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Clinical pain research

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Predicting the outcome of persistent sciatica using conditioned pain modulation: 1-year results from a prospective cohort study

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Abstract

Background and aims: Recovery in patients hospitalised with severe sciatica is unpredictable. Prognostic tools to aid clinicians in the early identification of patients at risk of developing chronic sciatic pain are warranted. Conditioned pain modulation (CPM) is a psychophysical measure of the endogenous pain modulatory pathways. Several studies have suggested CPM as a potentially important predictive biomarker for the development of chronic pain. The aim of the study was to determine whether CPM effect in patients still suffering from leg pain 6 weeks after hospital discharge for severe sciatica is associated with persistent leg pain at 12 months. A potential association would suggest that measuring CPM effect could be a valuable prognostic tool in the hospital management of sciatica.

Methods: A prospective cohort study in which CPM effect was measured 6 weeks after hospital discharge following an acute admission with sciatica as the main complaint. The impact of CPM effect on the outcome was analysed using logistic regression. The outcome measured was self-reported leg pain score of ≥1 in the past week on a 0–10 numeric rating scale (NRS) at 12 months post discharge.

Results: A total of 111 patients completed the entire study, 51 of whom received non-randomised surgical treatment. Crude and confounder adjusted analyses showed no significant association between CPM effect and leg-pain measured at 12 months, crude Odds Ratio 0.87, 95% CI 0.7–1.1, $p = 0.23$.

Conclusions: Our results suggest that CPM assessment has limited prognostic value for the long-term outcome in severe sciatica when measured 6 weeks after hospital discharge.

Implications: The present study adds important knowledge concerning the limited clinical use of late CPM testing in sciatica patients. The heterogeneity in patients, the wide range of treatments received and a generally favourable outcome are factors that may affect CPM's clinical value as a prognostic factor for severe sciatica.

Keywords: conditioned pain modulation; sciatica; disc herniation; pain; prognostic factor; neuropathic pain.

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1 Introduction

The treatment of lumbar spinal disorders constitutes a large portion of hospital costs, but the economic impact of work-absenteeism continues long after patients have been discharged [1]. Long-term recovery in patients hospitalised with severe sciatica is unpredictable and warrants better prognostic tools to aid clinicians in the identification of patients at risk of developing chronic sciatic pain and disability [2, 3].

Conditioned pain modulation (CPM) effect is a psychophysical measure of the endogenous pain modulatory pathways. This is demonstrated by a painful test stimulus (TS) being perceived as less painful in the presence of, or shortly after, a second painful stimulus [conditioning stimulus (CS)]. The difference in perceived pain of the TS with and without the CS is termed the CPM effect [4]. Impaired inhibitory CPM effect has been associated with a variety of chronic pain disorders [5], and has been suggested as a potentially important predictive biomarker for the development of chronic pain and a predictor of analgesic response to neuropathic pain [6, 7]. To our knowledge, the predictive value of CPM in sciatica has not been studied. The primary aim of this study was to determine whether CPM effect in patients still suffering from leg pain 6 weeks after hospital discharge for severe sciatica is associated with persistent leg pain at 12 months post hospital discharge. A potential association would suggest that measuring CPM effect could be a valuable prognostic tool in the hospital management of sciatica.

2 Methods

2.1 Study design

This was a prospective cohort study with assessments at three different time points: (1) questionnaire, clinical examination and lumbar MRI upon hospital admission, (2) CPM testing and questionnaire 6 weeks after hospital discharge, (3) a postal questionnaire at 12 months (Fig. 1).

2.2 Participants

Between December 2012 and March 2018, eligible patients were consecutively recruited from a larger cohort study aimed at patients suffering from sciatica that required acute hospitalisation at the Neurological Department of Oslo University Hospital [8]. This hospital provides care to all Oslo residents who require acute surgical or non-surgical treatment of sciatica. All physicians responsible for hospital admission were working independently of the study program and patients were not hospitalized for the purpose of inclusion in the study. Upon hospital admission, most patients were treated with a combination of paracetamol, non-steroidal anti-inflammatory drugs and mild or strong opioids. Lumbar surgery was typically offered to patients with severe sciatic pain refractory to analgesics or with a severe motor deficit. No other forms

