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Pertovaara, Antti

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Editorial comment

Pain treatment with intrathecal corticosteroids: Much ado about nothing? But epidural corticosteroids for radicular pain is still an option

Antti Pertovaara[a], Harald Breivik[b,c,d,*]

[a] Department of Physiology, Faculty of Medicine, University of Helsinki, Helsinki, Finland
[b] Department of Pain Management and Research, Oslo University Hospital, Norway
[c] Department of Anesthesiology, Oslo University Hospital, Norway
[d] Faculty of Medicine, University of Oslo, Norway

The Nobel Prize in Physiology or Medicine 1950 was given to Edward C. Kendall, Tadeus Reichstein and Philip S. Hench for their discoveries relating to the hormones of the adrenal cortex, their structure and biological effects. The pioneering work by these three scientists paved the way for medical use of glucocorticoids in inflammatory conditions. Interestingly, as pointed out in a recent review [1], findings by Scandinavian medical scientists as early as six decades ago suggested that inflammation associated with nerve compression is an important component of sciatic pain [2,3]. This proposal together with the discovery of glucocorticoids inspired a large number of clinical studies in which back pain was treated with epidural glucocorticoids (see for review [1]).

1. Actions of glucocorticoids that attenuate pain experiences are not in the spinal cord

While glucocorticoids are known to have multiple molecular actions that can contribute to pain modulation [1], it is still unclear which of these multiple mechanisms are critical for the analgesic action of glucocorticoids in back pain. Nor is it quite clear whether an action on tissues around the nerves or direct action on nerves and spinal cord might have a key role in the effect of glucocorticoids in back pain [1]. It has been hypothesized that if the cause of analgesic effect by glucocorticoids in back pain patients is predominantly due to action on the spinal cord, then glucocorticoids should be applied intrathecally rather than epidurally. Since 1960 [4], a number of clinical studies were performed using intrathecal administration of glucocorticoids in neuropathic pain syndromes, particularly in sciatica and postherpetic neuralgia. As summarized in a recent review [1], the results were variable. Many studies reported serious adverse effects, due to which the use of intrathecal glucocorticoid administration declined until the turn of the millennium, when a Japanese group published two studies reporting that intrathecal glucocorticoid (methylprednisolone) combined with lidocaine is a highly effective treatment in intractable postherpetic neuralgia when compared with lidocaine alone [5,6]. Unfortunately, many investigators elsewhere have failed in their attempts to replicate this most promising clinical finding, the treatment has had severe side-effects, or both [1].

2. Finally a decisive study excluding subdural and subarachnoid site of analgesic effects

To find out potential explanations for the variable results that have been obtained in clinical trials with intrathecal glucocorticoids, Rijsdijk and co-workers performed a preclinical study that is reported in this issue of *Scandinavian Journal of Pain* [7]. Rijsdijk et al. postulated that the aetiology of postherpetic neuralgia is not clear and may add to variability in clinical studies. Therefore, they assessed the effect of intrathecal corticosteroid treatment in three well-established experimental models of sustained pain that were induced by

(1) an inflammatory compound carrageenan,
(2) the neurotoxic compound formalin, or
(3) spinal nerve ligation.

Moreover, to find out whether formulation of the glucocorticoid might contribute to the variability in clinical findings, they compared results induced by two different methylprednisolone formulations: (1) one with depot characteristics and reduced preservative concentrations and (2) one methylprednisolone formulation without depot effect and without preservatives.

In addition to assessing the effect of glucocorticoid treatment on *pain behaviour*, they assessed the treatment effect on *biomarkers of neuronal injury* and *glial activation*.

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* Corresponding author at: Oslo University Hospital, Dept Anesthesiology, Pbox 4950 Nydalen, 0424 Oslo, Norway. Tel.: +47 23073691.
E-mail addresses: antti.pertovaara@helsinki.fi (A. Pertovaara), harald.breivik@medisin.uio.no (H. Breivik).

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3. No therapeutic effect by intrathecal methylprednisolone on pain behaviour

Among the main findings of the study are that the maximum tolerable doses of intrathecally administered methylprednisolone, independent of the formula, had no effect on pain behaviour in the inflammatory model or the spinal nerve ligation model. In the formalin model, only the delayed mechanical hypersensitivity one week after the formalin treatment was attenuated, while the sustained formalin-induced pain behaviour was not influenced by the intrathecal corticosteroid treatment. In the spinal nerve model, effects of systemic and perineural as well as intrathecal corticosteroid treatments were shown to have no effects on pain behaviour.

4. Methylprednisolone reduced activation of spinal cord microglia but not astrocytes by spinal nerve ligation

In the spinal nerve ligation model but not in other pain models, the activation of spinal microglia was reduced by intrathecal corticosteroid treatment, while corticosteroids failed to influence activation of spinal astrocytes or the index of injury in spinal neurons, independent of the pain model.

