MINIMALLY INVASIVE TREATMENT FOR LUMBAR SPINE RELATED PAIN DISORDERS

Minimaal invasieve behandeling voor wervelkolomgerelateerde pijnklachten van de lage rug

Proefschrift

ter verkrijging van de graad van doctor aan de Erasmus Universiteit Rotterdam op gezag van de rector magnificus, prof.dr. H.A.P. Pols, en volgens besluit van het College voor Promoties.

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For all patients suffering from chronic low back pain

Contents

"The development of science and of the creative activities of the spirit in general requires still another kind of freedom, which may be characterized as inward freedom. It is this freedom of the spirit, which consists in the independence of thought from the restrictions of authoritarian and social prejudice as well as from unphilosophical routinizing and habit in general."

Albert Einstein (1879-1955)

Chapter

1

Introduction and outline
of the thesis

Introduction

Chronic low back pain is defined as an unpleasant sensory and emotional experience in the lumbosacral area lasting more than 3 months, with some people reporting referred pain to the upper leg.

When the pain experience lasts less than 3 months we call it "acute pain", whereas "chronic pain" represents pain lasting longer than 3 months[1]. The percentage of people changing from acute over to chronic low back pain is much higher than previously documented; instead of 8% as presented by the Quebec task force[2], more recent studies report up to 65%[3-6].

Low back pain was and continues to be a very common problem globally and its prevalence will increase over the next years[7,8]. Low back pain causes more global disability than any other condition and ranks highest in terms of disability and sixth in terms of overall burden[8,9]. The mean prevalence is estimated to be 9.4-11.9%, the one year prevalence 22-65% and the lifetime prevalence 84%[8,10]. With these numbers we can say that this burden poses a problem due to the health care consultations and working days lost. Besides being common, treatment of low back pain is also costly; 2% of all physician office visits are for low back pain complaints[11].

Low back pain can be classified using a diverse set of classification systems. One such classification system distinguishes between "non-specific" and "specific" low back pain. The term "specific" low back pain is used when the pain is caused by a specific pathophysiological mechanism and "non-specific" when a specific somatic cause can't be identified. In primary care, most of low back pain is classified as "non-specific" because the underlying pathology cannot be identified; however, a "specific" low back pain problem is present in cases such as hernia nuclei pulposi, vertebral compression fracture, infection or tumour.
Regarding the spine related pain disorders, the vertebrae, intervertebral discs, facet joints and sacroiliac (SI) joints can act as a major cause of low back pain and of referred pain. The worldwide burden of osteoporotic vertebral fractures in the year 2000 was estimated to be 1.4 million[12]. The incidence of clinical osteoporotic vertebral fractures in The Netherlands was 0.7% in women and 0.2% in men aged 55 years or older[13]. Traumatic spinal fractures occur in 11.8 to 16.4 per 100000 population (0.012 to 0.016%)[14,15]. Being a frequent site of bone metastasis, spinal involvement occurs in up to 40% of patients with cancer[16]. Vertebral compression fractures occur in 55 to 70% of patients with

multiple myeloma[17]. The prevalence of internal disc disruption, facet joint pain or SI joint pain amongst the patients with chronic low back pain was estimated to be 39-42%[18,19], 15-31%[19,20] and 10-38%[19,21-23], respectively. The younger the patient, the more likely low back pain is discogenic in origin[19].
Ruling out red flags is an important part of the diagnostic process[24]. Patients with low back pain can be referred to secondary care when they do not benefit from usual (conservative) treatment or when symptoms persist. Medical history, physical examination and additional tests performed by the pain physician (or another specialist) together may lead towards the working diagnosis of a "specific" (low back) pain source. A classification merely between "non-specific" and "specific" may provide insufficient insight and other classification systems are currently being introduced, e.g. between "degenerative" and "non-degenerative" disorders[25].

Low back pain can occur as a result of conditions affecting the bony lumbar spine, the discs between the vertebrae, the ligaments around the spine and discs, the spinal cord and nerves, the muscles of the low back, internal organs of the pelvis and abdomen, and the skin covering the lumbar area. The assessment and interpretation of tests used to diagnose low back pain subtypes are often not standardized[26]. Identification of the pain-producing structure is not easy in (degenerative) spinal disease. Ageing affects the spinal elements and causes a certain degree of degeneration of these elements[27].
In assessing the association between deviations on spinal imaging and low back pain, the scientific research data yielded various results[28]. Patients with nerve compression due to disc herniation may report no pain[29-32], while other patients without nerve root compression may report severe pain[33-35]. Apparently, the severity of pain is not correlated with the size of the herniation[36-39]. Features on imaging tests may have little prognostic value regarding the cause of the symptoms[40-44].
Routine imaging tests are associated with radiation exposure and increased expenses and can possibly be unnecessary procedures[45]. Clinical practice guidelines for the diagnosis and treatment of low back pain have been developed in the past[46]. Appropriateness criteria for low back pain were issued by the American College of Radiology (1996, last revision 2011), rating the radiologic procedures and also taking into consideration the relative radiation level[47].
In men, the cross-sectional diameter of the erector spinae and multifidus muscles at the lower lumbar level can be considered to be prognostic factors for chronic low back pain after acute trauma[48].

Young et al. demonstrated that, regarding the diagnostic criteria, pain when rising from sitting, as well as axial, mid-line pain is associated with disc pain and that absence of pain when rising from sitting is associated with facet joint pain; SI joint pain appeared to be associated with three or more positive pain provocation tests, pain when rising from sitting, unilateral pain and absence of lumbar pain[49]. Hancock et al. found that axial, mid-line pain was the only clinical feature to increase the likelihood of the disc as being the source of pain. A combination of SI joint tests was informative, but single tests were not[50]. Arnbak et al. reported that, on examining the diagnostic value of three SI joint provocation tests, these tests were associated with sacroiliitis identified by MRI[51]. A systematic review of patient history and physical examination to diagnose chronic low back pain originating from the facet joints found that the evidence for the diagnostic accuracy is inconclusive and that therefore patient history and physical examination cannot be used as a substitute for the need of a diagnostic block[52].

When a patient with low back pain complaints visits his or her general physician or medical officer in the Dutch primary care setting and red flags are not suspected, a conservative period of six weeks is widely used. If the patient does not improve, he or she can be referred to secondary care. Long waiting times exist for appointments with pain physicians (or other specialties) in regular hospital settings. This health care system could be partly responsible for the chronification of low back pain. However, at this moment it is unknown whether treating the patient with low back pain in secondary care earlier in the process leads to better results.

Several reasons highlighting the need for change in the multidisciplinary management of chronic pain are presented in the consensus report by Kress et al.[53], i.e. medical training, improvements in training for team members, adopting a patient-centered approach, universal guidelines and influencing political will on a national as well as international level. We have to know first what to offer our patients suffering from this burden of chronic low back pain. However, high-quality evidence of treatment possibilities that provide a good and long lasting treatment outcome (e.g. pain reduction and physical restoration) is lacking.

There is moderate-quality evidence that self-management programmes have a moderate effect on pain intensity, and a small to moderate effect on disability[54].

Although differing in design, studies on the effectiveness of multidisciplinary treatment of chronic low back pain reported patients to have benefitted from treatment, including experiencing pain reduction[55-61]. Studies on massage interventions and yoga indicate short-term improvement[62-66]. There is no high quality evidence to support the use of Pilates exercise programmes[67]. Combined physical and psychological treatments, medical yoga, information and education programmes, spinal manipulation and acupuncture appear to be cost-effective options for low back pain when compared with the study-specific comparators[68]. Spinal fusion should not be favoured when multidisciplinary programmes are available[69].

In patients with chronic, axial low back pain, there is a lack of effectiveness of interlaminar epidural steroid injections. In the case of radicular pain a statistically significant short-term improvement in pain is observed[70]. There is no conclusive high quality evidence supporting the effectiveness of radiofrequency (RF) in patients with chronic low back pain[71-78]. Cement augmentation provides better clinical outcome compared to non-surgical management[79-82], although other studies demonstrate lack of effectiveness as compared to placebo[83,84]. In patients with cancer, balloon kyphoplasty (BKP) proved to be effective and safe[85-91].

Modern telehealth interventions are not more effective than minimal interventional treatment for reducing pain and disability[92].

Rationale and aims of the thesis

In view of the conflicting evidence for effectiveness of RF treatment in patients with chronic low back pain, a study was setup consisting of three RCTs investigating the effect of RF treatment of the SI joint, disc and facet joint in terms of pain relief and GPE. The RCTs studied the effect of respectively a RF lesion of the ramus dorsalis of the segmental nerve root for facet joint pain, an RF lesion with the Simplicity© III tool for SI joint pain and an RF lesion of the ramus communicans for disc pain. In a fourth study, the inter-rater reliability of the diagnostic parameters of the physical examination was assessed and in a fifth study we evaluated the predictive validity of lumbar X-ray images and MRIs in determining the somatic source of low back pain. Finally, we observed the effectiveness of BKP in patients with painful vertebral compression fractures.

Outline of this thesis

This thesis is divided into eight chapters. After this introduction and problem formulation, Chapter 2 describes the randomised sham-controlled double blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment for sacroiliac joint pain. Chapter 3 describes the randomised sham-controlled double blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment for lumbar facet joint pain. In Chapter 4 the randomised sham-controlled double blind multicentre clinical trial to ascertain the effect of percutaneous radiofrequency treatment at the ramus communicans for lumbar disc pain is described. Chapter 5 describes the inter-rater reliability of the diagnostic criteria for SI joint –, disc – and facet joint pain and Chapter 6 discusses the predictive validity of lumbar X-ray images and MRIs for chronic LBP subtypes. Chapter 7 describes the case series study on the effectiveness of BKP for painful vertebral compression fractures. Chapter 8 provides for a general discussion of the main findings, strengths and limitations of all studies in this thesis.

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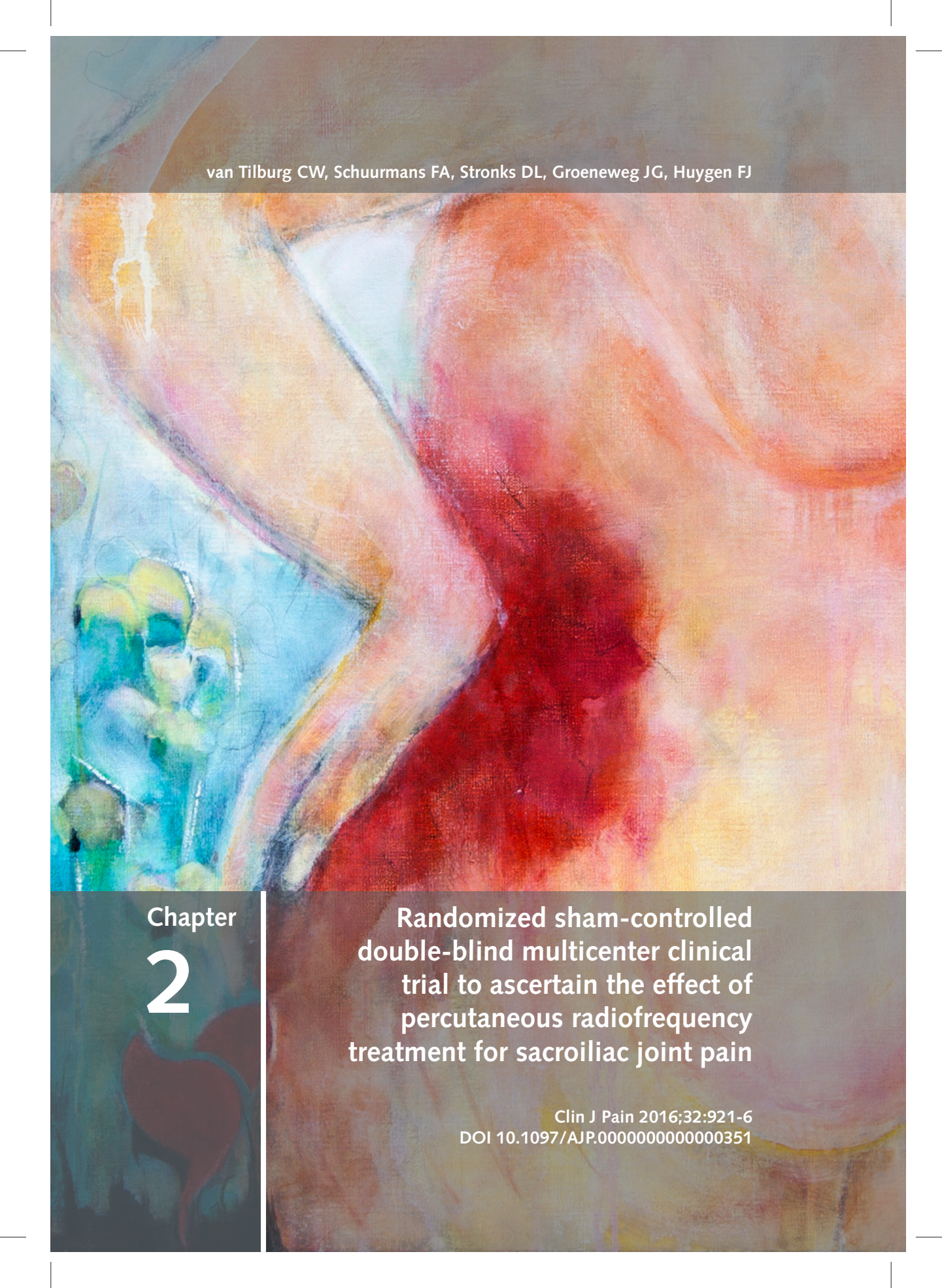
"Bitter Acid" (Beyond the surface)
April 27, 2008
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Chapter

2

Randomized sham-controlled double-blind multicenter clinical trial to ascertain the effect of percutaneous radiofrequency treatment for sacroiliac joint pain

Abstract

Objectives

To investigate the effect of a percutaneous radiofrequency heat lesion compared to a sham procedure, applied to the lateral branches of L5, S1, S2, S3 and S4 nerve roots.

