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Epidural steroid injections: our experience and a review of the new controversies

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Abstract

Since the FDA alert regarding the steroid epidural injections, there have been new controversies about this technique. We review the clinical evidence about epidural steroid injections and we comment our three decades experience with the interlaminar approach. Indications, efficacy and possible complications are also reviewed. *Anestezjologia i Ratownictwo 2015; 9: 315-326.*

Keywords: epidural steroid injections, low back pain, radicular pain, interlaminar, transforaminal, caudal, FDA alert

Introduction

Epidural steroid injections (ESI) are one of the most (if not the most) commonly performed interventions to manage subacute and chronic low back pain. ESI have been used for decades [1-3] for the treatment of discogenic and radicular pain originating from the cervical, thoracic and lumbar spine as well as for spondylosis, non-specific radiculitis and spinal stenosis.

In our region, Navarre (Spain), an anaesthesiologist and pain practitioner was sued by a patient after the performance of one ESI with triamcinolone acetonide (Trigon Depot® Bristol-Myers Squibb Spain) because in the directions for use it was specified that the epidural use of this drug was not approved by the manufacturer. This claim was rejected. Since then, triamcinolone acetonide was the corticosteroid of choice in our clinical practice. The specification of not approving the use of triamcinolone acetonide for epidural used was added in 2011, without any specific communication by the manufacturer to the medical community. A few weeks later, on April 2014, the FDA published its alert about ESI [4]. According to many physicians, it can be considered too alarmist and inaccurate [5], to say the least.

It is important to add to the confusion created by the claim (although it was rejected) and the FDA alert, that ESI have always been surrounded by some degree of controversy about their efficacy. This controversy is generated by the multiple uses that ESI have been given, as well as by the disparity of controlled and/or randomized trials to assess their efficacy. Moreover, the different ways that the epidural space can be reached (interlaminar, caudal and transforaminal) and the multiple steroids employed contribute to this.

Nevertheless, in the last two decades, there had been many efforts to establish evidence-based indications for the ESI, which has notably improved their outcomes. In the same way, there has been an effort to evaluate the best epidural approach, on the basis of patient condition and previous treatments [6-9].

The Anaesthesia section for Trauma and Orthopaedic surgery of our hospital has a large experience with ESI. ESI is a daily performed technique in our Hospital since 1990, with an average of 900-1200 ESI / year. However it is not rare that ESI must be performed in other hospitals from time to time, so we think it could be of interest to expose our protocols concerning ESI, especially since the FDA alert. Our aim is to resume the indications of ESI with better outcomes, as well as the steroids used and the approach chosen and emphasise the security and usefulness of the ESI with interlaminar or caudal approach when the

indication is met. In the same way, we also include our patient informed consent and discharge information (Appendix 1 and 2).

Discussion

The rationale for the ESI is based on the anti-inflammatory properties of the steroids, along with their ability to inhibit the synthesis of prostaglandins and the ectopic discharges from injured sensory nerves [10-12], and, on the other hand, on the particularity of the diffusion of any drug injected into the epidural space [13-19]. The former will allow to reduce swelling, inflammation and pain, and, although it will not treat the cause, it will, at least theoretically, shorten the clinical course of the causing disease, keep the patient out of the hospital and provide symptomatic relief which will improve the quality of life. The latter is related to the theory that injecting a drug into the epidural space allows a concentrated amount of medication to be retained in the target area, exposing the nerves involved in the procedure to this drug for a longer period of time than if the same drug was administered by another way [20,21].

Many steroids have been used for this purpose, the most commonly preparations available are: methylprednisolone acetate (Depo-Medrol® Pfizer USA), triamcinolone acetonide (Kenalog® Bristol-Myers Squibb USA, Trigon Depot® Bristol-Myers Squibb Spain), betamethasone (both acetate and sodium phosphate) (Celestone Soluspan® Schering-Plough USA, Celestone Cronodose® Schering-Plough Spain) and dexamethasone sodium phosphate (Decadron® Merck USA, Fortecortín® Merck Spain). They are all prednisolone derivatives with a different degree of water solubility. The more corticosteroids esters they contain, the less water-soluble they will be and more microcrystalline suspensions they will form [22-24]. The potential advantage of the ester preparations is that hydrolysis by cellular esterases is required to release the active part, so its effect should last longer in the place where it is administered [25]. Nevertheless, the microcrystalline suspensions formed are related to one of the feared adverse outcomes, which is the likelihood of microvascular embolization of these particles. Among the steroid preparations mentioned above, only dexamethasone sodium phosphate and betamethasone sodium phosphate are freely water soluble: they have a quicker onset of action with a concomitant reduced duration of action [26,27].

In 2002, Cluff et al [28] did already outline, "the ideal dose and type of steroid has yet to be determined". Even if this affirmation remains true, there have been many efforts to compare the different doses and, nowadays, according to the studies published, we can say that these are the most common doses and type of corticosteroids employed for ESI [29,9]:

- Methylprednisolone acetate either 40 or 80 mg
- Triamcinolone acetonide either 40 or 80 mg
- Betamethasone (both acetate and sodium phosphate) 6 mg or 12 mg of each compound (the most popular formulations employed are the ones that contain 6 mg of each preparation)
- Dexamethasone sodium phosphate 4 mg is the most common dose

The other hot topic about ESI is the approach to the epidural space. There are three options: transforaminal, interlaminar and caudal. The first must be accomplished under fluoroscopic vision whereas the other two can be done either under fluoroscopic vision or under a blind technique. The theoretical advantage of the transforaminal approach is that the admixture of steroid plus saline or local anaesthetic is injected directly into the dural sleeve and spreads into the epidural space covering a greater area of nerve root inflammation [21].

