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Safety of Epidural Steroid Injections for Lumbosacral Radicular Pain

Unmet Medical Need

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Objective: Epidural steroid injections (ESIs) are a commonly utilized treatment for lumbosacral radicular pain caused by intervertebral disc herniation or stenosis. Although effective in certain patient populations, ESIs have been associated with serious complications, including paralysis and death. In 2014, the US Food and Drug Administration (FDA) issued a safety warning on the risk of injecting corticosteroids into the epidural space. The aims of this article were to review the neurological complications associated with ESIs and to compare the formulations, safety, and effectiveness of commercially available corticosteroids given by transforaminal, interlaminar, or caudal injection.

Methods: Serious adverse events associated with ESIs were identified by a search of the FDA Adverse Event Reporting System (FAERS) database. A MEDLINE search of the literature was conducted to identify clinical trials comparing the safety and effectiveness of nonparticulate and particulate corticosteroid formulations.

Results: Neurological complications with ESIs were rare and more often associated with the use of particulate corticosteroids administered by transforaminal injection. Among the 10 comparative-effectiveness studies reviewed, 7 found nonparticulate steroids had comparable efficacy to particulate steroids, and 3 studies suggested reduced efficacy or shorter duration of effect for nonparticulate steroids.

Discussion: The risk of complications for transforaminal ESI is greater with particulate corticosteroids. Nonparticulate corticosteroids, which are often recommended as first-line therapy, may have a short duration of effect, and many commercial formulations contain neurotoxic preservatives. The safety profile of ESIs may continue to improve with the development of safer, sterile formulations that reduce the risk of complications while maintaining efficacy.

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Low back pain is the leading cause of disability in the world, with a lifetime prevalence rate estimated between 51% and 84%.[1,2] Lumbosacral radiculopathy is a common type of back pain that affects the lumbosacral nerve roots and causes radicular symptoms radiating into the lower extremities. The lifetime incidence is estimated at 13% to 40%.[3] In one systematic review, it was estimated that 36.6% of patients with chronic low back pain had predominantly neuropathic pain.[4]

Lumbosacral radicular pain can be managed with several different treatments, and a multimodal treatment strategy is often employed. Conservative management includes bedrest and physical therapy. Pharmacological options include antidepressants, membrane stabilizers, nonsteroidal anti-inflammatory drugs, muscle relaxants, oral steroids, and opioids, which have significant side effects and limited (if any) efficacy.[5,6] Surgery is an option once noninvasive options have been exhausted.

Epidural steroid injections (ESIs) are a cornerstone for the treatment of radicular pain and represent the most commonly performed pain management procedure in the United States.[7] ESIs have been shown to be effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery, and may provide relief for several years when strategically repeated.[8–13] The risks of ESIs are lower than other pharmacological approaches such as opioids that have the potential for abuse and less invasive, risky and costly than surgical intervention.

The mechanism for ESI-induced pain relief is thought to be multifactorial. Corticosteroids inhibit phospholipase A2, which converts membrane phospholipids into arachidonic acid and lysophospholipids.[14] Arachidonic acid is then further converted to proinflammatory eicosanoids, including prostaglandins, prostacyclins, thromboxanes, and leukotrienes. These inflammatory mediators can exacerbate pain and sensitize peripheral nociceptors. In addition to their anti-inflammatory effects, corticosteroids may inhibit ectopic discharges from nerve fibers[15] and depress conduction of unmyelinated fibers.[16] Corticosteroids are frequently coinjected with local anesthetics, which block neural transmission in normal nociceptive C-fibers and may enhance blood flow to ischemic nerve roots in neurogenic claudication.[17] In addition to drug-mediated effects, the injection procedure itself is thought to contribute to efficacy.

Epidural injections may work, in part, by lavage of the epidural space or possibly by lysing epidural and nerve root adhesions. In one systematic review, Rabinovitch et al[18] found a strong correlation between epidural injection volume and outcome, irrespective of steroid dose. In another systematic review and meta-analysis evaluating the effect of the control group in randomized controlled trials, Bicket et al[19] found that epidural nonsteroid injections afforded greater benefit than nonepidural injections, estimating that most of the early effect of epidural injections may be from the injection itself, rather than the steroids.

Whereas ESI is frequently used for the treatment of lumbosacral radiculopathy and is recommended in several guidelines and by multiple pain societies,[20–24] US Food and Drug Administration (FDA) has not approved any corticosteroid for epidural administration and has required warnings on all labels of injectable corticosteroid products. Safety issues with ESIs and associated procedures include the potential for infection as well as rare but serious neurological injuries. In the early 2000s, the Centers for Disease Control (CDC) began investigating reports of meningitis caused by a rare fungus in patients who had received ESIs in outpatient pain management clinics.[25] A decade later, another multistate outbreak of meningitis occurred, also in connection with patients who received ESIs for the treatment of spine pain.[26,27] This outbreak affected over 20 states and resulted in over 700 infections and hundreds of cases of meningitis, at least 24 of which are known to have resulted in death.[28] The outbreaks in 2002 and 2012 were caused by contamination of methylprednisolone acetate preparations with *Exophiala dermatitidis* and *Exserohilum rostratum* fungi, respectively. CDC and FDA investigations found that these steroid preparations were produced by compounding pharmacies. These compounded formulations were in demand as they could be formulated without potentially irritating or toxic preservatives, and preservative-free formulations were not available from commercial drug companies' depot steroid preparations.[29] As a result of these and other outbreaks, the Drug Quality and Security Act was passed in 2013 and granted the FDA greater authority to regulate and monitor the manufacture of compounded drugs.[30]

