Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections

Consensus Opinions from a Multidisciplinary Working Group and National Organizations

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ABSTRACT

Background: Epidural corticosteroid injections are a common treatment for radicular pain caused by intervertebral disc herniations, spinal stenosis, and other disorders. Although rare, catastrophic neurologic injuries, including stroke and spinal cord injury, have occurred with these injections.

Methods: A collaboration was undertaken between the U.S. Food and Drug Administration Safe Use Initiative, an expert multidisciplinary working group, and 13 specialty stakeholder societies. The goal of this collaboration was to review the existing evidence regarding neurologic complications associated with epidural corticosteroid injections and produce consensus procedural clinical considerations aimed at enhancing the safety of these injections. U.S. Food and Drug Administration Safe Use Initiative representatives helped convene and facilitate meetings without actively participating in the deliberations or decision-making process.

Results: Seventeen clinical considerations aimed at improving safety were produced by the stakeholder societies. Specific clinical considerations for performing transforaminal and interlaminar injections, including the use of nonparticulate steroid, anatomic considerations, and use of radiographic guidance are given along with the existing scientific evidence for each clinical consideration.

Conclusion: Adherence to specific recommended practices when performing epidural corticosteroid injections should lead to a reduction in the incidence of neurologic injuries. (Anesthesiology 2015; 122:974–84)

EPIDURAL injections of corticosteroids are widely used as a treatment for radicular pain caused by disc herniation and other conditions that affect spinal nerves. These injections are associated with a number of minor complications and side effects, such as exacerbation of pain, vasovagal reaction, headache, and unintentional dural puncture,1–7 that do not involve any permanent impairment. Of great concern, however, are rare injuries to the central nervous system that occur as a result of epidural corticosteroid injections. These rare neurologic injuries can be catastrophic and include stroke and spinal cord injury that can result in increased pain, severe permanent disability, or death. An expert working group with facilitation from the U.S. Food and Drug Administration’s Safe Use Initiative (SUI) and representatives from leading specialty societies reviewed the existing scientific evidence and assembled consensus clinical considerations aimed at reducing the risk of severe neurologic complications.
Background

The evidence that neurologic injury is associated with epidural injection of steroids is limited to case reports and reports of closed malpractice claims, and this evidence will be reviewed in the paragraphs that follow. The incidence of these rare complications cannot be calculated from the limited data because there is little information on the numbers of patients undergoing the procedures. The reports show us that these catastrophic injuries do occur, and the number of cases reported in the literature suggests that the risk is not negligible. The most commonly used routes of administration are the interlaminar route, in which the needle is placed between adjacent spinal laminae into the posterior epidural space (figs. 1 and 2), and the transforaminal route, in which the needle is placed in an intervertebral foramen (figs. 3 and 4).

The cardinal neurologic complication of cervical interlaminar injections is direct needle injury to the spinal cord (fig. 1). Case reports of such injuries are few in the literature; additional evidence is available from reviews of closed malpractice claims. An earlier review of malpractice claims identified 14 cases of spinal cord injury after epidural injection of steroids, among 276 claims relating to chronic pain management between 1970 and 1999. A more recent review looked at malpractice claims between January 1, 2005 and December 31, 2008. Of 294 claims relating to chronic pain management, 64 involved cervical interventions, with 20 cases of direct spinal cord injury. There has also been one report of indirect spinal cord injury, ostensibly due to a transient increase in pressure within the epidural space during injection causing ischemia. Direct spinal cord injury has been reported once after cervical transforaminal injections, but the cardinal neurologic complications of this procedure are infarctions of the spinal cord, brainstem, cerebrum, or cerebellum. These have been described in several case reports and a survey of 1,340 physicians. A review of closed claims identified nine instances of spinal cord infarction although the overlap with the published case reports could not be determined. Circumstantial evidence, and some direct evidence,
implicates a variety of possible mechanisms for these complications, involving either the vertebral artery or a radicular artery—more precisely termed a radiculomedullary or spinal medullary artery—an artery that reinforces the anterior or posterior spinal artery (fig. 3). For thoracic and lumbar injections, reports of injuries have been fewer although no less devastating. One case of paraplegia has been reported after a thoracic interlaminar injection of steroids (fig. 2), ostensibly due to direct injury of the spinal cord. In the four cases after lumbar injections, the mechanisms of neurologic injury are unclear, but variously may have involved swelling of an unrecognized epidural space-occupying lesion, injury to a radiculomedullary artery, or hematoma.

