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REVIEW ARTICLE

# Epidural steroid injections in the management of low-back pain with radiculopathy: an update of their efficacy and safety

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**Abstract**
*Introduction* Epidural steroid injections (ESIs) have been widely used for over 50 years in the treatment of low-back pain with radiculopathy. Most interventional pain physicians strongly believe in their efficacy and safety. Recent Cochrane systematic reviews have disclosed controversial results and have questioned the effectiveness of ESIs. Moreover, a few neurological adverse events have been reported recently.
*Methods* A literature search of systematic reviews analysing the effectiveness and complications of ESIs was carried out. The scientific quality of the reviews was assessed using the validated index of Oxman and Guyatt. We relied on data abstraction and quality ratings of the placebo-controlled trials as reported by high-quality systematic reviews.
*Results* Two types of systematic reviews were found. The Cochrane high-quality systematic reviews combining the three approaches and different pathologies were predominantly non-conclusive. The second type of review, emanating from the US Evidence-based Practice Centers, distinguishing between the routes of administration and between the principal pathologies found a moderate short-term benefit of ESIs versus placebo in patients with disc herniation and radiculitis, in keeping with the clinical experience. ESIs are generally well tolerated and most complications are related to technical problems. Cases of paraplegia, complicating the foraminal route and related to the violation of a radiculomedullary artery, have been recently reported. They are predominantly observed in previously operated patients.
*Conclusions* Epidural steroid injections have a moderate short-term effect in the management of low-back pain with radiculopathy. Severe neurological complications are exceptional, but call for research for alternative approaches to the foramen as well as for means to detect an eventual arterial injury.

**Keywords** Epidural · Steroid injection · Radiculopathy · Discal herniation · Radiculitis · Lumbar canal stenosis

**Abbreviations**

| | |
|---|---|
| ESI | Epidural steroid injection |
| ODI | Oswestry disability index |
| RCT | Randomized controlled trial |
| LBP | Low-back pain |
| NA | Not available |
| P | Positive |
| N | Negative |
| U.S.P.S.T.F | U.S. Preventive Services Task Force |

## Introduction

Since the first report of the use of epidural steroid injections (ESIs) by Lievre et al. [41, 42] in 1953, corticoid injection therapy has been commonly and increasingly

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used in the treatment of lumbosacral radiculopathies. Injection of steroids in the epidural space was initially empirical and developed progressively following the observation of the beneficial effects of intra-articular steroid injections in osteoarthritic joints. Epidural steroids have been used extensively throughout the world with the majority of experts supporting their use. However in recent years, several systematic reviews [39, 44, 51, 68] have disclosed controversial results regarding the efficacy of ESIs, creating a lack of consensus in the medical community. Recently, neurological complications have been reported creating a controversy with regard to neural toxicity and other adverse events and side effects of ESIs.

## Rationale

It is now admitted that interrelated mechanical and biochemical factors are involved in the genesis of nerve root pain [11]. In clinical practice, ESIs are essentially used in the treatment of radiculopathies caused by discal herniation or by lumbar canal stenosis. In the case of discal herniation, cells from the degenerated disc fragments produce numerous inflammatory mediators including TNF and various other inflammatory cytokines [52]. High levels of phospholipase A2, precursor of prostaglandins E2, have also been found in herniated discs [61]. All these neurotoxic substances may penetrate within the intraneural capillaries causing axonal ischemia, which in turn is responsible for nerve root pain. Moreover, the abundant inflammatory cells present in the granulation tissue surrounding the disc fragment are a strong marker of inflammation demonstrated by intense peripheral enhancement on gadolinium-enhanced magnetic resonance imaging (MRI) [31, 71]. It has also been shown experimentally that a small incision of the annulus fibrosus with minimal leakage of nucleus pulposus was sufficient to induce nerve root injury [37]. In the clinical setting, sciatica or femoral neuralgia can occur in the absence of nerve root impingement on radiologic studies. The chemical radiculitis without compression is related to exposure of the nerve root to irritant substances released in the epidural space from the degenerated disc. In the case of lumbar canal stenosis, inflammation of the nerve root is induced by chronic, slowly progressive mechanical compression. Experimentally, chronic compression of the nerve root induces an intraradicular edema and vascular changes. Moreover, an experimental model of chronic compression in pig has demonstrated the production of substance P inside the nerve root and the ganglion. This neuropeptide can induce inflammation and pain [22].