The corticosteroid can be diluted either in saline or local anaesthetic or in an admixture of both. There are many studies that report different results. However, there is a tendency towards the local anaesthetic/corticosteroid admixture, especially for the lumbar spine. The rationale of this election is probably the fact that local anaesthetics exert their analgesic effects by blocking the conduction in nerves via their effects on Na^+ channels and suppressing the ectopic signal generation in injured nerves. In addition to providing temporary pain relief, local anaesthetics may provide prolonged benefits by putatively interrupting the cycle of pain [30-37]. The total volume injected is also an arguable topic: the transforaminal approach will allow smaller volumes as well as the fluoroscopic techniques, whereas greater amounts will rise the chances of reaching the target in a blind technique [21].

Taking into account all these items, in 2013, Manchikanti et al [9] published an update of comprehensive evidence-based guidelines for interventional pain techniques in chronic spinal pain. Among their conclusions, it is interesting to cite the following ones

Table I. Summary of evidence for ESI [9]

Site of ESI	Approach	Degree of evidence	Indication
Cervical	Interlaminar	Good	Cervical disc herniation or radiculitis
		Fair	Axial or discogenic pain Spinal stenosis Post cervical surgery syndrome
Thoracic	Interlaminar	Fair	Thoracic discogenic pain Disc-related pain Post-surgery syndrome pain Spinal stenosis
Lumbar	Caudal, interlaminar or transforaminal	Good	Disc herniation Radiculitis
		Fair	Spinal stenosis
	Caudal or interlaminar	Fair	Axial or discogenic pain **without** disc herniation, radiculitis or facet joint pain
	Transforaminal	Limited	Axial or discogenic pain **without** disc herniation, radiculitis or facet joint pain
			Post-surgery syndrome
	Caudal	Fair	Post-surgery syndrome

Table II. Complications of ESI (excluding the direct effects of corticosteroids)

Frequency	Complications	Examples	References
Frequent	Infectious	Epidural abscess, Discitis, Osteomyelitis	[38-45]
	Intravascular injection	Intravenous or Intraarterial	[46-48]
	Subdural injection		[58]
	Dural puncture	Post dural puncture headache	[59-61]
	Nerve damage	Transitory or Permanent	[62-64]
	Vasovagal reactions		[65]
	Intracranial	Intracranial air injection Increased intracranial pressure	[66]
Rare	Ocular	Transient blindness	[67,68]
	Retinal	Serous corioretinopathy, Retinal necrosis, Retinal hemorrhage	[69-72]
	Diaphragm disorders	Persistent recurrent intractable hiccups	[73]
	Meningitis	Chemical or infectious (fungal meningitis because of contaminated prednisolone)	[74,75]
	Arachnoiditis	After intrathecal injection of corticosteroids	[76-78]
	Central nervous system injury	Stroke, spinal cord injury/infarction, paraplegia (specially with cervical and thoracic transforaminal approach)	[79-91]

related to ESI (Table I).

The complications of ESI can be related either to the needle placement (so they will be the same than in other epidural techniques (Table II) or to the drugs injected (Table III).

The adverse effects derived from the corticosteroids are the reason why it is necessary to limit the number of ESI. The last recommendations are to space them at least a week and to repeat them on the basis of the clinical status of the patient rather than on a fixed basis [9].

In fluoroscopically guided ESI, it is also important to underline the potential risk due to radiation exposure. There is a risk of damaging the eyes, skin and gonads [111,112].

Although it may seem alarming, Manchikanti et al [113], in evaluating 10000 fluoroscopically guided epidural injections, concluded that:

- In 2376 performed on the cervical region with an interlaminar approach, there were intravascular entry in 4.2%, return of blood in 1.2%, profuse bleeding in 0.7%, bruising in 0.3%, vasovagal reaction in 0.04%, transient nerve root irritation in 0.21%, dural puncture in 1%, postdural puncture headache in 0.08% and facial flushing in 0.08%

- Among the 301 performed in the thoracic region, there were intravascular entry in 4%, return of blood in 2.7%, profuse bleeding in 1.3%, local hematoma in 0.7%, bruising in0.3%, vasovagal reaction, transient nerve root irritation, postdural puncture headache and facial flushing in 0.33%, transient spinal cord irritation in 1%, dural puncture in 1.3% and profuse bleeding in 1.33%
- Among the ESI in the lumbar region with an interlaminar approach, the data were a 0.5% of intravascular and return of blood, a 0.8% of profuse bleeding and dural puncture, a 0.28% of local hematoma and transient nerve root irritation, a 0.07% of postlumbar puncture headache and a 0.13% of facial flushing.

With all the data exposed, and returning to the FDA drug safety communication [4] regarding the ESI, it is necessary to outline two points. The first one is that, among the complications cited by the FDA, 6 are related to transforaminal cervical ESI or nerve root blocks [62,87,88,114-116]; 4 are related to lumbar transforaminal ESI or selective nerve root blocks [117-120]; 1 is related to thoracic interlaminar [121]; 2 are related to cervical interlaminar ESI [91,122] and another one is a C1-C2 intrarticular facet steroid injection [123] (as Manchikanti et al [5] pointed in their paper in August 2014). And as these authors state, the FDA and its advisors have not reviewed all of the relevant literature and have reached inappropriate conclusions. In fact, as it has already been claimed by many physicians, the FDA has not mentioned the theoretical complications related to the ESI with either caudal or interlaminar approach (which remain the most widely utilized in interventional pain management). The second one is that it is inappropriate to extrapolate the evidence of the sometimes devastating consequences of transforaminal cervical, thoracic or even lumbar ESI to caudal or interlaminar approaches, especially in the lumbar spine. The techniques are completely different and so are the risks and the theoretical complications.

