

Cumulative Lifetime Steroid Exposure via Epidural Administration

Byron J. Schneider, MD¹; Ryan Mattie, MD²; and Clark C. Smith, MD, MPH³ on behalf of the Spine Intervention Society's Patient Safety Committee

¹Vanderbilt University, Department of Physical Medicine and Rehabilitation, Nashville, Tennessee, U.S.A;

² Providence Cedars-Sinai Tarzana Medical Center, Comprehensive Spine & Interventional Pain Management, Tarzana, California, U.S.A;

³Columbia University Medical Center, Rehabilitation and Regenerative Medicine, New York, New York, U.S.A.

Myth: There is a set number of epidural steroid injections (ESI) that is "safe" over the course of a patient's life.

Fact: Each exposure to steroid via epidural injection introduces risk of potential systemic side effects due to steroid. There may be a dose response effect or cumulative dose threshold for increased risk of certain potential side effects. There is no set number of ESIs that is "safe", nor a specific threshold known to be incrementally more "dangerous" over the course of a patient's life.

Glucocorticoids are a commonly employed medical treatment, which can be administered via a variety of routes and dosing schedules. One use of corticosteroid is via ESIs. While there are some gaps in the literature on the systemic risks of epidural steroids, the potential effects of chronic oral administration of glucocorticoids have been well documented. The oral steroid literature clearly demonstrates that long-term exposure to higher doses of glucocorticoids may result in adverse effects. The European League Against Rheumatism recently concluded that for daily prednisone and the risk of osteoporosis, infection, hyperglycemia, and glucocorticoid induced cardiovascular disease, the risk for harm is "low" with 5mg [equivalency: 0.8 mg dexamethasone, 4mg methylprednisolone (MP), 0.7mg betamethasone] or less, but for 10mg or greater there is elevated risk of harm [1]. All patients are expected to display adrenal insufficiency after more than one year of daily systemic oral glucocorticoid administration [2]. The literature on epidural glucocorticoid injections demonstrates some of these same systemic side effects. This is thought to be due to absorption of corticosteroid from the epidural space [3]. These effects can be immediate, long-term, or both.

Potential immediate complications are due to the direct effect of the exogenous corticosteroid on peripheral tissue. These include hyperglycemia and blood pressure elevation, which if present, are usually limited to 48-72 hours [4-6]. These must be considered for each individual injection. There is a paucity of literature regarding a cumulative lifetime risk of persistent hypertension or hyperglycemia due to multiple ESI.

Long-term adverse effects of ESI are most commonly due to Hypothalamic-Pituitary-Axis (HPA) suppression, a pathophysiologic event that occurs in some patients following ESI. In patients receiving lumbar ESI, one study found that 20.3% of subjects had greater than 50% decrease from baseline of cortisol level at three

weeks [7]. However, when compared to a lidocaine control group, this effect was seen only in those treated with methylprednisolone or triamcinolone (TC) but not dexamethasone or betamethasone [7]. Another study found that the mean time to have return to baseline HPA function after a single injection of 40mg TC was 19.9 +/- 6.8 days [8]. Limited evidence suggests a dose response effect, with 86% of patients demonstrating cortisol suppression one week after ESI with 80mg MP compared 53% of those who received 40mg MP [9]. Duration of HPA suppression did not appear to be dose dependent, however, as by week three there was no significant difference between the two groups [9]. The concept of allowing the HPA to "recover" between dosing seems to stem from a study that demonstrated that compared to controls, patients receiving daily oral glucocorticoid therapy showed evidence of HPA suppression, while patients receiving alternate day oral steroid therapy did not [10]. In theory, appropriate spacing of ESI may limit cumulative lifetime risk of certain systemic side effects of steroids.

