July 23, 2018

CareSource
P.O. Box 8738
Dayton, OH 45401-8738

Re: Epidural Steroid Injections (Interlaminar, Transforaminal, or Caudal Epidural Injections); MM-0007

To Whom It May Concern:

The Spine Intervention Society (SIS), a multi-specialty association of over 2,800 physicians dedicated to the development and promotion of the highest standards for the practice of interventional procedures in the diagnosis and treatment of spine pain, would like to take this opportunity to comment on your policy Epidural Steroid Injections (Interlaminar, Transforaminal, or Caudal Epidural Injections); MM-0007.

The Society's membership includes many of the clinicians and academicians whose published literature provides the seminal references upon which the practice of evidence-informed interventional spine care is based. Our organization has a strong record of working to eliminate fraudulent, unproven, and inappropriate procedures. At the same time, we are equally committed to assuring that appropriate, effective, and responsible treatments are preserved so that patients do not have to suffer or undergo more invasive and often unnecessary surgical procedures.

CareSource’s policy indicates that cervical transforaminal injections are contraindicated, citing the Food and Drug Administration’s (FDA) safety communication from 2014. CareSource is correct in understanding that these epidural steroid injections have been associated with rare but devastating complications, including spinal cord injuries -- a risk that the members of the Spine Intervention Society are very well aware of and take seriously. While we commend CareSource for considering the risks associated with cervical transforaminal epidural steroid injections, we wish to clarify several points.

In response to an invitation from Dr. James Rathmell and the FDA’s Safe Use Initiative, the Spine Intervention Society convened the Multisociety Pain Workgroup (MPW) in 2014 to review the evidence on safety and effectiveness of epidural steroid injections and submitted the attached comment letter to the FDA’s Anesthetic and Analgesic Drug Products Advisory Panel (AADPAC). The recommendations were subsequently published as a consensus recommendation of the MPW under the auspices of the Safe Use Initiative. (1) Contrary to what is indicated in the coverage policy, we have never criticized the 17 recommendations made, but wholeheartedly support their implementation and rigorous application.
In reviewing the 17 recommendations, you will note that nowhere are cervical transfornaminal injections prohibited. Serious neurological complications have been attributed not to the transfornaminal approach, but to the use of particulate steroid via the transfornaminal approach, and are mitigated by the use of non-particulate steroid.

We also wish to highlight the FDA’s response from October 2015, following careful consideration of the FDA’s AADPAC recommendations. The FDA’s Dr. Judith Racoosin, Deputy Director for Safety Division of Anesthesia, Analgesia, and Addiction Products, specifically stated in the New England Journal of Medicine that, “We find that available data do not currently support either a contraindication or a warning focused only on cervical transfornaminal injection of suspension glucocorticoids.” (2)

The transfornaminal approach has many advantages over the interlaminar approach depending on the particular pathology of the spinal condition. Given the evidence, we strongly believe it would be a mistake to completely disallow this approach. It is the only means whereby an anesthetic can be delivered selectively to a cervical spinal nerve for diagnostic purposes (selective nerve block), a critical procedure given the demonstrable lack of segmental specificity of imaging, physical exam or electrophysiology. (3) We believe your policy should be amended to allow selective nerve root blocks for diagnosis, and transfornaminal epidural steroid injections for therapy, the latter where a non-particulate steroid such as dexamethasone is utilized.

We hope that this information, as well as any dialogue and collaboration between CareSource and the Spine Intervention Society, will lead to the establishment of a reasonable coverage policy that will eliminate inappropriate utilization while preserving access in appropriately selected patients. We offer our ongoing input and expertise in this matter. If we may answer any questions or provide any assistance, please feel free to contact Belinda Duszynski, Senior Director of Policy and Practice at bduszynski@SpineIntervention.org.