In our clinical practice, we consider ESI if the following conditions are met:

- The pain symptoms are radicular in nature (usually associated with an herniated disc) as evidenced by physical examination, MRI/CT imaging, electromyogram or nerve conduction study.
- An intraspinal tumour or other space-occupying lesion has been ruled out by MRI/CT imaging as the cause of pain.
- A trial of conservative measures for at least one month has failed or is not feasible because the patient´s pain is too severe.
- There are no contraindications to receiving ESI (co-morbidities that can be exacerbated by steroid use, infection in the site of injection, systemic infection, bleeding disorders that can not be corrected, allergy to the medication that should be injected etc.).

In our case, we use a local anaesthetic, usually bupivacaine 0.25% (4-5 mL) or 0.125% (8-10 mL) with an admixture of betamethasone acetate and sodium phosphate 6 mg + 6 mg. Using this dose, in case of an unnoticed subdural or dural puncture, the volume injected slowly does not produce an extended blockade. When a transforaminal approach is chosen, the steroid injected is dexamethasone 4 mg with lidocaine 1%, with a total volume or 2 or 3 mL. Although with the appropriate precautions there is not more embolization risk with non-particulate steroid in the transforaminal approach (Manchikanti 2014 [5]), a decision was made by consensus to use non-particulate steroid for the transforaminal approach.

All of our patients are separately advised on the risks of an epidural technique both by interlaminar or transforaminal approach (not many caudal approaches are performed) and on the risks of an ESI. In the same way, when they sign the informed consent for this technique, it is explained that ESI is an off-label use

Table III. Major theoretical complications specifically related to corticosteroids reported after ESI

Endocrine	Cardiovascular	Musculoskeletal	Dermatologic	Metabolic	Other
- Suppression of pituitary adrenal axis [92,93] - Hypercorticism [94] - Cushing´s syndrome [95,96] - Menstrual disturbances [97]	- Fluid retention (and even heart failure, very rare) [95]	- Osteoporosis [98,99] - Avascular necrosis of the bone [100,101] - Steroid myopathy [102]	- Flushing [103-105]	- Weight gain [99] - Hyperglicemia [106]	- Epidural lipomatosis [107-110]

of the drug. In our experience, for more than three decades using the ESI, we have not experienced any of the dramatic consequences mentioned in the FDA alert, and our level of common complications is similar to the one described by Manchikanti et al [113], being the facial flushing (0.6%) and the postlumbar puncture headache (1%) (our data are not reported) the more frequent adverse outcomes.

Usually, we consider ESI an ambulatory procedure except in the case of serious pathology of the patient (ASA III or IV), need to reintroduce anticoagulation therapy or patients with big risk of diabetes mellitus decompensation. Before the hospital discharge, they all received some instructions where they are advised about the most frequent secondary effects as well as about the most serious complications that can appear and how to act in the case they appear.

In conclusion, we completely agree that there must be a modification in the information provided to the patients. It is important to outline the off-label use of the corticosteroids in the epidural space. It must also be remarked that, in some rare cases, epidural steroid injections have caused serious neurologic problems following transforaminal cervical and thoracic techniques, and this risk may also exist in transforaminal lumbar ESI. Nevertheless, none of these reasons should hinder the practice of an interventional pain technique that has demonstrated to be of value, not only in the management of pain, but also in the improvement of the life quality of thousands of patients. And finally, it is worth to remember that any physician is allowed to use off-label corticosteroids or any drug for any purpose they see fit.

Conflict of interest
None

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Appendix 1.

INFORMED CONSENT FOR EPIDURAL STEROID INJECTION PROCEDURES

Department of Anaesthesia

(Patient name and family name)

Address and identification number

Physician who informs:
(Name and family name, physician identification number)

It is a legal duty of compulsory observance.

Information: What is an epidural steroid injection (ESI)?
ESI consists on the introduction of a local anaesthetic and an anti-inflammatory drug in the epidural space, the closest to the swelling zone by the means of an epidural puncture. The epidural space is located just before the spinal cord (out of it). It is mostly indicated in radicular pain with sciatica.

What is the aim of ESI?
The aim is to allow the long-term anti-inflammatory drug working in the swelling area. We intend to break the muscle contraction-pain-inflammation circle. Improvement is obtained, generally temporal, but, in some cases, after the repetition of ESI, it can be permanent or, at least, it can achieve patient better quality of life. In many cases, a surgical procedure can be avoided.

Are ESI a secure procedure?

ESI procedures are not risk-free. Risks are due either to the epidural puncture technique or to the drugs injected. It is important to distinguish among minor and serious complications. Patients condition may also influence. Minor complications in some patients can be deleterious in others with cardiac pathology etc...

Minor complications:

The most frequent are: headache, urinary retention, pain in the puncture site, numbness and cramps (usually temporary).