In addition to issues with microbial contamination, in 2009, FDA initiated a review of the safety of ESIs based on serious neurological adverse events (AEs) reported in the FDA Adverse Event Reporting System (FAERS) database. In 2011, the FDA's Safe Use Initiative facilitated the organization of an external multidisciplinary working group to develop recommendations for minimizing the risk of serious neurological events with ESIs. Around that same time (2013), Pfizer asked the FDA to ban the use of Depo-Medrol (methylprednisolone acetate) injections near a patient's spinal cord, noting that the company had received hundreds of complaints about patients experiencing complications and injuries related to drug administration near the spinal cord. Pfizer wrote that Depo-Medrol "must not be given by intrathecal, epidural, intravenous, or any other unspecified routes."[31]

In April 2014, the FDA issued a requirement that all injectable corticosteroid product labels carry a warning stating that "serious neurological events, some resulting in death, have been reported with epidural injection of corticosteroids" and that the "safety and effectiveness of epidural administration of corticosteroids have not been established and corticosteroids are not approved for this use."[32] FDA convened an Advisory Committee meeting in November 2014 to discuss the safety and efficacy of ESIs with external experts to determine whether further regulatory action was necessary.[33] The Committee voted on whether they believed there were any clinical situations for which a contraindication should be added to the labeling of corticosteroids regarding their injection in the epidural space. The vote was 15 in favor of adding a contraindication to the labeling for cervical transforaminal injections performed with particulate steroids with 7 against (and 1 abstention). After the meeting, the FDA declined to implement a contraindication to restrict the injection of corticosteroids into the epidural space. FDA also chose not to modify the language of the class warning to limit it to specific injection approaches (interlaminar [IL], caudal, transforaminal [TF]), locations of spinal injections (cervical, thoracic, lumbar, sacral), or to specific steroid formulations (solutions or suspensions), because they concluded that each approach, location, and the formulation was associated with some risk of neurological injury.[34,35] In 2021, the FDA published a review of the Medicare database from 2009 to 2015 demonstrating that cervical injections carry a greater risk than lumbar injections. Paradoxically, while cervical transforaminal steroid injections were associated with a greater risk of an adverse spinal event than nontransforaminal injections, in the lumbar spine transforaminal injections were associated with a lower risk. Overall, there was no significant difference in risk between particulate and nonparticulate ESIs.[36] The regulatory discourse continues to this day, with the American Patient Defense Union (APDU) recently expressing concerns to Pfizer about devastating neurological injuries caused by the widespread epidural injection of Depo-Medrol, without patients' specific consent to its use. The APDU requested that Pfizer risk managers immediately issue a warning to all practitioner associations setting standards for spinal pain management, and to consider placing an absolute contraindication on the neuroaxial injection of Depo-Medrol in the United States. Back in 2013, Pfizer also proposed a contraindication that was rejected by the FDA in lieu of the class warning.[37]

This review summarizes the data on the neurological safety issues surrounding ESIs as well as data supporting the efficacy of corticosteroid injections for the treatment of lumbar radicular pain. Properties of the ideal formulations for this procedure are also discussed. Whereas complications can arise even in ideal circumstances (eg, digital subtraction angiography does not reliably prevent neurologically devastating complications[38]), the risks can be mitigated by the use of safe injection techniques and sterile formulations free of particulates and neurotoxic preservatives.

NEUROLOGICAL COMPLICATIONS ASSOCIATED WITH ESIs

In 2009, FDA began evaluating serious neurological complications associated with ESIs. Between 1997 and 2014, a total of 90 serious and sometimes fatal neurological events were reported to the FAERS, including cases of paraplegia, quadriplegia, spinal cord infarction, and stroke.[34] Potential causes of these AEs included technique-related issues such as unintentional intrathecal injection, epidural hematoma, injury to the spinal cord, direct injury to the arteries feeding the spinal cord, and embolic infarction due to inadvertent intra-arterial injection. Several potential risk factors, procedure-related and patient-related, were identified, including the level of spinal injection, the method of approaching the

epidural space (whether it be caudal, interlaminar, or transforaminal), and the degree of patient sedation. Cervical injections, in particular, were associated with these AEs, especially spinal cord injury, some of which were due to the vascular anatomy of the cervical region whereby unintentional intra-arterial injection with the transforaminal approach is more likely than in the lower lumbar region.

In 2011, a multidisciplinary working group was convened as part of FDA's Safe Use Initiative to determine recommendations to minimize the risk of ESIs. The working group included a range of experts from 13 subspecialties including representatives from anesthesiology, pain medicine, physical medicine and rehabilitation, neurosurgery, orthopedic surgery, and radiology organizations. The group agreed on 17 statements aimed at reducing the risk of neurological complications with ESIs.[39] Among the key suggestions was that all cervical and lumbar interlaminar epidural steroid injections (ILESIs) be performed using image guidance and with a test dose of contrast medium. For cervical and lumbar transforaminal epidural steroid injections (TFESIs), real-time fluoroscopy, and/or digital subtraction imaging should be performed before injecting any substance that could be hazardous to the patients. Patient sedation also emerged as an important recommendation, particularly in the cervical spine, as more heavily sedated patients may not be able to provide feedback during the procedure.[40] The group recommended against using particulate steroid formulations for cervical transforaminal injections and suggested using nonparticulate steroids for initial lumbar transforaminal injections. Other safeguards included the use of low-volume extension tubing for transforaminal injections, the use of digital subtraction angiography if available, and use of appropriate personal protective equipment.[39] In 2019, updated recommendations were published by the World Institute of Pain (WIP) Benelux Work Group.[41] Additional recommendations from the Benelux Work Group included dose limits on injectable steroids (eg, $\leq$20 mg triamcinolone acetate, 40 mg methylprednisolone acetate and 10 mg of dexamethasone), the injection of local anesthetic before transforaminal corticosteroid administration, limiting the volume of lumbar transforaminal and cervical interlaminar injections to $\leq$4 mL, and needle placement in the "safe triangle" for lumbar transforaminal injections. Notably, the work group did not mandate that initial lumbar TFESIs be done with soluble steroids. Apart from procedure-related and patient-related factors, the precise role of corticosteroids themselves in these AEs has been the subject of debate.

