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Neurological Complications Associated with Epidural Steroid Injections

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Abstract Multiple case reports of neurological complications resulting from intraarterial injection of corticosteroids have led the Food and Drug Administration (FDA) to issue a warning, requiring label changes, warning of serious neurological events, some resulting in death. The FDA has identified 131 cases of neurological adverse events, including 41 cases of arachnoiditis. A review of the literature reveals an overwhelming proportion of the complications are related to transforaminal epidural injections, of which cervical transforaminal epidural injections constituted the majority of neurological complications. Utilization data of epidural injections in the Medicare population revealed that cervical transforaminal epidural injections constitute only 2.4 % of total epidural injections and <5 % of all transforaminal epidural injections. Multiple theories have been proposed as the cause of neurological injury including particulate steroid, arterial intimal flaps, arterial dissection, dislodgement of plaque causing embolism, arterial muscle spasm, and embolism of a fresh thrombus following disruption of the intima.

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Introduction

On April 23, 2014, the Food and Drug Administration (FDA) issued a drug safety communication warning that injection of corticosteroids into the epidural space of the spine may result in rare, but serious adverse events, and required label changes to warn of rare, but serious neurological problems [1, 2•]. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. This warning resulted from a rapidly expanding body of the literature illustrating the potential for catastrophic neurological complications including brain and spinal cord infarction following the intraarterial injection of corticosteroids [1, 2•, 3, 4, 5•, 6, 7•]. Since the introduction of epidural steroid injections in 1952 [8, 9] for the treatment of lumbar radiculopathy, there have been a few publications warning of potential serious complications from epidural steroid injections, which included cases of arachnoiditis, septic meningitis, bacterial meningitis, and conus medullaris syndrome, most of which were associated with subarachnoid injections [10]. In recent years, neurological complications related to the intraarterial injection of particulate steroids have been reported [1, 2•, 3, 4, 5•, 6, 7•]. An outbreak of fungal meningitis, with 751 cases and 64 deaths associated with contaminated methylprednisolone acetate, occurred in 2012 [11]. Based on a request from the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) and the Division of Pharmacovigilance (DPV), an up-to-date assessment of the FDA Adverse Event Reporting System (FAERS) data and the medical literature, which describes epidural steroid injections and serious neurological events have been provided [3].

The DPV identified 131 FAERS cases of neurological adverse events, including 41 cases of arachnoiditis and other serious neurological adverse events [3]. These data provided an assessment of the potential association of arachnoiditis with injectable corticosteroids along with paraparesis/paraplegia, quadriplegia, spinal cord infarction, stroke, thrombosis/thromboembolism, sensory disturbances, nerve injury, blindness, seizures, bowel/bladder dysfunction, and psychological/behavioral changes. They also concluded that the use of imaging does not eradicate the risk of serious neurological outcomes, though it may reduce the risk. In the midst of this growing prevalence, disability, and economic impact [12–17], numerous modalities of treatment ranging from simple over-the-counter (OTC) medications to complex surgical fusions are increasing at an explosive rate [17–34]. Spinal interventional techniques, specifically epidural injections, are one of the most prominent and extensively used interventions [17, 19]. However, complications are associated not only with off-label use of epidural steroid injections, but also surgery and drug therapy.

Complications of Chronic Pain Therapy

The cost of chronic pain has been misunderstood and misstated. An Institute of Medicine (IOM) report [13] stated that chronic pain affects 100 million persons in the USA and costs $560 billion to $635 billion per year with direct costs ranging from $261 billion to $300 billion. However, other estimates have indicated that chronic persistent pain appears to be present in approximately >30 million persons in the USA. The IOM report is predicated on the work of Gaskin and Richards [13, 14] and indicated that moderate pain is prevalent in 10 % of the population, whereas severe pain is prevalent in 11 %. The remaining pain breaks into 33 % for joint pain, 25 % for arthritis, and 12 % for functional disability. These conditions are typically not considered as chronic noncancer pain, but are separate entities involving expensive surgical interventions and rehabilitations. These numbers are significant.

Recently, the FDA approved Zohydro™ ER (Zogenix, Inc., San Diego, CA, USA). This was a controversial decision against the recommendations of the Scientific Advisory Committee to support the approval of Zohydro [26]. Among the medical therapies, opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptic drugs, and antidepressants, along with benzodiazepines, have been used extensively in chronic pain treatment [18, 26–31, 35, 36].

