Radiculopathy and radiating low back pain in general practice

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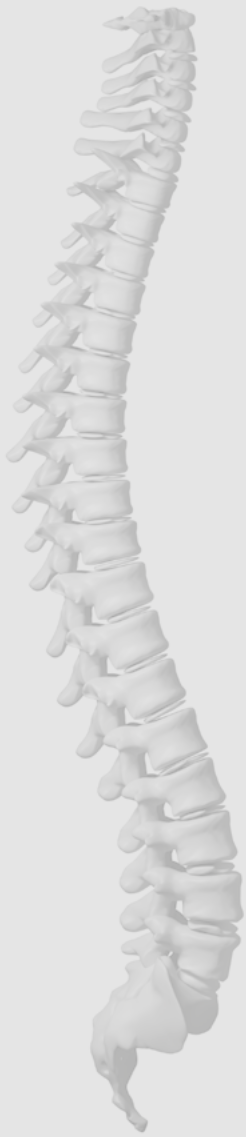
Chapter 3

Steroid injections added to the usual treatment of lumbar radicular syndrome. A pragmatic randomized controlled trial in general practice



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ABSTRACT

Background

Lumbosacral radicular syndrome (LRS) is a self-limiting, benign, painful and impairing condition caused by lumbar disc herniation and inflammatory processes around the nerve root. Segmental epidural steroid injections (SESIs) are helpful to reduce radicular pain on a short-term basis. It is unknown whether SESIs are an effective addition to usual pain treatment of LRS in general practice. In our study, we assessed the effectiveness of SESIs on pain and disability as an addition to usual care for acute LRS in general practice.

Method

A pragmatic, single-blinded, randomized controlled trial in Dutch general practice was conducted. Usual care was compared to usual care combined with a SESI in 63 patients in the acute phase of LRS. The primary outcome measure was the NRS back pain score at 4 weeks. To detect a minimal clinically important difference of 1.2 points and a common within-group standard deviation of 1.7 with a two-tailed alpha of 0.05 and a power of 0.80, we needed 33 subjects in each group. Statistical analysis was carried out using mixed models.

Results

A small significant effect in favour of the intervention, corrected for age, sex and baseline values, was found for the NRS back pain score, self-reported impairment and Roland-Morris disability score. The differences did not reach our threshold for clinical relevancy. Patients from the intervention group were significantly more satisfied with the received treatment than patients from the control group.

Conclusion

We found a statistically significant but small positive effect of SESIs on back pain, impairment and disability in acute LRS. Based on these outcomes, we cannot recommend implementing SESIs as an additional regular treatment option in general practice.

INTRODUCTION

Lumbosacral radicular syndrome (LRS) is defined as pain, radiating from the back into the leg, ("sciatica") in combination with a positive straight leg raising test and/or neurological symptoms originating from a single nerve root. In the Netherlands, LRS is treated by general practitioners (GPs) who adhere to the Dutch College of General Practitioner's Guideline on LRS.[1] According to this guideline, treatment of LRS consists of pain treatment by taking analgesics as needed, and maintaining normal daily activities as much as possible. The prognosis of LRS is favourable: within eight weeks, 80% of patients have reached bearable pain levels and resumed their work.[1] Some patients, however, do not adequately respond to conservative therapy during and after this period.[2] In 25% of patients, radicular pain becomes chronic.[1]

LRS is most commonly caused by protrusion of a lumbar intervertebral disc, which results in an inflammatory response around the nerve root.[1, 4] This inflammatory process is the cause of the radicular pain, rather than mechanical compression.[5-8] Local anti-inflammatory drugs may lessen inflammation and pain, making it easier for patients to profit from the favourable prognosis. Segmental epidural steroid injections (SESIs) are an example of local anti-inflammatory treatment. SESIs are not recommended in the Dutch guidelines for GPs, but the intervention is widely applied as a pain treatment for LRS in the Netherlands.

