

Health Policy Review



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On April 23, 2014, the Food and Drug Administration (FDA) issued a letter of warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, including "loss of vision, stroke, paralysis, and death." The advisory also advocated that patients should discuss the benefits and risks of epidural corticosteroid injections with their health care professionals, along with the benefits and risks associated with other possible treatments. In addition, the FDA stated that the effectiveness and safety of the corticosteroids for epidural use have not been established, and the FDA has not approved corticosteroids for such use.

To raise awareness of the risks of epidural corticosteroid injections in the medical community, the FDA's Safe Use Initiative convened a panel of experts including pain management experts to help define the techniques for such injections with the aim of reducing preventable harm. The panel was unable to reach an agreement on 20 proposed items related to technical aspects of performing epidural injections. Subsequently, the FDA issued the above referenced warning and a notice that a panel will be convened in November 2014.

This review assesses the inaccuracies of the warning and critically analyzes the available literature. The literature has been assessed in reference to alternate techniques and an understanding of the risk factors when performing transforaminal epidural injections in the cervical, thoracic, and lumbar regions, ultimately resulting in improved safety.

The results of this review show the efficacy of epidural injections, with or without steroids, in a multitude of spinal ailments utilizing caudal, cervical, thoracic, and lumbar interlaminar approaches as well as lumbar transforaminal epidural injections. The evidence also shows the superiority of steroids in managing lumbar disc herniation utilizing caudal and lumbar interlaminar approaches without any significant difference as compared to transforaminal approaches, either with local anesthetic alone or local anesthetic and steroids combined.

In conclusion, the authors request that the FDA modify the warning based on the evidence.

Key words: Chronic pain, epidural injections, epidural steroids, local anesthetic, radicular artery, complication.

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The US Food and Drug Administration (FDA) was established in 1906 through the passage of the Federal Food and Drugs Act. It seems that for almost as long, controversy has existed with multiple

organizations criticizing either over- or under-regulation. The FDA is an agency of the US Department of Health and Human Services (HHS), currently separated into 5 centers which oversee a majority of

the organizations' obligations involving food, drugs, cosmetics, animal food, dietary supplements, medical devices, biological goods and blood products (1,2). Every year, the FDA monitors the testing of 3,000 new drugs on nearly 200 million people to determine their effects. The FDA also issues numerous warnings, on a daily basis, over drug safety. A 2006 Institute of Medicine (IOM) report on pharmaceutical regulations in the US found major deficiencies in the FDA system for insuring the safety of drugs in the American market. The \$1.8 million IOM report called for an increase in the regulatory powers, funding, and independence of the FDA (3,4). However, others claim that the FDA possesses excessive regulatory and expanding authority without much evidence and consistency (5-11).

Among the myriad of approvals, warnings, criticisms, and praises; 2 recent actions by the FDA (12,13) related to the management of chronic, persistent, intractable pain have elicited enormous criticism – 1) approval of Zohydro despite an 11 to 2 decision against it by their own advisory committee and 2) the unprecedented warning related to corticosteroid epidural injections without scientific analysis of the evidence or even reliance on consensus. This discussion is related to the latter– the warning on epidural corticosteroids.

THE WARNING

On April 23, 2014, the FDA sent a letter of warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, including “loss of vision, stroke, paralysis, and death” (12). This warning also stated that the injections are given to treat neck and back pain, and radiating pain in the arms and legs. The FDA is requiring the addition of a warning to the drug labels of injectable corticosteroids to describe these risks. The advisory also advocates that patients should discuss the benefits and risks of epidural corticosteroid injections with their health care professionals, along with the benefits and risks associated with other possible treatments.

Furthermore, the FDA warning also comments that injectable corticosteroids are commonly used to reduce swelling or inflammation and injecting corticosteroids into the epidural space of the spine has been a widespread practice for many decades; however, the effectiveness and safety of the drugs for this use have not been established, and the FDA has not approved corticosteroids for such use (12). They also allude to the history of FDA involvement which led to their investigation of the safety issues when they became aware of

medical professionals' concerns about epidural corticosteroid injections and the risk of serious neurologic and adverse events (14). This concern prompted the FDA to review cases in the FDA Adverse Event Reporting System (FAERS) database and in the medical literature (15-29). The FDA alluded to the fact that to raise awareness over the risks of epidural corticosteroid injections in the medical community, the FDA Safe Use Initiative (12) convened a panel of experts, including pain management experts to help define the techniques for such injections which would reduce preventable harm. However, this warning has not included any of the expert panel's recommendations (12). Further, the FDA has included in the warning that as part of the FDA's ongoing effort to investigate this issue, the FDA plans to convene an advisory committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.

INACCURACIES OF WARNING

While it is accurate that the FDA has not approved the use of epidural steroids to manage painful spinal conditions, these injections have been used to treat radicular types of pain since 1952 and have been safely administered to hundreds of millions of patients not only in the US, but also worldwide (30-35). The FDA Drug Safety Communication contains 15 references supporting their stance (15-29). Of these 15 references, 6 of them were related to cervical transforaminal epidural injections or nerve root blocks (16-18,22,25,28); 4 were related to lumbar transforaminal or selective nerve root blocks (15,19,26,27); one was related to thoracic interlaminar (20); 2 were related to cervical interlaminar epidural injections (21,29); with one case report of cervical paravertebral injection (24); and one C1-C2 intraarticular facet steroid injection (23). Table 1 is an analysis of these reports.

We believe that the FDA and its advisors have not reviewed all of the relevant literature. Further the authors believe that the reviewed literature was improperly assessed leading to inappropriate conclusions. As stated by the FDA, an editorial (14) published in 2009 was in response to a manuscript describing potential intraarterial flow patterns in 15% of cervical transforaminal epidural injections (36). Increased intravascular flow patterns in transforaminal epidural injections have been demonstrated in multiple manuscripts with significantly higher flow rate or intravascular penetration in the cervical spine as compared to the lumbar spine (37-

