ANESTHESIA & PAIN MEDICINE

Anesth Pain Med 2021;16:16-27
https://doi.org/10.17085/apm.21002
pISSN 1975-5171 • eISSN 2383-7977

Review

Safety of epidural steroids: a review

Min Soo Lee and Ho Sik Moon

Department of Anesthesiology and Pain Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Received January 1, 2021
Revised January 18, 2021
Accepted January 18, 2021

Corresponding author
Ho Sik Moon, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 1021 Tongil-ro, Eunpyeong-gu, Seoul 03312, Korea
Tel: 82-2-2030-3864
Fax: 82-2-2030-3861
E-mail: mhsjshcat@catholic.ac.kr

Spine disease is one of the most common musculoskeletal diseases, especially in an aging society. An epidural steroid injection (ESI) is a highly effective treatment that can be used to bridge the gap between physical therapy and surgery. Recently, it has been increasingly used clinically. The purpose of this article is to review the complications of corticosteroids administered epidurally. Common complications include: hypothalamic-pituitary-adrenal (HPA) axis suppression, adrenal insufficiency, iatrogenic Cushing's syndrome, hyperglycemia, osteoporosis, and immunological or infectious diseases. Other less common complications include psychiatric problems and ocular ailments. However, the incidence of complications related to epidural steroids is not high, and most of them are not serious. The use of nonparticulate steroids is recommended to minimize the complications associated with epidural steroids. The appropriate interval and dosage of ESI are disputed. We recommend that the selection of appropriate ESI protocol should be based on the suppression of HPA axis, which reflects the systemic absorption of the corticosteroid.

Keywords: Drug-related side effects and adverse reactions; Epidural injections; Glucocorticoids; Guideline; Review; Safety.

INTRODUCTION

Corticosteroids are very attractive as drugs for many musculoskeletal diseases because of their potent anti-inflammatory effect. Epidural steroid injection (ESI) is widely used to treat various back pain conditions such as herniated intervertebral disc and spinal stenosis. Corticosteroids have been used to treat spinal diseases for a long time. Initially, they were delivered into intrathecal space in 1954 [1]. However, because of the transient pharmacological effect, the injection route of corticosteroids was changed into epidural space. Several studies have supported the efficacy of ESI in spinal disease [2–4]. Transforaminal epidural steroid injection (TFESI) is used to relieve pain and reduce the potential need for surgery [5,6]. Radicular pain is caused not only by mechanical compression but also due to inflammation of the affected nerve roots because the nucleus pulposus of the intervertebral disc evokes an immune reaction mediated via inflammatory molecules [7]. Thus the rationale for using corticosteroids in epidural block is established [8].

The complications associated with corticosteroid use are as many as their therapeutic effects. However, most complications related to ESI are not serious. Lee et al. [9] analyzed 52,935 ESI procedures performed in 22,059 patients and found no major adverse events. Similarly, no major adverse events were detected in another single-center study of 1,300 lumbar transforaminal epidural injections. Kang et al. [10] surveyed complications of 825 patients who were treated with dexamethasone epidurally. Forty patients (4.8%) showed systemic but minor and transient side effects of corticosteroids including facial flushing (1.5%),

urticaria (0.8%), and insomnia (0.8%). Serious complications such as adrenal insufficiency (AI), Cushing's syndrome, neurological accidents, and osteonecrosis have been reported rarely [11,12]. Because these complications cause irreversible sequelae, pain physicians need to be cognizant of the side effects of corticosteroids and their prevention.

ESI is a valuable procedure used to treat spinal pain. Although systemic side effects of treatment with long-term oral administration of steroids are well established, the pharmacology and side effects associated with ESI are poorly understood. This review summarizes the complications of epidural steroids and techniques as well as related mechanical injury.

PHARMACOLOGIC PROPERTIES OF EPIDURAL STEROIDS

Pathophysiology of radiculopathy

Radiculopathy is caused by inflammation and the mechanical compression of the nerve root. Inflammation plays a major role in the evolution of radiculopathy [13]. Clinically, a large herniation of an intervertebral disc associated with significant neural compression may be asymptomatic, whereas severe radicular pain may exist without detectable root compression. Also, the size or shape of herniation, and eventual change in size or shape does not correlate with clinical presentation or course [14,15]. This shows the importance of inflammation in the pathophysiology of radiculopathy. The damaged structures release various inflammatory mediators, which trigger inflammatory reaction in the spine. For instance, the damaged facet joints release bradykinin, serotonin, norepinephrine, and interleukin (IL)-1. Also, the nerve endings of the posterior longitudinal ligament, outer annulus, facet capsule, or periosteum release substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide. The nucleus pulposus generates inflammatory mediators, including phospholipase A2 (PLA2), prostaglandin E2, IL-1α, IL-1β, IL-6, tumor necrosis factor, and nitric oxide, and it is well known that discogenic pain is mediated by these inflammatory mediators and neovascularization induced by chemical signaling [8,16]. PLA2 is the rate-limiting factor involved in the synthesis of arachidonic acid, which is the principal substrate in the cyclo-oxygenase and lipo-oxygenase pathways. Prostaglandins, along with other arachidonic acid byproducts, can cause or exacerbate pain mediated via inflammatory mechanisms and sensitization of peripheral nociceptors [17,18]. Among the inflamed structures, the dorsal root ganglion is more sensitive to mechanical pressure than the nerve root [16].

Rationale for the use of epidural corticosteroids in radiculopathy

The therapeutic effects of corticosteroids in radiculopathy are yet to be fully understood. Until now, several mechanisms have been proposed: inhibition of leukocyte function; alleviation of inflammatory events such as edema, fibrin deposition, capillary dilatation, leukocyte aggregation, phagocytosis, capillary and fibroblast proliferation, collagen deposition and cicatrization; inhibition of the synthesis of pro-inflammatory substances like PLA2; inhibition of the activity of lymphokines; inhibition of the display of chemotactic molecules on the surface of the endothelial cells; and minimization of endothelial injury [16]. In addition to their anti-inflammatory effects, corticosteroids may inhibit pain via suppression of ectopic discharges from injured nerves and decreased conduction in normal unmyelinated C fibers [19].