Efficacy of SESIs in LRS is controversial. Some studies are underpowered, others lack methodological quality to justify definite conclusions.[2,9-12] In trials that included patients in the acute phase of well-defined radicular syndrome ("sciatica"), SESIs turned out to be more effective than placebo in reducing pain and hastening return to normal daily activities.[2, 5, 8, 13-22]

Since patients in the acute phase of LRS are cared for by GPs, SESIs are a possibly useful treatment option in general practice. Most RCTs, however, have been conducted to assess efficacy rather than effectiveness (i.e. placebo-controlled double blinded trials rather than pragmatic trials), in specialist practice, in heterogeneous patient groups, with a short-term follow-up and using a single measuring moment. To our knowledge, no study has assessed effectiveness in general practice, with multiple measuring points and a long term follow-up, in a homogeneous patient group. We assessed the effectiveness of adding SESIs to usual pain treatment for patients with acute LRS in general practice, by means of a pragmatic randomized controlled trial measuring pain, disability and recovery in acute LRS patients with profound sciatica.

METHOD

We conducted a pragmatic randomized controlled trial in Dutch general practice. Our trial took place in and around the city of Groningen, the Netherlands, in 41 general practices with 76 participating GPs. Patients were recruited between January 1st 2005 and December 31st 2007 and followed for one year. This study was approved by the Medical-Ethical Committee of the University Medical Center Groningen in 2005, (code 2005/154), and was registered in the Dutch trial register as SLURP, code NTR342. Our institution funded this study. There was no additional funding from external sources.

Our research question calls for a pragmatic study design, which demands that real life conditions are followed as closely as possible. Usual care was therefore not standardized but defined as the treatment decided on by the patients and their GPs. Since Dutch GPs generally adhere to the Dutch College of General Practitioner's guidelines, usual care consisted of advice and analgesic medication and/or referral as needed.[1, 23] The GPs' diagnosis of LRS was not evaluated by further specialist physical examination, except to determine the level at which the SESI was to be administered. Patients and caregivers were not blinded.

Inclusion criteria were a diagnosis of LRS established by the GP, complaints of LRS for at least two weeks and no more than four weeks duration and patient age between 18 and 60 years. The upper age limit of 60 was chosen because complications of epidural injections are more common in the over 60 age group, due to osteoporosis. Exclusion criteria were a history of spinal surgery or spinal trauma, maintenance therapy with corticosteroids or anticoagulants, bleeding disorder, cauda equina syndrome, a body mass index of more than 35 kg/m^2, inadequate mastery of the Dutch language, allergy to corticosteroids, pregnancy or a wish to conceive, breastfeeding and mental disability. Patients with insulin-dependent diabetes mellitus were not excluded but instructed to measure their serum glucose levels regularly in the 48 hours after the intervention.

Patients in whom the GP established the diagnosis of LRS were given written information on the study, an informed consent form and a baseline symptom questionnaire containing numerical rating scales for pain and impairment, the SF-36 and the Roland-Morris disability questionnaire. Patients were asked to complete the questionnaire and the informed consent form and send them to the research centre. Upon receiving this information, subjects were contacted by the primary researcher to check inclusion and exclusion criteria with a protocolled inclusion form. In the absence of exclusion criteria, the inclusion form was completed.

Randomization was performed by a colleague with no further involvement in the study. Pre-prepared, sequentially numbered, opaque, sealed envelopes containing stickers labelled either "SESI" or "CAU", balanced after 40 assignments, were used. Upon randomisation, the consecutive envelope was opened and the sticker with the allocated treatment was fixed on the completed inclusion form. Inclusion forms, containing personal patient information, were coded and kept separately from follow-up questionnaires. To keep the researchers blinded until after the final analysis of the results, follow-up questionnaires were provided with the same codes but contained no personal patient information.

Patients allocated to the intervention group were presented to the department of anaesthesiology of the University Medical Centre Groningen (UMCG). An anaesthesiologist with no further involvement in the study administered the SESIs within 48 hours after randomisation. The SESIs consisted of 80 milligrams of triamcinolone in 10 millilitres of normal saline and were administered using a lumbar translaminar approach without additional imaging, one level above the presumed LRS in either sitting or lateral position. The skin was anaesthetised with lidocaine, but no local anaesthetics were injected epidurally to avoid problems with mobility and bladder emptying. After the injection, patients were referred back to their GPs for further usual care. When a patient was randomized to the CAU-group the GP provided usual care from the start. The translaminar injection technique without additional imaging, rather than a transforaminal approach with fluoroscopic guidance and administering of local anaesthetics, was chosen because of the pragmatic study design - given the shorter waiting time and better accessibility, the intervention would be applied this way in normal practice as well.