CHEMICAL COMPOSITION OF FDA-APPROVED PARENTERAL CORTICOSTEROIDS

Corticosteroids are synthetic derivatives of the endogenous adrenal hormone, cortisol. Synthetic corticosteroids vary in their degree of water solubility, with several supplied as suspensions (eg, triamcinolone acetate, methylprednisolone acetate, betamethasone acetate). Sodium salt forms are water-soluble and supplied as solutions (eg, betamethasone sodium phosphate, dexamethasone sodium phosphate, methylprednisolone sodium succinate). Betamethasone is FDA-approved in both soluble (sodium phosphate) and nonsoluble (acetate) forms. The properties of currently marketed corticosteroid injections as of 2021 are provided in Table 1. All of these drug products have been genericized in the United States; the formulations vary only in use and types of preservatives. None are approved for epidural administration.

Light microscopy studies have shown corticosteroid particle sizes vary depending on the formulation. Among the suspension corticosteroids, triamcinolone particles range in size from 0.5 to >100 μm. The largest triamcinolone particles are >12 times bigger than red blood cells. Triamcinolone particles aggregate extensively and are densely packed.[42] Betamethasone particles are smaller but still tend to form large aggregates (>100 μm) in solution.[42] Methylprednisolone particles are smaller than red blood cells but densely packed. In contrast, dexamethasone sodium phosphate formulated at 4 or 10 mg/mL is freely soluble in water and forms small particles measuring about 0.5 μm, <1/10th the diameter of red blood cells, with no evidence of aggregation. Using a sensitive laser scanning confocal microscope, Benzon and colleagues noted that both dexamethasone and the short-acting betamethasone sodium phosphate did not contain any particles. However, the longer acting betamethasone sodium acetate contained small particles.[43] Based on these solubility and particulate characteristics, dexamethasone may be less likely to cause arterial or capillary obstruction if inadvertently injected intra-arterially. The ability to occlude a small radiculomedullary artery feeding the spinal cord is theoretically increased by particle size, aggregability, and possibly density.

The preparation may also affect particle properties. For example, Benzon and colleagues found that compounded betamethasone contained a higher proportion of particles >50 and 1000 μm than the commercially manufactured betamethasone, and that depo-methylprednisolone concentrations of 80 mg/mL contained a higher percentage of large particles than 40 mg/mL concentrations. Diluting the steroid mixture with lidocaine or saline, as is common in clinical practice, resulted in a smaller percentage of large particles (>50 μm) for betamethasone and depo-methylprednisolone 40 mg/mL, but a higher percentage for depo-methylprednisolone concentrations of 80 mg/mL.[43]

NEUROLOGICAL INJURY ANIMAL MODELS

The hypothesis that physical characteristics of corticosteroid solutions are related to the development of neurological AEs has been borne out in animal models. In one study, direct injection of particulate methylprednisolone into the vertebral artery of pigs resulted in hypoxic/ischemic damage.[44] All animals in the methylprednisolone group failed to regain consciousness after the injection and required ventilatory support. In contrast, pigs injected with dexamethasone solution showed no evidence of neurological injury.[44] In another study, dexamethasone or saline caused no neurological injuries when injected directly into the carotid artery of rats, whereas particulate methylprednisolone caused a cerebral hemorrhage.[45] Interestingly, injection of the nonparticulate methylprednisolone sodium succinate and the carrier of methylprednisolone acetate (the supernatant of the centrifuged suspension) also resulted in hemorrhagic brain lesions in half (3/6 rats for the carrier and 8/8 rats for methylprednisolone sodium succinate) of the rats. The authors considered factors other than embolization of the particulate steroid as etiologies, including endothelial toxicity via direct cellular effects resulting in impairment of the blood-brain barrier with hemorrhagic injury.

TABLE 1. Food and Drug Administration (FDA)-approved Injectable Corticosteroids

Corticosteroid	Tradename(s) (Manufacturer)	Suspension/ Solution	Solubility	Notable Excipients	Approved Routes of Administration
Betamethasone acetate, betamethasone sodium phosphate	Celestone Soluspan (Merck Sharp & Dohme)	Suspension	Acetate insoluble; sodium phosphate soluble	Benzalkonium chloride (for multidose use)	Intramuscular Intra-articular Soft tissue Intralesional
Methylprednisolone acetate	Depo-Medrol (Pharmacia and Upjohn Co.)	Suspension	Insoluble	Benzyl alcohol Polyethylene glycol Polysorbate 80 (for multidose use) Or Polyethylene glycol Myristyl-gamma-picolinium-chloride (for single-dose use)	Intramuscular Intra-articular Soft tissue Intralesional
Triamncinolone acetonide	Kenalog-10 Kenalog-40 Kenalog-80 (Bristol Myers Squibb)	Suspension	Insoluble	Benzyl alcohol Polysorbate 80 (for multidose use)	Intra-articular Intralesional Intramuscular*
Methylprednisolone sodium succinate	Solu-Medrol (Pharmacia and Upjohn Co.)	Solution	Soluble	Benzyl alcohol (for multidose use) Or Preservative-free (for single-dose use)	Intravenous Intramuscular
Dexamethasone sodium phosphate	Decadron (Merck)	Solution	Freely soluble	Benzyl alcohol with or without sodium sulfite (for multidose use) Or Methylparaben Propylparaben Edetate disodium (for multidose use) Or Preservative-free (for single-dose use)	Intravenous Intramuscular (intra-articular, intralesional, soft tissue)†