Thus, an inflammatory process is observed in the main causes of common sciatica: disc herniation, radiculitis and lumbar canal stenosis. It has then been postulated that local injection of potent anti-inflammatory drugs (i.e., steroids) could reduce inflammation by inhibiting the formation and/or release of the inflammatory cytokines and thereby reduce pain. Although the various possible mechanisms of action in the neural blockade are not completely elucidated, the clinical use of ESIs in the treatment of lumbar radiculopathies has a strong pathophysiologic basis.

## Efficacy

### Clinical experience

It is now admitted that the strength of evidence of efficacy is based on a close correlation between clinical experience and data of evidence-based literature. Until the advent of "evidence-based medicine" based on evidence whose importance was recognized in the early seventies of the past century [17], the efficacy of the procedures was based on traditional observational studies, and on judgements and opinions of experts. Clinical studies and expertise generally considered ESIs as effective in the treatment of inflammatory radiculopathies and most open studies disclosed positive results [63]. Since their introduction, ESIs have been increasingly used in clinical practice. In an opinion survey among French rheumatologists, it was found that ESIs was an important part of the conservative treatment of sciatica in 65% of the 84 specialized centers participating in the survey [40]. In a study performed in the US Medicare population, an increase in the number of lumbar ESIs from 553 out of 100,000 to 2,055 out of 100,000 patients was disclosed between 1994 and 2001, inducing a large increase of expenditures [27]. Taken together, these observations point to a rather positive estimate of ESI efficacy by experts and practitioners, and the overall clinical experience favors continuation of their use. However at the end of the last century, a few systematic reviews [7, 39] concluded that there was no clear evidence that epidural steroid injections were effective in managing lumbar radicular pain. Since these early Cochrane systematic reviews, the effectiveness of ESIs remains controversial, the majority of the evidence-based literature being predominantly non-conclusive.

As a consequence of the controversy between clinical experience and data of evidence-based literature, debate persists as to the value of ESIs in managing lumbar radiculopathies. The ongoing debate prompted us to update the present state of the art regarding the benefits of ESIs and their complications. Our objective was to evaluate whether an agreement could be found between scientific evidence and the lengthy clinical experience after reviewing the most recent systematic reviews and RCTs.

## Review of evidence-based literature

### *Methods*

It is now recognized that systematic reviews and meta-analyses of randomized trials are the best sources of evidence [9, 46]. By synthesizing a large and increasing amount of studies, they provide the most concise summaries of research evidence [29]. We carried out a literature search of high-quality systematic reviews, analyzing effectiveness and complications of ESIs up to 2009 using the Pubmed Database. We critically evaluated the quality of the reviews using the criteria proposed by Coulter [23] and advocated by Manchikanti [46, 49]: Who did the review? What was the objective of the review? How was the review done? To assess the scientific quality of the reviews, we used a validated quality instrument described by Oxman and Guyatt [53]. We reviewed the placebo-controlled trials, but relied on data abstraction and quality ratings as reported by high-quality systematic reviews to produce a comprehensive narrative review.

### *Results*

Two types of systematic reviews were disclosed. Although reviewing the same data of literature, they differ first of all by the strategy adopted in analyzing RCTS. The first type, referred to as "global", evaluates evidence by combining the three approaches (interlaminar, caudal, foraminal) and several pathologic conditions into one category: the "lumbosacral radicular syndrome". Most of these reviews point out the position of the Cochrane Collaboration Group. In contrast, the second type distinguishes between the three routes of administration as well as between different pathologic entities, mainly discal herniation, radiculitis and lumbar canal stenosis. As discussed below, they also differ in the methods used in quality assessment and data synthesis. We will examine in turn these two categories of systematic reviews.

