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Steroids for LBP – from rationale to inconvenient truth

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Summary

Low back pain (LBP) and sciatica are highly prevalent and their treatment remains a clinical challenge. Systemic or local administration of corticosteroids is frequently prescribed for this indication, partly because its pathogenesis is believed to be a mix between mechanical and inflammatory phenomenon, and because corticosteroids do have some analgesic properties. Although there is some biological and animal data in favour of the use of corticosteroids in LBP and sciatica, clinical evidence remains scarce. Local epidural injection can have some short term benefit. However, we found no support for any type for systemic administration of corticosteroids, a practice that should definitively be banned.

Key words: *corticosteroids; low back pain; sciatica*

Introduction

Low back pain (LBP) is a common and almost universal symptom, and in most cases, its origin remains unclear even after extensive investigations [1]. Sciatica is another disorder frequently encountered in clinical practice, whose management often poses a problem to clinicians. The concept of sciatica remains unclear and imprecise, mixing true radicular pain with ordinary lower limb radiating pain. Moreover, even if numerous recommendations are available for the clinical diagnosis and management of LBP, the treatment of sciatica and sciatic pain remains poorly defined despite their high prevalence.

Nevertheless, these facts do not prevent therapists from daily prescribing all kinds of treatments, with more than 200 different therapies recorded for back pain in a non-exhaustive review [2], a plethora which emphasizes the lack of a universally effective treatment. As already mentioned, the situation is not more encouraging for sciatica, for which the only systematic review of the literature published in 2007 [3] depicts a grim picture of the effectiveness of the available therapeutic arsenal.

In this context, with a lack of any definitive evidence for a specific treatment, which would rapidly establish itself,, physicians gladly use, by analogy, treatments that are effective in other pathologies and for which they have positive experience. This phenomenon is even more pronounced when there is some pathophysiological rationale. Corticosteroids are widely used in a variety of medical conditions, despite a lack of evidence, an observation that prompted an interesting discussion by Huntoon [4]. In the context of LBP, and sciatica in particular, this phenomenon is fairly typical. Despite its high prevalence, the pathophysiology of sciatic pain remains controversial, described as a mix between compression and inflammation, the relative importance of these varying in each patient [5, 6]. We intend to summarize the arguments for each respective mechanism in table 1. Interestingly, in a study comparing percutaneous decompression to transforaminal epidural steroid injection, decompression showed superior efficacy, suggesting a predominance of the mechanical component. However, one inclusion criterion was failed conservative treatment, which included epidural steroid injection [7].

The shortcut inflammation – corticosteroids is almost an engraved reflex in the medical subconscious mind. Indeed, it is easy to find a pathophysiological rationale for the use of corticosteroids, as an inflammatory component is always possible. This trend is so strong that despite the absence of clear clinical evidence, this practice is common and almost universal. However, there are side effects to the use of steroids, and in this period of medical rationalisation, it is important to rigorously re-evaluate the scientific and experimental data behind the rationale for such an approach, and especially the clinical evidence available.

Pharmacological and experimental data

The anti-inflammatory effects of steroids are well known [8]. However, a preliminary reflection on their analgesic effects is also critical in the context of LBP and sciatica. The effects of these drugs are complex because they regulate transcriptional pathways in different cellular contexts and affect not only inflammation, but also development, homeostasis, metabolism and cognition [9].

All corticosteroids are not interchangeable. They can be classified based on their relative potencies in terms of sodium retention and anti-inflammatory action (table 2), and are mainly used in medicine for their anti-inflammatory

and immunosuppressive properties. However, they also interact with many metabolic pathways (glucose, lipids), exert catabolic effects in some tissues (bone, muscle), and play a role in the response to stress.

Glucocorticoids (GC) reach all tissues, including the nervous system, and easily penetrate into cells. In the cytosol, GC exert classical genomic effects by binding either to the mineralocorticoid receptor or the glucocorticoid receptor (GCR). For the latter, two isoforms are described: (1) the alpha isoform is expressed in almost all cell types and is activated by GC; and (2) the beta isoform which does not bind GC and acts as an inhibitor, potentially playing a role in GC resistance [10]. After binding, the GCR becomes activated and the complex translocates into the nucleus, where it binds to specific DNA binding sites, triggering the genomic effects of GC, consisting of switching off pro-inflammatory transcription factors (transrepression), thus reducing the synthesis of pro-inflammatory cytokines in a dose-dependent manner, while switching on other anti-inflammatory and regulatory genes (transactivation).

