Radiculopathy and radiating low back pain in general practice

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Chapter 1

General Introduction

LUMBOSACRAL RADICULAR SYNDROME

Lumbosacral radicular syndrome (LRS) is defined, according to the Dutch college of general practitioner's (NHG) guideline, as a shooting, burning pain radiating from the back into the leg to below the knee ("sciatica"), in combination with a positive straight leg raising test and/or segmental (= originating from a single nerve root) neurological symptoms such as paresis, paraesthesia and diminished reflexes.[1] This definition by the NHG guideline is in accordance with the one provided by the Dutch college of neurologists in their multidisciplinary guideline.[2]

LRS is, according to these guidelines, a clinical syndrome diagnosis, most commonly caused by protrusion of a lumbar intervertebral disc. Radiological investigations such as magnetic resonance imaging or computed tomography are not required to establish the diagnosis. In fact, they are advised against, if deployed for reasons other than the consideration of surgery or the presence of alarm symptoms. Scan results bear little relation to symptoms and seem to add no prognostic value.[1-4] Establishing the clinical diagnosis of LRS can therefore be done in general practice, by means of anamnesis and physical examination.

The annual incidence of LRS in Dutch general practice is estimated at 9 new cases per 1,000 persons, and the prevalence 15 cases per 1,000, according to large registry databases from Dutch general practices.[5] The prognosis of conservatively treated LRS is favourable: within eight weeks, 80% of patients have reached tolerable pain levels and resumed their work.[6] However, this does not mean that they have all recovered completely. It is estimated that in 25% of patients, radicular pain lasts for more than three months.[1]

LRS is an expensive condition in terms of medical costs as well as in terms of productivity loss. In a cost of illness study, Lambeek *et al* found annual Dutch society costs for low back pain of 3.5 billion Euros in 2007, mostly due to the indirect costs of work absenteeism (1.7 billion Euros) and disability (1.4 billion Euros).[7] Since ten per cent of low-back pain patients are thought to suffer from radiculopathy, and considering LRS is most prevalent among working-aged male patients (25 to 64 years), it may be assumed that LRS contributes largely to the economic impact of low back pain in The Netherlands.[1]

TREATMENT OF LUMBOSACRAL RADICULAR SYNDROME

In the Netherlands, GPs treat LRS. According to their guideline on LRS, the treatment consists of analgesic medication as needed and maintaining normal daily activities as much as possible. Although the evidence for efficacy of non-steroidal anti-inflammatory drugs and opiates in LRS is not profound, these analgesics are recommended by the guideline as therapy of first choice.[1, 6, 8] Physical therapy, chiropraxy and manual therapy are not recommended since there is insufficient evidence for efficacy.[8]

Referral is necessary in the presence of alarm symptoms that may indicate:

- cauda equina syndrome (urine retention or incontinence, increasing pain in both legs, profound or rapidly progressive paresis),
- a serious underlying cause of the radicular pain, such as malignancy (unintended weight loss, increased erythrocyte sedimentation rate, medical history of cancer),
- osteoporotic vertebral fracture (age of onset higher than 60, female, low body mass index).

Referral can be considered if the radicular pain remains bothersome in spite of analgesic treatment, or if it lasts for more than six weeks.[1]

CORTICOSTEROID INJECTIONS IN LUMBOSACRAL RADICULAR SYNDROME

In LRS, compression of a low lumbar nerve root by a protruding intervertebral disc results in an inflammatory response, primarily mediated by phospholipase-A2 and tumour necrosis factor α.[9,10] The combination of this inflammatory process and the mechanical compression causes the radicular pain, the neurological symptoms and the loss of functionality in LRS.[11-14] Corticosteroids are medicines with powerful anti-inflammatory and analgesic properties, which include inhibition of prostaglandin and neuropeptide synthesis, blockage of phospholipase A and impairment of nociceptive C-fiber conduction.[15] Injecting corticosteroids epidurally at the level of the inflamed nerve root may therefore diminish pain and disability in LRS. This intervention is called a segmental epidural steroid injection. In current medical practice, epidural steroid injections are widely applied as a pain treatment for LRS. The exact frequency of which the intervention is applied in The Netherlands is, to our knowledge, unknown, but is estimated to be more than

seven million procedures in 2005 in the US.[16] The NHG guideline on LRS, however, advises against epidural steroid injections in LRS, since the evidence for efficacy is deemed unconvincing.[1] The Dutch college of neurologists guideline on LRS, on the other hand, states that epidural corticosteroid injections can be deployed if other treatment options do not adequately relieve radicular pain.[2]