Epidural Steroid Warning Controversy Still Dogging FDA

Table 1. Description of literature presented by the FDA

References used in the FDA letter	Type of Article	Number of Patients	Approach	Type of Steroids	Imaging guidance
Rathmell, 2009 (14)	Editorial	N/A	Transforaminal		
Kennedy et al, 2009 (15)	Case Reports	1 1	Lumbar transforaminal	6 mg betamethasone + 1 mL 0.75% bupivacaine 160 mg methylprednisolone + 6 mL 0.375% bupivacaine	Fluoroscopy CT
Windsor et al, 2003 (16)	Case reports Literature review	1 1 1	Cervical transforaminal	First case: Not specified Second case: 6 mg of Celestone plus 1.5 mL of solution from a total of 2.5 mL of 0.75 bupivacaine and 6 mg of Celestone Third case: 1.5 mL of injection of solution derived from 2% lidocaine and 6 mg of Celestone	Fluoroscopy
Beckman et al, 2006 (17)	Case Report	1	Cervical transforaminal	60 mg methylprednisolone + 0.75 mL 1% lidocaine	Fluoroscopy
Ludwig & Burns, 2005 (18)	Case Report	1	Cervical transforaminal	0.75 mL triamcinolone + 0.75 mL 0.75% bupivacaine	Fluoroscopy
Somayaji et al, 2005 (19)	Case Report	1	Lumbar nerve root injection (transforaminal)	40 mg triamcinolone + 1 mL 0.5% bupivacaine	CT
Tripathi et al, 2005 (20)	Case Report	1	Thoracic interlaminar	40 mg triamcinolone + 10 mL 0.125% bupivacaine	Fluoroscopy
Bose B, 2005 (21)	Case Report	1	Cervical interlaminar	80 mg methylprednisolone acetate	Fluoroscopy (no films?)
Tiso et al, 2004 (22)	Case Report	1	Cervical transforaminal	80 mg triamcinolone + 2 mL 0.25% bupivacaine	Fluoroscopy
Edlow et al, 2010 (23)	Case Report	1	Cervical facet joint injection	80 mg triamcinolone	None
Meyer et al, 2005 (24)	Case Report	1	Cervical paravertebral injection	5 mL cortisone and Xylocaine	None
Suresh et al, 2007 (25)	Case Report	1	Cervical transforaminal	40 mg triamcinolone	CT
Deshpande et al, 2005 (26)	Case Report	1	Lumbar nerve root injection (transforaminal)	6 mg betamethasone + 1 mL 0.5% bupivacaine/epinephrine	
Lyders et al, 2009 (27)	Case Report	1	Lumbar transforaminal	1 mL triamcinolone + 0.25% bupivacaine	Fluoroscopy
Popescu et al, 2007 (28)	Conference Abstract Case Report	1	Cervical transforaminal	methylprednisolone	Fluoroscopy
Ziai et al, 2006 (29)	Case Report	1	Cervical interlaminar	40 mg methylprednisolone acetate	

Adapted and modified from: Candido KD, Knezevic NN, Chin GC, Deer TR. The Food and Drug Administrations recent action on April 23, 2014 failed to appropriately address safety concerns about epidural steroid use. *Pain Physician* 2014; 17:E509-E524(11).

45). In response, Rathmell (14) offered digital subtraction technology as the solution. Further, he also posed critical questions: should we move to the routine use of non-particulate steroid or abandon the transforaminal technique altogether. Among the remaining 15 references (15-29) utilized in the FDA warning, 6 of them were concerned with cervical transforaminal epidural injections or nerve root blocks (16-18,22,25,28).

Windsor et al (16) reviewed the literature concerning complications and suggested an alternate technique in performing cervical transforaminal epidural injections. They reported 3 case reports, with one fatality and 2 disabling complications. All 3 procedures were performed under fluoroscopy at the C6 level on the left side injecting bupivacaine with betamethasone in 2 cases and lidocaine with betamethasone in another. More importantly, these authors discussed the reasons for the complications and suggested an alternate technique. Windsor et al (16) described entering the foramen adjacent to the caudal half. Huntoon (46) described the anatomy of the cervical intervertebral foramina along with vulnerable arteries and distinct neurologic changes after transforaminal epidural injections. Beckworth et al (47) also described the anomalous location of the vertebral artery in relation to the neural foramen and showed that the severity of foraminal stenosis and loss of disc height correlated with vertebral artery proximity to typical needle location. Huntoon (46) also concluded that the artery would only be injured by anterior needle misplacement. In addition, Hoefl et al, (48) utilizing pre-mortem angiography and post-mortem latex-injection into vasculature to trace radicular arteries entering the foramen either anteriorly or posteriorly to supply the anterior and posterior spinal arteries, noticed that the artery was of a large enough caliber to be entered by a 22-gauge needle. They further described that in the presence of wide anatomic variation in the origin and location of these vessels, it is possible that an appropriately placed needle could penetrate the radicular artery, despite adherence to strict and correct technique of fluoroscopically guided needle insertion (48). Consequently, multiple alternate techniques were described utilizing solely an extraforaminal approach (49-51); a dorsal approach with the patient in the prone position (52); a posterior approach (53); with the needle location at the outer edge of the posterior foramen (54,55); a blunt needle technique (56); an anterolateral approach (57,58); approach in an upright sitting position; and utilizing a TRUCATH (59,60). Essentially, none of these issues were considered in issuing the FDA warning.

The second manuscript was related to a cerebellar herniation after cervical transforaminal epidural injection by Beckman et al (17). In this report, the patient underwent a right C8 nerve root injection for a C7-T1 herniated nucleus pulposus using a 25-gauge 2½" short-bevel needle under propofol sedation with injection of 60 mg of methylprednisolone combined with 1% lidocaine. The patient developed a cerebellar infarct and brainstem herniation. The patient survived with residual deficits of persistent diplopia and difficulties with short-term memory loss and concentration. The authors considered sedation and lack of digital subtraction capability on the C-arm as crucial factors. This report elicited 2 letters to the editor (61,62). Provenzano and Fanciullo (61) reviewed the issues related to this case while the primary author of the letter expressed that he was convinced that cervical transforaminal epidural steroid injections should not be performed. The second letter by de Leon-Casasola (62) pointed to the 2 critical points that were noteworthy, which included that the patient did not have symptoms immediately after the steroid/local anesthetic injection and difficulty of explanation of a 25-gauge 2.5" short-bevel needle resulting in dissection of the vertebral artery and postulated that the patient already had a small dissection of the vertebral artery and that there was an unintentional artery puncture during the procedure that resulted in a small hemorrhage between the intima and the wall of the artery that led to further dissection and thrombosis that may better explain the mechanism of injury.

The third report of cervical transforaminal epidural injections relates to the case report by Ludwig and Burns (18) with a single case report of C6 cervical transforaminal epidural injection resulting in spinal cord infarction without direct spinal cord trauma with the procedure being performed with the patient alert, conscious and intravenously sedated and during which there was injection of 0.75 mL of 0.75% bupivacaine and 0.575 mL of triamcinolone.

