

Laboratory Evaluation

Determination of the Particulate Size and Aggregation of Clonidine and Corticosteroids for Epidural Steroid Injection

Halena M. Gazelka, MD¹, Abram H. Burgher, MD², Marc A. Huntoon, MD³,
Carlos B. Mantilla, MD¹, and Bryan C. Hoelzer, MD¹

From: ¹Mayo Clinic, Rochester, MN; ²The Pain Center of Arizona; and ³Vanderbilt University, Nashville, TN.

Dr. Gazelka is with the Department of Anesthesiology, Division of Pain Medicine, Mayo Clinic, Rochester, MN. Dr. Burgher is with The Pain Center of Arizona, Phoenix, AZ. Dr. Huntoon is Chair of the Division of Pain Medicine, Vanderbilt University. Dr. Mantilla is with the Department of Anesthesiology, Division of Pain Medicine, Mayo Clinic, Rochester, MN. Dr. Hoelzer is with the Department of Anesthesiology, Division of Pain Medicine, Mayo Clinic, Rochester, MN.

Address correspondence:
Halena M. Gazelka, MD
200 First Street SW
Rochester, MN 55905
Email: gazelka.halena@mayo.edu

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: None.

Manuscript received: 08/23/2011

Revised manuscript received:
10/14/2011

Accepted for publication:
10/18/2011

Free full manuscript:
www.painphysicianjournal.com

Background: Epidural injection of corticosteroids is a commonly used treatment for radicular pain. However, the benefits are often short lived, and repeated injections are often limited secondary to concerns of side effects from cumulative steroid doses. In addition, rare, catastrophic complications, including brain and spinal cord embolic infarcts have been attributed to particulate steroid injections. A previous study has shown that dexamethasone has less particulate than other corticosteroids, possibly reducing embolic risk. Furthermore, a recent study indicated that clonidine may be useful in the treatment of radicular pain when administered via epidural steroid injection. The combination of corticosteroid and clonidine is an intriguing, yet unstudied, alternative to traditional treatment.

Objective: Our study examines whether mixing clonidine and various corticosteroids results in increased particle size or aggregation.

Methods: Evaluations under light microscopy for particle size were made of samples of clonidine alone and clonidine mixed with equal parts of 3 corticosteroids solutions: dexamethasone sodium phosphate injection, triamcinolone acetonide injectable suspension, and betamethasone sodium phosphate and betamethasone acetate injectable suspension. Four mL each of clonidine (100 µcg/mL), clonidine (100 µcg/mL) + dexamethasone sodium phosphate injection (4 mg/mL), clonidine (100 µcg/mL) + triamcinolone acetonide injectable suspension (40 mg/mL), and clonidine (100 µcg/mL) + betamethasone sodium phosphate and betamethasone acetate injectable suspension (6 mg/mL) were examined. Their particle sizes were compared to measurements taken when each steroid solution was examined alone.

Results: Clonidine was determined to be nonparticulate when examined by light microscopy. Clonidine mixed with equal parts of each of the 3 corticosteroids mentioned above did not result in increased clumping or increased particle size over each of the corticosteroids measured alone.

Conclusion: Mixing clonidine with corticosteroids did not increase particulation compared to corticosteroids alone. Combining clonidine and corticosteroids for epidural injection may prove to be a useful treatment for radicular pain. The combination of these is unlikely to result in a solution that is more likely to cause embolic infarcts than the use of corticosteroids alone.

Key words: steroid, epidural, clonidine, injection, particulate, aggregation

Pain Physician 2012; 15:87-93

Injection of epidural steroids is a widely practiced intervention for the treatment of back pain with radicular symptoms (1). Indeed, epidural steroid injections are the most commonly performed intervention used in the United States to manage

chronic and subacute low back pain (2-8). There is sufficient evidence regarding the short-term efficacy of epidural steroid injections but few trials have evaluated long-term outcomes (3-7). Further, the well known complications of cumulative steroid dosing

limit the frequency of administering epidural steroids (9). Epidurally administered steroids are known to cross into the systemic circulation and affect nearly every major organ system in the body (10).

