Curr Phys Med Rehabil Rep (2015) 3:151–158
DOI 10.1007/s40141-015-0086-1

Ideal Corticosteroid Choice for Epidural Steroid Injections: A Review of Safety and Efficacy

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Published online: 29 March 2015

Abstract Spine pathology and pain are common. Epidural injections for radicular pain are a common treatment option. While effective for certain populations, these injections have been associated with rare but significant complications including paralysis. The mechanism of injury is felt to be an embolic event following an injection of non-soluble particulate corticosteroids inadvertently into an artery that perfuses the spinal cord or brain. This dire complication has varying risks based on the anatomic considerations of a given route of injection and the corticosteroid utilized. This article will review the proposed mechanism of injury, anatomy principles of the routes of epidural injections, and the solubility and efficacy research on the different commonly utilized corticosteroid options.

Keywords Epidural · Steroid · Injections · Particulate · Non-particulate · Radiculopathy

Introduction

Spine pain is a common phenomenon in the United States, and epidural steroid injections (ESIs) are a very commonly utilized and efficacious treatment in appropriately selected patients [1, 3]. There is, however, an increasing burden of evidence of a wide array of adverse events following cervical and lumbar ESIs including but not limited to spinal cord infarction with subsequent paralysis [4–7], cerebellar and brainstem infarction with and without herniation [8, 9], cortical blindness [10], and death [11, 12]. In a voluntary retrospective survey of pain physicians, Scanton et al. described 78 complications from cervical transforaminal ESIs alone including 16 vertebrobasilar brain infarcts and 12 cervical spinal cord infarcts [7]. The prevailing theory regarding the mechanism of injury is an embolic effect of inadvertently injected particulate corticosteroids into an artery during epidural injections. This mechanism of injury arises from several key pieces of evidence including light microcopy data, anatomic data, animal studies, and the literature on the complications themselves. Given the preponderance of evidence with these complication sis affiliated with the use of particulate corticosteroids, the use of non-particulate steroid such as dexamethasone has gained popularity with the theoretical benefit of mitigating some of these risks. However, the vast majority of studies that have historically established the efficacy of ESI have mainly used particulate steroids [13, 14•]. This has lead to a continued debate on which steroid option should be utilized [15]. This article will therefore review corticosteroid options available, as well as their solubility and efficacy. It will also review the complications associated with these procedures and their mechanisms of injury. Additional discussions will be had regarding the anatomy considerations that vary between procedures specifically in regards to the vascular anatomy.

Corticosteroid Options

First, it is crucial to understand the corticosteroid options. There are currently several options of commercially available corticosteroids including methylprednisolone acetate (Depo-Medrol), triamcinolone acetate (Kenalog), betamethasone

This article is part of the Topical Collection on *Interventional Pain Management*.

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acetate and phosphate (Celestone Soluspan), and dexamethasone phosphate (Decadron). The first three are generally considered particulates, while dexamethasone is considered non-particulate.

This stratification is based on a corticosteroid particle size and aggregation via light microscopy data in relationship to red blood cells [16]. Specifically, if a corticosteroid has particles larger than or aggregates larger than a red blood cell, then it is labeled a particulate. Given the proposed embolic nature of a complication, this definition and grouping makes logical sense. A typical red blood cell (RBC) diameter is 6–8 μm, and theoretically, particles smaller than this would eliminate the risk of embolic infarction in the event of inadvertent intravascular injection. Derby et al. in a light microscopy study observed that triamcinolone particles range in size from 0.5 mm to greater than 100 μm and aggregate extensively [16]. Methylprednisolone has also been shown to have large particles in excess of 50 mm [17, 18]. Both triamcinolone and methylprednisolone also tend to coalesce into large aggregates in excess of 100 μm [18]. Betamethasone, while having extremely small particles, was also considered a particulate due to fact that it was densely packed and had extensively aggregates with size greater than 100 μm [16]. This was all in contrast to dexamethasone particles. Dexamethasone was viewed after being dissolved in both water and lidocaine at concentrations of both 4 and 10 mg/ml, and the majority particles were only 0.5 μm, and that even the largest particles were much small than the observed size of RBCs of 7.5–7.8 μm [16]. Furthermore, aggregation of dexamethasone particles was not observed [16]. This corroborated previous findings that dexamethasone is essentially pure liquid with no identifiable particles [17]. Dexamethasone is thus the only commercially available steroid that appears to be both small enough and not to aggregate so that, at least in theory, inadvertent intravascular injection does not carry the risk of embolic infarction. Of note compounded betamethasone phosphate would also be labeled a non-particulate given its soluble nature. Similar to dexamethasone there have been no reported cases of permanent neurologic injury with its use. However, it is not commercially available, and the commercially available preparation of betamethasone (Celestone Soluspan) contains both betamethasone phosphate (soluble) and betamethasone acetate (non-soluble). This formulation has light microscopy data showing extensive aggregation of particles and also reported cases of paralysis in the literature.