Many adverse effects related to GC seem to be mediated through the same direct genomic effects [10, 11], explaining the relationship observed between doses, the percentage of CGR saturation and the severity of adverse effects in clinical situations. For these reasons, the classical recommendation is to use the lowest efficacious dose for the shortest duration [11].

Apart from these genomic effects, high GC doses also usually induce faster non-genomic effects that are ubiquitous, affecting membrane lipids and proteins, as well as intracellular proteins from many tissues in the cardiovascular, endocrine, immune, muscular or nervous systems [12]. The mechanisms of action not only implicate the classical GCR receptor without transcriptional and/or translational processes, but also non-classical membrane-bound receptors [10, 12, 13].

Differences in efficacy and adverse effects can be observed between different GC, depending on the chemical structure, hepatic clearance and half-life (table 2), as well as on CGR binding affinity, the ratio between glucocorticoid and mineralocorticoid activity and the relative potencies of genomic and non-genomic effects [11, 14]. Furthermore, differences of efficacy, or even relative resistance to GC treatment or effects, as observed in some patients with inflammatory diseases or fibromyalgia, may also be related to genetic factors [15, 16].

In the present LBP setting, the potential beneficial effects of GC appear to be mediated mainly through their analgesic actions, while their anti-inflammatory effects seem to be limited to an adjuvant role. The analgesic actions of GC are mediated through several mechanisms, including both genomic and non-genomic effects, and appear to be brain site-specific [12]. GC seem to play an important role in the modulation of painful stimuli at the level of the spinal cord, as confirmed by studies in rats, where a decrease of neuropeptide expression and increased availability of GABA receptors were observed after chronic GC treatment [17]. It was suggested that the genomic and non-genomic effects on neuronal excitability, for example through Ca2+ currents, were observed only when neurons were activated [12].

Thus, GC have an analgesic effect and their potential benefit has been assessed in numerous animal studies using different animal models of neuropathic “pain”, especially in rats. The results are not clear, as the effects differ depending on the dose of corticosteroids and type of pain,

Table 1: Arguments for mechanical or inflammatory mechanisms of LBP.

Mechanical factors	Inflammatory factors
The nerve root is a fine structure not well isolated to withstand compressions [6].	There is a high prevalence of disc herniation in asymptomatic patients, revealed by the use of imaging in epidemiological studies [6].
The root is attached to the vertebrae by ligaments, which adds tension in case of a herniated disc [6].	The tolerance of nerves to compression significantly decreases when there is inflammation [6].
Animal models showed that mechanical root compression reduces blood flow and distribution of nutritional intake [6].	The application of nucleus pulposus on a nerve, without compression, results in electrophysiological and anatomopathological alterations [6].
The oedema induced by compression could lead to a compartment syndrome, aggravating nerve ischaemia [6].	Response to anti-TNFα in case of acute sciatica [45].
Some studies suggest that decompression is more effective than steroid injection [7].	In a significant percent of sciatica cases (30%, according to [63]), imaging does not show compression but can highlight inflammatory processes [63].
Some surgeons believe that the rapid pain relief after surgery is due to the decrease in compression.	A successful spinal procedure does not always result in a clinically perfect result [5].
Experience shows that some patients who do not respond to conservative treatment are quickly relieved by discectomy.	There is not necessarily a perfect correlation between the severity of symptoms and the size of the hernia [5].
	The analysis of surgical specimens of periradicular fat [64] or disc material [65, 66] reveals the presence of pro-inflammatory cytokines.

Table 2: Characteristics of corticosteroids (adapted from Schimmer BP, Funder JW. ACTH, Adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, editor. Goodman and Gilman’s The pharmacological basis of therapeutics. 12th ed. New-York: McGraw-Hill; 2011. p. 1209–35 [67]).

