A Prospective Randomized Controlled Trial

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

Research Question(s):

Primary: Does lidocaine versus saline as a steroid diluent affect objective upper extremity strength following cervical epidural steroid injection in patients being treated for cervical radicular pain?

Secondary: Does lidocaine versus saline as a steroid diluent affect short-term pain, function, medication use, and global impression of change outcomes of cervical epidural injection for the treatment of radicular pain?

Null Hypothesis:

1. Cervical epidural steroid injections that include local anesthetic as a diluent have no effect on objective upper extremity strength following the injection.
2. Cervical epidural steroid injections for radicular pain that include lidocaine compared to saline as a diluent do not improve short-term pain, function, medication use, and global impression of change outcomes.

Introduction

Cervical radicular pain is a common problem that is often treated by epidural steroid injection (1). While clinical practice guidelines do not specifically recommend or discourage the use of local anesthetic in the epidural injectate (2), the majority of the published literature on clinical outcomes of cervical epidural steroid injection includes the use of lidocaine in the epidural injectate (3-11). Consequently, many practitioners elect to use local anesthetic in the epidural injectate in order to obtain additional diagnostic information when the precise source of pain is not clear from clinical presentation and imaging. Local anesthetic may also be included in order to provide immediate pain relief in cases of painful acute radicular symptoms.

Local anesthetic injection into the epidural space has the potential to cause transient weakness of the upper extremities. High dose local anesthetic in the cervical epidural space (12) and inappropriately placed low-dose local anesthetic in the subdural space or subarachnoid space (13, 14) are known to cause motor weakness. Appropriately placed, low-dose local anesthetic injected into the epidural space via a transforaminal approach, in close proximity to the exiting spinal nerve root, causes motor block in a small proportion of patients (15). However, the effect of low-dose injection of local anesthetic in the cervical interlaminar epidural space on objective upper extremity strength has not been characterized in the published literature. This proposition affects post-procedure instructions, as even mild weakness may pose a hazard during performance manual activities that require the upper extremity/extremities such as using a handrail or cane handle for support.

Dynamometry is an established and validated method for assessing muscle strength and motor neuron function with high reliability, and has been used to objectively assess changes in upper extremity strength.

This study aims to determine whether a standard dose of 2 mL 1% lidocaine included as a steroid diluent in a C7-T1 cervical interlaminar epidural steroid injection (CESI) causes an objective change in strength as measured by dynamometry. We hypothesized that cervical epidural lidocaine will cause an objective decrease in strength in functional movements of the upper extremity.

Significance:
Cervical radicular pain is relatively common, often treated with epidural steroid injection (ESI), when conservative treatments like oral analgesics, physical therapy, and activity modification have failed. There are no universal clinical practice guidelines for the use of diluents when CESI are performed.

Interlaminar CESI may be performed with or without the use of local anesthetics, due to training bias or theoretical concerns of weakness. CESI without the benefit of local anesthetic as a steroid diluent increases the latency of pain relief and may decrease diagnostic information immediately after a CESI with regard to pain generators responsible for symptoms, and may potentially decrease patient satisfaction.

By evaluating the effects of local anesthetic as a diluent during interlaminar cervical ESI, we will enhance the safety of this treatment with regard to expectations of objective motor weakness as well as post procedure pain control in the recovery phase after the injection procedure.

Additionally, investigation of short-term pain, function, medication use, and global impression of change following use of local anesthetic versus saline as a diluent during interlaminar cervical ESI will provide evidence to inform the optimization of clinical outcomes related to steroid diluent choice.

Subjects
A total of 104 subjects, aged 18-80 on the day of enrollment, will be recruited for participation in this study. Patients will be randomized to one of two groups based on a random computer-generated schedule.

Those assigned to Group #1 will undergo a interlaminar cervical ESI with local anesthetic as a steroid diluent. Those in Group #2 will receive a interlaminar cervical ESI with saline as a steroid diluent.

De-identification
All subjects will be assigned a unique alphanumeric identifier. No personally identifiable information will be used in the final database, in order to ensure compliance with HIPPA and hospital policy. 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. We intend to recruit participants primarily through word-of-mouth and from a database or participant pool for which participants have given prior permission to be contacted for research studies. Additionally, recruiting will take place through the distribution of flyers to the Health Sciences Education Building, University of Utah Student Life Center, the University of Utah South Jordan Health Center, the University of Utah Orthopaedic 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 and current athletic participation. Interested volunteers who qualify will be asked to report to the University of Utah Orthopaedic 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) Age 18-80.
2) Clinical diagnosis of cervical radicular pain.
3) Magnetic resonance imaging pathology consistent with clinical symptoms/signs.
4) Numerical Rating Scale (NRS) pain score of 4 or higher.
5) Pain duration of more than 6 weeks despite trial of conservative therapy (medications, physical therapy, or chiropractic care).
6) Patients who will undergo CESI for treatment of cervical radiculitis.