The "global" type will be considered first. From 1995 to 2008, we found ten systematic reviews of this category, of which five were of high quality. In 1995, Koes et al. [39] were the first to systematically assess the efficacy of ESIs for low-back pain and sciatica. They developed a list of criteria for methodological assessment of RCTs, ending with a numerical scoring of maximum 100 points. In their review, six RCTs were considered positive i.e., more effective than the reference treatment, and six were negative i.e., no better or worse than the reference treatment. They noted flaws in the design of most studies and concluded that, because of conflicting results, the efficacy of ESIs was not established.

In the same year, Watts et al. [68] published a meta-analysis of 11 RCTs, 9 of which had been evaluated by Koes. A total of 907 patients were involved in the assessment of efficacy. Results of the meta-analysis indicated clearly that ESIs were effective in the management of sciatica.

In the following years, further systematic reviews by Rozenberg et al. [59, 60] and Nelemans et al. [51] also concluded that the methodological quality of the RCTs was low and that there was insufficient evidence for the effectiveness of ESIs. Nelemans [51] also concluded that because of the tendency toward positive effects, there was no justification for abandoning epidural steroid injection therapy.

In 2007, Luijsterburg et al. [44] reviewed 14 RCTs published up to 2004. They were all negative at long term, five positive and nine negative at short term, providing conflicting evidence for the benefits of ESIs versus controls. In the last Cochrane review, Henscheke et al. [32] have excluded a large number of reviews, leaving only three studies rated as low quality. The major cause of exclusion was related to the duration of the radicular syndrome, which was either not reported or less than 3 months. Overall, the results of the above systematic reviews indicate that there is no strong evidence for or against the efficacy of ESIs, due to the low quality of the primary RCTs. For this reason, the European Guidelines published in March 2006 [2] made no recommendations. They indicated, however, that ESIs could be considered in contained discs, and that they should be X-ray guided, preferably through the foraminal route. The need for high-quality RCTs of sufficient sample size with long-term follow-up and appropriate outcome measures and controls was stressed.

We will now examine the second type of systematic reviews, using a different methodology and analyzing additional RCTs. The methodologic quality of the reviews was assessed using the Oxman and Guygatt criteria index [53]. All reviews had scores of 5 or over in a scale of 1–7. These reviews, emanating from several US evidence-based centers, evaluate evidence of efficacy according to the route of administration and to specific pathologic entities.

Chou et al. [19] have evaluated the main results of placebo-controlled trials of ESIs for radiculopathy depending on the mechanisms. Concerning disc herniation and radiculitis, the authors found a moderate short-term benefit of ESIs versus placebo with a fair quality of evidence. Their conclusions were based on 21 controlled trials, of which 9 were of high quality. In contrast, on the basis of three controlled trials of which only one was of high quality, the authors were unable to determine the efficacy or non-efficacy for spinal stenosis.

The lumbar interlaminar approach is the most commonly used, as its entry directly targets the radicular lesion. Three systematic reviews have evaluated the effectiveness of interlaminar ESIs. Boswell et al. [8] in 2003 and Abdi et al. [1] in 2007 concluded that the overall effectiveness of interlaminar ESIs was, respectively, moderate or strong for

**Table 1** Effectiveness of blind interlaminar ESIs in disc herniation and radiculitis

| Study | Scoring (max. 100) | Participants | Controls | Results, short term | Results, long term |
|---|---|---|---|---|---|
| Snoeck [62] | 72 | 51 | Epidural saline | N | N |
| Cuckler [24] | 60 | 36 | Epidural procaine | N | N |
| Carette [16] | 77 | 158 | Epidural saline | P | N |
| Arden [4] | 86 | 228 | Saline in interspinous ligament | P | N |
| Wilson Macdonald [69] | 68 | 61 | Intramuscular and interspinous ligament steroid injection | P | N |