The fourth case is related to adverse central nervous system sequelae following selective transforaminal block by Tiso et al (22). In this case report, the authors accessed the right C5-C6 foramina with a 25-gauge 2-inch Quincke tip spinal needle and injected 2 mL of contrast medium, followed by 2 mL of 0.25% bupivacaine mixed with 80 mg of triamcinolone injected through micro-bore tubing with frequent negative aspirations. In this patient, quadriplegia ensued shortly after injection of the corticosteroid solution with brainstem herniation. The authors proposed corticosteroid particulate

embolus as a potential mechanism, during unintended intra-arterial injection. In a letter to the editor, Aprill and Dumitrescu (63) described multiple reasons, including significant obesity of the patient (5'2" and 300 lb), and without a lateral radiograph which would be extremely difficult to obtain in a patient of such size, and a fluoroscopy time of 7 seconds. It was also questioned whether if the figure presented in the manuscript itself was a true picture of this particular patient or just a typical fluoroscopic pattern; the cervical spine was rotated to 90° which was considered a poor technique, and finally was criticized for the description of nonionized contrast medium, which should be nonionic contrast medium. The letter also suggested that even though digital subtraction is important, and should be employed if available, it does not replace careful visualization of the active fluoroscopically controlled injection, along with stressing the importance of the test dose of lidocaine.

The fifth manuscript by Suresh et al (25) described cerebellar and brainstem infarction as a complication of CT-guided transforaminal cervical nerve root block. In this case, a left C5 nerve root block was performed in a 60-year-old man under CT-guidance, using a 25-gauge spinal needle and injection of 0.3 mL of contrast medium followed by 1 mL of triamcinolone without local anesthetic. Immediately, the patient became unresponsive, and later developed a cerebellar and brainstem infarct affecting the left vertebral artery territory. The authors described it as the first report of a major complication of a cervical root injection under CT-guidance reported in the literature (article published in 2007); however, only a very small proportion of procedures are performed under CT-guidance (64).

The final manuscript was a case report of stroke following epidural injection (28) and subsequent publication of a literature review by Popescu et al (65). In this case, the authors described a 66-year-old woman undergoing transforaminal epidural steroid injection with a 22-gauge Quincke needle at the C5-C6 level developing flaccid quadriplegia following injection of 40 mg of methylprednisolone acetate. The authors' review also described the seminal report by Scanlon et al (66), which reported 78 complications following cervical transforaminal epidural injections including 30 infarction cases of which 13 cases resulted in fatalities, which also was not included in the FDA advisory. In addition, Popescu et al (65) found 6 cases of posterior circulation infarction and 10 cases of spinal cord ischemia following cervical transforaminal epidural steroid injections.

They postulated that the injury was likely due to ischemia in the distribution of the radicular artery that feeds the anterior spinal artery.

Scanlon et al (66), in a survey of 287 physicians, reported 78 complications, including 16 vertebral brain infarcts, 12 cervical spinal cord infarcts, and 2 combined brain/spinal cord infarcts. Of the 30 major complications (infarcts) reported, 13 cases resulted in fatal outcomes: 5 with brain infarcts, one with combined brain/spinal cord infarct, one following high spinal anesthesia, one associated with a seizure, and 5 with unspecified etiology (66). All 4 cases with corticosteroid alone involved methylprednisolone, resulting in 3 cerebellar infarcts and one posterior cerebral territory infarct. Of these, 3 had fatal outcomes and 2 autopsies revealed no vertebral artery trauma. Vertebral artery trauma was found in 3 cases, resulting in a fatal brain stem infarct, cervical spinal cord infarct, and death of unspecified etiology. In addition, one case had possible vertebral artery dissection, resulting in brain edema, dysarthria, and vertigo, which resolved after 5 days. Popescu et al (65), in a review of the literature, identified 16 cases of spinal cord and posterior circulation ischemia. Of these, 2 cases had transient symptoms and 10 had long-term sequelae with 4 resulting in death.

Engel et al (67), in a 2014 manuscript, systematically reviewed and analyzed the published data with effectiveness and risks of fluoroscopically guided cervical transforaminal injections of steroids. Their search yielded 21 articles with primary reports of serious complications, including 13 deaths and many catastrophic neurological injuries. They also included the findings from Scanlon et al (66); however, Engel et al (67) were unaware of how many of the 24 case reports described by them were included in the complications related to Scanlon et al's survey (66). They assumed that all 15 that occurred until 2007 were included. Thus, the results by Engel et al added another 10 fatal events and 53 other serious consequences to the complications reported specifically in the literature. Table 2 shows the reported complications of cervical transforaminal epidural injections as shown by Engel et al (16,22,17,18,67-83).

We believe it critical to point out that, the FDA has missed significant and valuable literature and a multitude of techniques with alternate approaches and other preventive modalities instead of focusing on only limited aspects (49-60,66,67).

The FDA warning also showed 4 reports of complications of lumbar transforaminal or selective nerve root blocks (15,19,26,27). The first case report was by Kenne-

Table 2. Reported risks of CTFIS, expressed as complications described specifically in the literature.

Brouwers et al, 2001 (68)	Spinal cord infarction leading to death
McMillan and Crumpton 2003 (69)	Cerebral injury and cortical blindness (persistent)
Rozin et al, 2003 (70)	Vertebral artery occlusion leading to death
Windsor et al, 2003 (16)	Lateral spinal cord infarction (persistent)
Windsor et al, 2003 (16)	Cerebral ischemia and hippocampal atrophy (persistent)
Windsor et al, 2003 (16)	Posterior spinal cord and cerebellar infarction (persistent)
Tiso et al, 2004 (22)	Cerebellar and cerebral infarction leading to death
Karasek and Bogduk 2004 (71)	Quadriplegia (transient)
Ludwig and Burns 2005 (18)	Spinal cord infarction leading to quadriplegia (persistent)
Beckman et al, 2006 (17)	Cerebellar infarction and brainstem herniation (persistent)
Wallace et al, 2007 (72)	Cortical blindness, paresis of face, and upper limbs (transient)
Muro et al, 2007 (73)	Spinal cord infarction leading to quadriplegia (persistent)
Ruppen et al, 2008 (74)	Paralysis of right leg (transient)
Lee et al, 2007 (75)	Epidural hematoma causing paraplegia (transient)
Schellhas et al, 2007 (76)	Grand mal seizure (transient)
Lee et al, 2008 (77)	Spinal cord injury leading to quadriparesis (persistent)
Lee et al, 2010 (78)	Quadriplegia (transient)
Kim et al, 2011 (79)	Cerebral edema and cortical blindness (transient)
Chung 2011 (80)	Grand mal seizure (transient)
Kaplowitz and Lee 2011 (81)	Horner's syndrome (persistent)
Tofuku et al, 2012 (82)	Flaccid paralysis (transient)
Chung et al, 2012 (83)	Causalgia (transient)
Chung et al, 2012 (83)	Horner's syndrome (transient)
Scanlon et al, 2007 (66)	10 additional complications causing death
Scanlon et al, 2007 (66)	53 additional serious but non-fatal complications
Total	13 deaths
	31 brain and spinal cord infarctions
	Numerous other serious and persistent CNS injuries

Adapted and modified from: Engel A, et al; Standards Division of the International Spine Intervention Society. The effectiveness and risks of fluoroscopically guided cervical transforaminal injections of steroids: A systematic review with comprehensive analysis of the published data. *Pain Med* 2014; 15:386-402 (67).

dy et al with Bogduk as the senior author (15) presenting 2 cases of transforaminal epidural injections, one of them performed under computed tomographic (CT) guidance. The first case involved an 83-year-old woman undergoing a fluoroscopically guided, left L3-L4 transforaminal injection of betamethasone and the second case involving a 79-year-old man undergoing a CT-guided right L3-L4, transforaminal injection of methylprednisolone). Both patients developed bilateral lower extremity paralysis, with neurogenic bowel and bladder, immediately after the procedure with magnetic resonance imaging (MRI) findings consistent with spinal cord infarction. Even though one case was performed

under fluoroscopy and the other one under CT guidance, in both cases the authors utilized the traditional safe triangle approach (84-86). In addition, a seemingly inordinately high incidence of intra-arterial injections has been reported with lumbar transforaminal epidural injections even though these are performed under CT guidance in a small proportion of patients (84). Further, in this case the authors also have performed the procedures at L3-L4 bilaterally which is considered as a high-risk zone along with injection of particulate steroids.