Sincerely,

Timothy Maus, MD
President
Spine Intervention Society
Attachments:

- MPW Letter to Dr. Randall Flick (AADPAC)
- Rathmell Article: Safeguards to Prevent Neurologic Complications After Epidural Steroid Injections: Consensus Opinions From a Multidisciplinary Working Group and National Organizations
- Racoosin Article: Serious Neurologic Events after Epidural Glucocorticoid Injection--The FDA's Risk Assessment

References:

November 7, 2014

Randall P. Flick MD, MPH
Chair
Anesthetic and Analgesic Drug Products Advisory Committee
c/o Stephanie L. Begansky, PharmD
Designated Federal Officer
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
W031-2417
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dear Dr. Flick and Members of the Committee:

The American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Disorders of the Spine and Peripheral Nerves, American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Section on Pain, American Academy of Pain Medicine, American Academy of Physical Medicine and Rehabilitation, American Association of Neurological Surgeons, American College of Radiology, American Pain Society, American Society of Anesthesiologists, American Society of Regional Anesthesia and Pain Medicine, Congress of Neurological Surgeons, International Spine Intervention Society, North American Neuromodulation Society, North American Spine Society, and Society of Interventional Radiology would like to take this opportunity to comment on the safety and effectiveness of epidural steroid injections. As medical specialty societies representing physicians who perform epidural steroid injections, we are deeply committed to ensuring that patients are safe and that their quality of life is greatly improved with interventional spine care. Our organizations have a strong record of working to eliminate fraudulent, unproven, and inappropriate procedures. At the same time, we are equally committed to assuring that safe and effective treatments are preserved so that patients do not have to unnecessarily suffer or undergo more invasive surgical procedures.

On April 23, 2014, the Food and Drug Administration (FDA) released a Drug Safety Communication warning that injection of steroids into the epidural space of the spine may result in rare but serious neurologic adverse events including stroke, loss of vision, paralysis, and death. We applaud the FDA on their effort to appropriately remind physicians and patients that they should be aware of the side effects and potential complications related to any and all drugs and medications that may be considered for treatment. The risks and benefits of treatments should be openly discussed by physicians, and considered by patients when determining how best to proceed. Unfortunately, the FDA’s Drug Safety Communication is also misleading. The statement indicates that the
safety and effectiveness of epidural administration of steroids have not been established. This is clearly not true based on robust literature on this topic.

Safety of Epidural Steroid Injections

While complications with epidural steroid injections (ESIs) have been reported, and are likely underreported, serious complications are limited to isolated case reports. This is despite the large number of injections performed annually.¹ No serious neurological complications have ever been reported in any prospective study of ESIs, regardless of approach or technique used, or anatomical area injected. A recently completed multi-institutional cohort of over 16,000 consecutive ESI procedures at all spine segments also reported no major complications.²⁻⁴

Particulate and Non-Particulate Steroids

Though rare, neurological complications are catastrophic and include stroke, blindness, paralysis, and death. These adverse events likely result from inadvertent injection of a radicular or vertebral artery that perfuses the spinal cord and brain. In all reported cases, particulate steroids have been used, and the mechanism of injury is presumed to be embolism of these particulates resulting in infarction. Light microscopy studies have demonstrated that the particles in these steroid preparations are either larger than red blood cells or form aggregates larger than red blood cells.⁵ Additionally, animal studies have shown central nervous system infarction with intra-arterial injection of particulate steroids.⁶

This is in contrast to dexamethasone, which has particles 5 to 10 times smaller than red blood cells on microscopic evaluation, and is effectively non-particulate in this context. Dexamethasone has been shown to have no adverse sequelae with direct injection into the arterial supply of the neuroaxis in animals.⁵⁻⁶ Non-particulate steroids have been routinely administered via the transforaminal epidural technical approach without a single report of a serious neurologic adverse event to date. It is logical to conclude that increased utilization of this medication will lead to decreased complication rates associated with these procedures. However, use of dexamethasone has not been universally adopted due to the fact that most published studies demonstrating the effectiveness of transforaminal injection of steroid (TFIS) have utilized particulate steroids. However, recent high quality studies have demonstrated the non-inferiority of dexamethasone to the most commonly injected particulate corticosteroid, triamcinolone acetate,⁷⁻⁸ which should further increase its utilization. Given that the risk of neurologic injury resulting from embolization of particulate steroid may be eliminated with the use of a non-particulate steroid, dexamethasone should be considered the preferred first-line medication option for TFIS. Particulate steroids could be considered as a second-line agent for lumbar TFIS (lumbar region only) if non-particulate steroids do not result in adequate duration of relief. This recommendation is consistent with the FDA Safe Use Initiative’s recommendations for safe injection practices which have been submitted for publication, and which all signatories to this letter support to help minimize risks associated with epidural steroid injections. Based on these data, and further supported by the consensus of experts representing fourteen
different specialty societies, we feel non-particulate steroids should be excluded from any FDA action as they have a robust safety profile.