Corticosteroids	Anti-inflammatory effect	Sodium-retaining potency	Biological half-life / duration of action	Elimination half-life	Equivalent dose mg (oral or intravenous)
Cortisol	1	1	8–12h	1h30	20
Prednisolone	4	0.8	12–36h	2h	5
Methylprednisolone	5	0.5	18–40h	2h	4
Triamcinolone	5	0	12–36h	2h	4
Dexamethasone	25	0	36–72h	3h	0.75

and overall the observations give limited support to GC use in sciatica and LBP. For example, glial activation and neuropathic pain development after ligation of two spinal nerves (L5 and L6) could be prevented in rats by systemic (continuous subcutaneous infusion at 4 mg/kg/day) or intrathecal (80 µg/kg/day) administration of methylprednisolone [18]. Another study in the rat, using a model of sciatic nerve compression by plastic cuff, showed that intraperitoneal administration of 1mg/kg of dexamethasone one hour after surgery led to a reduction of inflammation at the site of compression, as well as a decrease in C-fibres in the sciatic nerve, mechanical allodynia and spinal cord levels of substance P (but not of other peptides) [19]. Similarly, in a third rat model of chronic pain induced by sciatic nerve ligation, other authors demonstrated that the subcutaneous administration of triamcinolone (at 3 mg/kg) five days after surgery reduced thermal hyperalgesia and mechanical allodynia, as well as the number of mast cells expressing TNFα, but not cold allodynia or mechanical hyperalgesia [20].

In the latter study, all data do not support the use of GC. Indeed, the systemic administration of methylprednisolone (intraperitoneal at 12 mg/kg or chronically up to 3 mg/kg/day for three weeks) to healthy rats that underwent a nerve section had no effect on mechanical or thermal nociceptive thresholds, although there was a benefit on the neurogenic oedema with chronic administration [21]. Similarly, a study with the nerve ligation model in rats showed that intrathecal administration of methotrexate could prevent allodynia and the activation of microglia in the spinal cord, although there was no benefit associated with the use of dexamethasone [22].

Other models have also been used to demonstrate the benefits of GC use for neuropathic pain, such as sciatic nerve section in rats, causing a pain syndrome known as causalgia, or complex regional pain syndrome Type II (CRPS). Here again, the administration of methylprednisolone as a continuous infusion (3 mg/kg/day) for three weeks accelerated recovery from mechanical and thermal hyperalgesia and decreased Fos expression in the posterior horn of the spinal cord. However, no effect was observed regarding substance P and NK1 receptors [23]. Similarly, the subcutaneous administration of four doses of triamcinolone acetonide (1.5 mg/kg one hour pre-surgery and then on days 1, 2 and 3 post-surgery) significantly reduced the increases in various cytokines and mechanical hypersensitivity induced by spinal nerve ligation in the rat. However, corticosteroid treatment had no effect if started seven days after surgery [24], so the transposition to humans of these animal findings with very early steroid administration, sometimes even pre-injury, is questionable.

Perhaps an animal model with closer resemblance to human pathology is the application of autologous nucleus pulposus to the dorsal root ganglion. Using this model in 174 rats, Tachihara et al. showed that periradicular GC injections prevent the development of mechanical allodynia induced by chemical irritation of the root due to the nucleus pulposus. However, no difference was observed between the injection of dexamethasone alone, in combination with lidocaine, or lidocaine alone, suggesting that the addition of steroids may not be necessary during periradicular injection [25]. Furthermore, a recent study using a model of disc degeneration in mice (by inactivation of the SPARC gene), causing changes in the behaviour of the animals in terms of movement discomfort and hypersensitivity to cold, revealed a beneficial effect of morphine, but not gabapentin or dexamethasone, administration.

Thus, it appears that these studies in animal models, although they differ in GC type, dosage and route of administration [26], confirm a certain analgesic effect of GC with a reduction in neuropathic pain. However, the effect reported is limited and depends on the very early introduction of treatment, which might be difficult to achieve in medical practice.