Methods

Sixty patients aged 18 or more with a medical history and physical examination suggestive for sacroiliac joint pain and a reduction of 2 or more on a numerical rating scale (NRS, 0-10) after a sacroiliac joint test block. Treatment group: percutaneous radiofrequency (RF) heat lesion at the lateral branches of S1, S2, S3 and S4 nerve roots and the posterior ramus dorsalis of L5; sham group: same procedure as the treatment group except for the radiofrequency heat lesion. Primary outcome measure: pain reduction (NRS). Secondary outcome measure: Global Perceived Effect (GPE).

Results

No statistically significant difference in pain level over time between the groups (Group x Period) ($F_{(1,58)}$=.353; p=0.56) nor in the factor Group ($F_{(1,58)}$=.212; p=0.65) was found. The Period factor however yielded a significant difference ($F_{(1,58)}$=61.67; p<0.001), i.e. when pooled together the mean pain level of the patients was significantly reduced at T1 compared to T0. In the crossover group, 42.1% experienced a reduction in NRS of 2 or more at 1 month (p=0.65). No statistically significant difference in satisfaction over time between the groups was found ($F_{(1,50)}$=2.1; p=0.15). The independent factors Group ($F_{(1,50)}$=2.02; p=0.16) and Period ($F_{(1,50)}$=0.95; p=0.33) also showed no statistically significant difference. The same applies to recovery: no statistically significant Group x Period effect ($F_{(1,51)}$=0.09; p=0.77) was found, neither an effect of Group ($F_{(1,51)}$=0.004; p=0.95) nor of Period ($F_{(1,51)}$=0.27; p=0.60).

Discussion

The hypothesis of no difference in pain reduction or in global perceived effect between the treatment and sham group cannot be rejected.

Level of evidence

1A.

Key words

Sacroiliac joint, Radiofrequency, RCT, Sham, Chronic pain.

Introduction

In patients with sacro-iliac (SI) joint pain (constituting 10%-38% of patients with chronic low back pain[1-3]), questions rise concerning the persons who might be more susceptible for these problems, how the diagnosis should be made and what comprises optimal treatment. For diagnosing SI joint problems, besides a suggestive medical history and a physical examination[4-8], an intra-articular injection with local anaesthetics is still being used. Every step has its limitations and the whole diagnostic cascade should lead towards sufficient evidence for treatment of the SI joint.

Several types of treatment for trying to diminish SI joint pain are described in the literature, one of them is applying radiofrequency (RF) current to the nerves that provide the innervation[9,10]. Several studies describe a success ratio between 64% and 80%[11-13]. The application of RF current can be provided in several ways (pulsed or continuous, side of the lesion, number of lesions)[3,10,14-17], the practicality of the application must always be considered. More recently evidence emerged about the use of cooled RF current in providing a significant and long lasting pain relief[18-23].

The Simplicity© III probe (Neurotherm®, Wilmington, Massachusetts, United States) is a multi-electrode radiofrequency probe that has a unique design which allows for positioning using a single percutaneous entry point. With this procedure the lateral branches of S1, S2, S3 and S4 are targeted at the same time (a L5 dorsal root ramus radiofrequency lesioning is performed separately). Up to now, there are no randomized controlled trials available concerning the use of this device in diminishing SI joint pain. In this randomised sham-controlled double-blind multicenter clinical trial (Current Controlled Trials ISRCTN45914408) the percutaneous radiofrequency treatment of SI joint pain with this probe was evaluated and compared to a sham procedure. A crossover was provided for the sham-operated group after three months if no significant pain relief was obtained.

Materials and Methods

Study design

We conducted a randomised sham-controlled double-blind multicenter clinical trial in patients with sacroiliac joint pain for more than 3 months. The medical ethics committee from Erasmus University Medical Centre approved the protocol. Written informed consent was obtained from all participants.

Participants

Suitable patients for the study were recruited from a population of patients referred to the multidisciplinary pain centres of two general hospitals with complaints of ongoing low back pain for more than 3 months. Conservative care (rest, analgesics and physiotherapy) had failed to improve their burden. These patients were managed according to the flowchart presented in Figure 1. When a SI joint problem was suspected (details of medical history, physical examination and - if necessary - additional tests[4-7] leading, either wholly or in part, to the diagnosis of SI joint pain) can be found in table 1), and patients met the in- and exclusion criteria[24] (table 2), and if the test SI joint injection with local anaesthetics was positive (decrease in NRS of 2 or more on a 0-10 point scale[25]), the patient was eligible for the RCT. Each patient received a general brochure containing information concerning scientific research involving human subjects (Ministry of Health, Welfare and Sports[26]) and a brochure (including the questionnaires) explaining the complete procedure. After giving written informed consent patients were enrolled in the study.

RANDOMIZED SHAM-CONTROLLED DOUBLE-BLIND MULTICENTER CLINICAL TRIAL TO ASCERTAIN
THE EFFECT OF PERCUTANEOUS RADIOFREQUENCY TREATMENT FOR SACROILIAC JOINT PAIN

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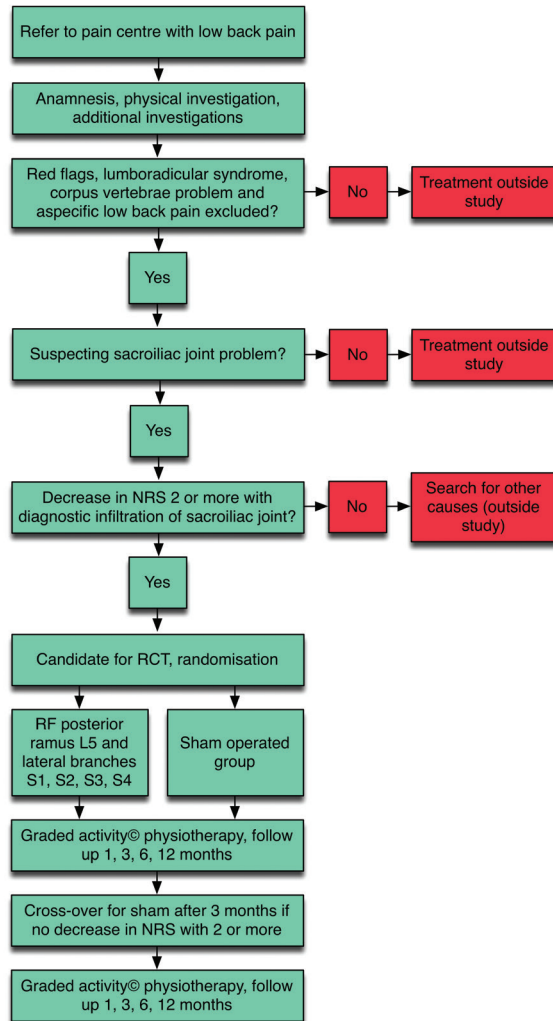
Figure 1: Study flowchart. NRS indicates numerical rating scale; RCT, randomized controlled trial; RF, radiofrequency.

Study interventions

Test SI joint injection: the injection was performed under fluoroscopy with a 10 cm Sluijter-Mehta Kit (SMK) needle (Cotop® via Neurotherm®, Wilmington, Massachusetts, United States). The patient lies in the prone position on the operating table with a pillow under the pelvis. From the anteroposterior (AP) view, the c-arm is rotated contralaterally until the medial cortical line of the posterior articulation is in focus. Local anesthesia with 1 mL lidocaine 2% was given for skin infiltration. Needle insertion is 1-2 cm cranially from the

lower border of the SI joint at the level of the zone of maximal radiographic translucency. Introduction of the needle into the SI joint is characterized by a change in resistance. On a lateral view, the needle tip should appear anterior to the dorsal border of the sacrum. The SI joint was injected with a total of 3 mL lidocaine 2%.

RF heat lesion of the ramus dorsalis of L5 and lateral branches of S1, S2, S3 and S4 with a RF probe with three independent active electrodes versus sham: when patients were candidates for the trial they were randomised in two study groups:

1. Treatment group: monitoring according to American Society of Anesthesiologists (ASA) House of Delegates Standards for Basic Anesthetic Monitoring[27]. Continuous intravenous (IV) propofol Target Controlled Infusion (TCI) 0,5 µg/mL and remifentanyl 0,05 µg/kg/min. Continuous oxygen 15 L/min (non-rebreather mask and bag). The patient lies in the prone position on the operating table with a pillow under the pelvis. Skin infiltration with 1 mL lidocaine 2% per level. The skin entry point for the RF probe with three independent active electrodes is identified at the ipsilateral, lateral, inferior border of the sacrum, 1 cm lateral of and below the S4 foramen. Infiltration over the course of the RF probe with three independent active electrodes with 10 mL lidocaine 2%, staying lateral to the sacral foramen, in contact with the sacrum, and medial to the SI joint. Inserting and advancing RF probe, maintaining continuous contact with the sacrum, on a cephalad and slightly lateral line, staying lateral to the sacral foramen, medial to the SI joint and ventral to the ilium, until contact with the sacral ala prevents further advancement. Percutaneous RF heat lesion (85°C, each step 90 s, total of five steps) with a radiofrequency lesion generator (NT2000, Neurotherm®, Wilmington, Massachusetts, United States) at the lateral branches of S1, S2, S3 and S4 nerve roots. Percutaneous RF heat lesion (85° C for 90 s, same lesion generator) of the L5 dorsal root primary ramus with a 10 cm SMK needle, placed to lie in contact with the S1 superior articular process just slightly above the groove formed between the superior articular process and sacral ala; then advanced with needle position confirmed using fluoroscopy (AP and lateral view) and motor stimulation (2 Hz and at least 1 V).

2. Sham-operated group: same procedure as in treatment group except for the RF heat lesions.

A crossover was provided for the sham-operated group after three months if no significant pain relief was obtained.

Diagnostic criteria for SI joint pain

Medical history
1. Unilateral pain
2. Patient fingerpoints to the location of the pain
3. Pain produced or increased when rising from sitting
4. Direct trauma to the SI joint
5. Buttock pain while turning over in bed
6. Sitting on opposite buttock
7. Hip feels unstable or has given way, some patients fall
8. Pain radiating into the groin or thigh
9. Sciatica (often S1)
10. Pregnancy, giving birth

Physical examination
1. Sitting exam shows no reflex, motor or sensory signs in the legs
2. Straight leg raising (Lasègue) negative between 30 and 70 degrees of passive flexion
3. Distraction (Gapping) test
4. Compression test
5. Sacral thrust test
6. Posterior shear (thigh thrust) test
7. Pelvic torsion (Gaenslen's) test
8. Cranial shear test
9. Patrick-Faber test
10. Bilateral internal rotation of the hip / unilateral rotation of the hip painful at SI joint(s)
11. Drop test
12. Yeoman's test

Additional tests (if available and/or necessary)
1. X-ray pelvis AP
2. CT
3. MRI
4. Diagnostic SI joint block

Table 1: Details about medical history, physical examination and additional tests in patients leading, either wholly or in part, to the diagnosis of sacroiliac joint pain[4-7].