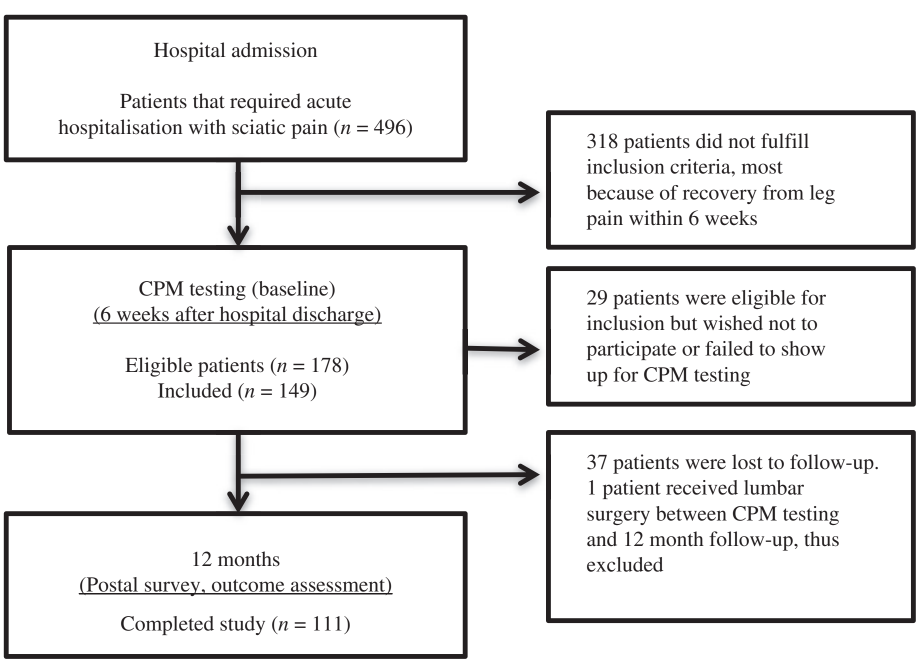

Fig. 1: Flow diagram of the study population.

of treatment were offered. Patients (surgical and non-surgical) that still suffered from sciatic pain [≥2 on a numeric rating scale (NRS)] 6 weeks post hospital discharge (baseline of the study/CPM testing) were further for the present study following a series of inclusion and exclusion criteria.

Inclusion criteria: Age 18–65; suffering from sciatica, defined as radiating leg-pain with dermatomal distribution graded ≥2 on a self-reported NRS ranging from 0 to 10 (0 = no pain, 10 = worst pain imaginable) at baseline; hospitalised with acute sciatica as their major complaint with self-reported leg pain of ≥4 on a NRS 6 weeks prior to baseline testing; and radiological confirmation of disc herniation on magnetic resonance imaging (MRI).

Exclusion criteria: Cauda-equina syndrome; pregnant or breastfeeding; drug or alcohol addiction; primary psychiatric disease; use of antipsychotics or antidepressants; limited Norwegian proficiency; chronic non-lumbar pain rated ≥4 on NRS for ≥3 months in the last 2 years; lumbar surgery between baseline CPM testing and 12 months post hospital discharge.

2.3 The predictor of interest (independent variable): mean CPM effect

All participants received written information concerning the test program, but were blinded to the study hypothesis and that CPM would be tested. Each test was conducted by experimenters wearing the same clothing in a laboratory with a consistent placement of instruments. During the experiment, the tester read slowly from a standardized instruction protocol, and all sessions followed the same procedure. The study procedure was adapted from a previously published protocol [9]. The CPM effect was measured following a 4-step procedure using a computerized temperature stimulation device [10] with a 30 × 30 mm Peltier thermode as TS and a container [11] of circulating water at 7 °C as CS (Fig. 2).

Step 1 (identifying TS temperature): After identifying heat pain threshold and heat pain tolerance level by the methods of limit (baseline 32 °C, rate of change 1 °C/s), the experimenter identified the individual patient's TS temperature (°C) scored as 6 cm on a 10 cm computerized visual analogue scale (VAS) with endpoints "no pain" and "worst imaginable pain".

Step 2 (TS): Patients received 120 s of continuous TS (baseline temperature: 32 °C, increase rate: 2 °C/s) to their right forearm. The perceived TS pain intensity was concurrently scored on a 10 cm computerized horizontal VAS (endpoints: "no pain" and "worst pain imaginable"), with the patients continuously scrolling the wheel on a computer mouse according to perceived pain. The TS pain scoring was sampled at 1 Hz.