The second report involves spinal cord infarction following therapeutic CT-guided left L2 nerve root injection (19). The procedure was performed in a 21-year-

old woman presenting with symptoms and signs of left L2 nerve root compression. One mL of 0.5% bupivacaine and 40 mg of triamcinolone was injected under CT guidance. Immediately after the injection the patient developed bilateral sensory loss and paraplegia. An MRI demonstrated spinal cord infarction. The authors reported this as their fourth case of spinal cord infarction following nerve root injection as of 2005. There was a letter to the editor from Martin and Huntoon (87). In this letter they alluded to the fact that CT guidance cannot distinguish entry into radicular vessels and thus is not necessarily superior to fluoroscopic placement.

The third case report of lumbar transforaminal epidural injections included in the FDA advisory was by Deshpande et al (26) reporting transverse myelitis after a lumbar steroid injection in a patient with Behçet disease. The report involved a 42-year-old woman with undiagnosed Behçet disease undergoing a CT-guided nerve root injection to alleviate L2 radicular pain. The procedure was performed with a 22-gauge needle utilizing one mL of 0.5% bupivacaine and 6 mg of betamethasone with the patient beginning to experience bilateral lower extremity weakness, urinary urgency and paresthesias, extending rostrally to a T12 level within 8 hours after the procedure. A spinal cord MRI the following day revealed edematous changes with gadolinium enhancement from the conus medullaris extending rostrally to T9. Subsequent treatment resulted in incomplete recovery. The authors believe that Behçet disease may correlate with complications following spinal punctures; however, the procedure was performed under CT guidance and was performed at L2.

In the fourth case report by Lyders and Morris (27), spinal cord infarction was reported following a lumbar transforaminal epidural steroid injection with MR imaging and angiographic findings. The injection was performed on a 54-year-old woman with an acute-on-chronic disc herniation at L1-2 presented for transforaminal epidural injection at L2-3 on the right side. The procedure was performed with a 22-gauge spinal needle and injection of 2 mL of contrast medium, followed by one mL of triamcinolone and 0.25% bupivacaine. Within minutes of the injection, the patient developed bilateral lower extremity weakness, which progressed into flaccid paralysis. The postprocedure CT of the thoracolumbar spine demonstrated no evidence of epidural hematoma within 1.5 hours of the injection. An MRI of the spine performed approximately 4 hours after the injection revealed spinal cord infarct. A catheter-directed spinal angiography showed presumed occlusion of

the L2 segmental artery with the right L3 segmental artery demonstrating collateral vessels coursing toward the right L2-3 foramen, with irregular attenuated reconstitution of the distal L2 segmental branch and radicular artery. This procedure was performed at the L2 level with injection of particulate corticosteroid and the safe triangle approach (84).

Thus, the FDA advisory has included only 5 cases from 4 reports (15,19,26,27), of which 2 of them were performed under CT guidance and all of them were performed above the L3 levels either on the left side or the right side utilizing particulate steroids and also utilizing the safe triangle approach in which the artery accompanies the nerve in the majority of the cases therefore targeting the artery as well as the nerve (84). The FDA warning did not cite the comprehensive review of lumbar transforaminal epidural injections by Atluri et al (84). In this comprehensive review, the authors reported 18 cases of paralysis from transforaminal epidural injections with ability to analyze the position of the needle within the neural foramen based on the available images and/or description among only 10 of the 18 cases. Surprisingly, 5 of the 18 cases were performed with CT guidance and 12 cases were performed with fluoroscopic guidance with one case of unknown imaging modality. Their data essentially showed that in 77.7% of the cases the needle was in the superior part of the foramen and in 71.4% of the cases the needle was in the anterior part of the foramen, coinciding with the location of the radicular artery in the foramen. Atluri et al (84) also provided extensive discussions on risk factors and alternate approaches improving the safety by avoiding the so-called safe triangle and entering into the foramen at the inferior aspect. The alternate approaches (84) are in contradiction to classic approaches and teaching (86,88,89). Table 3 shows the features of lumbar transforaminal epidural injections resulting in complications (15,19,27,85,90-96).

The next report in the FDA advisory relates to a thoracic interlaminar epidural injection (20). Tripathi et al (20) reported paraplegia following injection into the spinal cord during attempted epidural steroid injection in an awake patient. The case involved a 62-year-old man patient weighing 172 lb, with unknown height, with distribution of pain from T12 to L2 nerve roots. Under fluoroscopic assistance, the T11-12 epidural space was identified by using an 18-gauge Tuohy needle and loss of resistance technique. A test dose of 3 mL of 1.5% lidocaine with epinephrine was used resulting in no hemodynamic or neurological changes after 3

Table 3. Variables related to location of needle placement.

Author	Steroid	Local Anesthetic Injected	Post-Procedure MRI
Houten & Errico (90)	Celestone (12 mg)	0.25% Bupivacaine (1 mL)	Edema in distal thoracic cord
Houten & Errico (90)	40 mg Depo-Medrol (1 mL)	1% Lidocaine (1 mL)	Edema in distal spinal cord
Houten & Errico (90)	40 mg Depo-Medrol (1 mL)	1% Lidocaine (1 mL)	Edema in lower thoracic cord
Glaser & Falco (92)	50 mg Triamcinolone (2 mL)	1% Ropivacaine (1 mL)	Spinal cord infarction from T5 to conus
Huntoon & Martin (91)	40 mg Triamcinolone	0.25% Bupivacaine (4 mL)	Altered T2 signal in T11-T12 cord
Somayaji et al (19)	40 mg Triamcinolone (1 mL)	0.5% Bupivacaine (1 mL)	Infarction of distal thoracic cord and conus
Quintero et al (93)	125 mg of Hydrocortisone	NI	No changes in MRI 3 months later
Kennedy et al (15)	6 mg Celestone (1 mL)	0.75% Bupivacaine (1 mL)	Infarction of grey matter of conus and distal thoracic cord
Kennedy et al (15)	120 mg Depo-Medrol (2 mL)	0.375% Bupivacaine (6 mL)	Infarction from T9 to tip of conus
Lyders & Morris (27)	Triamcinolone (1 mL)	0.25% Bupivacaine (Quantity Unknown)	Increase T2 signal in distal thoracic cord
Wybier et al (94)	Prednisolone 125 mg (Quantity Unknown)	None	Central dot in conus medullaris
Glaser & Shah (85)	NI	NI	NI
Glaser & Shah (85)	NI	NI	MRI changes consistent with artery of Adamkiewicz injury
Wybier et al (94)	125 mg Prednisolone	None	T2 high intensity signal in conus
Wybier et al (94)	125 mg Prednisolone	None	T2 high intensity signal in conus
Murthy et al (96)	no name given	NI	NI
Chang Chien et al (95)	80 mg Kenalog	1 mL 1% Lidocaine	Ischemic changes in spinal cord from T6-T10