Outcomes

The main study parameter was pain reduction (Numerical Rating Scale (NRS)[28-32]). The 0–10 verbal numeric rating scale (NRS-11) is a tool that enjoys widespread clinical use due to its ease of administration. When using the NRS-11 patients are asked to rate their pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including zero). Often the value of "4" is used to confirm clinical nursing judgment as to the need for further intervention or documentation that the patient's goals for analgesia have been achieved.

Inclusion
1. Age 18 years or older
2. Anamnesis and physical investigation suggestive of SI joint pain
3. Decrease in NRS of 2 or more / 10 on diagnostic SI joint block

Exclusion
1. Presence of red flags[28]
2. Lumboradicular syndrome
3. Aspecific low back pain
4. Corpus vertebrae problem
5. Progressive neurological defects
6. Major psychiatric disorder (according to psychiatrists opinion)
7. Anticoagulation cannot be stopped
8. Active infection
9. Pain in other parts of the body that is more severe
10. Allergies to any medication used in the study
11. Pregnancy
12. Communication (language) difficulties (according to physicians opinion)

Table 2: In- and exclusion criteria[24] for patients with SI joint pain eligible for RCT.

The secondary study parameter was Global Perceived Effect (GPE)[33-35]. The type of rating of perceived effect is a "transition scale" or Global Perceived Effect (GPE) scale. The GPE scale asks the patient to rate, on a numerical scale, how much their condition has improved or deteriorated since some predefined time point. The GPE has several qualities that make it an appealing tool for use in clinical practice and research; being a single question, it is easy and quick to administer and the results are seemingly simple to interpret. Such scales have been recommended for use as a core outcome measure for chronic pain trials and been advocated to increase the relevance of information from clinical trials to clinical practice.

Follow-up

The results of the crossover group were analysed separately, and compared with those who received the actual treatment in the first case. Time periods for follow-up are presented in table 3. Both groups received graded activity[36,37] physiotherapy, which constitutes an individual, submaximal, gradually increased exercise program, with an operant-conditioning behavioral approach, based on the results of the tests and the demands of the patient's work.

Statistical considerations

Difference in patients' gender between the experimental groups was analysed using Fisher's Exact Test. Difference in age was analysed using the Independent-Samples Mann-Whitney U test; the difference in BMI using

the Independent-Samples T-test. The data on the NRS-11, GPE (subscales "Satisfaction" and "Recovery") were analysed by means of a MANOVA for repeated measurements using as independent variables Group (treatment and sham) and Time (in case of the NRS-11 Period T0-T1, in case of the GPE subscales Period T1-T2 as independent variables).

For the skewed distributed variables we nevertheless decided to use MANOVA for repeated measurements analysis of variance. We did so, because, although the MANOVA test requires that each dependent variable entered into the analysis be normally distributed it can still be used in case of skewly distributed dependent variable(s). The Monte Carlo experiments have shown that for sample size 3 or 5 it is still possible to analyse leptokurtic, rectangular, J-shaped, moderately, and markedly skewed distributions. These experiments demonstrated that the empirically determined rejection region of the F-distribution would be no larger than $\alpha = 0.08$ when the usual 5% rejection is used[38].

The percentage of patients requesting crossover and subsequently reporting a significant pain relief was analysed using the One-Sample Binomial Test (reference probability 0.5). Only patients in the sham group could switch to the intervention.

Period	Description
T0	Day of first consultation: medical history, physical examination, additional tests if necessary. Excluding red flags[28], aspecific low back pain and corpus vertebrae problems. Obtaining NRS.
T1	1 month after treatment: NRS and GPE.
T2	3 months after treatment: NRS, GPE.
T1c	1 month after treatment for crossover group: NRS and GPE.
T2c	3 months after treatment for crossover group: NRS, GPE.

Table 3: Time periods for follow-up (NRS: Numerical Rating Scale; GPE: Global Perceived Effect).

The sample size was computed using the NRS-11 as the primary outcome parameter. A statistically detectable and clinically relevant within / between interaction effect size (f(V)) of 0.2 on this scale was chosen. The power of the study $(1 - \beta)$ was chosen to be 0.8, an allocation ratio of 1:1 and the two-sided level of significance (α) to be 0.05. The required a priori total sample size computed by this method is 60.

Data were analysed using SPSS for Mac, version 22 (International Business Machines (IBM) Corporation, Software Group, Route 100, Somers, NY, 10589, United States of America). The primary comparison was done at T1.

Blinding

Based upon the required sample size calculation, sixty envelopes (30 "treatment group" and 30 "sham group") were prepared, sealed, mixed and placed together in a box. Patients chose an envelope randomly. Patients as well as their pain physicians were completely unaware of the content of the envelope during any stage (or T2 in case of sham procedure without reduction in NRS of 2 or more) of the investigation. The pain research nurse was the only one aware of the contents and performed the treatment accordingly. Regarding the radiofrequency lesion generator, all sound indicators were turned off and the generator itself was visually hidden from the patient by means of a linen cloth, hung between two metal infusion poles. The pain physician left the operating theatre when the actual treatment (RF current or sham) took place. The same time period was taken for an actual – or a sham treatment.

Results

Patients were included and treated between February 2012 and June 2014. Out of 79 eligible patients (one patient entered the study without a written informed consent) a total of 19 patients resigned due to various reasons: no significant pain reduction after diagnostic block (9), no more pain after diagnostic block (2), afraid of unemployment (1), not enough time (1), shortly after signing the informed consent form, no reason specified (1), second opinion (1), cumbersome sedation (1), chronic pain turned bearable (1), fear of needles (1) and without reporting a cause (1).

The flowchart of the progress through the phases of the RCT is presented in figure 2. The demographic data of the treatment and sham groups are presented in table 4. There was no statistically significant difference between the parameters of the groups.
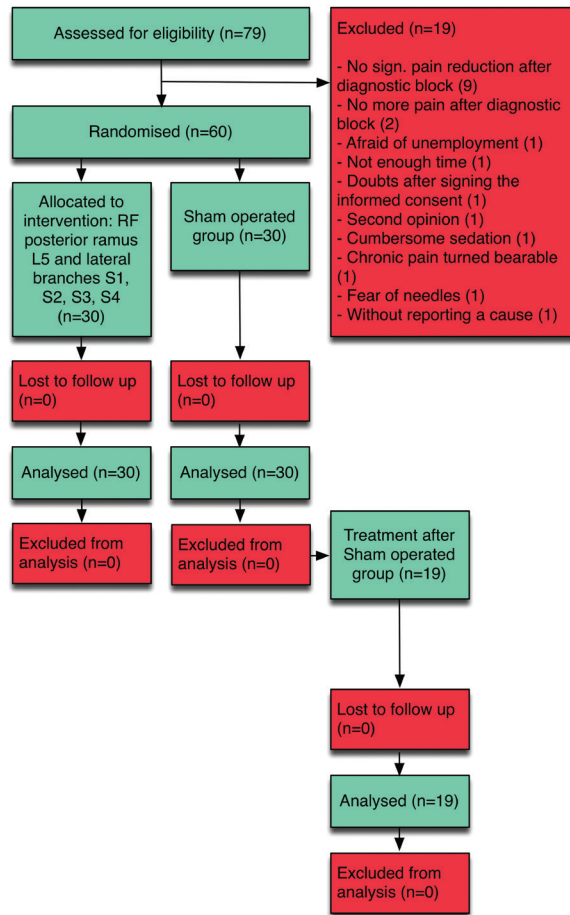
*Figure 2: Flow diagram of the progress through the phases of the randomized controlled trial.
RF indicates radiofrequency.*

Parameter	Treatment	Sham	p
Age (years), median, (IQR)	59.5 (27)	62 (18)	0.89
BMI (kg/m²), mean, (sd)	28.1 (5.2)	28 (4.9)	0.87
Male gender (number, %)	5 (16.7)	5 (16.7)	1
Female gender (number, %)	25 (83.3)	25 (83.3)	1
Caucasian race (number, %)	30 (100)	30 (100)	1

*Table 4: Demographic data of the treatment – and sham groups (IQR: interquartile range (25,75); sd:
standard deviation; p: level of significance; BMI: Body Mass Index).*

Outcome parameter	Treatment group mean (sd)	Sham group mean (sd)	Results MANOVAs	
NRS T0	7.2 (1.4)	7.5 (1.2)	Group Period Group x Period	$F_{(1,58)}$=0.212; p=0.65 $F_{(1,58)}$=61.76; p<0.001 $F_{(1,58)}$=0.353; p=0.56
NRS T1	5.4 (1.7)	5.4 (1.9)		
GPE satisfaction T1	3.2 (1.1)	3.3 (1.0)	Group Period Group x Period	$F_{(1,50)}$=2.02; p=0.16 $F_{(1,50)}$=0.95; p=0.33 $F_{(1,50)}$=2.1; p=0.15
GPE satisfaction T2	3.1 (1.6)	3.8 (1.5)		
GPE recovery T1	3.3 (1.0)	3.3 (1.0)	Group Period Group x Period	$F_{(1,50)}$=0.004; p=0.95 $F_{(1,50)}$=0.27; p=0.60 $F_{(1,50)}$=0.09; p=0.77
GPE recovery T2	3.4 (1.6)	3.4 (1.5)		

Table 5: Numerical rating scale (NRS) and global perceived effect (GPE) scales of the treatment – and sham groups (sd: standard deviation; T0: Day of first consultation; T1: 1 month after treatment; T2: 3 months after treatment).

No statistically significant difference in pain level over time between the groups (Group x Period) ($F_{(1,58)}$=.353; p=0.56) nor in the factor Group ($F_{(1,58)}$=.212; p=0.65) was found. The Period factor however yielded a significant difference ($F_{(1,58)}$=61.67; p<0.001), i.e. when pooled together the mean pain level of the patients was significantly reduced at T1 compared to T0 (figure 3). In the crossover group, 8 out of 19 patients experienced a reduction in NRS of 2 or more at 1 month crossover (p=0.65).

Figure 3. Boxplot of NRS-11 scores by group and by moment of measurement
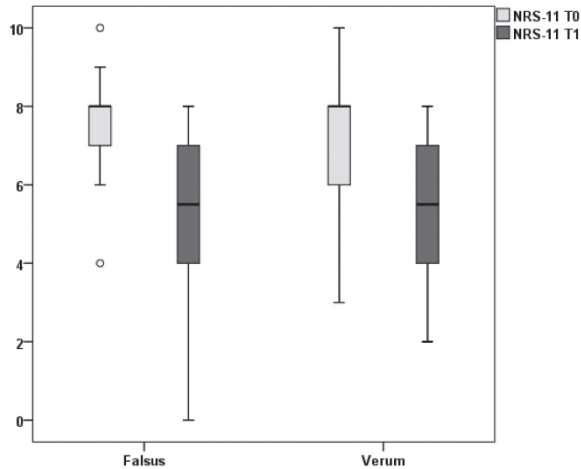
Figure 3: Boxplot of numerical rating scale (NRS)-11 scores by group and by moment of measurement (verum=treatment group; falsus=sham group).

No statistically significant difference in satisfaction over time between the groups (Group x Period) was found ($F_{(1,50)}$=2.1; p=0.15). The independent factors Group ($F_{(1,50)}$=2.02; p=0.16) and Period ($F_{(1,50)}$=0.95; p=0.33) also showed no statistically significant difference (eight missing cases on T2). The same applies to recovery: no statistically significant Group x Period effect ($F_{(1,51)}$=0.09; p=0.77) was found, neither an effect of Group ($F_{(1,51)}$=0.004; p=0.95) nor of Period ($F_{(1,51)}$=0.27; p=0.60) (seven missing cases on T2) (table 5).

During the trial we noted one unexpected and unsuspected serious adverse event, due to a fall from the stairs during the follow up period.

Discussion

In this randomised controlled trial the proportion of patients who reported a significant pain relief (NRS ≥ 2) after the sham procedure was even higher (but not statistically significant) than those after the actual treatment. In the crossover group (3 months after the sham procedure) the number of people that demonstrated a statistically significant reduction after the RF treatment was 42.1%, which equals the number of positive results (43.3%) from the primary treatment group.

