BEST PRACTICES FOR EPIDURAL STEROID INJECTIONS IN THE SETTING OF A PRESERVATIVE-FREE DEXAMETHASONE SHORTAGE

The Spine Intervention Society (SIS) supports the following best practice recommendations and statements for the performance of epidural steroid injections in the setting of a preservative-free dexamethasone shortage:

- While preservative-free dexamethasone is preferred, dexamethasone with preservative may be used for transforaminal epidural injections (TFESI).
- Physicians who elect to use preservative-free steroids from a compounding pharmacy must carefully weigh the risks and benefits, as sterility assurance concerns exist.
- Only non-particulate steroids should be used for cervical TFESI.
- In the absence of dexamethasone, particulate steroids (e.g. methylprednisolone, betamethasone, triamcinolone) can be considered for lumbar TFESI (although at higher risk).*
- If a lumbar TFESI with particulate steroid is performed, physicians should strongly consider use of all available risk-mitigation strategies to minimize the possibility of intra-arterial injection including the use of an infraneural approach, a local anesthetic test dose, and use of digital subtracting imaging (DSI) beyond requisite live-fluoroscopic observation of contrast medium injection through extension tubing. It should be noted that commercially available particulate steroids contain preservatives, so use of particulate steroid does not eliminate the possible effects of preservative excipients (PEs).
- Because the risk profile is indistinguishable, either particulate or non-particulate steroids may be used in the performance of interlaminar or caudal epidural injections at any spinal level. Clinical judgment on a case-by-case basis is recommended when selecting the optimal route of epidural injection to balance safety and effectiveness.

Physicians should carefully weigh the risks and benefits of using an alternative agent or approach for epidural steroid injection and involve each patient in the process of shared decision making before proceeding.

*Procedures should be performed following **SIS Guidelines**. The operator should confirm placement of the needle in at least two planes and confirm appropriate contrast medium spread under fluoroscopic observation. Please refer to the **SIS Guidelines** for the full details and standards related to each unique procedure.*

Background

It is well established that the risk of neurologic injury associated with TFESI is reduced by the use of non-particulate steroid (i.e. dexamethasone) as opposed to particulate steroid preparations. Particulate steroids cause red blood cell agglutination and the steroid particles themselves are large enough to obstruct arterioles; however, dexamethasone does not have these properties. As such, if dexamethasone is inadvertently injected into the vertebral artery or a radiculomedullary artery, the risk of an ischemic neurological event is substantially reduced, if not completely obviated. In large cohort studies of TFESIs performed according to practice guidelines, there is a zero prevalence of ischemic neurological events.

In the case of a preservative-free dexamethasone shortage, providers must carefully consider various options to optimize safety and effectiveness during an epidural steroid injection. Guideline-concordant alternative choices include:

1) TFESI of dexamethasone with preservative.
2) TFESI of particulate steroid.*
3) Epidural injection of particulate steroid via an alternative route (interlaminar or caudal).
4) Provide a treatment other than epidural steroid injection

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Currently, there are no published guidelines addressing the advisability of using steroids from compounding pharmacies.

*The Multisociety Pain Workgroup's (MPW) **Safe Use Initiative** guidelines state: "A nonparticulate steroid (e.g., dexamethasone) should be used for the initial injection in lumbar transforaminal epidural injections. There are situations where particulate steroids could be used in the performance of lumbar TFESIs."

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SEVERAL FACTORS MUST BE CONSIDERED THAT MAY AFFECT THE RISK PROFILE OF AN EPIDURAL INJECTION:

RECOMMENDATION 1: Preservative-free dexamethasone remains the preferred corticosteroid for TFESI, but given the paucity of evidence of neurotoxicity associated with benzyl alcohol, the use of dexamethasone containing preservative is a reasonable alternative.

Risks Associated With The Use Of Steroid Preparations Containing Preservatives

Concern exists surrounding the use of steroid preparations that contain PEs for epidural injection ESIs. This is largely due to the possibility of neurotoxicity if the PE is inadvertently injected into the intrathecal space. Neurotoxicity has been reported in association with benzyl alcohol, polyethylene glycol, and benzalkonium chloride, among other PEs. The body of literature regarding neurotoxicity due to spinal administration of medication was summarized in 1999 and suggested that neurotoxicity due to PEs is unlikely at the dosages and concentrations used in humans. Since this review was published, no significant new literature has emerged to further guide clinical decision making.

