SYSTEMATIC REVIEW

Safety of Epidural Corticosteroid Injections

Ippokratis Pountos1 • Michalis Panteli1 • Gavin Walters2 • Dudley Bush3 • Peter V. Giannoudis1

Abstract
Background and Objective Epidural corticosteroid injections (ESIs) have been used for several decades and now represent the most common intervention performed for the management of back pain with a radicular component. However, several reports have presented devastating complications and adverse effects, which fuelled concerns over the risk versus clinical effectiveness. The authors offer a comprehensive review of the available literature and analyse the data derived from studies and case reports.

Methods Studies were identified by searching PubMed MEDLINE, Ovid MEDLINE, EMBase, Scopus, Google Scholar and the Cochrane Library to retrieve all available relevant articles. Publications from the last 20 years (September 1994 to September 2014) were considered for further analysis. Studies selected were English-language original articles publishing results on complications related to the technique used for cervical and lumbar ESIs. The studies had to specify the approach used for injection. All studies that did not fulfil these eligibility criteria were excluded from further analysis.

Results Overall, the available literature supports the view that serious complications following injections of corticosteroid suspensions into the cervical and lumbar epidural space are uncommon, but if they occur they can be devastating.

Conclusions The true incidence of such complications remains unclear. Direct vascular injury and/or administration of injectates intra-arterially represent a major concern and could account for the vast majority of the adverse events reported. Accurate placement of the needle, use of a non-particulate corticosteroid, live fluoroscopy, digital subtraction angiography, and familiarisation of the operator with contrast patterns on fluoroscopy should minimise these risks. The available literature has several limitations including incomplete documentation, unreported data and inherent bias. Large registries and well-structured observational studies are needed to determine the true incidence of adverse events and address the safety concerns.

Ippokratis Pountos
pountos@doctors.org.uk

1 Academic Department of Trauma and Orthopaedics, Leeds General Infirmary, Clarendon Wing Level A, Great George Street, Leeds LS1 3EX, UK
2 University of Leeds, Leeds, UK
3 Anaesthetic Department, Leeds Teaching Hospitals, NHS Trust, Leeds, UK

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Key Points

Serious complications including damage to the neural elements, stroke and death have been reported with epidural corticosteroid injections (ESIs) but are mostly anecdotal. Their true incidence is unknown, but such outcomes seem to be rare.

Vascular penetration is possible, relatively more frequent in the cervical segments and potentially hazardous. Intravascular injection can be reduced by use of injected contrast media.

The use of a blunt needle, live fluoroscopy, digital subtraction angiography and the administration of a small test dose initially could help reduce the adverse effects.

Many complications can be avoided by a thorough understanding of the anatomy, accurate placement of the needle and familiarisation of the contrast patterns on fluoroscopy.

More research must be performed regarding the benefits versus risk, techniques and outcome of ESIs.

1 Introduction

Epidural corticosteroid injections (ESIs) have been used for decades as a therapeutic modality in the management of spinal pain syndromes attributed to disc pathology and spinal stenosis. Although the exact pathophysiology of these conditions remains obscure, it has been suggested they occur through an ectopic “firing action potentials” mechanism in nerve roots derived from the mechanical compression [1]. This mechanical compression could stimulate a local inflammatory process, which forms the rationale behind the administration of the corticosteroids. This theory is further strengthened by findings suggesting that the lavage of inflammatory mediators may reduce pain and inflammation [2].

Epidural injections can be administered through a transforaminal, interlaminar or caudal route. The interlaminar route is considered to be non-specific and the injectate is free to spread within the posterior epidural space with possible flow anteriorly, cephalad and caudally [3]. This could be influenced by tissue fibrosis, scarring or hypertrophy, which may occur in spinal pathology [4]. Transforaminal ESIs are more specific and selected nerves can be targeted. ESI administered through this route could in theory deposit a larger mass of corticosteroid close to the pain generators at the ventral epidural space allowing a greater degree of drug diffusion, so transforaminal ESI may be more efficacious in alleviating patients’ pain [4]. However, several prospective randomised studies have failed to demonstrate a statistically significant difference in terms of pain reduction and functional score improvement between the transforaminal and interlaminar approaches [5, 6]. In a recent systematic literature review of comparative studies involving patients with lumbar sacral radicular pain, Chang-Chien et al. [5], suggested that both approaches are equally effective and demonstrated only minor non-significant differences between them. In contrast to the interlaminar and transforaminal routes, caudal epidural injections require relatively higher volumes of corticosteroids but are considered to be easier and safer and are preferred in patients after spinal surgery.

The modality of imaging may influence the efficacy of ESI. Currently, fluoroscopy, ultrasound and computed tomography (CT) imaging have been used and their utilisation continues to increase. The choice amongst them partly lies in personal preference but also on the availability and prior training on the device. Limited evidence currently exists in terms of the effectiveness and safety differences between these techniques. For instance, a recent literature review by Bui and Bogduk [7] concluded that CT-guided lumbar transforaminal injection of corticosteroids is neither more effective nor safer than the fluoroscopy-guided injections but that CT is associated with significantly higher radiation doses than conventional fluoroscopy. Ultrasound has gained popularity and maybe a safe alternative to the other radiological imaging modalities [8].