Exclusion criteria:

1) Refusal to participate, provide consent, or provide communication and follow-up information for duration of the study.
2) Inability to perform handgrip or arm strength testing.
3) Contraindications to Cervical ESI (active infection, bleeding disorders, current anticoagulant or antiplatelet medication use, allergy to medications used for CIESI, and pregnancy).
4) Cervical spinal cord lesions; cerebrovascular, demyelinating, or other neuro-muscular muscular disease.
5) Patient request for or requirement of conscious sedation for the injection procedure.

Study design:

Prospective, randomized, controlled, double blinded trial in patients undergoing CESI for symptoms of cervical radicular pain.

Patients will be randomized to group #1 or #2 based on a random computer-generated schedule.

Group #1: Interlaminar cervical ESI at the C7-T1 level with triamcinolone 80 mg (40 mg/mL) + 2 mL 1% lidocaine (total volume 4 mL).

Group #2: Interlaminar cervical ESI at the C7-T1 level with triamcinolone 80 mg (40 mg/mL) + 2 mL preservative saline (total volume 4 mL).

Adults who are eligible and scheduled to have an epidural steroid injection with triamcinolone for treatment of cervical radicular pain at the University of Utah Orthopaedic Center or University of Utah South Jordan Health Center will be approached by authorized research personnel. All eligible patients will be offered to participate in the study and all patients will sign a written informed consent form before proceeding and will also be consented for the procedure. Participating in the study is voluntary. The patients may choose not to enroll in the research. Patients will be presented with the same options of treatment whether they enroll or decide not to.

Power Analysis
Statistical Plan & Sample Size Calculation:
Size of study groups:
Group 1: n = 52
Group 2: n = 52

A power analysis was performed based upon previous observations of UE strength (28) using Fisher's Exact Test. Sample sizes of 52 in each of the two treatment groups will achieve > 80% power to detect a group different in proportions, assuming 20% of patients in the Lidocaine group will demonstrate a motor deficit after the CESI and those in the Saline group will demonstrate no difference in motor strength after the CESI, assuming a 2% measurement error with the strength testing method described. The alpha level of this test statistic is set at 0.05, but the significance level actually achieved by this study design is 0.0004.

Procedure
All patients evaluated in the University of Utah Orthopaedic Center who will have a CESI with triamcinolone will be considered for participation in the study. Subjects will be consented for participation in the study and informed consent will be obtained. Each subject will be randomized into a group assignment in a 1:1 manner, #1 or #2, as outlined in the Methods section above. All documentation will be stored using a unique coded identifier to ensure compliance with HIPPA.

A Report Form will be used to record all pre- and post-procedure data (See Appendix)

In every participant in Control Cohort, Group 1 and Group 2, a pre-procedure NRS pain score, pain medication use, and presence of subjective or objective symptoms of UE weakness will be recorded. Bilateral handgrip, wrist extension, elbow flexion, and elbow extension strength (myotomes C5-T1) will be measured by a trained research assistant prior to the injection procedure using a handheld JAMAR® PLUS+ digital dynamometer (Sammons Preston, Bollingbrook, IL) for hand grip strength and a Lafayette Manual Muscle Testing System model 01163 (Lafayette Instrument Company, Lafayette, IN) for arm strength assessment. Three baseline strength measurements will be recorded for each strength test (20,21). Validation studies using similar protocols for upper extremity functional strength measurement show a high degree

of test-retest reliability with a narrow range of variability [22–26]. Additionally, light touch and pinprick sensory testing in the C5-T1 dermatomes will performed with a tapered whisp of cotton and a disposable safety pin, respectively, in accordance with the methods described when performing an American Spinal Injury Association (ASIA) examination in accordance with the international standards for neurological classification of spinal cord injury (27).

Measurements will be taken prior to and 30 minutes following the injection procedure. Participants in Group #1 and Group #2 will also be queried with the Upper Extremity Functional Index (UEFI) before the injection procedure and again 1 day after the procedure (administered via telephone).

For Group 1 and Group 2, patients will be randomized to treatment group based on a random computer-generated schedule. Participants will be blinded to the group to which they are randomized. All standard procedures for CESIs will be followed as is standard practice including time out, skin prep, hemodynamic monitoring, image guidance, etc.