Opioid-related poisoning deaths have been escalating, reaching almost 17,000 in 2011 with an increase of 300 % since 1999, with methadone alone contributing to 4418 deaths in 2011 [28]. A simple OTC product such as acetaminophen has been linked to as many as 980 deaths a year based on data from the FDA [34]. In addition to acetaminophen, NSAIDs, in prescription and OTC formulations, are very commonly and extensively used in chronic pain and are assumed to be well tolerated when used on a long-term basis [30]. The chronic use of NSAIDs leads to multiple gastrointestinal (GI), cardiovascular and renal complications, and hearing loss [30]. It is estimated that 60 million Americans regularly use NSAIDs, causing clinically significant upper GI complications in up to 2 % of users, apart from numerous lower GI complications, resulting in over 120,000 hospital admissions annually in the USA due to GI hemorrhages. Based on data from 1990, more than 16,500 persons die from NSAID-related GI adverse events each year in the USA alone. In addition, significant cardiovascular and renal complications also have been reported.

Antiepileptic drugs are also used extensively; however, their efficacy results are rather disappointing with only 7–11 % of patients with fibromyalgia and 9–17 % of patients with painful diabetic neuropathy reporting a 50 % reduction in pain [31]. Overall, deaths and serious adverse patient outcomes from FDA-approved drugs were reported to be almost 82,000 and 471,000, respectively, in 2010 [36]. Spinal surgical interventions have been shown to be responsible for 1286 deaths in 2008, with fusions increasing 137 % from 1998 to 2008 [25]. Thus, the theoretically numerous complications reported secondary to epidural steroid injections that prompted FDA action may actually be considered a relatively small number compared with the complications of other therapies for the same disease state.

Epidural Steroid Injections

Epidural steroid injections have been utilized in managing spinal pain since 1952 [8, 9] and have been relatively safely administered to hundreds of millions of patients in the USA and across the globe [10, 17, 19]. The debate continues on the efficacy of epidural injections in managing chronic spinal pain of various origins, utilizing multiple approaches, and using various drugs, including particulate steroids [17, 36–40, 41•, 42, 43, 44•, 45, 46•, 47–53]. There are multiple systematic reviews utilizing appropriate methodological quality assessment of included studies and grading of evidence [5•, 17, 38–40, 41•, 44•], multiple high-quality randomized trials with appropriate outcome parameters, and follow-up for as long as 2 years showed significant evidence of effectiveness [54–73]. There is no evidence derived either from randomized controlled trials or from observational studies indicating the efficacy nor even effectiveness of therapeutic cervical transforaminal epidural injections and also there is a lack of evidence for the diagnostic accuracy of cervical transforaminal epidural injections and nerve root blocks [5•, 39, 40].

Epidural injections with or without steroids are the most commonly performed procedures in interventional pain

management, comprising almost half of all interventional techniques excluding implantables, trigger point injections, intraarticular injections, and vertebral augmentation procedures [19]. Epidural injections showed an overall increase of 169 or 106 % per 100,000 Medicare beneficiaries with an annual increase of 8 or 6 % from 2000 to 2013 [19]. Lumbosacral interlaminar or caudal epidural injections (CPT 62311), the most commonly performed procedures, have increased 11 % during this same period, with an annual increase of 1 %, increasing from 1560 per 100,000 Medicare beneficiaries in 2000 to 1737 in 2013. Cervical and thoracic interlaminar epidural injections increased substantially from 2000 to 2013 by 119 % per 100,000 Medicare fee-for-service beneficiaries, with an annual increase rate of 6 % as shown in Table 1. However, cervical and thoracic transforaminal epidural injections covered by CPT 64479 and CPT 64480 increased at a rate of 84 % with an annual increase of 5 %. Major fatalities have been described with transforaminal epidural injections, specifically with cervical transforaminal epidural injections, without proven clinical efficacy. Furthermore, the increase in lumbosacral transforaminal epidural injections has been exceptional with CPT code 64483 and CPT 64484 at a rate of 577 % per 100,000 population, with an overall increase of 787 %, with an annual rate of 16 % or 18 %, increasing from 309 to 2092 per 100,000 Medicare fee-for-service beneficiaries from 2000 to 2013, exceeding CPT 62311 per 100,000 Medicare beneficiaries in 2011 (Table 1). Thus, cervical and thoracic transforaminal epidural injections constituted 2.4 % of all epidural injections and <5 % of total transforaminal epidural injections.