Major complications:

Puncture infection, meningitis and pus formation. This can be generally be solved, but it requires the patient hospital admission. Hemorrhage, called epidural haematoma, is another of the major complications, it can cause spinal cord compression, with serious neurologic consequences: legs palsy, sphincter incontinence, perineum, genitals or legs numbness. If epidural haematoma occurs, a surgical procedure must be undergone to evacuate it. Patients taking blood thinners must interrupt their treatment before ESI because ESI ESI can not be done under these drugs effects. Such drugs are:

1 Anticoagulants:
   - Dicumarol: Sintrom®
   - Warfarine: Aldocumar®
   - Dabigatran: Pradaxa®
   - Apixaban: Eliquis®
   - Rivaroxaban: Xarelto®
2 Platelet anti-aggregant:
   - Clopidogrel: Plavix®, Iscover®
   - Ticlopidine: Tiklid®, Ticlodone®
   - Cilostazol: Pletal®, Ekistol®
   - Aspirin 100mg + Clopidogrel 75 mg: Duoplavin®

The following platelet anti-aggregant should be discontinued or adjusted:

- Acetylsalicylic acid: Adiro®, AAS®, Inyesprin®, Tromalyt®
- Trifusal: Disgren®
- Dipiridamol: Persantin®, Asasantin®
- Ditazol: Ageroplas®

During the anaesthetic visit you will be told how to proceed with these drugs.

The anti-inflammatory drug that will be used is Celestone Cronodose®:

- It is an injectable admixture with Betamethasone acetate and Betamethasone sodium phosphate. This allows a very fast diffusion in the tissues reducing the swelling.
- It is recommended for the treatment of major and moderate diseases that respond to systemic therapy with corticosteroids and in the cases that they can not be administrated orally.

Celestone Cronodose® is recommended for: intramuscular, intraarticular, periarticular, intrabursal, intradermal o intralesional use.

The epidural use of this drug is not approved by the manufacturer and can produce serious adverse effects as: vision loss, stroke, paralysis and death.

You can check www.fda.gov/Drugs/DrugSafety/ucm395191.htm for further information.

Seek emergency medical attention immediately if you experience any unusual symptoms after receiving an epidural Celestone Cronodose® injection, such as loss of vision or vision changes; tingling in your arms or legs; sudden weakness or numbness of your face, arm, or leg on one or both sides of the body; dizziness; severe headache; or seizures.

In case you have taken a drug you do not know the composition, please reach your physician to find out if it can interfere with your coagulation.

Customized risks
They are related to the patient condition and the most noteworthy are:

Do not hesitate to ask if you need any further information.

Statement and signatures
I state that:
1. I understand the need of the proposed procedure.
2. I have been explained with an intelligible language and in detail the risks and possible complications linked to the proposed procedure.
3. Some not foreseen circumstances can occur during the procedure and may involve the need of using different techniques. In this case, I consent to care provided by the anaesthesiologist according to his critrerion.
4. I understand they can not give me any guarantee about the outcome.
5. I have had a chance to ask questions.
6. I have been informed I can revoke this consent at any time before the procedure.
7. I have received a copy of this document.
8. Taking into account risks and benefits, I consent to receive the proposed procedure.

Date:

Patient signature ***Physician signature***

This consent can be given or revoke by the patient legal representative, in case the patient indicates so or it is a minor patient or there is a patient handicap. The relationship to patient will be specified (legal representative, relative etc.)

Name and family name: ..... Form of identification: .....

Signature

As ..... I consent to the procedure
CONSENT Rejection / Revocation
After being informed about the risks and type of procedure, I freely and consciously state the **rejection** ☐ **revocation**

☐ **of the procedure consent**, and I assume the consequences that can be derived from this decision

Patient signature ***Physician signature***

This consent can be given and/or revoke by the patient legal representative, in case the patient indicates so or it is a minor patient or there is a patient handicap. The relationship to patient will be specified (legal representative, relative etc…)

Name and family name: ..... Form of identification: .....

Signature

As ..... I reject/revoke the procedure consent.

Appendix 2.

Epidural Steroid Injection Discharge Instructions

You have undergone an epidural steroid injection. You must take into account the following considerations once you leave the hospital:

- You may experience increased discomfort for 24 hours after the injection.
- Limited activity and rest is recommended for this time period.
- You may gradually resume regular activities as your discomfort subsides.
- Do not drive or operate machinery for 24 hours.
- You will not modify your pain medication since your pain physician tells you
- You may take analgesics if required
- You will need a responsible adult with you for the next 24 hours.
- You may remove the Band-Aid tonight.
- Steroid medications take 2-5 days to become effective; therefore, you may not experience immediate pain relief.
- If you are a diabetic, the steroid may increase your blood sugar for 7-14 days. Should your blood sugar increase, please call the physician that manages your diabetes.
- Women may experience alterations in their menstrual cycle (an increase or decrease in blood loss or even a delay in the following cycle)
- You may experience facial flushing.
- You may experience fluid retention and arterial hypertension (if symptoms do not weaken in 12 hours, call the physician that manages your hypertension).
- If you are taking blood thinners, you may resume it as you are told in the instructions you have been given at your discharge.

Notify the hospital if any of the following occurs:

- Discomfort that becomes severe and/or interferes with normal movement or feeling.
- Signs of infection at injection site, which may include warmth, redness, swelling, foul odour and drainage.
- Increase in temperature above 38º degrees orally.
- Excessive bleeding from injection site.
- New changes in sensation or motor function such as new areas of numbness, weakness, or changes in bowel or bladder function.
- Headache that prevents you from standing up or sitting down, and that improves when lying down. Nausea and vomiting, blurred vision and dizziness can accompany it.