Follow-up in both groups was performed using postal questionnaires regarding pain, disability, and satisfaction with treatment, measured at 2, 4, 6, 13, 26 and 52 weeks after the start of the treatment. The 24-point Roland-Morris Disability Questionnaire (RMDQ) was used for measuring disability.[24, 25] For measuring pain and self-perceived impairment, a numeric rating scale (NRS) from 0 to 10 was used, where 0 meant no pain/impairment and 10 meant the worst pain/impairment imaginable. For measuring satisfaction with treatment, we asked patients to grade their treatment on a scale from 0 to 10, where 0 meant very poor and 10 meant excellent. All variables were measured at every time point. As minimal clinically important differences in the interpretation of the results, a reduction of 30% from baseline was used for the RMDQ-score and 2.0 was used for the NRS pain and impairment scores.[24-28]

Power calculations were based on the NRS back pain score at four weeks from the start of the treatment. A difference in NRS back pain score of 1.2 – 2.0 is considered clinically relevant in primary care attendants with low back pain.[29-32] The mean standard deviation of VAS scores in patients with moderate pain is approximately 1.7.[33] To detect a difference of 1.2 and a common within-group standard deviation of 1.7 with a two-tailed alpha of 0.05 and a power of 0.80, we needed 33 subjects in each group.

All analyses were performed using an intention-to-treat basis. Mixed model regression analysis was performed using SAS 9.2 PROC MIXED. No data imputation is necessary using this model.[34] Patients were a random factor in the model and treatment a fixed factor. For every outcome variable, treatment and time of measurement as independent variables were tested with sex, age and baseline-values as covariates to account for non-balance in the randomization.

RESULTS

Eighty-four patients were presented to us by their GPs, of whom 73 patients were eligible and included in the study. A flow schedule is presented in figure 3.1.

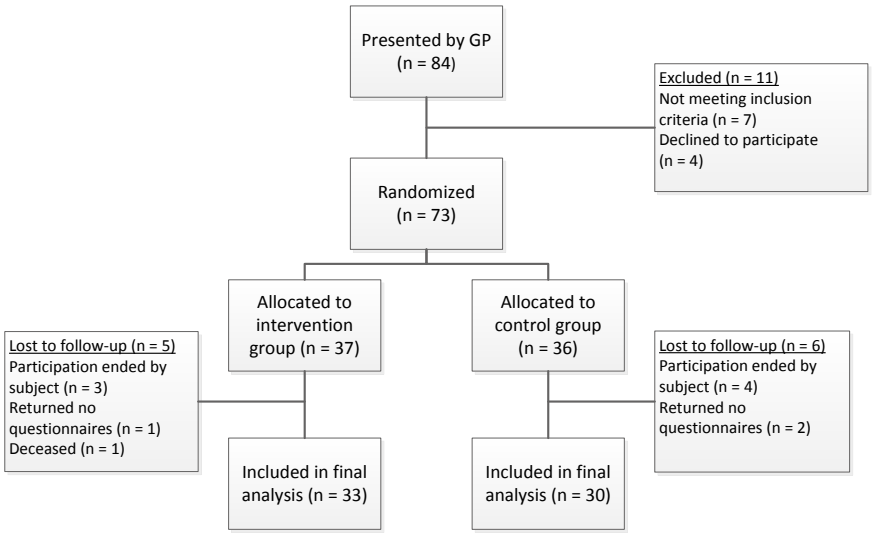


Figure 3.1: Population flow schedule

Of the 73 randomized patients, ten were not included in the analysis. Seven subjects ended their participation shortly after enrolment and three subjects did not send back any questionnaires despite repeated requests. Of one subject the follow-up was incomplete. She died during the study period due to Burkitt lymphoma, which initially caused radicular pain. The subjects lost to follow-up did not differ significantly in sex, age, randomization group or baseline values from the 63 subjects who were included in the analysis. Of these 63 subjects, 30 were men. The mean age of the study participants at the time of the inclusion was 43.7 years (SD 9.8).