Pharmacokinetics of epidural steroids

The elimination half-life of triamcinolone acetonide 80 mg following interlaminar epidural injection is 506 ± 255 h, and the time to maximum concentration (T_{max}) is 37.5 ± 37.5 h [20]. These pharmacokinetic properties of epidural steroids vary depending on the route of administration. The elimination half-life after oral, intravenous, intraarticular, and intravitreal injection of triamcinolone varies: oral, 2.6 h [21]; intravenous, 2.0 h [21]; intraarticular knee injection, 77–154 h [22]; and intravitreal, 446 h [23]. The differences between oral/intravenous and intraarticular/intravitreal/epidural administration of triamcinolone appear to be due to its particulate form. Interestingly, in the case of cervical interlaminar epidural injection with triamcinolone acetonide 80 mg, the elimination half-life was 310 ± 212 h and T_{max} was 22.8 ± 13.1 h, which was shorter than that of lumbar ESI due to the cervical epidural vasculature [24]. Current evidence suggests that more soluble glucocorticoids have shorter duration of systemic effect than less soluble glucocorticoids [25]. Intramuscular administration of dexamethasone is followed by partial absorption into the

systemic circulation and the biological half-life of dexamethasone is 5.2 ± 0.4 h [26]. Unfortunately, there has been no study on the pharmacokinetic features of epidural dexamethasone, and further research is required.

ENDOCRINOLOGICAL COMPLICATIONS

HPA axis suppression, AI, and iatrogenic Cushing's syndrome

Glucocorticoids are synthesized in the adrenal cortex under the regulation of the HPA axis. They are produced on demand and not stored in body. The glucocorticoid synthesis is inhibited by three mechanisms. First, the rapid feedback (less than 10 min) is sensitive to changes in circulating glucocorticoids and not to the absolute levels of steroid. Second, early delayed feedback (30 min to 2 h) is associated with the suppression of adrenocorticotropic hormone (ACTH) synthesis, which is affected by the concentration of circulating glucocorticoids. Third, late delayed feedback (about a day) is related to high concentration of glucocorticoids, persisting for days or weeks [27].

HPA axis suppression occurs in most of the patients who receive ESI, and most of them recover within 2–4 weeks [28–32]. This complication is likely to be asymptomatic and does not require treatment in most cases. Studies involving orally administered corticosteroids have shown that the treatment dose or duration is not correlated with the severity of HPA axis suppression and reported substantial individual variation in clinical effects depending on age and co-existing disease [33]. However, the results of ESI differed from the effects of oral corticosteroid intake. Sim et al. [30] conducted a randomized controlled trial comparing the HPA axis suppression under different dosages of epidural triamcinolone (40 mg vs. 20 mg) and showed that the HPA suppression in the triamcinolone 40 mg group (19.7 ± 3.1 days) was longer than in the group treated with triamcinolone 20 mg (8.0 ± 2.4 days), and the recovery rate of the triamcinolone 40 mg group was lower than in the triamcinolone 20 mg group (P = 0.015). However, the extent of HPA axis reduction, i.e., the difference between salivary cortisol (SC) concentration before ESI and SC concentration on day 1 after ESI was not affected by the dosage of corticosteroid [30]. The type of corticosteroid also affects the HPA axis suppression. Friedly et al. [25] reported that HPA axis suppression was more likely with longer-acting insoluble corticosteroid formulations such as methylprednisolone or triamcinolone than betamethasone and dexamethasone. However, patient demographics did not influence the duration of HPA axis suppression [25].

Secondary AI is known as a rare disease (0.00015–0.00028%) [34]. Its mortality is two-fold higher than in general population, which is associated with infection or adrenal crisis [34]. The common symptoms of AI are fatigue, loss of appetite, weight loss, nausea, vomiting, abdominal pain, and muscle and joint pain, which are nonspecific and therefore do not facilitate easy diagnosis. Moreover, specific symptoms such as hyperpigmentation, salt craving, and postural hypotension are uncommon in AI induced with exogenous glucocorticoids because of intact mineralocorticoid axis [35]. Therefore, an early diagnosis of iatrogenic AI is challenging for physicians. Park et al. reported that 11.8% of patients who were treated with long-term ESI beyond 6 months developed secondary AI, although they did not show AI symptoms [28]. The average number of ESIs per year in the AI group was 7.7 ± 1.3/yr and in the Non-AI group was 7.4 ± 3.3/yr.

The risk of iatrogenic Cushing's syndrome after ESI is unknown. No well-controlled study about its incidence after ESI is available, and only several cases have been reported [36–38]. Interestingly, a few cases were associated with ritonavir treatment of patients with human immunodeficiency virus [37,38]. Park et al. [28] reported that none of the 18 subjects who were treated long-term with ESI beyond 6 months manifested iatrogenic Cushing's syndrome. The authors used the late-night salivary cortisol (LNSC) test, which is usually performed between 23:00 and 24:00, and is known to be very sensitive and specific for the diagnosis of Cushing's syndrome [39]. Sim et al. [30] also conducted an LNSC test in 30 subjects who received triamcinolone acetate 40 mg or 20 mg and showed the absence of iatrogenic Cushing's syndrome in either group.

Effects on glucose metabolism & hyperglycemia

Glucocorticoids decrease insulin sensitivity and peripheral glucose uptake as well as hepatic gluconeogenesis. Hyperglycemia may be one of the annoying side effects after ESI, especially in patients with diabetes.

In a study by Ward et al. [40], 10 healthy volunteers were administered 80 mg of triamcinolone (equivalent to dexamethasone 16 mg) via caudal ESI. Fasting insulin and glucose levels rose significantly one day after ESI and returned to normal by 1 week. In a study of patients receiving ESI or

glenohumeral joint injection, serum glucose was elevated for approximately 1 day [41]. Maillefert et al. [42] followed nine healthy subjects for 21 days after a single epidural injection of dexamethasone 15 mg and found no changes in fasting glucose. These studies dispute the hypoglycemic effect of ESIs in healthy individuals.

ESIs appear to have a greater effect on glucose control in diabetics. Diabetic patients may have significantly reduced cytochrome p450 3A4 expression and activity [43]. Thereby, a decreased clearance of glucocorticoids and increased duration of systemic side effects are observed. Gonzalez et al. [44] followed 12 patients with diabetes after epidural injection of betamethasone 12–18 mg via transforaminal and caudal route and reported statistically significant elevations in blood glucose levels in diabetic subjects. This effect peaked on the day of the injection and lasted approximately 2 days. A study of 100 patients with pre-existing diabetes by Kim et al. [45] reported that ESIs were associated with significant elevations in postprandial blood glucose in diabetic patients for up to 4 days after the procedure. The higher dose of triamcinolone increased the glucose levels greater than the lower dose regardless of pain control, employment status, or clinical outcome. Thus, they recommended lower doses in patients with diabetes [45]. Based on the above studies, the elevation in blood glucose among diabetic subjects was observed for two to three days following ESI, and therefore diabetic patients are advised to control their blood sugar levels tightly until three days after the procedure.