Step 3 (TS and CS): After a 300 s break, patients received another 120 s of TS on the same arm while the other arm was immersed in a container of 7 °C circulating water (CS). As in step 2, TS pain was scored simultaneously.

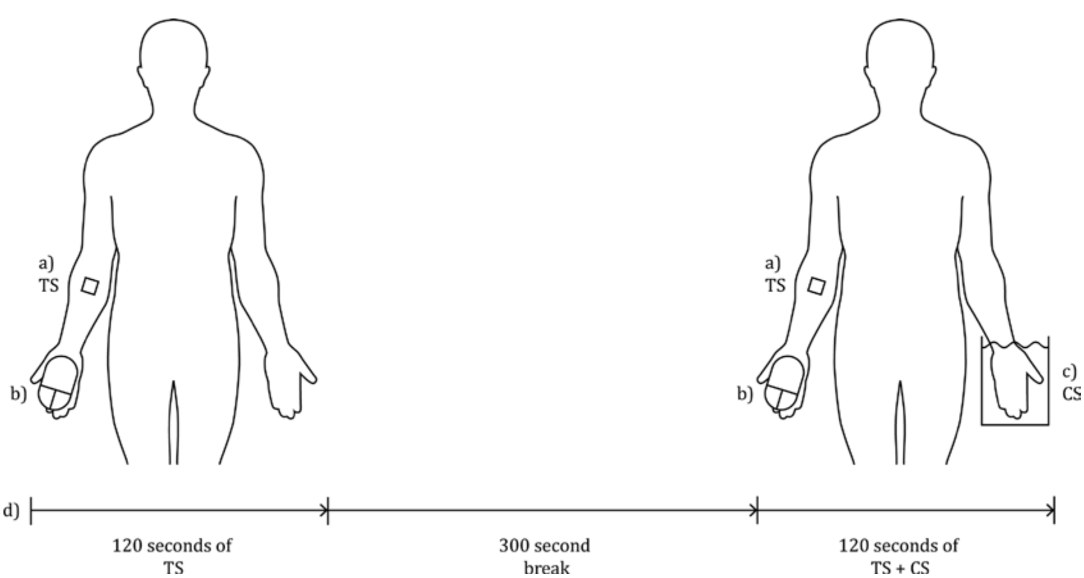

Fig. 2: The method of testing conditioned pain modulation (CPM). [a]TS: painful heat applied by a peltier thermode on the participants right forearm. [b]Pain rating: participants scrolled the wheel on a computer mouse according to perceived TS heat pain (10 cm horizontal VAS on a computer). [c]CS: left hand immersed in a container of painful cold (7 °C) circulating water. [d]Timeline. TS = test stimulus; VAS = visual analogue scale; CS = conditioning stimulus.

Step 4 (CPM calculation): The average pain score from the 120 s of TS in both step 2 and step 3 was applied when calculating the CPM effect, defined as the difference between the two means ($VAS_{(TS\ and\ CS)}$–$VAS_{(TS)}$). Accordingly, a negative value represents an inhibitory CPM effect.

2.4 Main outcome (dependent variable): leg pain at 12 months post hospital discharge

At 12 months, a leg pain score of ≥1 in the past week on a self-reported 0–10 NRS was set as the cut-off value for persistent leg pain and the present study's final outcome. Patients with a leg pain NRS score of 0 were considered to have recovered from leg-pain. Leg pain does not give a direct measure of patient function or quality of life, but it is found to be one of the most responsive outcomes for capturing disabling symptoms in patients suffering from sciatica [12].

2.5 Statistical analysis

All data analyses were performed using SPSS 24.00 (IBM, Armonk, NY, USA). Significance level was set to 5%. Continuous data were described with mean and standard deviation (SD). Associations between pairs of categorical data were analysed using the χ^2 test and associations between pairs of continuous data were analysed using independent samples *t*-tests. Logistic regression analysis was used to investigate the association between the independent variables (CPM, age, sex, baseline leg pain) and the dependent variable (leg pain ≥1 scored on a 0–10 NRS at 12 months). All independent variables were entered simultaneously, and all significant associations were described with Odds Ratios (OR) and 95% confidence intervals (95% CI). No missing values were imputed. Finally, three sensitivity regression analyses were carried out in which more severe cut-off values for the main outcome were investigated; (1) leg pain ≥2 on a 0-10 NRS measured at 12 months, (2) leg pain ≥6 on a 0–10 NRS measured at 12 months, (3) a reduction in leg pain of ≥2 on a 0–10 NRS at 12 months.