Mechanism of Injury: Anatomic Considerations

Give the light microscopy studies mentioned above, it is at least theoretically possible that injection of a particulate corticosteroid into an artery could cause an embolic effect. This mechanism is supported by anatomic plausibility given the known presence of arteries around the spinal column. The majority of permanent neurologic deficits are thought to occur with injection of particulate steroids inadvertently into either the vertebral artery, artery of Adamkiewicz, or radiculomedullary artery resulting in infarction of territory of nervous tissue supplied by that artery. An understanding of these vascular structures is essential in both performing and understanding the risks associated with these injections. In the cervical spine, the vertebral artery most often arises from the subclavian artery then enters the transverse foramina at the C6 level and then ascends ventral to the accepted target of cervical transforaminal (TFESI), through the transverse foramen until it curves medially and dorsally behind the superior articulate process of C1 [19]. The vertebral artery can give rise to a number of the segmental medullary arteries that feed the spinal cord while it ascends. The ascending cervical artery branches must also be considered during cervical TFESIs, as after it branches off from the subclavian artery, it can form an anastomosis with the vertebral artery. This vessel most often runs along the anterior tubercles of the transverse processes before supplying spinal branches. Additionally, the deep cervical artery not only gives branches to the brachial plexus and certain muscles but also supplies medullary arteries which feed the anterior spinal artery [19]. In a series of cadaveric dissections, Huntoon et al. found that in 21 of 95 foraminal areas examined, the parent ascending or deep cervical artery, or a large branch of it, was within 2 mm of the needle path for a CTFES procedure [19].

In the thoracolumbar spine, the artery of Adamkiewicz is the primary vascular supply to the spinal cord. It branches off the medial trunk of the segmental artery prior to entering the anterior spinal artery [20]. It can arise as high as T5, but more commonly from T9 to T12, and more rarely from L1, L2, or L3. It has, however, been reported as far caudal as the S2 foramen [21]. Cadaveric studies have shown that the artery of Adamkiewicz and radicular arteries are most commonly located in the anterior or anterosuperior aspects of the transvertebral foramen, which is part of what is commonly considered the "safe triangle" [22]. Studies of lumbar TFESI have shown that more than 75 % of the time, the needle is placed in the superior foramen, and more than 70 % of the time, the needle is placed in the anterior portion of the foramen [23]. Clearly there is a risk of cannulating arterioles that feed the spinal cord during TFESI at all levels of the spine, though greater risks at the L3 spinal level and above with only 1 % of people having an artery at risk below L3 [24]. This is also reflected in the complications literature, where although there have been cases of paralysis reported following injections at all levels from L1 through S1, the majority of cases are at the L3 level or higher. This is despite the majority of injections likely occurring at the lower levels (L4 through S1) due to the higher rates of pathology affecting these levels.

Mechanism of Injury: Animal Studies and Case Reports

The proposed mechanism of injury is thus possible based on light microscopy data and is plausible based on vascular anatomic considerations of the spinal column. It is additionally corroborated by animal studies that further demonstrate biologic plausibility. One study performed direct injection of steroids into the vertebral artery of pigs. It showed that the group injected with the particulate methylprednisolone suffered from permanent neurologic hypoxic/ischemic damage, while the group injected with dexamethasone showed no evidence of neurologic injury and recovered fully [25]. Another study demonstrated that direction injections of dexamethasone into the carotid artery of rats brains also did not result in any neurologic injury, while particulate corticosteroids had permanent neurologic complications [26]. These studies collectively show the safety of the non-particulate dexamethasone phosphate and the serious adverse effects of the particulate preparations.

Lastly, the literature on these complications offers further insights. Currently, all of the literatures on permanent neurologic complications due to these procedures is exclusively associated with the use of particulate corticosteroids. Ahadian et al. listed 18 serious adverse events in the literature that occurred following TFESIs, and of those ten involved methylprednisolone, five used triamcinolone, and two used betamethasone [4, 5, 9, 27–35]. Recently, the United States Food and Drug Adminstration (FDA) reviewed the closed claims data on adverse events following epidural injections. In their report, they cited three complications with dexamethasone. Upon review of these complications, two were transient numbness and weakness that had no abnormalities on post-procedure MRI and their symptoms resolved. This would be consistent with the reported concurrent injection of the local anesthetic lidocaine and not consistent with the other cases of paralysis. The third case involved the development of seizures 1 month after a cervical epidural injection. This case also lacks a biologic plausibility and is more consistent with the probable scenario of someone who spontaneously developed seizures and happened to receive an injection in the preceding month. This FDA statement resulted in appropriate rebuttals given its imprecision [2].