Neurological Complications

The neurological complications from off-label use of epidural steroids have been extensively reported in the medical literature as well as by the FDA [1, 2•, 3, 4, 5•, 6, 7•, 8–12, 74–84]. The FAERS data, medical literature, and liability claims all have limitations. Thus, there is no certainty that a reported event was actually due to the product. The FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Many factors can influence whether or not an event will be reported to the FDA, be published in the literature or in the court system. Thus, the available data

Table 1 Utilization of epidural injections in the Medicare population from 2000 to 2013

Year	Interlaminar epidurals				Transforaminal epidurals								Total epidural injections	
					Cervical/Thoracic				Lumbar/Sacral					
	Cervical/ thoracic CPT 62310		Lumbar/sacral CPT 62311		CPT 64479	CPT 64480	Total		CPT 64483	CPT 64484	T,otal			
	Services	Rate	Services	Rate	Services	Services	Services	Rate	Services	Services	Services	Rate	Services	Rate
2000	75,741	191	618,362	1560	13,454	9434	22,888	58	85,006	37,477	122,483	309	839,474	2118
2001	84,385	211	702,713	1755	14,732	8537	23,269	58	125,534	53,133	178,667	446	989,034	2470
2002	99,117	245	786,919	1943	18,583	10,835	29,418	73	177,679	79,115	256,794	634	1,172,248	2894
2003	109,783	267	838,858	2040	21,882	15,769	37,651	92	242,491	114,046	356,537	867	1,342,829	3265
2004	130,649	313	878,174	2104	25,182	18,094	43,276	104	363,744	196,044	559,788	1341	1,611,887	3863
2005	141,652	333	945,350	2225	27,844	20,525	48,369	114	395,508	216,892	612,400	1441	1,747,771	4113
2006	146,748	339	946,961	2185	29,822	23,073	52,895	122	452,125	245,453	697,578	1610	1,844,182	4255
2007	156,415	353	926,029	2092	29,938	22,266	52,204	118	506,274	274,305	780,579	1764	1,915,227	4327
2008	165,636	365	905,419	1994	32,286	24,003	56,289	124	572,340	317,448	889,788	1959	2,017,132	4442
2009	175,503	383	888,166	1939	37,012	27,487	64,499	141	632,658	351,685	984,343	2149	2,112,511	4612
2010	184,750	394	888,421	1894	40,003	29,888	69,891	149	679,117	383,128	1,062,245	2264	2,205,307	4701
2011	200,134	414	914,324	1893	38,970	26,628	65,598	136	710,638	398,519	1,109,157	2296	2,289,213	4740
2012	213,390	424	925,176	1839	35,945	21,293	57,238	114	718,437	390,749	1,109,186	2205	2,304,993	4582
2013	217,393	419	901,468	1737	34,699	20,409	55,108	106	700,820	385,098	1,085,918	2092	2,259,887	4354
Change	187 %	119 %	46 %	11 %	158 %	116 %	141 %	84 %	724 %	928 %	787 %	577 %	169 %	106 %
Average annual change	8 %	6 %	3 %	1 %	8 %	6 %	7 %	5 %	18 %	20 %	18 %	16 %	8 %	6 %

Rate—per 100,000 Medicare beneficiaries. Change from 2000 to 2013. Modified and updated from Manchikanti et al. [19]

cannot be used to calculate the incidence of an adverse event from a medication error in the US population. The FAERS search retrieved 476 reports with 389 related to serious neurological adverse events and 87 reports related to arachnoiditis. Figure 1 shows FAERS case selection as reported by the FDA after the exclusion of duplicate reports; 90 cases were included in the case series of a serious neurological adverse event and 41 cases were included in the case series of arachnoiditis with epidural steroid injection used for a total of 131 cases.

Reports included both particulate and non-particulate steroid administration with or without local anesthetic and with or without fluoroscopy. Even though serious neurological adverse events were reported with both types of preparation, the case series for FAERS review contained many more reports for particulate steroids (n=116) compared with non-particulate steroids (n=4), with 11 cases not reporting a formulation. All five of the cases reporting a fatal outcome in the case series reported the use of particulate steroids even though the cause of death in two cases reporting arachnoiditis was due to suicide. Overall, it appears that the majority of the reports are related to cervical transforaminal injections with particulate steroids. There have been a multitude of other reports in the peer-reviewed literature [2•, 3, 4]. As described in the epidural steroid warning controversy [2•] and other reports [2•, 3, 4, 5•, 6, 7•], there were 13 deaths and 31 brain and spinal cord infarctions with numerous other serious and persistent neurological injuries in the cervical spine alone related to cervical transforaminal epidural steroid injections. The majority of the patients were treated with particulate steroids [2•, 5•, 6]. In the lumbar spine 18 case reports, 2 cervical interlaminar epidural injections and one thoracic interlaminar epidural injection have been reported. In addition, multiple cases of meningitis, arachnoiditis, and deaths have been reported in the literature [2•, 3, 4, 5•, 6, 7•, 10, 11, 75].