RESEARCH ON CORTICOSTEROID INJECTIONS FOR LRS

Several systematic reviews and meta-analyses that included clinical efficacy trials on segmental epidural steroid injections have been performed. The most relevant of these are listed below, in order of publication date (most recent first):

In 2012, Pinto *et al* reviewed epidural corticosteroid injections in the management of sciatica including 25 published reports, among which were 23 clinical trials.[17] The pooled results of the 14 trials included in the meta-analysis (1,316 patients) showed a significant short-term positive effect compared to placebo for pain and disability and no statistically significant long-term effects. The overall quality of evidence was rated as high. The authors raised the question whether the intervention has clinical utility since the effects were small.

Buenaventura *et al* included four randomized trials with a combined study population of 502 patients in a systematic review assessing the effectiveness of lumbar transforaminal steroid injections for low back pain and sciatica in 2009. All studies showed sizeable positive results for short-term pain relief and two of those were also positive for long-term pain relief.[18]

In a systematic review in 2007, Luijsterburg *et al* distinguished the 30 included studies with 2,780 patients by the control groups that were used. Groups compared were epidural corticosteroid injections versus placebo, epidural steroids versus usual care and epidural steroids versus another kind of injection.[8] Data were not pooled. Evidence was deemed to be conflicting and a definite conclusion was not reached. The overall advice regarding the application of epidural steroids in LRS was therefore negative, although it was remarked that targeted injections under radioscopic guidance (transforaminal injections) were more efficacious than epidural injections (interlaminar approach).

Abdi *et al* performed a systematic review assessing the efficacy of epidural corticosteroid injections in the management of chronic lumbar (and cervical) radicular pain in 2007.[16] The authors distinguished the included studied by the various injection techniques. All 63 studies were included in a vote count from

which the end conclusion was derived: strong evidence exists for the short-term efficacy of interlaminar, transforaminal and caudal epidural steroid injections in the case of chronic lumbar radicular pain, and moderate evidence for long-term relief. Six studies about transforaminal injections were included by DePalma *et al* in their systematic review of 2005.[11] The authors conclude that level III (= moderate) evidence is available in support of selective nerve root injections for lumbosacral radiculopathy. They deemed the intervention a "minimally invasive and safe treatment for a painful syndrome".

Vroomen *et al* included four clinical trials in their systematic review in 2000, applying rigorous selection criteria which resulted in small heterogeneity of patients, control groups and outcome measures.[6] The authors did not distinguish between injection techniques or between short-term and long-term effects. Data were pooled. The pooled odds ratio for the four RCTs was 2.2 (95% CI 1.0 – 4.7). The end conclusions were that epidural steroid injections are more effective in acute than in chronic complaints, more effective in carefully selected than in heterogeneous patient populations (i.e. clear signs of radiculopathy rather than non-specific low back pain) and that the highest-quality studies showed the lowest odds ratios for efficacy. Their overall conclusion was that epidural steroids lack serious side effects and may be beneficial for radiculopathy.

Two older systematic reviews by Watts and Koes were published in 1995.[19, 20] Koes *et al* included 12 randomized controlled trials with 534 patients on the efficacy of epidural steroid injections in low back pain and sciatica, six of which reported positive results. The overall conclusion was that efficacy of epidural steroids in radiculopathy had not yet been established. Watts *et al* included 11 trials in their meta-analysis, (9 of which were also reviewed by Koes) with 907 patients. They concluded that epidural steroid injections were efficacious on both short-term and long-term (OR 2.61 and 1.87 respectively). The difference in conclusions between these reviews that made use of practically the same set of studies has been reflected upon by Kevork Hopayian and Miranda Mugford, who concluded that it was probably due to differences in assessing methodological quality of the papers and the methods for summing up the evidence.[21] Also, the fact that a more heterogeneous population was included in the review by Koes *et al* may have played a role.