Per randomization, triamcinolone acetonide 80 mg (Kenalog) (E. R. Squibb & Sons Limited, Uxbridge UK) will be combined with 2mL Lidocaine 1% or 2 mL preservative free saline and will be injected during the CESI procedure. In all cases, the total injectate volume will be 4 mL. All injections will be image guided with fluoroscopy, as is the current standard practice. Fluoroscopy time will be recorded.

The participant will be discharged from the clinic with written discharge instructions (current standard practice).

Participants will be telephoned and emailed by clinic personnel 1 day after the CESI to assess for subjective weakness in the hands or arms as well as any other adverse reactions. As above, the UEFI will be administered at this time.

Participants will only be recruited for this study for a single CESI. Those who require repeat injections will not be recruited a second or third time.

Data Collection:

1 Data evaluation (See Case report form)

2 Interpretation of Anticipated Results:

Statistical analysis
Differences in strength as measured by dynamometry pre-and post-injection will be assessed by Fishers exact test.
Means and standard deviations of subject demographic data, as well as pain scores and UEFI scores will be calculated.

Data Storage

Hard copy data will be collected and stored in a password-protected computer located in the Division of PM&R. Subjects will each be assigned an ID number that will be used as the sole identifier on any documents. Subject 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.[31] The responder analysis will include the proportion of patients with 30% or greater improvement on the NDI-5,[32,33] 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),[34] and the proportion of participants who undergo surgical spine surgery.

Primary outcome:

- Change in strength for each individual in each treatment group before and 30 minutes after CESI
- Categorical analysis based on a minimally clinically important change of 19.5% for upper extremity strength assessment (29).

Secondary outcomes:

- Change in mean arterial pressure prior to, 30 minutes after CESI, via automated blood pressure cuff measure.
- Change in HR prior to, 30 minutes after CESI
- Change in NRS pain score from pre-injection to post injection (immediate) and 1-day.
- Change in UEFI score from pre-injection to post injection (immediate) and 1-day.
- Change in pain medication use from pre-injection to post injection (immediate) and 1-day.
- Procedure complications or adverse reactions to medications used

Risks/Benefits:

Risks of study participation are the same as those for any standard fluoroscopically guided cervical ESI performed for management of cervical radiculitis when more conservative methods have been exhausted or failed. These risks 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 to decrease pain levels, allergy to latex,

iodine/chlorhexidine, adhesives or any medications used during the procedure. 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 risks associated with the pre- and post-injection grip and arm strength testing with dynamometry. In this study, the length of stay and length of recovery is no longer than that of a standard CESI performed in the Orthopaedic Center at present.

There are no direct benefits to the individual by participating in this study. The patients will be presented with the same treatment options whether they enroll in the study or decide not to participate. The information gained from this study may provide the investigators a better understanding of a patient's pain and strength 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, MD

The Principal Investigator is an MD at the University of Utah Orthopaedic Center and University of Utah South Jordan Health Center. 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 Orthopaedic Center; all members have research experience.

References

1. Peloso P, Gross A, Haines T, Trinh K, Goldsmith CH, Burnie S, et al. Medicinal and injection therapies for mechanical neck disorders. Cochrane Database Syst Rev. 2007(3):CD000319.
2. Bogduk N. Practice Guidelines for Spinal Diagnostic and Treatment Procedures. 2nd ed. Bogduk N, editor. San Francisco: International Spine Intervention Society ; 2013.
3. Purkis I. Cervical epidural steroids. The Pain Clinic. 1986;1:3-7.
4. Stav A, Ovadia L, Sternberg A, Kaadan M, Weksler N. Cervical epidural steroid injection for cervicobrachialgia. Acta Anaesthesiol Scand. 1993;37(6):562-6.