Adapted from [54]

short-term pain relief, but limited for long-term pain relief. In a high-quality systematic review, Parr et al. [54] have evaluated the effectiveness of blind interlaminar epidural injections in general. However as shown on Table 1, all interventions selected for efficacy assessment in this review were steroid epidurals. The level of evidence was classified as I, II or III, with three sub-categories of level II (moderate), according to the classification developed by the U.S. Preventive Services Task Force (U.S.P.S.T.F.). Results based on five RCTs in the evidence synthesis for disc herniation and radiculitis are shown in Table 1 with the controls used. They provide moderate evidence of efficacy (level II-2) for short-term pain relief and limited evidence for long-term pain relief (level III). The study by Cuckler et al. [24] listed in Table 1 is a randomized placebo-controlled trial that compares the efficacy of epidural steroid injection with that of saline, both in combination with procaine in patients with a radiculopathy related to either a discal herniation ($n = 36$) or lumbar spinal stenosis ($n = 37$). In both discal herniation and stenosis patients, results were better than those obtained in the saline-treated group. However, it was a trend: the difference was not significant. The number of patients included in this study is small in both the discal and stenosis group, which reduces the discriminant power.

Concerning efficacy of ESIs administered by the interlaminar route in spinal stenosis, the literature is sparse. Observational studies have shown positive short-term effects [10, 20, 34]. In the prospective study performed by Rivest et al. [58], 38% of patients with lumbar canal stenosis ($n = 105$) reported improvement compared with 61% of disc herniation patients ($n = 107$). In a prospective study reported by Campbell et al. [15], 84 patients with lumbar canal stenosis received an ESI once a week for 3 weeks, performed without fluoroscopy, using an interlaminar approach. With a minimum of 24 months of follow-up, 50 patients had surgical decompression after ESI and 34 (40.5%) had relief of their symptoms without surgery at the latest follow-up. The results were compared with the spinal canal dimensions, which were not predictive of success or failure of ESIs.

The efficacy of ESIs by the caudal route has been evaluated in two systematic reviews by Boswell et al. [8] and Abdi et al. [1]. Both reviews concluded that the evidence of efficacy for discal pathology was strong for short-term and moderate for long-term pain relief. Similar conclusions were reported in the recent systematic review by Conn et al. [21], dealing with epidural injections in general. The results of this review are shown in Table 2. Four of the six included trials [12, 14, 33, 50] are in fact a comparison of ESIs with a control. The study by Dashfield [25] compared steroid epidurals to targeted steroid placement during spinal endoscopy. The study by Manchikanti [48] is an equivalence trial that compares two groups of 30 patients receiving either caudal lidocaine or lidocaine mixed with a small amount of steroid (only 1 ml). With regard to the latter two studies, the degree of evidence disclosed in this review for disc herniation and radiculitis may be questioned.

The evidence synthesis for lumbar stenosis (Table 3) was based on one RCT, positive at short and long term, and two prospective studies, both positive at short term. In the positive RCT by Manchikanti et al. [47], two groups of 20 patients received either lidocaine caudal epidural injections as a control or lidocaine mixed with a steroid. The fluid volume injected was 10 ml in each group. Multiple outcome measures were used, including numeric rating scale and ODI. There was no significant difference between the two groups. Approximately, 40% of patients had no treatment effect. In the responder group, a significant improvement in pain and functional status was observed with approximately three to four procedures in the 1 year follow-up. The authors conclude that this positive, often transitory, effect is particularly useful in elderly, fragile patients often with comorbidities, considering that the natural evolution of lumbar spinal stenosis is unpredictable and not always pejorative [47].