The number of positive SI joint test blocks was 86.1% (62 out of 72 blocks), which is higher than expected when considering the available literature[1,2,8] on the subject. Possible reasons could be (the combination of) multidisciplinary assessment, rating of the decrease in NRS as a result of the test injection with local anaesthetics according to Ostelo et al. (positive test injection with local anaesthetics when a decrease in NRS of 2 or more on a 0-10 point scale is obtained)[25] instead of a decrease of 50% in NRS, using only local anesthetics instead of corticosteroids and the probability that, based on the diagnostic cascade used, the patients did not have SI joint pain. The false-positive rate of a single, uncontrolled, SI joint injection with local anaesthetics is around 20%[2], but can be a high as 54%[1]. The local anaesthetic diffuses out of the joint in 61% of cases, becoming an intra- as well as extra-articular injection[12].

The presence of pain distal to the knee in patients with SI joint pain is described but not often found and SI joint denervation often won't relieve this type of pain when present. Instead of using "sciatica (often S1)" as inclusion criterion it would have been better to use "pain predominantly below L5". As stated the whole diagnostic cascade should be taken into account and not a single item. Another limitation of this study is the fact that we used only one diagnostic test block instead of using a double diagnostic test block. Having considered the daily practice in pain management, this sham RCT was completed with one diagnostic test block.

Regarding the internal validity of this study: (1) Due to the anatomy of the sacrum, we sometimes didn't reach the S4 branch with the radiofrequency probe with three independent active electrodes, performing a L5 to S3 radiofrequency procedure. How much does the S4 branch attributes to SI joint pain? The size of the lesion by the radiofrequency probe with three independent active electrodes might be smaller than the one from the cooled RF treatment variant[39] but, again, what is the (exact) influence of that? (2) Age was nonnormally (bimodally) distributed (figure 3); this might reflect differences in disease type, encompassing different structures (anatomical changes, disorders of the capsuloligamentous structures, and diastasis from pregnancy and childbirth and disorders from the vascular plexus or complex neural network) and operative procedures[1,5]; (3) Pain scores were measured during follow-up at specific time periods (table 3). Using average pain scores over certain time periods (i.e. past month), based on pain diaries might have led to a different result; (4) All patients received graded activity[36-37] physiotherapy, but not at a single centre; as a consequence gaining evidence of equal quality of physiotherapy accompaniment was difficult and we therefore do not know whether – and if so to which extend – this factor has confounded the treatment outcome.

On the basis of this RCT the hypothesis of no difference in pain reduction or in global perceived effect between the treatment and sham group cannot be rejected (level of evidence 1A[40]).

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"Pool of Darkness" (Beyond the surface)
April 14, 2008
With permission of the painter Julie Meese
juliemeese@hotmail.com

van Tilburg CW, Schuurmans FA, Stronks DL, Groeneweg JG, Huygen FJ

Chapter

3

Randomised sham-controlled
double blind multicentre clinical
trial to ascertain the effect
of percutaneous radiofrequency
treatment for lumbar facet joint pain

Abstract

Aims

The aim of this study was to compare the effect of a percutaneous radiofrequency heat lesion at the medial branch of the primary dorsal ramus with a sham procedure, for the treatment of lumbar facet joint pain.

Patients and Methods

A randomised sham-controlled double blind multicentre trial was carried out at the multidisciplinary pain centres of two hospitals. A total of 60 patients aged > 18 years with a history and physical examination suggestive of facet joint pain and a decrease of ≥ 2 on a numerical rating scale (NRS 0 to 10) after a diagnostic facet joint test block were included. In the treatment group, a percutaneous radiofrequency heat lesion (80°C during 60 seconds per level) was applied to the medial branch of the primary dorsal ramus. In the sham group, the same procedure was undertaken without for the radiofrequency lesion. Both groups also received a graded activity physiotherapy programme. The primary outcome measure was decrease in pain. A secondary outcome measure was the Global Perceived Effect scale (GPE).

Results

There was a statistically significant effect on the level of pain in the factor Period (T0-T1). However, there was no statistically significant difference with the passage of time between the groups (Group x Period) or in the factor Group. In the crossover group, 11 of 19 patients had a decrease in NRS of ≥ 2 at one month crossover (p = 0.65). There was no statistically significant difference in satisfaction with the passage of time between the groups (Group x Period). The independent factors Group and Period also showed no statistically significant difference. There was no statistically significant Group x Period effect for recovery, neither an effect of Group or of Period.

Conclusion

The null hypothesis of no difference in the decrease in pain and in GPE between the treatment and sham groups cannot be rejected. Post hoc analysis revealed that the age of the patients and the severity of the initial pain significantly predicted a positive outcome.

Introduction

In 1911 Goldthwait[1] proposed that in patients with chronic low back pain (LBP), the facet joints were a potential source of pain. Several reviews have subsequently described difficulties in diagnosing facet joint pain,[2-4] when based on the medical history, physical examination and radiological findings. However, in 1976, Mooney and Robertson described the injection of local anaesthetic in an attempt to confirm the diagnosis.[5] Recently, radiofrequency has been described as a possible form of treatment for lumbar facet joint pain.[6] Radiofrequency causes the localised destruction of neural tissue and interruption of neural signaling. This is known as the radiofrequency heat lesion.[6] Fluoroscopically guided percutaneous radiofrequency denervation of the lumbar facet joints have been associated with an overall incidence of minor complications of 1% per lesion site such as ongoing localised pain or neuritic pain and no major complications have been reported.[7]

Recently two systematic reviews addressed radiofrequency treatment for patients with LBP. Leggett et al.[8] analysed six sham-controlled randomised control trials (RCTs) involving lumbar facet joint pain, performed between 1994 and 2008. There were many differences between the trials including the duration of LBP before the patients entered the study, which was between three months and more than two years, and which specialty performed the examination. Also there were variations in the exclusion criteria, such as previous spinal surgery in three RCTs and previous radiofrequency treatment in one. They reported differences in the way the diagnostic blocks were performed, how the results were interpreted, the number of treatments given and of patients entered into the trial. Poetscher et al.[9] evaluated nine RCTs comparing the effect of radiofrequency treatment with other forms of treatment and with a placebo and found that radiofrequency denervation was more effective than a placebo and steroid injections. They concluded, however, that the evidence should be interpreted with caution.
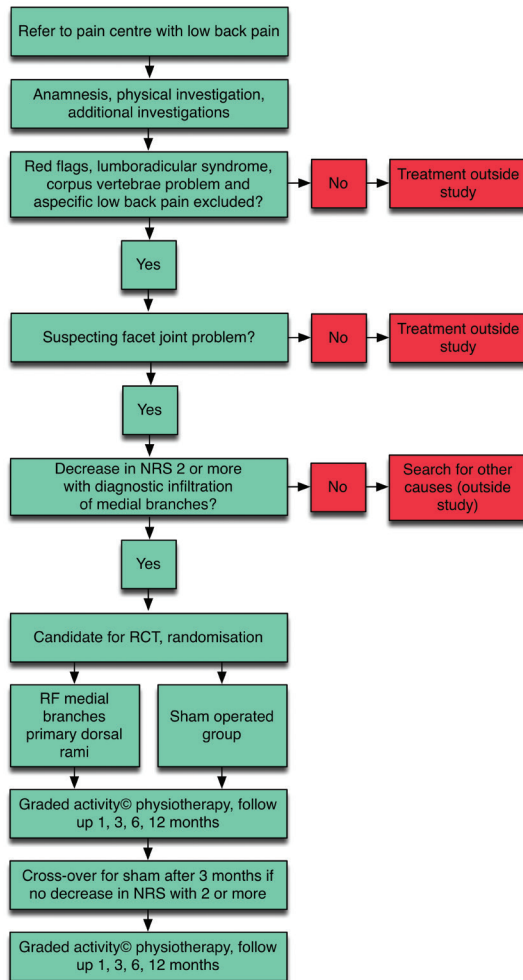
Fig 1. Study flowchart (NRS, Numerical Rating Scale; RCT, Randomised Clinical Trial; RF, Radio Frequency).

In a review article dealing with the treatment of facet joint pain, Cohen, Huang and Brummett[10] described even more differences in these various studies. The results of these RCTs are therefore inconsistent and do not resolve the debate about the role of radiofrequency treatment in chronic LBP. In an attempt to answer these issues, a randomised sham-controlled double blind multicentre clinical trial (RCT; Current Controlled Trials ISRCTN17868852) was constructed. Its aim was to investigate the effect of a percutaneous radiofrequency heat lesion compared with a sham procedure, when applied to the medial branch of the primary dorsal ramus, for treatment of lumbar facet joint pain. The effect on the intensity of pain and on perceived effectiveness of this treatment was compared with a sham procedure.

A crossover was provided for the sham-operated group after a minimum of three months if no significant pain relief was reported. The null hypothesis was that there was no difference in the reduction of pain or in Global Perceived Effect (GPE) scale between the two groups.

Period	Description
T0	Day of first consultation: medical history, physical examination, additional tests if necessary. Excluding red flags[28], nonspecific low back pain and corpus vertebrae problems. Obtaining NRS.
T1	1 month after treatment: NRS and GPE.
T2	3 months after treatment: NRS, GPE.
T1c	1 month after treatment for crossover group: NRS and GPE.
T2c	3 months after treatment for crossover group: NRS, GPE.

Table I: time periods for follow-up (NRS: Numerical Rating Scale; GPE: Global Perceived Effect).

Patients and Methods

The Erasmus University Medical Centre Rotterdam ethical committee, which is approved by the Dutch Central Committee on Research Involving Human Subjects, and the local hospital both approved the protocol. All patients gave written informed consent.

Patients were recruited from those with a history of LBP for more than three months, who had been referred to the multidisciplinary pain centres of Lievenberg Hospital, Bergen op Zoom, The Netherlands and Franciscus Hospital, Roosendaal, The Netherlands. Conservative care which included rest, analgesics and physiotherapy had failed to improve the pain. These patients were managed as shown in Figure 1. The medical history and clinical findings were recorded, along with radiographs, CT and MRI scans. The inclusion and exclusion criteria were based on the New Zealand LBP Guide.[11] A test injection at the medial branch of the primary dorsal ramus with local anaesthesia was performed and if it induced a decrease in the Numerical Rating Scale (NRS) for pain of ≥ 2 on a 0 to 10 point scale,[12] the patient was eligible for inclusion. Each patient then received a brochure containing general information about research involving humans (Ministry of Health, Welfare and Sports)13 and one, including the questionnaires, explaining the procedure.

The test injection at the medial branch of the primary dorsal ramus was performed under fluoroscopy with three 10 cm Sluijter-Mehta Kit needles (Cotop via Neurotherm, Wilmington, Massachusetts) at the facet joint that was presumed to be the source of the pain and into the two adjacent levels. For the L5/S1 level, the adjacent L4/L5 level was also treated. The patient lay prone on the operating table with a pillow under the abdomen in order to flatten the lumbar lordosis. From the anteroposterior (AP) view, the C-arm was rotated obliquely to the ipsilateral side so that the junction between the superior articular process and the transverse process was more easily accessible. Local anaesthesia with 1 mL lidocaine 2% per level was infiltrated into the skin. Contact was made with the transverse process as close as possible to the superior articular process. After contacting bone, the needle was advanced slightly in a cranial direction so that its tip slid over the transverse process. In the lateral view, the tip of the electrode lay at the base of the superior articular process at the lower aspect of the intervertebral foramen, approximately 1 mm dorsal to its posterior border. After sensory (50 Hz) - and motor (2 Hz) stimulation with contraction of the ipsilateral multifidus muscle and excluding too close proximity to the segmental nerve, a total of 0.5 mL lidocaine 2% was introduced around each medial branch.

The patients were randomised into two groups:
1) Treatment group: the same procedure as the test was used except that a percutaneous radiofrequency heat lesion (80ºC for 60 seconds per level, total of three steps) was given with a radiofrequency generator (NT2000, Neurotherm)® into the medial branches of the primary dorsal ramus;
2) sham group: the same procedure as in treatment group was used except without the radiofrequency heat lesions.
A crossover for the sham group was provided after a minimum of three months if no significant pain relief (without a decrease in NRS for pain of ≥ 2) was obtained.