On the other hand, there are also experimental data from human studies, showing results as ambivalent as in animals, but which could constitute a rationale for GC use in LBP and sciatica. In a study using quantitative measures of sensitivity after surgical treatment of disc herniation, systemic perioperative administration of methylprednisolone demonstrated some benefit regarding pain at two weeks, and a protective effect on C-fibres in combination with surgery was also observed for up to two years [27]. Similarly, the administration of dexamethasone combined with bupivacaine for brachial plexus block prolonged the duration of sensory and motor block, and reduced the consumption of analgesics and verbal pain score for 24 hours [28].

However, in a model of skin burn in healthy volunteers, the systemic intravenous administration of dexamethasone (8 mg) two hours before the test did not reduce the changes induced by inflammatory mediators in terms of sensory threshold, pain perception and skin rash, in comparison with placebo [29].

Finally, a review published in 2005 on the treatments available for postherpetic neuralgia as a model of neuropathic pain revealed only one study favourable to the use of corticosteroids [30]. This study, published in 2000, evaluated the intrathecal administration of methylprednisolone combined with lidocaine. However, the results obtained were never confirmed, probably because of the risks inherent to this route of administration [31]. Moreover, a recent Cochrane review on postherpetic pain prevention with corticosteroids showed negative results [32].

Other experimental studies in humans provided more indirect evidence of the possible link between corticosteroids and pain perception. Indeed, the induction of hypocorticism by administrating metyrapone to healthy subjects has been shown to be associated with a lower pain threshold (mechanical stimulus) and a reduction of sensitisation in the short term [33]. Furthermore, in subjects with depression, the increase in thermal pain threshold after intravenous treatment with clomipramine seemed to be associated with a low neuroendocrine response to antidepressants. Indeed, in this study on a small group of patients (n = 19) suffering from moderate to severe depression treated intravenously with clomipramine and stratified according to their blood levels of cortisol and prolactin in response to clomipramine, Kundermann et al. revealed a decrease in thermal sensitivity in patients with low neuroendocrine response to antidepressants. There was only a significant difference in terms of response to cortisol, but prolactin did not appear to play a role, suggesting a link between

cortisol secretion in response to clomipramine, and serotonergic dysfunction in pain perception in depressed patients. However, the authors found no difference between subgroups in terms of clinical variables such as number of pain sites, pain intensity and "unpleasantness" of pain [34]. Overall, the pharmacological and experimental data, in animal and human studies, demonstrated a role for GC as analgesics by mechanisms certainly not fully understood, although the effect remains modest. Therefore, these results can constitute a rationale for the use of GC in sciatica and LBP, although it is unlikely that their widespread use is based on such data.

Clinical evidences (the inconvenient truth)

Although the use of GC in sciatica and LBP can be rationalized, their widespread use remains difficult to understand today in light of the evidence revealing a lack of significant clinical efficacy. In the hierarchy of therapeutic measures for LBP, the local use of GC remain the gold standard for many physicians, although it is usually performed by specialists. Nevertheless, and despite over a century of use, the effectiveness of epidural GC injections remains controversial, and at best, its use is considered as reasonably safe [35].

A comprehensive review was published in December 2010 as part of a Health Technology Assessment. At the lumbar level, epidural injections (caudal, foraminal or interspinous) carried out for LBP with or without radicular syndrome, spinal stenosis, failed back surgery syndrome and several other indications were evaluated. Similarly, facet, medial branch blocks, sacroiliac and intradiscal injections were also analysed in a voluminous report of 299 pages with more than 200 scientific references. The authors sought to answer four questions: (1) what was the evidence available for the efficacy and effectiveness of these injections; (2) what was the evidence available for their safety; (3) what was the evidence available for their effectiveness and/or safety in some specific subgroups of the population; and (4) what were the cost implications and cost-effectiveness [36]. In response to the impact of this work and its subsequent publication, health authorities in the state of Washington decided not to reimburse intradiscal or facet injections, or medial branch block injections. A recent Swiss review, which focused only on the radicular syndrome, did not find many more arguments to recommend this type of procedure, with some room for spinal injections. For the authors, "Spinal injection using radiographic guidance appears to provide some beneficial short-term effect on pain. It might be offered when pain treatments according to the WHO steps have failed" [37]. However, this approach appears to be unfavourable in terms of cost-effectiveness [38].