Proposed Alternative Mechanisms of Injury

Alternative causes of neurologic compromise have also been proposed, such as chemical vascular injury or direct neurotoxic effects of additives and preservatives that are included in the steroids used for ESIs. These additives include benzyl alcohol, polyethylene glycol (PEG), polysorbate 80, and ethylenediaminetetraacetate (EDTA) [36]. Direct injection of the carrier molecule PEG (found in the commercially available form of methylprednisolone, Depo-Medrol) into carotid arteries of rats has been shown to cause hemorrhagic brain injury [26]. On the other hand, Benzon et al. has shown that PEG does not cause neurolysis at concentrations up to 40 % [37]. Case reports of severe flaccid paralysis following epidural anesthesia have been attributed to the 1.5 % benzyl alcohol contained in a saline solution [38]. However, the only common trait between the various steroids that have been implicated in permanent neurologic deficits when used in ESI—methylprednisolone, betamethasone, and triamcinolone—is particle size, as none of the carriers or additives that have been suggested to be causative in injury are common to all three. Additionally, some have proposed arterial dissection following needle trauma, however, even this one reported case utilized a particulate corticosteroid, thus calling into question the true effects of the vertebral artery dissection [11].

Therefore, collectively given the light microscopy data, the animal studies, and the case reports, it appears that all commercially available particulate corticosteroids can cause serious neurologic injury. This does not appear to be the case for dexamethasone phosphate. While the risks are clearly different for the corticosteroid options, the relative effectiveness must be considered to make an informed risk to benefit decision for a particular patient.

Efficacy Overview

A full review of the literature on the efficacy of ESIs in and of themselves is a separate topic. Readers must understand the efficacy of a particular treatment varies based on the pathology treated, the route of injection and possibly even the steroid utilized. The best review of the literature that takes these factors into consideration is by MacVicar et al. through the International Spine Intervention Society on lumbar TFESI. They concluded that lumbar TFESI is a legitimate treatment for lumbar radicular pain caused by disk herniation or foraminal stenosis that is effective, cost-effective, and reduces the burden of illness on patients and the population at large [14•]. Specifically, estimates of lumbar efficacy are that up to 70 % of patients get at least 50 % relief at 1–2 months and 30 % have complete pain relief [39]. A similar review by the International Spine Intervention Society by Engel et al. on the effectiveness of cervical TFESIs is less convincing but still concludes that cervical TFESI helps some patients with short-term relief of radicular pain and is associated with reduced rates of spinal surgery [40]. Specifically they conclude that approximately 40 % of patients have 50 % improvement of

radicular pain at 4 weeks [40]. In both of the above reviews, the vast majority of literature that support the efficacy of TFESI utilize particulate steroids [14•, 40]. The evidence for other forms of epidural injection such as interlaminar and caudal approaches is less robust [41–43]. Additionally, the procedures are likely less safe and less efficacious without the use of appropriate image guidance to help assure accuracy and decrease the risk of inadvertent injection of a particulate corticosteroid into the artery.

Given the apparent dichotomy in risk between particulate and non-particulate steroids, there is not surprisingly increasing interest in comparative of efficacy between the two classes of steroids and their use in ESI. It is theorized that the particulate steroids stay in the epidural space longer due to their size and aggregation properties, while the soluble steroids are washed out of their target region readily. Reports of crystal deposition in the epidural space found intra-operatively months after an epidural steroid injection with a particulate steroid seem to confirm this. This, in theory, creates an argument that particulate steroids may be more efficacious than non-particulate steroids. Fortunately, this theoretical superior efficacy has been examined in multiple studies over the past decade.

Cervical Spine

In 2006, Dreyfuss et al. were the first to investigate the relative effectiveness of the steroid preparations by conducting a prospective randomized trial between 60 mg Triamcinolone versus 12.5 mg dexamethasone with single cervical TFESI in 30 patients with 4-week follow-up. Using appropriate categorical outcomes defining success as at least 50 % relief, they found no difference between groups with 60 % of the dexamethasone group and 67 % of the triamcinolone group achieving relief. Other non-significant findings were that a greater proportion in the dexamethasone group (27 %) achieved complete relief compared to the triamcinolone group (7 %). It is likely that findings in this study lacked statistical significance due to it lacking power, though ultimately the authors concluded that the "effectiveness of dexamethasone was slightly less than that of triamcinolone, but the difference was neither statistically nor clinically significant" [44].

In 2009, Lee et al. published findings from a non-randomized comparison between 40 mg triamcinolone versus 10 mg dexamethasone use in single cervical TFESI in 259 consecutive patients with minimum 4-week follow-up [44]. The study used a 5-point scale to perform categorical analysis but failed to explicitly define what was success or failure. Nonetheless, they found no significant difference between the two groups with 43 of 62 patients (69 %) in the dexamethasone group versus 78 out of 97 (80 %) in the triamcinolone group being categorized as success ($p = 0.129$) [44]. The mean duration of being symptom free was 298 days in the dexamethasone group and 185 days in the triamcinolone group, but again the findings were non-significant. There was no difference in rates of progressing to surgery between the two groups [44].

