Epidural steroid injections: An update on mechanisms of injury and safety

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Epidural steroid injections (ESIs) are the most commonly performed intervention in the United States to manage chronic and subacute low back and neck pain with radiculopathy. ESIs have been used for decades for the treatment of discogenic and osteoarthritic radicular conditions originating from the cervical, thoracic, and lumbar spine, as well as spondylosis, nonspecific radiculitis, and spinal stenosis.

With the ever-increasing use of epidural steroids, there has been a disproportionate increase in popularity of transforaminal ESIs in particular. Since 2002, there has been a growing body of largely transforaminal epidural steroid case report literature that describes paralysis, stroke, and death that immediately follows the performance of these procedures. These complications are thought to be related to a combination of factors, which may include the technique used, underlying pathophysiology that is being treated, anatomical variations in the blood supply, as well as the specific injectate used.

This article discusses the pathogenesis of these complications and puts the role of steroids in their causation into perspective.

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Background

Epidural steroid injections (ESIs) are the most commonly performed intervention in the United States to manage chronic and subacute low back pain. ESIs have been used for decades for the treatment of discogenic and osteoarthritic radicular pain originating from the cervical, thoracic, and lumbar spine, as well as spondylosis, non-specific radiculitis, and spinal stenosis. Other reported uses of epidural steroids include the treatment of pain from post-herpetic or post-traumatic neuralgia, muscle contraction headaches, or subacute inflammatory spinal pain syndrome that has not responded to more conservative treatments.

The therapeutic effects of epidural steroids are a combination of the primary physiological changes that result from the procedure and the secondary results arising from the enhanced pain control that allow integration of other therapeutic modalities. A spectrum of direct effects may provide therapeutic benefit. For example, most investigators believe the predominant benefit of epidural steroids is their anti-inflammatory effect, although their neurolytic effect on unmyelinated C-fibers has also been demonstrated. Various publications between controlled and uncontrolled trials describe success rates varying between 19% and 100%.

The epidural space entry can be accomplished via interlaminar, transforaminal, or caudal approaches. Interlaminar and transforaminal epidural steroids in the lumbar and cervical spine are the most commonly performed types of ESIs. The type and amount of steroid to inject as well as the specific mixture that may contain normal saline or local anesthetic has always been based largely on personal preferences rather than published evidence. There is no consen-
sus on the optimum steroid type or standard steroid dose in epidural injections (e.g., Depo-Medrol, Aristocort, Kenalog 40-120 mg).

The interlaminar approach is the most commonly used approach, as its performance is well-known by the greatest number of physicians. The interlaminar ESI has the advantage of providing multilevel and bilateral, albeit dorsal and not transforaminal, spread of the injectate in the epidural space that may make the interlaminar technique the more logical approach in a patient with multilevel spinal disease. The interlaminar ESI, although performed with or without fluoroscopic guidance, is largely considered a safe and effective procedure.

An alternative approach to the epidural space is the transforaminal injection. In contrast to the interlaminar technique, the transforaminal approach always uses fluoroscopy to guide a needle adjacent to or into the intervertebral foramen on one side. The steroid solution is injected directly onto the dural sleeve and spreads transforaminally into the epidural space, thus covering a greater area of nerve root inflammation than can be achieved by the interlaminar approach. In addition, the medication is deposited more anterolaterally in the epidural space, close to the area of greatest inflammation and pain production with, for example, more common posterolateral herniations. A transforaminal peridural nerve root sleeve and central canal epidural steroid spread has the potential to treat the inflammation at the injected nerve roots and the dorsal root ganglions, anterolateral dura, posterior longitudinal ligament, and at the nerve supply of the intervertebral disc. Therefore, relief of axial and/or radicular pain can occur. This arguably technically improved injection at the site of the lesion and the improved spread of the steroid may therefore be more effective. The transforaminal epidural steroids may also have utility in diagnosis of clinically significant foraminal stenosis and prognosticating surgical outcomes of foraminotomy.6

With the ever-increasing use of epidural steroids, there has been an increase in popularity of transforaminal ESIs in particular. There are several reasons for the increased popularity of transforaminal epidural steroids. Although randomized, prospective, comparative studies looking at outcomes between fluoroscopic interlaminar and transforaminal epidural steroids are lacking, there is a general opinion that a transforaminal epidural steroid provides superior steroid spread in terms of laterality, anterior epidural space, and nerve root.