3 Results

Of the 149 patients included in the study, 111 patients responded to the follow-up questionnaire at 12 months (Fig. 1). Table 1 shows the baseline patient characteristics

Table 1: Characteristics and measured CPM effect for the different patient subgroups.

	N (% of all patients)	Mean CPM effect in cm (CI)
All patients	111	−2.4 (−2.8, −2.1)
Males	72 (65)	−2.4 (−2.8, −2.0)
Females	39 (35)	−2.4 (−3.1, −1.7)
Education >12 years	79 (72)	−2.2 (−2.6, −1.8)
Education <12 years	32 (28)	−2.9 (−3.6, −2.1)
Living with spouse/partner	85 (77)	−2.3 (−2.7, −1.9)
No spouse/partner	26 (23)	−2.7 (−3.7, −2.0)
Actively employed	83 (75)	−2.5 (−2.9, −2.1)
Not actively employed	28 (25)	−2.3 (−3.0, −1.5)
European Caucasian	103 (94)	−2.7 (−2.7, −2.0)
Not European Caucasian	6 (6)	−3.5 (−5.3, −1.7)
Disc herniation surgery within 6 weeks prior to CPM testing	51 (54)	−2.5 (−3.1, −1.9)
No disc herniation surgery within 6 weeks prior to CPM testing	60 (46)	−2.3 (−2.8, −1.9)
Any previous lumbar surgery	45 (41)	−2.3 (−2.8, −1.8)
No previous lumbar surgery	66 (59)	−2.5 (−3.0, −2.0)
Sporadic use of analgesics for leg-pain	91 (82)	−2.3 (−2.7, −1.9)
No use of analgesics for leg pain	20 (20)	−2.8 (−3.5, −2.1)
Daily use of analgesics	47 (42)	−2.4 (−2.9, −1.9)
Non daily use of analgesics	64 (58)	−2.4 (−2.9, −2.0)
Current smoker	13 (12)	−3.2 (−4.4, −2.0)
Non smoker	97 (88)	−2.3 (−2.7, −1.9)
Poor quality of life last week, yes	24 (22)	−2.5 (−3.3, −1.8)
Poor quality of life last week, no	85 (78)	−2.4 (−2.8, −2.0)

CI = confidence interval; CPM = conditioned pain modulation.

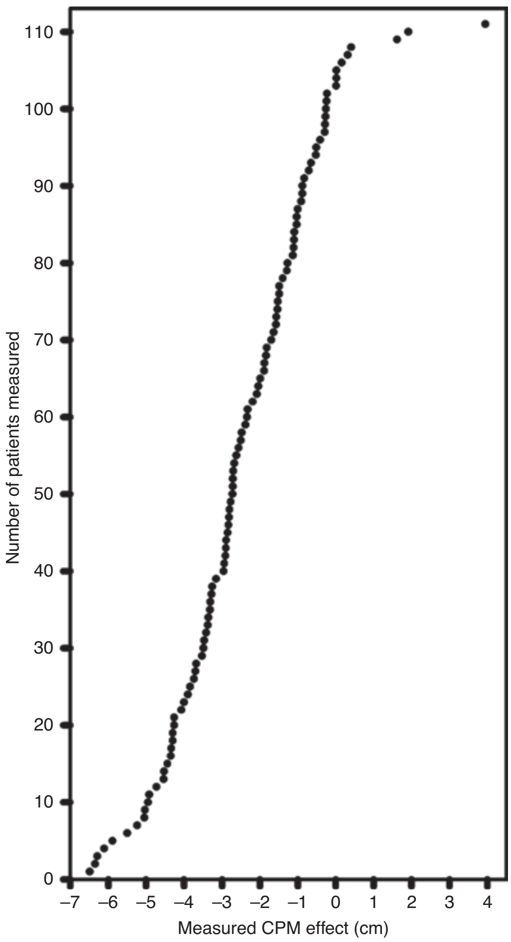

Fig. 3: Dispersion of CPM scores for each of the 111 patients.