Multiple other complications including nerve damage, hemorrhage, and epidural abscess [10, 19, 75–84] have been reported; however, these complications are extremely rare and overall epidural injections are considered safe, specifically, without including transforaminal epidural injections in the equation.

In a comprehensive review of the risks of fluoroscopically guided cervical transforaminal injections of steroids, Engel et al. [5•] described the resultant complications including spinal cord infarction leading to death and paralysis; cerebral and cerebellar ischemia and infarction, cortical blindness, and vertebral artery occlusion leading to death. In addition, he described multiple other complications including epidural hematoma, grand mal seizures, transient or permanent Horner syndrome, and transient causalgia, or complex regional pain syndrome type II.

Data Based on Liability Claims

Injury and liability associated with cervical procedures for chronic pain have taken center stage in recent years [78–80, 84]. From January 1, 2005 through December 31, 2008, claims related to cervical interventions represented 22 % (64/294) of chronic pain treatment claims [78]. Of the patients who underwent a cervical procedure, 59 % experienced spinal cord damage, compared with 11 % of patients with other chronic pain, with direct needle trauma as the predominant cause. Unfortunately, general anesthetic or unspecified sedation was used in 67 % of cervical procedure claims associated with spinal cord injuries, but in only 19 % of cervical procedure claims not associated with spinal cord injuries. However,

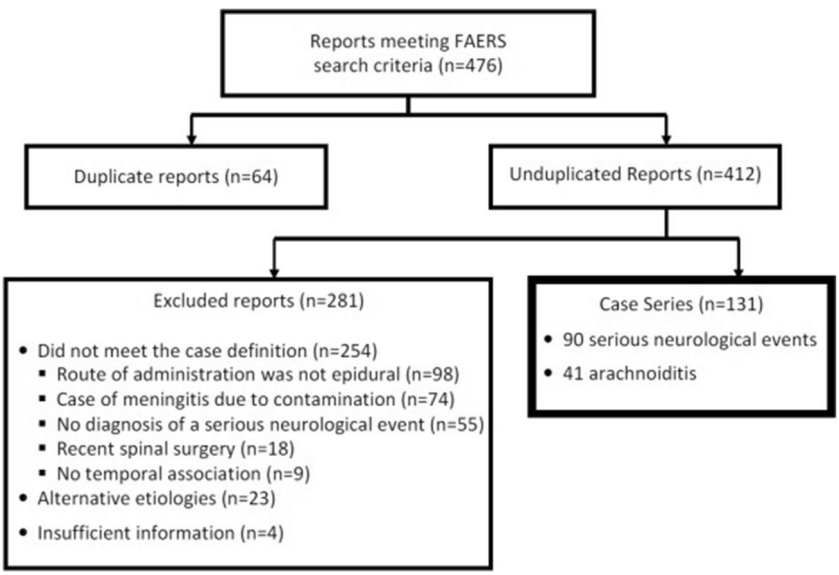

Fig. 1 Adverse events of epidural steroid injections. Adapted and modified from: Food and Drug Administration. Anesthetic and Analgesic Drug Products Advisory Committee Meeting. November 24–25, 2014. Epidural steroid injections (ESI) and the risk of serious neurological adverse reactions. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AnestheticAndAnalgesicDrugProductsAdvisoryCommittee/UCM422692.pdf [3]

in another closed claims analysis spanning from 1970 through 2007, which included all general anesthesia claims, cervical injury claims were <1 % of all claims [80]. Cord injury was more commonly seen than root and/or bony spine injuries typically resulting in quadriplegia. Other assessments evaluating medication-related claims, as well as opioid-related claims, showed that medication management represented 70 % of 295 chronic non-cancer pain claims [83].

