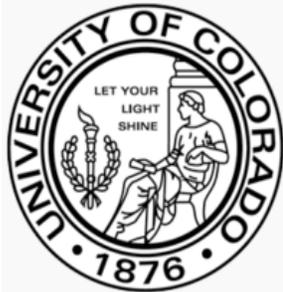


# Epidural Steroid Injections: Recent history, FDA Safe Use Initiative, and Multi-Society Pain Workgroup



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# Objectives

- ▶ Discuss why medications are injected
- ▶ Discuss risks: past and more recent
- ▶ Describe FDA Safe Use Initiative
- ▶ Discuss current areas of consensus
- ▶ Outline recent studies



# Disclosures

- ▶ I perform ESIs
- ▶ My wife is a pharmacist: not compounding
- ▶ No other pertinent financial disclosures
  - No ownership in Spine Centers/Injection Facilities
  - No ownership/stocks in C-arm manufacturers



FUTURE - DENVER VA MEDICAL CENTER - AURORA, COLORADO

# Disclosures: past year

- ▶ NASS: Honorarium and Expenses  
Board Meeting, Coding Workshops, Emerging  
Technology Summit, RUC Advisor <\$5000/year



# Rationale for Anesthetics

- ▶ **Disrupt afferent sensory impulses thus reducing pain; depending on anesthetic flow, may confirm symptomatic nerve roots**
- ▶ **With test dose, substantial LE effects or CNS effects warn of inadvertent sub-arachnoid, sub-dural, or vascular spread**
- ▶ **Psychological advantage of “relief of symptoms”**



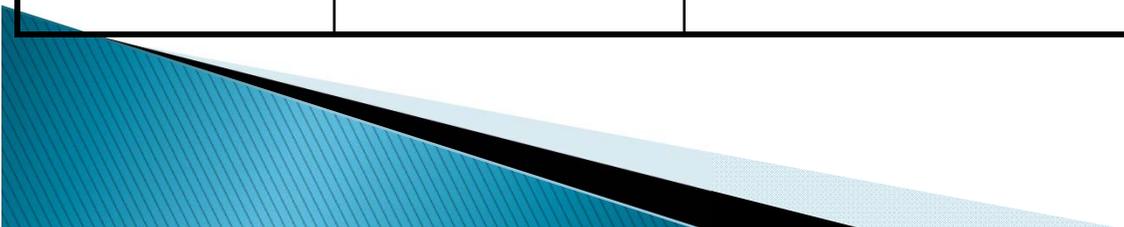
# Effect of Corticosteroids

- ▶ Inhibit prostaglandin synthesis (Flower, *Nature*, 1979)
- ▶ Suppress superoxide radicals
- ▶ Stabilize lysosomal enzymes at supraphysiologic concentrations
- ▶ Block C-fiber transmission (Siddall, *Spine*, 1997)
- ▶ Reduces capillary permeability
- ▶ Reversible local anesthetic effect (Siddall, *Spine*, 1997)



# Corticosteroid Agents

<b>Generic Name</b>	<b>Betamethasone</b>	<b>Methylprednisolone</b>	<b>Triamcinolone</b>	<b>Dexamethasone</b>
<b>Brand Name</b>	<b>Celestone</b>	<b>Depomedrol</b>	<b>Kenalog</b>	<b>Decadron</b>
<b>Benzyl Alcohol</b>	<b>NO</b>	<b>YES</b>	<b>YES</b>	<b>YES</b>
<b>Potency</b>	<b>25</b>	<b>5</b>	<b>5</b>	<b>30</b>
<b>Duration</b>	<b>Long</b>	<b>Intermediate</b>	<b>Intermediate</b>	<b>Long</b>



# Corticosteroid Side Effects

- ▶ Insomnia (39%), facial erythema (20%), nausea (20%), rash/puritis (8%) with Celestone Soluspan
- ▶ Temperature <100F, euphoria, depression, mood swings, pain flare, fluid retention, headache, hyperglycemia, hypertension, gastritis, menstrual irregularities
- ▶ No persistent complaints noted over 14 days (Andrade, ISIS Newsletter, 1993)



# Corticosteroid Side Effects

- ▶ True Cushingoid effect (facial edema, bruising, fat pad development) very rare and resolves within several weeks (Abram, *Reg Anesthesia*, 1996)
- ▶ Suppression of plasma cortisol can occur for usually 2 and up to 3 weeks (Jacobs, *Anesthesia*, 1993 and Burn, *Am J Phys Med*, 1974)