Shakir et al. published the most recent study, which was a retrospective review comparing 40 mg triamcinolone versus 15 mg dexamethasone in 441 patients. There were statistically significant differences in mean pain score reduction (triamcinolone 2.33 vs. dexamethasone 2.38) between groups [45]. Review of the data in the study also reveals that in the dexamethasone group 73 received 1 injection, 95 received 2 injections, and 53 received 3 injections. Compared to the triamcinolone group in which 55 received 1 injection, 92 received 2 injections and 73 received 3 injections [45]. The study also reported there was no difference between groups when comparing those with benefit (any improvement) versus no benefit (0 reduction in pain). Re-evaluation of the data by comparing those who demonstrated a decrease in VAS by score of 2 more (minimal clinical significant decrease for VAS) 126/220 (57 %) of the triamcinolone group demonstrated improvement compared to 134/221 (61 %) of the dexamethasone group also shows a no significant difference between groups. Evaluation of the three studies that compare particulate versus non-particulate steroids for cervical TFESI does not demonstrate superiority of particulate or non-particulate steroid in terms of efficacy.

Lumbar Spine

There are four additional studies that compare particulate to non-particulate steroids for lumbar ESI, of which two were randomized prospective trials. The 2011 study by Kim and Brown evaluated their use in interlaminar steroid injections and found smaller mean VAS decrease in the dexamethasone group (19.7 % VAS decrease) compared to the methylprednisolone group (27.2 % VAS decrease), but their results were not statistically significant and even more both groups demonstrated the same likelihood of improvement [46]. In 2013, El-Yahchouchi et al. published the largest study to date comparing particulate and non-particulate steroids for TFESI [47••]. This retrospective study was set up as a non-inferiority study between dexamethasone 10 mg compared to triamcinolone 80 mg and betamethasone 12 mg for lumbar TFESI [47••]. A chart review of 2634 patients with 2-month follow-up was performed and categorical analysis of both pain relief defined as success with 50 % pain relief on VAS as well as functional improvement defined as success with >40 % improvement on Roland Morris was performed. With respect to pain relief, 52.4 % in the dexamethasone group were defined as success compared to 44.2 % in the particulate

group. On Roland Morris, 46.4 % of the dexamethasone group achieved greater than 40 % improvement compared to 39 % in the particulate steroid group [47••]. Further subgroup analysis was performed, and in some cases, dexamethasone was found to actually be superior to the particulate steroids. Overall, the authors concluded that there was no evidence that dexamethasone is less effective than particulate steroids in lumbar TFESIs [47••]. While not randomized nor prospective, the large number of injections evaluated in the El-Yahchouchi study is perhaps the most significant evidence that particulate and non-particulate steroids are similar in efficacy for TFESI.

The first prospective study in the lumbar spine was published in 2010 by Park et al. [48]. In this study, 106 patients were randomized to either 7.5 mg of dexamethasone or 40 mg of triamcinolone for a lumbar TFESI and followed for 1 month. When evaluating the mean decrease in VAS pain score at 4 weeks, the triamcinolone group had a decrease of 4.1 ± 1.9 which was statistically greater than that found in the dexamethasone group of 2.4 ± 0.9 (Mann–Whitney U $p < 0.00$). However, by stricter criteria, the 95 % confidence overlapped lessening the significance of the findings somewhat. For the outcome of pain relief, a statistically significant greater percentage of patients in the triamcinolone group achieved complete relief as well. However, for functional outcomes including the McGill pain questionnaire and the Oswestry Disability Index, there was no difference between the groups [48]. To date, this is the only study demonstrating a statistically significant outcome favoring particulate corticosteroids. This finding, however, was only for pain outcomes and not for functional outcomes. Also when re-evaluating the data using categorical outcome the difference between the two groups, triamcinolone was still favored but the difference was no longer statistically significant [48, 49]. In 2013, Kennedy et al. compared 40 mg triamcinolone versus 10 mg dexamethasone for lumbar TFESI for radicular pain due to disk herniation in 78 patients [50••]. At 2-week follow-up, there was a non-statistically significant trend toward a greater percentage of patients in the triamcinolone group achieving >50 % relief (43.2 % triamcinolone vs. 31.7 % dexamethasone), but this trend disappeared at 3- and 6-month follow-up. Similarly, there was a small trend favoring triamcinolone when evaluated for 51 % reduction in ODI at 2 weeks (35 % triamcinolone vs. 27 % dexamethasone), which also disappeared and actually reversed by 6 months (65 % triamcinolone vs. 71 % dexamethasone). When evaluating the number of injections required, there was a small but statistically significant difference favoring triamcinolone with 7/41 (17 %) patients in the dexamethasone group receiving 3 injections compared to only 1/37 (3 %) in the triamcinolone group ($p = 0.005$) [50••]. The authors concluded that dexamethasone appears to possess reasonably similar effectiveness when compared with triamcinolone but noted that the dexamethasone group required slightly more injections than the triamcinolone group to achieve the same outcomes [50••]. Clearly, this body of evidence demonstrates that dexamethasone is an effective treatment for lumbar radicular pain.