Effects on bone metabolism & osteoporosis

In general, corticosteroid therapy results in bone loss and osteoporosis, which could be a challenge, especially in postmenopausal women. Corticosteroids affect bone remodeling by increasing bone resorption via apoptosis of osteocytes and enhanced osteoclast activity. Many studies have investigated bone mineral density (BMD) in patients taking oral corticosteroids. However, orally administered corticosteroids exhibit different absorption characteristics and effects compared with those associated with epidural injections. Therefore, a direct comparison between the two is difficult.

Dubois et al. [46] reported the absence of a relationship between cumulative epidural steroid dose and BMD in healthy men and women pretreated with at least 3 g of methylprednisolone. However, in postmenopausal women, an ESI with triamcinolone 80 mg induced a significant decrease in hip BMD at 6 months compared with baseline ($P = 0.002$) and an age-matched control group ($P = 0.007$) [47]. Similarly, Kim and Hwang [48] reported a retrospective study in which multiple ESIs with an approximate cumulative dose of triamcinolone 400 mg reduced hip BMD in postmenopausal women. The average duration between the first and last ESIs was 34.4 ± 2.6 months. The risk of osteoporotic fracture appears to increase due to ESI. Mandel et al. [49] conducted a large retrospective cohort study comparing 3,415 patients who received at least one ESI with 3,000 patients who did not receive any ESI. ESI increased the risk of fractures by a factor of 1.21 (95% confidence interval, 1.08–1.30) after adjustment for covariates ($P = 0.003$). Therefore, physicians should keep in mind that ESI increases the risk of osteoporosis and fracture in postmenopausal women.

Abnormal uterine bleeding

Abnormal uterine bleeding (AUB) is not infrequent in women treated with ESI. The incidence of AUB in women (70% premenopausal and 30% postmenopausal) who received ESI was 2.5% of 8,166 ESIs [50]. However, the exact relationship between AUB and ESI was not revealed exactly and sex hormone levels after ESI have yet to be measured. In the case of intra-articular injection, corticosteroid therapy induces a temporary, but considerable suppression of sex hormone secretion [51].

IMMUNOLOGICAL/INFECTIOUS COMPLICATIONS

Immunosuppression and infection

Immunosuppression is one of the most serious side effects associated with iatrogenic corticosteroid use. Corticosteroids suppress inflammatory genes, upregulate anti-inflammatory genes, decrease the production of proinflammatory cytokines, and inhibit phagocyte function [52]. Preoperative intra-articular corticosteroid injection is associated with an increased risk of postoperative periprosthetic infection [53]. Preoperative ESI also appears to be related to infection after spine surgery. The overall rate of postoperative infection related to single-level lumbar decompression after ESI was reported to vary between 0.8% and 1.7%, which was more common within 1 month and 1–3 months

before surgery than within 3–6 months and 6–12 months before surgery [54]. Therefore, the optimal interval between the last preoperative ESI and surgery should be at least 3 months to prevent postoperative infection. Singla et al. [55] also reported similar results suggesting that preoperative ESI within 3 months of lumbar fusion was associated with an increased rate (1.6%) of postoperative infection in a retrospective cohort of 88,540 patients.

Allergic reaction & anaphylaxis

Despite the anti-inflammatory and anti-allergic effects of corticosteroids, no systemic hypersensitivity was detected, paradoxically [56]. The allergic reactions or hypersensitivity usually occur due to exposure to preservatives or steroids. The incidence of anaphylaxis was 0.5% in the study of patients injected with intravenous corticosteroids [57]. However, no study analyzed the incidence of anaphylaxis in patients using epidural corticosteroids except in a few cases. Most of the cases are associated with triamcinolone or methylprednisolone treatment and symptoms include sneezing, angioedema, tachycardia, marked hypotension, itching, redness, and peri-orbital edema [58–60].

Facial flushing is a common side effect of ESI, and is associated immunoglobulin E and histamine-mediated reaction [61]. Most types of corticosteroids used in ESI cause facial flushing. Cicala et al. [61] reported that 9.3% of patients who received cervical ESI with methylprednisolone acetate manifested facial flushing. In the retrospective cohort study of Kim et al. [62], the overall incidence of facial flushing was 28% among 150 subjects who received ESI with 16 mg of dexamethasone. In this study, the female subjects were vulnerable to facial flushing (64%) and all cases of flushing were resolved within 48 h.

MISCELLANEOUS COMPLICATIONS

Psychiatric complications

Corticosteroid-induced psychiatric complications are not infrequent. Wada et al. [63] reported that corticosteroid-induced psychiatric syndrome including depression, mania, psychosis, and delirium occurred in 0.87% of 2,069 patients (15 patients with a mood disorder and 3 patients with a psychotic disorder), who showed a relatively good outcome with full remission within 1–3 months. However, the pathophysiology of this complication was not clear. Corticosteroid is suggested to affect dopaminergic or cholinergic systems, reduce serotonin release, and induce toxic effects in the hippocampus or other brain regions [64]. Most of the studies involved oral or intravenous administration of corticosteroid, but not ESI. Benyamin et al reported a case of a 67-year-old male who received multiple corticosteroid injections including ESI, and developed psychotic symptoms such as racing thoughts, anger, agitation, pressured hyper-verbal speech, and paranoia, which spontaneously resolved in 7–10 days [65].

Ocular complications

Corticosteroid therapy can increase intraocular pressure (IOP), which is known as steroid-induced ocular hypertension, steroid-induced glaucoma (SIG), and at worst blindness. The prevalence of SIG is not reported yet, but non-responders to corticosteroid was accounted for 61–63% (IOP elevation < 5 mmHg), moderate responders 33% (IOP elevation ranging 6 to 15 mmHg), and high responders constituted 4–6% (IOP elevation > 15 mmHg) [66]. However, these results are based on corticosteroid administration through the topical, intraocular, periocular, oral, intravenous, inhaled, nasal, and transcutaneous routes. A single case report involved a patient who experienced sudden bilateral blurred vision due to increased IOP after ESI, warranting immediate ophthalmic intervention. The symptom resolved within three and one half months [67]. In addition, a few case reports involved other ophthalmological complications such as retinal venous hemorrhage, amblyopia, transient bilateral vision defect, central serous chorioretinopathy, and subcapsular cataracts after ESI [68,69].