2 Risk Versus Efficacy of Epidural Corticosteroid Injections (ESIs)

Several authors have questioned the overall efficacy of ESIs for the management of radicular pain [9–12]. In a systematic review of the available literature in 2009 by Chou et al. [9], ESIs were moderately effective for short-term symptom relief in patients with low back pain but conferred no long-term benefit. In a similar manuscript, Pinto et al. [11] concluded that epidural corticosteroid injections offer only short-term relief of leg pain and disability for patients with sciatica. The authors questioned the clinical justification of this procedure when comparing the benefits with the risks. Furthermore, in a systematic review including data from the Cochrane Central Register of Controlled Trials, Staal et al. [12] concluded that there is insufficient evidence to support the use of injection therapy in subacute and chronic low back pain. These conclusions have been challenged by several other trials and systematic reviews [13–18]. In patients with lumbar radicular pain caused by contained disc herniations, MacVicar et al. [16] suggested that lumbar transforaminal
injection of corticosteroids is effective in reducing pain, restoring function, reducing the need for other healthcare modalities and avoiding surgery [16]. In line with these deductions, Quraishi [18] concluded that in patients with lumbar radiculopathy, ESIs result in an improvement in pain but not disability. Friedly et al. [10] suggested that epidural injection of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine in the treatment of lumbar spinal stenosis alone. ESIs were found to have significant effect in relieving chronic intractable pain of cervical origin, providing long-term relief [14]. Some meta-analyses suggested that there is good evidence for the effectiveness of cervical interlaminar epidural injections in managing radiculitis secondary to disc herniation and fair evidence in managing axial or discogenic pain, pain of central spinal stenosis and pain of post-surgery syndrome [15, 17]. The same authors concluded that the evidence is poor for cervical transforaminal epidural injections. It should be mentioned, however, that several of these studies have been criticised for flaws and deficiencies, adding further overall confusion.

In addition to the controversy surrounding the efficacy of ESIs, some authors have raised concerns regarding potential adverse events. On 23 April 2014 the US Food and Drug Administration (FDA) issued a warning to the medical community covering the potential risks of these injections [19]. The warning states that “injection of corticosteroids into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death”.

This systematic review aims to scrutinise the available literature, present the available data and documentation from several authors, and analyse the risks involved with the ESIs in the cervical and lumbar spine.

3 Methods

This review was carried out in accordance to the PRISMA guidelines [20]. Data were documented according to a standardised protocol, where objectives and inclusion criteria were specified in detail.

Publications from the last 20 years (September 1994 to September 2014) were considered for further analysis. Studies selected were original articles, in the English language, publishing results on complications related to the technique used for the ESIs. Only cervical and lumbar ESIs were included and the studies had to specify the approach used for injection. All studies that did not fulfil these eligibility criteria were excluded from further analysis.

Studies were identified by searching the following resources/databases to retrieve all available relevant articles: PubMed MEDLINE, Ovid MEDLINE, EMBASE, Scopus, Google Scholar and the Cochrane Library. The terms used for the search included ‘epidural’, ‘injection’, ‘corticosteroid’ and ‘steroid’ both isolated or in combination with specific words including ‘transforaminal’, ‘interlaminar’, ‘adverse events’, ‘complication’ and ‘side effect’. The identified articles and their bibliographies including any relevant reviews were manually searched for additional potential eligible studies.

Two of the authors (Ippokratis Pountos and Gavin Walters) of this systematic review performed 208 the assessment, in an independent, unblinded and standardised manner. Most citations were excluded on the basis of information provided by their respective title or abstract. In any other case, the complete manuscript was obtained and scrutinised by two reviewers.

4 Results

Of 3255 papers initially identified, 162 met the inclusion criteria (Fig. 1). This included 58 studies, of which 38 recorded complications while the remaining 20 state that 217 no complications were encountered [21–78]. 101 case reports were also found [79–179].

4.1 Interlaminar Cervical ESIs

The review of the available literature identified 11 manuscripts presenting complications following interlaminar cervical ESIs (Table 1) [21, 22, 24, 26, 28–34]. One
**Table 1** Complications reported with interlaminar cervical epidural corticosteroid injections