**Comparison to Alternative Treatments for Back Pain**

For further comparison, the rates of serious complications from alternative treatments for spine pathology are significantly higher. There were 14,800 opioid related deaths in the United States in 2008.9 More than 103,000 individuals are hospitalized annually in the United States for NSAID-related serious GI complications, with 16,500 NSAID-related deaths occurring each year in the United States among patients with rheumatoid arthritis and osteoarthritis.10 Based on these data, we request that the FDA warning be modified to reflect the extremely low risk involved with lumbar ESI in comparison to significantly higher risks of alternative treatment option such as opioids and NSAIDs.

**Effectiveness of Epidural Steroid Injections**

The second area of concern with the FDA statement is the misleading sentiment that the effectiveness of ESIs has not been determined. While there is always room for more research, there is ample evidence demonstrating the effectiveness of ESIs in reducing and eliminating pain, improving function, decreasing reliance on opioids, and eliminating the need for surgery for many patients.11

**Particulate and Non-Particulate Steroids**

Multiple high quality studies have demonstrated efficacy of ESIs when performed on patients with appropriate indications. A double blind randomized controlled trial (RCT) by Riew et al investigated the effect of TFIS on avoidance of surgery for lumbar radicular pain.12 Only 29% of patients who were treated with transformaminal injection of betamethasone and bupivacaine required surgery during the 13-28 month post-procedure follow-up time period compared with 66% of those who received transformaminal injection of bupivacaine alone (P < 0.004). Corroboration of the surgery-sparing effect of lumbar TFIS has been provided in a recent study in which injections were offered to patients with radicular pain who were on a surgical waiting list. A successful outcome, and avoidance of surgery, was achieved in 51/91 (56%, 95% CI ± 10%) patients.13 Lumbar TFIS have also been shown to be effective for the treatment of radicular pain that has not responded to surgical intervention. Of 156 patients whose radicular pain was not relieved by surgery, 38 (31%, 95% CI ± 7%), responded to TFIS and none of these patients required revision surgery.14 Another RCT found that after an average follow-up period of 1.4 years, the patients receiving TFIS had an 84% success rate compared to only 48% for the group receiving deep lumbar paraspinal muscle injection with saline (P < 0.005).15 The most scientifically rigorous double blind RCT compared the efficacy of TFIS with transformaminal injection of local anesthetic, transformaminal injection of saline, intramuscular steroids, or intramuscular saline for the treatment of lumbar radicular pain.16 The authors found that success rates for providing at least 50% pain relief from the various control treatments were statistically indistinguishable at 15% (95% CI +/- 7%) while 54% (+/- 18%) of patients who received TFIS achieved a successful outcome both at 1- month and at 12-month follow-up. Collectively these studies have led to recent systematic reviews17,18 with meta-analyses that have summarized the large volume of research on this topic. Up to 70%
of patients achieve 50% pain relief for 1-2 months; 30% achieve complete pain relief.\textsuperscript{18} For patients with disc herniations, up to 70% may achieve 50% pain relief for six months.\textsuperscript{7} Pain relief is accompanied by functional recovery and reduced reliance on other health care resources.\textsuperscript{7,18,19}