Steroid-induced myopathy

Steroid-induced myopathy is a rare complication characterized clinically by proximal lower extremity weakness, normal creatine kinase, normal electromyogram, and loss of type IIa fibers [52]. There is no research or case report on steroid-induced myopathy associated with ESI. Therefore, further research is needed to address this problem.

Epidural lipomatosis

A few case reports suggest epidural lipomatosis, which is characterized by excessive accumulation of unencapsulated fat in the spinal canal [70–72]. This complication is usu-

ally associated with long-term ESI and can cause symptoms of spinal cord or nerve root compression. The prognosis of epidural lipomatosis is not good. Two of the cases required spine surgery [71,72].

MISCELLANEOUS ISSUES FOR SAFE ESI

Corticosteroids: particulate vs. nonparticulate steroids

The corticosteroids for ESI are divided into particulate (triamcinolone and methylprednisolone) and nonparticulate (dexamethasone and betamethasone) formulations. Several cases of spinal cord ischemia after ESI have been reported since they were first described in 2002 by Houten and Errico [73]. Reports of spinal cord ischemia, paralysis, permanent blindness, and death after ESI have raised concerns about the potential embolization of particulate corticosteroids. Proposed mechanisms include direct injury to the spinal arteries and embolization. Specifically, the transforaminal approach entails needle insertion in close proximity to the spinal cord arteries. Inadvertent arterial injection of a particulate corticosteroid may result in embolic infarction and subsequent permanent neurologic compromise. Recent investigations demonstrate an alternative mechanism of injury. Several particulate steroids have been shown to exert immediate and massive effect on microvascular perfusion in a mouse model via formation of red blood cell (RBC) aggregates associated with the transformation of RBCs into spiculated RBCs [74,75].

However, dexamethasone does not form particles or aggregates large enough to cause an embolism, based on published case reports of paraplegia, quadriplegia, or stroke following ESI [74]. However, a mixture of dexamethasone or betamethasone and ropivacaine induced a pH-dependent crystallization in vitro [76,77]. In 2011, the Food and Drug Administration (FDA) required a label change for triamcinolone, stating that it should not be used for ESI. Nonetheless, particulate steroids continue to be used because of a theoretical advantage of pain relief secondary to delayed clearance from the spinal canal [78]. Three randomized studies investigated the effectiveness of different steroid preparations. Two studies reported no evidence that nonparticulate steroids such as dexamethasone at 10 mg were less effective than particulate steroids such as methylprednisolone, triamcinolone, or betamethasone in lumbar TFESI [79,80]. Conversely, Park et al. [81] reported that the nonparticulate steroid dexamethasone was statistically less effective than the particulate steroid in terms of pain relief. In 2020, Donohue et al. [82] reported that there was no significant difference in pain relief at any point between nonparticulate and particulate steroids and recommended the use of nonparticulate corticosteroids in ESI given the safety concerns associated with particulate corticosteroids. Considering the potential risk of catastrophic complications, nonparticulate steroid preparations should be considered as first-line agents when performing ESI. Further studies are necessary to compare corticosteroid preparations.

Optimal interval and dosage of ESI

Unfortunately, there is no definite consensus on what constitutes the appropriate regimen of ESIs, and little information concerning recommendations or practice guidelines is available to date. A significant variation in dose, frequency, and ESI interval was attributed to physician preference. In a survey conducted by Vydra et al. [2], most physicians (56.0%) preferred 10 mg of dexamethasone for ESI, followed by 8 mg (12%), 4 mg (9%), 15 mg (8%), 20 mg (6%), 6 mg (6%), and 12 mg (3%). Also, many of the doctors (40%) allowed 4 ESIs annually, followed by 3 (29%), 6 (17%), 5 (6%), 2 (3%), 8 (2%), 10 (2%), 9 (1%), and > 10 injections (1%) [2]. Kim et al. [83] published a survey of 122 pain centers adopting the current ESI regimen. More than half (55%) of Korean pain physicians used dexamethasone for ESIs. The minimum interval of subsequent ESIs is 3.1 weeks at academic institutions and 2.1 weeks at private pain clinics [83].

Determining the optimal steroid dose, duration, and interval for ESIs is essential to develop a treatment protocol with minimal complications without compromising the treatment effectiveness. Above all, a consensus is needed to determine the major complications associated with steroids indicating limited corticosteroid use. Rare complications, such as epidural lipomatosis, steroid-induced myopathy, and iatrogenic Cushing's syndrome or complications that are patient-specific such as allergic reactions cannot be used as a criterion for limited ESI use. Most epidural steroid complications are associated with systemic absorption of corticosteroids, which is reflected by HPA axis suppression. The HPA axis suppression as an indicator of a ESI limitation has several advantages. First, it is observed in all patients who receive ESI [28,30–32]. Second, the recovery

curve of HPA function after ESI is similar to that of the elimination of epidurally injected steroid [20,24]. Third, it represents a dose-response relationship, which provides important information about minimal dosage of epidural steroids [30]. Finally, the recovery of HPA axis function is closely related to AI, one of the serious complications of ESI [28].