*The 10 mg/mL strength is only approved for intra-articular and intralesional use. The 40 and 80 mg/mL strengths are only for intramuscular and intra-articular use.

†Intra-articular, intralesional, and soft tissue administration is only approved for the 4 mg strength of dexamethasone.

NEUROTOXIC PRESERVATIVES

Direct neurotoxic effects of the additives and preservatives in commercially available corticosteroid formulations have also been proposed as a potential mechanism for neurological complications that can arise after ESI. As shown in Table 1, formulations on the market today contain additives including benzyl alcohol, polyethylene glycol, polysorbate 80, edetate disodium, sodium sulfite, and myristyl-gamma-picolinium chloride. There are reports in the literature, mainly from animal studies, that suggest these additives have potential neurological toxicity. Table 2 describes some of the observed neurotoxic effects with commonly used preservatives and other additives in the manufacture of commercial corticosteroid injections.

Preservatives such as benzyl alcohol and to a lesser extent benzalkonium and polyethylene glycol are particularly important for certain aqueous-based parenteral products to prevent against microbial contamination. The selected preservative (and amount used) is typically based on the need for antimicrobial activity (greater in in parenteral products labeled for multiuse), and physical and chemical compatibility properties.[51] A key factor in preservative use and selection is whether the parenteral product is designed for single-dose or multidose use.

Because most studies evaluating neurotoxicity with corticosteroids used formulations with preservatives, it is unclear which ingredient (ie, drug or preservatives) specifically caused the neurotoxicity. Further research in this area is needed, while in the interim, class-specific warnings for neurotoxicity are labeled for all corticosteroid products. Although most commercially available formulations contain preservatives, there are also preservative-free options available for dexamethasone and methylprednisolone sodium succinate that contain warnings on the potential for neurotoxicity. It is important to note that preservative-free corticosteroid formulations contain ingredients besides the drug itself, such as sodium hydroxide, hydrochloric acid, citric acid, phosphoric acid, acetic acid, etc. for pH adjustment or buffering, and other excipients to maintain suspensions (if applicable) and prolong the shelf-life. Future studies should examine the frequency of AEs observed in patients treated with preservative-free formulations versus preservative-based formulations.

NEUROLOGICAL AEs: FINDINGS FROM THE FAERS DATABASE

FDA's analysis of serious neurological AEs reported to FAERS revealed that most serious neurological AEs were associated with particulate formulations, consistent with the observed aggregation in vitro and an embolic mechanism. Dexamethasone sodium phosphate solution was associated

TABLE 2. Preservatives in Corticosteroid Injections

Additive	Neurotoxic Effects	References
Polyethylene glycol	Direct injection into carotid arteries in rats caused hemorrhagic brain injury	Dawley et al[45]
	Reversible dose-related depression of compound action potentials of rabbit vagus nerves: 20%-30% caused, while 40% caused abolition of compound action potentials (concentrations above 40% not studied as it was too viscous)	Benzon et al[46]
Benzyl alcohol	Neurotoxic effects in rodents after oral administration	National Toxicology Program[47]
	Flaccid paraparesis in mother after postdelivery epidural injection containing 1.5% benzyl alcohol in a 0.9% saline solution	Craig et al[48]
	Seizures were observed following injection of 4.5% benzyl alcohol and death occurred following injection of 9% benzyl alcohol in dogs. There is a single case report of paralysis following inadvertent subarachnoid injection of 40 mL of normal saline that contained 1.5% benzyl alcohol	Duszynski[49]
EDTA	Convulsions in mice after spinal injection	Van Boxem et al[41]
Sodium sulfite	Irreversible paralysis after subarachnoid administration in rabbits	Van Boxem et al[41]
Benzalkonium chloride	Arachnoid fibrosis after intrathecal injection in sheep	Van Boxem et al[41]
Myristyl-gamma-picolinium chloride	Toxicity in rat dorsal root ganglia sensory neurons	Knezevic et al[50]

with 3 events, with none resulting in permanent injury or death.[33] In 1 case, a 30-year-old female experienced "new pain and numbness" and "new tingling in left leg" after receiving a "lumbosacral injection" of dexamethasone (route, dose, and formulation base unknown) for an unspecified condition. Her magnetic resonance imaging (MRI) showed no change from a baseline/previous MRI. The event outcome was unknown at the time of reporting. In a second case, a 50-year-old female experienced sudden neck pain, hypotension, headache, and a burning sensation in her neck, shoulder, and legs after receiving a cervical ESI with dexamethasone 10 mg (injection approach and formulation base unspecified). The patient's medical history included chronic degenerative disease of cervical spine and asthma. Concomitant medications included iohexol contrast administration, which was ostensibly used to confirm the adequate needle placement. An MRI revealed no acute changes. The patient fully recovered from the events. The third case reported an 89-year-old male who experienced numbness in the left leg, increased pain in both legs, and dizziness within 24 hours after receiving a lumbar injection of dexamethasone (route of injection and dose unknown). Medical history included Parkinson disease, degenerative joint and disc disease of the lumbar spine, and radicular left leg pain. He was treated with a Medrol dose pack, and at the time of reporting, the adjudication and outcome of the event was ongoing. Reasons for the discrepancy between the FAERS database and the Medicare database regarding the effect of steroid solubility include the failure of the latter to control for confounding variables and the type of AE.[36]

