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Systemic effects of epidural steroid injections

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ABSTRACT

The aim of this study was to review all the published articles in the English language literature regarding the systemic effects of epidural corticosteroid injections (ESIs) in humans. ESIs are among the procedures that are most commonly used to manage chronic back pain. However, there has been no conclusive review on the systemic effects of this popular procedure. Reports were searched for in MEDLINE and EMBASE using the terms 'epidural' and 'steroids', 'corticosteroids' or 'glucocorticosteroids' up to and including the year 2012. Reports were also located by examining the references in the identified articles. We concluded that even if epidural steroid injection is one of the most widely-used techniques to treat radicular pain, it must be administered cautiously, with careful monitoring for systemic side effects. At the very least, a standardised protocol is necessary.

Key words: chronic pain, treatment, side effects, epidural injections, steroids, systemic effects

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Epidural steroid injections (ESIs) are commonly used to help reduce radicular pain, which is frequently described as a sharp, lancinating, radiating pain. Radicular pain is often the result of nerve root inflammation [1] and/or irritation emanating from the cervical, thoracic or lumbar spine. Corticosteroids, in combination with local anaesthetics, are used to treat painful spinal disorders by epidural administration due to their powerful anti-inflammatory effect [2–4]. The first documented epidural medication injection was performed in 1901 when cocaine was injected to treat sciatica [5], and the epidural injection of corticosteroids into the epidural space to manage lumbar radicular pain was first recorded in 1952 [6]. Several routes of epidural steroid administration are currently helpful, including caudal, interlaminar and transforaminal approaches [7]. The epidural administration of corticosteroids is one of the subjects most studied in interventional pain management [8]. In contrast to oral steroids, ESIs offer the advantage of a more localised medication delivery to the area of the affected nerve roots, thereby decreasing the likelihood of potential systemic side effects. The most commonly used agents for administration in neural blockade are methylprednisolone acetate, triamcinolone diacetate, triamcinolone actinide, betamethasone acetate and phosphate mixture [9, 10], with a variation of usage of 82% for methylprednisolone, 13% triamcinolone and 5% betamethasone. Absolute contraindications to perform epidural injections include known hypersensitivity to the administered agents, systemic infection or local infection at the planned site of injection, local malignancy and bleeding diathesis/anticoagulation therapy. Relative contraindications are related to the systemic effects of steroids on the heart, diabetes, immune system deficiency and glaucoma [11]. ESIs should not be performed in pregnant women, particularly under fluoroscopic control, due to radiation exposure during the procedure, which can be a risk for foetal development [11].

The aim of this review is to present the systemic effects of steroid epidural injections because they are commonly used for treatment in a wide variety of patient populations.

METHODS

In this review, we present all data published on the systemic effects of steroids following ESIs in humans in the English language literature up to and including the year 2012. Reports were searched for in MEDLINE and EMBASE, using the terms 'epidural' and 'steroids', 'corticosteroid' or 'glucocorticosteroid systemic effects'. Reports were also located by examining the references of the identified articles. Only objective findings outside the epidural space were included, and subjective findings, such as patient or

physician global assessment and pain following ESI, were not included.

RESULTS

METABOLIC EFFECTS

GLUCOSE, CHOLESTEROL AND TRIGLYCERIDE METABOLISM

All studies excluded epidural steroid injections within the previous two months and peripheral corticosteroid injections within the previous two weeks

Even et al. [12] noted a statistically significant increase in blood glucose levels in 30 diabetic patients after ESI (an average 125.96 ± 100.97 mg dL^{-1} increase in blood glucose levels after injection). The patients returned to their normal standard deviation mean glucose levels within two days of injection.

Gonzalez et al. [13] studied the effects of betamethasone lumbosacral, transforaminal and caudal epidural injections on blood glucose levels in diabetic subjects, but only transient changes occurred for 12 patients. The blood glucose elevation (106 mg dL^{-1}) remained statistically significant for three days after injection.