Table 3.1: Mean NRS and Roland-Morris scores of study participants for every measuring moment in the follow-up period.

Follow-up time (weeks)	0	2	4	6	13	26	52
RMDQ score							
Intervention group mean (SD)	16.5 (4.2)	10.7 (7.1)	8.9 (6.8)	8.0 (6.8)	5.3 (5.9)	3.0 (4.5)	2.3 (3.7)
Control group mean (SD)	14.5 (6.1)	12.3 (6.1)	10.5 (7.0)	8.1 (6.3)	7.6 (6.3)	5.4 (6.5)	4.1 (6.2)
NRS back pain							
Intervention group mean (SD)	6.2 (2.6)	3.3 (2.9)	3.3 (3.0)	2.5 (2.6)	2.1 (2.5)	1.9 (2.5)	1.3 (1.9)
Control group mean (SD)	4.5 (2.7)	4.1 (3.0)	3.6 (2.7)	2.8 (2.3)	3.0 (3.0)	2.0 (2.4)	2.0 (2.9)
NRS leg pain							
Intervention group mean (SD)	7.8 (1.7)	4.2 (3.1)	3.8 (3.3)	2.6 (2.5)	1.6 (2.5)	1.6 (2.4)	1.0 (2.0)
Control group mean (SD)	6.4 (2.3)	4.7 (3.1)	3.9 (2.8)	2.9 (2.5)	2.7 (2.8)	1.9 (2.5)	1.4 (2.2)
NRS pain during day							
Intervention group mean (SD)	7.7 (1.6)	4.9 (3.1)	4.5 (3.2)	3.1 (2.7)	2.4 (2.7)	2.2 (2.6)	1.2 (2.0)
Control group mean (SD)	6.2 (2.1)	5.1 (2.8)	4.2 (2.6)	3.3 (2.4)	3.1 (2.9)	2.2 (2.3)	2.2 (3.0)
NRS pain during night							
Intervention group mean (SD)	6.4 (2.6)	3.6 (3.2)	3.7 (3.0)	2.5 (2.5)	1.7 (2.6)	1.8 (2.3)	0.8 (1.7)
Control group mean (SD)	5.7 (2.7)	4.3 (3.0)	3.0 (2.8)	2.6 (2.5)	2.6 (2.9)	1.9 (2.5)	1.8 (2.9)
NRS total pain							
Intervention group mean (SD)	7.7 (1.2)	5.0 (2.9)	4.2 (3.0)	3.3 (2.5)	2.5 (2.5)	2.3 (2.5)	1.3 (2.0)
Control group mean (SD)	6.9 (1.7)	5.3 (2.6)	4.5 (2.8)	3.7 (2.5)	3.2 (2.8)	2.3 (2.4)	2.1 (3.0)
NRS impairment							
Intervention group mean (SD)	7.8 (1.6)	5.2 (3.2)	4.0 (3.1)	3.0 (2.8)	2.6 (2.9)	1.7 (2.2)	1.0 (1.6)
Control group mean (SD)	6.7 (2.2)	5.2 (2.8)	4.7 (2.8)	3.3 (2.9)	3.2 (2.9)	2.1 (2.3)	1.9 (2.6)