NI = No information available

Adapted and modified from: Atluri S, Glaser SE, Shah RV, Sudarshan G. Needle position analysis in cases of paralysis from transforaminal epidurals: Consider alternative approaches to traditional techniques. *Pain Physician* 2013; 16:321-334 (84).

minutes, followed by injection of triamcinolone 40 mg in 10 mL of bupivacaine 0.125%. Even though the patient reported pain relief in 5 minutes and was able to move his toes bilaterally, the authors described that the weakness in his limbs remained undetected because of his restricted mobility after hip joint fixation and weakness. Further, the patient had no pain and was also hemodynamically stable and was discharged. The next day, the patient developed paralysis at physical therapy and an MRI confirmed injection into the spinal cord. The patient's symptoms failed to improve over 4 months. This report was followed by multiple letters to the editor (97-101); however, Tripathi et al declined response to 2 letters (100,101). The majority of the criticism surrounded the improper patient selection in this case with pain location from T12 to L3 and the approach involving T11-12 and a very unusual occurrence of pain as well as injection location, questions on fluoroscopic guidance and lack of observation under lateral views, injection of local anesthetic of 10 mL of bupivacaine and the issue of development of sequelae of injection into the spinal

cord with a late onset. This case obviously suffers from incomplete data reporting and a poor technique with no relationship to injected corticosteroids. Thus, the inclusion of thoracic interlaminar epidural injections in the warning is not warranted.

The FDA warning also included 2 cervical interlaminar epidural injection reports (21,29). The first case involves quadriplegia following cervical epidural steroid injection with literature review. The case involved a 47-year-old man receiving cervical epidural injection in the C6-C7 space by a pain management specialist under fluoroscopy with no complications for the first 2 times, with the previous injection 2 weeks prior to the injection in question, using a 22-gauge Tuohy needle in the prone position and injecting methylprednisolone 80 mg/mL and iopamidol 200, 1 mL, without local anesthetic. The patient had significant degenerative vertebral column disease. The patient developed quadriplegia and respiratory arrest. The patient's symptoms improved somewhat with supportive care; the quadriplegia appeared to be reversible. The authors

claim that there were no reports of quadriplegia after cervical epidural injection in the literature until the publication of this manuscript in 2005. The authors (21) described various potential mechanisms with none providing an appropriate explanation. Most importantly the MRIs 6 hours after the injury and 6 months after the injury showed no evidence of direct trauma to the spinal cord. Their recommendation and strong theory of the effect was based on stenosis, which must be assessed prior to performing an epidural injection, perhaps, limiting the injection volume and exercising care in the speed at which it is administered. In a letter to the editor, Singh and Panagos (102), recommended performing the interlaminar epidural injection below the level of stenosis.

The second report was by Ziai (29) about a brainstem stroke following uncomplicated cervical epidural steroid injection in a 41-year-old man with a history of left-sided neck pain having received 3 cervical epidural procedures at the C5-C6 level one week apart. The injection included contrast medium and 40 mg of methylprednisolone acetate and 1 mL of preservative-free saline. No anesthetic was injected either locally or epidurally. During the third procedure, within minutes of injection, the patient developed nausea, vomiting, and headache without respiratory distress and without focal neurologic deficits. The patient was discharged home 2 hours after the procedure with some improvement in his symptoms. Approximately 7 to 8 hours after the injection the patient reported slurred speech and progressive weakness in all 4 extremities with continued deterioration in his condition including becoming unconscious and developing respiratory arrest. An initial MRI revealed diffuse ischemic infarction of the midbrain, pons, medulla, and left thalamus. The results of a cranial-cervical magnetic resonance angiography (MRA) were normal and showed patency of both vertebral arteries and basilar artery. There was no thrombus, hematoma, or dissection. Subsequent MRI showed progression of ischemia with extensive edema throughout the midbrain, pons, medulla, thalamus, right internal capsule, and medial aspect of the right temporal lobe. On autopsy, the brain demonstrated edema and hemorrhage along with microscopic hemorrhagic necrosis of the basil thalamus, hypothalamus, midbrain, pons, and medulla bilaterally consistent with infarction. There was no evidence of atherosclerosis of intracranial arteries, which were normal and patent; however, soft tissue examination showed a small area of hemorrhage within the adventitia of the left vertebral artery

at the level of C5-6 vertebrae with no evidence of dissection or vasospasm of the vertebral arteries. Based on the close proximity of the procedure and the onset of symptomatology and causal relationship established to cervical epidural steroid injection, it was postulated that in the absence of vertebral artery dissection, the procedure triggered an event such as vascular spasm of the vertebral and basilar arteries or brainstem perforators, which resulted in decreased cerebral blood flow and subsequent brainstem ischemic infarct. The spasm may have been transient, thus it was not observed on MRI, transcranial Doppler ultrasound, or autopsy. Reperfusion injury may have likely contributed to edema and hemorrhagic conversion. Vasospasm may have been caused by inadvertent intravascular needle entry, despite the use of fluoroscopic guidance with contrast medium. There is also a possibility of intradural entry of the needle and methylprednisolone acetate within the cerebral intravascular or subarachnoid space could have produced intracranial vascular spasm.

These 2 cases of cervical interlaminar epidural injections reported in the FDA advisory were without proven causal relationship to the steroid injections. Thus, the inclusion of cervical interlaminar epidural injections may not be justifiable.