Since 2002, there have been a growing number of transforaminal epidural steroid case reports that describe paralysis, stroke, and even death that follow these procedures. They are thought to be related to a combination of factors that may include the approach used, underlying pathophysiology that is being treated, anatomical variation of the blood supply, as well as the specific injectate used.1-7,12

Prospective, randomized trials comparing outcomes after fluoroscopic interlaminar and transforaminal ESIs are lacking. Despite abundant anecdotal experience around the country, the evidence for transforaminal efficacy and superiority over interlaminar ESI is scant.13 Thus, any discussion of risk versus benefit of interlaminar versus transforaminal epidural steroids must weigh the growing body of transforaminal complication literature against the lack of prospective, randomized literature evidence of superior efficacy when compared with the interlaminar approach.

Case reports and the resultant steroid controversy

In essentially all reported cases, the common thread is that the procedural physicians had longstanding experience in performing spinal steroid injections. Furthermore, despite a high level of technical competence, accepted technique, and proper injectate confirmation (supported, for example, by biplanar fluoroscopy, negative repeat aspirations, and injection of myelographic contrast), sudden or delayed-onset neurological complications occurred that have resulted in spinal cord infarctions, paraplegia, tetraplegia, brain herniation, and death.14-16

Most of these cases occurred after cervical transforaminal ESIs, although similar adverse outcomes have been described after lumbar transforaminal ESIs in operated spines as well.7

For example, prompt onset of quadriplegia after an apparently unremarkable selective cervical transforaminal ESI has been reported. This was due to a massive cerebellar and occipital cortex infarction that was followed by brainstem herniation and death. The potential role of particulate corticosteroids and its potential for microvascular embolization was entertained. Because a radicular artery embolization would not result in the type of infarction that has occurred in this case, a vertebral artery or terminal branch injury or occlusion was suspected.17

Several cases of paraplegia after lumbar transforaminal ESIs in operated lumbar spines have been reported by Houten and Errico. The proposed mechanism was vascular injury or embolization.7

Despite using standard of care technique, immediate major complications still occur. Various conclusions have been reached by authors of these and other case reports that ultimately implicate nerve ischemia and infarction as the final common pathway that resulted in the reported neural injury and, in some cases, brain edema, herniation, and death.

The exact mechanism or combination of mechanisms that may contribute to such neural injury may be due to one or more of the following factors.

1. Sustained compressive effect of the injectate that exceeds the local arterial pressure or neural perfusion pressure in the area injected producing neural ischemia.
2. Mechanical needle injury to the vasculature that disrupts the neural blood supply.
Inflammatory arterial vascular irritability that predisposes the local vasculature to vasospasm from an advancing needle or from the mechanical effect of the injectate itself.

A comparative model to this theory could be Prinzmetal’s angina (vasospasm of the coronary circulation). Such vasospasm can produce sufficient ischemia to produce myocardial infarction, and by the same mechanism, an inflamed epidural space and vasculature can be provoked into vasospasm by an advancing needle or injectate producing infarction in the more susceptible noncollateralized neural tissue.

4. Undetected embolization of a particulate steroid intrarterial injection.

5. Previous spine surgery appears to be an independent risk factor for spinal cord infarction. Almost all the cases of lumbar transforaminal epidural steroids resulting in spinal cord infarction were patients who had prior lumbar spine surgery. This brings up the possibility of altered anatomy, vascular relocation, neovascularization, and scar tissue vascularization that anastomoses with the existing spinal or radicular blood supply.