Recent studies have also demonstrated that non-particulate medications are just as effective as particulate preparations. A large retrospective review of over 3600 lumbar transforaminal injections from the Mayo Clinic showed dexamethasone to be non-inferior to particulate preparations.\textsuperscript{8} Also a prospective double blind RCT showed dexamethasone was equivalent to triamcinolone, with over 70% of subjects that received an ESI experiencing at least 50% pain relief and avoiding surgery through the study’s 6 month follow-up period.\textsuperscript{7}

\textit{Diagnosis/Indications}
Some studies and reviews, however, do report negative results with ESIs. There are multiple potential reasons for this. First while there is a large preponderance of evidence supporting the effectiveness of image-guided ESIs for radicular pain due to disc herniations, ESIs may not be as effective for other pathologies. Unfortunately, a significant number of studies simply study low back or radicular pain without identifying the underlying etiology. These are merely symptoms and not a diagnosis. For perspective, imagine a hypothetical systematic review of prescription medication for the treatment of cough, a symptom. A few studies may show beneficial effects from antibiotics in a group of patients with bacterial pneumonia, a specific diagnosis, whereas pooled data from heterogeneous groups – including viral bronchitis, chemical pneumonitis, asthma, lung cancer, etc. – would produce different effects. If these pooled effects showed that many different medications had minimal impact on cough from various sources, it would still be a disservice to abandon prescription antibiotics for pneumonia.

\textit{Technique/Image Guidance}
Second, when reviewing the literature regarding the effectiveness of ESIs, it is of utmost importance to know what technique was utilized. Multiple studies have demonstrated that non-image guided ESIs have unacceptably high miss rates with as many as 74% of these injections placing medication either outside the epidural space or not reaching the targeted site of pathology within the epidural space.\textsuperscript{20} Since placebo controlled studies of intramuscular steroid injections failed to show any benefits,\textsuperscript{21,22,23} it should be no surprise that prospective randomized comparisons of image-guided ESIs to intramuscular steroid injections\textsuperscript{16,24} and to blind ESIs\textsuperscript{25} unanimously favor image-guided ESIs. In a clinically relevant context, studies of non-image guided ESIs show no benefit over sham treatment with a collective number needed to treat of >90.\textsuperscript{26,27,28,29,30,31} In stark contrast, a large number of controlled studies of image-guided TFIS for patients with radiculopathy demonstrate robust positive outcomes\textsuperscript{16,32,33,34,35,36,37,38,39,40,41} with a number needed to treat of 3.\textsuperscript{18}

\textit{Data Analysis}
While imprecision in diagnosis and inaccuracy in injections are major contributors to poor reported outcomes, negative studies and reviews are also reported for other reasons.
Unfortunately a preponderance of studies have opted to report clinical relevance by comparing group means for a minimum clinically important difference. While appealingly simplistic, this approach is inherently flawed. This method can result in a misinterpretation of the data, and dismisses clinically important information about the treatment effects of spine injections. Comparison between group means assumes a normal Gaussian distribution of pain and disability in response to spinal injections. In the context of ESIs, the clinical result is often bimodal, with some patients who respond and others who do not. Thus, the treatment effects are best-assessed using categorical data to compare proportions of responders to non-responders. A clear example of the utility of this approach is revealed in a study comparing TFIS to placebo. Comparison of group mean data failed to find any difference between treatment groups, but categorical analysis demonstrated both statistically and clinically meaningful differences in favor of TFIS.

It has also been suggested by some that epidural injections of local anesthetic alone are equivalent to epidural injections that include steroid. We reject this claim. When two treatment arms have similar results, the appropriate conclusion is not necessarily that both treatments are equally effective. Just as likely, the treatments may be equally ineffective. For several indications, the latter is more likely. As cited above, multiple high quality, well-designed studies have demonstrated statistically and clinically significant differences favoring ESIs over local anesthetic alone.

In conclusion it is clear that indication, technique, data analysis, and treatment medication are all vitally important in determining the effectiveness of ESIs. The data collectively show that for appropriate pathologies, image-guided ESIs with non-particulate steroids are an effective and safe treatment, and it would be inappropriate and biased to conclude that all ESIs are ineffective and unsafe.

