Optimizing care in lumbar radiculopathy and neurogenic claudication: from injection to inference, and from clinician to algorithm

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Part I

Optimizing care for lumbar radiculopathy

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General introduction and outline

Lumbosacral radiculopathy, often used interchangeably with sciatica in the literature despite referring more broadly to a condition of the lumbar or sacral nerve roots, is a neurological disorder with a reported lifetime prevalence of up to 43% [1]. Generally, it is characterized by unilateral radicular pain extending along one of the exiting nerve roots and is caused by either lumbosacral disc herniation (LDH) or degenerative spinal stenosis (LSS) due to age-related disc degeneration, hypertrophy of the ligamentum flavum and zygapophyseal joint, and osteophyte formation [2]. Radicular pain is frequently accompanied by functional impairments, back pain and motor-sensory deficits [3]. Originally, nerve root compression was assumed to be the primary cause of symptoms. However, research over the past decades has demonstrated that a significant proportion of patients exhibit severe symptoms despite the absence of nerve root compression on imaging. Conversely, some patients present with clear radiological evidence of nerve root impingement but experience little to no symptoms [4-6]. As a result, the general idea has changed and it is now accepted that the pathophysiology of lumbosacral radiculopathy is a multifaceted interplay involving inflammatory processes and immunological responses in conjunction with mechanical compression [7-10]. Exposure of the nerve root to nucleus pulposus material has been shown to elicit an inflammatory response, including cytokine release and recruitment of pro-inflammatory cells, which exacerbates pain and neural dysfunction. Stenosis can result in nerve root oedema and inflammation caused by local ischemia as a result from congestion of venous blood around the nerve root inducing cytokine release. Additionally, vertebral end plate devascularization may strengthen this response [10-13].

Disease progression, however, usually differs as patients with LDH are younger on average and have a more acute onset of symptoms which may aggravate when coughing, sneezing or leg-straightening, while patients with LSS often are older and experience gradually increasing symptoms that may exacerbate during standing or walking. However, for both patient groups, the impact on daily functioning can be severe, necessitating effective management strategies [14]. Since lumbosacral radiculopathy due to LDH may follow a favorable, self-limiting course, and patient outcomes after one year of follow-up have been shown to be similar between surgical and non-surgical groups, initial treatment is conservative for several weeks to months before considering imaging and non-conservative interventions [15-18]. There is less consensus on the optimal treatment approach for LSS, as its symptoms usually follow a more chronic course, though some patients may still experience spontaneous resolution of their symptoms [19-21]. In both patient groups, oral pain medication often provides inadequate relief, and the substantial impact of the condition leads to significant medical and socio-economic costs [22].

One of the primary interventional treatments for lumbosacral radiculopathy is an epidural steroid injection (ESI), which aims to mitigate inflammation and provide symptomatic relief. The origins of this technique date back to 1895 when Bier anesthetized the lower body of one of his residents by injecting a cocaine solution into the intrathecal space [23]. Building on this, Cathelin and Sicard in the early 1900s adapted the approach by using the caudal route to remain within the epidural space [24,25], and it was not until the 1950s that Robecchi and Capra introduced the first periradicular steroid injection with hydrocortisone, laying the foundation for modern ESI [26]. In addition to the caudal approach, interlaminar and transforaminal techniques have been developed. Particularly the transforaminal epidural steroid injection (TEI) approach is now widely employed as it is considered the most selective one of techniques to deliver corticosteroids near the affected nerve root.

Given its potential to reduce inflammatory mediators and modulate immune responses [11,27-29], TEI is commonly administered as a minimally invasive alternative for patients with lumbar radiculopathy who do not respond adequately to conservative treatment [30]. However, its efficacy remains a topic of debate due to inconsistent findings in the literature. While some studies report significant pain relief and functional improvement, others suggest only limited benefits compared to placebo treatments. A 2012 systematic review and meta-analysis by Pinto et al. found a slight favour for corticosteroids but questioned the clinical utility [31]. Since then, several additional randomized controlled trials have been conducted, specifically for the transforaminal approach, highlighting the need for a renewed evaluation of the effectiveness of TEI.