There was a case report of cervical paravertebral injection (24) with fatal embolism of the anterior spinal artery after local cervical analgesic infiltration. This appears to be similar to cervical nerve root block or transforaminal epidural injection with misplacement of the needle. The case report involved a 66-year-old man with a radicular infiltration of cortisone and lidocaine 5 mL in the left paravertebral C5-6 region as well as in the region of the left shoulder without fluoroscopy with development of acute respiratory failure 2.5 hours after the treatment resulting in tetraplegia with concurrent full consciousness with assisted ventilation up to the patient's death. An MRI confirmed an ischemic lesion of the upper anterior cervical myelon with autopsy revealing pneumonia as a cause of death. Neuropathology confirmed anterior infarction at the C2-3 level of the cervical spinal cord, with obstruction of the anterior spinal artery with an embolus. This was a tragic procedure performed by a general practitioner without fluoroscopy and not related to epidural corticosteroid injections.

The final case (23) involved a C1-C2 intraarticular facet steroid injection. This case report involved a 64-year-old man with chronic cervical pain receiving a C1-C2 intraarticular facet steroid injection using a

25-gauge needle under radiographic guidance utilizing 2 mL of a 40 mg/mL triamcinolone acetone suspension. The patient immediately lost consciousness and was briefly apneic and was intubated. At autopsy, dissection of the posterior neck revealed soft tissue hemorrhage overlying the left C1-C2 facet joint. However, the cervical dura mater was intact. The vertebral arteries were also patent, with no microscopic evidence of injury to the cervical portions of the vertebral arteries. There was no arthrosclerosis, dissection, or other vascular abnormality in the intracranial cerebral arteries. Examination of the brain showed diffuse tissue softening throughout the posterior circulation territory, including the pons, inferomedial left temporal lobe, left occipital lobe, cerebellar hemisphere, and bilateral thalami. The authors discussed various mechanisms of intravascular injection with particulate steroid and postulated that devastating neurologic injury can occur not only during cervical transforaminal epidural injection, but also with facet injection as a result of particulate steroids entering the posterior cerebral circulation. In a letter to the editor, Datta and Manchikanti (103) and Tang (104) described anatomic perspectives and procedural considerations and recommended the best course of action may be to abandon the practice of performing C1-C2 or atlanto-axial injections. Thus, the inclusion of this case report is also likely not related to cervical epidural injection. Moreover, it involves an extremely risky procedure without any evidence of efficacy or effectiveness.

The FDA also quoted a reference which demonstrates the safety of these injections (105). The FDA has not provided any references in relation to the complications of either lumbar interlaminar or caudal epidural injections which are the most widely utilized epidural injections in interventional pain management. Indeed, in a prior review we reported that it constituted 74% of epidural injections during 2000; however, it decreased to 40% in the fee-for-service Medicare population during 2011 (106).

EMERGING TECHNICAL REGULATIONS

The FDA in their desire to increase awareness of the risks of epidural corticosteroid injections is also contemplating releasing multiple regulations affecting the technical aspects of performance of epidural injections. This is widely considered to be beyond the scope of FDA drug safety and is under the jurisdiction of the states.

To raise awareness of the risks of epidural corticosteroid injections in the medical community, the FDA's Safe Use Initiative convened a panel of experts, in-

cluding pain management experts, to help define the techniques for such injections which would reduce preventable harm (12). This statement may not be quite accurate. The Safe Use Initiative panel included multiple organizations including the American Society of Interventional Pain Physicians (ASIPP), which initially discussed the Safe Use Initiative in reference to the complications and the type of warning to be posted. Voting results were inconclusive, leading to an additional set of questions with standards to be established in providing all procedures, just not epidural injections. Appropriate answers were provided by ASIPP and others. Table 4 shows a questionnaire considered in the revoting performed in October 2013. We consider these questions to be repetitive, not based on evidence, often irrelevant, and occasionally harmful for the practice of medicine and physician decision-making. The net result is increased expenses, and above all, and arguably, reduced safety by imposing standards that are not universally agreed upon. (107).

During the waiting period the FDA released the drug safety communication (12) with warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events and epidural injections do not have effectiveness. To add to the challenge, the Multisociety Pain Workgroup (MPW) has been involved. Briefly, MPW was formed from an extension of the Noridian Pain Group (NPG) to develop nationwide local coverage determinations (LCDs) (108). These activities created significant issues related to LCDs. Subsequently, ASIPP withdrew from the MPW and an investigation was started by the Oversight and Investigations Committee of Energy and Commerce of the US Congress. As a result, some LCDs were released which are utilized by Noridian, and approved or considered by others to replace highly functional LCDs in over 30 states with new LCDs which are incomplete and dysfunctional (109-120). During this process, multiple recommendations made by ASIPP have been considered and these LCDs developed by the MPW were significantly improved. The final product of the MPW was not based on evidence, leading to increased utilization and disruption of a smooth process, which has been established for many years.

The MPW consists of 16 societies, including 5 surgical societies: American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS), American Academy of Orthopaedic Surgeons (AAOS), North American Spine Society (NASS), North American Neuromodulation Society (NANS); 4 radiology societies:

Table 4. Proposed technical standards in performance of interventional techniques.

1.	All cervical interlaminar (IL) injections should be performed using image-guidance, with appropriate lateral or contralateral oblique views, and a test-dose of contrast medium.
2.	Particulate steroids may be used with cervical IL ESIs that are performed using image-guidance, with appropriate lateral or contralateral oblique views, and a test-dose of contrast medium.
3.	Particulate steroids may be used with lumbar IL ESIs that are performed using image-guidance, with appropriate lateral or contralateral oblique views, and a test-dose of contrast medium.
4.	Cervical transforaminal (TF) ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient.
5.	Lumbar TF ESIs should be performed by injecting contrast medium under real-time fluoroscopy and/or DSA, in a frontal plane, before injecting any substance that may be hazardous to the patient.
6.	TF ESI is associated with a risk of catastrophic neurovascular complications.
7.	Particulate steroids appear to be inordinately represented in case reports of neurovascular complications following TF ESI.
8.	Cervical interlaminar injections should preferably be performed at C7-T1, but not higher than the C6-C7 level.
9.	No cervical interlaminar injection 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
10.	Cervical interlaminar ESIs are recommended over cervical TF ESIs
11.	Lumbar TF ESIs are recommended over lumbar interlaminar ESIs when a unilateral single nerve root is involved
12.	Lumbar IL ESI is recommended over TF ESI when there is involvement of several nerve roots unilaterally or bilaterally
13.	Dexamethasone, a non-particulate steroid, should be used for the initial injection in lumbar transforaminal epidural injections.
14.	Particulate steroids should not be used in lumbar TF ESIs.
15.	DSA is recommended for cervical TF ESIs.
16.	DSA is recommended for lumbar TF ESIs.
17.	Extension tubing is required for all TF ESIs.
18.	A local anesthetic injection is recommended before injection of the steroid with all TF ESIs.
19.	Chlorhexidine is preferable as the skin prep solution over iodine-based solutions.
20.	A face mask and sterile gloves must be worn during the procedure.