Before discussing appropriate ESI interval, physicians should consider the need to repeat ESI multiple times. Repeated ESIs within 3 months provide cumulative benefit [84]. If multiple ESIs are considered, an appropriate interval between ESIs should be decided based on the average duration of HPA axis suppression after ESI without affecting the physiological restoration. Another rationale for an appropriate interval is to wait until the peak effects of epidural steroid treatment are detected to avoid needless additional ESI [85]. Chon and Moon [31] reported that the HPA axis suppression period after ESI with triamcinolone 40 mg was 19.9 ± 6.8 days, which was similar to that of Sim et al. [30] (19.7 ± 3.1 days). Accordingly, the minimum recommended interval between ESIs using triamcinolone 40 mg might be 3 to 4 weeks for safety. The HPA axis suppression period is affected by the dose of epidural steroid administered. In the study of Sim et al. [30], the HPA suppression period after the epidural injection of triamcinolone 20 mg was 8.0 ± 2.4 days. Therefore, the smaller the dose of epidural steroid, the closer is the ESI minimum interval. The type of corticosteroid also affects the duration of HPA axis suppression. Friedly et al. [25] reported that particulate corticosteroids such as methylprednisolone and triamcinolone showed relatively longer HPA axis suppression than the non-particulate forms like betamethasone and dexamethasone. In the case of methylprednisolone and triamcinolone, the HPA suppression lasted an average of 3 weeks; however, the serum cortisol concentrations following 3-week treatment with betamethasone and dexamethasone was not significantly different from the control group. Similarly, Chutatape et al. [86] reported that epidural dexamethasone 8 mg decreased both ACTH and serum cortisol concentrations below 7 days. These results may be associated with the characteristics of the particulate steroid formulations, suggesting that long-acting and insoluble types can cause sustained systemic absorption of the corticosteroid. In summary, multiple ESIs using particulate steroid require sufficient interval of about 3–4 weeks because of long-lasting HPA axis suppression, while non-particulate steroids require shorter periods.

The types of corticosteroids, treatment effectiveness and duration, and the incidence of complications should be considered to determine the optimal dosage of ESI. In the case of oral corticosteroid intake, a multidisciplinary European League Against Rheumatism (EULAR) task force group of experts recommended that the risk of long-term corticosteroid therapy depended on dosage: treatment with less than 5 mg prednisone equivalent per day had low risk, whereas patient-specific characteristics should be considered between 5 mg and 10 mg/day, and levels greater than 10 mg/day could increase the risk of harm [87]. However, in the case of ESI, it is controversial whether there is a relationship between systemic complications and the dosage of corticosteroids. Habib et al. [88] conducted a randomized, single-blind, controlled trial that showed no significant difference between the two ESI doses of methylprednisolone (80 mg and 40 mg) in terms of the rate of secondary AI (P = 0.715) at 3 weeks, except for the visual analog scale (VAS) (P = 0.049) at 3 weeks. However, in the double-blind, randomized controlled trial of Sim et al. [30], there was a significant difference between ESIs with 40 mg and 20 mg doses of triamcinolone in terms of HPA suppression period (19.7 ± 3.1 days vs. 8.0 ± 2.4 days, P = 0.0005) and the slope in the linear mixed-effects model denoting the recovery rate of HPA axis (0.00431 ± 0.00043 vs. 0.00647 ± 0.00069, P = 0.015) at 4 weeks. However, there were no differences in VAS (P > 0.99) and AI incidence (P = 0.220) at 4 weeks between the two groups in Sim's study.

The World Institute of Pain (WIP) Benelux working group recommended that the number of ESIs should be adjusted according to the clinical response, suggesting that a 2-week interval for additional ESI may be appropriate for proper evaluation and minimization of endocrine side effects, and the lowest effective dose should be used for ESI (40 mg for methylprednisolone, 10 to 20 mg for triamcinolone acetate, and 10 mg for dexamethasone phosphate) [68].

ESI for a pregnant or breastfeeding patient

Approximately 50% of pregnant women experience low back pain. Despite its prevalence, low-back pain (LBP) in pregnancy is considered normal by many patients and physicians. Also, safe treatment options in pregnancy are still disputed. Concerns regarding maternal and fetal well-being restrict the use of interventional treatment regimens by pain physicians, resulting in a higher incidence of obstetric complications.

Sehmbi et al. [89] reviewed 56 studies investigating management strategies for LBP in pregnancy. According to this review, three case reports involved ESI to alleviate symptoms of LBP, but all pregnant patients eventually required operative intervention due to recurrence or progression of neurological symptoms. In brief, there is weak evidence supporting the analgesic and surgery-delaying effect of ESI in pregnant patients with LBP, which is consistent with observations involving non-pregnant patients. Although a single dose of epidural steroid appears to be associated with a low risk to the fetus, it is recommended that ESI should be reserved for pregnant patients with new onset of signs or severe symptoms of lumbar nerve root compression before surgery.

The use of ESI during breastfeeding has yet to be investigated comprehensively. The secretory function of prolactin in humans is sensitive to changes in the activity of the HPA axis in a dose-dependent manner [90]. McGuire reported a case of 35-year-old mother treated with ESI and facet joint injection with triamcinolone 80–120 mg resulting in temporary reduction of lactation [91]. Although a detailed study is needed, patients should be informed that the amount of breast milk may decrease from day 3 to day 9 after ESI. Karahan et al. [92] reported that methylprednisolone concentrations in breast milk and maternal serum following high-dose (1,000 mg) methylprednisolone IV pulse therapy showed a similar trend at all time points. Eight hours after the injection, the concentrations of methylprednisolone in the milk and maternal serum were low; the transfer of methylprednisolone into breast milk is low. They recommended that mothers need to wait for 2–4 h to further limit the level of exposure although the risk to the infant seems low. Currently, no information on the effect of epidural steroids on breast milk or breastfed infants is available.

CONCLUSIONS

The complications caused by epidural corticosteroids are relatively rare and rarely serious. However, pain physicians should be aware of the complications because a growing number of patients with various diseases are treated with ESI. Although the relationship between the degree of systemic absorption and the side effects of ESI are not well known, and most ESI-related complications appear to be associated with systemic absorption of corticosteroids. Thus, the complications of ESI differ from those administered via oral or venous routes and depend on the type of steroids used. The duration of HPA axis suppression adequately reflects the systemic absorption of epidural corticosteroids. In terms of safety, non-particulate steroids are preferred over particulate steroids. The ESI interval should be at least 3–4 weeks for a particulate steroid, but non-particulate steroids may be administered more frequently. The ESI dosage is controversial and should be designed to minimize HPA axis suppression for each drug.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conceptualization: Min Soo Lee, Ho Sik Moon. Formal analysis: Min Soo Lee. Writing - original draft: Min Soo Lee, Ho Sik Moon. Writing - review & editing: Ho Sik Moon. Supervision: Ho Sik Moon.