The lack of demonstrable evidence does not seem to deter the advocates of GC injection, although studies are regularly published showing similar results. A recent randomized, controlled and double-blind study showed no benefit, using statistic and clinical thresholds of significance, at six, 12 and 52 weeks of follow-up. Indeed, caudal epidural steroid injections in patients suffering from lumbar radicular syndrome for more than 12 weeks were not more effective than caudal epidural injections of NaCl or even subcutaneous injections of NaCl [39]. Another recent study comparing the effectiveness of caudal epidural injections of anaesthetic or corticosteroids in patients with disc herniation and radiculitis did not reveal any significant difference [40]. The same group demonstrated an identical observation for discogenic pain without disc herniation or radiculitis [41], post surgery syndrome [42] and even spinal stenosis [43]. Finally, a recent study in patients with lumbar spinal stenosis and monoradicular involvement showed that epidural injection of etanercept was superior to dexamethasone [44] and the inflammatory component alone could not explain the results obtained with anti-TNFα [45], compared to those with GC.

However, the proponents of this approach always find flaws in a given study to which they attribute the lack of efficacy observed, giving them a reason to perform new studies. Among the most classical critics, the choice of product is sometimes discussed. However, it is known that epidural injection of 15 mg of non-particulate dexamethasone phosphate and 80 mg of particulate methylprednisolone in two groups of 30 patients showed no significant difference in terms of efficacy or tolerance [46].

Another example, the presence or absence of inflammatory lesions does not seem to explain the response to GC. A study published in 2004 evaluated the effectiveness of interlaminar or foraminal epidural injections under fluoroscopy in 232 patients with degenerative disc disease, including 93 with end-plate inflammatory reactions as identified on magnetic resonance imaging (MRI), corresponding to MODIC type I changes. This study showed greater improvement in Oswestry score in patients with MODIC I [47]. However, the difference was small, and most importantly, a recent systematic review [48] highlighted the methodological limitations of this work. The same review revealed that only one other study, of better quality, on the relationship between type I or II MODIC lesions and response to intradiscal GC injections, showed a short-term effect (at one month) on pain, but not on function [49].

In summary, although the infiltration of GC, more or less guided, is often considered the "gold standard," there is no evidence to recommend their use for LBP or radicular pain, and certainly not as first-line strategy. A comprehensive discussion of the different routes of administration and efficiency would go well beyond the purpose of this article, but none has emerged as an approach with effectiveness greatly superior to others.

In general, the practitioner is more directly concerned with the use of steroids in a form that he can prescribe himself, that is to say, oral, intramuscular or intravenous. However, in this case also, the literature is clear. A recent systematic review with meta-analysis on the use of various types of oral or parenteral steroids came to the conclusion that there was a lack of superiority of steroids over placebo in sciatica and clearly discouraged their use in view of the poor effectiveness-tolerance ratio [50].

Let us remind the reader, who may wonder about insufficient dosing, that patients received oral doses up to 64 mg/day of dexamethasone on the first day, for a total, cumulative dose of 144 mg of dexamethasone in decreasing doses

over one week [51], 160 mg of methylprednisolone acetate for single intramuscular dose [52] and 500 mg methylprednisolone as a single intravenous dose [53]. There was no clinically meaningful benefit in any case that could be demonstrated in the short, medium or long term, regarding symptoms, function or return to work. Although in the literature there is still a reasonable doubt on the short-term efficacy of epidural use, there is definitely no evidence to support the systematic use of GC for LBP or sciatica, a common practice that should thus be avoided.