# Medical Complications

- ▶ Vasovagal most common
- ▶ Allergic and anaphylactic reactions
- ▶ Direct nerve or cord trauma should not occur
- ▶ Compression of nerve roots or cord by epidural hematoma/abscess



# Medical Complications

- ▶ Prospective and retrospective studies found no long term complications in over 350 consecutive transforaminal epidurals (Huston: *Arch Phys Med Rehabil*; 77:937,1996, Botwin KP: *Arch Phys Med Rehabil*; 81 (8) : 1045, 2000)



# Post-ESI Headache

- ▶ Maybe due to inadvertent dural puncture
- ▶ Dural puncture occurs in 1-3% with interlaminar and in 0.5% with caudal ESIs
- ▶ Incidence of post-dural puncture headaches ranges from 7.5-75% with needle size reported as the greatest determinant
- ▶ Transforaminal approach unlikely (Botwin, 2000)



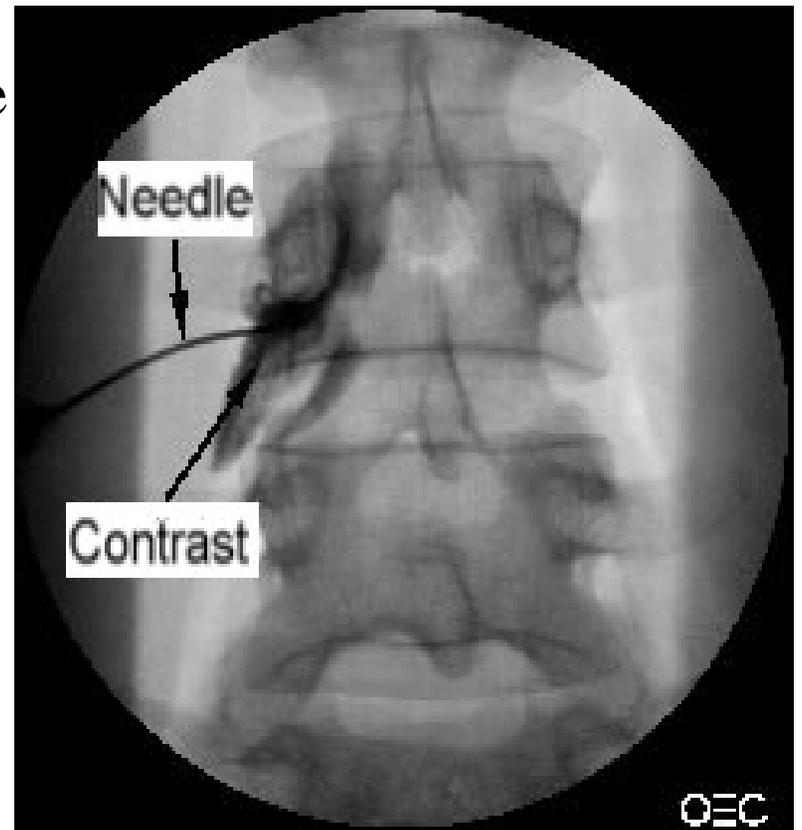
# Real Risks

Houten, *Spine J*, 2002

Paraplegia after lumbosacral nerve root block: report of three cases

Sudden onset of paraplegia with injection of steroid

Vascular injury (artery of Adamkiewicz) or particulate?