Obviously, the risks of epidural steroid injections are not limited to complications from systemic absorption of the steroid. Entry to the epidural space can be achieved via interlaminar, transforaminal, or caudal approaches. The route with which epidural steroids are delivered often depends on the anatomy of the patient and the experience of the clinician providing care. Studies have shown that fluoroscopically directed epidural injections with or without steroids may offer greater efficacy (11-23). However, transforaminal epidural injections are considered more effective than caudal and interlaminar but are associated with an increased risk of ischemic neurologic injury (24-29). Multiple mechanisms of injury have been hypothesized. Cortisone-induced vasospasm of the vascular endothelium may be one mechanism (29,30). Another possibility is that particles in the steroid itself may embolize, jeopardizing blood flow to the anterior spinal artery, resulting in spinal cord injury (29,31). While the risks of transforaminal injection in the cervical cord may seem more obvious (32-38), there are reports of significant neurological injury and paraplegia after lumbar transforaminal injection as well (39-46).

With embolization and possible obstruction of the anterior spinal artery as a potential mechanism for the serious complications that have been reported after transforaminal epidural steroid injection, an obvious response may be to search for injectable anti-inflammatories that are less particulate. A study by Derby et al (47) delineated the size and potential to aggregate of various steroid preparations that are most commonly used in the United States for epidural injection. The study compared preparations of dexamethasone, triamcinolone, betamethasone, and methylprednisolone microscopically, examining each for particulate matter and tendency to form aggregates. Next, particles and aggregates were compared to red blood cell size. Presumably, if smaller than red blood cells, the particles and/or aggregates should pass more easily through small vessels. They found that dexamethasone contained particles 10 times smaller than red blood cells and without obvious potential to aggregate, while both triamcinolone and betamethasone contained particles that tended to aggregate, with many aggregates larger in size than red blood cells.

The risks and limits of corticosteroids have contributed to a continued search for novel epidural therapy.

A recent study by Burgher et al (48) indicates that clonidine may be useful in the treatment of radicular pain when administered epidurally. Clonidine, an alpha 2 agonist, is both an analgesic and an anti-inflammatory. Alpha-2 receptors, where clonidine exerts its effect, are located in the central nervous system, as well as on peripheral nerves. There is evidence that the analgesic effects of clonidine are exerted at the level of the spinal cord, but other potential mechanisms exist, including the blockade of C and A-delta fibers, increasing potassium conductance, and augmenting local anesthetic blockade. Multiple studies support the safety and efficacy of clonidine for epidural use (49). Furthermore, clonidine is not anticipated to be associated with cumulative dose toxicity. The study by Burgher et al (48) randomized patients receiving transforaminal epidural steroid injections to either lidocaine + clonidine injections or lidocaine + triamcinolone injections. No differences were noted between the 2 groups on measurements of pain intensity rating at one month. Functional measures revealed additional improvement in the triamcinolone group at one month (48). The use of clonidine for epidural injection, either alone or as an adjunct to corticosteroid, has potential for patient benefit both from the standpoint of improving pain control and perhaps allowing for decreased dosing and/or the frequency of steroid injections. Both of these would have obvious advantages for patient care.

Given the positive results of Burgher et al's study (48), future studies may focus on the efficacy of combining corticosteroids and clonidine. Prior to undertaking such a study it is important to know if the addition of clonidine has any effect on corticosteroid particle size and/or aggregation. We hypothesized that mixing clonidine at a standard concentration with various commonly used preparations of 3 corticosteroids would not result in increased particle size or aggregation over that seen when corticosteroids are examined alone.

METHODS

Three common steroid preparations were utilized in this study: Celestone Soluspan (Schering, Kenilworth, NJ), a trade name of betamethasone; Kenalog-40 (Bristol-Meyers Squibb Company, Princeton, NJ) a trade name of triamcinolone; and Dexamethasone Sodium Phosphate (American Regent, Inc, Shirley, NY). One formulation of clonidine, Duraclon (Xanodyne Pharmaceuticals, Inc, Newport, KY), was utilized for the study. Each of the above agents was examined alone, along with each of the steroids with equal parts clonidine.

The preparations studied were: Dexamethasone Sodium Phosphate, 4 mg/mL; Celestone Soluspan, 6 mg/mL; and Kenalog-40, 40 mg/mL. Clonidine 0.1 mg/mL was also examined. Initially, one mL of each steroid preparation was examined alone. Then, clonidine one mL was examined alone. Further, each steroid solution was mixed 1:1 with clonidine (one mL steroid with 1 mL clonidine) and examined.