Zuffery et al. [14] treated five patients with 80 mg of acetate methylprednisolone to treat spinal stenosis. Following steroid injection via two routes, urinary excretion was analysed. None of the patients demonstrated a renal impairment that could interfere with renal elimination of the injected steroids. A single steroid injection had no effect on the glycaemic profile. The absence of blood glucose modification was coincident with very low urinary excretion of the drug. The mean excretion was approximately ten-fold lower compared to patients who had received intra-articular infiltration and intramuscular injection; methylprednisolone remained localised in the epidural space, and only small amounts entered the system. Epidural injection of soluble betamethasone and soluble cortisol resulted in significantly increased glycaemia the evening following the injection. The glucose concentration remained increased for two days, although the increase was no longer significant.

Wars et al. [15] examined ten patients with sciatica who underwent a caudal epidural injection of 80 mg triamcinolone. A short insulin tolerance test was performed before and twice following (at 24 h and one week) the injection; fasting glucose, insulin and cortisol were also evaluated. They observed potent suppression of insulin activity, but it returned to the pre-treatment value within one week.

Maillefert et al. [16] admitted nine patients for sciatica. A single epidural injection of 15 mg dexamethasone acetate was administered. They evaluated serum cortisol, ACTH (adrenocorticotropin), free cortisol, sodium, potassium and fasting glucose, triglycerides and cholesterol as well as 24-hour urine collection. Serum cortisol, ACTH and urinary cortisol were profoundly decreased after two and seven days but had returned to normal by day 21. No changes in fasting serum glucose, triglycerides, cholesterol, sodium or potassium levels were observed.

Contrasting results for diabetic and non-diabetic patients with sciatica were obtained by Younes et al. [17]. Each patient was administered three injections of 1.5 mL of cortivazol at intervals of three days. Plasma cortisol and ACTH were measured at 8am, and urinary free cortisol excretion over 24 hours as well as fasting and postprandial blood glucose, serum cholesterol, triglycerides, sodium and potassium were evaluated. The mean postprandial blood glucose was significantly higher at day 1 post-treatment (10.1 ± 5.4 mmol L^{-1}). At day 7 post-treatment, blood glucose remained significantly elevated in diabetic patients compared to non-diabetic patients. In both diabetic and non-diabetic patients, plasma cortisol, ACTH and urinary free cortisol were markedly reduced at days 1 and 7 post-treatment. At day 21, a decrease was observed. No significant variations in fasting blood glucose or the serum levels of cholesterol, triglycerides, sodium or potassium were observed.

OSTEOPOROSIS AND BONE CHANGES

The relationship between ESIs, bone mineral density (BMD) and vertebral fracture remains to be determined.

Yi et al. [18] established a relationship between ESIs, BMD and vertebral fracture in 352 postmenopausal women with low back pain. They observed no correlations, similar to some previous studies [19, 20]. Other studies have shown that patients treated with high-dose glucocorticoid therapy are at risk for lower BMD [21–23]. Manchikanti et al. [24] described 100 patients treated with epidural steroid injections of 146 mg of methylprednisolone acetate. The baseline BMD was 0.4967, and after one year of intermittent epidural corticosteroid treatment, the BMD did not change.

VASCULAR EFFECTS

FLUSHING

Everett [25] compared flushing as a side effect of betamethasone acetate/betamethasone sodium phosphate vs methylprednisolone after epidural steroid injections in 240 patients. Compared to 9% of methylprednisolone patients, 16% of patients who underwent ESIs with betamethasone acetate/betamethasone sodium phosphate reported a flushing reaction. The overall incidence of flushing was approximately 11%. Botwin et al. [26] reported a 2.3% incidence of facial flushing in 139 patients with radiculopathy who were treated with caudal epidural steroid injections. DeSio et al. [27] reported that 12 of 1,399 patients experienced flushing following both cervical and lumbar epidural injections, while Cicala et al. [28] reported that 11%

of patients experienced flushing after cervical methylprednisolone acetate injections.