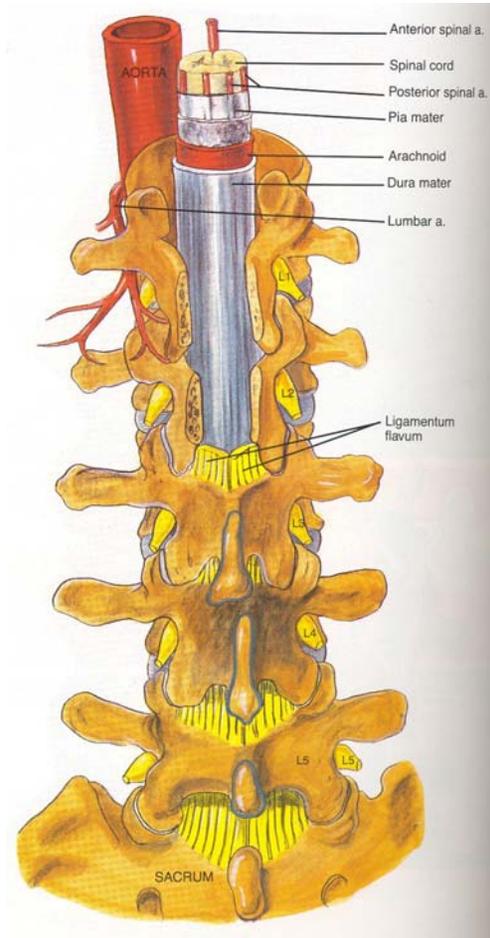


# Real risks

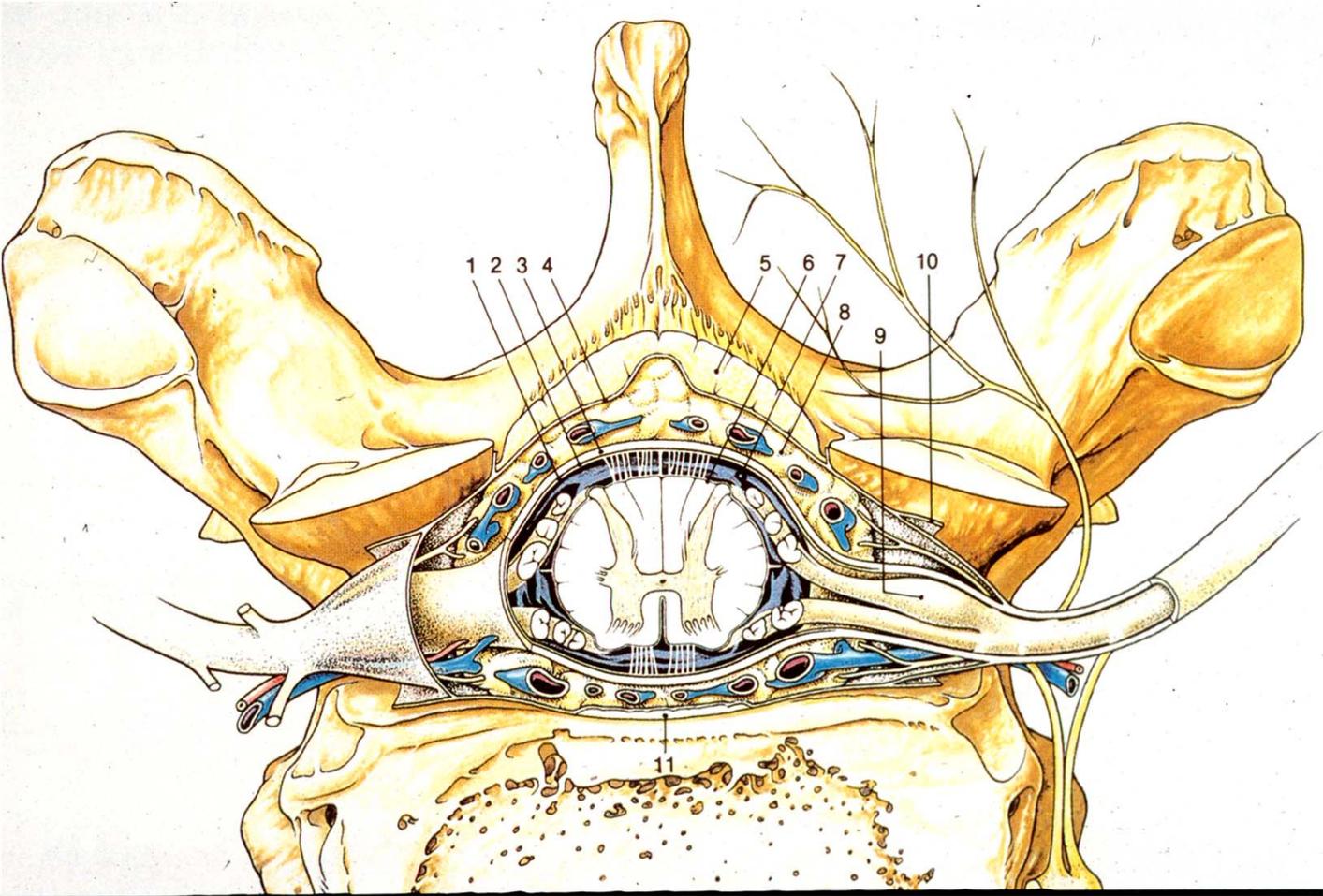
Huntoon, *Reg Anesth  
Pain Med*, Sept 2004