The main outcome was a decrease in pain using the NRS-11[14-18]. When using this scale, patients are asked to rate their pain from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible", using whole numbers (11 integers including zero). The secondary outcome was the GPE scale,[19-21] for which the patient is asked to rate, numerically, how much their condition has improved or deteriorated from some predefined time point. The test-retest reliability of the GPE scale is excellent,[19-21] but the ratings are influenced by the current status of the patient.

The results of the crossover group were analysed separately and compared with those who received the actual treatment initially. The periods of time at which the patients were reviewed are shown in Table I.

The patients in both groups were also treated with graded activity physiotherapy[22,23], containing an individual, submaximal, gradually increasing exercise programme and an operant-conditioning behavioural approach. This is based on the results of the tests and the demands of the patient's work.
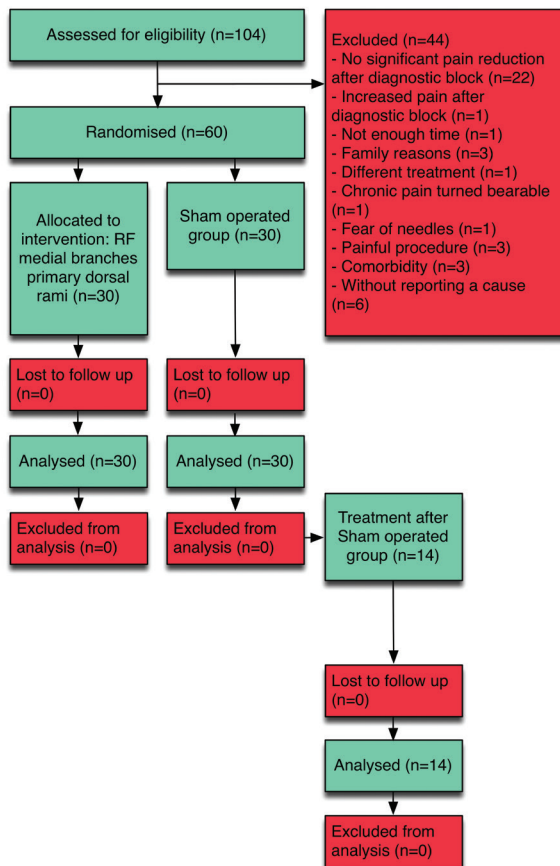

Fig. 2 Flow diagram of the progress through the randomized controlled trial (RF, radiofrequency).

Statistical analysis

The differences in gender, age and body mass index (BMI) between the groups were analysed using Fisher's exact test, the Mann-Whitney U test and the independent samples t-test, respectively. The data on the NRS-11 and GPE

(subscales "Satisfaction" and "Recovery") were analysed using multivariate analysis of variance (MANOVA) for repeated measurements using, as independent variables, Group (treatment versus sham) and Time (with the NRS-11 Period T0-T1, and the GPE subscales Period T1-T2).

We also used MANOVA for repeated measurements analysis of variance for the variables whose distribution was skewed. We did this, because, although the MANOVA test requires that each dependent variable entered into the analysis be normally distributed, it can still be used for variables whose distribution is skewed. The Monte Carlo experiments[24-26] have shown that for sample size three or five it is still possible to analyse leptokurtic (clustering along the x-axis with higher peak), rectangular, J-shaped, moderately, and markedly skewed distributions. These experiments showed that the empirically determined rejection region of the F-distribution would be < α = 0.08 when the usual 5% rejection is used.

The percentage of patients requesting crossover and subsequently reporting significant pain relief was analysed using the one-sample binomial test (reference probability 0.5). Only patients in the sham group could switch to the intervention.

The required *a priori* sample size for the trial was computed using the NRS-11 as the primary outcome measure. A statistically detectable and clinically relevant with/between interaction effect size (f(V)) of 0.2 on the scale was chosen. The power of the study (1 - β) was chosen to be 0.8, an allocation ratio of 1:1 and the two-sided level of significance (α) 0.05. The required sample size was 60.

Data were analysed using SPSS for Mac, version 22 (International Business Machines (IBM) Corporation, Software Group, Route 100, Somers, New York). The primary comparison was done at T1, which was one month after the treatment.

Parameter	Treatment	Sham	p
Age (years), median, (IQR)	65 (12)	58 (12)	0.004
BMI (kg/m²), mean, (sd)	29.7 (4.7)	29.4 (5.9)	0.42
Male gender (number, %)	14 (*46.7*)	12 (*40*)	
Female gender (number, %)	16 (*53.3*)	18 (*60*)	
Caucasian race (number, %)	30 (*100*)	30 (*100*)	

Table II: demographic data of the treatment – and sham groups (IQR: interquartile range (25,75); sd: standard deviation; p: level of significance; BMI: Body Mass Index).

Outcome parameter	Treatment group mean (sd)	Sham group mean (sd)	Results MANOVAs	
NRS T0	7.2 (1.4)	7.4 (0.8)	Group Period Group x Period	$F_{(1,58)}$=0.194; p=0.66 $F_{(1,58)}$=39.95; p<0.001 $F_{(1,58)}$=0.393; p=0.53
NRS T1	5.3 (1.8)	5.5 (1.9)		
GPE satisfaction T1	3.4 (1.0)	3.5 (1.2)	Group Period Group x Period	$F_{(1,51)}$=0.445; p=0.51 $F_{(1,51)}$=0.40; p=0.53 $F_{(1,51)}$=1.23; p=0.27
GPE satisfaction T2	3.4 (1.0)	3.7 (1.3)		
GPE recovery T1	3.3 (1.0)	3.4 (1.2)	Group Period Group x Period	$F_{(1,52)}$=0.456; p=0.50 $F_{(1,52)}$=0.80; p=0.38 $F_{(1,52)}$=0.09; p=0.77
GPE recovery T2	3.4 (1.0)	3.6 (1.1)		

Table III: numerical rating scale (NRS) and global perceived effect (GPE) scales of the treatment – and sham groups (sd: standard deviation; T0: Day of first consultation; T1: 1 month after treatment; T2: 3 months after treatment).

	Experimental group	
Duration (yrs)	Treatment n (%)	Sham n (%)
< 0,5	4 (*13.3*)	5 (*16.7*)
0,5-1	2 (*6.7*)	6 (*20*)
1-5	10 (*33.3*)	10 (*33.3*)
>5	13 (*43.3*)	6 (*20*)
Unknown	1 (*3.3*)	3 (*10*)
Total	30 (*100*)	30 (*100*)

Table IV: duration of low back pain before entering the study by group (T0).

Based on the calculation of the sample size, 60 envelopes (30 for each group, treatment and sham) were prepared, sealed, mixed and placed in a box. Patients chose an envelope randomly. Patients and physicians were unaware of the content of the envelope at all stages of the investigation.

The pain research nurse (F. Schuurmans) was the only one aware of the contents and arranged the treatment accordingly. All sound indicators of the radiofrequency lesion generator were turned off and the generator itself was hidden from the patient by means of a linen cloth, hung between two infusion poles. The pain physician left the operating theatre when the actual treatment (radiofrequency or sham) took place. The same time period was taken for an actual or a sham treatment. In this way the physicians, investigators and patients were blinded for the intervention. At time periods T1 and T2, the patient was asked by the physician and or the investigator to rate the pain and the recovery, the research nurse played no part here.

Results

The trial took place between February 2012 and June 2014. Out of 104 eligible patients, 44 withdrew for a variety of reasons: no significant decrease in pain after the diagnostic test (22), increased pain after the diagnostic test (one), not enough time (three), family reasons (three), alternative treatment (one), chronic pain which became bearable (one), fear of needles (one), painful procedure despite local anaesthesia (three), comorbidity (three) and without reporting a reason (six).

Progress through the trial is shown in Figure 2. The demographic data of the patients in both groups are shown in Table II. The age distribution was skewed but other parameters were normally distributed.
A statistically significant effect on the level of pain of the factor Period (T0-T1) was found. However, there was no statistically significant difference with the passage of time between the groups (Group x Period) nor in the factor Group. In the crossover group, 11 of 19 patients had a decrease in the NRS of ≥ 2 at one month crossover (p = 0.65). There was no statistically significant difference with the passage of time in satisfaction between the groups (Group x Period). The independent factors Group and Period also showed no statistically significant difference. The same applied to recovery, no statistically significant Group x Period effect was found, neither an effect of Group nor of Period (Table III).

The duration of LBP before entering the study (T0) for the patients is shown in Table IV and the description of the relative frequency of severity of the LBP is shown in Table V, with the patients' age in Table VI.

NRS	Treatment frequency (%)	Sham frequency (%)
1	0 (*0*)	0 (*0*)
2	0 (*0*)	0 (*0*)
3	0 (*0*)	0 (*0*)
4	2 (*6.7*)	0 (*0*)
5	2 (*6.7*)	0 (*0*)
6	3 (*10*)	3 (*10*)
7	11 (*36.7*)	13 (*43.3*)
8	8 (*26.7*)	13 (*43.3*)
9	4 (*13.3*)	1 (*3.3*)
10	0 (*0*)	0 (*0*)

Table V: (relative) frequency distribution of severity of low back pain before entering the study (T0).
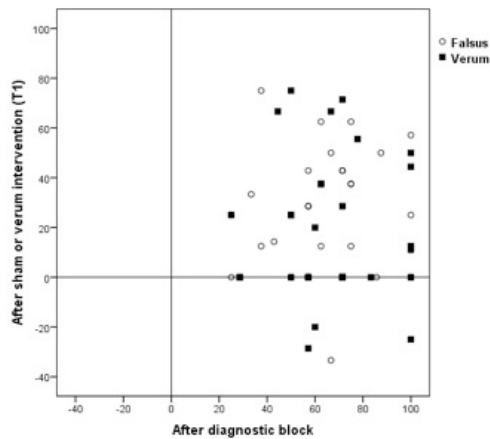
Fig. 3 Size of the decrease in pain due to the diagnostic test (%) compared with the rate of success of the intervention (%).

A total of 50 patients (83.3%) had a decrease of > 50% after the diagnostic test. Post hoc, the validity (in terms of sensitivity) of the percentage decrease in pain after the diagnostic test, in predicting the percentage which would have a decrease after the intervention at T1 (treatment or sham), was analysed. There was no statistically significant correlation between these parameters, neither in the treatment (r = 0.003; p = 0.99) nor sham group (r = 0.16; p = 0.40). The size of the decrease in pain due to the diagnostic test did not seem to influence the rate of success of the intervention (Fig. 3).

A total of 29 patients (48.3%) reported a significant decrease in pain (by NRS of ≥ 2). Our analysis showed that these patients cannot be predicted by the interventional procedure (treatment or sham). In order to evaluate the possible contribution of other parameters than the intervention to the prediction of a significant decrease in pain at T1, binary logistical regression analysis was used. The parameters entered into this analysis were gender, BMI, duration of symptoms, the level of pain at baseline, age and the interaction between group and age (Group x Age) because of the imbalance in age between the groups. In order to prevent overfitting of the model, univariate binary logistic regression analysis of these parameters was performed. Only age and the level of pain at T0, the parameters with a level of significance of $p \leq 0.2$, were entered into the final multivariate stepwise binary logistic regression analysis (Backward Wald method) with a probability of $p = 0.1$. This analysis revealed that age ($p = 0.01$) and the initial level of pain ($p = 0.08$) significantly contributed to the prediction of a significant decrease in pain (Table VII). This resulted in a sensitivity of 62.1%, a specificity of 67.7% (overall classification 65%), with a cutoff value of 0.5, being a moderate performance.
No serious adverse events were encountered during the trial.

Discussion

In 2003, following a critical review, Slipman et al.[27] emphasised the need for RCTs to provide recommendations on the treatment of facet joint pain, because of the moderate to limited evidence available. Recent systematic reviews have identified six randomised, placebo-controlled trials investigating the efficacy of the radiofrequency lesion on the medial branch of the primary dorsal ramus.[8-10] Among these, three small studies were positive[28-30], two were equivocally positive,[31] and one[32] was negative[10]. The overall quality of the evidence of the studies was low to moderate.