After mixing, each of the steroid solutions and mixtures was distributed on a glass slide in an area of approximately one cm in diameter. Each slide was examined by light microscopy at a magnification of 200X in 4 areas. Initial sites for examination were selected by random number generator. Photographs were taken in each of the 4 areas selected, and particle sizes were measured.

RESULTS

The various steroid preparations exhibited different properties in terms of particle size, shape, and the prevalence and size of aggregates. For comparison, the

size of red blood cells has previously been determined as 7.5 – 7.8 μm in diameter, providing a reference for the size of our particles and aggregates (48).

Dexamethasone

At 200X magnification, the dexamethasone 4 mg/mL solution had no measurable particles, and there was no apparent aggregation in the solution. The clonidine and dexamethasone solution also had no measurable particles or evidence of aggregation.

Triamcinolone

The triamcinolone 40 mg/mL solution contained particles measuring 2.3 μm to 200 μm . The particles were densely packed with extensive aggregation observed. These measurements were similar to those reported by Derby et al (47). The clonidine:triamcinolone mixture resulted in particles measuring 3.1 – 82 μm , with many clumps and aggregates noted (Fig. 1). There was no increased size or aggregation noted when clonidine was added to triamcinolone 40mg/mL. (Fig. 1.)

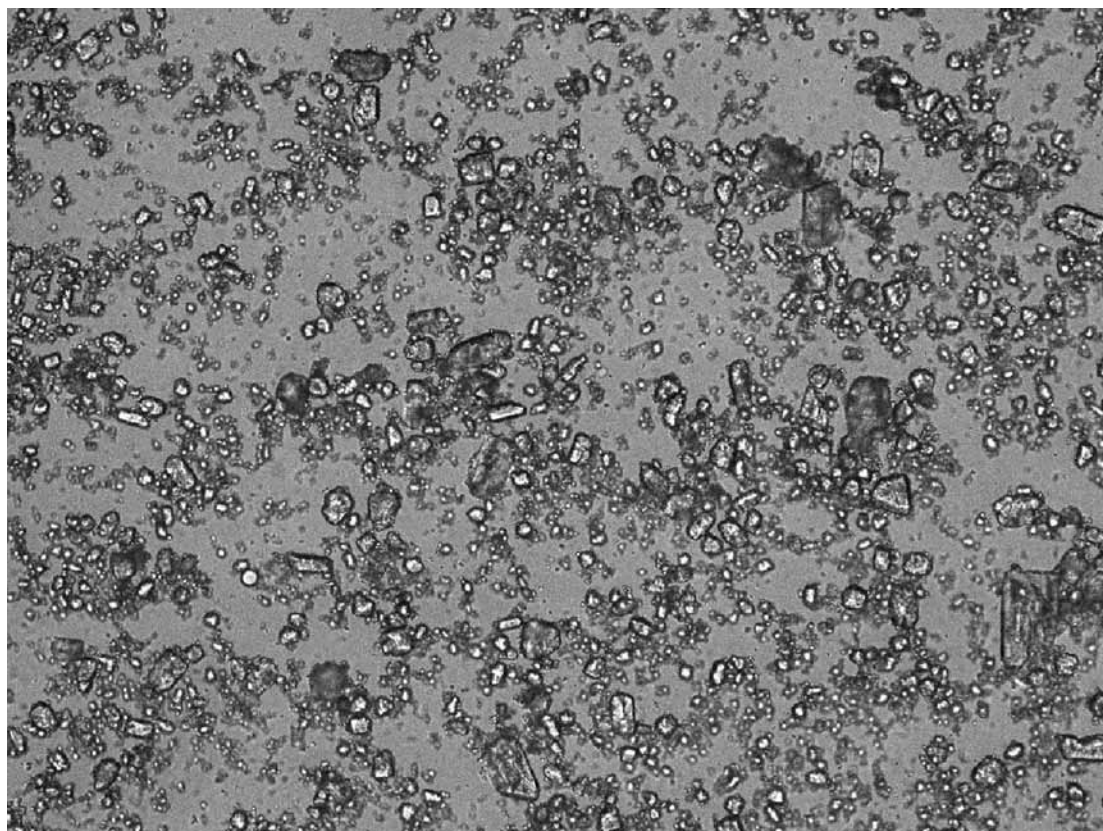


Fig. 1. *Microscopic findings of triamcinolone 40 mg/mL mixed with clonidine 100 $\mu\text{g/mL}$.*