BLOOD PRESSURE

Younes et al. [17] monitored blood pressure and reported a significant increase compared to baseline, although it returned to baseline values by the third post-treatment visit (day 21). A transient increase in mean systolic blood pressure of 5 mm Hg returned to baseline three weeks after injection. By contrast, dexamethasone [16] resulted in no difference in blood pressure one week after an epidural corticosteroid injection.

CARDIOPULMONARY EFFECTS

One case of cardiopulmonary arrest has been reported [29]. After a corticosteroid injection at the C6–C7 level, the patient experienced immediate arrest, including cardioacceleratory centre blockade, a severe vasovagal response, iatrogenic pneumocephalus and involvement of the phrenic nerve followed by apnoea. This could be a rare but potentially deadly side effect, even if the mechanism remains unclear. The authors could not relate the arrest to the epidural procedure or to a systemic side effect of the corticosteroid.

ENDOCRINE EFFECTS

Hypothalamic-pituitary-adrenal (HPA) axis

Younes et al. [17] reported suppression of the corticotropic axis after three local cortivazol injections, and it persisted beyond 21 days after the epidural injection. A profound decrease in serum ACTH and free cortisol levels was observed on post-injection days 1 and 7. Normal ACTH levels were found on day 21.

A single epidural injection of 15 mg of dexamethasone acetate has been associated with transient adrenal suppression [16]. Weekly ESIs over a three-week period caused a dramatic acute and chronic suppression of the HPA axis [30], with a median suppression of less than 1 month. A single lumbar epidural steroid injection of 80 mg of methylprednisolone acetate [31] did not result in absorption of the corticosteroid into the systemic circulation. Marked suppression of plasma cortisol levels was documented for up to three weeks following the injection, and the capacity of the adrenal cortex to secrete cortisol in response to ACTH was diminished. Cortisol measured 14 days after epidural steroid injection [32] resulted in deficient ACTH stimulation tests with depressed baseline plasma cortisol values in 19 to 22 patients. Hsu et al. [33] compared plasma cortisol and ACTH profiles and concluded that a single epidural injection of 40 mg of triamcinolone markedly decreased plasma cortisol for only 24 hours, while 80 mg resulted in a decrease for up to 14 days post-treatment; HPA axis function returned to normal within 35 days in both groups. Botwin et al. [34] reported that HPA suppression lasted for nearly three weeks. Epidural injections performed simultaneously with other injections (e.g. facet, piriformis) also have the potential to increase the length of serum ACTH suppression [35]. Finally, Chon et al. [36] showed that HPA axis function was suppressed after ESI until day 21 and returned to normal after approximately 19.9 days and that the minimal interval between ESI treatments should be at least one month.

HYPOTHALAMIC-PITUITARY-OVARIAN AXIS

Gitkind et al. [37] reported a case of heavy and painful menstrual bleeding after epidural steroid injections, and the bleeding was thought to be due to inhibition of the hypothalamic-pituitary-ovarian axis.

CUSHING'S SYNDROME AND HYPERCORTICISM

Stambough et al. [38] reported a case of transient hypercorticism after an epidural steroid injection of 80 mg methylprednisolone acetate with two doses administered one week apart; the hypercorticism resolved within six weeks.

Cushing's syndrome was described [39] after a cervical injection of 60 mg of epidural methylprednisolone, but the syndrome disappeared within four months.

LIPOMATOSIS

Several authors [40–45] have reported cases of symptomatic epidural lipomatosis following epidural injections of corticosteroids. Roy Camille et al. [46] reported two cases of symptomatic epidural lipomatosis following 103 epidural injections of 40 mg of methylprednisolone acetate in a paraplegic patient. Camacho [43] reported a 74 year-old obese patient with rheumatic pseudomyalgia who was treated for three years with 10 to 20 mg of prednisone for intermittent radicular claudication and low back pain. Gupta et al. [47] reported a progressively worsening weakness of the lower extremities due to canal stenosis lipomatosis extending from C7 to T10. Tok et al. [48] reported a 45 year-old diabetic man with claudication that was most likely due to symptomatic lumbar spinal lipomatosis resulting from a single local epidural steroid injection.