5. Intrathecal glucocorticoids for neuropathic pain is ineffective and risky

The thorough and carefully performed experimental study by Rijsdijk et al. using three different types of pain models and two different methylprednisolone formulations indicates that intrathecal corticosteroids have poor, if any analgesic effect [7]. Earlier, when analysing results of randomized controlled clinical trials, Rijsdijk et al. proposed that the efficacy of intrathecally administered corticosteroids is at best doubtful and associated with a measurable risk of adverse effects [1]. Their present experimental results are in line with this proposal. Together the earlier clinical findings [1] and present experimental results indicate that intrathecal administration of corticosteroids may not provide a promising treatment strategy for chronic pain.

6. Interlaminar (or trans- or intra-foraminal) epidural corticosteroids can relieve radicular back pain

When epidural injections of corticosteroids for lumbar radicular pain became widely used in the 1970s and later, based on the observations by Lindahl and Rexed that there is inflammatory changes in and around lumbar nerve roots/spinal nerves of operated cases of sciatica [3], convincing clinical results were reported [8]. Inflamed nerve roots or oedema from prolapsed disc content creates restricted space for the spinal nerve-roots. A spinal nerve in the intervertebral foramen may even be compressed. Corticosteroids placed in the epidural space are effective in reducing these inflammatory reactions and pain [8]. This pain relief lasts for days to weeks and even months.

7. Epidural corticosteroids will NOT relieve back pain

Already in 1975 we realized that it is radicular pain that epidural corticosteroids can relieve, while low-back pain is not relieved (for reference [8,12]). The opinions about the effects of epidural corticosteroids were confused and muddled by epidural and even intrathecal injections of corticosteroids for "low-back pain." Patients with both low-back pain and radicular-sciatic pain are relieved from the latter by epidural corticosteroids, leaving the back-pain unchanged [8]. This was a clue to the mechanisms of epidural corticosteroids: It is the local anti-inflammatory effect, not a specific spinal cord effect. A study in which we gave the same dose of methylprednisolone epidurally or intramuscularly again indicated a local effect (for reference, see [8]).

8. Transforaminal epidural corticosteroid injections may be too risky.

Transforaminal epidural corticosteroid injection (or intraforaminal injection) is more effective than interlaminar epidural injections because the injectate comes closer to where the pathology is [9]. But cases of intra-arterial injections during such trans- or intra-foraminal injections have caused catastrophic complications leading to permanent paraplegia. Particulate corticosteroids can obstruct lumen of segmental arteries to the spinal cord; especially unfortunate when one of the main supply arteries to the anterior spinal artery (e.g. Adamkiewicz artery) is obstructed [9]. This has happened even during so-called "safe" transforaminal injections and during radiologically controlled needle placement [9]. These are rare complications, but catastrophic events when they do happen.

9. Recommendations for transforaminal corticosteroid injections

Non-particulate corticosteroids with contrast, injected transforaminally during real-time fluoroscopy may be safer [9]. However, this is no guarantee against serious complications. Therefore, the less effective but safer interlaminar epidural injection is what is recommended and only when there is clear radicular pain [9]. The pain relief obtained in this way is an anti-inflammatory effect, creating mechanically more room for the nerve-roots and spinal nerves, and this is possibly associated with a direct effect on the cell membranes of spinal nerves and nerve-roots that contributes to pain suppression.

10. Epidural corticosteroids do NOT relieve radicular pain via spinal cord mechanisms.

Corticosteroids do not have a direct analgesic action on the spinal cord as demonstrated by the present research-report in the *Scandinavian Journal of Pain* by Mienke Rijsdijk, Camilla I. Svensson and co-workers in Tony Yaksh's research group [7]. They placed the corticosteroid directly on the spinal cord, close to the spinal dorsal horn, so that if corticosteroids were inducing analgesia due to a direct action on spinal cord mechanisms (e.g. via corticosteroid receptors expressed by inter-neurons of the "pain-gate"), it should show up as a significant analgesic effect. It did not, and therefore, an epidural corticosteroid injection will be even less likely than an intrathecal injection to cause pain relief via direct spinal cord mechanisms.

The study by Rijsdijk et al. [7] together with clinical evidence reviewed by the same group [1] should impress "interventionalists," preventing the clinical use of intrathecal injections, even for intractable postherpetic neuralgia [1,5–7]. Intrathecal injections of corticosteroid are not only INEFFECTIVE, they are also HAZARDOUS, with a risk of spinal cord damage and catastrophic permanent neurological injury.

11. Do not inject epidural corticosteroids if there is an increased risk of bleeding

Tragic neurological complications to epidural injections have occurred in patients on vitamin-K antagonists, the new oral antihaemostatic drugs (NOAHs), or platelet inhibitors. Therefore, spinal

interventions should not be attempted in patients who have increased risk of bleeding due to any antihaemostatic drug [10,11].

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