We appreciate the opportunity to provide these comments and insights for consideration.

Sincerely,

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36 Wang JC, Lin E, Brodke DS, Youssef JA. Epidural injections for the treatment of symptomatic


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.

This article is featured in “This Month in Anesthesiology,” page 1A. Corresponding article on page 964. The preliminary clinical considerations from this working group were presented orally in a panel session titled Transforaminal Epidural Steroid Injections and the Food and Drug Administration Use Initiative that was held at the American Society of Anesthesiologists 2013 Annual Meeting in San Francisco, California, on October 12, 2013, and during a meeting of the Food and Drug Administration Anesthetic and Analgesic Drug Products Advisory Committee held on November 24 and 25, 2014, in Silver Spring, Maryland.

Submitted for publication September 21, 2014. Accepted for publication December 30, 2014. From the Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts (J.P.R., N.S.R.); Northwestern University Feinberg School of Medicine, Chicago, Illinois (H.T.B.); EvergreenHealth, Kirkland, Washington (P.D., R.B.); Vanderbilt University School of Medicine, Nashville, Tennessee (M.H.); University of California San Diego, San Diego, California (M.W.); Washington University School of Medicine, St. Louis, Missouri (K.D.R.); Cleveland Clinic Lerner College of Medicine, Cleveland, Ohio (R.W.R.); Interventional Spine Specialists, Kenner, Louisiana (C.A.); Rush Medical College, Chicago, Illinois (A.B.); Ahwatukee Sports and Spine, Phoenix, Arizona (D.S.K.); University of Newcastle, Newcastle, Australia (N.B.); University of Saskatchewan, Saskatoon, Saskatchewan, Canada (D.R.F.); Southside Pain Solutions, Danville, Virginia (E.F.); APM Spine and Sports Physicains, Virginia Beach, Virginia (S.H.); Mayo Clinic Florida, Jacksonville, Florida (J. Stone); Virginia Mason Medical Center, Seattle, Washington (K.V.); Neuroimaging and Interventional Spine Services, LLC, Ridgefield, Connecticut (G.L.); NewSouth NeuroSpine, Flowood, Mississippi (J. Summers); Danbury Hospital, Danbury, Connecticut (D.K.); University of North Carolina School of Medicine, Winston Salem, North Carolina (D.O.); and Medical College of Wisconsin/Froedtert Hospital, Milwaukee, Wisconsin (S.T.).
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 extended by 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).24

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.25 In the four cases after lumbar injections,26–29 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).30–37 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).38 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 injections, showing that it is possible to cannulate these small vessels unintentionally.24,39

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.15,40,41 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.40
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. Such injuries did not occur after the injection of dexamethasone.

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. Direct evidence is lacking for these alternate mechanisms for neurologic injury.

Other potential mechanisms of injury involving the vertebral artery include perforation and traumatic aneurysm caused by penetration with the needle. 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). 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. 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.

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 provide guidance to the healthcare community.
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. The working group presented findings from these studies to the consulting organizations, which revoted 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 transformaminal 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 *therapeutic cervical* transformaminal injections. Although the initial use of nonparticulate steroid dexamethasone in *lumbar* transformaminal 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 transformaminally. One clinical consideration that received a negative vote involves the use of extension tubing for transformaminal 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 transformaminal injections. Two organizations could not reach consensus on two clinical considerations: the initial use of nonparticulate steroid dexamethasone in lumbar transformaminal 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). 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 epidural space is often narrow, making the dural sac and spinal cord more susceptible to penetration and injury. 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 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 transformaminal 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. 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 transformaminal 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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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.”