Paralysis after  
transforaminal epidural  
steroid injection and  
previous surgery

MRI → Infarct



# Anatomic considerations



# Cervical ESI Complications

Baker, Dreyfuss,  
Mercer, Bogduk, *Pain*,  
May 2003

Observation of contrast  
injection into radicular  
artery

Proposed mechanism for  
spinal cord injury



# Cervical ESI Complications

Rozin, *Am J Forensic  
Med Pathol*, Dec 2003

44 y/o C7 transforaminal

25 g spinal needle

Massive cerebral edema

Death due to dissection  
of the left vertebral artery  
with subsequent  
thrombosis



# Cervical ESI Complications

Weiskopf, Rathmell, Aprill, and Bogduk  
*Anesthesiology*, June 2004

Clinical Concepts and Commentary

Cervical Transforaminal Injection of Steroids

- 1 published report of spinal cord infarct
- 3 Australia, 1 European, 11 United States unpublished
- Spinal cord and brainstem infarct
- Few radiographic records
- Conjecture: radicular artery penetrated



# Cervical ESI Complications

Karasek and Bogduk,  
*Pain Med*, June 2004

- C7 Transforaminal
- Injection of test dose local anesthetic
- Transient quadriplegia
- Likely injection into cervical radicular artery



# ESI Complications

Tiso, *Spine Journal*, July 2004

Adverse central nervous system sequelae after selective transforaminal block: the role of corticosteroids