ORCID

Min Soo Lee, https://orcid.org/0000-0002-9968-1998
Ho Sik Moon, https://orcid.org/0000-0003-2298-7734

REFERENCES

1. Lucherini T. [First findings in the use of hydrocortisone by endospinal route]. Policlinico Prat 1954 61: 841-6. Italian.
2. Vydra D, McCormick Z, Clements N, Nagpal A, Julia J, Cushman D. Current trends in steroid dose choice and frequency of administration of epidural steroid injections: a survey study. PM R 2020; 12: 49-54.
3. Mordhorst TR, McCormick ZL, Presson AP, Collier WH, Spiker WR. Examining the relationship between epidural steroid injections and patient satisfaction. Spine J 2020; 20: 207-12.
4. Sabbaghan S, Mirzamohammadi E, Ameri Mahabadi M, Nikouei F, Rahbarian F, Ahmadichaboki S, et al. Short-term efficacy of epidural injection of triamcinolone through translaminar approach for the treatment of lumbar canal stenosis. Anesth Pain Med 2020; 10: e99764.
5. Manson NA, McKeon MD, Abraham EP. Transforaminal epidural steroid injections prevent the need for surgery in patients with sciatica secondary to lumbar disc herniation: a retrospective case series. Can J Surg 2013; 56: 89-96.

6. Bicket MC, Horowitz JM, Benzon HT, Cohen SP. Epidural injections in prevention of surgery for spinal pain: systematic review and meta-analysis of randomized controlled trials. Spine J 2015; 15: 348-62.
7. Maus TP, Bogduk N. Epidural steroid injections. In: Bonica's management of pain. 5th ed. Edited by Ballantyne JC, Fishman SM, Rathmell JP: Philadelphia, Wolters Kluwer. 2019, pp 1611-22.
8. Cohen SP, Bicket MC, Jamison D, Wilkinson I, Rathmell JP. Epidural steroids: a comprehensive, evidence-based review. Reg Anesth Pain Med 2013; 38: 175-200.
9. Lee JW, Lee E, Lee GY, Kang Y, Ahn JM, Kang HS. Epidural steroid injection-related events requiring hospitalisation or emergency room visits among 52,935 procedures performed at a single centre. Eur Radiol 2018; 28: 418-27.
10. Kang WY, Lee JW, Lee E, Kang Y, Ahn JM, Kang HS. Systemic effects of fluoroscopically guided epidural steroid injection with dexamethasone. Korean J Pain 2019; 32: 178-86.
11. McGrath JM, Schaefer MP, Malkamaki DM. Incidence and characteristics of complications from epidural steroid injections. Pain Med 2011; 12: 726-31.
12. Berthelot JM, Le Goff B, Maugars Y. Side effects of corticosteroid injections: what's new? Joint Bone Spine 2013; 80: 363-7.
13. Mulleman D, Mammou S, Griffoul I, Watier H, Goupille P. Pathophysiology of disk-related sciatica. I.--Evidence supporting a chemical component. Joint Bone Spine 2006; 73: 151-8.
14. Boden SD, Davis DO, Dina TS, Patronas NJ, Wiesel SW. Abnormal magnetic-resonance scans of the lumbar spine in asymptomatic subjects. A prospective investigation. J Bone Joint Surg Am 1990; 72: 403-8.
15. Boos N, Rieder R, Schade V, Spratt KF, Semmer N, Aebi M. 1995 Volvo Award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations. Spine (Phila Pa 1976) 1995; 20: 2613-25.
16. McLain RF, Kapural L, Mekhail NA. Epidural steroid therapy for back and leg pain: mechanisms of action and efficacy. Spine J 2005; 5: 191-201.
17. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. Orthop Clin North Am 1991; 22: 181-7.
18. Olmarker K, Størkson R, Berge OG. Pathogenesis of sciatic pain: a study of spontaneous behavior in rats exposed to experimental disc herniation. Spine (Phila Pa 1976) 2002; 27: 1312-7.
19. Johansson A, Hao J, Sjölund B. Local corticosteroid application blocks transmission in normal nociceptive C-fibres. Acta Anaesthesiol Scand 1990; 34: 335-8.
20. Hooten WM, Nicholson WT, Gazelka HM, Reid JM, Moeschler SM, Lamer TJ. Serum triamcinolone levels following interlaminar epidural injection. Reg Anesth Pain Med 2016; 41: 75-9.
21. Derendorf H, Hochhaus G, Rohatagi S, Möllmann H, Barth J, Sourgens H, et al. Pharmacokinetics of triamcinolone acetonide after intravenous, oral, and inhaled administration. J Clin Pharmacol 1995; 35: 302-5.
22. Derendorf H, Möllmann H, Grüner A, Haack D, Gyselby G. Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. Clin Pharmacol Ther 1986; 39: 313-7.
23. Beer PM, Bakri SJ, Singh RJ, Liu W, Peters GB 3rd, Miller M. Intraocular concentration and pharmacokinetics of triamcinolone acetonide after a single intravitreal injection. Ophthalmology 2003; 110: 681-6.
24. Lamer TJ, Dickson RR, Gazelka HM, Nicholson WT, Reid JM, Moeschler SM, et al. Serum triamcinolone levels following cervical interlaminar epidural injection. Pain Res Manag 2018; 2018: 8474127.
25. Friedly JL, Comstock BA, Heagerty PJ, Bauer Z, Rothman MS, Suri P, et al. Systemic effects of epidural steroid injections for spinal stenosis. Pain 2018; 159: 876-83.
26. Jobe AH, Milad MA, Peppard T, Jusko WJ. Pharmacokinetics and pharmacodynamics of intramuscular and oral betamethasone and dexamethasone in reproductive age women in India. Clin Transl Sci 2020; 13: 391-9.
27. Scherer J, Rainsford KD, Kean CA, Kean WF. Pharmacology of intra-articular triamcinolone. Inflammopharmacology 2014; 22: 201-17.
28. Park J, Kwak J, Chung S, Hong HJ, Chon JY, Moon HS. Incidence of adrenal insufficiency and Cushing's syndrome after long-term epidural steroid injections over six months or longer: a preliminary study. J Pain Res 2020; 13: 1505-14.
29. Stout A, Friedly J, Standaert CJ. Systemic absorption and side effects of locally injected glucocorticoids. PM R 2019; 11: 409-19.
30. Sim SE, Hong HJ, Roh K, Seo J, Moon HS. Relationship between epidural steroid dose and suppression of hypothalamus-pituitary-adrenal axis. Pain Physician 2020; 23(4S): S283-94.
31. Chon JY, Moon HS. Salivary cortisol concentration changes after epidural steroid injection. Pain Physician 2012; 15: 461-6.
32. Abdul AJ, Ghai B, Bansal D, Sachdeva N, Bhansali A, Dhatt SS. Hypothalamic pituitary adrenocortical axis suppression following a single epidural injection of methylprednisolone acetate. Pain Physician 2017; 20: E991-1001.
33. Liu D, Ahmet A, Ward L, Krishnamoorthy P, Mandelcorn ED,