The transforaminal route is target specific and reaches the ventrolateral section of the epidural space. The review by Boswell et al. [8] based on three randomized trials showed a short- and long-term effectiveness for lumbar nerve root pain. Similarly, Abdi et al. [1] reviewing six randomized trials showed that the evidence of efficacy was

**Table 2** Effectiveness of caudal ESIs in disc herniation and radiculitis

| Study | Scoring (max. 100) | Participants | Controls | Results, short term | Results, long term |
|---|---|---|---|---|---|
| Manchikanti [48] | 72 | 84 | Epidural lidocaine | P | N |
| Dashfield [25] | 50 | 60 | Spinal endoscopy lidocaine + steroid | P | NA |
| Bush and Hillier [14] | 55 | 23 | Epidural saline | P | N |
| Mathews [50] | 62 | 57 | Lidocaine sacral hiatus or sacral tender point | N | P |
| Hesla and Breivik [33] | 58 | 69 | Caudal bupivacaine and saline | P | P |
| Breivik [12] | 68 | 35 | Caudal bupivacaine and saline | P | NA |

Adapted from [21]

**Table 3** Efficacy of caudal ESIs in spinal stenosis

| Study | Scoring (max. 100) | Participants | Results, short term | Results, long term |
|---|---|---|---|---|
| Manchikanti [47] | 70 | 40 | P | P |
| Ciocon [20] prospective | 57 | 30 | P | NA |
| Botwin [10] prospective | 61 | 34 | P | P |

Adapted from [21]

**Table 4** Transforaminal ESIs in disc herniation and radiculitis

| Study | Scoring (max. 100) | Participants | Controls | Results, short term | Results, long term |
|---|---|---|---|---|---|
| Karppinen [36] | 81 | 160 | Epidural saline | P | N |
| Riew [56, 57] | 68 | 55 | Epidural anesthetic | P | P |
| Jeong [35] | 63 | 239 | Epidural steroid ganglionic versus preganglionic | P | NA |
| Vad [66] | 58 | 48 | Saline trigger-point injection | P | P |

Adapted from [13]

strong for short-term (<6 weeks) and moderate for long-term results (>6 weeks). Buenaventura et al. [13] have specifically evaluated the efficacy of transforaminal ESIs in discal herniation and radiculitis. The results based on four RCTs are shown in Table 4. They provide moderate evidence (Level II-1) for short-term pain relief and moderate evidence (level II-2) for long-term improvement. One can question, however, the inclusion of Jeong et al.'s trial as they essentially compared transforaminal preganglionic ESIs to ganglionic ESIs.

No specific systematic review of transforaminal ESIs for lateral stenosis could be found in literature. A prospective evaluation by Botwin et al. [10] in 34 patients with lateral stenosis showed positive short-term and long-term pain relief. In a randomized double-blind controlled trial, Tafazal et al. [65] compared the effect of corticosteroids combined with bupivacaine in peri-radicular infiltration with bupivacaine only in patients with foraminal prolapsed disc or foraminal stenosis. They were able to show a significant short-term effect at 3 months, persisting at 6 months in both populations. Interestingly, the results were equivalent whether using steroids with local anesthetic or local anesthetic alone. The beneficial effects were more frequent in discal pathology than in osteoarthritic lateral stenosis.

## Complications

ESIs are generally well tolerated. However, severe and worrisome complications may occur, imposing observance of a strict protocol during the procedure. In addition to minor side effects, the major complications are related to the needle placement, steroid or chemical entities used in the formulations of injected steroids.

Dural puncture may happen with a varying frequency between 2 and 5% according to the authors [18, 19]. In addition to the post-dural puncture syndrome including headache, nausea and vertigo, there is a risk of subdural injection of the steroid, its buffers and preservatives

carrying a potential neurotoxic effect and a risk of brain thrombophlebitis [26]. Utmost precautions are mandatory to avoid intrathecal injections.

Infectious complications are rare. They comprise epidural abscess or septic meningitis if the needle has violated the dura. In addition to the strict observance of the asepsis rules, ESIs must be postponed if clinical or biological signs evoking an infection elsewhere are present. Epidural hematomas are also rare, but can be catastrophic. Prior to epidural injection, it is mandatory to verify the absence of coagulation disorders, constitutional or drug-related.