Quadraparesis, massive brainstem infarct

Corticosteroid preparation occluding metarterioles and arterioles



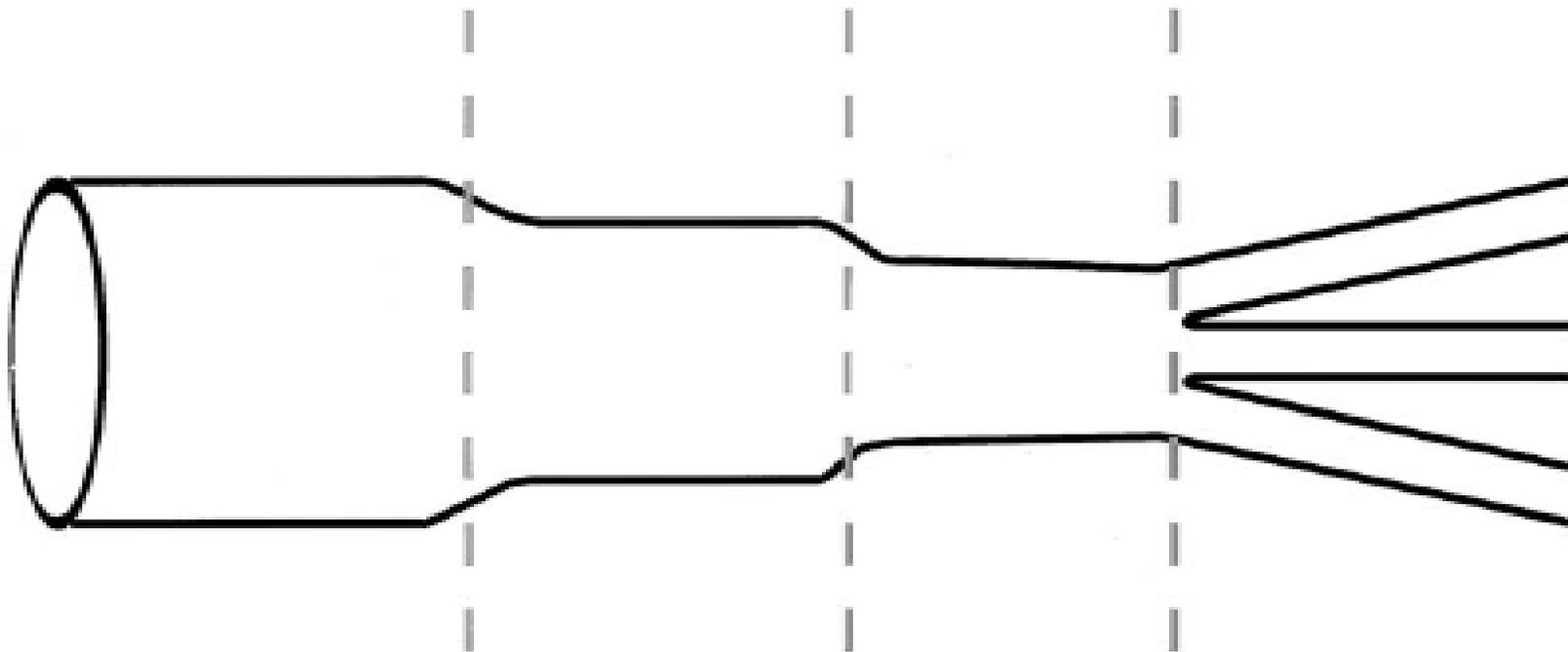
# Corticosteroid and Particulate

*Tiso et al, Spine Journal, July 2004*

<b>BSP-BA (Celestone)</b>	<b>TA (Kenalog)</b>	<b>MPA (Depo-Medrol)</b>	<b>DSP (Decadron)</b>
<b>Rodlike</b>	<b>Amorphous, Clumping</b>	<b>Amorphous, Clumping</b>	<b>Rodlike</b>
<b>Lucent</b>	<b>Opaque</b>	<b>Opaque</b>	<b>Lucent</b>
<b>&gt;50 um 1.14%</b>	<b>&gt;50 um 3.7% Aggregates &gt;100 um</b>	<b>&gt;50 um 8.57% Aggregates &gt;100um</b>	<b>20-50 um 66% &gt;50 um 3.7%</b>



# Vascular Anatomy



ARTERY

>50 $\mu$ m.

METARTERIOLE

20-50 $\mu$ m.

ARTERIOLE

10-15 $\mu$ m.

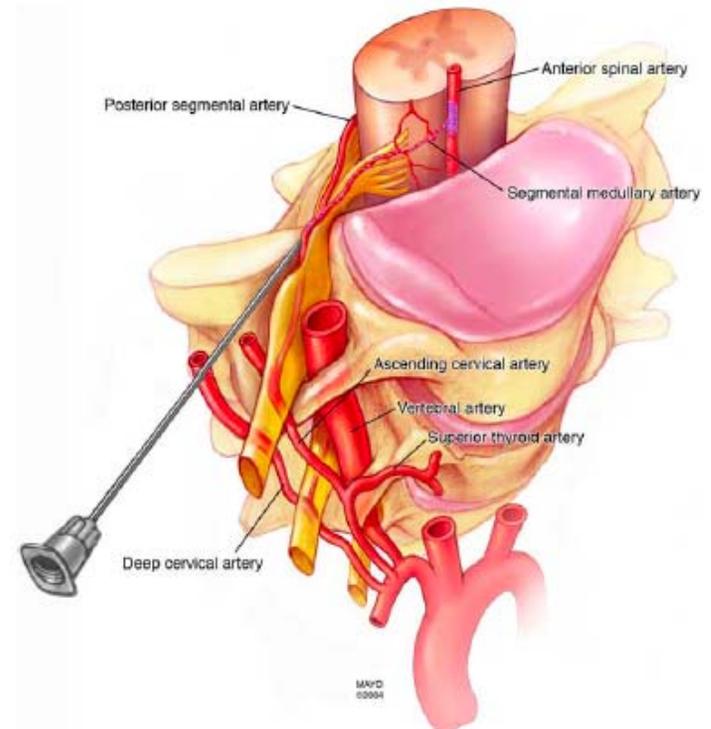
CAPILLARY

5-8 $\mu$ m.



# Risk

- ▶ Proposed MOA
  - Occlusion from Particulate (imaging)
  - Chemical Injury (animal model)
  - Vasospasm?
  - Arterial Dissection?
- ▶ <1:10,000
- ▶ Concerned Practitioner contacted FDA
  - Neural Injury



# FDA Safe Use Initiative

- ▶ Launched in 2009
- ▶ Mission: minimizing the risks associated with non-optimal use of FDA approved medications.
- ▶ Goal: reduce preventable harm by identifying specific, preventable medication risks
- ▶ Developing, implementing and evaluating cross-sector interventions with partners who are committed to safe medication use.
- ▶ *Safe Use Initiative's* efforts are of non-regulatory nature; but can align with, complement and/or reinforce FDA's regulatory efforts.