Telephone numbers provided.

References

1. Robecchi A, Capra R. Hydrocortisone (compound F); first clinical experiments in the field of rheumatology. Minerva Med 1952; 98:1259-63.
2. Lievre JA, Bloch-Michael H, Pean G. L'hydrocortisone en injection locale. Rev Rhum 1953;29:310-11.
3. Harley C. Extradural corticosteroid infiltration. A follow-up study of 50 cases. Ann Phys Med 1966;9:22-8.
4. U.S. Food and Drug Administration. Drug Safety Communications. FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain. April 23, 2014. Avalaible at: www.fda.gov/downloads/Drugs/Drug-Safety/UCM394286.pdf
5. Manchikanti L, Candido KD, Singh V, et al. Epidural steroid warning controversy still dogging FDA. Pain Physician 2014;17:E451-E474.
6. Arden NK, Price C, Reading I, et al. A multicentre randomized controlled trial of epidural corticosteroid injections for sciatica: The WEST study. Rheumatology (Oxford) 2005;44:1399-406.
7. Wilson-MacDonald J, Burt G, Griffin D, et al. Epidural steroid injection for nerve root compression: a randomized, controlled trial. J Bone Joint Surg Br 2005;87:352-5.
8. Lee JH, An JH, Lee SH. Comparison of the effectiveness of interlaminar and bilateral transforaminal epidural steroid injections in treatment of patients with lumbosacral disc herniation and spinal stenosis. Clin J Pain 2009;25:206-10.
9. Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. Pain Physician. 2013;16(2 Suppl):S49-283.
10. Devor M, Govrin-Lippmann R, Raber P. Corticosteroids suppress ectopic neural discharge originating in experimental neuromas. Pain 1985;22:127-37.
11. Johansson A, Hao J, Sjölund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. Acta Anaesthesiol Scand 1990;34:335-8.
12. Hirata F, Schiffmann E, Venkatasubramanian K, et al. A phospholipase A2 inhibitory protein in rabbit neutrophils induced by glucocorticoids. Proc Natl Acad Sci USA 1980;77:2533–2536.
13. Manchikanti L, Boswell MV, Datta S, et al. Comprehensive review of therapeutic interventions in managing chronic spinal pain. Pain Physician 2009;12:123-98.
14. Manchikanti L, Boswell MV, Singh V, et al. Comprehensive evidence-based guidelines for interventional techniques in the management of chronic spinal pain. Pain Physician 2009;12:699-802.
15. Buenaventura RM, Datta S, Abdi S, ET al. Systematic review of therapeutic lumbar transforaminal epidural steroid injections. Pain Physician 2009;12:233-251.
16. Young IA, Hyman GS, Packia-Raj LN, et al. The use of lumbar epidural/ transforaminal steroids for managing spinal disease. J Am Acad Orthop Surg 2007;15:228-38.
17. Schaufele MK, Hatch L, Jones W. Interlaminar versus transforaminal epidural injections for the treatment of symptomatic lumbar intervertebral disc herniations. Pain Physician 2006;9:361-6.
18. Vad VB, Bhat AL, Lutz GE, et al. Transforaminal epidural steroid injections in lumbosacral radiculopathy: A prospective randomized study. Spine 2002;27:11-6.
19. Ghahreman A, Ferch R, Bogduk N. The efficacy of transforaminal injection of steroids for the treatment of lumbar radicular pain. Pain Med 2010;11:1149-68.
20. Kang SS, Hwang B, Son H, et al. The dosages of corticosteroid in transforaminal epidural steroid injections for lumbar radicular pain due to a herniated disc. Pain Physician. 2011;14:361-70.
21. Gharibo C, Koo C, Chung J, et al. Epidural steroid injections: An update on mechanisms of injury and safety. Tech Reg Anesth Pain Manag 2009;13:266-71.
22. Tiso RL, Cutler T, Catania JA, et al. Adverse central nervous system sequelae after selective transforaminal block: the role of corticosteroids. Spine J 2004;4:468-74.
23. Benzon HT, Chew TL, McCarthy RJ, et al. Comparison of the particle sizes of different steroids and the effect of dilution: a review of the relative neurotoxicities of the steroids. Anesthesiology 2007;106:331-8.
24. Derby R, Lee SH, Date ES, et al. Size and aggregation of corticosteroids used for epidural injections. Pain Med 2008;9:227-34.
25. Wright JM, Cowper JJ, Page Thomas DP, et al. The hydrolysis of cortisol 21-esters by a homogenate of inflamed rabbit synovium and by rheumatoid synovial fluid. Clin Exp Rheumatol 1983;1:137-41.
26. Blankenbaker DG, De Smet AA, Stanczak JD, et al. Lumbar radiculopathy: treatment with selective lumbar nerve blocks—comparison of effectiveness of triamcinolone and betamethasone injectable suspensions. Radiology 2005;237:738-41.
27. Stanczak J, Blankenbaker DG, De Smet AA, et al. Efficacy of epidural injections of Kenalog and Celestone in the treatment of lower back pain. AJR Am J Roentgenol 2003;181:1255-8.
28. Cluff R, Mehio A-K, Cohen SP, et al. The Technical Aspects of Epidural Steroid Injections: Anesth Analg 2002;95:403-8.
29. Manchikanti, L. Role of neuraxial steroids in interventional pain management. Pain Physician 2002;5:182-99.
30. Arner S, Lindblom U, Meyerson BA, et al. Prolonged relief of neuralgia after regional anesthetic blocks: a call for further experimental