While there is a growing body of literature regarding particulate versus non-particulate use of steroids for ESI, available literature to guide other decisions that may be faced such as dosing is very limited. The most appropriate dose of all corticosteroids including dexamethasone has yet to be established. In general, dexamethasone is thought to have only slightly less anti-inflammatory effect than betamethasone per mg, and both of these are roughly fivefold more potent per mg of triamcinolone or methylprednisolone [51]. In the comparative studies above, doses of dexamethasone used included 7.5, 10, 12.5, and 15 mg [44, 45, 47••, 48, 50••, 52]. Of note, the study that utilized 7.5 mg of dexamethasone was the only one that found statistically significant superiority of particulate steroids over dexamethasone [48], possibly brining into questions if the results would have been different had a higher dose of dexamethasone been utilized. There is one study to date that looked at the optimal dose of dexamethasone for ESI. Ahadian et al. compared improvements in radicular pain score as well as multiple secondary functional at 4, 8, and 12 weeks in prospective randomized double blind trial of 98 subjects after lumbar TFESI of either 4, 8, or 12 mg of dexamethasone [53]. All three groups showed significant improvement from baseline at 12 weeks but no significant difference between groups, suggesting that TFESI with dexamethasone provides significant and meaningful improvement at doses of 4, 8, and 12 mg and that the optimal dose may be even lower than 4 mg [53]. Conversely, the ideal dose may also be greater than 12 mg as the studies with the best results have utilized larger doses.

In cases where particulate steroids still may be preferred, consideration must also be made regarding the dosing of particulate steroids and comparative efficacy of different particulate steroids. Again the literature evaluating these topics is sparse. No standard dose of steroid exists for ESI, though in the aforementioned review article on lumbar TFESI by MacVicar, it was noted that most studies that investigated TFESI used either low (40 mg) dose methylprednisolone or high (80 mg) dose methylprednisolone, or "equivalent" dosing of triamcinolone (1:1 equivalency) or betamethasone (5:1 equivalency) [14•, 51]. In a retrospective chart review of lumbar ESI, one study showed 40 mg of triamcinolone to be more efficacious than 6 mg of betamethasone at 2 weeks (71 vs. 54 % subjects demonstrating improvement in low back, buttock, or leg pain respectively, $p < 0.001$) [54]. A much smaller study also performing interlaminar ESI showed that a purely

aqueous (non-particulate) form of 15 mg betamethasone (betamethasone sodium phosphate, not commercially available) was less effective than 80 mg methylprednisolone in treating patients with lumbar pain at 4 weeks [55]. However, another retrospective chart review that evaluated 40 mg of triamcinolone and 6 mg of betamethasone via the transforaminal approached failed to show a significant difference in the percentage of those demonstrating improvement at 2 weeks between the two groups (49 % of triamcinolone vs. 55 % of betamethasone with improvement in radicular pain, $p = 0.69$) [56]. Collectively, while there are multiple studies demonstrating efficacy of TFESI using differing doses of methylprednisolone, betamethasone, or triamcinolone, the only study that compared use of two different particulate corticosteroids showed no difference in efficacy.

Additional Safe Guards

Many safeguards have been developed to avoid or identify intravascular injection with the goal of aborting the procedure. These include use of proper technique according to the International Spine Intervention Society guidelines, injection of contrast under real time fluoroscopy, anesthetic test dose, use of low volume extension tubing, an infraneural approach, and potential use of digital subtraction angiography [5, 57–61]. It is imperative that a physician performing these injections has knowledge of the inherent risks of the procedure and strategies to reduce those risks.

Conclusions

Transforaminal epidural administration of steroids is a proven method of symptom relief for both cervical and lumbar radicular pain [14•, 40]. These procedures overall have very low rates of complications [14•, 40, 47••, 62–66]. Regardless of steroid choice, minor transient adverse events such as vasovagal events, increased pain, and systemic side effects such as elevated blood glucose may occur [47••, 62–66]. Of greatest concern though, is permanent neurologic compromise including paraplegia, quadriplegia, and even death [5, 7, 28]. The is a large volume of evidence that these particular neurologic complications arise after the injection of a particulate corticosteroid into an artery that perfuses the central nervous system [2, 5, 16, 30, 49, 67].

Given the anatomic considerations, light microcopy data, case reports of complication, and the comparative efficacy data several recommendations clearly emerge. These recommendations vary by route and location of the injection.

Interlaminar and Caudal ESI

While interlaminar and even caudal injections have case reports of paralysis in the literature [68], these procedural routes clearly have a lower risk of this particular complication due to the known vascular anatomy of the spinal column. Therefore, the main consideration with these approaches is the efficacy of the corticosteroid. There are currently insufficient data to give a clear recommendation on which corticosteroid should be utilized for these procedures.

Cervical and Thoracic Transforaminal ESI

Given the known presence of the vertebral artery in the foramen at every level in the cervical spine, a cervical transforaminal ESI should only be completed utilizing a non-particulate corticosteroid due to the unfavorable risk to benefit ratio with a particulate corticosteroid. For the thoracic spine, the presence of an artery is higher than the lumbar spine but lower than the cervical spine. However, the thoracic spine does have additional anatomic features such as the ribs obscuring the ability to detect vascular flow on fluoroscopy, which may result in an increased risk in this area. Therefore, it is the recommendation of the authors to utilize a non-particulate corticosteroid exclusively for a thoracic transforaminal ESI.