AP = anteroposterior; C6-C7 = the interspace between the sixth and seventh cervical vertebrae; C7-T1 = the interspace between the seventh cervical and first thoracic vertebrae; ESI = epidural steroid injection; IL = interlaminar; TF = trasforaminal.
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

Fig. 5. (A) Bony anatomy relevant to cervical interlaminar epidural injection. Three-dimensional reconstruction computed tomography of the cervical spine as viewed in the lateral projection. Inset matches the anatomic area in the radiographs shown in B and C. (B) Lateral radiograph of the cervical spine near the cervicothoracic junction during interlaminar cervical epidural injection. A 22-gauge Touhy needle is in place in the C7/T1 interspace extending toward the dorsal epidural space. (C) Labeled image after injection of radiographic contrast. The anterior most extent of the spinous process and the posterior most extent of the ligamentum flavum and spinal canal coincide with the “J-point” or the point where the inferior margin of the spinous process begins to arc in a cephalad direction, taking the appearance of the letter “J.” The area outlined to the left of the image in the dashed box has been enlarged in the inset to the right, where the approximate borders of the ligamentum flavum have been outlined. The contrast extends in a linear stripe in a cephalad and caudad direction from the needle tip that outlines the dorsal (posterior) border of the dura mater. 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.
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.59

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,60 placement of the needle at the inferior aspect of the intervertebral foramina instead of the superior “safe triangle,”61–64 and use of specific needle tip types.65,66

The working group felt that there were not enough quality publications to discuss these logical but largely untested safeguards. The use of chlorhexidine in alcohol for antiseptics67 was also omitted in view of the controversy surrounding possible neurotoxicity of the antiseptic solution.68 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. 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 treatment. 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.

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 No­cimed and Relievant. Dr. Riew receives royalties from Biomet, Medtronic, and Osprey. He is a stock holder with Aedmedica, 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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Serious Neurologic Events after Epidural Glucocorticoid Injection — The FDA’s Risk Assessment

Judith A. Racoosin, M.D., M.P.H, Sally M. Seymour, M.D., Laurelle Cascio, Pharm.D., and Rajdeep Gill, Pharm.D.

At times, the Food and Drug Administration (FDA) must grapple with safety concerns related to off-label uses of FDA-approved medications. Over the past several years, we have sought to understand the risk of serious neurologic events that occur after the epidural injection of glucocorticoids (corticosteroids) — a procedure that is commonly performed in the United States in an effort to manage radicular neck and back pain. The FDA has not approved any injectable glucocorticoid product for epidural administration, so any such use is considered off-label — part of the practice of medicine and not regulated by the FDA.

In 2009, the FDA began evaluating serious neurologic events associated with epidural glucocorticoid injections. Between 1997 and 2014, a total of 90 serious and sometimes fatal neurologic events were reported to the FDA Adverse Event Reporting System (FAERS), including cases of paraplegia, quadriplegia, spinal cord infarction, and stroke. (Compounded glucocorticoids used in epidural injections have been associated with fungal meningitis, but cases involving contaminated products were not included in the case...
A central question is the role of the glucocorticoids themselves in these adverse events. There is concern that in glucocorticoids formulated as suspensions rather than solutions, particulate matter may pose an increased risk of embolism after inadvertent intra-vascular injection. All catastrophic events (those resulting in permanent disability or death) reported to FAERS were associated with injection of a suspension, whereas only a few cases involving temporary symptoms were reported with glucocorticoid solutions.

To evaluate the relative use in the United States of these different glucocorticoid formulations in epidural injections, the FDA analyzed health care claims data from IMS Health (projected to the U.S. commercially insured population) and Medicare. Among beneficiaries of Medicare Parts A and B who were 65 years of age or older in 2013, more than 1.3 million epidural glucocorticoid injections were performed in approximately 426,000 patients. IMS Health data indicate that an estimated 604,000 commercially insured U.S. patients less than 65 years of age received an epidural glucocorticoid injection in 2013 (see graph). Although we do not have access to information about the extent of utilization of compounded products used for such injections because they are not regulated by the FDA, Medicare and IMS Health data show that suspension formulations accounted for more than 80% of utilization of commercially available products. Because the use of solutions is so limited, it’s difficult to assess the relative safety of solutions as compared with suspensions on the basis of the existing data. The increasing use of solutions for epidural injections by the transforaminal approach between 2009 and 2013, from 5% to 15% of patients younger than 65, may reflect increased concern regarding the safety of suspensions administered by the transforaminal route (see graph). A similar but smaller trend was observed in the Medicare population (an increase from 4% to 9%).