Lack of concealment of allocation and failure to blind patients was reported in several trials, and the risk of selective reporting in all trials[9]. The number of positive lumbar facet joint test blocks was 77.8% (81 of 104). Several studies reported a high percentage of false positive blocks[33-36] due to reasons such as placebo response, sedation, the liberal use of superficial local anaesthesia, spread of the injected material to pain generating structures other than those targeted and using only local anaesthetics instead of including corticosteroids. Furthermore, the combination of multidisciplinary treatment and the criteria chosen for the diagnostic test to be called positive differ between studies (decrease in NRS of ≥ 2,12,50% or 80%[37] pain relief).

A limitation of our study is the use of one instead of two test blocks, which was chosen because it is our pain management practice. Also pain scores were measured during follow-up at specific moments in time. Using mean pain scores over certain periods of time, for example the past month, and based on pain diaries might lead to a different result. Depending on the median duration of the symptoms, decrease in pain is unlikely to be due to spontaneous recovery. In addition, the regression analysis revealed no statistically significant effect of the interaction of group and age. Therefore, a possible overall effect of treatment due to the imbalance in age between the two groups, is unlikely. The injection of local anaesthetics is a different procedure than inducing a radiofrequency heat lesion. When the heat lesion does not lead to a significant decrease in pain, does that mean that the diagnostic block is a false positive? Or does it mean that the treatment cannot provide significant decrease in pain, contrary to the diagnostic test? Another limitation is that we did not test the patients for the success of blinding. However, since the results of the crossover, when the patients knew that they would receive the real radiofrequency heat lesion, were comparable, we do not think this compromised the results.

Age (yrs)	Treatment n (%)	Sham n (%)
30-39	0 (0)	2 (6.7)
40-49	2 (6.7)	5 (16.7)
50-59	5 (16.7)	11 (36.7)
60-69	15 (50)	9 (30)
70-79	8 (26.7)	3 10)
Total	30 (100)	30 (100)

Table VI: patients' age before entering the study by group.

| | B (SE) [p-value] | 95% CI for Odds Ratio | | |
		Lower	Odds Ratio	Upper
Included				
Constant	1.6 (3.15) [.61]			
Age	-0.09 (.035) [.01]	.85	0.914	0.98
Pain level at baseline	0.53 (.3) [.08]	.94	1.69	3.03

Table VII: results of multivariate binary logictic regression analysis (R^2=0.21 (Cox & Schnell), 0.28 (Nagelkerke). Model X^2(2)=14.32, p=0.001).

All patients had physiotherapy, but not at a single centre, and as a consequence we do not know if and to what extent this factor confounded the outcome. Whilst 11 of 19 patients in the crossover group had a clinically but not statistically significant decrease in pain at T1 (p = 0.65), this would support the results from the primary analysis. Post hoc analysis revealed that age and the initial severity of pain significantly predicted a positive outcome.

In conclusion, following this RCT we are unable to reject the null hypothesis, of no difference in either decrease in pain or in the GPE scale between the treatment and sham groups when using radiofrequency for lumbar facet joint pain.

Supplementary material

Tables showing details about medical history, physical examination and additional tests in patients with facet joint pain (Table 1) and inclusion/exclusion criteria for patients with facet joint pain eligible for RCT (Table 2).

Diagnostic criteria for facet joint pain

Medical history
1. Age > 65 years
2. Trauma (fall, auto accident)
3. Dull and deep ache
4. Localised unilateral or bilateral back pain
5. Low back pain associated with groin or thigh pain
6. Pain, if referred to the leg, is above the knee
7. Unilateral or bilateral muscle spasm over the affected joints
8. Pain not exacerbated by coughing
9. Pain relief by recumbency
10. Lack of radicular features

Physical examination
1. Pain in extension
2. Pain eased in flexion
3. Pain when rising from forward flexion
4. Pain in extension, lateral flexion or rotation manoeuvers to the ipsilateral side
5. Replication or aggravation of pain by unilateral or bilateral pressure over the facet joints or transverse process
6. Local unilateral or bilateral passive movements show reduced range of motion or increased stiffness on the side of facet joint pain
7. Tight or facilitated muscles (psoas, hip adductors, hamstring muscles)
8. Weak or inhibited muscles (gluteus maximus, gluteus medius muscles)

Additional tests (if available and/or necessary)
1. X-ray lumbar spine AP / lateral
2. CT
3. MRI
4. Diagnostic medial branch block

Table 1: details about medical history, physical examination and additional tests in patients with facet joint pain.

Inclusion
1. Age 18 years or older
2. Medical history and physical examination suggestive of facet joint pain
3. Decrease in NRS of 2 or more / 10 on diagnostic medial branch block
Exclusion
1. Presence of red flags[22]
2. Lumboradicular syndrome
3. Aspecific low back pain
4. Corpus vertebrae problem
5. Progressive neurological defecits
6. Major psychiatric disorder (according to psychiatrists opinion)
7. Anticoagulation cannot be stopped
8. Active infection
9. Pain in other parts of the body that is more severe
10. Allergies to any medication used in the study
11. Pregnancy
12. Communication (language) difficulties (according to physicians opinion)

Table 2: in- and exclusion criteria for patients with facet joint pain eligible for RCT.
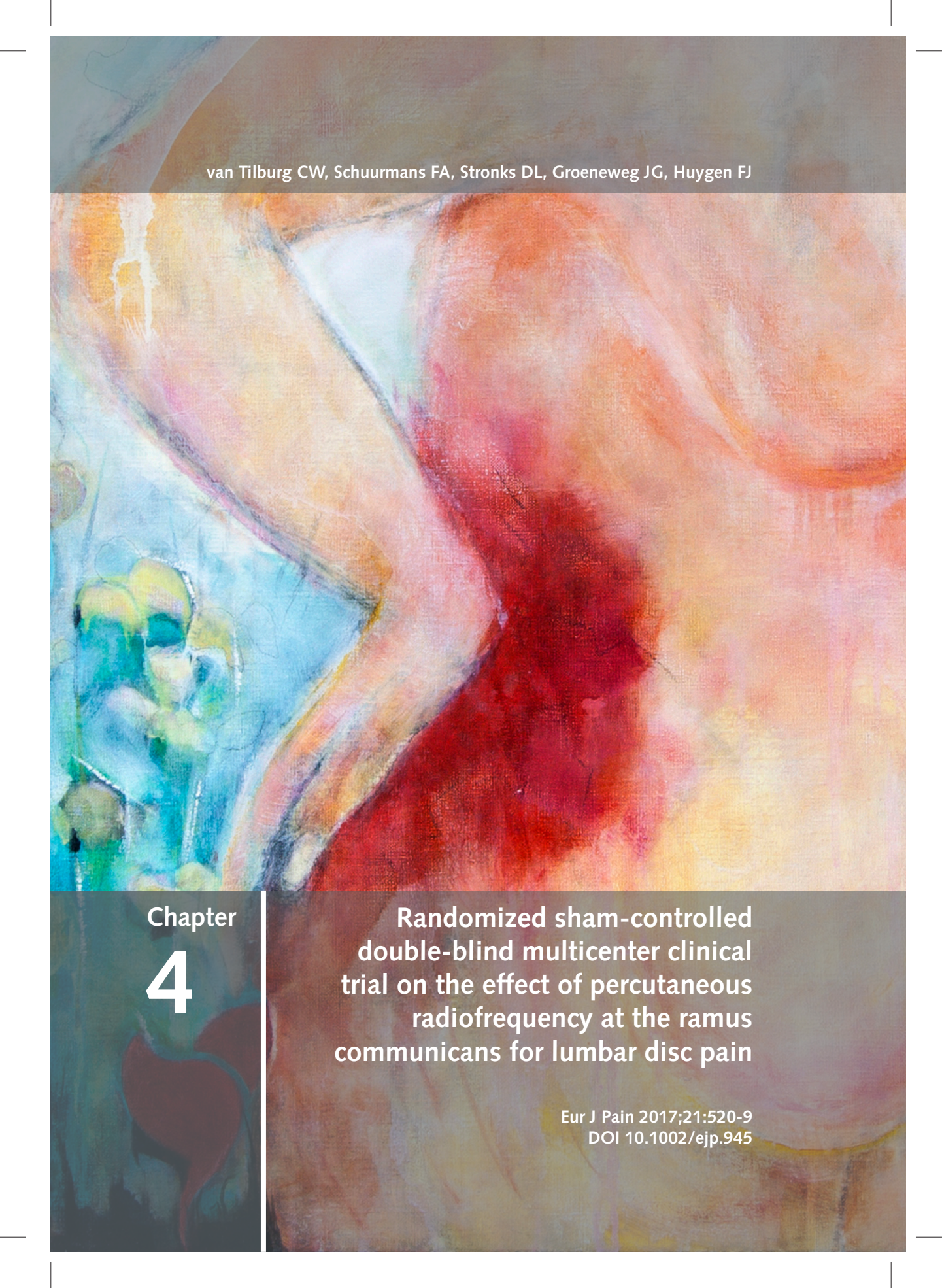
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Chapter

4

Randomized sham-controlled
double-blind multicenter clinical
trial on the effect of percutaneous
radiofrequency at the ramus
communicans for lumbar disc pain

Abstract

Background

Investigate the effect of percutaneous radiofrequency compared to a sham procedure, applied to the ramus communicans for treatment of lumbar disc pain.

Methods

Randomized sham-controlled double blind crossover multicenter clinical trial. Multidisciplinary pain centers of two general hospitals. Sixty patients aged 18 or more with medical history and physical examination suggestive for lumbar disc pain and a reduction of 2 or more on a numerical rating scale (0-10) after a diagnostic ramus communicans test block. Treatment group: percutaneous radiofrequency treatment applied to the ramus communicans; sham: same procedure except radiofrequency treatment. Primary outcome measure: pain reduction. Secondary outcome measure: Global Perceived Effect.

Results

No statistically significant difference in pain level over time between the groups, as well as in the group was found; however, the factor period yielded a statistically significant result. In the crossover group, 11 out of 16 patients experienced a reduction in NRS of 2 or more at 1 month (no significant deviation from chance). No statistically significant difference in satisfaction over time between the groups was found. The independent factors group and period also showed no statistically significant effects. The same applies to recovery: no statistically significant effects were found.

Conclusions

The null hypothesis of no difference in pain reduction and in global perceived effect between the treatment and sham group cannot be rejected. Post-hoc analysis revealed that none of the investigated parameters contributed to the prediction of a significant pain reduction.

Introduction

In patients with chronic low back pain, the discs represent a potential pain generator[1-3]. Disc pain can occur as a result of genetic implications, together with degenerative marks and start at an early age[4-8]. Low back disc pain uses the sympathetic nervous system; pain impulses coming from the intervertebral disc join the L2 spinal ganglion via the rami communicantes and the sympathetic trunk[9-10]. In patients with chronic lumbar disc pain, symptoms can show no improvement over time[11]. One of the treatment possibilities is applying high frequency energy at specific sites in or around the lumbar discs. Applying radiofrequency (RF) is a possible, but not generally accepted option for chronic low back pain. When a continuous radiofrequency (CRF) current is used, the tissue heating can lead to localized destruction of neural tissue and consequent interruption of neural signaling[12].

Interrupting signalling through the ramus communicans may interfere with the transition of painful information from the discs to the central nervous system[13]. To evaluate the efficacy of a RF treatment at the ramus communicans, a few studies were performed[14-15]. Methodological differences exist in these studies concerning the inclusion criteria, outcome parameters and follow-up. In a systematic review addressing RF treatment for low back pain subtypes, three sham-controlled RCT's involving lumbar disc pain[16] were included; differences between the studies were observed regarding RF technique, duration of low back pain before entering the study, the exclusion criteria and the number of participants. The results of these studies are inconsistent and do not help to settle the continuing debate about the role of this specific treatment in chronic lumbar disc pain.

Therefore, we set up a randomized sham-controlled double blind multicenter clinical trial (Current Controlled Trials ISRCTN48011364). The aim of the study is to investigate the effect of a percutaneous RF treatment compared to a sham procedure, applied at the ramus communicans; we investigated the effect on pain intensity and on global perceived effect of this interventional treatment compared to a sham procedure. A crossover was provided for the sham-operated group after a minimum of three months if no significant pain relief was reported.

Methods

Study design

We conducted a randomized sham-controlled double blind multicenter clinical trial in patients with lumbar disc pain for more than 3 months. The medical ethics committee from Erasmus University Medical Center approved the protocol. Written informed consent was obtained from all participants.