6. Although least likely, an intraosseous injection (due to osteopenia) with a particulate steroid has been demonstrated to travel to the inferior vena cava. It is questionable whether such communication can occur with the arterial circulation leading to cerebrovascular or spinal embolization or whether venous embolism of steroid particles would be of sufficient caliber to result in neural damage.

The pathogenesis of the final injury may be due to any one of the above factors alone or a combination of them. There has been much discussion of types of steroids injected in the epidural space and specific focus on particulate steroid size in relation to the inner blood vessel diameter in the region. However, when the particulate steroid embolization is put into perspective, it is only one of many potential explanations for neural injury.

In all the reported cases, the exact nature of the events that led to these complications (vasospasm, disruption, embolic occlusion) is unknown. Therefore, even with strict adherence to proper technique arterial spasm, arterial disruption or embolization is still a rare but real possibility.

The commonly used technique of detecting a flashback of blood in the needle hub is only 44.7% sensitive when used to identify intravascular penetration.

In a separate study involving 191 fluoroscopically guided lumbosacral transforaminal ESIs, using intermittent fluoroscopy to identify proper segmental positioning followed by live anteroposterior fluoroscopy during injection of contrast, there was a reported 8.9% incidence of simultaneous epidural and vascular injection pattern, as well as a 4.2% incidence of vascular injection alone, totaling a 13.1% incidence of vascular penetration. The study recommended that live fluoroscopy, as opposed to intermittent imaging, be used during injection so as not to miss simultaneous epidural plus intravascular injection.

Any performance of transforaminal ESI potentially puts the radicular artery at risk of puncture, vasospasm, disruption, or occlusion. This fact is made more problematic by the variations in the location of the radicular artery within the cervical or lumbar intervertebral foramina.

As documented by multiple investigators, there is wide anatomical variation of the vascular presence within the foramen. In essence, no absolute, valid, and consistent anatomical advice can be given with respect to needle placement, and larger anatomical studies are needed to ascertain the exact extent of the anatomical vascular variability within the neural foramina. Due to this lack of anatomical consistency, there is little cogent information regarding level of entry, extent of entry into the foramen, and vertical location of the needle tip in the foramen.

**Anatomy**

The spinal cord receives its vascular supply from one anterior spinal artery and two posterior spinal arteries.

A single anterior spinal artery feeds the anterior two-thirds of the spinal cord along its entire length and receives its supply near the cervicomedullary junction from the vertebral arteries via two anterior spinal branches. The spinal cord and the nerve roots also receive their blood supply from radicular arteries, which take off from the aorta and travel at each of the vertebral levels through the neural foramen along with each nerve root bilaterally. These radicular arteries primarily supply the nerve root, entering the intervertebral foramina just inferior to the exiting spinal nerve and travel a tortuous path in the anterior inferior aspect of the foramina. Further, in a cadaveric dissection, it was found that radicular arteries that arise from vertebral arteries tend to course in the anteromedial portion of the foramen. The most likely area in which an injection would interfere with radicular vasculature was found to be in the lower cervical levels.

There are on average three larger radicular arteries that supply the anterior spinal cord by giving off branches superiorly and inferiorly to feed the anterior spinal artery called radiculomedullary arteries. These radiculomedullary arteries often predominate in the cervical spinal region. At the thoracolumbar levels, these arteries take off from intercostals and lumbar artery branches, which enter the foramina and continue on to supply the anterior spinal artery. Below the level of T8, there is often one large radiculomedullary branch that supplies the anterior spinal artery, called the artery of Adamkiewicz. Although its origin is variable, 85% of the time it takes off from the left side between the levels of T9 and L2, at times as low as at lower lumbar levels, rarely as low as S1 and most often at L1. There have been noted cases where the artery of Adamkiewicz has a higher thoracic take-off point and supplies...
the anterior spinal artery via an iliac radiculomedullary branch.23