Pathoanatomy

Neurological complications include meningitis, arachnoiditis secondary to infection, vascular trauma, injection into radicular medullary arteries, and direct needle trauma to neural structures with or without involvement of steroids. Of all pathophysiological mechanisms, the vascular theory has been shown to be the most common mechanism and has received extensive attention. While vascular complications can occur in all areas of the spine and are of grave concern, they are most commonly seen in the cervical spine with a transforaminal approach, followed by lumbar transforaminal epidural steroid injections. Arachnoiditis is seen predominantly in the lumbar spine. Direct neural trauma, specifically to the spinal cord, is observed in only the thoracic or cervical region; whereas nerve root trauma can occur in all 3 regions.

The spinal cord receives its vascular supply from an anterior spinal artery and two posterior spinal arteries. The anterior spinal artery feeds the anterior two thirds of the spinal cord along its entire length and generally receives its supply near the cervicomedullary junction most commonly from the vertebral arteries via the anterior spinal branches. The spinal cord and nerve roots are supplied by radicular arteries, which originate from the aorta and travel at each of the vertebral levels through the neuroforamen [5•, 6, 7•, 85–88]. These radicular medullary arteries often predominate in the cervical spinal region. At the thoracolumbar regions, these arteries take off from intercostals and lumbar artery branches, which enter the foramina and continue on to supply the anterior spinal artery. There is often a dominant radiculomedullary branch that supplies the anterior branch, called the Artery of Adamkiewicz, typically below the level of T8, generally with its origin in 85 % of individuals on the left side between T9 and L2, but at times as low as the lower lumbar levels and rarely at S1. Thus, there is a lower margin of safety in the cervical spine because of the proximity of the artery supplying the brain and the location of the vascular feeder arteries to the spinal cord within the cervical foramen. However, in the thoracolumbar spine, the arterial supply follows a regular and recurring path along the vertebra and within the neural foramina. Specifically, in the thoracolumbar spine, the arteries are located predominantly in the superior and middle part of the foramina with the inferior part without radicular arteries the majority of the time [7•].

Thus, based on anatomic variations, cervical transforaminal epidural injections are associated with a relatively high risk without a proven methodology to prevent these complications, whereas in the thoracic and lumbar spine, the majority of the complications may be avoided by utilizing an infraneural approach to the foramen [7•].

Intrathecal injection of steroids may lead to meningitis and arachnoiditis. In addition, infections can lead to meningitis specifically overwhelming fungal infections. Meningitis is predominantly reported after dural puncture in a small number of patients after epidural corticosteroid injections. In the overwhelming number of cases, meningitis has been reported to be secondary to infected injectate material. While meningitis may lead to arachnoiditis, intrathecal injection of corticosteroids also has been reported to cause arachnoiditis because of the chemicals contained in the preparations.

There have been several clinical reports and animal studies assessing the neurotoxicity of intrathecal glucocorticoids [10, 85, 89–93]. Neurotoxicity has been implicated due to the presence of preservatives; however, others [94] reported no adverse events with intrathecal injection of methylprednisolone with 7-day intervals of four injections in treating postherpetic neuralgia.

Mechanism of Injury

Several mechanisms have been proposed to account for brain and spinal cord infarction following epidural injections secondary to vascular trauma or injection into the artery. Even though the leading theory is that of embolism of particulate steroid, other mechanisms including arterial intimal flaps, arterial dissection, dislodgement of plaque causing an embolism, arterial muscle spasm, and embolism of a fresh thrombus following disruption of the intima have been proposed.

The leading hypothesis is that inadvertent intraarticular injection of a particulate corticosteroid acts as an embolus and causes a stroke [5•, 6, 7•, 85]. The intraarterial injection of particulate steroid leading to an embolus is supported by a high prevalence of intravascular contrast medium injections, specifically with cervical transforaminal epidural injections [86, 95, 96]. In addition, there are case reports of steroids being injected into the vertebral artery [6, 97]. Considering the extensive distribution of radiculomedullary arteries in the cervical spine, it is conceivable that particulate steroid injected into an ascending or deep cervical artery could also result in spinal cord infarction, brainstem infarction, or cerebellar infarction. Thus far, the majority of case reports and experimental evidence points to particulate steroids [5•, 6, 7•]. Among all the corticosteroids, methylprednisolone was the most commonly used drug; it consists of the largest particles [97]. Further, it also has been shown that methylprednisolone and triamcinolone particles tend to coalesce into larger aggregates far in excess of 100 microns, increasing their embolic potential [97].