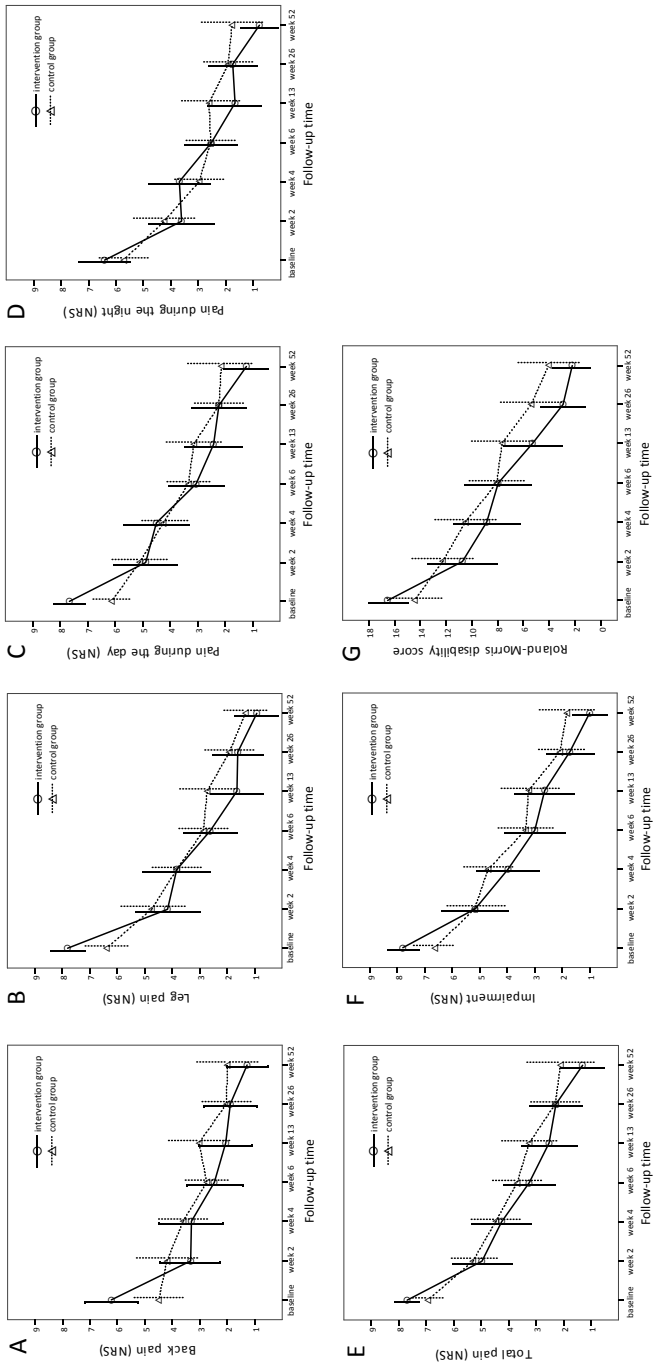
For the 63 study participants, we sent out 441 questionnaires, of which 408 were returned. Means and standard deviations of all variables in both groups for every time point of measurement are presented in table 3.1. Despite randomization, the intervention group was in a worse initial condition than the control group for all baseline values. We adjusted for these differences by including the baseline values as covariates in the mixed models regression analysis. In table 3.2 and in figures 3.2a-g, we report the results of the mixed models regression analysis. Both groups experience a significant decline over time for all symptoms. When analysed over the entire follow-up time, the intervention group experienced significantly less symptoms than the control group for the NRS back pain score ($p = 0.0115$), the NRS score for self-perceived impairment ($p = 0.0361$) and the the RMDQ-score ($p = 0.0173$). These differences between the groups remained constant during the whole follow-up period. In figures 3.2a-g, the courses over time of all variables for the entire study period are shown graphically.

Finally, we found a significant difference in mean patient satisfaction between the two groups. The intervention group rated their treatment 9.0 on a 0 to 10 scale, and the control group rated their treatment 7.2 on a 0 to 10 scale ($p = 0.006$). No complications or adverse effects of the intervention were reported.

Table 3.2: Estimated differences between group means.

Variable	Estimated difference	Standard error	P |t|	95% CI -	95% CI +
RMDQ-score	2.5004	1.0435	0.0173	0.4551	4.5456
NRS back pain	1.1165	0.4389	0.0115	0.2562	1.9767
NRS leg pain	0.6717	0.5100	0.1890	-0.3279	1.6713
NRS pain during the day	0.6563	0.5186	0.2068	-0.3601	1.6727
NRS pain during the night	0.5285	0.4741	0.2659	-0.4007	1.4577
NRS total pain	0.6890	0.4729	0.1463	-0.2378	1.6158
NRS impairment	1.0254	0.4867	0.0361	0.0714	1.9793

In this repeated measures regression analysis, differences between groups are calculated based on the study outcomes, corrected for baseline values, to estimate true values in the random population. We found significant differences between group means for RMDQ-score, NRS back pain score and NRS score for self-perceived impairment. These differences are statistically significant but too small to be considered clinically relevant.