A more recent review of data in the FAERS database from 1978 to 2020 is summarized in Table 3. These findings are based on a simple online dashboard query as follows:

- The drug (limited to 5 search terms per drug) which included betamethasone, dexamethasone, methylprednisolone, and triamcinolone.
- Drug search terms focused on those specific for injectable formulations.
- Excluded suspected drugs identified as given in combination with other drugs (eg, methylprednisolone acetate/lidocaine) as these were typically captured within the selected search terms.
- Excluded parent drug name for betamethasone and dexamethasone only, as the search otherwise resulted in an inordinate number of product types (eg, oral, topical, and ophthalmic) not typically associated with epidural injection (these were included for methylprednisolone and triamcinolone as the description of AEs in these instances infer that they were associated with epidural injection).
- Included events associated with pharmacy-compounded products.
- Did not include events that noted procedural errors deemed likely to cause the AE.
- Included indications for use: back pain, back injury, and back disorder.

It should be noted that most of the incidents involved coadministration of other drugs. In general, these events are in-line with earlier FDA findings. Given the number of ESI procedures performed annually (estimated to be over 9 million per year in the United States), this FAERS evaluation is consistent with the FDA's findings and literature suggesting that neurological events are indeed rare but serious, debilitating, and sometimes lethal.[52] The large majority of permanent neurological complications associated with ESIs have resulted from particulate corticosteroid use (eg, methylprednisolone and triamcinolone) administered by transforaminal injection.[33] Most neurological complications after nonparticulate corticosteroid use (ie, dexamethasone injections) were transient and less severe than with those associated with particulate corticosteroids, although 1 case of spinal cord infarction after a lumbar transforaminal injection of dexamethasone in a 60-year-old patient has been reported.[53] However, this case report had several limitations including no available fluoroscopy images, no identification of the type of contrast agent used, and no information about whether the injected dexamethasone was preservative-free.

In summary, there are no means to reliably discern in most cases whether serious neurological AEs associated with ESIs are due to the formulation, drug, technique, or a combination of these factors. The incidence of neurological complications from different formulations cannot be calculated without knowing the denominator; however, the severity of AEs from particulate corticosteroids differs significantly from nonparticulate formulations (eg, betamethasone sodium phosphate and dexamethasone sodium phosphate), which warrants further investigation. Less

TABLE 3. Corticosteroid Serious Neurological Adverse Events (1978-2020): FDA Adverse Event Reporting System (FAERS) Database Analysis

		Reported Adverse Events				
Suspected Drug	Period (y)	Total	Serious	Life-threatening	Deaths	Examples of Serious Neurological Adverse Events Potentially Associated With Epidural Injection (Not Identified as Associated With Procedural Error or Infection)
Betamethasone acetate and sodium phosphate Betamethasone sodium phosphate	1998-2020	51	48	3	4	Amnesia, coordination abnormal, confusional state, fall, delusion, dizziness, dysarthria, gait disturbance, gait inability, intention tremor, loss of consciousness, mental impairment, nerve injury, pain in extremity, paresthesia, paralysis, paraplegia, perineal pain, peripheral nerve lesion, neuralgia, neuritis, neurological examination abnormal, neurological symptom, Romberg test positive, sensorimotor disorder, sensory disturbance, sensory loss, sciatic nerve injury, spinal cord injury thoracic, visual impairment
Dexamethasone acetate Dexamethasone phosphate Dexamethasone sodium phosphate	2008-2020	47	46	4	3	Dizziness, fall, neuropathy peripheral
Methylprednisolone Methylprednisolone acetate Methylprednisolone sodium succinate	1983-2020	429	359	26	23	Arachnoiditis, blindness unilateral, dizziness, gait disturbance, headache, loss of libido, meningitis chemical, muscle spasms, muscle twitching, musculoskeletal stiffness, nerve root injury, neuralgia, neurosarcoidosis, neurotoxicity, optic ischemic neuropathy, paresthesia, pain in extremity, paralysis, photophobia, pneumocephalus, psychotic disorder, spinal pain, vertigo, vision blurred, visual impairment
Triamcinolone Triamcinolone acetate Triamcinolone diacetate Triamcinolone hexacetonite	1978-2020	283	239	15	4	Balance disorder, burning sensation, cauda equina syndrome, dizziness, dysstasia, fall, gait disturbance, headache, loss of control of legs, migraine, monoplegia, muscle spasms, muscle twitching, nausea, neck pain, neuropathy peripheral, paralysis, paraplegia, peripheral sensorimotor neuropathy, photosensitivity reaction, sensorimotor disorder, sensory loss, tinnitus, tremor, unresponsive to stimuli, vision blurred

obvious in these data is the role that preservatives play in neurological events.