Participants

Suitable patients for the study were recruited from a population of patients with complaints of ongoing low back pain for more than 3 months and referred to the multidisciplinary pain centers of Lievensberg Hospital (Bergen op Zoom, The Netherlands) or Franciscus Hospital (Roosendaal, The Netherlands). Conservative care (rest, analgesics and physiotherapy) had failed to improve their burden. These patients were managed according to the flowchart presented in Fig. 1. When a disc problem was suspected (table 1) and patients met the in- and exclusion criteria[17] (table 2), and if the test injection at the ramus communicans with local anesthetics was positive (decrease in Numerical Rating Scale (NRS) of 2 or more on a 0-10 point scale[18]), the patient was eligible for the RCT. Each patient received a general brochure containing information concerning scientific research involving human subjects (Ministry of Health, Welfare and Sports[19]) and a brochure (including the questionnaires) explaining the complete procedure. After giving written informed consent patients were enrolled in the study.
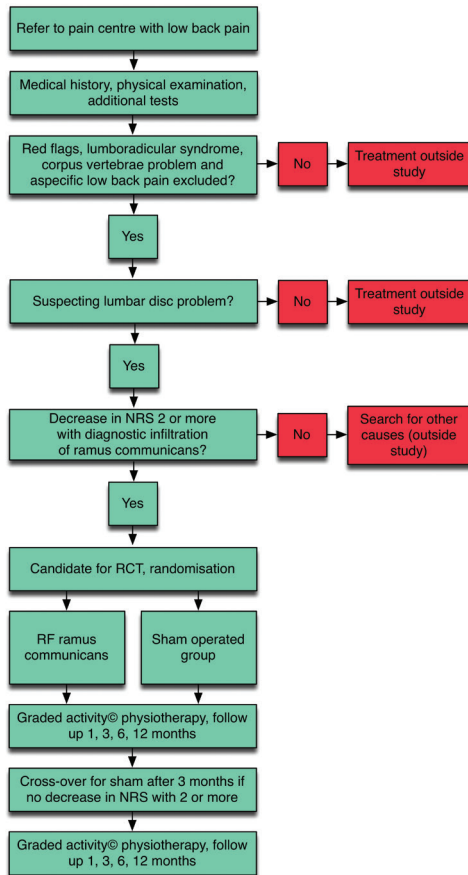
Figure 1: Study flowchart.

Diagnostic criteria for disc pain
Medical history
1. Centralization of pain
2. Pain when rising from sitting
3. Low back pain, worse after prolonged sitting, flexion, coughing, sneezing
4. Referred pain to the groin, buttock and thigh
5. Chronic muscle imbalance patterns
6. Repeated episodes of low back pain (onset may be sudden or may result from overuse or unidentified causes)
7. Fear or be unable to flex during the episodes
Physical examination
1. Gait deviation
2. Abnormal sensory and motor examination, hyperactive or diminished reflexes
3. Digital interspinous pressure (DIP) test positive
4. Straight leg raising (Lasègue) positive between 30 and 70 degrees of passive flexion
Additional tests (if available and/or necessary)
1. CT (degeneration)
2. MRI (degeneration)
3. Diagnostic block at ramus communicans

Table 1: details about medical history, physical examination and additional tests in patients with disc pain.

Inclusion
1. Age 18 years or older
2. Medical history and physical examination suggestive of lumbar disc pain
3. Decrease in NRS of 2 or more / 10 on diagnostic ramus communicans block
Exclusion
1. Presence of red flags[15]
2. Lumboradicular syndrome
3. Aspecific low back pain
4. Corpus vertebrae problem
5. Progressive neurological defecits
6. Major psychiatric disorder (according to psychiatrists opinion)
7. Anticoagulation cannot be stopped
8. Active infection
9. Pain in other parts of the body that is more severe
10. Allergies to any medication used in the study
11. Pregnancy
12. Communication (language) difficulties (according to physicians opinion)

Table 2: in- and exclusion criteria for patients with disc pain eligible for RCT.

Study interventions

Test injection at the ramus communicans: the injection was performed under fluoroscopy with 15 cm Sluijter-Mehta Kit (SMK) needles (Cotop® via Neurotherm®, Wilmington, Massachusetts, United States). The patient lies prone on the operating table with a pillow under the abdomen to flatten the lumbar lordosis. From the anteroposterior (AP) view, the c-arm is rotated obliquely to the ipsilateral side so that facet joints are projected away and the vertebral column is clearly visible. From the sagittal plane, the c-arm is rotated to let the transverse process change its location relative to the vertebral body and, as a result, the axis of the transverse process lies slightly above the middle of the vertebral body. The injection point is marked just caudally to the transverse process and somewhat medially to the lateral border of the vertebral body. Local anesthesia with 1 mL lidocaine 2% was given for skin infiltration. The needle is advanced until contact is made with the vertebral body. On the lateral view, the tip of the needle should be somewhat ventral to the posterior side of the lateral body. After sensory (50 Hz) and motor (2 Hz) stimulation as an adjunct to confirm correct needle placement, the ramus communicans was surrounded with a total of 0.5 mL lidocaine 2%.

RF treatment at the ramus communicans versus sham: when patients were candidates for the trial they were randomized in two study groups:

1. Treatment group: treatment was performed under under fluoroscopy with 15 cm Sluijter-Mehta Kit (SMK) needles (Cotop® via Neurotherm®, Wilmington, Massachusetts, United States). The patient lies prone on the operating table

with a pillow under the abdomen to flatten the lumbar lordosis. From the anteroposterior (AP) view, the c-arm is rotated obliquely to the ipsilateral side so that facet joints are projected away and the vertebral column is clearly visible. From the sagittal plane, the c-arm is rotated to let the transverse process change its location relative to the vertebral body and, as a result, the axis of the transverse process lies slightly above the middle of the vertebral body. The injection point is marked just caudally to the transverse process and somewhat medially to the lateral border of the vertebral body. Local anesthesia with 1 mL lidocaine 2% was given for skin infiltration. The needle is advanced until contact is made with the vertebral body. On the lateral view, the tip of the needle should be somewhat ventral to the posterior side of the lateral body. After sensory (50 Hz) and motor (2 Hz) stimulation, the ramus communicans was surrounded with a total of 0.5 mL lidocaine 2% and a RF treatment (80° C during 60 s per level) with a radiofrequency lesion generator (NT2000, Neurotherm®, Wilmington, Massachusetts, United States) was carried out;

2. Sham-operated group: same procedure as in the treatment group except for the RF treatment.

A crossover was provided for the sham-operated group after three months if no significant pain relief was obtained.

Both groups received graded activity[20,21] physiotherapy, which constitutes of an individual, submaximal, gradually increased exercise program, with an operant-conditioning behavioral approach, based on the results of the tests and the demands of the patient's work.

Outcome parameters

The primary study parameter was pain reduction (NRS[22-26]). The 0–10 verbal numeric rating scale (NRS-11) is a tool that enjoys widespread clinical use due to its ease of administration. When using the NRS-11 patients are asked to rate their pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including zero). Often the value of "4" is used to confirm clinical nursing judgment as to the need for further intervention or documentation that the patient's goals for analgesia have been achieved.

The secondary study parameter was Global Perceived Effect (GPE)[27-29]. The type of rating of perceived effect is a "transition scale". This numerical scale

asks the patient to rate how much their condition has improved or deteriorated since some predefined time point. The GPE has several qualities that make it an appealing tool for use in clinical practice and research; being a single question, it is easy and quick to administer and the results are simple to interpret. This scale is recommended for use as a core outcome measure for chronic pain trials and advocated to increase the relevance of information from clinical trials to clinical practice.

Follow-up

The results of the crossover group were analyzed separately. Time periods for follow-up are presented in table 3.

Statistical considerations

The Kolmogorov-Smirnov test was used to analyze whether or not parameters were normally distributed. Difference in patients' gender between the experimental groups was analyzed using Fisher's Exact Test. Difference in age and in BMI was analyzed using the Independent-Samples T-test. The data on NRS-11, GPE (subscales "Satisfaction" and "Recovery") were analyzed by means of a MANOVA for repeated measurements using independent variables Group (treatment or sham) and Time (in case of the NRS-11 Period T0-T1, in case of the GPE subscales Period T1 and T2 as independent variables). For the skewed distributed variables we nevertheless decided to use MANOVA for repeated measurements analysis of variance. We did so, because, although the MANOVA test requires that each dependent variable entered into the analysis be normally distributed it can still be used in case of skewly distributed dependent variable(s). The Monte Carlo experiments[30] have shown that for sample size 3 or 5 it is still possible to analyze leptokurtic, rectangular, J-shaped, moderately, and markedly skewed distributions. These experiments demonstrated that the empirically determined rejection region of the F-distribution would be no larger than $\alpha=0.08$ when the usual 5% rejection is used.

The percentage of patients requesting crossover and subsequently reporting a significant pain relief was analysed using the One-Sample Binomial Test (reference probability 0.5). Only patients in the sham group could switch to the intervention.

The required a priori sample size was computed using the NRS-11 as the primary outcome parameter. A statistically detectable and clinically relevant

with / between interaction effect size (f(V)) of 0.2 on the scale was chosen. The power of the study (1 - β) was chosen to be 0.8, an allocation ratio of 1:1 and the two-sided level of significance (α) 0.05. The required a priori total sample size computed by this method is 60.

Data were analyzed using SPSS for Mac, version 22 (International Business Machines (IBM) Corporation, Software Group, Route 100, Somers, NY, 10589, United States of America). The primary comparison was done at T1.

Period	Description
T0	Day of first consultation: medical history, physical examination, additional tests if necessary. Excluding red flags[28], aspecific low back pain and corpus vertebrae problems. Obtaining NRS.
T1	1 month after treatment: NRS and GPE.
T2	3 months after treatment: NRS, GPE.
T1c	1 month after treatment for crossover group: NRS and GPE.
T2c	3 months after treatment for crossover group: NRS, GPE.

Table 3: time periods for follow-up (NRS: Numerical Rating Scale; GPE: Global Perceived Effect).

Blinding

Based upon the required sample size calculation, sixty envelopes (30 "treatment group" and 30 "sham group") were prepared, sealed, mixed and placed together in a box. Patients chose an envelope randomly. Patients as well as their pain physicians were completely unaware of the content of the envelope during any stage of the investigation. The pain research nurse was the only one aware of the contents and performed the treatment accordingly. Regarding the radiofrequency generator, all sound indicators were turned off and the generator itself was visually hidden from the patient by means of a linen cloth, hung between two metal infusion poles. The pain physician left the operating theatre when the actual treatment (RF current or sham) took place. The same time period was taken for an actual – or a sham treatment.

Results

Patients were included and treated between March 2012 and December 2014. Out of 116 eligible patients a total of 56 patients resigned due to various reasons: no significant pain reduction after diagnostic block (33), not enough time (2), communication problems (4), chronic pain turned bearable (2), painful needle insertion procedure despite local anesthetics (3), technique not possible (1), comorbidity (4), pregnancy (1) and without reporting a cause (6).

The flowchart of the progress through the phases of the RCT is presented in Fig. 2. The demographic data of the treatment and sham groups are presented in table 4. There were no statistically significant differences in the parameters between both groups.
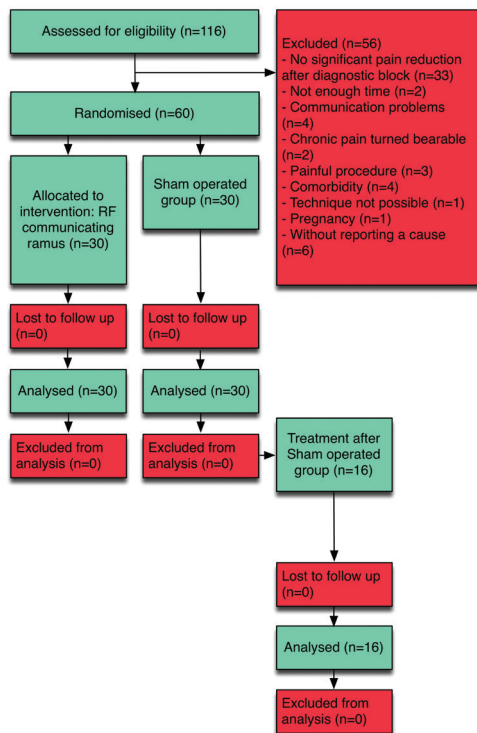
Figure 2: Flow diagram of the progress through the phases of the RCT.