More extensive is the literature reporting paraplegia after lumbar transforaminal injections (fig. 4). In all cases, particulate steroids were used, and the suspected mechanism of injury is either injection of steroids into a radiculomedullary artery or spasm of such an artery when perturbed by the needle.

Anatomy, Laboratory, and Animal Studies

Anatomic studies have shown that the vertebral artery lies in close proximity to needles inserted into the cervical intervertebral foramen, along with other arteries, such as the ascending cervical and deep cervical arteries, which can contribute to the supply of the central nervous system (fig. 3). The diameter of those arteries is sufficient to admit the tip of a needle. In the case of radicular arteries, investigators have captured images of contrast medium injected into cervical radicular arteries in the course of transforaminal injection, showing that it is possible to cannulate these small vessels unintentionally.

Laboratory studies have shown that certain steroid preparations contain particles and form aggregates. Methylprednisolone has the largest particles, triamcinolone is intermediate, and betamethasone has the smallest. These particles or their aggregates can act as emboli if injected into an artery and are of sufficient size to block small terminal arterioles supplying the brain or spinal cord. Dexamethasone does not form particles or aggregates.

...
Possible Mechanisms of Injury

Collectively, these studies suggest that intraarterial injection of particulate steroids is a likely mechanism of spinal or cerebrovascular complications of cervical transforaminal injections. In this regard, it is conspicuous that in virtually all case reports of infarction after cervical transforaminal injection of steroids, particulate steroids were used. In cases where nonparticulate medication was injected, such as lidocaine or contrast (iopamidol), paralysis of the extremities or blindness was temporary.14,44 Such injuries did not occur after the injection of dexamethasone.

Other potential mechanisms of injury involving the vertebral artery include perforation22 and traumatic aneurysm caused by penetration with the needle.22 Direct contact between an advancing needle and a small artery could theoretically cause spasm of that vessel or create an intimal flap (i.e., dissection).23,35,40 Direct evidence is lacking for these alternate mechanisms for neurologic injury.

Animal studies have shown that the carrier used in some steroid preparations might be directly toxic to the central nervous system, resulting in injury.43 A review of the animal studies showed that the concentrations of the preservatives polyethylene glycol and myristyl-gamma-picolinium chloride needed to cause morphologic or nerve conduction changes must be 2 to 10 times the concentrations found in these commercial drug preparations, thus toxicity resulting directly from the low concentrations of preservative appears to be unlikely.40

Role of the Food and Drug Administration Safe Use Initiative

To address concerns related to medication-related risks, the U.S. Food and Drug Administration created its SUI in 2009 to create and facilitate public and private collaborations within the healthcare community.* The goal of the SUI is to reduce preventable harm by identifying specific, preventable medication risks and developing, implementing, and evaluating cross-sector innovations with partners who are committed to safe medication use. It works with stakeholders to respond to the challenges of managing risks associated with the way medications are used.

Safe Use Initiative facilitated the organization of an expert working group of key stakeholders created to understand the causes of the neurologic injuries associated with epidural steroid injections and devise strategies to mitigate their risk. The working group consisted primarily of experts external to the Food and Drug Administration who have published scientific studies or scholarly works on the topic of epidural steroid injections, and SUI representatives have helped convene and facilitate meetings without actively participating in the deliberations or decision-making process. The working group drafted, discussed, and formulated a set of clinical considerations to minimize the risk of catastrophic neural injury associated with epidural steroid injections, which has resulted in the development of studies and publication of reports to provide guidance to the healthcare community.

Methods

The SUI convened and facilitated teleconferences conducted by the working group, which drafted, discussed, and formulated a set of clinical considerations designed to minimize the risk of catastrophic neural injury associated with epidural steroid injections. Clinical considerations were formulated with reference to the best available scientific evidence, and when evidence was lacking, expert opinion was sought both within the working group and from leading scientific societies or associations with interest or expertise in the subject of epidural injections. The clinical considerations of the working group primarily considered complications arising from the administration of epidural steroid injections reported in the literature and were designed to

Fig. 4. Axial view of lumbar transforaminal and selective nerve root injection. The anatomy and proper needle position (axial view) for right L3/L4 transforaminal. IVC = inferior vena cava. Reproduced, with permission, and modified from original figures, from Rathmell JP: Atlas of Image Guided Intervention in Regional Anesthesia and Pain Medicine, 2nd edition. Philadelphia, Lippincott Williams & Wilkins, 2012. Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Animal studies have shown that injection of particulate methylprednisolone into the vertebral artery or internal carotid artery can lead to severe neurologic injuries (strokes) similar to those seen in published human case reports.42,43 Such injuries did not occur after the injection of dexamethasone.