EFFICACY AND SAFETY OF ESIs IN LUMBOSACRAL RADICULAR PAIN

The efficacy of ESIs has been investigated in over 45 randomized, placebo-controlled trials,[54] making it one of the most well-studied procedures. Several systematic reviews have shown at least moderate evidence for both short-term and long-term benefits of ESI in managing back and leg pain due to disc herniation and spinal stenosis.[55–59]

SAFETY BENEFIT OF NONPARTICULATE CORTICOSTEROIDS IN TFESI

Although caudal and interlaminar injections have been shown to be superior to placebo, TFESI have emerged as the preferred injection approach for lumbar radicular pain caused by disc herniation and foraminal stenosis.[54] Systematic reviews focused on the transforaminal approach have shown strong evidence that TFESI is effective for radicular pain due to intervertebral disc herniation.[8,59] When observational and pragmatic studies permitting multiple injections are considered, up to 63% of patients with disc herniations achieve at least 50% pain relief after 1 month and 59% at 1 year.[59] Comparisons between transforaminal and interlaminar epidural injections for lumbosacral disc herniation have shown that short-term pain control is better with TFESI, and there are trends for superiority in long-term outcomes (4 to 6 mo) as well.[60] For ILESI, there is scant evidence to support the increased safety of nonparticulate steroids in any region[39,41]; however, the use of particulate steroids and their preservatives has been postulated to be an etiology for arachnoiditis after inadvertent dural puncture, with 39 of the 41 cases reported to the FDA at the time of the 2014 meeting attributed to intrathecal particulate steroid injection.[33,61]

Regarding spinal stenosis, a systematic review by Smith et al[59] found TFESI success rates of 49% at 1 month, 43% at 6 months and 59% at 1 year when uncontrolled studies evaluating repeat injections were considered, though the authors acknowledge a lack of corroboration with placebo-controlled trials. There is also evidence that ESI treatment can reduce the need for surgical intervention[9–12] and the use of other health care, though the benefit is somewhat mitigated by the lack of standardization for patients seeking surgery and other interventions.[8] For example, while systematic reviews and subgroup analyses of randomized surgical trials demonstrate that ESI may reduce the need for surgery, database reviews have found a positive correlation between geographic utilization of spine surgeries and ESI.[10,62,63] Most studies and meta-analyses evaluating ESI studies have utilized data from particulate steroid formulations.[8,59,60]

Studies in animals and humans suggesting that nonparticulate formulations are safer for transforaminal injections raise the question of whether nonparticulate formulations are as effective as particulate formulations. Whereas head-to-head

comparative pharmacokinetic studies are lacking, it has been postulated that suspension ESIs have a longer duration of effect compared with nonparticulate steroids such as dexamethasone, which possess high aqueous solubility and very small particle size, and that the time the steroid remains in the epidural space correlates with efficacy. This is supported by a randomized trial performed in 160 patients with cervical radiculopathy that demonstrated a greater reduction in pain scores when epidural bupivacaine, with intermittent steroids, was administered via a continuous infusion rather than via boluses administered every 4 to 5 days.[64] Currently, there are no placebo-controlled trials evaluating nonparticulate steroids for any form of spinal pain, so evidence of efficacy must derive from randomized studies comparing dexamethasone to particulate steroids, which have been shown to be efficacious in randomized controlled studies.

NARRATIVE REVIEW OF STUDIES COMPARING PARTICULATE AND NONPARTICULATE EPIDURAL STEROIDS FOR LUMBOSACRAL RADICULOPATHY

To address the question of whether soluble steroids are as effective as particulate formulations, numerous comparative-effectiveness studies have been performed comparing the 2 types of steroids in patients with lumbosacral radicular pain with TFESI (Table 4).

In 2010, Park and colleagues published a study in which 106 patients with lumbar radiculopathy secondary to a herniated disc were randomized to receive transforaminal epidural dexamethasone or triamcinolone. At 1-month follow-up, the triamcinolone group experienced a mean reduction in Visual Analog Scale (VAS) pain score of 4.1 ± 1.9, which was statistically greater than the pain reduction observed with dexamethasone (2.4 ± 0.9). Differences in functional outcomes were not statistically significant.[65]

El-Yahchouchi and colleagues conducted the largest comparative study done to date, retrospectively analyzing treatment outcomes for 2634 patients treated with dexamethasone, triamcinolone, or betamethasone for lumbosacral radicular pain. At 2-month follow-up, 52.4% of dexamethasone-treated patients experienced $\geq 50\%$ pain reduction on a VAS compared with 44.2% of particulate steroid-treated patients. For function, 46.4% of the dexamethasone group experienced $> 40\%$ improvement compared with 39% in the particulate steroid group. The authors concluded that dexamethasone was noninferior to particulate steroids for lumbar TFESIs.[66] Limitations of this study include not only its retrospective nature but also the nonconcurrent use of the steroids: betamethasone and triamcinolone were used between 2006 and 2010 and dexamethasone exclusively after 2010.

Two more recent retrospective analyses comparing the effectiveness of dexamethasone to triamcinolone have been performed, with both studies favoring triamcinolone over dexamethasone at the 4-week follow-up in patients with lumbar radiculopathy.[70,71] In the Bensler and colleagues' study, 44.3% of triamcinolone-treated patients experienced improvement at 1 month versus 33.1% of dexamethasone-treated patients. At 1 week, significantly more patients in the dexamethasone group reported "worsening" symptoms.[70] In the Tagowski et al's[71] study, 34.9% of dexamethasone-treated patients experienced $\geq 50\%$ pain reduction in Numerical Rating Scale (NRS) score compared with 49.2% of triamcinolone-treated patients 4 weeks after treatment. The superiority of the particulate steroid was dependent on the baseline pain level, as the proportion of patients with $\geq 50\%$ pain reduction was similar for dexamethasone and triamcinolone in patients with low levels of baseline pain. This discrepancy may be due to the nonlinear nature of NRS pain scales,[72] and suggests that there may be no advantage for using particulate steroids in ESI for mild to moderate lumbar radiculopathy. Similar to the El-Yahchouchi and colleagues' analysis, both of these studies are limited by their retrospective nature and nonconcurrent use of the steroids.