Leigh R, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol 2013; 9: 30.
34. Chabre O, Goichot B, Zenaty D, Bertherat J. Group 1. Epidemiology of primary and secondary adrenal insufficiency: prevalence and incidence, acute adrenal insufficiency, long-term morbidity and mortality. Ann Endocrinol (Paris) 2017; 78: 490-4.
35. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol 2015; 3: 216-26.
36. Leary J, Swislocki A. Hypothalamic-pituitary-adrenal suppression and iatrogenic Cushing's syndrome as a complication of epidural steroid injections. Case Rep Endocrinol 2013; 2013: 617042.
37. Grierson MJ, Harrast MA. Iatrogenic Cushing syndrome after epidural steroid injections for lumbar radiculopathy in an HIV-infected patient treated with ritonavir: a case report highlighting drug interactions for spine interventionalists. PM R 2012; 4: 234-7.
38. Albert NE, Kazi S, Santoro J, Dougherty R. Ritonavir and epidural triamcinolone as a cause of iatrogenic Cushing's syndrome. Am J Med Sci 2012; 344: 72-4.
39. Elias PC, Martinez EZ, Barone BF, Mermejo LM, Castro M, Moreira AC. Late-night salivary cortisol has a better performance than urinary free cortisol in the diagnosis of Cushing's syndrome. J Clin Endocrinol Metab 2014; 99: 2045-51.
40. Ward A, Watson J, Wood P, Dunne C, Kerr D. Glucocorticoid epidural for sciatica: metabolic and endocrine sequelae. Rheumatology (Oxford) 2002; 41: 68-71.
41. Younes M, Neffati F, Touzi M, Hassen-Zrour S, Fendri Y, Béjia I, et al. Systemic effects of epidural and intra-articular glucocorticoid injections in diabetic and non-diabetic patients. Joint Bone Spine 2007; 74: 472-6.
42. Maillefert JF, Aho S, Huguenin MC, Chatard C, Peere T, Marquignon MF, et al. Systemic effects of epidural dexamethasone injections. Rev Rhum Engl Ed 1995; 62: 429-32.
43. Dostalek M, Court MH, Yan B, Akhlaghi F. Significantly reduced cytochrome P450 3A4 expression and activity in liver from humans with diabetes mellitus. Br J Pharmacol 2011; 163: 937-47.
44. Gonzalez P, Laker SR, Sullivan W, Harwood JE, Akuthota V. The effects of epidural betamethasone on blood glucose in patients with diabetes mellitus. PM R 2009; 1: 340-5.
45. Kim WH, Sim WS, Shin BS, Lee CJ, Jin HS, Lee JY, et al. Effects of two different doses of epidural steroid on blood glucose levels and pain control in patients with diabetes mellitus. Pain Physician 2013; 16: 557-68.
46. Dubois EF, Wagemans MF, Verdouw BC, Zwinderman AH, Van Boxtel CJ, Dekhuijzen PN, et al. Lack of relationships between cumulative methylprednisolone dose and bone mineral density in healthy men and postmenopausal women with chronic low back pain. Clin Rheumatol 2003; 22: 12-7.
47. Al-Shoha A, Rao DS, Schilling J, Peterson E, Mandel S. Effect of epidural steroid injection on bone mineral density and markers of bone turnover in postmenopausal women. Spine (Phila Pa 1976) 2012; 37: E1567-71.
48. Kim S, Hwang B. Relationship between bone mineral density and the frequent administration of epidural steroid injections in postmenopausal women with low back pain. Pain Res Manag 2014; 19: 30-4.
49. Mandel S, Schilling J, Peterson E, Rao DS, Sanders W. A retrospective analysis of vertebral body fractures following epidural steroid injections. J Bone Joint Surg Am 2013; 95: 961-4.
50. Suh-Burgmann E, Hung YY, Mura J. Abnormal vaginal bleeding after epidural steroid injection: a paired observation cohort study. Am J Obstet Gynecol 2013 209: 206.e1-6.
51. Weitoft T, Larsson A, Rönnblom L. Serum levels of sex steroid hormones and matrix metalloproteinases after intra-articular glucocorticoid treatment in female patients with rheumatoid arthritis. Ann Rheum Dis 2008; 67: 422-4.
52. Gensler LS. Glucocorticoids: complications to anticipate and prevent. Neurohospitalist 2013; 3: 92-7.
53. Schairer WW, Nwachukwu BU, Mayman DJ, Lyman S, Jerabek SA. Preoperative hip injections increase the rate of periprosthetic infection after total hip arthroplasty. J Arthroplasty 2016; 31(9 Suppl): 166-9.e1.
54. Yang S, Werner BC, Cancienne JM, Hassanzadeh H, Shimer AL, Shen FH, et al. Preoperative epidural injections are associated with increased risk of infection after single-level lumbar decompression. Spine J 2016; 16: 191-6.
55. Singla A, Yang S, Werner BC, Cancienne JM, Nourbakhsh A, Shimer AL, et al. The impact of preoperative epidural injections on postoperative infection in lumbar fusion surgery. J Neurosurg Spine 2017; 26: 645-9.
56. Barbaud A, Waton J. Systemic allergy to corticosteroids: clinical features and cross reactivity. Curr Pharm Des 2016; 22: 6825-31.
57. Klein-Gitelman MS, Pachman LM. Intravenous corticosteroids: adverse reactions are more variable than expected in children. J Rheumatol 1998; 25: 1995-2002.
58. Mace S, Vadas P, Pruzanski W. Anaphylactic shock induced by intraarticular injection of methylprednisolone acetate. J Rheumatol 1997; 24: 1191-4.
59. Amin N, Brancaccio R, Cohen D. Cutaneous reactions to inject-