VISUAL EFFECTS

Pizzimenti et al. [49] reported two patients who developed central serous chorioretinopathy (CSC) after receiving a corticosteroid injection in the epidural space for the treatment of back pain. The accumulation of subretinal fluid spontaneously resolved within several weeks. Lida et al. [50] described three patients who developed bilateral CSC with diffuse retinal pigment epitheliopathy after the treatment of back pain with epidural corticosteroid injection. Vision loss following epidural injections has been described [51–59] due to necrosis and retinal haemorrhage.

DYSPHONIA

Slipman et al. [60] reported a 46 year-old patient with left-side low back pain who developed symptoms of dysphonia and throat irritation 24 hours after receiving a fluoroscopically guided steroid injection into the epidural space. A direct laryngoscopy performed before a second injection detected no abnormalities. When dysphonia reappeared 48 hours after the second injection, laryngoscopy revealed oedema in the anterior vocal cord with thick surrounding mucous. Full clinical resolution was apparent 15 days after the second injection. Bath et al. [61] reported a 12% incidence of transient dysphonia and/or associated throat symptoms in 100 patients after a therapeutic ESI.

OTHER EFFECTS

Only minor gastrointestinal disturbances were reported following the epidural administration of steroids [62, 63].

A single case of steroid myopathy has been reported following a single-dose epidural injection of triamcinolone [64].

Less common side effects have included elevated temperature, euphoria, depression, mood swings, local fat atrophy, depigmentation of the skin and pain flare [65]. Insomnia (39%), facial erythaema (20%), nausea (20%) and rash and pruritus (8%) have been observed following betamethasone injection [65].

Finally, ESIs did not induce weight gain [66].

DISCUSSION

Epidural steroid injections have been endorsed by the North American Spine Society and the Agency for Healthcare of the Department of Health and Human Services as an integral part of the nonsurgical management of radicular pain from lumbar spine disorders. Although the primary indication for ESIs is radicular pain associated with a herniated nucleus pulposus, a variety of other indications have been reported in the literature: lumbosacral disk herniation, spinal stenosis with radicular pain, compression fracture of the lumbar spine with radicular pain, and facet or nerve root cyst with radicular pain. Because radicular pain may originate from inflammation of the epidural space and the nerve root, the analgesic effects of corticosteroids are most likely related to the inhibition of phospholipase 2 (PLA2) and inflammation, the inhibition of neural transmission in nociceptive C-fibres, and the reduction of capillary permeability [67]. The potential side effects from glucocorticoids administered into the epidural space are numerous and are dose-, location- and duration-dependent. Considering the types of preparations, both particulate and nonparticulate steroids have been used in epidural injections for decades. Particulate corticosteroid preparations have been associated with adverse central nervous system sequelae [68, 69], which are most likely more related to the type of preparation [4, 70] than to the glucocorticoid effects [71]. Only a few papers have compared the clinical efficacy of particulate versus nonparticulate steroids [72–74]. ESIs result in the elevation of blood glucose for a limited period of time (2–7 days). The difference could be related to the type of steroid used, which has been shown to have different effects on metabolism and the speed of elimination in humans. Glucocorticoids are important stress hormones with hyperglycaemic effects, and they are enhanced in disease states in which insulin secretion is limited, such as diabetes mellitus. This is the result of decreased sensitivity to insulin and the modulation of pancreatic insulin secretion and hepatic and extrahepatic responses to insulin. Patients with diabetes should be given specific advice for the management of their condition after the administration of epidural glucocorticoids. Additional studies examining hyperglycaemia specifically after an epidural corticosteroid injection have confirmed that it may potentially contribute to the development of insulin resistance [16, 17]. However, there is no data in the literature demonstrating how corticosteroids injected into the epidural space are metabolised. ESIs have been shown to cause an increase in the blood glucose levels in diabetics [12–15].