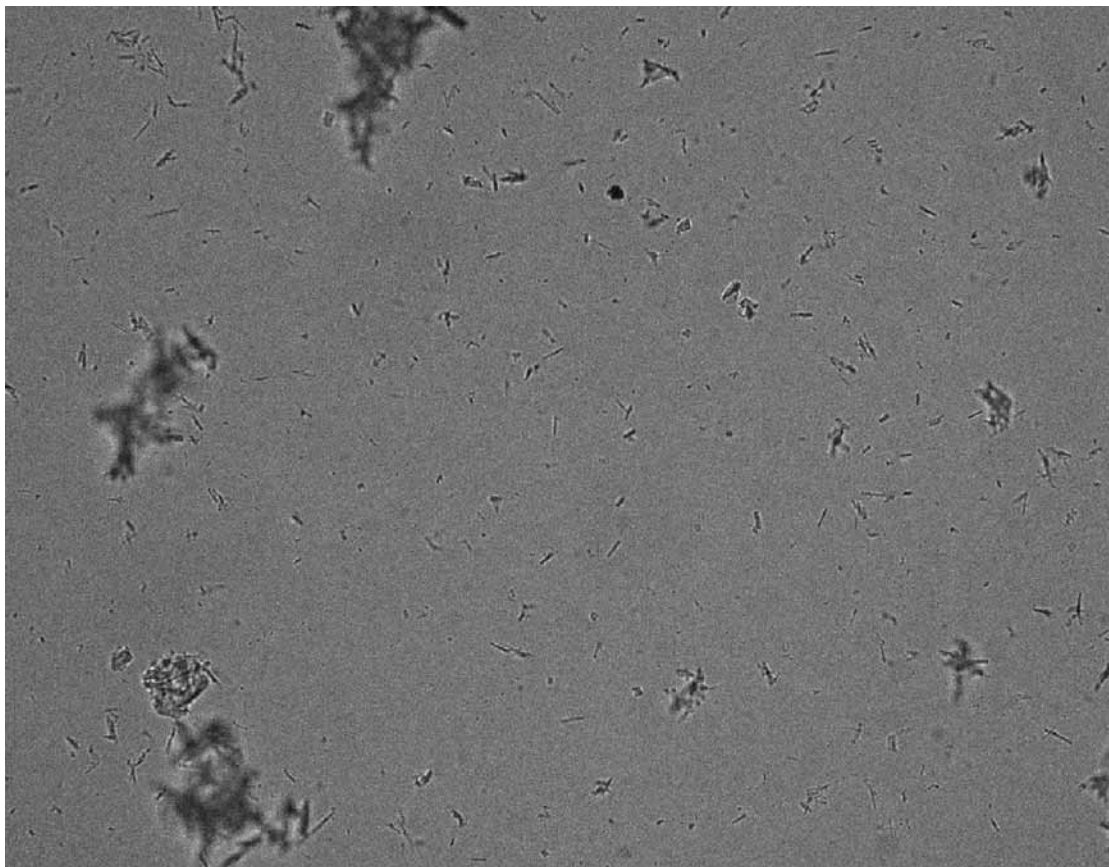


Fig. 2. Microscopic finding of betamethasone 6 mg/mL mixed with clonidine 100 µg/mL.

Betamethasone

The betamethasone 6mg/mL solution contained long, rod-shaped particles of varying sizes. The particles formed extensive aggregates. These measured from 1.5 to 77 µm, but most were much smaller than the maximum measurement. These measurements were similar to those reported by Derby et al (47). Mixed with clonidine, the betamethasone solution resulted in more long particles with aggregates from 2.2 to 54.6 µm (Fig. 2). There was no increased size or aggregation noted when clonidine was added to betamethasone 6 mg/mL (Fig. 2).

Clonidine

Clonidine (100 µg/mL) alone resulted in no measurable particles and thus, no aggregates.

DISCUSSION

This study examined whether clonidine, when used alone or added to steroid preparations commonly utilized for epidural steroid injection, resulted in increased particles or aggregation over what is seen with the steroids themselves. We found that not only were there no particles in clonidine alone, this medication also did not contribute to increase in particulate size or aggregation when mixed with steroid.