and systematic clinical studies. Pain 1990;43:287-97.
31. Hayashi N, Weinstein JN, Meller ST, et al. The effect of epidural injection of betamethasone or bupivacaine in a rat model of lumbar radiculopathy. Spine 1998;23:877-85.
32. Benzon HT. Epidural steroid injections for low back pain and lumbosacral radiculopathy. Pain 1986;24:277-95.
33. Lavoie PA, Khazen T, Filion PR. Mechanisms of the inhibition of fast axonal transport by local anesthetics. Neuropharmacology 1989;28:175-81.
34. Bisby MA. Inhibition of axonal transport in nerves chronically treated with local anesthetics. Exp Neurol 1975;47:481-9.
35. Katz WA, Rothenberg R. Section 3: the nature of pain—pathophysiology. J Clin Rheumatol 2005;11(suppl 2):S11–S15.
36. Melzack R, Coderre TJ, Katz J, et al. Central neuroplasticity and pathological pain. Ann N Y Acad Sci 2001;933:157–174.
37. Cassuto J, Sinclair R, Bonderovic M. Antiinflammatory properties of local anesthetics and their present and potential clinical implications. Acta Anaesthesiol Scand 2006;50:265–282.
38. Manchikanti L, Malla Y, Wargo BW, et al. Infection control practices (safe injection and medication vial utilization) for interventional techniques: Are they based on relative risk management or evidence? Pain Physician 2011;14:425-34.
39. Simopoulos TT, Kraemer JJ, Glazer P, et al. Vertebral osteomyelitis: A potentially catastrophic outcome after lumbar epidural steroid injection. Pain Physician 2008;11:693-7.
40. McGrath JM, Schaefer MP, Malkamaki DM. Incidence and characteristics of complications from epidural steroid injections. Pain Med 2011;12:726-31.
41. Saigal G, Donovan Post MJ, Kozic D.Thoracic intradural Aspergillus abscess formation following epidural steroid injection. AJNR Am J Neuroradiol 2004;25:642-4.
42. Kabbara A, Rosenberg SK, Untal C.Methicillin-resistant staphylococcus aureus epidural abscess after transforaminal epidural steroid injection. Pain Physician 2004;7:269-72.
43. Hooten WM, Kinney MO, Huntoon MA. Epidural abscess and meningitis after epidural corticosteroid injection. Mayo Clin Proc 2004;79:682-686.
44. Waldman SD. Cervical epidural abscess after cervical epidural nerve block with steroids. Anesth Analg 1991;72:717-8.
45. Huang RC, Shapiro GS, Lim M, et al. Cervical epidural abscess after epidural steroid injection. Spine (Phila Pa 1976) 2004;29:E7-E9.
46. Kaplan MS, Cunniff J, Cooke J, et al. Intravascular uptake during fluoroscopically guided cervical interlaminar steroid injection at C6-7: A case report. Arch Phys Med Rehabil 2008;89:553-8.
47. Derby R, Lee SH, Kim BJ, et al. Complications following cervical epidural steroid injections by expert interventionalists in 2003. Pain Physician 2004;7:445-9.
48. Rozin L, Rozin R, Koehler SA, 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;24:351-355.
49. Ozdemir O, Calisaneller T, Yildirim E, et al. Acute intracranial subdural hematoma after epidural steroid injection: A case report. J Manipulative Physiol Ther 2007;30:536-8.
50. Yoo HS, Park SW, Han JH, et al. Paraplegia caused by an epidural hematoma in a patient with unrecognized chronic idiopathic thrombocytopenic purpura following an epidural steroid injection. Spine (Phila Pa 1976) 2009;34:E376-E379.
51. Xu R, Bydon M, Gokaslan ZL, et al. Epidural steroid injection resulting in epidural hematoma in a patient despite strict adherence to anticoagulation guidelines. J Neurosurg Spine 2009;11:358-64.
52. Shanthanna H, Park J. Acute epidural haematoma following epidural steroid injection in a patient with spinal stenosis. Anaesthesia 2011;66:837-9.
53. LaBan MM, Kasturi G, Wang IM. Epidural corticosteroid injections precipitating epidural hematomas with spinal paresis. Am J Phys Med Rehabil 2007;86:166-7.
54. Ain RJ, Vance MB. Epidural hematoma after epidural steroid injection in a patient withholding enoxaparin per guidelines. Anesthesiology 2005;102:701-3.
55. Manchikanti L, Malla Y, Wargo BW, et al. A prospective evaluation of bleeding risk of interventional techniques in chronic pain. Pain Physician 2011;14:317-29.
56. Williams KN, Jackowski A, Evans PJ. Epidural haematoma requiring surgical decompression following repeated cervical epidural steroid injections for chronic pain. Pain 1990;42:197-9.
57. Stoll A, Sanchez M. Epidural hematoma after epidural block: Implications for its use in pain management. Surg Neurol 2002;57:235-40.
58. Lehmann LJ, Pallares VS. Subdural injection of a local anesthetic with steroids: Complication of epidural anesthesia. South Med J 1995;88:467-9.
59. Abdi S, Datta S, Trescot AM, Schultz DM, et al. Epidural steroids in the management of chronic spinal pain: A systematic review. Pain Physician 2007;10:185-212.
60. Thomas R, Thanthulage S. Intracranial hypotension headache after uncomplicated caudal epidural injection. Anaesthesia 2012;67:416-9.
61. Mosaffa F, Karimi K, Madadi F, et al. Post-dural puncture headache: A comparison between median and paramedian approaches in orthopedic patients. Anesth Pain 2011;1:66-9.
62. Tiso RL, Cutler T, Catania JA, et al. Adverse central nervous system sequelae after selective transforaminal block: The role of corticosteroids.