Glucocorticoids are known to alter calcium homeostasis, affecting bone through a reduction in bone formation and an increase in bone breakdown [19]. Fortunately, glucocorticoid injections, when administered into the epidural space, have not been shown to change bone mineral density (BMD) or increase fracture risk [21–23]. The ESI number and mean duration and mean total dose of glucocorticoids are not associated with a low BMD or fracture [24], even if cumulative glucocorticoid administration might be associated with decreased BMD. All patients initiating long-term treatment with epidural glucocorticoids should obtain appropriate baseline BMDs of the spine and hip.

A flushing reaction is an immunoglobulin IgE-mediated side effect [25]. A portion of the reaction is mediated by histamine, and the reaction tends to be self-limiting [26]. However, the flushing reaction may mimic the signs and symptoms of an anaphylactic reaction and create concern for patients and physicians.

Glucocorticoid secretions are approximately 5 to 10 mg m^{-2} per day of cortisol secretions. These estimates of glucocorticoid secretion are equivalent to approximately 20 to 30 mg per day of hydrocortisone or 5 to 7 mg per day of oral prednisone. The synthesis of cortisol can increase five- to ten-fold under conditions of severe stress, to a maximal level for 100 mg m^{-2} per^{-1} day. Patients who receive 5 mg per day or less of prednisone continue to have an intact HPA axis. The dose and frequency of ESIs should be kept to a minimum to prevent suppression of the HPA axis [31]. The recovery of the HPA axis after the discontinuation of

exogenous glucocorticoids may take up to one year, and physiologic reductions in serum adrenocorticotropic hormone can be observed for 1–2 weeks after a single epidural steroid injection. Mineralocorticoid function via the renin angiotensin aldosterone system is usually intact [34].

Evidence of hypercorticism is usually lacking, but it may be observed [38, 39] following exceptionally high doses of corticosteroid given over a short period of time.

Induced by long-term steroid treatment, lipomatosis is an uncommon condition in which unencapsulated fat accumulates within the epidural space, causing overgrowth in the vertebral canal [41]. Lipomatosis is rare but can cause significant morbidity, with symptoms identical to those of more common disorders such as vertebral and disc disease and cord lesions (e.g. transverse myelitis, multiple sclerosis and syringomyelia) [43, 47, 75].

Central serous chorioretinopathy (CSC) is a condition characterised by serous detachment of the neurosensory retina in the posterior pole. Retinal haemorrhage has primarily been attributed to rapid epidural injections of high volumes, causing a sudden increase in intracranial pressure resulting in the increase of retinal venous pressure [49, 50].

CONCLUSIONS

Ultimately, to predict the systemic effects of epidural steroid injections, it is fundamental to define the timing, frequency and doses of glucocorticoid administrations; indeed, the majority of daily clinical practice is based on empirical clinical protocols.

The optimal timing is unknown, but as long as there are no signs of progressive neurological deficits, epidural injection is indicated for pain control.

The interval between injections varies with the steroid preparation used. Because injected methylprednisolone has been reported to remain in situ for approximately two weeks, clinicians should consider waiting approximately two weeks after an injection to assess the patient's response. The ideal number of epidural injections to administer is often unclear because there is no clear data in the current literature on the exact number of ESIs in clinical practice patterns. However, the data suggests that up to 3–4 injections may be used for acute radicular pain syndromes. Some authors recommend one injection for diagnostic and therapeutic purposes, whereas others recommend three injections in a series followed by a repeat course of three injections after 3-, 6-, and 12-month intervals.

Depending on the particular clinical scenario, the total dose of methylprednisolone should most likely not exceed approximately 3 mg/kg of body weight to prevent salt and water retention. In interlaminar ESI, the typical corticosteroid doses are 12–18 mg for betamethasone and 80–120 mg for methylprednisolone; half of these steroid doses are used for transforaminal ESIs [76].

More in-depth investigations on the systemic effects, pharmacokinetics and pharmacodynamics of epidurally administered steroids will be helpful to identify evidence-based medicine protocols for epidural steroid injections.

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