An evaluation of steroids with intraarterial injection in the rat brain [98] sought to differentiate between the postulated mechanisms of injury. These mechanisms include a mechanical injury to arteries supplying the spinal cord, direct neurotoxicity of the steroid injected, and embolization of particulate material due to inadvertent intravascular injection of particulate steroid, based on the leading hypothesis and circumstantial support for inadvertent intravascular of particulate steroid. In this trial [98], cerebral hemorrhage occurred in animal test subjects administered Depo-Medrol or Solu-Medrol, ranging from 3 of 6 in the Depo-Medrol carrier group, 8 of 11 in the Depo-Medrol group, and 7 of 8 in the Solu-Medrol group. However, there were no lesions identified in the Decadron or saline group. This study provided in vivo evidence of intraarterial steroid injection of Depo-Medrol, its carrier, or Solu-Medrol.

Multiple procedural factors have been described along with precautions to avoid intraarterial injection of particulate steroids. The evidence shows that none of these precautions or combinations of them are entirely protective against the serious complications of cervical transforaminal epidural injections [4]. However, even though at present adequate proof does not exist, it does make sense that placing the needle in the inferior part of the triangle in the thoracic and lumbar regions, described as an infraneural approach, may eliminate the risks in the lumbosacral spine. Use of non-particulate steroids has also been suggested, but not proven to be equivalent in effectiveness if epidural steroids are indicated. Precautions such as live fluoroscopy, digital subtraction angiography, and using a blunt needle may be useful. In addition to the various precautions, previous spine surgery appears to be an independent risk factor for spinal cord infarction because of altered anatomy, vascular relocation, neovascularization, and scar tissue vascularization anastomosis with the existing spinal or radicular blood supply [87].

The exact mechanism or combination of mechanisms that may contribute to vascular or neural injury is uncertain and could be multifactorial. Considering the embolic theory as the major cause, other mechanisms include sustained compressive effect of the injectate that exceeds the local arterial pressure or neural profusion pressure in the area injected producing neural ischemia, mechanical needle injury to the vasculature that disrupts the neural blood supply, and the inflammatory arterial irritability that predisposes the local vasculature to vasospasm from an advancing needle or from the mechanical effect of the injectate itself [85, 87].

Discussion

Neurological complications of epidural steroid injections include rare, but serious adverse reactions including spinal cord infarction, paralysis, and death. Based on the available literature, an overwhelming number of complications were related to cervical transforaminal epidural injections, with some complications coming from lumbar transforaminal epidural injections and intraarticular injections. Meningitis and arachnoiditis have occurred most commonly secondary to fungal meningitis. Based on utilization data, overall cervical and thoracic transforaminal epidurals together constitute 2.4 % of all epidural injections, <5 % of all transforaminal epidural injections, and contribute to over 99 % of the complications related to intraarterial injection of particulate steroids. Thus, these complications have not been convincingly seen with cervical or thoracic interlaminar epidural injections. There are no reports of lumbar or caudal epidural injections causing these complications. The FDA has extrapolated evidence from cervical and thoracic transforaminal epidural injections. These constitute a very small proportion of procedures leading to overwhelming reports of injury inappropriately attributed to all corticosteroid injections. While there are no proven safety measures to perform cervical transforaminal epidural injections, coupled with a lack of efficacy, thoracolumbar transforaminal epidural injections may be modified with an infraneural approach and safely performed.

Conclusion

Neurological complications from the epidural administration of steroids have been reported following cervical transforaminal epidural injections, which constitute approximately 2.4 % of total epidural injections and <5 % of all transforaminal epidural injections. To a lesser extent, neurological complications have also been reported following lumbar transforaminal epidural injections. Neurological complications are related to not only intraarterial injection of particulate steroid but also infection, nerve damage, hemorrhage, and epidural abscess. Based on anatomic variations, cervical transforaminal epidural injections are associated with an extremely high risk without a proven methodology to prevent these complications. Further, there is no evidence illustrating the therapeutic efficacy or diagnostic accuracy of cervical transforaminal epidural injections. Various mechanisms have been proposed to account for brain and spinal cord infarction following epidural injections secondary to vascular trauma and injection into the artery. The leading theory is an embolism caused by particulate steroid, whereas other mechanisms, including arterial intimal flaps, arterial dissection, dislodgement of plaque causing an embolism, arterial muscle spasm, and an embolism from a fresh thrombus following disruption of the intima, have been proposed.

To minimize neurological complications, non-particulate steroids should be considered in cervical transforaminal epidural injections or in lumbar transforaminal epidural

injections in high risk patients as well as when a so-called "safe triangle" approach is utilized.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Laxmaiah Manchikanti and Dr. Joshua A. Hirsch each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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