Lumbar Transforaminal ESI

In the lumbar spine, while the risk of arterial presence is lower than the cervical and thoracic spine, it is clearly a possibility that the treating physician must be aware of. Given the large volume of literature showing efficacy, dexamethasone should now be considered the first line treatment for those receiving a lumbar transforaminal ESI. The higher risk particulates should be reserved for special cases, such as those that are non-responsive to the non-particulate formulation. Additional safe guards could be considered for this group including the use of an infraneural approach or digital subtraction technology [3, 5, 7, 28], and given the much greater risks of surgery over TFESI regardless of steroid selection, optimizing chances of successful TFESI would likely. For the time being though, non-particulate steroids such as dexamethasone should be used as first line steroid choice for TFESI in all cervical injections and lumbar injections at L3 and above where risk of permanent neurologic compromise is greatest. Moreover, the literature is equivocal as to demonstrating the theoretically greater efficacy of particulate steroids and as such, even for TFESI at L4 and below, using dexamethasone likely confers equal or close to equal efficacy without the added risk of using particulate steroids.

Compliance with Ethics Guidelines

Conflict of Interest Byron Schneider and Neal Varghis declare that they have no conflict of interest. David J. Kennedy reports non-financial support from ISIS, AAP, grants from ISIS, and personal fees from NASS/ISIS.

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.

References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Kennedy DJ, Baker RM, Rathmell JP. Use of spinal injections for low back pain. JAMA. 2013;310(16):1736.
2. Kennedy DJ, Levin J, Rosenquist R, Singh V, Smith C, et al. Epidural steroid injections are safe and effective: multisociety letter in support of the safety and effectiveness of epidural steroid injections. Pain Med. 2015;. doi:10.1111/pme.12667.
3. Karppinen J, Ohinmaa A, Malmivaara A, Kurunlahti M, Kyllönen E, Pienimäki T, et al. Cost effectiveness of periradicular infiltration for sciatica: subgroup analysis of a randomized controlled trial. Spine. 2001;26(23):2587–95.
4. Ludwig MA, Burns SP. Spinal cord infarction following cervical transforaminal epidural injection: a case report. Spine. 2005; 30(10):E266–8.
5. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: two case reports. Pain Med. 2009;10(8):1389–94.
6. Bose B. Quadriparesis following cervical epidural steroid injections: case report and review of the literature. Spine J. 2005; 5(5):558–63.
7. Scanlon GC, Moeller-Bertram T, Romanowsky SM, Wallace MS. Cervical transforaminal epidural steroid injections: more dangerous than we think? Spine. 2007;32(11):1249–56.
8. Suresh S, Berman J, Connell DA. Cerebellar and brainstem infarction as a complication of CT-guided transforaminal cervical nerve root block. Skeletal Radiol. 2007;36(5):449–52.
9. Beckman WA, Mendez RJ, Paine GF, Mazzilli MA. Cerebellar herniation after cervical transforaminal epidural injection. Reg Anesth Pain Med. 2006;31(3):282–5.
10. McMillan MR, Crumpton C. Cortical blindness and neurologic injury complicating cervical transforaminal injection for cervical radiculopathy. Anesthesiology. 2003;99(2):509–11.
11. Rozin L, Rozin R, Koehler SA, Shakir A, Ladham S, Barmada M, et al. Death during transforaminal epidural steroid nerve root block (C7) due to perforation of the left vertebral artery. Am J Forensic Med Pathol. 2003;24(4):351–5.
12. Brouwers PJ, Kottink EJ, Simon MA, Prevo RL. A cervical anterior spinal artery syndrome after diagnostic blockade of the right C6-nerve root. Pain. 2001;91(3):397–9.
13. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. Pain Med. 2010;11(8):1149–68.
14. • MacVicar J, King W, Landers MH, Bogduk N. The effectiveness of lumbar transforaminal injection of steroids: a comprehensive review with systematic analysis of the published data. Pain Med. 2013;14(1):14–28. *A well done review of efficacy for a single procedure with appropriate stratification based on underlying pathology*.
15. Depalma MJ, Stout A, Kennedy DJ. Corticosteroid choice for epidural injections. PM R. 2013;5(6):524–32.
16. Derby R, Lee S-H, Date ES, Lee J-H, Lee C-H. Size and aggregation of corticosteroids used for epidural injections. Pain Med. 2008;9(2):227–34.
17. Benzon HT, Chew T-L, McCarthy RJ, Benzon HA, Walega DR. Comparison of the particle sizes of different steroids and the effect of dilution: a review of the relative neurotoxicities of the steroids. Anesthesiology. 2007;106(2):331–8.
18. Tiso RL, Cutler T, Catania JA, Whalen K. Adverse central nervous system sequelae after selective transforaminal block: the role of corticosteroids. Spine J. 2004;4(4):468–74.
19. Huntoon MA. Anatomy of the cervical intervertebral foramina: vulnerable arteries and ischemic neurologic injuries after transforaminal epidural injections. Pain. 2005;117(1–2):104–11.
20. Alleyne CH, Cawley CM, Shengelaia GG, Barrow DL. Microsurgical anatomy of the artery of Adamkiewicz and its segmental artery. J Neurosurg. 1998;89(5):791–5.
21. Kroszczynski AC, Kohan K, Kurowski M, Olson TR, Downie SA. Intraforaminal location of thoracolumbar anterior medullary arteries. Pain Med. 2013;14(6):808–12.
22. Kroszczynski AC, Kohan K, Kurowski M, Olson TR, Downie SA. Intraforaminal location of thoracolumbar anterior medullary arteries. Pain Med. 2013;14(6):808–12.
23. Atluri S, Glaser SE, Shah RV, Sudarshan G. Needle position analysis in cases of paralysis from transforaminal epidurals: consider alternative approaches to traditional technique. Pain Physician. 2013;16(4):321–34.
24. Lo D, Valleé JN, Spelle L, Cormier E, Saillant G, Rancurel G, et al. Unusual origin of the artery of Adamkiewicz from the fourth lumbar artery. Neuroradiology. 2002;44(2):153–7.
25. Okubadejo GO, Talcott MR, Schmidt RE, Sharma A, Patel AA, Mackey RB, et al. Perils of intravascular methylprednisolone injection into the vertebral artery. An animal study. J Bone Joint Surg Am. 2008;90(9):1932–8.
26. Dawley JD, Moeller-Bertram T, Wallace MS, Patel PM. Intra-arterial injection in the rat brain: evaluation of steroids used for transforaminal epidurals. Spine. 2009;34(16):1638–43.
27. Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: a prospective, randomized, double-blind, dose-response trial. Reg Anesth Pain Med. 2011;36(6):572–8.
28. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: report of three cases. Spine J. 2002;2(1):70–5.
29. Huntoon MA, Martin DP. Paralysis after transforaminal epidural injection and previous spinal surgery. Reg Anesth Pain Med. 2004;29(5):494–5.
30. Karasek M, Bogduk N. Temporary neurologic deficit after cervical transforaminal injection of local anesthetic. Pain Med. 2004;5(2):202–5.
31. Glaser SE, Falco F. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. Pain Physician. 2005;8(3):309–14.
32. Muro K, O'Shaughnessy B, Ganju A. Infarction of the cervical spinal cord following multilevel transforaminal epidural steroid injection: case report and review of the literature. J Spinal Cord Med. 2007;30(4):385–8.
33. Ruppen W, Hügli R, Reuss S, Aeschbach A, Urwyler A. Neurological symptoms after cervical transforaminal injection with steroids in a patient with hypoplasia of the vertebral artery. Acta Anaesthesiol Scand. 2008;52(1):165–6.
34. Lyders EM, Morris PP. A case of spinal cord infarction following lumbar transforaminal epidural steroid injection: MR imaging