| Study, year          | Design                      | Pts                          | Medications                  | Imaging | Complications                                      |
|----------------------|-----------------------------|------------------------------|------------------------------|---------|---------------------------------------------------|
| Botwin et al., 2003  | Retrospective cohort study  | 157 pts, 345 injections, C6–7 or C7–T1 | Triamcinolone acetonide 80 mg | FL      | Overall 16.8 %:  
23 Increased neck pain (6.7 %)  
16 Non-positional headaches (4.6 %)  
6 Insomnia (1.7 %)  
6 Vasovagal reactions (1.7 %)  
5 Facial flushing (1.5 %)  
1 Pyrexia (0.3 %)  
1 Dural puncture (0.3 %)  
3 Dural punctures (0.07 %)  
17 Vagal symptoms (0.4 %)  
3 Paraesthesia and numbness (0.07 %) |
| Derby et al., 2003   | Retrospective survey        | 4389 Injections              | NA                           | NA      | 16.9 % headaches  
21.5 % insomnia, flushing of the face, temperature  
6.2 % of increased pain |
| Goel and Pollan, 2006| Prospective cohort study    | 29 pts, 65 injections        | NA                           | FL      | 16.9 % headaches  
21.5 % insomnia, flushing of the face, temperature  
6.2 % of increased pain |
| Kwon et al., 2007    | Retrospective cohort study  | 76 pts, 76 injections        | Triamcinolone acetonide 40 mg | FL      | 100 Intravascular placement of needle (4.2 %)  
24 Dural puncture (1 %)  
6 Transient nerve root irritation (0.25 %)  
5 Transient spinal cord irritation (0.21 %)  
16 Profuse bleeding (0.7 %)  
1 Vasovagal (0.04 %)  
2 Facial flushing (0.08 %)  
1 Vasovagal and syncope (0.8 %) |
| Kranz et al., 2011   | Retrospective cohort study  | 50 pts, 53 injections        | Betamethasone                | CT      | 1 Intrathecal injection |
| Manchikanti et al., 2012 | Prospective cohort study | 2376 Injections            | NA                           | FL      | 100 Intravascular placement of needle (4.2 %)  
24 Dural puncture (1 %)  
6 Transient nerve root irritation (0.25 %)  
5 Transient spinal cord irritation (0.21 %)  
16 Profuse bleeding (0.7 %)  
1 Vasovagal (0.04 %)  
2 Facial flushing (0.08 %)  
1 Vasovagal and syncope (0.8 %) |
| Lee et al., 2012     | Prospective cohort study    | ~127 Injections              | Dexamethasone sodium phosphate 10 mg | FL      | 100 Intravascular placement of needle (4.2 %)  
24 Dural puncture (1 %)  
6 Transient nerve root irritation (0.25 %)  
5 Transient spinal cord irritation (0.21 %)  
16 Profuse bleeding (0.7 %)  
1 Vasovagal (0.04 %)  
2 Facial flushing (0.08 %)  
1 Vasovagal and syncope (0.8 %) |
| Beyaz and Eman, 2013 | Retrospective cohort study  | 65 pts                       | NA                           | FL      | 100 Intravascular placement of needle (4.2 %)  
24 Dural puncture (1 %)  
6 Transient nerve root irritation (0.25 %)  
5 Transient spinal cord irritation (0.21 %)  
16 Profuse bleeding (0.7 %)  
1 Vasovagal (0.04 %)  
2 Facial flushing (0.08 %)  
1 Vasovagal and syncope (0.8 %) |
| Manchikanti et al., 2013 | RCT                        | 120 pts, 654 injections      | Betamethasone 6 mg (n = 60)  | FL      | 2 Subarachnoid punctures (0.3 %)  
4 Intravascular penetrations (0.6 %)  
5 Nerve root irritations (0.76 %)  
1 Pain lasting 1 week (0.15 %)  
1 Itching sensations  
1 Facial flushing  
1 Dry mouth  
1 Erectile dysfunction |
| Lee et al., 2014     | Retrospective cohort study  | 143 pts                      | Triamcinolone acetonide 40 mg | FL      | 2 Subarachnoid punctures (0.3 %)  
4 Intravascular penetrations (0.6 %)  
5 Nerve root irritations (0.76 %)  
1 Pain lasting 1 week (0.15 %)  
1 Itching sensations  
1 Facial flushing  
1 Dry mouth  
1 Erectile dysfunction |
manuscript that reports no complications has also been identified but only includes 14 interlaminar cervical ESIs [23].

Based on the available studies, the incidence of dural puncture ranged between 0.07 and 2.6 %. Vasovagal reactions ranged between 0.04 and 1.7 %. In a prospective study including 2376 injections, Manchikanti et al. [34] reported 100 cases where intravascular placement of the needle occurred [34]. However, complications that could potentially be correlated with inadvertent intravascular injection of corticosteroids were low and included 11 cases of transient nerve root or spinal cord irritation, one vasovagal event and two cases of facial flushing. In a retrospective analysis of the results of 345 C6–7 or C7–T1 injections, Botwin et al. [22] reported an overall incidence of complications of 16.8 %. A large proportion of these adverse events were related to an increase of neck pain, headache, insomnia and vasovagal reactions.

### 4.2 Transforaminal Cervical ESIs

There are limited studies analysing the complications from this approach. Furman et al. [25] presented 504 cervical (C3–C8) transforaminal ESIs performed on 337 patients [25]. They reported identification of 98 intravascular injections that did not result in any adverse effects. Similarly, other authors have reported no complications [27, 31, 37–39]. In a retrospective review of 1579 injections, Derby et al. [24] reported two cases of aggravated radicular pain, two cases of prolonged paraesthesias and the development of skin rash in one patient. In another study including 43 ESIs with prednisolone, 19 % of patients experienced minor neurovegetative manifestations [43]. Scanlon et al. [41] conducted an anonymous survey asking the US physician members of the American Pain Society about their experience with regards to serious complications following cervical transforaminal epidural corticosteroid injections (TESIs) [41]. From the 287 replies, 78 complications were reported, among which there were 30 brain or spinal cord infarcts and 24 neurologic complications including death of unsuspected aetiology (n = 3), high spinal anaesthesia (n = 3), transient ischaemic attacks (n = 3), and spinal cord or brainstem oedema (n = 3). Overall, the survey revealed 13 cases with a fatal outcome [41].