For other systemic effects such as a decrease in bone mineral density (BMD) and osteoporotic compression fracture, a cumulative dose effect may be present. A recent meta-analysis on this topic found that significant reductions in BMD were associated with a cumulative MP dose of 200mg over a one-year period and 400mg over three years, but not with doses of less than 200mg of MP equivalents for postmenopausal women or less than 3g for healthy men [11]. This is consistent with one specific study that found approximately 14 ESIs with a cumulative TC dose of approximately 400mg can reduce BMD in postmenopausal women with low back pain [12]. Another study found an increasing number of ESIs was associated with an increasing likelihood of fractures; each successive ESI increased the risk of fracture by a factor of 1.21 [13]. Conversely, some studies have not shown such a relationship, with one even reporting that the risk of osteoporotic compression fracture decreases with each

While iatrogenic Cushing's disease is typically associated with prolonged exposure to high dose steroids, there is a case report of Cushing's disease after a single ESI [15]. Other case reports of systemic endocrine disorders have been reported to occur after repeated spine steroid injections. One patient was reported to have 15 ESI over three years with an estimated cumulative dose of TC upwards of 600mg. Another patient had a total of 510mg TC and 40mg MP over a 28-month period administered via axial spine intra-articular injections [16]. Such complications appear rare, existing in case report form only.

Conclusions & Recommendations:

- The possibility of short-term and long-term systemic effects of corticosteroids should be discussed with the patient prior to the procedure during the informed consent process.
- It is clear that ESI can result in unwanted systemic steroid effects. Regardless of route of administration, prolonged exposure to higher doses of steroid confers increased risk of such side effects.
- Specific to ESI, there is inconclusive evidence to suggest a specific "threshold" number of injections over a patient's lifetime that is "safe". Conversely, for every single ESI, the systemic effects of steroids must be considered.
- Spacing ESIs at least three weeks apart to allow for recovery after potential HPA suppression may limit long-term sequelae of cumulative steroid exposure.
- There may be a cumulative dose of steroid from ESI that confers greater risk of decrease BMD or osteoporotic compression fracture: 400mg MP over three years for postmenopausal women and greater than 3g for healthy men.
- Limited evidence suggests that complications of osteoporotic compression fracture or endocrinopathies may be more likely to occur after 14 or more ESI exposures.
- Patients should be counseled on the potential long-term adverse effects of multiple corticosteroid injections and educated on the potential value of tracking how many steroid injections they receive over time.

References

1. Strehl C, Bijlsma JWJ, 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.
2. Bertouch JV, Meffin PJ, Sallustio BC, Brooks PM. A comparison of plasma methylprednisolone concentrations following intra-articular injection in patients with rheumatoid arthritis and osteoarthritis. *Aust N Z J Med* 1983;13:583-6.
3. Schneider B, Zheng P, Mattie R, Kennedy DJ. Safety of epidural steroid injections. *Expert Opin Drug Saf* 2016;15:1031-9.
4. Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine* 2012;37:E46-50.
5. Gonzalez P, Laker SR, Sullivan W, Harwood JEF, Akuthota V. The effects of epidural betamethasone on blood glucose in patients with diabetes mellitus. *PM R* 2009;1:340-5.
6. 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. *Jt Bone Spine Rev Rhum* 2007;74:472.
7. 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;159:876-883.
8. Chon JY, Moon HS. Salivary cortisol concentration changes after epidural steroid injection. *Pain Physician* 2012;15:461-6.
9. 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.
10. Ackerman GL, Nolan CM. Adrenocortical responsiveness after alternate-day corticosteroid therapy. *N Engl J Med* 1968;278:405-9.
11. Kerezoudis P, Rinaldo L, Alvi MA, Hunt CL, Qu W, Maus TP, et al. The effect of epidural steroid injections on bone mineral density and vertebral fracture risk: a systematic review and critical appraisal of current literature. *Pain Med* 2018;9:569-579.
12. 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 J Can Pain Soc J Société Can Pour Trait Douleur* 2014;19:30-4.
13. 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.
14. Carreon L, Ong K, Lau E, Kurtz S, Glassman S. Risk of osteoporotic fracture after steroid injections in Medicare patients. *Scoliosis* 2014;9:O46.
15. Leary J, Swislocki A. Hypothalamic-pituitary-adrenal suppression and iatrogenic cushing's syndrome as a complication of epidural steroid injections. *Case Rep Endocrinol* 2013;1-4.
16. Lansang MC, Farmer T, Kennedy L. Diagnosing the unrecognized systemic absorption of intra-articular and epidural steroid injections. *Endocr Pract* 2009;15:225-8.