The effectiveness of TEI in patients with lumbosacral radiculopathy may depend on the underlying etiology; however, this remains uncertain. The majority of studies have focused on patients with MRI-confirmed LDH, while relatively few have evaluated TEI outcomes in those with radiculopathy due to other etiologies or in the absence of a compressive lesion on imaging [32,33]. The studies that have compared the effect of TEI between patients with LDH and those with other etiologies suggest comparable outcomes, though findings vary based on the outcome measure and duration of follow-up [34-36]. If TEI provides symptom relief independent of the underlying pathology, routine pre-treatment MRI scans may not be necessary. One study specifically indicated that MRI prior to TEI may be redundant, as it did not significantly influence treatment effectiveness or clinical decision-making [36]. However, the overall body of evidence remains constrained by the small number of studies and the lack of prospective data.

Beyond the underlying etiology of symptoms, no consensus exists regarding other factors associated with TEI effectiveness. Some studies suggest that patients with a shorter duration of symptoms may experience greater benefit from TEI compared to those with a more chronic history [32], or that early pain relief following TEI could serve as a prognostic indicator of long-term outcomes [37,38]. Various demographic, clinical, and radiological variables have been explored; however, no strong conclusions have been drawn, largely due to the considerable heterogeneity in patient populations, epidural steroid techniques, and outcome measures. This lack of consistency has precluded the development of a predictive model for TEI treatment success and, consequently, the implementation of more patient-tailored therapeutic strategies for patients suffering from lumbosacral radiculopathy.

AIMS AND OUTLINE OF THIS THESIS:

1. The only systematic review and meta-analysis comparing the effectiveness of a transforaminal epidural steroid injection (TEI) to placebo – either a transforaminal injection with saline or a sham-injection in the para-spinal muscle – dates back to 2012 [31]. Since then, multiple randomized controlled trials have been conducted, primarily evaluating transforaminal injections. Given these new studies, a reassessment is warranted to determine whether the additional data alter the existing conclusions. Therefore, this first aim is to systematically review and update the current evidence on TEI efficacy compared to placebo in patients with lumbosacral radiculopathy (Chapter 2).
2. TEI has become an increasingly popular treatment for patients with lumbosacral radiculopathy. Since this condition can be caused by a variety of spinal pathology, it is essential to determine whether TEI effectiveness depends on the underlying etiology. Hence, the second aim is to assess the effectiveness of TEI in patients with MRI-confirmed lumbar disc herniation (LDH) compared to those with alternative causes or no compressive lesion on imaging, using data from a large retrospective cohort (Chapter 3).
3. To optimize treatment strategies, it is essential to identify factors that positively or negatively affect patient outcome after treatment with TEI. Therefore, the third aim is to comprehensively review all studies that have examined demographic, clinical, or radiological parameters and their association with the outcome of a single transforaminal injection in patients with lumbar radiculopathy secondary to disc herniation or spinal stenosis (Chapter 4).
4. Current literature suggests that patients with a shorter duration of symptoms may benefit more from TEI. Moreover, there is some evidence that

routine MRI before TEI may be redundant. At present, patients are treated conservatively for several weeks to months before referral to a neurologist and subsequent MRI examination. It is usually only after these steps that they become eligible for TEI or surgical intervention. During this period, symptoms often remain inadequately managed, impairing daily function and contributing to absenteeism. Given these findings, our fourth aim is to investigate whether patients may benefit from early TEI administration. To address this, we present the protocol for a randomized controlled trial comparing the effectiveness of TEI to usual care in patients experiencing acute lumbar radiculopathy symptoms (Chapter 5).

5. The identification of prognostic factors for TEI is significantly limited by the lack of large cohorts and prospective data. Furthermore, substantial heterogeneity in study designs and treatment protocols—combining outcomes from caudal, interlaminar, and transforaminal injections using various corticosteroids—complicates personalizing treatment strategies. To achieve this, the fifth aim is to develop a prediction model for TEI success. We present the protocol for a large, multi-center, prospective cohort study designed to assess the effects of TEI in patients with MRI-confirmed disc herniation or stenosis, congruent with clinical findings, and to identify demographic, clinical and radiological parameters associated with treatment outcomes (Chapter 6).
6. Vertebral endplate changes, known as Modic changes (MC), have been proposed as markers of inflammatory processes and are associated with disc herniation and less favorable outcomes after surgery [39-46]. It has been suggested that the absence of MC correlates with reduced radicular pain and improved clinical outcomes, whereas their presence may aggravate symptoms [46]. Consequently, in patients with MC at the level of disc herniation, inflammation may play a more significant role, and TEI may be more effective. The sixth aim is to assess this association using prospective data from our large cohort study (Chapter 7).

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