Cost-effectiveness and safety

There is globally little evidence for efficacy, effectiveness and cost-effectiveness. Moreover, the risks associated with the prescription of GC are often underestimated. The systemic risks induced by steroids on the metabolic, endocrine, cardiovascular, infectious, bone (not only osteoporotic fractures, but avascular necrosis of the femoral head), neuropsychiatric, ophthalmological and cutaneous systems are well known. Thus, it would be wrong to believe that the administration schemes for GC used in LBP and sciatica are safe. Regarding the specific problem at hand, a few things are worth noting. Firstly, there are two types of adverse effects of corticosteroid administration: (1) those resulting from withdrawal (acute adrenal insufficiency or flare ups of the underlying disease), and (2) those resulting from continued use of supraphysiological doses (table 3). Indeed, hypothalamic-pituitary-adrenal suppression, ranging between four days to six weeks, has been described even after a single epidural or intramuscular GC injection [35]. Secondly, other unexpected side effects have also been reported immediately after epidural injection, such as menorrhagia [54], hiccups [55], cauda equina syndrome [56] or even intraspinal lipomatosis [57]. More surprising and disturbing is the possibility of worsening neuropathic pain by methylprednisolone injection [58], or the possible interference with the herniated disc resorption by a corticosteroids-induced reduction of metalloproteinase-3 expression [59]. Finally, even the most enthusiastic physicians now fear medullary infarction, a very rare but dramatic complication described in cases of foraminal injection [37], not to mention the "simple" complications such as infection, haemorrhage, etc., associated with any invasive procedure.

Finally, it is worth noting that the analgesic effects of GC are not yet recognized by health authorities. GC have no official indication for LBP with or without a radicular component, at least in Switzerland. Thus, their use in these conditions should be considered off-label. Moreover, the epidural use of particulate forms of GC is usually formally contraindicated by the manufacturers.

Conclusions

Corticosteroids are powerful anti-inflammatory and analgesic adjuvants for certain chronic pain conditions [29]. Even if there is an inflammatory component in the pathogenesis of discogenic radicular syndromes, and even if animal studies can bring a theoretical rationale for their use, the clinical evidence available do in no way support the systemic use of GC for LBP. Thus, in view of the lack of demonstrable benefit, the risk of use is unacceptable.

The discrepancies between animal and human studies have been the subject of a recent systematic review. The authors mostly pointed out the limitations of animal studies because of differences between species, of the methodology of animal studies itself and of factors that may explain the discrepancy between animal experiments and clinical trials (e.g, bias, random error, differences between animal and human models, etc.) [60]. Moreover, in light of the recent literature, the place of GC in syndromes, painful or not, of the nervous system seems to be increasingly reduced. However, the question remains regarding whether there is a place for the use of locoregional GC in LBP and sciatica. There are probably some "desperate" clinical situations in which the physician will feel more comfortable prescribing infiltration than systemic analgesics, NSAIDs or morphine treatment, although systemic GC do not have a place even in these cases. Nevertheless, we should bear in mind the reason why we move away from the evidence, and data supporting the use of infiltration remain poor. It is possible that some patients are actually better candidates than others for such treatment, and a group from the United States recently published data showing that the presence of a fibronectin and aggrecan complex in the epidural cleaning fluid was a predictor for the response to epidural corticosteroid injection in patients with lumbar radiculopathy on disc herniation [61]. However, it seems unlikely that such a complex approach could find a clinical application in the near future. Above all, any approach demonstrating the existence of a subgroup of LBP targets for GC treatment should start with a definition and scientific identification of such a subgroup, with a secondary unequivocal demonstration of treatment efficacy in this subgroup, and not the reverse. Ultimately, we must learn to question our secular practices because the evidence does not support the current widespread use of GC for LBP and sciatica. Although such a challenge can be difficult, we can learn from the experience of our colleagues from the centre for para-

Table 3: Principal adverse effects (adapted from Schimmer BP, Funder JW. ACTH, Adrenal steroids, and pharmacology of the adrenal cortex. In: Brunton LL, editor. Goodman and Gilman's The pharmacological basis of therapeutics. 12th ed. New-York: McGraw-Hill; 2011. p. 1209–35 [67]).

Withdrawal	**Long-term treatment with supraphysiological doses**
Acute adrenal insufficiency	Hypokalaemic alkalosis
Flare-up of the underlying disease	Hypertension
	Hyperglycaemia
	Increased susceptibility to infection
	Osteoporosis
	Myopathy
	Behavioural disturbance

plegics in Nottwil, who were able to change their practice of management of spinal cord injury by drastically decreasing the doses of GC administered, with no difference in neurological outcome [62].

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