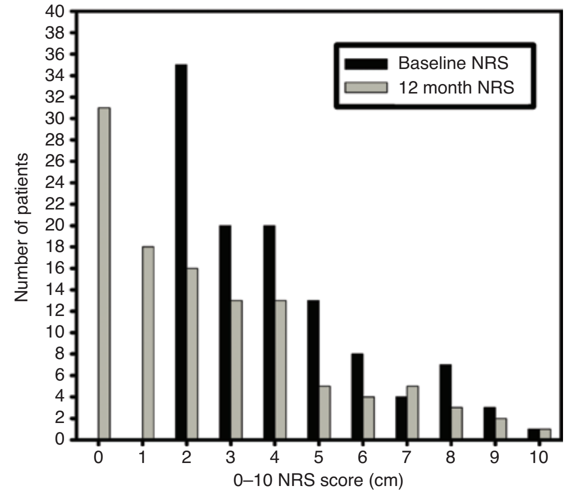

Fig. 4: Mean NRS leg pain measured at baseline and 12 months.

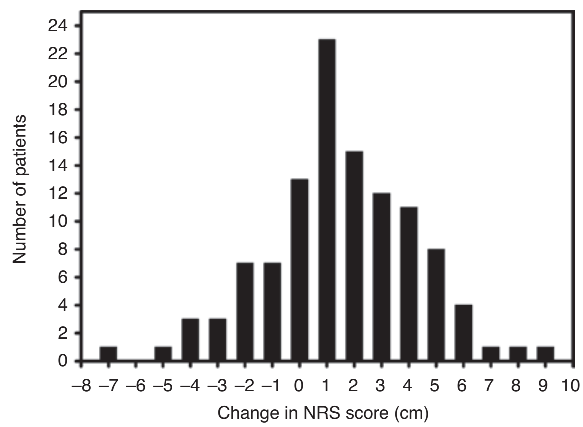

Fig. 5: The change in leg pain measured between baseline and 12 months (NRS $score_{(baseline)}$–NRS $score_{(12\ months)}$) for each patient. A positive value represents a decrease in pain from baseline to 12 months.

and the different CPM values. The patients were hospitalized for a mean (SD) of 5.2 (4.4) days. A total of 51 patients (54%) received surgical treatment in the 6-week period between hospital admission and CPM testing (baseline). Mean CPM value was measured to –2.4 cm (95% CI –2.8, –2.1).

Figure 3 shows the general dispersion of CPM scores among the patients. No statistically significant difference in mean CPM effect was evident when comparing surgically and non-surgically treated patients, –2.3 cm vs. –2.5 cm, t(109) = 0.56, $p = 0.59$. Mean NRS leg pain was 4.0 (SD 2.1) measured at baseline and 2.5 (SD 2.5) at 12 months (Fig. 4). The mean (SD) change in leg pain measured between baseline and 12 months for each patient (NRS $score_{(baseline)}$–NRS $score_{(12\ months)}$) was 1.5 (2.8) (Fig. 5).

3.1 Association between CPM effect and main outcome

Crude analysis did not reveal any statistically significant association between CPM effect and leg pain ≥1 on a 0–10 NRS measured at 12 months, OR 0.87, 95% CI 0.7–1.1, $p = 0.23$. Further, no significant association was found when adjusting individually or concurrently for the following: age, sex, baseline leg-pain and surgical treatment (Table 2). Sensitivity analysis of the main outcome revealed no association between CPM effect and; (1) leg pain ≥2 on a 0–10 NRS measured at 12 months, (2) leg pain ≥6 on a 0–10 NRS measured at 12 months, (3) a reduction in 0–10 NRS leg pain of ≥2 at 12 months (logistic regression analysis, results not shown).

4 Discussion

This prospective cohort study on patients admitted to hospital due to acute sciatica revealed no statistically significant

Table 2: The association between CPM effect and persistent leg-pain at 12 months, adjusted for age, sex, baseline leg pain and surgical treatment.