Spine J 2004;4:468-474.

63. Abbasi A, Malhotra G, Malanga G, et al. Complications of interlaminar cervical epidural steroid injections: A review of the literature. Spine (Phila Pa 1976) 2007;32:2144-51.
64. Lee SH, Kim KT, Kim DH, et al. Clinical outcomes of cervical radiculopathy following epidural steroid injection: A prospective study with follow-up for more than 2 years. Spine (Phila Pa 1976) 2012;37:1041-7.
65. Trentman TL, Rosenfeld DM, Seamans DP, et al. Vasovagal reactions and other complications of cervical vs. lumbar translaminar epidural steroid injections. Pain Pract 2009;9:59-64.
66. Ammirati M, Perino F. Symptomatic air trapped in the spine after lumbar epidural corticosteroid injection. Case report. J Neurosurg Spine 2006;5:359-61.
67. Young WF. Transient blindness afterlumbar epidural steroid injection: A case report and literature review. Spine (Phila Pa 1976) 2002;27:E476-E477.
68. Purdy EP, Ajimal GS. Vision loss after lumbar epidural steroid injection. Anesth Analg 1998;86:119-22.
69. Browning DJ. Acute retinal necrosis following epidural steroid injections. Am J Ophthalmol 2003;136:192-4.
70. Kusher FH, Olson JC. Retinal hemorrhage as a consequence of epidural steroid injection. Arch Opthalmol 1995;113:309-13.
71. Iida T, Spaide RF, Negrao SG, et al. Central serous chorioretinopathy after epidural corticosteroid injection. Am J Ophthalmol 2001;132:423-5.
72. Pizzimenti JJ, Daniel KP. Central serous chorioretinopathy after epidural steroids. Pharmacotherapy 2005;25:1141-6.
73. McAllister RK, McDavid AJ, Meyer TA, et al. Recurrent persistent hiccups after epidural steroid injection and analgesia with bupivacaine. Anesth Analg 2005;100:1834-6.
74. Gutknecht DR. Chemical meningitis following epidural injections of corticosteroids (Letter). Am J Med 1987;82:570.
75. Kainer MA, Reagan DR, Nguyen DB, et al. Tennessee Fungal Meningitis Investigation Team. Fungal infections associated with contaminated methylprednisolone in Tennessee. N Engl J Med 2012;367:2194-203.
76. Latham JM, Fraser RD, Moore RJ, et al. The pathologic effects of intrathecal betamethasone.Spine (Phila Pa 1976) 1997;22:1558-62.
77. Lima RM, Navarro LH, Carness JM, et al. Clinical and histological effects of the intrathecal administration of methylprednisolone in dogs. Pain Physician 2010;13:493-501.
78. Wilkinson HA. Intrathecal Depo-Medrol. A literatura review. Clin J Pain 1992;8:49-56.
79. Lenoir T, Deloin X, Dauzac C, et al. Paraplegia after interlaminar epidural steroid injection: A case report. Rev Chir Orthop Reparatrice Appar Mot 2008;94:697-701.
80. Linn AJ, Desilva C, Peeters-Asdourian C.Thromboembolic stroke: A rare complication associated with peri-procedural management of an epidural steroid injection. Pain Physician 2009;12:159-62.
81. Usta B, Muslu B. Sedation during cervical vs. lumbar translaminar epidural steroid injections. Pain Pract 2009;9:480; author reply 480-1.
82. Thefenne L, Dubecq C, Zing E, et al. A rare case of paraplegia complicating a lumbar epidural infiltration. Ann Phys Rehabil Med 2010;53:575-83.
83. Benzon HT, Iqbal M, Tallman MS, et al. Superior sagittal sinus thrombosis in a patient with postdural puncture headache. Reg Anesth Pain Med 2003;28:64-7.
84. Hetts SW, Narvid J, Singh T, et al. Association between lumbar epidural injection and development of acute paraparesis in patients with spinal dural arteriovenous fistulas. AJNR Am J Neuroradiol 2007;28:581-3.
85. Glaser SE, Falco FJE. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. Pain Physician 2005;8:309-14.
86. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: Report of three cases. Spine J 2002;2:70-5.
87. Ludwig MA, Burns SP. Spinal cord infarction following cervical transforaminal epidural injection: A case report. Spine (Phila Pa 1976) 2005;30:E266-E268.
88. Beckman WA, Mendez RJ, Paine GF, et al. Cerebellar herniation after cervical transforaminal epidural injection. Reg Anesth Pain Med 2006;31:282-5.
89. Chung JY, Han JH, Kang JM, et al. Paraplegia after epidural steroid injection. Anaesth Intensive Care 2012;40:1074-6.
90. Singh R, Panagos A. Quadriparesis following cervical epidural steroid injections. Spine J 2006;6:349.
91. Ziai WC, Ardelt AA, Llinas RH. Brainstem stroke following uncomplicated cervical epidural steroid injection. Arch Neurol 2006;63:1643-6.
92. Kay JK, Findling JW, Raff H. Epidural triamcinolone suppresses the pituitary-adrenal axis in human subjects. Anesth Analg 1994;79:501-505.
93. Hsu D, Fu P, Gyermek L, et al. Comparison of plasma cortisol and ACTH profile after a single lumbar epidural dose of triamcinolone 40 mg, 80 mg respectively in low back pain patients. Anesth Analg 1996;82:S191.
94. Stambough JL, Booth RE, Rothman RH. Transient hypercorticism after epidural steroid injection. J Bone and Joint Surg 1984;66-A:1115-6.
95. Tuel SM, Meythaler JM, Cross LL. Cushing's syndrome from epidural methylprednisolone. Pain 1990;40:81-4.
96. Edmonds LC, Vance ML, Hughes JM. Morbidity from paraspinal Depo-Corticosteroid injections for analgesia. Cushing's syndrome and adrenal suppression. Anesth Analg 1991;72:820-2.
97. Gitkind AI, Shah B, Thomas M. Epidural corticosteroid injections as a possible cause of menorrhagia: A case report. Pain Med