American College of Radiology (ACR), American Society for Neurorehabilitation (ASNR), American Society of Spine Radiology (ASSR), Society of Interventional Radiology (SIR); 2 anesthesiology societies: American Society of Anesthesiologists (ASA) and American Society of Regional Anesthesia and Pain Medicine (ASRA); 2 pain management societies, both of which are under investigation by the US Senate: American Pain Society (APS) and American Academy of Pain Medicine (AAPM); one physiatry society: American Academy of Physical Medicine and Rehabilitation (AAPMR); one international society: International Spine Intervention Society (ISIS), and finally, the only interventional pain management society: ASIPP, which has subsequently withdrawn.

INADEQUATE LITERATURE REVIEW

There are multiple issues with the literature review as appropriate literature research was not performed. The wide array of literature related to complications and safety considerations of epidural injections has not

been included, thus we are unaware if it was reviewed (36-68,70-73,76,77,82,84-86,87,90,92-95,97-104,121-190). Further, multiple warnings and the initiation of alternate techniques to classic and traditional teachings (86,88,89) avoidance of particulate steroids, utilization of a blunt needle, and a multitude of other precautions have not been discussed or mentioned. Thus, without completely assessing evidence, the FDA has proposed the limited evidence from cervical transforaminal epidurals to all other techniques of epidural injections including caudal, lumbar interlaminar, thoracic interlaminar, cervical interlaminar, and lumbar transforaminal. Further, as the FDA has reported, these can occur even with injections which are not included in the warnings such as facet joint injections or paravertebral injections without appropriate technical expertise and caution.

The FDA warning has described 6 reports of cervical transforaminal epidural injections or nerve root blocks (16-18,22,25,28); however, there are a multitude of other reports describing not only complications, but

also anatomic considerations, technical considerations, alternate approaches, and limited effectiveness of cervical transforaminal epidural injections in the diagnosis and therapy of cervical radicular pain syndromes (16,36-38,46-65,66,71,70,72,76,95,121-126,133-137,139,141-145,147-149,152,154-158,162,163,167-171,173-175,180-184,187,188,190)

Mechanisms of brain injury and spinal cord infarction that have been suggested to account for the brain and spinal cord infarctions include the leading hypothesis that inadvertent intraarterial injection of particulate corticosteroid creates an embolus, causing a distal infarct (18,22,66,71,72,84,92,191). In addition to infarction, a variety of other complications were reported which include vasospasm, ischemic events, cortical blindness, high spinal anesthesia, and seizures. Safety considerations for cervical transforaminal are crucial. Multiple techniques have been described to improve safety with posterior placement of the needle, including positioning of the needle, performing the procedure with a posterior approach with the patient in the prone position, and performing the procedure with a blunt needle or utilizing the TRUCATH (49-60).

There have been complications reported for thoracic transforaminal epidural injections (92). Even though there are some anecdotal reports and modification of technique to incorporate an infraneural approach, the literature is scant in relation to thoracic transforaminal epidural injections. However, considering the arterial blood supply of the spinal cord and the anatomy of radicular arteries, thoracic transforaminal epidurals are equally dangerous as cervical transforaminal epidural injections (96,191-204).

The FDA advisory also included 4 reports including 5 cases related to lumbar transforaminal or selective nerve root blocks (15,19,26,27); however, a literature search yields multiple other reports, alternate techniques, and efficacy assessments (71,73,84,85,90,93-95,127-138,140-142,145-147,149-151,153,160-163,164-170,172,178-180).

Atluri et al (84) reviewed the literature and analyzed the reported cases of paralysis from lumbar transforaminal epidural steroid injections to possibly establish a causal relationship leading to possible prevention of this complication. They found 18 reported cases of paralysis from transforaminal epidural injections. They were able to analyze the position of the needle within the neural foramen based on the available images and/or description among 10 of these 18 cases. Five cases were performed under CT guidance and 12 cases were

performed under fluoroscopic guidance (unknown in one case). Additionally, other variables associated with the procedure, including the technique, were also examined. They analyzed the needle position in the neural foramen in cases of paralysis from transforaminal epidural steroid injections. This analysis was based on images and/or description provided in published reports. Their case reviews revealed an association between paralysis and well performed traditional safe triangle approach with good epidural contrast medium spreads. Analyzed data showed that in 77.7% of the cases, the needle was in the superior part of the foramen. In 71.4% of the cases, the needle was in the anterior part of the foramen. This coincided with the location of the radicular artery in the foramen. In 22.2% of cases, the needle was in the midzone (neither in the superior nor inferior zone). No level was spared as this event occurred at every foramen from T12 to S1. Ten of these events happened during a left-sided procedure and 8 during a right-sided procedure. No relationship was noted between this complication and other variables like type and size of the needles, side of the injection, local anesthetic, contrast medium, or volume of injectate. They concluded that in light of the anatomical and radiological evidence in the literature, radicular arteries dwell in the superior part of the foramen along the traditional needle position. Therefore, the authors suggested that the traditional technique of placing the needle in the superior and anterior part of the foramen must be reexamined (96,202-204).

Ischemic complications seem to occur in cases of needles placed in the superoanterior part of the foramen (where the radicular artery usually resides) using the traditional safe triangle technique (TSTT) associated with good reported and observed contrast medium spreads. Glaser and Falco (92) were the first to question the TSTT. They suggested that the needle should be placed in the inferior and anterior part of the foramen. Jasper (205) described the above technique more elaborately and named it "retrodiscal transforaminal" injection. Lee et al (206) have also critiqued the TSTT, questioning the need to cross the nerve in order to place the needle anteriorly in the foramen. They proposed an alternative approach placing the needle in the superoposterior part of the foramen. Murthy et al (96) also advocated inferior placement of the needle in the foramen, posterior to the nerve. Glaser and Shah (85) went to the extent of stating that the TSTT is not safe. They advocated targeting Kambin's triangle—the inferoanterior aspect of the foramen. More recently Zhu et al

(207) proposed placing the needle in the posterior part of the foramen. The common denominator for all these alternative approaches is avoidance of the superoanterior part of the foramen.

Based on the analysis of the available anatomical studies and radiological studies, Atluri et al (84) have identified the "Inferior Triangle." In the oblique fluoroscopic view, its boundaries are as follows: the lateral border of the superior articular process forms one side of the triangle and the transverse process is the base. This is diametrically opposite of the traditional Safe Triangle

There is an argument that replacing particulate steroids with nonparticulate dexamethasone will avoid an embolization event but it won't thwart injury from needle trauma, dissection, or spasm of the artery. Avoiding the artery seems more prudent than using nonparticulate steroids. Theoretically, particulate steroids seem to be more efficacious than nonparticulate steroids. Some have advocated measures like using digital subtraction, dye injection using real time fluoroscopy, using blunt needles, and using test doses before injecting steroid (15,208). One case of paralysis has been reported in spite of using a test dose and digital subtraction (95).