The anterior spinal artery may also receive blood supply from ascending and deep cervical arteries that anastomose with the vertebral and other arteries. The ascending cervical artery often takes off either from the inferior thyroid artery or straight from the thyrocervical trunk or subclavian artery. Of note, in one case, it was found to be large enough to be cannulated by a 22-gauge needle. The ascending cervical artery can then form anastomotic connections with the vertebral, deep cervical, or occipital arteries. The deep cervical artery is one of two divisions of the costocervical trunk that takes off from the posterior subclavian artery; the other division is the superior intercostal artery. This deep cervical artery will provide spinal branches from levels C7 to T1, the cervical radiculomedullary arteries. At the point of cervical enlargement (C5 or C6), there is a larger medullary branch that joins with the anterior spinal artery. These radiculomedullary arteries are of great clinical importance as they traverse the entire length of the intervertebral foramen medially and can be compromised during injection.

The posterior one-third of the spinal cord is supplied by two posterior spinal arteries, which are smaller and less contiguous compared with the single anterior spinal artery, and these travel in the posterolateral areas of the spinal cord.

**Comparison of particulate and nonparticulate steroid injectate formulations**

The commonly injected synthetic corticosteroids include betamethasone sodium phosphate (BSP), BSP and betamethasone acetate (BSP-BA), triamcinolone acetonide (TA), dexamethasone sodium phosphate (DSP), and methylprednisolone acetate (MA).18 They are all derivatives of the cortisol analog prednisolone and have greater anti-inflammatory properties than cortisol.20,26 The half-life of these formulations ranges from 36 to 72 hours, which is related to particulate steroid size. The solutions with larger particles, and therefore a presumably longer half-life, would seem to be the preferred choice of injectate. These depot formulations would provide several weeks of sustained anti-inflammatory effect over the injected area and therefore presumably a greater degree of therapeutic effect.

In a microscopic comparative analysis between the various formulations, there were significant differences found between the synthetic compounds. It is apparent that the BSP formulations have the fewest proportions of the largest sized particles in excess of 50 μm, whereas MA has the greatest amount of large particles. Of the two injectates with intermediate amounts of large particles—TA and DSP—TA tended to aggregate into larger particles measuring greater than 100 μm.

Some have suggested that the larger the particulate size, the more likely it is that vessels which lie in the path of a transforaminal injection will become occluded and cause ischemia or infarction of the supplied area, potentially explaining the reported complications.

There are little data that compare outcomes with particulate and nonparticulate steroids. Donnell and coworkers compared 8 mg dexamethasone with 80 mg triamcinolone mixed with 2 cc 1% lidocaine. All patients received 2 level lumbar transforaminal ESIs. The average change in the visual analog scale was analyzed at the end of treatment. The triamcinolone group had an average visual analog scale decrease of 2.87 versus 1.21 for the dexamethasone group (P = 0.0037). The pain completely resolved in 15 patients receiving triamcinolone versus 4 of those patients who received dexamethasone and experienced complete pain relief.27

The epidural steroids efficacy literature has almost exclusively used particulate steroids in achieving favorable outcomes. Prospective, randomized, comparative analyses of particulate and nonparticulate steroids are lacking. In the absence of data to the contrary, use of nonparticulate steroids in ESIs likely compromises efficacy and may be no safer than the more popular and standard of care particulate steroids due to other mechanisms of injury that are still present when nonparticulate steroids are used.

**Conclusions and considerations to improve epidural steroid injection safety**

While making recommendations to enhance safety, it should be noted that there is incomplete evidence to formulate guidelines for a specific type of technique, practice modification, or type of steroid used. Given the potential for various types of vascular neural injury that range from vasospasm to mechanical injury to particulate matter embolization and the essential absence of efficacy or safety data on nonparticulate steroids, such as dexamethasone, it would be inappropriate to advocate use of one category of steroid over another or one particular type of steroid over another. It is also notable that neural injury that is explained by vascular injury was also described in the absence of steroid injection.28

The sustained duration of the anti-inflammatory effect of particulate steroids is postulated to be responsible for the weeks and months of improvement our patients report with epidural steroids. Nonparticulate steroids such as dexamethasone do not provide sustained anti-inflammatory effects and have virtually no data supporting their use in ESIs. Because the nonparticulate steroids would be promptly absorbed systemically and dissipate from the injected area, they are likely no better than if they were injected intravascularly.