No randomized controlled clinical trials from a later date than the abovementioned reviews were found. Complications of epidural steroids in LRS are uncommon and predominantly mild and transient. The most frequently occurring

complication of the intervention is accidental puncturing of the dural sac, which happens in 1-5% of cases.[22-24] This complication sometimes results in headache due to liquor loss, for which a short hospital admission and closing of the puncture hole with a blood patch may be required. Rare complications include meningitis, epidural abscess or hematoma, extradural abscess, cerebrospinal fluid-cutaneous fistula, retinal haemorrhage and an increased chance of vertebral fractures in patients with osteoporosis after multiple injections.[25-27]

We concluded, based on the available literature, that epidural corticosteroid injections, as a pain treatment in LRS, are probably efficacious and safe on the short-term for patients in the acute phase of well-defined radiculopathy.

UNEXPLORED AREAS

GPs are the main caregivers for patients with LRS, but most of the abovementioned studies have been performed in hospital settings with a short-term follow up. Little is known about the treatment strategies they employ or about the clinical course of illness in LRS on the long term. Interventions that are efficacious in carefully controlled circumstances (efficacy) may not have a beneficial effect in normal daily circumstances (effectiveness). Whereas short-term efficacy of epidural steroid injections in LRS, provided they are administered to the right patient group, is probable (see above), effectiveness, -the extent to which a beneficial effect can be expected in practice-, has yet to be studied.

STUDY DESIGN

We performed a pragmatic randomized controlled trial in general practice, in which we investigated the clinical effectiveness of segmental epidural steroid injections for acute LRS with a follow-up period of one year. Outcome measures were pain, disability, quality of life, utility and costs. Pragmatic trials are the preferred design form to measure effectiveness. In order to produce results that are generalizable as well as reliable, researchers need to achieve a balance between external and internal validity. We instructed the participating GPs to include patients in the acute phase of well-defined LRS because this subgroup benefits the most from segmental epidural steroid injections according to the literature. On the other hand, we entrusted establishing the diagnosis to the physicians without confirmatory tests, because this

is what happens in real life. In the same manner, the participating GPs were allowed the choice of treatments constituting 'usual care'. It was recommended however, that the national guidelines be followed. More detailed information on the design of our trial is given in the method sections of chapters three to five.

RESEARCH QUESTIONS AND OUTLINE OF THIS THESIS

- Which treatment strategies are employed by Dutch GPs in LRS? What is the clinical course of illness in LRS in Dutch general practice? In Chapter 2, a historic prospective cohort study researching incidence, prevalence, long-term course of illness and treatment strategies for radiating low back pain (which includes LRS) in general practice is described to provide a timely overview of the status quo.
- Are segmental epidural steroid injections effective as an additional analgesic treatment compared to the usual care, in the acute phase of LRS, in Dutch general practice? This question is addressed in Chapter 3.
- What is the influence of adding epidural steroid injections to the usual care of LRS in Dutch general practice on the direct and indirect medical costs of this condition? Are epidural steroid injections cost-effective when implemented as an additional pain treatment for LRS in Dutch general practice? In Chapter 4, an economic evaluation is presented.
- Do segmental epidural steroid injections enhance the quality of life in patients with acute LRS, when applied as an additional pain treatment in Dutch general practice? What will the costs per QALY gained be, if epidural corticosteroid injections are added to the usual treatment of acute LRS in Dutch general practice? The influence of adding epidural corticosteroid injections to the usual pain treatment of LRS in general practice on patients' quality of life, including a cost-utility analysis, is described in Chapter 5.
- In Chapter 6, the results of the research presented in the previous chapters is summarized and reflected upon.

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