2010;11:713-715.
98. Healey JH. Glucocorticoid-induced osteoporosis. Curr Opin Orthop 1994;5:33-8.
99. Manchikanti L, Pampati VS, Beyer C et al. The effect of neuraxial steroids on weight and bone mass density: A prospective evaluation. Pain Physician 2000;3:357-66.
100. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992;326:1473-9.
101. Kelman GJ, Williams GW, Colwell CW et al. Steroid related osteonecrosis of the knee. Clin Orthop 1990;257:171-6.
102. Boonen S, Van Distel G, Westhovens R et al. Steroid myopathy induced by epidural triamcinolone injection. Brit J Rheumatol 1995;34:385.
103. Everett CR, Baskin MN, Novoseletsky D, et al. Flushing as a side effect following lumbar transforaminal epidural steroid injection. Pain Physician 2004;7:427-9.
104. Kim CH, Issa MA, Vaglienti RM. Flushing following interlaminar lumbar epidural steroid injection with dexamethasone. Pain Physician 2010;13:481-4.
105. De Sio JM, Kahn CH, Warfield CA. Facial flushing and/or generalized erythema after epidural steroid injection. Anesth Analg 1995;80:617-9.
106. Gonzalez P, Laker SR, Sullivan W, et al. The effects of epidural betamethasone on blood glucose in patients with diabetes mellitus. PMR 2009;1:340-5.
107.Roy-Camille R, Mazel CH, Husson JL et al. Symptomatic spinal epidural lipomatosis induced by a longterm steroid treatment. Spine 1991;16:1365-71.
108. Giuffre R. Intradural spinal lipomas. Review of the literature (99 cases) and report of an additional case. Acta Neurochi 1966;14:69-95.
109. Fessler RG, Johnson DL, Brown FD et al. Epidural lipomatosis in steroid-treated patients. Spine 1992;17:183-8.
110. Rawlins BA, Di Giacinto GV. Epidural compression in the spinal canal caused by excessive adipose tissue. A case report. Clin Orthop 1992;275:140-3.
111.Manchikanti L, Cash KA, Moss TL, et al. Risk of whole body radiation exposure and protective measures in fluoroscopically guided interventional techniques: A prospective evaluation. BMC Anesthesiol 2003;3:2.
112. Park CH, Lee SH, Park HS. Lumbar retrodiscal versus post-ganglionic transforaminal epidural steroid injection for the treatment of lumbar intervertebral disc herniations. Pain Physician 2011;14:353-60.
113. Manchikanti L, Malla Y, Wargo BW, et al. A prospective evaluation of complications of 10,000 fluoroscopically directed epidural injections. Pain Physician 2012;15:131-40.
114. Windsor RE, Storm S, Sugar R, et al. Cervical transforaminal injection: review of the literature, complications, and a suggested technique. Pain Physician 2003;6:457-65.
115. Suresh S, Berman J, Connell DA. Cerebellar and brainstem infarction as a complication of CT-guided transforaminal cervical nerve root block. Skeletal Radiol 2007;36:449-52.
116. Popescu A, Gardner K. An usual mechanism for spinal cord infarction – case report. Ann Neurol 2007;62:32.
117.Kennedy DJ, Dreyfuss P, Aprill CN, et al. Paraplegia following image guided transforaminal lumbar spine epidural steroid injection: two case reports. Pain Med 2009;10:1389-94.
118. Somayaji HS, Saifuddin A, Casey AT, et al. Spinal cord infarction following therapeutic computed tomography- guided left L2 nerve root injection. Spine (Phila Pa 1976) 2005;30:E106-E108.
119. Deshpande DM, Krishnan C, Kerr DA. Transverse myelitis after lumbar steroid injection in a patient with Behcet's disease. Spinal Cord 2005;43:735-7.
120. 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;30:1691-3.
121. Tripathi M, Nath SS, Gupta RK. Paraplegia after intracord injection during attempted epidural steroid injection in an awake-patient. Anesth Analg 2005;101:1209-11.
122. Bose B. Quadriparesis following cervical epidural steroid injections: case report and review of the literature. Spine J 2005;5:558-63.
123. Edlow BL, Wainger BJ, Frosch MP, et al. Posterior circulation stroke after C1-C2 intraarticular facet steroid injection: evidence for diffuse microvascular injury. Anesthesiology 2010;112:1532-5.