Figures 3.2a-g: In figures a-g, the numerical rating scale (NRS) scores and the Roland-Morris Disability Questionnaire (RMDQ) scores for the entire follow-up time are shown for both groups. When corrected for baseline values, there is a significant effect of the intervention on the RMDQ score and on the NRS scores for back pain and self-perceived impairment (the curve for the intervention group 'lies below' the curve for the control group). Differences between groups remain constant (the two curves are parallel)

DISCUSSION

In this study, SESIs yielded a statistically significant overall effect on back pain, self-perceived impairment and disability as an additional treatment for LRS in a pragmatic general practice setting. Small differences between pain severity scores and other outcomes, however, may be statistically significant but clinically trivial. Since differences of 1.2 – 2.0 on the NRS pain scales, and a 30% reduction from baseline (which amounts to 4.5 points in our study) in RMDQ score can be considered clinically important to patients, the effects of our intervention are probably too small to be relevant.[24-32]

The intervention group was significantly more satisfied with their treatment than the control group, rating a mean of 9.0 versus 7.2 on a 0 to 10 scale ($p = 0.006$). As no clinically relevant effect was yielded in our study, the more positive evaluation of the intervention by patients should probably be attributed to the effect of receiving extra attention and care.

Our study is the first pragmatic trial undertaken in general practice, where most patients with LRS are seen and treated in an early stage. It is one of the few studies aimed to assess effectiveness rather than efficacy of SESIs. To our knowledge this has been done only once before, 15 years ago and in a hospital setting.[22] Outcomes of that study suggested that adding SESIs as a first-line treatment to rest and a nonsteroidal anti-inflammatory drug for LRS resulted in additional costs and no gain in efficacy. Our study is the first to evaluate the effect of SESIs on LRS with mixed models multiple regression analysis, which enabled us to assess the effect of this intervention over the whole course of the follow-up time rather than evaluating its effect on a single moment. Whereas most trials in this field are underpowered, we included enough patients to yield a statistically significant effect.

This study has some possible limitations. One is the fact that the intervention group unfortunately differed from the control group in baseline values. Since randomization was adequately performed, we have no explanation for these differences other than coincidence. In the mixed model regression analysis we corrected for the baseline differences including the baseline values as a covariate. Baseline differences between groups do, however, raise questions about whether those groups are truly comparable. The MCIDs of measuring instruments may vary between categories of baseline severity in symptoms. According to the literature, our groups were comparable in that respect.[28, 33] We are therefore convinced that the difference in baseline values between our study groups are not a problem for the analyses and the ultimate interpretation of our trial results.

It can be argued that for our study goals, the NRS leg pain score would have been a more appropriate primary outcome measure than the NRS back pain score. We chose back pain for calculating our sample sizes because the MCID of the NRS back pain score is extensively used and well described in primary care back pain patients.[24, 29, 30, 32, 33] However, leg pain is more specific for radiculopathy.[34,35] Since our study had the statistical power to detect a difference of 1.2 on a numerical rating scale with a power of 0.80 and an alpha of 0.05, and since the minimal clinically important difference for leg pain on the numerical rating scale is 1.3 to 3.5, it would have detected a relevant difference in leg pain if present. A different choice of primary outcome measure would therefore not have led to different conclusions.

Our subjects reported no adverse effects of our intervention. One of the subjects, however, died during our study period due to Burkitt lymphoma, which initially caused radicular pain. Epidural steroids are known to relief symptoms of spinal cord compression caused by tumours or metastases.[36] It is conceivable that administering epidural steroids to a patient whose radicular complaints are caused by cancer, delays diagnosis and treatment. To our knowledge, no reports about this problem have been published.

Placebo-controlled double-blinded randomized trials have yielded positive results for the efficacy as a pain treatment of SESIs on LRS. Our study shows that the intervention has a statistically significant beneficial effect as an additional treatment in general practice as well. This effect however, is too small to be considered clinically relevant to patients. Based on the outcomes of this study, we cannot recommend that administering SESIs for the pain treatment of LRS be implemented as a regular intervention in general practice. Further research should be aimed at adequately treating pain in patients with acute LRS and possibly at identifying patient subgroups that might benefit the most from SESIs, with additional focus on complications and side effects.

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