# A Consensus Statement

United States Food and Drug Administration Safe Use Initiative

- ▶ **Physicians : Workgroup**
  - Experts
  - Published Literature
- ▶ **Professional medical societies: Comments related to Agreement/Disagreement**



U.S. Department of Health and Human Services

**Food and Drug Administration**



# Contaminated Steroids

- ▶ Summer of 2012
- ▶ Multiple cases of fungal meningitis linked to ESI; primarily TN, MI
- ▶ Contaminated steroid from compounding pharmacy



CDC

# Step 1

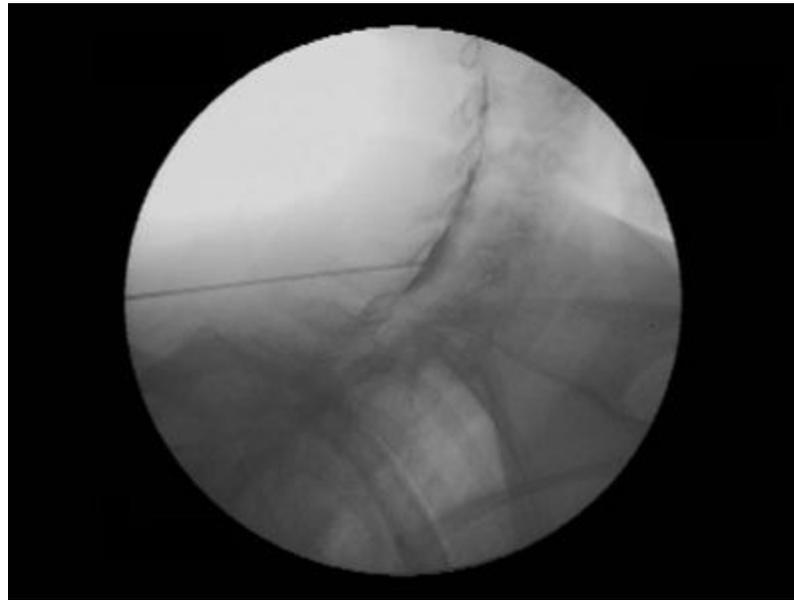
- ▶ Expert Panel



# Core areas of consensus

- ▶ There is an increased chance of neurologic injury with transforaminal epidural approach compared to the interlaminar approach (1–8).

Main Premise



# Core areas of consensus

- ▶ There is an increased chance of neurologic injury when particulate steroids are used for transforaminal injections (6–9).



CDC

# Core areas of consensus

- ▶ Use of image-guidance is mandatory when performing transforaminal injections.



# Core areas of consensus

- ▶ The unique risks specifically associated with interlaminar and transforaminal injections warrant separate recommendations for each technique.
- ▶ The unique risks associated with conducting the same techniques at different anatomic levels of the spine warrant separate recommendations.



# Work Group Concensus

- ▶ **All Interlaminar injections**
  - Particulate steroids may be used



# Work Group Consensus

## ▶ Cervical interlaminar injections

- There is significant risk of direct spinal cord injury during needle placement (10).
- Fluoroscopy including lateral view and use of radiographic contrast medium is mandatory.
- Entry at the C7–T1 or C6–C7 vertebral level is recommended (11).
- The interlaminar approach above C6 is not recommended.



# Work Group Consensus

- ▶ **Cervical transforaminal injections**
  - Use of image guidance and radiographic contrast injected with live fluoroscopy or digital subtraction angiography is mandatory.
- ▶ **Lumbar transforaminal injections**
  - Use of image guidance and radiographic contrast injected with live fluoroscopy or digital subtraction angiography is mandatory.



# Work Group Consensus Lacking

- ▶ An interlaminar approach should be utilized in preference to a transforaminal approach in most circumstances (a transforaminal approach may be preferred in patients who had spinal fusion).
- ▶ For lumbar transforaminal injections, non-particulate steroids should be used before particulate steroid (if clinical improvement does not ensue after a first injection, a second injection using particulate steroid may be considered) (12).