Back bleeding is unreliable in detecting intravascular entry. Live fluoroscopy while the myelographic contrast is being injected can be used to exclude intra-arterial needle location before injection of particulate steroid.29
Contrast injection and digital subtraction analysis is an imaging technology that can enhance the detection of intravascular contrast uptake during transforaminal ESIs.

Real-time digital subtraction technology digitally "subtracts" the baseline radiograph from serial images. It has been demonstrated to reduce the incidence of intravascular injection. It is important to note that, although the incidence of detection of intravascular injection is statistically significantly higher with digital subtraction analysis, it is still not 100%. For example, the needle could move after the real-time imaging before the injectate is given. Furthermore, use of this imaging technology may be providing us with a capability that does not address other mechanisms of ischemic insult, such as mechanical injury to the blood supply or vasospasm.

Hodges and coworkers emphasize the dangers of sedation when performing cervical ESIs. Sedation increases the possibility that the patient may not be able to verbalize pain or other abnormal sensations that might occur during the procedure that could indicate a complication.

Despite general discussion in the literature about excluding patients with preexisting vascular disease or spinal surgery from getting a transforaminal epidural steroid, there is no real information to base this conclusion on. It would be unfortunate to exclude and limit the use of these techniques to nonoperated spines, for example. What would we do with those patients with disabling recurrent disc herniations and stenotic adjacent segment disease? Furthermore, vascular anomalies occur even in nonoperated patients with lumbar-sacral radiculopathy.

Another safety factor that has been mentioned is use of blunt-tip needles that may reduce the probability of arterial entry, although this has never been proven to be the actual source of the problem. Furthermore, it can’t be stated with certainty that a blunt needle would eliminate intravascular entry or prevent vasospasm or vessel injury.

There is absence of comparative outcome studies that favor one type of ESI approach over another. Therefore, given the higher incidence of vascular complications reported in the literature with the performance of transforaminal ESIs, the interlaminar ESI can be considered a safer alternative. An argument can also be made to provide the first injection consistently as an interlaminar ESI. If the patient response is inadequate in 1-2 weeks, only then can a transforaminal ESI be considered.

When a transforaminal ESI is being performed, consideration should be given to the extent of the needle entry into the neuroforamen. The needle tip can be placed at the entrance to the foramen, paraforaminal, or as far away from the foramen as possible while also allowing the injectate to disperse on to the dural sleeve so the steroid can spread into the foramen and the anterior epidural space.

During the performance of a transforaminal ESI, the needle should be completely immobilized during and after contrast injection as well as while connecting the syringe or the microbore extension to eliminate any subsequent needle movement after final placement and therefore potential entry into a vascular space.

Should the number of attempts in a transforaminal injection be limited in presence of vascular spread? The answer to this question is likely affirmative. Although the authors are unable to provide a specific number, one or two instances of arterial spread should probably result in termination of procedure without further attempts.

ESIs are considered by many to be an important part of the multidisciplinary plan of care in the radiculopathy patient. As discussed in this article, limiting the resulting controversy over the case reports to the type of steroid injected oversimplifies the pathophysiology complexity and ignores many of the other factors that can also contribute to similar injury and the role of the transforaminal approach in these cases.

In our efforts to maximize epidural steroid efficacy and safety, the type of steroid injected should be part of the greater discussion that includes discussion of relative safety of interlaminar versus transforaminal techniques and the multiple plausible alternative mechanisms of neural injury discussed in this article.

References