Systemic effects resulting from oral or intravenous administration of steroids are rarely observed after epidural injections. However, side effects and complications have been reported [38]. They have been extensively and recently reviewed by Manchikanti [45]. They principally include complications related to the endocrine system: hyperglycemia or worsening of diabetes; adrenal suppression biologically detected following a series of ESIs performed with short intervals. Hypertension with fluid retention and gain of weight may happen and the patient must be aware of this possibility. The musculoskeletal (osteonecrosis, osteoporosis) ocular or gastrointestinal complications of prolonged oral therapy are exceptional following ESIs.

Recently, a case of sudden paraplegia immediately following ESIs has been reported. Since 2002, 12 such cases have been observed. They have been analyzed in detail by Wybier et al. [70]. The clinical pattern is similar in all cases: within a few minutes after the procedures, acute abdominal and leg pain are followed by a complete sensorimotor deficit of the lower limbs. MRI performed a few hours after the procedure is usually normal. In contrast, MRI obtained 24–96 h later disclose a central high-intensity zone of the spinal cord consistent with an acute ischemia. Of the 12 patients reported by Wybier, 8 had previous surgery and in 10 patients the injection route was foraminal; this route was the only one used in the 4 non-operated patients. The most probable mechanism of this severe, although exceptional, complication is the violation of a radiculomedullary artery with embolization of macroaggregates of steroid, and subsequent deprivation of the arterial supply of the cord. The radiculomedullary artery, also known as Adamkiewicz artery usually arises from the left between T9 and L2. In a minority of individuals, it may arise at a lower level of the lumbar spine [6, 30, 43]. At the level concerned, the nerve root runs in the foramen parallel to the artery, which can be damaged by the needle in the foraminal approach. The high prevalence of this complication in operated patients may be related to the abundant vasculature and neoangiogenesis of the scar tissue, enhancing the risk of vascular damage.

## Discussion

Regarding the efficacy of ESIs in the treatment of lumbar radiculopathies, we have three main sources of information: clinical experience, Cochrane systematic reviews, and systematic reviews using methods adapted from the U.S. Preventive Services Task Force (U.S.P.S.T.F.).

Most interventional pain physicians strongly believe that ESIs are effective in the treatment of patients with sciatica. This belief, based on judgments and opinions of experts, is reinforced by the observation that ESIs have been widely used for over half a century and are still a current therapeutic tool used internationally in many specialized centers. It is therefore difficult to conceive that the absence of efficacy could have been missed over the years by so many practitioners. However, traditional clinical experience can be misleading. It is well known in other domains of medicine that the opinions of clinicians and conclusions of experts can be biased, inducing the continuation of useless, costly and possibly harmful therapies [3]. A scientific approach is clearly needed.

The other principal sources of information are provided by the two types of evidence-based systematic reviews: the Cochrane reviews and the reviews emanating from the U.S. Evidence-based Pratice Centers. The two types of reviews have adopted a different strategy in analyzing RCTs. They also differ in the methods used to assess the quality of each individual study. Variations of methodology are also detected in each of the two types. This is particularly noticeable in the Cochrane reviews. For example, concerning the methodologic quality assessment, Luijsterburg et al. [44] used a Delphi list and Staal et al. [64] the criteria recommended by the Cochrane Back Review Group. The three principal systematic reviews separating techniques and pathologies used similar methodologic criteria adapted from Koes et al. [39] to evaluate the quality of the RCTs. Concerning the analysis of evidence, variations are also observed between the two types of review: the Cochrane reviews usually summarize evidence according to a rating system with five levels of evidence (best evidence synthesis), whereas Henschke et al. [32] used a different grading quality of evidence as recommended by Guyatt and Osman; the non-Cochrane systematic reviews used a system adapted from the U.S. Preventive Services Task Force with five levels of evidence ranging from level I–III, with three subcategories of evidence in level II.

The inconclusive results of the Cochrane reviews have cast doubt on the therapeutic role that ESIs had for over 50 years in the treatment of sciatica. One can question the reasons for the absence of meaningful conclusions generated by the high-quality Cochrane systematic reviews, creating a difficult situation of uncertainty. The impossibility to conclude for or against effectiveness of ESIs has a

multifactorial origin mainly related to the low quality of the RCTs.