### 4.3 Interlaminar Lumbar ESIs

The literature search found 11 studies that present adverse effects following interlaminar lumbar ESIs (Table 2) [34–36, 40, 42, 44, 45, 47–52]. In addition, four studies that involve more than 250 patients have reported no adverse events following interlaminar lumbar epidural ESIs [46, 54, 55, 60]. In a prospective cohort study including 1450 injections, Manchikanti et al. [34] reported an incidence of 0.8 % for dural puncture and profuse bleeding following the injection [34]. A prospective, randomised blinded study including 106 patients has reported a rather high number of minor adverse effects [35]. In particular, 26 % of the patients experienced discomfort and pain at the injection site, 18 % had non-positional headache and 10 % suffered from nausea after the injection. In an analysis of 6631 interlaminar lumbar ESIs, Huang et al. [48] found 42 cases of inadvertent lumbar facet joint injection [48]. In 31 cases the physician recognised the lumbar facet joint injection. A similar study design reported by Candido et al. [46] reported the incidence of intradiscal injection to be one in 4723 [46].

### 4.4 Transforaminal Lumbar ESIs

Fourteen studies were identified that presented adverse effects following transforaminal ESIs (Table 3) [34, 50, 53, 56–59, 61, 63, 65–69]. In contrast, no adverse events were presented by a number of other authors [25, 62, 70–78]. McGrath et al. [59] retrospectively reviewed the charts of patients receiving ESIs over a 7-year period [59]. Of the 3964 injections included, only minor complications were reported in 84 injections. The most common complication reported was increased pain, which was encountered in half of the patients. Two prospective studies analysing a large number of transforaminal lumbar ESIs reported an incidence of intravascular penetration of between 7.4 and 7.9 % [34, 35].

| Study, year | Design | Pts | Medications | Imaging | Complications |
|------------|--------|-----|-------------|---------|---------------|
| Manchikanti et al., 2014 [32] | RCT | 120 pts, 688 injections | Betamethasone 6 mg (n = 60) | FL | 6 Subarachnoid punctures (0.3 %) 10 Intravascular penetrations (0.6 %) 3 Nerve root irritations (0.76 %) 1 Pain lasting 1 week (0.15 %) |

CT computed tomography, FL fluoroscopy, NA not available, pts patients, RCT randomised controlled trial

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The main difference was an 8.7% rate of vasovagal episodes reported by Karaman et al. [57]. A similar rate was reported by Ploumis et al. [61], although only 20 patients were included in that study. Hong et al. [56] identified six intradiscal injections among 249 transforaminal ESIs, which represents an incidence of 2.4% [56]. A lower incidence of one in 402 injections was reported by Candido et al. [46], although this was tenfold higher than after interlaminar ESI [46].

### 4.4.5 Adverse Event Case Reports According to the Approach Used

A large number of case reports presenting rare adverse events following ESIs exist (Fig. 2) [79–179]. The available literature has described deaths following ESIs [89, 93, 97]. Reviewing the available case reports, the most common and devastating complication was infarction of the spinal cord, cerebellum, brain and brainstem [97, 141].

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**Table 2** Complications reported with interlaminar lumbar epidural corticosteroid injections