Derby et al (47) have shown that some of the steroid preparations commonly used for epidural injections contain particles and aggregates that, when compared in size to red blood cells, could be sizable enough to occlude small vessels of the microcirculation. Dexamethasone contained no appreciable par-

ticles or aggregations. However, both triamcinolone and betamethasone alone contained large particles and aggregates. Interestingly, no adverse neurologic events have been reported when nonparticulate steroids have been used. This lends evidence to the theory that the neurologic compromise seen after transforaminal steroid injections is secondary to particle embolization (47). Furthermore, a recent study has shown no difference in efficacy when comparing particulate to nonparticulate corticosteroids in treating cervical radiculopathy (50) which raises the question of whether or not particulate steroids should ever be used in neuroaxial injections.

Clonidine may be a useful adjunct or single agent treatment in epidural injections for multiple reasons. Analgesia is mediated by its action at alpha 2 receptors in the central nervous system. Clonidine may also possess significant anti-inflammatory activity that would also decrease pain (51). Further, clonidine is known to be a safe to administer epidurally (49). A recent study by Burgher et al (48) reveals that clonidine may result in pain relief that is comparable, when administered in the epidural space, to steroid. Further studies are needed to determine if the combination of clonidine with corticosteroids offers any clinical advantage to either medication injected alone.

The risks associated with inadvertent injection of particulate steroids into the arteries supplying the central nervous system, particularly with transforaminal injections, have come under discussion in recent years. Multiple case reports have surfaced citing significant morbidity following these injections when particulates were utilized (37,39).

Clearly, safe adjunctive medications that decrease

steroid utilization while maintaining efficacy may find a role in epidural steroid injection.

The present study was limited to observing various dissolved corticosteroid preparations with clonidine in vitro under a microscope. Making the observations in vivo in blood would be difficult, given that the visual density of blood would make observation and photography of particles and aggregates of steroids virtually impossible. However, since clonidine alone and with the steroids did not result in any increase in particulate matter, and since clonidine is soluble in water, it is logical to conclude that the addition of clonidine to epidural steroid injectate would not result in any increase in risk for arterial or capillary obstruction over the use of the individual steroids alone.

CONCLUSION

Derby et al (47) have shown that commonly used steroid preparations vary greatly in particulate size and tendency to aggregate. Dexamethasone does not tend to form particles or to clump. Both triamcinolone and betamethasone contain particles and form extensive aggregates which tend to be much larger than red blood cells. Thus, it is logical to deduce that epidural steroid injections containing dexamethasone may be less likely to cause arterial or capillary obstruction. Furthermore, a recent study by Burgher et al (48) indicates that clonidine may be useful in the treatment of radicular pain when administered via epidural steroid injection. The combination of steroid and clonidine may be a logical next step in the evolution of epidural steroid therapy. In this study, clonidine was noted not to increase particulate matter or aggregation when combined with dexamethasone, triamcinolone, or betamethasone.

REFERENCES

1. Practice Guidelines for Chronic Pain Management: An updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology* 2010; 112:810-833.
2. Gharibo C, Koo C, Chung J, Moroz A. Epidural steroid injections: An update on mechanisms of injury and safety. *Tech Reg Anesth Pain Mgmt* 2009; 13:266-271.
3. Manchikanti L, Pampati V, Boswell MV, Smith HS, Hirsch JA. Analysis of the growth of epidural injections and costs in the Medicare population: A comparative evaluation of 1997, 2002, and 2006 data. *Pain Physician* 2010; 13:199-212.
4. Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976)* 2009; 34:1078-1093.
5. Manchikanti L, Datta S, Derby R, Wolfer LR, Benyamin RM, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part 1. Diagnostic interventions. *Pain Physician* 2010; 13:E141-E174.
6. Manchikanti L, Datta S, Gupta S, Munglani R, Bryce DA, Ward SP, Benyamin RM, Sharma ML, Helm II S, Fellows B, Hirsch JA. A critical review of the American Pain Society clinical practice guidelines for interventional techniques: Part