# Work Group Consensus Lacking

- ▶ For cervical transforaminal injections, only non-particulate steroids should be used (13, 14).
- ▶ Should digital subtraction be mandatory for all transforaminal injections?



# Step 2: Multi-Society Input

- ▶ AANS/CNS
- ▶ AAPM
- ▶ AAPMR
- ▶ ACR
- ▶ APS
- ▶ ASA
- ▶ ASNR
- ▶ ASRA
- ▶ ASSR
- ▶ ISIS
- ▶ NANS
- ▶ NASS
- ▶ SIR



# Current Working Statement

1. Cervical interlaminar (IL) ESIs are associated with a rare risk of catastrophic neurologic injury.
2. Transforaminal (TF) ESI using particulate steroid is associated with a rare risk of catastrophic neurovascular complications.
3. All cervical interlaminar (IL) epidural steroid injections should be performed using image-guidance, with appropriate AP, lateral or contralateral oblique views, and a test-dose of contrast medium.



4. Cervical transforaminal ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient. (1 NO)

5. Cervical interlaminar epidural steroid injections are recommended to be performed at C7-T1, but preferably not higher than the C6-C7 level.

6. No cervical interlaminar epidural steroid injection should be undertaken, at any segmental level, without reviewing, before the procedure, prior imaging studies that show there is adequate epidural space for needle placement at the target level.



7. Particulate steroids should not be used in cervical TF injections.

8. All lumbar IL ESIs should be performed using image-guidance, with appropriate AP, lateral or contralateral oblique views, and a test-dose of contrast medium.

9. Lumbar TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient. (1 NO)

10. A non-particulate steroid (e.g. dexamethasone) should be used for the initial injection in lumbar transforaminal epidural injections. (2 URC)



11. There are situations where particulate steroids could be used in the performance of lumbar TF ESIs.

12. Extension tubing is recommended for all TF ESIs.

13. A face mask and sterile gloves must be worn during the procedure.

14. The ultimate choice of what approach or technique (IL vs. TF ESI) to use should be made by the treating physician by balancing potential risks vs. benefits with each technique for each given patient



15. Cervical and lumbar IL-ESIs can be performed without contrast in patients with documented contra-indication to use of contrast (e.g. significant history of contrast allergy or anaphylactic reaction) (2 URC)

16. TF ESIs can be performed without contrast in patients with documented contra-indication to use of but in these circumstances, particulate steroids are contra-indicated and only preservative free, particulate free steroids should be used.

17. Moderate to heavy sedation is not recommended for epidural steroid injections, but if light sedation is employed, the patient should remain able to communicate pain or other adverse sensations or events.



# Does steroid choice matter?

- ▶ The Noninferiority of the Nonparticulate Steroid Dexamethasone vs the Particulate Steroids Betamethasone and Triamcinolone in Lumbar Transforaminal Epidural Steroid Injections
- ▶ Christine El-Yahchouchi MD<sup>1</sup> et al
- ▶ Pain Medicine Volume 14, Issue 11, pages 1650–1657, November 2013



- ▶ **Objective**

To assess whether a nonparticulate steroid (dexamethasone, 10 mg) is less clinically effective than the particulate steroids (triamcinolone, 80 mg; betamethasone, 12 mg) in lumbar transforaminal epidural steroid injections (TFESIs) in subjects with radicular pain with or without radiculopathy.

- ▶ **Design**

Retrospective observational study with noninferiority analysis of dexamethasone relative to particulate steroids.

- ▶ **Setting**

Single academic radiology pain management practice.

- ▶ **Subjects**

Three thousand six hundred forty-five lumbar TFESIs at the L4–5, L5–S1, or S1 neural foramina, performed on 2,634 subjects.



- ▶ **Methods/Outcome Measures**

Subjects were assessed with a pain numerical rating scale (NRS, 0–10) and Roland–Morris disability questionnaire (R–M) prior to TFESI, and at 2 weeks and 2 months follow-up. For categorical outcomes, successful pain relief was defined as either  $\geq 50\%$  reduction in NRS or pain 0/10; functional success was defined as  $\geq 40\%$  reduction in R–M score. Noninferiority analysis was performed with  $\delta = -10\%$  as the limit of noninferiority. Continuous outcomes (mean NRS, R–M scores) were analyzed for noninferiority with difference bounds of 0.3 for NRS scores and 1.0 for R–M scores.