| Study, year          | Design                        | Pts, injections | Medications                       | Imaging | Complications                                      |
|---------------------|-------------------------------|-----------------|-----------------------------------|---------|---------------------------------------------------|
| Carette et al., 1997 [36] | Prospective randomised blinded study | 78 pts, 162 injections | Methylprednisolone 80 mg | BL      | 1 Dural puncture (0.6%)                            |
|                      |                               |                 |                                   |         | 27 Transient headache                              |
| Kraemer et al., 1997 [51] | RCT                          | 87 pts, 87 injections | Triamcinolone 10 mg | CT      | 1.9–3.6 % headache                                 |
| Valat et al., 2003 [42] | RCT                          | 39 pts, 117 injections | Prednisolone acetate 50 mg | BL      | 2 Headache                                        |
| Arden et al., 2005 [44] | RCT                          | 115 pts, 3 injections each | Triamcinolone acetonide 80 mg | BL      | 4 Non-specific headache                            |
|                      |                               |                 |                                   |         | 2 Postdural puncture, headache, nausea             |
|                      |                               |                 |                                   |         | 5 Other                                           |
| Kim et al., 2010 [49] | Retrospective cohort study    | 150 pts, 150 injections | Dexamethasone 16 mg | FL      | 42 Facial flushing (28%)                           |
| Kim et al., 2011 [50] | Prospective randomised study  | 60 pts, 120 injections | Dexamethasone phosphate 15 mg or methylprednisolone acetate 80 mg | FL      | 1 Intrathecal injection                            |
| Manchikanti et al., 2012 [34, 40] | Prospective randomised blinded study | 120 pts, 213 injections | Betamethasone 1 mL (n = 60) | FL      | 3 Subarachnoid punctures (1.4%)                     |
| Manchikanti et al., 2012 [34] | Prospective cohort study      | 1450 Injections | NA | FL     | 7 Intravascular placement of needle (0.5%)        |
|                      |                               |                 |                                   |         | 4 Transient nerve root irritation (0.28%)          |
|                      |                               |                 |                                   |         | 11 Dural punctures (0.8%)                          |
|                      |                               |                 |                                   |         | 11 Profuse bleeding (0.8%)                         |
|                      |                               |                 |                                   |         | 4 Local haematoma (0.28%)                          |
|                      |                               |                 |                                   |         | 1 Headache (0.07%)                                 |
|                      |                               |                 |                                   |         | 2 Facial flushing (0.13%)                           |
|                      |                               |                 |                                   |         | 1 Dural puncture                                   |
|                      |                               |                 |                                   |         | 1 Transient paraparesis                            |
|                      |                               |                 |                                   |         | 26 % discomfort and pain at the injection site     |
|                      |                               |                 |                                   |         | 18 % non-positional headache                        |
|                      |                               |                 |                                   |         | 10 % nausea                                       |
|                      |                               |                 |                                   |         | 15 Dizziness or pain at injection site or facial flushing |
| Bartynski et al., 2013 [45] | Retrospective cohort study    | 276 pts, 392 injection | Methylprednisolone acetate 80 mg | FL      | 1 Intrathecal injection                            |
| Candido et al. 2013 [35] | Prospective randomised blinded study | 106 pts, L3–S1 | Methylprednisolone acetate 120 mg | FL      | 26 % discomfort and pain at the injection site     |
|                      |                               |                 |                                   |         | 18 % non-positional headache                        |
|                      |                               |                 |                                   |         | 10 % nausea                                       |
|                      |                               |                 |                                   |         | 15 Dizziness or pain at injection site or facial flushing |
| Evansa et al., 2015 [47] | Prospective randomised study  | 120 pts, 120 injections | Methylprednisolone acetate 80 mg | FL (n = 56), US (n = 56) | 1 Intrathecal injection |

**BL** blind, **CT** computed tomography, **FL** fluoroscopy, **NA** not available, **pts** patients, **RCT** randomised controlled trial, **US** ultrasound
Infarctions could occur due to damage to the blood vessels, or either to vasospasm or an emboli from particulate matter associated with the corticosteroid injection. Damage to the blood vessels could result in haematomas, and subdural and epidural haematomas have been reported [124, 135, 144, 146, 155, 162, 164]. Permanent paralysis can occur following such haematomas [145]. Direct damage to the spinal cord by trauma or direct injection of ESI medications into the cervical spinal cord has been also documented [140, 148, 160, 173]. Such a complication can

| Study, year | Design | Pts | Medications | Imaging | Complications |
|-------------|--------|-----|-------------|---------|---------------|
| Botwin et al., 2000 [53] | Retrospective cohort study | 207 pts, 322 injections | Either betamethasone 9–12 mg or methylprednisolone 80 mg | FL | 10 Non-positional headaches (3.1 %) 8 Increased back pain (2.4 %) 2 Increased leg pain (0.6 %) 4 Facial flushing (1.2 %) 1 Vasovagal reaction (0.3 %) 1 Increased blood sugar (258 mg/dL) in an insulin-dependent patient with diabetes mellitus (0.3 %) 1 Intraoperative hypertension (0.3 %) 1 Pain at injection site 5 Vascular uptake 6 Paraesthesia during procedure |
| Ahadian et al., 2011 [62] | Prospective randomised study | 98 pts, 98 injections | Dexamethasone 4, 8 or 12 mg FL | | 42 Increased pain 6 Numbness 9 Pain at injection site |
| Karaman et al., 2011 [57] | Prospective cohort study | 562 pts, 1305 injections | Triamcinolone acetonide FL | | 97 Vascular penetration (7.4 %) 8.7 % vasovagal episodes 5 Transient erectile dysfunction (0.9 %) 5 Facial flushing (0.9 %) |
| McGrath et al., 2011 [59] | Retrospective cohort study | 1667 pts, 3964 injections | NA FL | | 41 Transient pain 104 Intravascular placement of needle (7.9 %) 16 Transient nerve root irritation (4.6 %) 8 Profuse bleeding (1 %) 1 Vasovagal (0.08 %) 2 Facial flushing (0.15 %) |
| Manchikanti et al., 2012 [34] | Prospective cohort study | 1310 Injections | NA FL | | 2 Discitis |
| Cansever et al., 2012 [63] | Prospective cohort study | 153 pts | Methylprednisolone 40 mg FL | | 3 Transient weakness 14 Increased low back pain 2 Low blood pressure post-injection |
| Wewalka et al., 2012 [69] | Cohort study | 37 pts, 65 injections | Triamcinolone 40 mg CT | | 10 Intravascular placement of needle (4.6 %) 16 Transient nerve root irritation (2.8 %) 8 Profuse bleeding (1 %) 1 Vasovagal (0.08 %) 2 Facial flushing (1.1 %) |
| Koh et al., 2013 [65] | RCT | 53 pts | Triamcinolone 20 mg FL | | 1 Burning at injection site (1.9 %) |
| Manson et al., 2013 [58] | Retrospective cohort study | 91 pts, 106 injections | Triamcinolone 40 mg FL | | 2 Vasovagal episodes |
| Hong et al., 2014 [56] | Prospective cohort study | 239 pts, 249 injections | Dexamethasone 5 mg and mepivacaine 3 mL FL | | 6 Intradiscal injection |
| Manchikanti et al., 2014 [67] | RCT | 120 pts, 601 injections | Betamethasone 3 mg FL | | 28 Intravascular infiltrations (4.6 %) 9 Nerve root irritations (1.5 %) |
| Krawijwantananong et al., 2014 [66] | Prospective cohort study | 38 pts, 72 injections | Methylprednisolone 80 mg FL | | 3 Worsening of leg pain |
| Ploumis et al., 2014 [61] | Prospective cohort study | 20 pts, L4–S1 | Betamethasone 9 mg FL | | 2 Vasovagal episodes (10 %) |
| Tauheed et al., 2014 [68] | RCT | 60 pts | Methylprednisolone 60 mg FL | | 3 Transient paraesthesia of nerve distribution |