The sample sizes of most of the primary RCTs were small, lowering their capacity to detect discrete but relevant differences. A strong heterogeneity exists between studies with respect to the type and dosage of the steroid, the fluid volume injected, the number of injections and their intervals. Symptom duration before treatment, not always mentioned in the RCTs, is another confounding variable: mechanisms of pain in acute, subacute or chronic situations are not similar. The nature of the controls varies between studies: it can be epidural injections of saline or anesthesic. In some RCTs, the effect of ESIs is compared with no treatment or with other treatments. As discussed below, inconsistency between trials may depend on the type of control used.

Other factors may also explain why beneficial effects could have been missed. Most primary RCTs were performed without X-ray guidance, with a risk of incorrect position of the needle. The importance of X-ray guidance has recently been emphasized by Barham and Hilton [5], who showed in a series of 137 patients treated by caudal ESIs that the miss rate without radioscopic control was 26%. The miss rate is lower in non-obese patients treated blindly by the interlaminar route [55]. The outcome criteria variable between studies can also be misleading. As suggested by Nelemans [51], the use of visual analog scales to measure the pain relief may miss small but true effects especially if the dichotomized results (improved/not improved) are used.

Efficacy may vary according to the pathology. In a 2008 updated Cochrane review on injection therapy for subacute and chronic low-back pain, Staal et al. [64] stated that "one of the main problems when studying the effects of injection therapy was the lack of diagnostic criteria for determining the injection site". In the case of radicular pain caused by discal herniation or lumbar canal stenosis, the diagnostic is known and the site of injections can be determined accordingly. Moreover, the natural evolution of radiculopathies related to discal herniation, radiculitis and stenosis is not the same. Interlaminar, caudal and transforaminal routes may have different efficacy rates. For example, Koes et al. [39] reviewed systematically 12 RCTs of lumbar ESIs combining five caudal and seven interlaminar injections. As pointed out by Boswell et al. [8], four of the five caudal were positive, while only two of the seven interlaminar were positive.

Taken together, these observations may explain why high-quality scientific assessment of efficacy of ESIs combining different techniques and diseases may produce inconclusive results. Systematic reviews including in a same overall evaluation such a heterogenous group of patients carries a risk of dilution of efficacy of the treatment method. A part of this risk is eluded when evidence is evaluated after separating the different techniques and pathologies, which also generates a better clinical relevance. It is recognized, however, that in the latter reviews, the other confounding factors discussed above were not eluded, thus illustrating the difficulty in synthesizing the evidence in this topic. As indicated above, the variations of methodology in quality assessment and analysis of evidence between reviews add to the difficultly.

The authors of systematic reviews adapted from the U.S.P.S.T.F. used a different methodological approach and reported more conclusive results. A short-term benefit of ESIs has been shown in patients with discal herniation and radiculitis by reviews analyzing the data separately: according to imaging [19] or according to the routes of administration [13, 19, 21, 54]. The duration of this effect is not clarified in all studies; approximately 6 weeks have been proposed by some authors [1, 51, 67]. The magnitude of the effect is considered as moderate by Chou et al. [19], who have noted inconsistency between studies. In a higher quality trial, Carette et al. [16] found that during the first 6 weeks of the trial, patients reported less leg pain than those receiving the placebo consisting of 1 ml of saline compared with 80 mg of methyl prednisolone acetate in 8 ml of saline. To evaluate the magnitude of the benefit, Carette et al., calculated the effect size and found 0.50 for the radicular pain. This value is considered as moderate (small effect 0.20, large effect 0.80), which is consistent with the conclusions of Chou et al. Few studies have evaluated the long-term effect, which is more difficult to assess owing to the natural evolution of a discal herniation, depending in part on its size and location. Some RCTs using the caudal or foraminal routes [48, 65] have reported long-term benefits, but it is not clear whether this effect is related or not to repeat injections. Additional ESIs may prolong the analgesic effect. This is an important goal in the management of nerve root pain to prevent peripheral and central sensitization and the risk of chronicity [11].

