Annual Maximum Dose of Epidural Steroid Injection

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Myth: It is standard practice to perform an initial series of three high-dose epidural steroid injections (ESI) separated by one week, and this treatment can safely be repeated several times in one year.

Fact: Effectiveness data and adverse effect profiles of epidurally administered glucocorticoids (GC) dispute both the need for and the safety of frequent high-dose ESI.

Patient selection criteria, interventional technique, steroid type, dose, injectate volume, outcomes, adverse effects, interval, and total number of injections are some of the important variables that factor into how much glucocorticoid (GC) may be administered in treating an individual with radicular pain. Interventional technique (interlaminar versus transforaminal) and steroid type (particulate versus non-particulate) have been covered in separate FactFinders. In consideration of the advisability of a maximum annual GC dose for ESI, this FactFinder will briefly examine the evidence concerning epidural steroid dose and injection interval as they relate to effectiveness data and adverse effects due to systemic corticosteroid absorption.

Currently, there is no consensus as to the most favorable GC dose for an initial or subsequent ESI [1]. Several recent systematic reviews concerning the effectiveness of ESI confirm the heterogeneity of clinical practices [2-4]. Differing guidelines also reflect this diversity of tradition, but do not go so far as to delineate safe GC doses for ESIs [5-7]. There are four commonly studied GC agents utilized in the performance of ESI with a range of doses that vary up to five times in potency.

AGENT	CORTICOSTEROID DOSE EQUIVALENTS*	EPIDURAL DOSE LOW (mg)	EPIDURAL DOSE HIGH (mg)	TRIAMCINOLONE EQUIVALENTS (mg)
Betamethasone	12	6	12	36-80
Dexamethasone	15	4	16	21-85
Methylprednisolone	80	40	80	20-120
Triamcinolone	80	20	100	20-100
Prednisone	100			

*https://emedicine.medscape.com/article/2172042-overview

Dose-response curves for the four common GC used in ESI have not been established. In the few published studies examining this issue, the reduced doses are as effective as moderate doses and the highest doses are no better than moderate doses [8,9]. In the systematic ESI reviews cited above, there was no attempt to stratify outcomes according to steroid type or dose. Therefore, the optimal agent and dose of GC for an initial ESI is yet to be established.

To compound the dosage uncertainty is the issue of if, or when, to perform a subsequent ESI. The time course for the demonstration of beneficial effects from ESI has not been precisely determined, but consensus opinion is that it occurs in 1-14 days. The historical recommendation to delay repeat injections at least two weeks may be grounded

in the expectation of waiting for the patient to gain the maximal beneficial effect of the first injection before proceeding with a second.

From the review by MacVicar *et al*. [2] comes a frequently cited figure that only 4% of ESI-treated patients require a second injection. That may be a misunderstanding of the review process, which necessarily excluded all of the studies that utilized repeat injections for a perceived deficiency in data reporting for categorical outcomes. The majority of the primary ESI effectiveness literature does not control for the number or timing of multiple injections. Repeat ESI may be performed for recurrence of radicular pain with the expectation of recovery of most or all previously achieved benefit. Acute pain patients will likely recover all prior benefit. Repeat ESI, within three months of the index injection, can provide cumulative benefit [8].

Adverse pharmacologic effects of ESI can be grouped into three categories. Immediate, generally minor transient effects include elevation of blood glucose, flushing, insomnia, and gastritis; intermediate effects include endocrinopathies, immunosuppression, alteration of mood, cardiovascular perturbation, and muscle weakness; and long-term, possibly serious problems include osteoporosis and issues related to iatrogenic Cushing's and/or hypothalamic–pituitary–adrenal (HPA) axis suppression. GC toxicity is generally related to both the dose and duration of exposure [9]. Cushing's (hypercorticolism) can be a debilitating condition and adrenal insufficiency may render patients unable to respond to physical or emotional stress. The onset of HPA axis suppression is often gradual and may go undetected until an illness, injury, or other stressor precipitates a life threatening adrenal crisis [10]. The incidence of Cushing's and clinical manifestations of HPA axis suppression as the result of ESI are rare, but theoretically possible. Studies designed to evaluate the frequency and types of complications following ESI failed to identify a single case [11].

The onset and duration of adverse effects from injected epidural GC are not related to their pharmacological half-lives. The degree and duration of HPA axis suppression following ESI may be dose-dependent. Habib *et al.* examined the magnitude and duration of HPA suppression following epidural injection of two dosing strategies of methylprednisolone: 80 mg verses 40 mg. The larger dose resulted in a greater percentage of patients with laboratory confirmed HPA axis suppression (86%) than did the smaller dose (53%) at one week post-injection. Furthermore, one-fifth remained suppressed at week 4 [12]. Longer-acting agents (triamcinolone and methylprednisolone) suppress cortisol production for a longer duration than do the more soluble agents (dexamethasone and betamethasone) [13]. Abdul et al. reported HPA axis suppression in 87% of subjects at post-injection day 7, 43% at day 14, and 7% at day 28 following epidural injection of 80 mg of methylprednisolone in those without co-morbidities [14]. Iranmanesh *et al*. reported laboratory confirmed suppression of adrenocorticotropic hormone (ACTH) and cortisol for 1-4 weeks and suppression of urinary free cortisol for more than 12 weeks following ESI with triamcinolone 80 mg [15]. These laboratory findings have an undetermined clinical relevance. Additionally, patient variables, comorbidities, and certain medications can significantly affect the amount and duration of HPA-axis suppression [16]. Certain patient populations are at significant risk from the adverse effects of corticosteroids, particularly the elderly and those with other comorbid conditions such as: immune system impairment, diabetes, congestive heart failure, poorly controlled hypertension, deficiencies in wound healing, myopathy, and osteopenia/osteoporosis [17, 18].

Long exposure and high-dose steroids are administered in many diverse clinical settings, but because the signs and symptoms of Cushing's and HPA axis suppression are vague, many go undiagnosed. The threshold to test for adrenal insufficiency should be low, especially for those patients at risk and those with new non-specific symptoms [17].

The most prudent principle is to utilize repeat steroid injections only in those who experience significant measurable benefit in pain and function from the index injection, and to space subsequent injections at intervals sufficient to allow full expression of the intended beneficial effect as well as recovery of adrenal function. Physicians should exercise caution when planning an ESI on patients who may have recent exposure to GC from other healthcare providers and for other medical conditions.

Conclusions & Recommendations:

- Systemic effects of epidurally administered GCs are inadequately studied and underappreciated.
- The administration of ESI should be based on patient response, the safety profile of the agent, the pharmacological profile of the injected GC, and up-to-date dosage guidelines established in the scientific literature.
- Because all adverse effects are dose dependent, moderate doses may be safer without compromising effectiveness.
- Dexamethasone and other more soluble GCs may have shorter duration of systemic effects than less soluble GCs.
- To minimize GC adverse effects, the interval between ESI should be at least 2-3 weeks and possibly longer for triamcinolone and methylprednisolone.
- Effectiveness data support an index ESI and two repeat injections in selected patients with an interval between three weeks and three months within an initial six-month period.
- At this time, no recommendation can be made for the proper dosing or injection interval beyond six months.
- Patients should be examined for the presence of signs and symptoms suggestive of Cushing's and HPA axis suppression in follow up from an index ESI, and repeat injections should be staged accordingly.
- Multiple high-dose (more than 40 mg equivalent of triamcinolone) injections in susceptible populations may pose increasing risk relative to potential benefit.

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