CT computed tomography, FL fluoroscopy, NA not available, pts patients, RCT randomised controlled trial
occur with an absence of pain being reported by the patient when the spinal cord structures were punctured [156]. Subdural and intrathecal spread or diffusion of the injected mixture of corticosteroids, anaesthetic and contrast dye could result in cauda equina and conus medularis syndromes, arachnoiditis, meningitis and temporary respiratory depression [139, 148, 153, 171]. Intracranial subdural haematoma after accidental dural puncture has also been presented [142]. Furthermore, cases of pneumocephalus, pneumorrhachis and cerebrospinal fluid (CSF) leak can occur [90, 94, 95, 147, 151, 153, 170]. Infections and abscesses have been also reported following ESI [108–114, 117–127, 130, 132, 133, 164]. With the exception of a fungal infection outbreak in the USA in 2012, infection rates are considered rare [109]. Infection rates vary following an epidural injection, but, on average, are reported to be one in 60,000–100,000 epidural injections [112]. The documented outbreak in 2012 was possibly caused by a contaminated glucocorticoid product used for epidural and paraspinal injection [108, 109]. In single case reports, cases of meningitis, vertebral osteomyelitis, and spinal and paraspinal abscesses have been reported that are caused by microorganisms including Aspergillus spp., Staphylococcus aureus and methicillin-resistant S. aureus [111, 113, 126]. Patients’ skin flora has been proposed to be the most common source of infection [125].

Blindness after ESI has been reported multiple times [82–84, 86, 87, 154, 167]. It has been hypothesised that this complication is caused by an abrupt rise in the CSF pressure caused by the volume of the injected pharmaceutical agents. In the cervical spine, this complication can be the result of the administration of radio contrast agents administered in the intracranial vasculature [84]. The patient’s vision returned to normal within 1 year of follow-up in some studies [82, 83], but permanent visual impairment in patients’ vision was reported by some authors [84, 86, 87, 167].

Vaginal bleeding has been reported as a potential complication of ESI [99, 101]. Sub-Burgmann et al. [116] have retrospectively reviewed 8166 ESI procedures and reported an incidence of 2.5 % (n = 201; 197 patients) for abnormal vaginal bleeding [116]. Of these women, 70 % were premenopausal and 30 % were postmenopausal. Suppression of the hypothalamic–pituitary–ovarian axis causing anovulatory cycles has been hypothesised to be the mechanism for this adverse effect [115].

Case reports have also presented other complications including iatrogenic Cushing’s syndrome [131, 166], persistent hiccups [128, 152], convulsions [129], reversible posterior leukoencephalopathy syndrome [82], epidural granuloma formation [150], subdural block [157], Brown–Séquard syndrome [159], herpes zoster outbreak [165],...
Steroid myopathy [166] and corticosteroid-induced psychosis [137] following ESI. Spinal epidural lipomatosis is a rare condition of adipose tissue hypertrophy in the epidural space and has been reported to occur after ESI [138, 143, 161]. In addition, cardiopulmonary arrest following ESI and anaphylaxis and other adverse events due to the epidural corticosteroid compounds can occur [134, 136, 149, 169, 175]. Complex regional pain syndrome and development of neuropathic pain following ESI have also occurred [158, 163].

5 Discussion

ESIs have been used for more than 60 years since Lievre et al. [180] reported the use of epidural hydrocortisone in a series of 20 patients. Over the years, their use has expanded significantly. In Medicare beneficiaries in the USA, the number of epidural injections has increased by 106.3% in the decade between 1997 and 2006 [181]. Currently, ESIs are the most common intervention performed for the management of chronic low back pain in the USA [182]. Nevertheless, their clinical need and effectiveness has been questioned by several studies [10]. Indications for ESI are not robust and the outcome could not be correlated with the extent of the underlying pathology, e.g. the degree of lumbar spinal stenosis, but could be determined by factors such as age, sex and the preceding opioid use [183–185].