In 2014, Kennedy and colleagues conducted a prospective study comparing triamcinolone to dexamethasone in 78 patients with lumbar radicular pain due to disc herniation. At the 2-week follow-up, there was a trend favoring triamcinolone (43.2% of triamcinolone patients experienced $\geq 50\%$ pain relief vs. 31.7% dexamethasone-treated patients). However, at the 3- and 6-month follow-ups, $> 70\%$ of the patients in both groups had at least 50% pain relief. The percentage of patients who needed surgery was also the same in both groups: 15% for dexamethasone at the 3- and 6-month follow-up and 16% and 19% at 3- and 6-month follow-up for triamcinolone, respectively. There was a statistically significant increase in the number of patients needing a repeat injection in the dexamethasone group. Seven of 41 dexamethasone-treated patients (17%) received 3 injections versus only 1 of 37 triamcinolone-treated patients (3%) ($P = 0.0005$). The authors concluded that dexamethasone is similar in effectiveness to particulate corticosteroids, but more dexamethasone injections were required to achieve the same outcomes.[67]

Another comparative-effectiveness study was conducted in 2015 by Denis et al[68] who found dexamethasone and betamethasone provided similar pain relief and functional improvement after 3 months in patients treated with TFESIs. At 6 months, functional improvement favored dexamethasone ($P = 0.050$).

In a randomized study conducted in 2011, Kim and Brown compared interlaminar injections of dexamethasone and methylprednisolone in patients with lumbosacral radicular pain (Table 5). Although they reported greater pain relief in the methylprednisolone group, the difference fell shy of statistical significance.[74]

A systematic review was performed by Mehta et al[76] that included 3 cervical studies (1 randomized) and 4 lumbar studies (2 randomized) comparing particulate and nonparticulate steroids for TFESI. The authors concluded that for patients with lumbar radiculopathy due to disc herniation or stenosis, the use of nonparticulate steroids is noninferior to the use of particulate steroids and, given their improved safety profile, should be recommended for lumbar TFESIs. In patients with cervical radiculopathy, the authors also recommended nonparticulate steroid use for TFESI based on safety concerns and noninferiority. For lumbar ILESI, a randomized trial demonstrated equivalence for particulate and nonparticulate steroids,[74] while a retrospective intra-individual comparison study demonstrated the superiority of particulate to nonparticulate steroids,[75] leading the authors to conclude the evidence was insufficient to provide any recommendation.

SAFETY ISSUES WITH DEXAMETHASONE SOLUTION

Based on safety data and comparative-effectiveness studies, several groups recommend dexamethasone as the first-line medication for TFESI.[39,49,77] The Benelux group of the

TABLE 4. Comparative-effectiveness of Dexamethasone Versus Particulate Steroids in the Treatment of Lumbar Radiculopathy With Transforaminal Epidural Steroid Injection

References	Study Type	Dexamethasone Dose (mg)	Comparator Dose	Patient Exposure	Results
Park et al[65]	Randomized, controlled trial comparing dexamethasone and triamcinolone in patients with lumbar disc herniation	7.5	40 mg triamcinolone	106	VAS pain score reduction: triamcinolone 4.1 ± 1.9 vs. dexamethasone 2.4 ± 0.9 No significant difference in functional outcomes at 1 mo
El-Yahchouchi et al[66]	Retrospective comparative-effectiveness outcomes study of dexamethasone vs. triamcinolone or betamethasone in patients with lumbar radicular pain	10	80 mg triamcinolone or 12 mg betamethasone	2634	52.4% of dexamethasone patients had ≥ 50% pain reduction at 2 mo vs. 44.2% of particulate steroid group
Kennedy et al[67]	Randomized, double-blind comparative-effectiveness study of dexamethasone vs. triamcinolone in patients with intervertebral disc herniation	10	40 mg triamcinolone	78	Trend favoring triamcinolone at 2-wk follow-up that was not observed at 3 or 6 mo Dexamethasone patients had more repeat injections (17%) than triamcinolone patients (3%) ($P = 0.005$)
Denis et al[68]	Randomized, double-blind controlled trial comparing the effectiveness of dexamethasone and betamethasone for lumbosacral radicular pain	7.5	6.0 mg betamethasone	56	No differences in VAS pain and ODI scores between the 2 groups at 3 mo. At 6 mo, improvement in ODI score marginally favored dexamethasone ($P = 0.050$)
McCormick et al[69]	Retrospective comparative-effectiveness study in patients with lumbar radicular pain	15	12 mg betamethasone 80 mg triamcinolone	78	No statistical difference in success rate between particulate steroids (35%) and nonparticulate steroids (28%) at short-term follow-up (< 30 d; $P = 0.50$) or intermediate follow-up, or the proportion who required repeat injections (27% vs. 39%)
Bensler et al[70]	Retrospective comparative-effectiveness outcomes study of particulate vs. nonparticulate corticosteroids in patients with lumbar radicular pain	4	40 mg triamcinolone acetonide	494	Higher proportion of patients treated with particulate steroids were improved at 1 wk (43.2% vs. 27.7%, $P = 0.001$) and at 1 mo (44.3% vs. 33.1%, $P = 0.019$) Patients receiving particulate steroids also had significantly higher NRS change scores at 1 wk ($P = 0.02$) and 1 mo ($P = 0.007$)
Tagowski et al[71]*	Retrospective comparative-effectiveness outcomes study of dexamethasone vs. triamcinolone in patients with lumbar radiculopathy	4	40 mg triamcinolone acetonide	418	Overall chance of pain reduction ≥ 50% was lower for dexamethasone-treated patients than triamncinolone-treated patients 4 wk postlumbar ESI (OR = 0.55; $P < 0.012$) Superiority of triamcinolone was dependent on baseline pain level, as low levels of baseline pain resulted in similar proportion of patients achieving ≥ 50% pain reduction