2. Therapeutic interventions. *Pain Physician* 2010; 13:E215-E264.
7. Staal JB, de Bie RA, de Vet HC, Hildebrandt J, Nelemans P. Injection therapy for subacute and chronic low back pain: An updated Cochrane review. *Spine (Phila Pa 1976)* 2009; 34:49-59.
 8. Friedly J, Chan L, Deyo R. Increases in lumbosacral injections in the Medicare population: 1994 to 2001. *Spine (Phila Pa 1976)* 2007; 32:1754-1760.
 9. Baqai A, Bal R. The mechanism of action and side effects of epidural steroids. *Tech Reg Anesth Pain Mgmt* 2009; 13:205-211.
 10. Lansang MC, Farmer T, Kennedy L. Diagnosing the unrecognized systemic absorption of intra-articular and epidural steroid injections. *Endocr Pract* 2009; 15:225-228.
 11. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 3. Post surgery syndrome. *Pain Physician* 2008; 11:817-831.
 12. Manchikanti L, Cash KA, McManus CD, Pampati V, Smith HS. One year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections with or without steroids in managing chronic discogenic low back pain without disc herniation or radiculitis. *Pain Physician* 2011; 14:25-36.
 13. Manchikanti L, Cash KA, McManus CD, Pampati V, Abdi S. Preliminary results of randomized, equivalence trial of fluoroscopic caudal epidural injections in managing chronic low back pain: Part 4. Spinal stenosis. *Pain Physician* 2008; 11:833-848.
 14. Manchikanti L, Singh V, Cash KA, Pampati V, Damron KS, Boswell MV. A randomized, controlled, double-blind trial of fluoroscopic caudal epidural injections in the treatment of lumbar disc herniation and radiculitis. *Spine (Phila Pa 1976)* 2011; 36:1897-1905.
 15. Dashfield AK, Taylor MB, Cleaver JS, Farrow D. Comparison of caudal steroid epidural with targeted steroid placement during spinal endoscopy for chronic sciatica: A prospective, randomized, double-blind trial. *Br J Anaesth* 2005; 94:514-559.
 16. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. Preliminary results of a randomized, double-blind, controlled trial of fluoroscopic lumbar interlaminar epidural injections in managing chronic lumbar discogenic pain without disc herniation or radiculitis. *Pain Physician* 2010; 13:E279-E292.
 17. Manchikanti L, Singh V, Falco FJE, Cash KA, Pampati V. Evaluation of the effectiveness of lumbar interlaminar epidural injections in managing chronic pain of lumbar disc herniation or radiculitis: A randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:343-355.
 18. NEw systematic review on lumbar interlam
 19. Lee JW, Shin HI, Park SY, Lee GY, Kang HS. Therapeutic trial of fluoroscopic interlaminar epidural steroid injection for axial low back pain: Effectiveness and outcome predictors. *AJNR Am J Neuroradiol* 2010; 31:1817-1823.
 20. Gharibo CG, Varlotta GP, Rhame EE, Liu ECJ, 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* 2011; 14:499-511.
 21. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A preliminary report of a randomized double-blind, active controlled trial of fluoroscopic thoracic interlaminar epidural injections in managing chronic thoracic pain. *Pain Physician* 2010; 13:E357-E369.
 22. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. *Anesth Analg* 2007; 104:1217-1222.
 23. Manchikanti L, Cash KA, Pampati V, Wargo BW, Malla Y. The effectiveness of fluoroscopic cervical interlaminar epidural injections in managing chronic cervical disc herniation and radiculitis: Preliminary results of a randomized, double-blind, controlled trial. *Pain Physician* 2010; 13:223-236.
 24. Buenaventura RM, Datta S, Abdi S, Smith HS. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. *Pain Physician* 2009; 12:233-251.
 25. Derby R. Cervical radicular pain: Transforaminal vs interlaminar steroid injections. *Spine* 2004; 6:16-21.
 26. Manchikanti L, Boswell MV, Singh V, Benyamin RM, Fellows B, Abdi S, Buenaventura RM, Conn A, Datta S, Derby R, Falco FJ, Erhart S, Diwan S, Hayek SM, Helm S, Parr AT, Schultz DM, Smith HS, Wolfer LR, Hirsch JA; ASIIPP-IPM. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. *Pain Physician* 2009; 12:699-802.
 27. Riew KD, Yin Y, Gilula L, Bridwell KH, Lenke LG, Laurusen C, Goette K. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg Am* 2000; 82:1589-1593.
 28. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. *Spine (Phila Pa 1976)* 2002; 27:11-16.
 29. Huntton MA. Anatomy of the cervical intervertebral foramina: Vulnerable arteries and ischemic neurologic injuries after transforaminal epidural injections. *Pain* 2005; 117:104-111.
 30. Rorie DK. Metabolism of norepinephrine in vitro by dog pulmonary arterial endothelium. *Am J Physiol* 1982; 243:H732-737.
 31. Tiso RL, Cutler T, Catania JA, Whalen K. Adverse central nervous system sequelae after selective transforaminal block: The role of corticosteroids. *Spine J* 2004; 4:468-474.
 32. Baker R, Dreyfuss P, Mercer S, Bogduk N. Cervical transforaminal injection of corticosteroids into a radicular artery: A possible mechanism for spinal cord injury. *Pain* 2003; 103:211-215.
 33. Brouwers PJ, Kottink EJ, Simon MA, Prevo RL. A cervical anterior spinal artery syndrome after diagnostic blockade of the right C6-nerve root. *Pain* 2001; 91:397-399.
 34. Karasek M, Bogduk N. Temporary neurologic deficit after cervical transforaminal injection of local anesthetic. *Pain Med* 2004; 5:202-205.
 35. Rosenkranz M, Grzycka U, Niesen W, Fuchs K, Schummer W, Weiller C, Röther J. Anterior spinal artery syndrome following periradicular cervical nerve root therapy. *J Neurol* 2004; 251:229-231.
 36. Rozin L, Rozin R, Koehler SA, Shakir A, Latham S, Barmada M, Dominick J, Wecht CH. Death during transforaminal epidural steroid nerve root block (C7) due to perforation of the left vertebral artery. *Am J Forensic Med Pathol* 2003; 24:351-355.
 37. Lee JH, Lee JK, Seo BR, Moon SJ, Kim JH, Kim SH. Spinal cord injury produced by direct damage during cervical transforaminal epidural injection. *Reg Anesth Pain Med* 2008; 33:377-379.