Addendum

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reduce harm resulting from one or more putative mechanisms of injury.

Once clinical considerations were drafted, representatives from a number of national pain organizations were invited to review and vote on them. After an initial vote, newer studies were published that provided further guidance on key issues.\textsuperscript{47,48} The working group presented findings from these studies to the consulting organizations, which revoked on the clinical considerations based on the new information.

**Results**

The representatives of the national organizations overwhelmingly approved all the clinical considerations of the working group, with board approval from their respective societies before rendering their final votes (table 1).

The working group and the advising national organizations unanimously agreed that epidural injections of steroids were rarely associated with serious complications due to injuries of the central nervous system. They agreed that transforaminal injections are associated with a risk of catastrophic neurovascular complications and that particulate steroids appear to be inordinately represented in case reports of these complications.

The representatives unanimously approved the clinical consideration that only nonparticulate steroids should be used in the\textit{therapeutic cervical} transforaminal injections. Although the initial use of nonparticulate steroid dexamethasone in\textit{lumbar} transforaminal injections was recommended (11 of 13 votes), the representatives unanimously agreed that there might be instances where particulate steroids could be used in this setting, for example, consideration to use of a particulate steroid might be given if a given patient had failed to improve after an initial treatment with nonparticulate steroid.

Clinical considerations involving technical aspects of the procedures included use of appropriate image-guided views, injection of contrast under real-time fluoroscopy, review of prior imaging studies, use of face mask and sterile gloves, use of extension tubing, and avoidance of heavy sedation.

Three clinical considerations received votes against adoption. Two clinical considerations involved the measures needed to prevent intravascular injection, the representative of one organization felt that digital subtraction imaging (DSI) should be made mandatory when injecting a potentially hazardous substance transforaminally. One clinical consideration that received a negative vote involves the use of extension tubing for transforaminal injections.

Three clinical considerations receive votes of “unable to reach consensus” among the officers, board of directors, or representatives of the organizations. One organization could not reach consensus on the issue of injection of contrast medium under real-time fluoroscopy and/or DSI before cervical transforaminal injections. Two organizations could not reach consensus on two clinical considerations: the initial use of nonparticulate steroid dexamethasone in lumbar transforaminal injections and the performance of interlaminar injections without contrast in patients with a significant history of contrast allergy or anaphylactic reaction.

**Discussion**

Image guidance for all cervical interlaminar injections was recommended to avoid penetration of the spinal cord as a result of improper insertion of the needle. Appropriate lateral or oblique views are essential to gauge depth of needle insertion (fig. 5).\textsuperscript{49,50} Relying on loss-of-resistance or on anteroposterior views alone does not protect patients from excessive depth of needle insertion, resulting in the risk that air, saline, or contrast medium might be injected into the spinal cord.

Similar precautions apply for lumbar interlaminar injections. Appropriate lateral or oblique views are required to ensure correct depth of needle insertion, lest the injection be into the subarachnoid space; contrast medium should be used to ensure injection correctly into the epidural space; and particulate steroids are acceptable because there is little risk of intraarterial injection.

The clinical consideration that needle entry for cervical interlaminar injections be performed at C7-T1 was based on reports that at other segmental levels the cervical epidural space is often narrow, making the dural sac and spinal cord more susceptible to penetration and injury.\textsuperscript{51-53} Based on similar rationale about the close anatomic proximity of the dura mater and spinal cord to the point of needle entry, the clinical consideration was adopted that cervical interlaminar injections should not be undertaken unless inspection of imaging taken before the procedure demonstrates that the epidural space at the segmental level at which the injection will be undertaken is sufficient in size to admit a needle safely. A recent study\textsuperscript{54} found that magnetic resonance imaging did not improve treatment outcomes for epidural steroid injections done in patients with a wide range of painful spinal disorders, yet suggested that magnetic resonance imaging may improve outcomes in the subset of patients with radiculopathy. This study did not examine the impact of imaging on safety, nonetheless the authors do emphasize that magnetic resonance imaging can detect rare contraindications to epidural injection, such as spinal metastases and infection.