and angiographic findings. AJNR Am J Neuroradiol. 2009; 30(9):1691–3.
35. Wybier M, Gaudart S, Petrover D, Houdart E, Laredo J-D. Paraplegia complicating selective steroid injections of the lumbar spine. Report of five cases and review of the literature. Eur Radiol. 2010;20(1):181–9.
36. Manchikanti L. Role of neuraxial steroids in interventional pain management. Pain Physician. 2002;5(2):182–99.
37. Benzon HT, Gissen AJ, Strichartz GR, Avram MJ, Covino BG. The effect of polyethylene glycol on mammalian nerve impulses. Anesth Analg. 1987;66(6):553–9.
38. Craig DB, Habib GG. Flaccid paraparesis following obstetrical epidural anesthesia: possible role of benzyl alcohol. Anesth Analg. 1977;56(2):219–21.
39. Ackerman WE 3rd, Ahmad M. The efficacy of lumbar epidural steroid injections in patients with lumbar disc herniations. Anesth Analg. 2007;104(5):1217–22 tables of contents.
40. Engel A, King W, MacVicar J, 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(3):386–402.
41. Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St-Pierre A, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. N Engl J Med. 1997;336(23):1634–40.
42. Valat J-P, Giraudeau B, Rozenberg S, Goupille P, Bourgeois P, Micheau-Beaugendre V, et al. Epidural corticosteroid injections for sciatica: a randomised, double blind, controlled clinical trial. Ann Rheum Dis. 2003;62(7):639–43.
43. Bush K, Hillier S. A controlled study of caudal epidural injections of triamcinolone plus procaine for the management of intractable sciatica. Spine. 1991;16(5):572–5.
44. Lee JW, Park KW, Chung S-K, Yeom JS, Kim K-J, Kim H-J, et al. Cervical transforaminal epidural steroid injection for the management of cervical radiculopathy: a comparative study of particulate versus non-particulate steroids. Skeletal Radiol. 2009;38(11):1077–82.
45. Shakir A, Ma V, Mehta B. Comparison of pain score reduction using triamcinolone vs. dexamethasone in cervical transforaminal epidural steroid injections. Am J Phys Med Rehabil. 2013;92(9):768–75.
46. Kim D, Brown J. Efficacy and safety of lumbar epidural dexamethasone versus methylprednisolone in the treatment of lumbar radiculopathy: a comparison of soluble versus particulate steroids. Clin J Pain. 2011;27(6):518–22.
47. •• El-Yahchouchi C, Geske JR, Carter RE, Diehn FE, Wald JT, Murthy NS, et al. The noninferiority of the nonparticulate steroid dexamethasone vs. the particulate steroids betamethasone and triamcinolone in lumbar transforaminal epidural steroid injections. Pain Med. 2013;14(11):1650–57. *This is a largest study to date comparing the outcomes after receiving various steroid options*.
48. Park CH, Lee SH, Kim BI. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. Pain Med. 2010;11(11):1654–8.
49. DePalma MJ, Stout A, Kennedy DJ. Corticosteroid choice for epidural injections. PM R. 2013;5(6):524–32.
50. •• Kennedy DJ, Plastaras C, Casey E, Visco CJ, Rittenberg JD, Conrad B, et al. Comparative effectiveness of lumbar transforaminal epidural steroid injections with particulate versus nonparticulate corticosteroids for lumbar radicular pain due to intervertebral disc herniation: a prospective, randomized, double-blind trial. Pain Med. 2014;15(4):548–55. *This reference is among the best prospective studies comparing the steroid choices in a single homogenous patient population with appropriate outcomes over an appropriate time frame*.
51. Lennard TA. Pain procedures in clinical practice. 3rd ed. Philadelphia: Elsevier/Saunders; 2011.
52. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. Pain Med. 2006;7(3):237–42.
53. Ahadian FM, McGreevy K, Schulteis G. Lumbar transforaminal epidural dexamethasone: a prospective, randomized, double-blind, dose-response trial. Reg Anesth Pain Med. 2011;36(6):572–8.
54. Stanczak J, Blankenbaker DG, De Smet AA, Fine J. Efficacy of epidural injections of Kenalog and Celestone in the treatment of lower back pain. AJR Am J Roentgenol. 2003;181(5):1255–8.
55. Noe CE, Haynsworth RF. Comparison of epidural Depo-Medrol vs. aqueous betamethasone in patients with low back pain. Pain Pract. 2003;3(3):222–5.
56. Blankenbaker DG, De Smet AA, Stanczak JD, Fine JP. Lumbar radiculopathy: treatment with selective lumbar nerve blocks–comparison of effectiveness of triamcinolone and betamethasone injectable suspensions. Radiology. 2005;237(2):738–41.
57. Park JW, Nam HS, Cho SK, Jung HJ, Lee BJ, Park Y. Kambin's triangle approach of lumbar transforaminal epidural injection with spinal stenosis. Ann Rehabil Med. 2012;25(1):833–43.
58. McLean JP, Sigler JD, Plastaras CT, Garvan CW, Rittenberg JD. The rate of detection of intravascular injection in cervical transforaminal epidural steroid injections with and without digital subtraction angiography. PM R. 2009;1(7):636–42.
59. Bogduk N, International Spine Intervention Society, Standards Committee. Practice guidelines for spinal diagnostic and treatment procedures. San Francisco: International Spine Intervention Society; 2004.
60. Chang Chien GC, Candido KD, Knezevic NN. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. Pain Physician. 2012;15(6):515–23.
61. Rathmell JP, Benzon HT, Dreyfuss P, Huntoon M, Wallace M, Baker R, et al. Safeguards to prevent neurologic complications after epidural steroid injections: consensus opinions from a multidisciplinary working group and national organizations. Anesthesiology. 2015. doi:10.1097/ALN.0000000000000614.
62. Kennedy DJ, Schneider B, Casey E, Rittenberg J, Conrad B, Smuck M, et al. Vasovagal rates in flouroscopically guided interventional procedures: a study of over 8,000 injections. Pain Med. 2013;14(12):1854–9.
63. Schneider BJ, Smuck M, Plastaras C, Nahm LS, Maus TP, Kennedy DJ. Poster 458 delayed complications following interventional pain procedures. PM R. 2014;6(9):S346.
64. Nahm LS, Smuck M, Plastaras C, Schneider BJ, Kennedy DJ. Poster 457 next day adverse events from interventional pain procedures. PM R. 2014;6(9):S346.
65. McCormick Z, Plastaras C, Garvan C, Macron DS, Joshi A, Chimes GP, et al. Poster 460 fluoroscopically guided lumbosacral transforaminal epidural steroid injections: adverse events and predictive factors. PM R. 2014;6(9):S347.
66. Schneider B, Kennedy DJ, Casey E, Smuck M, Conrad B, Plastaras C. Trainee involvement in transforaminal epidural steroid injections associated with increased incidence of vasovagal reactions. PM&R. 2014. http://linkinghub.elsevier.com/retrieve/pii/S1934148214001713.
67. Bogduk N, Dreyfuss P, Baker R, Yin W, Landers M, Hammer M, et al. Complications of spinal diagnostic and treatment procedures. Pain Med. 2008;2(9):S11–34.
68. Shetty SR, Shankaranarayana RU, Mehandale SG. Paraplegia following caudal block in a child with Burkitt's lymphoma. Paediatr Anaesth. 2011;21(10):1087–8.