- ▶ **Results**

With categorical outcomes, dexamethasone was demonstrated to be noninferior to the particulate steroids in pain relief and functional improvement at 2 months. Using continuous outcomes, dexamethasone was demonstrated to be superior to the particulate steroids in both pain relief and functional improvement at 2 months.

- ▶ **Conclusion**

This retrospective observational study reveals no evidence that dexamethasone is less effective than particulate steroids in lumbar TFESIs performed for radicular pain with or without radiculopathy.



# Does steroid choice matter?

- ▶ Comparative Effectiveness of Lumbar Transforaminal Epidural Steroid Injections with Particulate vs. Nonparticulate Corticosteroids for Lumbar Radicular Pain due to Intervertebral Disc herniation: A Prospective, Randomized, Double-Blind Trial.
- ▶ Kennedy DJ, et al.
- ▶ Pain Medicine, 2014; 15: 548–555



- ▶ **Objective**

This study aims to determine if there was a major difference in effectiveness between particulate and nonparticulate corticosteroids for acute radicular pain due to lumbar disc herniation.

- ▶ **Design**

A multicenter, double blind, prospective, randomized trial on 78 consecutive subjects with acute uni-level disc herniation resulting in unilateral radicular pain. All subjects received a single level transforaminal epidural steroid injection with either dexamethasone or triamcinolone. Repeat injections were allowed as determined by the blinded physician and subjects. Primary outcomes included: number of injections received, surgical rates, and categorical pain scores at 2 weeks, 3 months, and 6 months. Secondary outcomes included mean Oswestry Disability Index.



## ▶ Results

Both triamcinolone and dexamethasone resulted in statically significant improvements in pain and function at 2 weeks, 3 months, and 6 months, without clear differences between groups. The surgical rates were comparable with 14.6% of the dexamethasone group and 18.9% of the triamcinolone group receiving surgery. There was a statistically significant difference in the number of injections received, with 17.1% of the dexamethasone group receiving three injections vs only 2.7% of the triamcinolone group.

## ▶ Conclusions

Transforaminal epidural corticosteroid injections are an effective treatment for acute radicular pain due to disc herniation, and frequently only require 1 or 2 injections for symptomatic relief. Dexamethasone appears to possess reasonably similar effectiveness when compared with triamcinolone. However, the dexamethasone group received slightly more injections than the triamcinolone group to achieve the same outcomes.



# A Randomized Trial of Epidural Glucocorticoid Injections for Spinal Stenosis

Janna L. Friedly, M.D. et al

N Engl J Med 2014; 371:11–21, July 3, 2014.

## ▶ METHODS

In a double-blind, multisite trial, 400 patients who had lumbar central spinal stenosis and moderate-to-severe leg pain and disability to receive epidural injections of glucocorticoids plus lidocaine or lidocaine alone. The patients received one or two injections before the primary outcome evaluation, performed 6 weeks after randomization and the first injection. The primary outcomes were the score on the Roland-Morris Disability Questionnaire (RMDQ, in which scores range from 0 to 24, with higher scores indicating greater physical disability) and the rating of the intensity of leg pain (on a scale from 0 to 10, with 0 indicating no pain and 10 indicating “pain as bad as you can imagine”).

## ▶ RESULTS

At 6 weeks, there were no significant between-group differences in the RMDQ score (adjusted difference in the average treatment effect between the glucocorticoid-lidocaine group and the lidocaine-alone group, –1.0 points; 95% confidence interval [CI], –2.1 to 0.1;  $P=0.07$ ) or the intensity of leg pain (adjusted difference in the average treatment effect, –0.2 points; 95% CI, –0.8 to 0.4;  $P=0.48$ ). A prespecified secondary subgroup analysis with stratification according to type of injection (interlaminar vs. transforaminal) likewise showed no significant differences at 6 weeks.

## ▶ CONCLUSIONS

In the treatment of lumbar spinal stenosis, epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone.



# Where are we Oct 8, 2014

- ▶ Basic premise: there are risks with ESI
- ▶ Likely increased risk with certain injections using particulate steroid
- ▶ Risk of SCI with Cervical IL ESI noted
- ▶ Imaging Guidance: increasing likelihood of recommendation
- ▶ Efficacy comments (IL vs. TF) were not felt to be part of MPW role
- ▶ Using non-particulate is still unclear, but gaining evidence



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# Thank You