Benzyl alcohol is the primary PE in commercially available preparations of dexamethasone. Animal studies demonstrate no difference in neurotoxicity for benzyl alcohol (doses ranging from 0.9% to 4.5%) compared to normal saline when directly injected into the cisterna magna of adult dogs. Seizures were observed following injection of a 4.5% concentration of benzyl alcohol and death occurred following injection of a 9% concentration of benzyl alcohol. There is a single case report of paralysis following inadvertent subarachnoid injection of 40mL of normal saline that contained 1.5% benzyl alcohol. In commercially available dexamethasone, which contains a 1% concentration of benzyl alcohol, evidence of neuronal toxicity has never been reported in humans.

Aside from neurotoxicity, concern has been raised with regard to the potential for a hypersensitivity (allergic) reaction to benzyl alcohol. It should be noted that allergy to benzyl alcohol is relatively rare. Furthermore, through the process of skin testing, all components of the dexamethasone solution have been identified as potential sources of hypersensitivity reactions. This includes dexamethasone in its native form (before esterification), the succinate ester moiety (added for solubility), sodium citrate, citric acid, sodium hydroxide, and other minor excipients such as lactose, carboxymethylcellulose, and polyethylene glycol. Elimination of the preservative component of dexamethasone, therefore, does not eliminate the risk of hypersensitivity reactions.

RECOMMENDATION 2: Physicians who elect to use preservative-free steroids from a compounding pharmacy must carefully weigh the risks and benefits, as sterility assurance concerns exist.

Risks Associated With The Use Of Compounding Pharmacies

It is possible to obtain preservative-free dexamethasone from a compounding pharmacy. However, significant concerns exist regarding sterility assurance in relation to agents prepared by compounding pharmacies, which were brought to light during the 2012 fungal meningitis outbreak that originated from the New England Compounding Company.

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RECOMMENDATION 3: **Only non-particulate steroids should be used for cervical transforaminal injections.**

RECOMMENDATION 4: **In the absence of preservative-free dexamethasone, particulate steroids (e.g. methylprednisolone, betamethasone, triamcinolone) can be considered for lumbar TFESI, although at higher risk.***

RECOMMENDATION 5: **If a lumbar TFESI with particulate steroid is performed, physicians should strongly consider use of all available risk-mitigation strategies to minimize the possibility of intra-arterial injection, including the use of an infraneural approach, a local anesthetic test dose, and use of DSI beyond the requisite live-fluoroscopic observation of contrast medium injection through extension tubing. It should be noted that commercially available particulate steroids contain preservatives, so use of particulate steroid does not eliminate the possible effects of PEs.**

RECOMMENDATION 6: **For interlaminar or caudal epidural steroid injections the evidence supports the use of either particulate or non-particulate corticosteroids as there is no evidence of superior safety for one agent over another. Clinical judgment on a case-by-case basis is recommended when selecting the optimal route of epidural injection to balance safety and effectiveness.**

Route Of Epidural Entry For Steroid Deposition

Multiple routes of access to the epidural space are possible. A complete review of the differences in the safety and effectiveness of epidural steroid injections via the transforaminal vs. interlaminar vs. caudal routes are beyond the scope of this position statement. However, there is no definitive consensus on the "best" approach for every patient regardless of clinical scenario. Physicians should carefully weigh the risks and benefits of using various steroid agents and approaches for epidural steroid injection and involve each patient in the process of shared decision making before proceeding.

Transforaminal Injections

Particulate steroid should never be injected via the cervical transforaminal route, leaving dexamethasone as the only safe steroid choice. In the absence of preservative-free dexamethasone, particulate steroids (e.g. methylprednisolone, betamethasone, triamcinolone) can be considered for lumbar TFESI, although at higher risk; anatomical studies have identified radiculomedullary arteries at various levels in the lumbar spine. If a lumbar TFESI with particulate steroid is performed, physicians should strongly consider use of all available risk-mitigation strategies to minimize the possibility of intra-arterial injection, including the use of an infraneural approach, a local anesthetic test dose, and use of DSI beyond the requisite live-fluoroscopic observation of contrast medium injection through extension tubing. It should be noted that commercially available particulate steroids contain preservatives, so use of particulate steroid does not eliminate the possible effects of PEs.

Interlaminar and Caudal Injections

When using an interlaminar or caudal route of entry, there is no evidence to suggest that use of non-particulate dexamethasone confers any safety benefit over particulate steroids such as triamcinolone, betamethasone, and methylprednisolone. To date, there have been no published cases of ischemic neurologic infarction related to a particulate steroid injected via the caudal or interlaminar epidural space. Notably, while the FDA has placed a "black box" warning on the use of epidural triamcinolone, there is no published evidence that indicates a difference in risk when using triamcinolone compared to other particulate steroid agents. Instead, the relevant increased risk associated with non-transforaminal routes of access is epidural hematoma. Epidural hematoma risk is considered equal for all corticosteroid agents, and is present regardless of anticoagulation status.

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