Concerning the therapeutic value of ESIs in managing radiculopathies related to spinal stenosis, the literature is sparse and controversial [28]. However, ESIs are commonly and increasingly used, owing to the aging of the general population. In the survey by Friedly et al. [27] in the U.S. Medicare population, spinal stenosis accounted for 23% of all ESIs. After reviewing the data of the literature, it is clear that the level of scientific evidence of efficacy of ESIs in spinal stenosis is yet to be determined. It relies now on observational studies and on one RCT [47].

The effect due to the intervention must be distinguished from the placebo effect related to the influence of the patient's expectation of the injection. The strength of evidence depends on the controls used. Systematic reviews emanating from U.S. Evidence-based Centers have disclosed

a short-term benefit of ESIs. Most of them have compared epidural steroid injections as the intervention with various controls. The placebo controls presented on Tables 1, 2 and 4 consist of epidural saline or local anesthetic injections, and of non-epidural controls, i.e., local intramuscular, ligamentous structures, painful trigger-point injections of saline, anesthetic or steroid. Chou et al. [19] have noted that trials using a sham soft-tissue placebo injection as controls reported short-term benefits more consistently than studies with epidural placebo injections. However in the Carette et al.'s trial already cited, the steroid was compared with a small quantity of epidural saline (1 ml), which excluded the possibility of a washout effect of saline, suggested by some authors [67]. The use of a local anesthetic as epidural placebo control may create a difficult issue, as an equivalent positive effect between steroid and lidocaine has been detected in studies using a local anesthetic as a control [47, 48, 65]. The effect of lidocaine, persisting a few weeks and outlasting the normal duration of a local anesthetic, is unexpected and difficult to understand. This finding, however, must be seriously considered in future studies. In addition, the use of an epidural anesthetic carries the risk of a subdural anesthesia in case of dural puncture during the injection and of accidental intravenous injections possibly followed by convulsions and arrhythmias. Chou et al. [19] have suggested that trials comparing epidural saline or anesthetic injection versus non-epidural placebo injection would be helpful to clarify the efficacy of non-steroid epidural injections. This recommendation is particularly important since the epidural steroid injected as an intervention is often diluted in saline or in anesthetic [4, 12, 36, 69].

In future X-ray guided RCTs, in addition to the many pertinent recommendations for research made by the Cochrane reviewers, an appropriate choice of the intervention of interest, i.e., epidural steroid injection and of the control will be of primary importance. The injected steroid must have a sufficient volume to correctly fill the epidural space, the diluent being a neutral ineffective fluid. For safety reasons, the steroid chosen must have the least tendency to coalesce [70]. The only way to clearly distinguish the efficacy of the procedure from a simple placebo effect is through the use of a sham ineffective control, such as a local intramuscular ineffective injection, simulating an epidural injection on a blinded randomized patient. In the course of this review, it was noted that many other aspects of this complex area must be clarified, confirmed and strengthened by additional research.

## Conclusions

The purpose of this narrative review was to summarize the present knowledge regarding efficacy and safety of epidural injections in the treatment of lumbosacral radiculopathies. We have presented qualitative evidence issued from primary RCTs and systematic reviews that injections of steroids in the epidural space have a moderate short-term pain relief effect in sciatica related to discal herniation and radiculitis. Clinical experience also favours their use in lumbar canal stenosis, but more research work is necessary to demonstrate scientific evidence. Concerning safety, ESIs are generally well tolerated and most complications are related to technical problems during the procedure. The safety of ESIs has been recently questioned after the report of several cases of paraplegia complicating the foraminal route, more and more used owing to its strong evidence of efficacy. Although quite exceptional, the seriousness of this adverse event implicates the research of alternative approaches to the foramen and means to detect an eventual arterial injury, as well as the use of a steroid agent with the least tendency to coalesce.

**Conflict of interest** None.

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