Collectively, this systematic review contains data from more than 100,000 ESIs reported in prospective or retrospective studies. The reported complications were minor in the vast majority. Major events have been reported anecdotally and it is impossible to comment on their true incidence based on the available results in the literature. Overall, the potential causes of adverse events could be categorised into three distinct categories: (1) direct damage to the blood vessels or adjacent anatomical structures during the procedure; (2) intravascular administration of the injectate; and (3) a local or systemic reaction including bacterial contamination.

Direct damage to the blood vessels or adjacent structure is an inherent risk for any injection, including ESIs. Direct damage to the spinal cord by the needle and the injection of corticosteroids into the cervical spinal cord has been also documented in a very limited number of case reports. Clinically significant haematomas derived from piercing or damage to the blood vessels can occur and the reported incidence for all epidurals is less than one in 150,000. This complication is increased in patients with coagulopathy and patients on anticoagulant medications [186–188]. Inadvertent dural punctures can occur after ESIs and CSF flashback is pathognomonic of this complication. Other complications, including intracranial subdural haematoma after accidental dural puncture and cases of pneumocephalus, pneumorrhachis and CSF leak, have been presented in case reports [90, 94, 95, 98].

Intravascular injection of the corticosteroids, carrier and/or the local anaesthetic could account for the large majority of the serious adverse effects. The reported incidence of inadvertent intravascular injection with fluoroscopically guided TESI is reported to range from 9% to as high as 32.8% [25, 189–192]. This incidence is related to the level at which the injection is performed. Furman et al. [25, 189] reported an incidence of fluoroscopically confirmed intravascular penetration of 19.4% for cervical TESIs, 8.1% for lumbar TESIs and 21.3% for TESIs at the S1 level. In addition, Sullivan et al. [192] suggested that intravascular uptake is twice as likely to occur in patients over rather than under 50 years of age [192]. Vascular embolic events from intra-arterial injection of particulate corticosteroids have been found to account for serious complications including spinal cord infarction, paraplegia and death [93, 100, 102, 103, 105]. Houten et al. [102] presented three cases of paraplegia which ensued suddenly after instillation of the corticosteroid solution in the artery of Adamkiewicz. Similar cases have been reported by others [34]. It should be mentioned that intra-articular injections pose a higher degree of danger, while venous uptake has been considered benign [193, 194]. In terms of the injectate, medium-sized particles between 51 and 1000 µm have the potential to enter and occlude a blood vessel [195]. Smaller particles (10–50 µm) may still be able to occlude capillaries [195]. Irrespective of the size, it has been suggested that when corticosteroid particles enter a blood vessel they could coalesce and precipitate, forming larger particles [195]. Non-particulate corticosteroids are soluble and should not cause embolic infarction. The injection of the particulate corticosteroid methylprednisolone into the vertebral artery of four pigs resulted in permanent loss of consciousness, while the animals receiving dexamethasone and prednisolone recovered fully [194]. Dawley et al. [193] demonstrated that methylprednisolone and its non-particulate carrier can produce significant injury to the blood–brain barrier when injected intra-arterially. The authors also suggested that in addition to the cerebral microvasculature occlusion by the particulate corticosteroids, damage can occur via toxicity of the carrier or the corticosteroid. Based on several observations that failed to highlight any difference in the efficacy of particulate and non-particulate corticosteroids, we would recommend the use of soluble non-particulate agents [196–198].

The local anaesthetic, corticosteroid or carrier can cause local and systemic reactions. Blockage of the neural elements by the local anaesthetic can occur. A transient blockage of the neural conduction is expected; however, the reported central canal, conus medularis and cauda
equiná syndrome must have an underlying cause, i.e., hematoma, infarct, etc. Transient systemic reactions including headaches, vasovagal reactions and facial flushing have been reported; these reactions occurred shortly after the ESI and could represent a reaction to the injected analgesic agents and/or corticosteroids. It is rather unclear whether ESIs pose a long-term risk of certain conditions and whether a cumulative effect of prolonged exposure exists. If that is true, epidural corticosteroids could have similar systemic effects to that of long-term corticosteroids administered through other routes. For instance, a significant number of the patients with chronic back pain conditions are treated with repeated injections over prolonged period of time. Corticosteroids are known to interfere with calcium homeostasis, reducing bone formation and increasing bone breakdown. Osteoporosis and an increased fracture risk could theoretically occur; however, the available literature does not support this theory. Manchikanti et al. [199] prospectively evaluated 100 patients receiving epidural injections and reported no change in bone mineral density. Insulin resistance is another adverse effect associated with corticosteroid administration; however, studies looking specifically at patients receiving ESIs did not find any changes in the fasting glucose levels [200, 201]. Hypothalamic–pituitary–adrenal axis suppression has been demonstrated to occur after ESIs [200, 202]. Maillefert et al. [200] showed that following ESI with dexamethasone a profound decrease in the serum levels of adrenocorticotropic hormone (ACTH) occurs. These levels of ACTH returned to normal 3 weeks after the injection [200]. Hypertension can also occur following ESIs; a mean systolic blood pressure increase of 5 mmHg has been previously reported following ESIs [201]. Finally, corticosteroid administration represents a risk factor for wound complications postoperatively and poses an increased risk for infections [203]. ESIs are frequently performed prior to spinal surgery, either as a diagnostic tool or for pain management, but their contribution to complications of such procedures is currently unknown.