Although inadvertent intraarticular injection is one mechanism for serious neurologic events, there are other potential causes. A study conducted as part of the American Society of Anesthesiologists’ Closed Claims Project showed that in cases of cervical procedures for chronic pain that led to malpractice claims, direct needle trauma to a nerve or the spinal cord was the most common procedure-related event. Although many observers believe that the risk of injury occurs primarily with transforaminal cervical injections, the authors of this analysis found that of the cervical epidural procedures that were associated with spinal cord injury, two thirds were performed with the interlaminar approach and one third with the transforaminal approach.

Because of the technical nature of epidural glucocorticoid injec-

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**Estimated Numbers of Patients under 65 Years of Age in the Commercially Insured U.S. Population Who Received an Epidural Glucocorticoid Injection (EGI), According to Method of Administration and Type of Formulation, 2009–2013.**

Data are from IMS Lifelink Health Plan Claims Database, November 2014.
tion, in 2011 the FDA’s Safe Use Initiative facilitated the organization of an external expert working group to engage the community that performs these procedures in developing recommendations for minimizing the risk of serious neurologic events. That group recently published its clinical considerations for health care providers. Although the FDA facilitated meetings, the recommendations come from the working group, not the agency.

In 2014, the FDA issued a requirement that all injectable glucocorticoid product labels carry a warning stating that “serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids” and that the “safety and effectiveness of epidural administration of corticosteroids have not been established and corticosteroids are not approved for this use.” The agency determined that the class warning was warranted on the basis of its analysis of FAERS cases and reports in the medical literature of serious neurologic events. The warning did not distinguish any difference in the risk associated with the various injection approaches (interlaminar, transforaminal, and caudal), locations of spinal injection (cervical, thoracic, lumbar, and sacral), or glucocorticoid formulations (solutions and suspensions), because the data suggested that each approach, location, and formulation was associated with some risk of neurologic injury.

We believe that it is important to warn patients and practitioners about the risk of these serious, albeit rare, adverse events and to remind providers that epidural injection is an off-label use of glucocorticoids.

The FDA held an advisory committee meeting in November 2014 to obtain external expert input on this matter and to discuss whether further regulatory actions were necessary. One key question for the committee was whether a contraindication was warranted to restrict the injection of glucocorticoids into the epidural space. Before and during the advisory committee meeting, the FDA received feedback regarding the scope of the class warning. There was a wide range of opinions, from support for stronger labeling, including such elements as a contraindication, to arguments that the warning was too broad and should focus on particular approaches, spinal regions, formulations, or some combination thereof. Many advisory committee members expressed concern about the risk of cervical transforaminal injection of suspension glucocorticoid formulas and recommended that the FDA contraindicate suspension products for this use. Some also thought that the FDA should modify its statement to say that safety and effectiveness of the injections have not been established “by the FDA.”

After carefully considering the feedback provided at the advisory committee meeting, the FDA has decided not to modify the warning about serious neurologic events. Without question, serious (sometimes fatal) neurologic events occur with epidural glucocorticoid injection. Given the large number of these procedures performed, these events appear to be rare; however, a population-based study would be needed to establish a valid estimate of their frequency. We find that available data do not currently support either a contraindication or a warning focused only on cervical transforaminal injection of suspension glucocorticoids. Although many experts believe the risk is greatest with suspensions, the available data do not support comparative safety labeling implying that solutions are safer. Such labeling could encourage practitioners to use solutions, even though their relative safety and effectiveness remain an open question. Regarding effectiveness, some published studies support the benefit of epidural glucocorticoid injection, but others call that benefit into question. Patient selection may be the key to optimizing the efficacy of epidural glucocorticoid injection, and we encourage the medical community to work to identify the types of patients who might benefit most.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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