UPDATE
Vanderbilt Pain Management Center

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Moving Forward: Epidurals After Fungal Meningitis Epidemic

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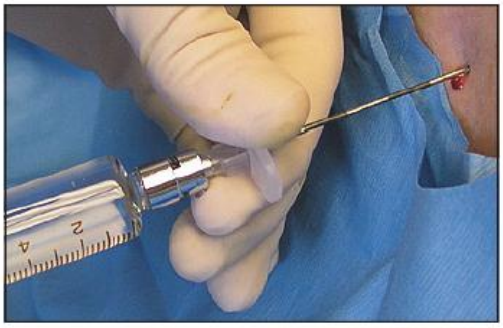
The latter part of 2012 was a dark time in the history of pain medicine. Tennessee was the state hardest hit by the fungal meningitis epidemic. Many patients were killed or injured after receiving epidural injections for spinal radicular pain, simply due to a tainted batch of corticosteroids from a now-disgraced and extinct pharmaceutical supplier.[1,2] Unfortunately, the procedure itself has subsequently been maligned by many, who have either incomplete or erroneous information.[3] Having spent my dinical and research efforts throughout a career focused on making pain interventional treatments safer and more efficacious, I feel it is important to clarify the risks and benefits of these injections.[4,5]



Are patients still at risk for fungal meningitis?

The best answer is yes, but the risk is extremely low, far less than 1/100,000. We know what the spontaneous rate for epidural abscess is (~8/100,000) from a population-based epidemiological study in Rochester, MN.[6] These cases were all MRI-confirmed bacterial, not fungal, organisms and occurred without obvious cause. Outside of the catastrophic type of pharmaceutical contamination seen last fall, the risk for fungal abscess is negligible. We know that the majority of bacterial epidural abscesses that occur after corticosteroid injections do not lead to meningitis, drawing from literature reviews of these complications.[7] In the medical literature, approximately half of the patients diagnosed with bacterial abscesses or meningitis after injections had some form of immune compromise, e.g., cancer, diabetes mellitus, collagen vascular disease. The best ways to mitigate these infectious risks are simple. First, epidural corticosteroid injections should not be performed in individuals who are actively infected. This might also include greater care than "usual" with patients who may be immunocompromised, e.g., hyperglycemic patients. Second, all potential safeguards should be used (proper hand washing; use of a chlorhexidine/alcohol skin prep instead of povidone/iodine; wearing a face mask; swabbing the top of "sterile" vials with alcohol prior to dispensing; sterile tray/gloves; and the use of pharmaceuticals approved by the FDA. [8,9,10] Note that all steroids used in the epidural space, despite greater than 50 years of practice, are used in an "off-label" manner, even if they are from a FDA-regulated pharmaceutical company. It is also very important that the interventionalist has extensive training and preferably board certification as well.

Are these injections efficacious?

Again, the best answer is yes, but to a point. Recent meta-analyses and extensive reviews support the efficacy of these procedures for short-term relief of symptoms of radicular pain, often due to disk protrusions/herniations and the result-

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ant inflammatory changes. [4,5,11,12] Epidural steroid injections have less efficacious/less clear effects for conditions such as post-spinal surgical pain, spinal stenosis, and simple low back pain. It is for these types of pain that confounding results dilute overall results. Thus patient selection is critical. It is far more important to refer patients early for conservative management and assessment, part of which might include an injection, than to start patients on opioids for indeterminate periods of time. The duration of relief from therapeutic epidurals tends to be from about 6-12 weeks in most of these large reviews. It is well recognized that the pathophysiology involves both mechanical factors and inflammation, with locally released inflammatory cytokines (interleukin 1, 6, 8 and tumor-necrosis factor-alpha) being important targets. The reason that corticosteroids work is that they reduce that inflammation better than many other agents.

Are there other things I need to worry about?

Yes. A small task force, organized through the FDA Safe Use Initiative, has been working for the last year to come up with guidelines for the safe performance of transforaminal epidural injections.[8] Our deliberations have focused on the use of particulate steroids (methylprednisolone, triamcinolone, betamethasone) in particular. Studies suggest that with well-localized pathology, e.g., a left L5 radiculopathy, that a transforaminal injection (injecting through the neural foramina instead of the posterior interlaminar epidural opening) is more efficacious. However, in a rare number of patients, particles have entered the blood supply to the spinal cord or brain stem, causing spinal cord infarcts, or brain stem strokes.[13] The likely action of our group will be to recommend to the FDA that these injections be performed at upper lumbar and all thoracic and cervical levels only with non-particulate corticosteroids, from which no cases of catastrophic injury have been noted in the world literature. It is important to realize that although this is a devastating complication, it is quite rare.