There have not been any studies of arterial injection or paralysis related to lumbar interlaminar or caudal epidural injections with or without steroids; however, multiple complications have been reported with lumbar interlaminar and caudal epidural injections.

EFFICACY OF EPIDURAL INJECTIONS

The efficacy and effectiveness of epidural injections has been described in numerous guidelines, systematic reviews, randomized trials, and observational studies (60,155,209-269). Utilizing high quality randomized controlled trials and appropriate methodologic quality assessment of randomized controlled trials utilizing Cochrane review criteria (270,271) and ASIPP Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria with high quality randomized controlled trials with qualitative best evidence synthesis utilizing grading of randomized trials (216,272), Level I evidence has been shown for managing disc herniation with epidural injections with or without steroids but superiority with steroids. Identification of evidence at vertebral levels also showed Level I evidence in the lumbosacral region for disc herniation and radiculitis with superiority of steroids over local anesthetic alone. Level II evidence has been demonstrated for individual

procedures with caudal, lumbar interlaminar, and lumbar transforaminal epidural injections with or without steroids with superiority of steroids with caudal and lumbar interlaminar epidural injections, with no significant difference among the 3 approaches. The evidence in managing cervical disc herniation with cervical interlaminar epidural injections has been shown to be Level II whereas it was a weak Level II for thoracic disc herniation with only one randomized controlled trial. There were no cervical or thoracic transforaminal epidural randomized trials for the assessment of the efficacy of epidural injections with or without steroids (67).

Level I evidence also has been shown to be present in managing spinal stenosis with multiple high quality randomized relevant trials. However, with individual spinal levels, the evidence was Level II in managing either lumbar spinal stenosis or cervical spinal stenosis with no significant difference with the addition of steroids to local anesthetics in central spinal stenosis.

The evidence for post lumbar surgery syndrome has been shown to be Level II with caudal epidural injections as well as cervical interlaminar epidural injections with no significant difference with the addition of steroids to local anesthetic.

Level II evidence also has been demonstrated with percutaneous adhesiolysis and administration of steroids with local anesthetic in spinal stenosis, post surgery syndrome, and recalcitrant disc herniation. The efficacy of epidural injection in discogenic pain in the lumbar and cervical regions has been shown to be Level II with caudal epidural injections, lumbar interlaminar epidural injections, and cervical interlaminar epidural injections.

DISCUSSION

This review emphasizes the high risk of spinal infarction, paralysis, and death involved with cervical and thoracic transforaminal steroid injections but a smaller risk with lumbar transforaminal epidural injections. However, these risks have not been proven to be true with cervical or thoracic interlaminar epidural injections with no reports for lumbar and caudal epidural injections. Thus, extrapolating the evidence from cervical and thoracic transforaminal epidurals, or even lumbar transforaminal epidurals, is inappropriate to use for all corticosteroid injections and different types of epidural injections. These techniques are vastly different. Consequently, the risks are also vastly different, thus providing warning to the public and physicians without providing pertinent evidence and based on limited input, is considered inappropriate for an agency such as the

FDA. Further, it is not only safety, but also efficacy has not been evaluated appropriately either. There was no mention of alternate approaches to transforaminal epidural injections. In essence, the FDA relied on some of their advisors from organizations recommending techniques that are not universally recognized as best practice in terms of patient safety. These actions by the FDA have raised significant controversy and debate among multiple organizations and members of Congress. In fact, ASIPP presented multiple letters to the FDA and a single letter signed by over 1,000 interventional pain physicians. Further, an official appeal is being planned with a request for rescinding or modifying the warning and calling for an open forum discussion of proposed regulations.

There is an obvious lack of communication among agencies, even the ones controlled by the HHS. As an example, the Centers for Medicare and Medicaid Services (CMS) has not agreed to any type of restrictions on performing epidural injections. In essence, empowering the nurses has been the motto to improve the access. Consequently, CMS has issued regulations liberalizing these procedures to be performed by certified registered nurse anesthetists (CRNAs), yet at the same time complaining about overutilization, abuse, and fraud. Appropriate training and qualifications are essential to perform these procedures. Even though these complications have occurred in the hands of well-trained physicians, the occurrence will be much more severe because of the lack of appropriate training and supervision.

It is also surprising that the FDA and other agencies continue to quote inaccurate chronic pain data from an IOM report which was essentially based on a study by Gaskin and Richard. It reported the total incremental medical expenditures for selected pain conditions exceeded \$650 billion and the dramatic number of people suffering with chronic pain— 100 million (273,274). Unfortunately, the data were utilized in a flawed manner. This study from Johns Hopkins defined persons with pain as follows:

- Persons who reported that they experienced pain limiting their ability to work, which is appropriate and includes 43.9 million of the total 100 million being estimated and discussed here with 21.3 million suffering with moderate pain and 22.6 million suffering with severe pain.
- However, the number 2 category is persons who were diagnosed with joint pain or arthritis, which is estimated to be 123.7 million.

- Finally, they also included 24.7 million persons who had a disability that limited their ability to work that had nothing to do with pain.

Thus, multiple conditions were not only repeatedly counted, but also included very costly arthritis and functional disability, which are not related to chronic non-cancer pain. A liberal estimate would be approximately 30 million requiring therapy for chronic non-cancer pain, either with interventional procedures, physical therapy, surgical interventions, or chronic opioid therapy.

In these regulations, the FDA is not only encroaching upon the other agencies within the HHS, it is also encroaching on the medical practice act. Even then, the authority of the FDA to regulate medical procedures continues to be disputed. The FDA Web site emphasizes that they regulate drugs and devices, but under these regulations, procedures are not listed. However, they also do not list the procedures under the items they do not regulate. In the case involving the injection of adult stem cells, the FDA argued that they had authority to regulate the procedure because it involved the injection of drugs (10). The FDA made the same argument regarding the injection of epidural steroids. Overall, it appears that the FDA will be exceeding their explicit statutory authority and are in fact trying to regulate the practice of medicine, which has traditionally been left to the states. Further, the FDA is also trying to control issues related to infection control which already have been regulated by the Centers for Disease Control and Prevention (CDC).

Even though the issue of contaminated epidural steroids and the mortality related to the failure to control appropriately has not been discussed, it is presumed that it had significant influence on the FDA warning; however, more regulations will not control failure to exercise implementation of the regulations which are already in place. In an era of extremely high regulations (275), continuing cuts, and increasing expenses, an additional burden is placed on patients' access to pain-relieving treatments.

CONCLUSION

In conclusion, the FDA should modify its statement replacing it with an evidence-based warning emphasizing the off-label use of epidural steroids which can cause rare, but serious neurologic problems following cervical and thoracic transforaminal epidural injections and also an increased risk with

lumbar transforaminal epidural injections when performed without appropriate precautions. This conclusion by the FDA is based on a lack of evidence and will hinder access to necessary treatments in managing chronic spinal pain.

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