*Injections were administered via the transforaminal and interlaminar routes in this study.
ESI indicates Epidural steroid injection; NRS, Numerical Rating Scale; ODI, Oswestry Disability Index; OR, odds ratio; VAS, Visual Analog Scale.

WIP, on the other hand, did not recommend a nonparticulate steroid as the first-line steroid.[41] Although most societies recommend dexamethasone as the first choice for TFESI, there is a need to develop safer options. Among the currently available dexamethasone formulations (Table 1), some contain benzyl alcohol, a preservative with known neurotoxic effects in high concentrations.[47–49] Multiple studies have also reported that the duration of pain relief for patients receiving epidural dexamethasone injections can be shorter than with particulate steroids.[67,78] One recent retrospective study of 94 consecutive patients undergoing TFESI with dexamethasone for lumbosacral radicular pain found one third of patients did not experience any meaningful pain relief after an initial dexamethasone injection—either they had no improvement at all (9.6%) or their pain returned to baseline within 3 days (23.4%).[78] None of the patients experienced complete pain relief 2 weeks after their first injection with dexamethasone, and all patients proceeded to a second steroid injection. The need to provide frequent injections to patients can pose additional safety risks, both from the nonstochastic effects of steroids and the cumulative risks of the procedures themselves.

CONCLUSIONS

ESIs are perhaps the most commonly used interventional treatment for lumbosacral radiculopathy and have

TABLE 5. Comparative-effectiveness of Dexamethasone Versus Particulate Steroids in the Treatment of Lumbar Radiculopathy With Interlaminar Epidural Steroid Injection and Caudal Injection Technique

References	Study Type	Injection Technique	Dexamethasone Dose (mg)	Comparator Dose	Patient Exposure	Results
Datta and Upadhyay[73]	Randomized trial comparing dexamethasone, triamcinolone and methylprednisolone mixed with bupivacaine to bupivacaine alone in patients with radicular pain secondary to lumbar disc herniation	Caudal	15	80 mg methylprednisolone 80 mg triamcinolone 10-15 mL bupivacaine 0.25% alone (similar bupivacaine volume to steroid treatment groups)	163	All 3 steroid groups had greater pain relief than the nonsteroid control group through 12 wk, with no differences between groups All steroid groups had less paravertebral muscle spasm At 12 wk but not 6 wk, the triamcinolone and methylprednisolone groups had greater improvement in finger-to-floor range of motion than the dexamethasone and bupivacaine-only groups Mean VAS pain score at 12 wk: bupivacaine alone (6.2), methylprednisolone +bupivacaine (4.9), triamcinolone+bupivacaine (4.8), dexamethasone +bupivacaine (5.2)
Kim & Brown[74]	Randomized controlled trial comparing dexamethasone and methylprednisolone in patients with lumbar radiculopathy	IL	15	80 mg methylprednisolone	60	VAS pain score reduction: dexamethasone 19.7% decrease; methylprednisolone 27.2% decrease; difference not statistically significant
Kim et al[75]	Retrospective crossover study in patients who previously underwent an ESI with triamcinolone	Caudal, IL, or TFESI	10	40 mg triamcinolone	162	62.6% reported that triamcinolone provided greater benefit than dexamethasone ($P = 0.004$)

ESI indicates Epidural steroid injection; IL, interlaminar; TFESI, transforaminal epidural steroid injection; VAS, Visual Analog Scale.

been shown to reduce pain and improve function in well-selected patients, often for months. ESIs play an integral role as part of a multimodal treatment strategy to treat lumbar and cervical radicular pain and theoretically present fewer risks than surgical interventions. Although mixed, some studies suggest that ESI may reduce opioid use in the short term.[79,80] Although no corticosteroids have received FDA approval for epidural injection, numerous studies over the past 50 years have demonstrated efficacy and safety leading to high utilization in treating lumbosacral radiculopathy. Overall, complication rates are low, with vasovagal reactions, increased radicular pain, and pain at the injection site being the most common. Systemic side effects such as elevated blood glucose may also occur. Temporary and permanent neurological complications are rare and most often associated with the use of particulate corticosteroids given via the transforaminal route. Whereas a causal relationship has only been established in animal models, numerous case reports allude to a higher risk with transforaminal particulate steroids. TFESI have been shown in multiple randomized studies and a meta-analysis to provide superior pain relief and functional improvement compared with ILESI for unilateral radicular pain,[60] and most guidelines and reviews recommend nonparticulate steroids such as dexamethasone as the first-line medication choice for TFESI due to their enhanced safety profile and comparable effectiveness. The safety of dexamethasone formulations may be improved using preservative-free, sterile formulations but this must be balanced against possible reduced efficacy or duration of effect. Hence, the development of new formulations with increased residency time at the injection site may provide the optimum balance needed to enhance safety and improve effectiveness.

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