For cervical procedures in general, irrespective of whether interlaminar or transforaminal injections were performed, analysis of closed claims reveals that having the patient heavily sedated during the procedure or being unresponsive at the time of injection are each significantly associated with an increased risk of spinal cord injury.\textsuperscript{10} Furthermore, some 45% of spinal cord injuries were deemed avoidable had suitable precautions been used. There was agreement by all societies that if sedation is used, it should be light enough to allow the patient to communicate pain or other adverse sensations or events during the procedure.

For cervical and lumbar transforaminal injections, the cardinal risk is intraarterial injection. Therefore, a test dose of contrast medium is essential to identify unintended entry into an artery before any other agent is injected (figs. 6 and 7). Dexamethasone was recommended as the first-line agent for lumbar
Table 1. Statements and Clinical Considerations of the Working Group Endorsed by the MultiSpecialty Work Group

<table>
<thead>
<tr>
<th>Statement/Clinical Consideration</th>
<th>Number of Organizations Agreeing</th>
<th>Number of Organizations Disagreeing</th>
<th>Number of Organizations Unable to Reach Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cervical IL ESIs are associated with a rare risk of catastrophic neurologic injury (fig. 1).</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. TF ESI using particulate steroid is associated with a rare risk of catastrophic neurovascular complications (fig. 3).</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3. All cervical IL ESIs should be performed using image guidance, with appropriate AP, lateral, or contralateral oblique views and a test dose of contrast medium (fig. 5).</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4. Cervical TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient (fig. 6).</td>
<td>11</td>
<td>1*</td>
<td>1</td>
</tr>
<tr>
<td>5. Cervical IL ESIs are recommended to be performed at C7-T1, but preferably not higher than the C6-C7 level.</td>
<td>13</td>
<td>0</td>
<td>0</td>
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<tr>
<td>6. No cervical IL ESI 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.</td>
<td>13</td>
<td>0</td>
<td>0</td>
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<tr>
<td>7. Particulate steroids should not be used in therapeutic cervical TF injections.</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>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.</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9. Lumbar TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or digital subtraction imaging, using an AP view, before injecting any substance that may be hazardous to the patient (fig. 7).</td>
<td>12</td>
<td>1*</td>
<td>0</td>
</tr>
<tr>
<td>10. A nonparticulate steroid (e.g., dexamethasone) should be used for the initial injection in lumbar transforaminal epidural injections.</td>
<td>11</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>11. There are situations where particulate steroids could be used in the performance of lumbar TF ESIs.</td>
<td>13</td>
<td>0</td>
<td>0</td>
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<tr>
<td>12. Extension tubing is recommended for all TF ESIs.</td>
<td>12</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>13. A face mask and sterile gloves must be worn during the procedure.</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>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.</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>15. Cervical and lumbar IL ESIs can be performed without contrast in patients with documented contraindication to use of contrast (e.g., significant history of contrast allergy or anaphylactic reaction).</td>
<td>11</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>16. TF ESIs can be performed without contrast in patients with documented contraindication to use, but in these circumstances, particulate steroids are contraindicated and only preservative-free, particulate-free steroids should be used.</td>
<td>13</td>
<td>0</td>
<td>0</td>
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<tr>
<td>17. Moderate-to-heavy sedation is not recommended for ESIs, but if light sedation is used, the patient should remain able to communicate pain or other adverse sensations or events.</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* The organization voting against questions 4 and 9 commented, "Digital Subtraction Imaging should be mandatory before injecting a potentially hazardous substance transforaminally."
transforaminal injections on two grounds. The first was to avoid particulate steroids, which have been implicated in all cases of severe neurologic complications from this procedure. The second was that studies have now shown that the effectiveness of dexamethasone is not significantly less than that of particulate steroids.47,48 Use of dexamethasone as a first-line agent for
lumbar transforaminal is the most controversial clinical consideration the group is putting forward. We acknowledge that there is no direct evidence that nonparticulate steroids are superior to sham injections, and studies that show no difference between particulate and nonparticulate steroids are underpowered.47,48

Digital subtraction imaging was endorsed for transforaminal injections on the grounds that it significantly increases the detection of vascular uptake of contrast medium55–57 and requires less contrast medium to detect vessels (figs. 6 and 7). One study showed the sensitivity of DSI to be 60% compared with 20% with aspiration.57 However, the working group acknowledged that DSI was not widely available, not necessarily essential for safety, and increases radiation exposure.58 Physicians who do not use DSI and rely instead on real-time fluoroscopy must carefully
view the images during the injection of contrast medium, lest the fleeting appearance of a small artery escapes notice.