Outcome (dependent variable) = leg pain score of ≥1 the past week on a 0–10 NRS at 12 months, n = 111, R^2 = 0.05				
Factors tested (independent variables entered simultaneously)	**B**	**Wald statistic**	***p*-Value**	***OR* (95% CI)**
CPM effect (cm)	−0.14	1.31	0.25	0.87 (0.69, 1.10)
Age (years)	0.01	0.26	0.61	1.01 (0.97, 1.05)
Sex (male)	0.36	0.65	0.42	1.43 (0.60, 3.42)
Baseline 0–10 NRS leg pain score	0.06	0.28	0.60	1.06 (0.86, 1.31)
Surgery prior to CPM testing	0.43	0.95	0.33	1.54 (0.65, 3.68)

R^2 = Nagelkerke R^2; NRS = 0–10 numeric rating scale; B = unstandardized β coefficient; OR = odds ratio; CI = confidence interval; CPM = conditioned pain modulation.

association between CPM effect measured 6 weeks post hospital discharge and persistent leg-pain at 12 months. However, it is important to bear in mind that the purpose of the study was not to explore the causal inference of CPM effect in sciatic pain chronicity or test the validity of the CPM paradigm, but to test its crude prognostic value in a clinical setting of heterogeneous sciatic patients whose pain persists despite pharmaceutical or surgical treatment. It is possible that further stratified analysis of different subgroups of sciatica patients or implementation of stricter inclusion criteria in terms of symptom debut, treatment and pain characteristics may demonstrate an association between the CPM effect and the outcomes that the present study failed to show. However, stricter inclusion criteria and stratification of this heterogeneous group of patients would limit the use of CPM to only a few selected patients, decreasing its value as a clinically useful prognostic tool, especially since few patients have persistent sciatica 6 weeks after hospital discharge.

One can argue that a limitation in the present study is that patients were CPM tested 6 weeks post admission rather than during the acute phase of the disease or prior to lumbar surgery. The present study's patients may have undergone both psychological and physical changes that could affect their CPM effect and its possible predictive properties. However, it is more practical, accurate and economically feasible to test patients in an outpatient laboratory setting, rather than a crowded hospital ward where patients are stressed, medicated, immobile and facing a limited number of days before discharge.

Currently, there is insufficient data to identify a superior CPM protocol [13–15]. Until such data is available, study validity and comparability of different CPM protocols will continue to be questioned. This may also apply to the present study. One can argue that the present study's CPM protocol may introduce attention bias in the form of distraction, since the second TS is applied in parallel to the CS and not in sequence as in other CPM protocols [16]. Further, the 0–10 NRS pain scale as the final outcome could not be preserved as a continuous variable in the regression analysis without violating the assumption of multivariate normality. Though other cutoffs values were tested and showed no significant results, the present study runs the risk of losing valuable information and making type II errors when data collected as continua were split into categories [17].

There is a limited and conflicting body of studies exploring CPM effect as a potential prognostic factor for persistent pain and disability in patients with sciatica and other spinal disorders. Supporting the present article's main findings is a cohort-study of 156 primary care patients with non-specific low-back pain who were CPM tested and subsequently assessed for chronic pain 4 months later [18]. The study failed to demonstrate CPM effect as a predictor for pain chronicity. Though the patient population was different in terms of disease mechanism and symptom severity, this previous study bears a methodological resemblance to the present study. The present findings are further supported by two additional CPM studies on low-back pain patients, which indicated that altered CPM is not a major determinant of hyperalgesia and pain in their patient population [19–21]. In contrast, CPM effect was shown to have predictive value for persistent postoperative pain in patients who had undergone surgical thoracotomy and abdominal surgery [22]. The obvious methodological difference in this case is that the CPM testing was performed prior to pain debut, and not after or during ongoing pain as in the present study. This suggests that measures of CPM effect have predictive value if measured prior to pain debut, but not after.

5 Conclusions

Our results suggest that CPM effect measured 6 weeks post hospital discharge has limited prognostic value for the long-term outcome in persistent sciatic pain. Despite this negative finding, CPM effect as a biomarker in the management of sciatica should not be entirely dismissed. The clinical value of CPM testing may lie in its ability to direct treatment or predict outcomes in more carefully selected sciatica patients than in the present study.

Authors' statements

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Conflict of interest: Authors state no conflict of interest.

Informed consent: Written informed consent was obtained prior to participation.

Ethical approval: Human testing was performed in accordance with the Declaration of Helsinki, and the Norwegian Regional Ethics Committee (REK) approved the study (project number 2012/1108).

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