5. Cicala RS, Thoni K, Angel JJ. Long-term results of cervical epidural steroid injections. Clin J Pain. 1989;5(2):143-5.
6. Ferrante FM, Wilson SP, Iacobo C, Orav EJ, Rocco AG, Lipson S. Clinical classification as a predictor of therapeutic outcome after cervical epidural steroid injection. Spine (Phila Pa 1976). 1993;18(6):730-6.
7. Botwin KP, Castellanos R, Rao S, Hanna AF, Torres-Ramos FM, Gruber RD, et al. Complications of fluoroscopically guided interlaminar cervical epidural injections. Arch Phys Med Rehabil. 2003;84(5):627-33.
8. Rowlingson JC, Kirschenbaum LP. Epidural analgesic techniques in the management of cervical pain. Anesth Analg. 1986;65(9):938-42.
9. 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. 1994;58(2):239-43.
10. Lee SH, Kim KT, Kim DH, Lee BJ, Son ES, Kwack YH. Clinical outcomes of cervical radiculopathy following epidural steroid injection: a prospective study with follow-up for more than 2 years. Spine (Phila Pa 1976). 2012;37(12):1041-7.
11. McCormick ZL, 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. 2016 Dec 5. [Epub ahead of print]
12. Capdevila X, Biboulet P, Rubenovitch J, Serre-Cousine O, Peray P, Deschodt J, et al. The effects of cervical epidural anesthesia with bupivacaine on pulmonary function in conscious patients. Anesth Analg. 1998;86(5):1033-8.
13. Bansal S, Turtle MJ. Inadvertent subdural spread complicating cervical epidural steroid injection with local anaesthetic agent. Anaesth Intensive Care. 2003;31(5):570-2.
14. Collier CB. Accidental subdural block: four more cases and a radiographic review. Anaesth Intensive Care. 1992;20(2):215-25.
15. Plastaras C, McCormick ZL, Garvan C, Macron D, Joshi A, Chimes G, et al. Adverse events associated with fluoroscopically guided lumbosacral transforaminal epidural steroid injections. Spine J. 2015;15(10):2157-65.
16. Ortiz MP, Godoy MC, Schlosser RS, Ortiz RP, Godoy JP, Santiago ES, Rigo FK, Beck V, Duarte T, Duarte MM, Menezes MS. Effect of endovenous lidocaine on analgesia and serum cytokines: double-blinded and randomized trial. J Clin Anesth. 2016 Dec;35:70-77.
17. Chiu KM, Lu CW, Lee MY, Wang MJ, Lin TY, Wang SJ. Neuroprotective and anti-inflammatory effects of lidocaine in kainic acid-injected rats. Neuroreport. 2016 May 4;27(7):501-7.
18. Gray A, Marrero-Berrios I, Weinberg J, Manchikalapati D, SchianodiCola J, Schloss RS, Yarmush J. The effect of local anesthetic on pro-inflammatory macrophage modulation by mesenchymal stromal cells. Int Immunopharmacol. 2016 Apr;33:48-54.
19. van der Wal SE, van den Heuvel SA, Radema SA, van Berkum BF, Vaneker M, Steegers MA, Scheffer GJ, Vissers KC. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2016 May;20(5):655-74.
20. Bohannon RW. Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. Arch Phys Med Rehabil. 1997;78(1):26-32.

21. Bohannon RW. Grip strength impairments among older adults receiving physical therapy in a home-care setting. Percept Mot Skills. 2010;111(3):761-4.
22. Hayes K, Walton JR, Szomor ZL, Murrell GA. Reliability of 3 methods for assessing shoulder strength. J Shoulder Elbow Surg. 2002 Jan-Feb;11(1):33-9.
23. Kolber MJ, Beekhuizen K, Cheng MS, Fiebert IM. The reliability of hand-held dynamometry in measuring isometric strength of the shoulder internal and external rotator musculature using a stabilization device. Physiother Theory Pract. 2007 Mar-Apr;23(2):119-24.
24. Awatani T, Mori S, Shinohara J, Koshiba H, Nariai M, Tatsumi Y, Nagata A, Morikita I. Same-session and between-day intra-rater reliability of hand-held dynamometer measurements of isometric shoulder extensor strength. J Phys Ther Sci. 2016 Mar;28(3):936-9. doi: 10.1589/jpts.28.936. Epub 2016 Mar 31.
25. Fieseler G, Molitor T, Irlenbusch L, Delank KS, Laudner KG, Hermassi S, Schwesig R. Intrarater reliability of goniometry and hand-held dynamometry for shoulder and elbow examinations in female team handball athletes and asymptomatic volunteers. Arch Orthop Trauma Surg. 2015 Dec;135(12):1719-26. doi: 10.1007/s00402-015-2331-6. Epub 2015 Sep 19.
26. Tsai YJ, Tu YK, Hsiao CK, Su FC. Within-session reliability and smallest real difference of muscle strength following nerve transfers in patients with brachial plexus injuries. J Hand Surg Am. 2015 Jun;40(6):1196-201.
27. Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, Johansen M, Jones L, Krassioukov A, Mulcahey MJ, Schmidt-Read M, Waring W. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med. 2016 Sep;39(5):504-12.
28. McCormick ZL, Nelson A, Kendall MC, McCarthy RJ, Nagpal G, Walega DR. Does Cervical Interlaminar Epidural Steroid Injection with Low-Dose Lidocaine Cause Objective Upper Extremity Weakness? A Preliminary Study. Pain Med. 2017 Mar 18.
29. Kim JK, Park MG, Shin SJ. What is the minimum clinically important difference in grip strength? Clin Orthop Relat Res. 2014;472(8):2536-41.