Extension tubing was recommended so that once a needle had been placed, it would no longer be touched, and risk being dislodged when syringes for successive agents are connected. This practice guards against a needle, shown to be in a safe location by a test dose of contrast medium, being dislodged to an unsafe location when the syringe for steroids is connected. Face masks and gloves were recommended to comply with generally accepted guidelines for aseptic technique.

Topics that have been discussed by some experts but were not considered by the working group include the use of a local anesthetic test dose, placement of the needle at the inferior aspect of the intervertebral foramina instead of the superior “safe triangle,” and use of specific needle tip types. The working group felt that there were not enough quality publications to discuss these logical but largely unstated safeguards. The use of chlorhexidine in alcohol for antiseptics was also omitted in view of the controversy surrounding possible neurotoxicity of the antiseptic solution. Finally, the issue of neuraxial injections in the anticoagulated patient was omitted because the American Society of Regional Anesthesia and Pain Medicine, in collaboration with some national and international organizations, is finalizing guidelines on interventional pain procedures for patients on anticoagulants (Honorio T. Benzon, M.D., Professor of Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, written communication, December 2014).

We acknowledge that catastrophic neurologic injuries can and do occur during epidural steroid injections. The actual incidence is unknown, but epidural steroid injections are common, and reports of these neurologic injuries are uncommon. The purpose of this multidisciplinary effort was to review the available evidence and assemble the best clinical considerations for reducing or eliminating these injuries. Although it is beyond the scope of this effort, it is equally important to closely examine the need for epidural injection in each patient who receives this therapy. The clinical considerations put forth herein are broadly supported by experts from many disciplines and stakeholder national medical organizations. We acknowledge that many of the clinical considerations are nothing more than the logical opinions of a group of experts and many remain untested through rigorous scientific research. Many, if not most of the clinical considerations will never be tested, as the incidence of these rare complications is so low that even large studies including thousands of patients are unlikely to detect meaningful differences after the implementation of the clinical considerations. For now, our hope is that these clinical considerations will help every practitioner who performs epidural injections of steroids to become familiar with the risk of neurologic complications and to adopt the best safeguards to avoid complications and provide the safest care for their patients.

Acknowledgments
The authors thank Salma Lemtouni, M.D., M.P.H., of the U.S. Food and Drug Administration Safe Use Initiative (Silver Spring, Maryland), who worked tirelessly with the working group to convene the meetings necessary to assemble the current set of expert clinical considerations aimed at improving patient safety. The authors also thank the representatives of national organizations (see the appendix for list of all participants), who shared their expertise and served to interface with each of their own organizations as we created the final clinical considerations. The American Society of Interventional Pain Physicians (Paducah, Kentucky) did participate in this project, but left the process voluntarily during our early deliberations; the authors acknowledge their participation, but their inclusion in the list of participants should not be misconstrued as an indication of their support for the final recommendations. This work was assembled through the voluntary efforts of the authors with scheduling and meeting facilitation provided by the U.S. Food and Drug Administration Safe Use Initiative.

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Competing Interests
Dr. Rathmell is a Director of the American Board of Anesthesiology. Dr. Benzon is a member of the Board of Directors of the American Society of Regional Anesthesia and Pain Medicine. Dr. Dreyfuss is past president of the International Spine Intervention Society. Dr. Huntoon is a member of the Board of Directors of the American Society of Regional Anesthesia and Pain Medicine. Dr. Baker is past president of the North American Spine Society, the past president of the International Spine Intervention Society, and a consultant to Medtronic, Mesoiblast, and Relievant MedSystems. He holds stock in Noximed and Relievant. Dr. Riew receives royalties from Biomet, Medtronic, and Osprey. He is a stock holder with Amedica, Benvenue, Expanding Orthopedics, Nexgen Spine, Osprey, Paradigm, Spine, Spinal Kinetics, Spineology, Vertiflex, and PSD. He is a board member on the CSRS, KASS, Global Spine Journal, Spine Journal, and AOSpine International. Dr. Rosenquist is past president of the American Society of Regional Anesthesia and Pain Medicine. Dr. Aprill is a founding member of the International Spine Intervention Society. Dr. Buvanendran is a member of the Board of Directors of the American Society of Regional Anesthesia and Pain Medicine. Dr. Bogduk is founding member of the International Spine Intervention Society. The other authors declare no competing interests.

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References


Appendix

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