38. Malhotra G, Abbasi A, Rhee M. Complications of transforaminal cervical epidural steroid injections. *Spine (Phila Pa 1976)* 2009; 34:731-739.
39. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: Two case reports. *Pain Med* 2009; 10:1389-1394.
40. Lyders EM, Morris PP. A case of spinal cord infarction following lumbar transforaminal epidural steroid injection: MR imaging and angiographic findings. *AJNR Am J Neuroradiol* 2009; 30:1691-1693.
41. Huntoon MA, Martin DP. Paralysis after transforaminal epidural injection and previous spinal surgery. *Reg Anesth Pain Med* 2004; 29:494-495.
42. Glaser SE, Falco F. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. *Pain Physician* 2005; 8:309-314.
43. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: Report of three cases. *Spine J* 2002; 2:70-75.
44. Somayaji HS, Saifuddin A, Casey AT, Briggs TW. Spinal cord infarction following therapeutic computed tomography-guided left L2 nerve root injection. *Spine (Phila Pa 1976)* 2005; 30:E106-108.
45. Wybier M, Gaudart S, Petrover D, Houdart E, Laredo JD. Paraplegia complicating selective steroid injections of the lumbar spine. Report of five cases and review of the literature. *Eur Radiol* 2010; 20:181-189.
46. Wybier M. Transforaminal epidural corticosteroid injections and spinal cord infarction. *Joint Bone Spine* 2008; 75:523-525.
47. Derby R, Lee SH, Date ES, Lee JH, Lee CH. Size and aggregation of corticosteroids used for epidural injections. *Pain Med* 2008; 9:227-234.
48. Burgher AH, Hoelzer BC, Schroeder DR, Wilson GA, Huntoon MA. Transforaminal epidural clonidine versus corticosteroid for acute lumbosacral radiculopathy due to intervertebral disc herniation. *Spine (Phila Pa 1976)* 2011; 36:E293-300.
49. Eisenach JC, De Kock M, Klimscha W. Alpha(2)-adrenergic agonists for regional anesthesia. A clinical review of clonidine (1984-1995). *Anesthesiology* 1996; 85:655-674.
50. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. *Pain Med* 2006; 7:237-242.
51. Wu CT, Jao SW, Borel CO, Yeh CC, Li CY, Lu CH, Wong CS. The effect of epidural clonidine on perioperative cytokine response, postoperative pain, and bowel function in patients undergoing colorectal surgery. *Anesth Analg* 2004; 99:502-509, table of contents.