Are there alternatives on the horizon?

Actually, yes. Several groups are looking at the use of other drugs with anticytokine activity to target the inflammatory changes around the spinal nerve. Initial studies with etanercept, a disease modifying anti-rheumatic drug (DMARD), have been conducted. A human trial of transforaminal epidural injection of etanercept was positive for intermediate pain relief.[14] Other groups have looked at monoclonal antibodies to interleukin-6, with good results in comparison to dexamethasone.[15] Finally, the use of clonidine, an FDA-approved agent for cancer-related neuropathic pain via the epidural route, has recently been trialed in comparison to triamcinolone.[16] Although triamcinolone had slightly greater effects on function than clonidine, pain scores were similar in both groups. Duration of action may have been one potential drawback, as clonidine's anticytokine effects peak at three days via this route. This agent has been extensively safety tested and recently was formulated as a long-acting pellet to attempt to overcome the durability issue. It is likely that in the future, corticosteroids will still have some role in therapeutic epidural injections, but these other agents or similar ones may emerge as effective therapies as well. It is entirely plausible that concomitant administration of a "soup" of different active agents will become the new normal.

Conclusion

The fungal meningitis crisis points out the necessity of a secure and safe drug supply. Nevertheless, therapeutic epidurals remain a viable and effective treatment for patients with spinal radicular pain who have been well evaluated.

REFERENCES

1. Pettit AC, Kropski JA, Castilho JL, et al. The index case for the fungal meningitis outbreak in the United States. *N Engl J Med.* 2012;367:2119–2125.
2. Kainer MA, Reagan DR, Nguyen DB, et al. Fungal infections associated with contaminated methylprednisolone in Tennessee. *N Engl J Med.* 2012;367:2194–2203.
3. Outterson K. Regulating compounding pharmacies after NECC. *N Engl J Med.* 2012;367:1969–1972.
4. Huntoon MA, Gazelka HM. Complications associated with chronic steroid use. In: Neal JM, Rathmell JP, eds. *Complications in Regional Anesthesia and Pain Medicine.* 2nd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2013: 401–411.
5. Huntoon MA, Burgher AH. Therapeutic epidural injections: interlaminar and transforaminal. In: Huntoon MA, Benzon HT, Narouze S. Deer T, eds. *Spinal Injections and Peripheral Nerve Blocks: Interventional and Neuromodulatory Techniques for Pain Management, Volume 4.* Philadelphia, PA: Elsevier/Saunders; 2012: 121–128.
6. Praszynski AE, Hooten WM, Huntoon MA. The incidence of spontaneous epidural abscess in Olmsted County from 1990 through 2000: a rare cause of spinal pain. *Pain Med.* 2007;8:338–343.
7. Hooten WM, Kinney MO, Huntoon MA. Epidural abscess and meningitis after epidural corticosteroid injection. *Mayo Clin Proc.* 2004;79:682–686.
8. Pain-Topics.org. News/Research UPDATES. http://updates.pain-topics.org/2012/01/harms-of-epidural-steroid-injections.html. Accessed February 28, 2013.
9. Centers for Disease Control and Prevention. http://www.cdc.gov/HAI/settings/outpatient/basic-infection-control-prevention-plan-2011/standard-precautions-d-f.html. Accessed November 12, 2012.
10. Centers for Disease Control and Prevention. http://www.cdc.gov/injectionsafety/PDF/Clinical_Reminder_Spinal-Infection_Meningitis.pdf. Accessed November 12, 2012.
11. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. *Reg Anesth Pain Med.* 2013 (In Press).
12. Pinto RZ, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections in the management of sciatica: a systematic review and meta-analysis. *Ann Intern Med.* 2012;157: 865–877.
13. Huntoon MA. Anatomy of the cervical intervertebral foramina: vulnerable arteries and ischemic neurologic injuries after transforaminal epidural injections. *Pain.* 2005;117:104–111.
14. Cohen SP, Bogduk N, Dragovich, et al. A randomized, double-blind, placebo-controlled, dose-response, and preclinical safety study of transforaminal epidural etanercept for the treatment of sciatica. *Anesthesiology.* 2009;110:1116–1126.
15. Ohtori S, Miyagi M, Eguchi Y, Inoue G, Orita S, Ochiai N, Kishida S, Kuniyoshi K, Nakamura J, Aoki Y, Ishikawa T, Arai G, Kamoda H, Suzuki M, Takaso M, Furuya T, Kubota G, Sakuma Y, Oikawa T, Toyone T, Takahashi K. Efficacy of epidural administration of anti-interleukin-6 receptor antibody onto spinal nerve for treatment of sciatica. *Eur Spine J.* 2012;21:2079–2084.