able corticosteroids. Dermatitis 2006; 17: 143-6.
60. Moran DE, Moynagh MR, Alzanki M, Chan VO, Eustace SJ. Anaphylaxis at image-guided epidural pain block secondary to corticosteroid compound. Skeletal Radiol 2012; 41: 1317-8.
61. Cicala RS, Westbrook L, Angel JJ. Side effects and complications of cervical epidural steroid injections. J Pain Symptom Manage 1989; 4: 64-6.
62. Kim CH, Issa MA, Vaglienti RM. Flushing following interlaminar lumbar epidural steroid injection with dexamethasone. Pain Physician 2010; 13: 481-4.
63. Wada K, Yamada N, Sato T, Suzuki H, Miki M, Lee Y, et al. Corticosteroid-induced psychotic and mood disorders: diagnosis defined by DSM-IV and clinical pictures. Psychosomatics 2001; 42: 461-6.
64. Kenna HA, Poon AW, de los Angeles CP, Koran LM. Psychiatric complications of treatment with corticosteroids: review with case report. Psychiatry Clin Neurosci 2011; 65: 549-60.
65. Benyamin RM, Vallejo R, Kramer J, Rafeyan R. Corticosteroid induced psychosis in the pain management setting. Pain Physician 2008; 11: 917-20.
66. Roberti G, Oddone F, Agnifili L, Katsanos A, Michelessi M, Mastropasqua L, et al. Steroid-induced glaucoma: epidemiology, pathophysiology, and clinical management. Surv Ophthalmol 2020; 65: 458-72.
67. Manjiani D, Said S, Kaye AD. Transient glaucoma after an epidural steroid injection: a case report. Ochsner J 2015; 15: 79-82.
68. Van Boxem K, Rijsdijk M, Hans G, de Jong J, Kallewaard JW, Vissers K, et al. Safe use of epidural corticosteroid injections: recommendations of the WIP Benelux work group. Pain Pract 2019; 19: 61-92.
69. Chen YC, Gajraj NM, Clavo A, Joshi GP. Posterior subcapsular cataract formation associated with multiple lumbar epidural corticosteroid injections. Anesth Analg 1998; 86: 1054-5.
70. Tok CH, Kaur S, Gangi A. Symptomatic spinal epidural lipomatosis after a single local epidural steroid injection. Cardiovasc Intervent Radiol 2011; 34 Suppl 2: S250-5.
71. Danielson KD, Harrast MA. Focal spinal epidural lipomatosis after a single epidural steroid injection. PM R 2011; 3: 590-3.
72. Sandberg DI, Lavyne MH. Symptomatic spinal epidural lipomatosis after local epidural corticosteroid injections: case report. Neurosurgery 1999; 45: 162-5.
73. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: report of three cases. Spine J 2002; 2: 70-5.
74. Derby R, Lee SH, Date ES, Lee JH, Lee CH. Size and aggregation of corticosteroids used for epidural injections. Pain Med 2008; 9: 227-34.
75. Laemmel E, Segal N, Mirshahi M, Azzazene D, Le Marchand S, Wybier M, et al. Deleterious effects of intra-arterial administration of particulate steroids on microvascular perfusion in a mouse model. Radiology 2016; 279: 731-40.
76. Watkins TW, Dupre S, Coucher JR. Ropivacaine and dexamethasone: a potentially dangerous combination for therapeutic pain injections. J Med Imaging Radiat Oncol 2015; 59: 571-7.
77. Hwang H, Park J, Lee WK, Lee WH, Leigh JH, Lee JJ, et al. Crystallization of local anesthetics when mixed with corticosteroid solutions. Ann Rehabil Med 2016; 40: 21-7.
78. Benzon HT, Chew TL, McCarthy RJ, Benzon HA, Walega DR. Comparison of the particle sizes of different steroids and the effect of dilution: a review of the relative neurotoxicities of the steroids. Anesthesiology 2007; 106: 331-8.
79. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. Pain Med 2006; 7: 237-42.
80. Kim D, Brown J. Efficacy and safety of lumbar epidural dexamethasone versus methylprednisolone in the treatment of lumbar radiculopathy: a comparison of soluble versus particulate steroids. Clin J Pain 2011; 27: 518-22.
81. Park CH, Lee SH, Kim BI. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. Pain Med 2010; 11: 1654-8.
82. Donohue NK, Tarima SS, Durand MJ, Wu H. Comparing pain relief and functional improvement between methylprednisolone and dexamethasone lumbosacral transforaminal epidural steroid injections: a self-controlled study. Korean J Pain 2020; 33: 192-8.
83. Kim EJ, Moon JY, Park KS, Yoo da H, Kim YC, Sim WS, et al. Epidural steroid injection in Korean pain physicians: a national survey. Korean J Pain 2014; 27: 35-42.
84. Murthy NS, Geske JR, Shelerud RA, Wald JT, Diehn FE, Thielen KR, et al. The effectiveness of repeat lumbar transforaminal epidural steroid injections. Pain Med 2014; 15: 1686-94.
85. Mattie R, Schneider BJ, Smith C. Frequency of epidural steroid injections. Pain Med 2020; 21: 1078-9.
86. Chutatape A, Menon M, Fook-Chong S, George JM. Metabolic and endocrinal effects of epidural glucocorticoid injections. Singapore Med J 2019; 60: 140-4.
87. Strehl C, Bijlsma JW, de Wit M, Boers M, Caeyers N, Cutolo M, et al. Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force. Ann Rheum Dis 2016; 75: 952-7.
88. Habib G, Jabbour A, Salman J, Hakim G, Haddad H. The effect

of epidural methylprednisolone acetate injection on the hypothalamic-pituitary-adrenal axis. J Clin Anesth 2013; 25: 629-33.
89. Sehmbi H, D'Souza R, Bhatia A. Low back pain in pregnancy: investigations, management, and role of neuraxial analgesia and anaesthesia: a systematic review. Gynecol Obstet Invest 2017; 82: 417-36.
90. Hubina E, Nagy GM, Tóth BE, Iván G, Görömbey Z, Szabolcs I, et al. Dexamethasone and adrenocorticotropin suppress prolactin secretion in humans. Endocrine 2002; 18: 215-9.
91. McGuire E. Sudden loss of milk supply following high-dose triamcinolone (Kenacort) injection. Breastfeed Rev 2012; 20: 32-4.
92. Zengin Karahan S, Boz C, Terzi M, Aktoz G, Sen S, Ozbudun B, et al. Methylprednisolone concentrations in breast milk and serum of patients with multiple sclerosis treated with IV pulse methylprednisolone. Clin Neurol Neurosurg 2020; 197: 106118.