Severe infections are rare after spinal injections and have an incidence of 0.1–0.01% [188]. The only exception is a fungal infection outbreak in the USA in 2012. According to the Centers for Disease Control and Prevention, 25 deaths due to epidural corticosteroid-related meningitis (many due to Aspergillosis) were identified; 337 patients were affected in 18 US states and 14,000 patients were probably exposed to contaminated corticosteroids [186].

In the authors’ opinion, several recommendations can be made with the aim of minimising the incidence of major complications after ESIs. First, ESIs should be performed under fluoroscopic guidance and the needle position should be confirmed in at least two planes, typically anteroposterior and either an oblique or lateral plane. Intravascular penetration has been the primary concern related to ESIs. Aspiration prior to the injection is specific but not sensitive at detecting intravascular needle placement, being unable to produce a flashback of blood in 74% of cases in which the needle was ultimately determined to be intravascular [192]. Injection of contrast media is recommended and operators must be able to distinguish between intravascular, epidural and subdural contrast flow patterns. The use of a blunt needle and the suggestion that a small ‘test’ dose of the medication should be injected initially has been proposed [204–207]. Fluoroscopy can detect unintentional vascular injections [208]. Dynamic live fluoroscopy was found to perform better than static intermittent fluoroscopy, which was found to miss 57% of the intravascular injections [208]. Digital subtraction angiography can be used as a radiologic adjunct to identify vascular compromise during the injection. However, in a case report by Chang et al. [80], an anaesthetic test dose and digital subtraction angiography performed twice did not prevent a catastrophic spinal cord infarction and the resultant paraplegia. It is under debate whether the transforaminal route poses a higher risk of serious complications when performed by an experience physician. Given the lack of evidence, one could argue that it is reasonable to consider the transforaminal approach only when the interlaminar route has failed. Finally, informed consent should be taken and the patient should be aware of the potential risk and benefits of this procedure.

The survey of cervical injections conducted by Scanlon et al. [41] is the only manuscript that presents a high number of serious and fatal cases. Possible mechanisms explaining these events include the intra-arterial injection of particulate corticosteroid or trauma causing embolisation to the distal basilar or vertebral arteries. Despite the fact that the study presents the extreme end of potential complications, it is unclear what the true incidence of these events is. As previously mentioned, it would be of enormous educational interest to have further details regarding these events, especially details of the technique and imaging used as well as the training and experience of the physician [209].

The warning issued by the FDA regarding ESIs merits further discussion and analysis, and the use of corticosteroids for injections in the epidural space for spinal pain syndromes is not FDA approved. The FDA mentions that, despite their use, the effectiveness of ESIs has been challenged and could potentially result in serious adverse events including death, stroke and paralysis. In support of these arguments, the FDA has published several case reports. Major adverse events can occur with ESIs, but such events are rare, their true incidence is unknown and they have only been presented in case reports. For instance, none of the studies included in Tables 1, 2 and 3 presents
such major devastating complications. Thus, several authors have criticised the FDA’s warning statement as inaccurate. Of note is Manchikanti et al. conclusion stating that the FDA’s warning is an additional burden on patient access to pain-relieving treatments [210]. Should the FDA’s warning letter be replaced by an evidence-based educational guidance to safeguard the best clinical practice?

Several limitations can be found in the available literature. A large proportion of the available case reports and studies provide insufficient documentation, i.e. the approach used for ESI, symptom duration, volume injected or even the number of injections. In addition, the majority of the studies report adverse effects incidentally as their main aim is to report the efficacy of the injections. Furthermore, the available studies were heterogeneous with regards to the outcome measures, and in several manuscripts the surgical technique, corticosteroid dosage and the addition of other medications are not reported. It is of note that many studies did not look at or record the complications or adverse effects of corticosteroid exposure but present results from several pain and functional scores. Therefore, it is possible that both the short- and long-term adverse effects of corticosteroid exposure remain unreported. As previously highlighted, there is a risk of bias.

6 Conclusions

ESIs are relatively safe; however, although major complications of ESIs have been reported, their true incidence remains obscure. Vascular penetration and administration of pharmaceutical agents intra-arterially could account for a large proportion of the adverse events reported. With accurate placement of the needle, use of non-particulate corticosteroids, live fluoroscopy, digital subtraction angiography and familiarisation of the contrast patterns on fluoroscopy these risks should be minimised. Further research is required to shed more light on the best clinical practice for the use of ESIs and the true incidence of complications relating to them.

Compliance with Ethical Standards

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