No statistically significant difference in pain level over time between the groups (Group x Period) ($F_{(1,58)}$=0.04; p=.84), nor in the factor Group ($F_{(1,58)}$=0.01; p=.92) was found; however, the factor Period yielded a statistically significant result ($F_{(1,58)}$=40.68; p<.001) (table 5). In the crossover group, 11 out of 16 patients experienced a reduction in NRS of 2 or more at 1 month crossover (p=.21).

No statistically significant difference in satisfaction over time between the groups (Group x Period) was found ($F_{(1,46)}$=0.95; p=.34). The independent factors Group ($F_{(1,46)}$=0.80; p=.38) and Period ($F_{(1,46)}$=0.002; p=.97) also showed no statistically significant difference. The same applies to recovery: no statistically significant Group x Period effect ($F_{(1,46)}$=0.33; p=.57) was found, neither an effect of Group ($F_{(1,46)}$=0.02; p=.89) nor of Period ($F_{(1,46)}$=2.43; p=.13) (table 5).

The duration of low back pain before entering the study (T0) in the treatment – and sham groups of this RCT is presented in table 6; the same applies to the description of the relative frequency distribution of severity of low back pain (table 7) and patients' age (table 8).

During the trial we noted no serious adverse events.

Parameter	Treatment	Sham	p
Age (years), mean, (sd)	50.5 (13.9)	50.1 (12.3)	.91
BMI (kg/m²), mean, (sd)	27.8 (4.3)	27.8 (4.0)	.67
Male gender (number, %)	10 (33.3)	11 (36.7)	1
Caucasian race (number, %)	30 (100)	30 (100)	1

Table 4: Demographic data of the verum – and sham groups (sd: standard deviation; p: level of significance; BMI: Body Mass Index).

Outcome parameter	Treatment group mean (sd)	Sham group mean (sd)	Results MANOVAs	
NRS T0	7.8 (1.05)	7.8 (1.05)	Group Period Group x Period	$F_{(1,58)}=0.01$; p=.92 $F_{(1,58)}=40.68$; p<.001 $F_{(1,58)}=0.04$; p=.84
NRS T1	5.8 (2.28)	5.7 (2.28)		
GPE satisfaction T1	3.5 (1.92)	3.7 (1.84)	Group Period Group x Period	$F_{(1,46)}=0.80$; p=.38 $F_{(1,46)}=0.002$; p=.97 $F_{(1,46)}=0.95$; p=.34
GPE satisfaction T2	3.3 (2.09)	3.8 (2.02)		
GPE recovery T1	3.7 (1.48)	3.6 (1.43)	Group Period Group x Period	$F_{(1,46)}=0.02$; p=.89 $F_{(1,46)}=2.43$; p=.13 $F_{(1,46)}=0.33$; p=.57
GPE recovery T2	3.4 (1.77)	3.5 (1.70)		

Table 5: numerical rating scale (NRS) and global perceived effect (GPE) scales of the treatment – and sham groups (sd: standard deviation; T0: Day of first consultation; T1: 1 month after treatment; T2: 3 months after treatment).

Duration (yrs)	Treatment group n (%)	Sham group n (%)
> 0.25 / < 0,5	4	3
0,5-1	3	1
1-5	11	11
>5	12	15
Unknown	0	0
Total	30 (100)	30 (100)

Table 6: duration of low back pain before entering the study by group (T0).

NRS	Treatment frequency (%)	Sham frequency (%)
£ 4	0 (0)	0 (0)
5	1 (3.33)	1 (3.33)
6	3 (10)	2 (6.67)
7	3 (10)	8 (26.67)
8	18 (60)	12 (40)
9	5 (16.67)	5 (16.67)
10	0 (0)	2 (6.67)

Table 7: (relative) frequency distribution of severity of low back pain before entering the study (NRS: Numerical Rating Scale).

Age (years)	Treatment group n (%)	Sham group n (%)
18-29	2 (6.67)	3 (10)
30-39	5 (16.67)	3 (10)
40-49	5 (16.67)	9 (30)
50-59	13 (43.33)	6 (20)
60-69	2 (6.67)	9 (30)
70-79	3 (10)	0 (0)
Total	30 (100)	30 (100)

Table 8: patients' age before entering the study by group.

Discussion

In this randomized, sham-controlled, double blind, multicenter RCT we have investigated the effect of a percutaneous RF treatment compared to a sham procedure, applied to the ramus communicans for treatment of lumbar disc pain. This study does not support this type of treatment; we cannot reject the null hypothesis of no difference in pain reduction or in global perceived effect between the treatment and sham group. In the crossover group, 11 of out of 16 patients experienced a clinically significant pain reduction at T1. This proportion is not statistically significant from chance (p=.21); this finding supports the results from the primary analysis, where we also did not find a statistically significant result from the treatment intervention compared to the sham intervention.

Considerations with respect to our findings: firstly, this RCT has possible methodological limitations: 1) having considered daily practice in pain management, we used one diagnostic test block; 2) pain scores were measured during follow-up at specific moments in time. Using average pain scores over certain time periods (e.g. past month), based on pain diaries might have led to a different result; 3) the injection of local anesthetics is a different procedure compared to a RF treatment. So, when the RF treatment does not lead to a significant pain reduction, does that mean that the diagnostic test block was an invalid predictor of the effect of a RF treatment (i.c. a false positive)? If so, one

might wonder how many false negative results of the diagnostic block there
(also) may have been. We are comparing different procedures with each other,
with a diagnostic instrument being hard to validate; 4) all patients received
graded activity[28-29] physiotherapy, but not at a single center; as a consequence
gaining evidence of equal quality of physiotherapy accompaniment was
difficult and we therefore do not know if – and if so to which extent – this
factor has confounded the treatment outcome.

It is difficult to compare our results to those of previous studies on this
subject[16] because of the many differences regarding 1) the RF technique used
(intra-discal, cooled RF trans-discal biacuplasty, intra-annular discTRODE
probe); 2) the duration of low back pain before entering the study (more than
6 months to more than 1 year); 3) the exclusion criteria and the number of
participants. For example, in one study the sham procedure was not the same
as the actual RF treatment[31]. Besides using a different anatomical structure by
Kapural et al., a positive response to diagnostic discography was used instead
of a decrease in NRS of 2 or more from a diagnostic test block at the ramus
communicans as an inclusion parameter, like we did in our study. Furthermore
5) the criterion for a clinically relevant reduction in pain (after the diagnostic
block and after the intervention) differed between the studies already
performed. Use was made of a decrease in NRS of 2 or more[20], 50% pain relief,
or 80% pain relief.

In our RCT 48 out of 60 patients experienced a reduction in NRS of 50% or
more after the diagnostic test block. Post hoc the predictive validity (in terms
of sensitivity) of the amount of pain reduction after the diagnostic block in
predicting the effectiveness of the intervention (in terms of the amount of
pain reduction) after the intervention at T1 (sham or verum) was analyzed. No
statistically significant correlation between these parameters was found, neither
in the sham group (r=0.02; p=.93), nor in the verum group (r=-0.27; p=.14).
So, in terms of predictive sensitivity, the size of the pain reduction after the
diagnostic test block appears not to be related to the size of the pain reduction
after the intervention (Fig. 3).

In addition, 6) the pain reduction over time of the patients pooled together,
might have been due to spontaneous recovery. However, based upon the
median duration of the complaints of the participating patients spontaneous
recovery is not likely.

Keeping the above mentioned difference in mind, two other RCT's on this topic found no statistically significant effect either, and one RCT[31] found a statistically significant improvement in physical function, pain and disability. In their systematic review on non-operative management for discogenic back pain[32], Lu et al. mention the study from Oh and Shim[14] as the only one targeting the ramus communicans. The RF treatment used in this study was the same as in our study; however, patients were eligible for this RCT only when their pain continued after intradiscal electrothermal annuloplasty (IDET). The diagnostic test block used had to generate a 50% pain reduction and not a decrease in NRS with 2 or more, as was our criterion for a clinical relevant pain reduction. Furthermore, the questionnaires used were different, as well as the number of participants.

In our RCT 34 out of 60 patients reported a significant decrease in pain of 2 or more on verbal NRS for pain. Analysis so far revealed that those patients cannot be predicted by the interventional procedure. In order to evaluate the possible contribution of other parameters than the interventional procedure to the prediction of a significant pain reduction at T1, post hoc a binary logistic regression analysis was performed (Backward Wald method). The parameters to be entered into this analysis were age, gender, BMI and the level of pain at baseline. To prevent over fitting of the model, we performed univariate binary logistic regression analysis of these parameters. This analysis revealed that none of the investigated parameters contributed to the prediction of a significant pain reduction.

A comprehensive understanding of spinal innervation is needed for the clinical evaluation of lumbar spinal pain. Any component that receives innervation can theoretically act as a source of pain[33]. The sinuvertebral nerves that innervate the lumbar discs are formed by a somatic root from a ventral ramus and an autonomic root from a grey ramus communicans; an ascending branch passes as far as the next higher intervertebral disc, while a descending branch supplies the disc at the level of entry. Two types of rami communicantes are observed, a superior oblique ramus and a deep transverse ramus[34]; sinuvertebral nerves originate from the deep transverse rami. These deep transverse rami run close to the vertebral bodies and along the lumbar arteries and veins; they run along the lateral side of each lumbar vertebral body and connect to the corresponding lumbar spinal nerve and sympathetic trunk in a segmental manner. All superficial oblique rami run upon the surface of the aponeurosis, while the deep transverse rami run beneath the aponeurosis. In this way, using fluoroscopic guidance, together with sensory – and motor stimulation, we have

tried to interrupt the pain impulses with high frequency energy at the site of origin.
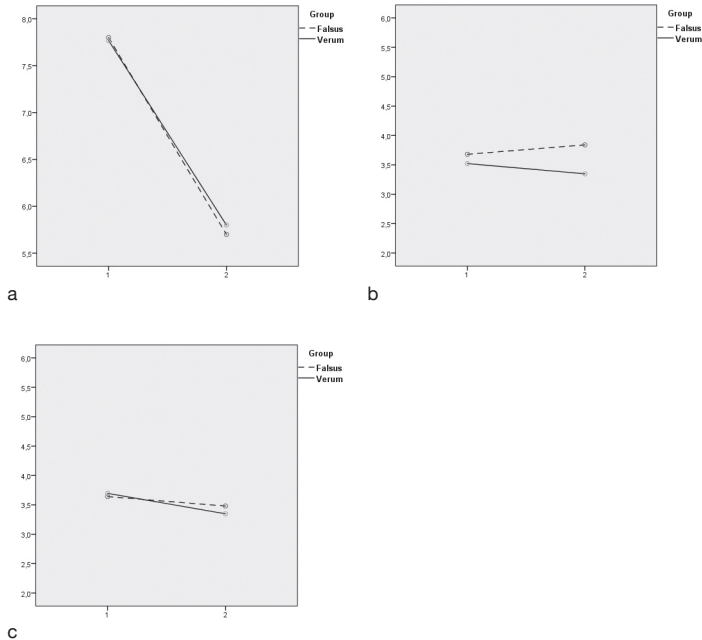
Figure 3: Comparison of the pain reduction (%) after the diagnostic block and the pain reduction at T1 after the RF or sham intervention (%).

Neural branches supplying the spinal column can arise from 1) the sympathetic trunk directly, 2) the superficial oblique rami, deep transverse rami, sinuvertebral nerves and splanchnic nerves and 3) directly from each lumbar vertebral primary ramus. Two types of innervation co-exist, a segmental (directly from the spinal nerve) and a non-segmental type (via the sympathetic nervous system). Discogenic low back pain occurs via visceral sympathetic afferents mainly through the L2 spinal nerve root[35]. Unilateral infiltration of this L2 nerve root was not predictive of provocative discography results; bilateral infiltration was not investigated[36]. In patients with L3 and L4 vertebral body fractures, L2 spinal nerve block was effective for two weeks[37]. The results from a prospective analysis on the assessment of pulsed radiofrequency treatment at the L2 dorsal root ganglion for providing pain relief in patients with chronic low back pain with or without lower limb pain showed that the procedure is safe and effective for treating chronic low back pain[38]. Targeting the L2 nerve root can possibly be used as a diagnostic tool and treatment opportunity[35,39], requiring further scientific research.

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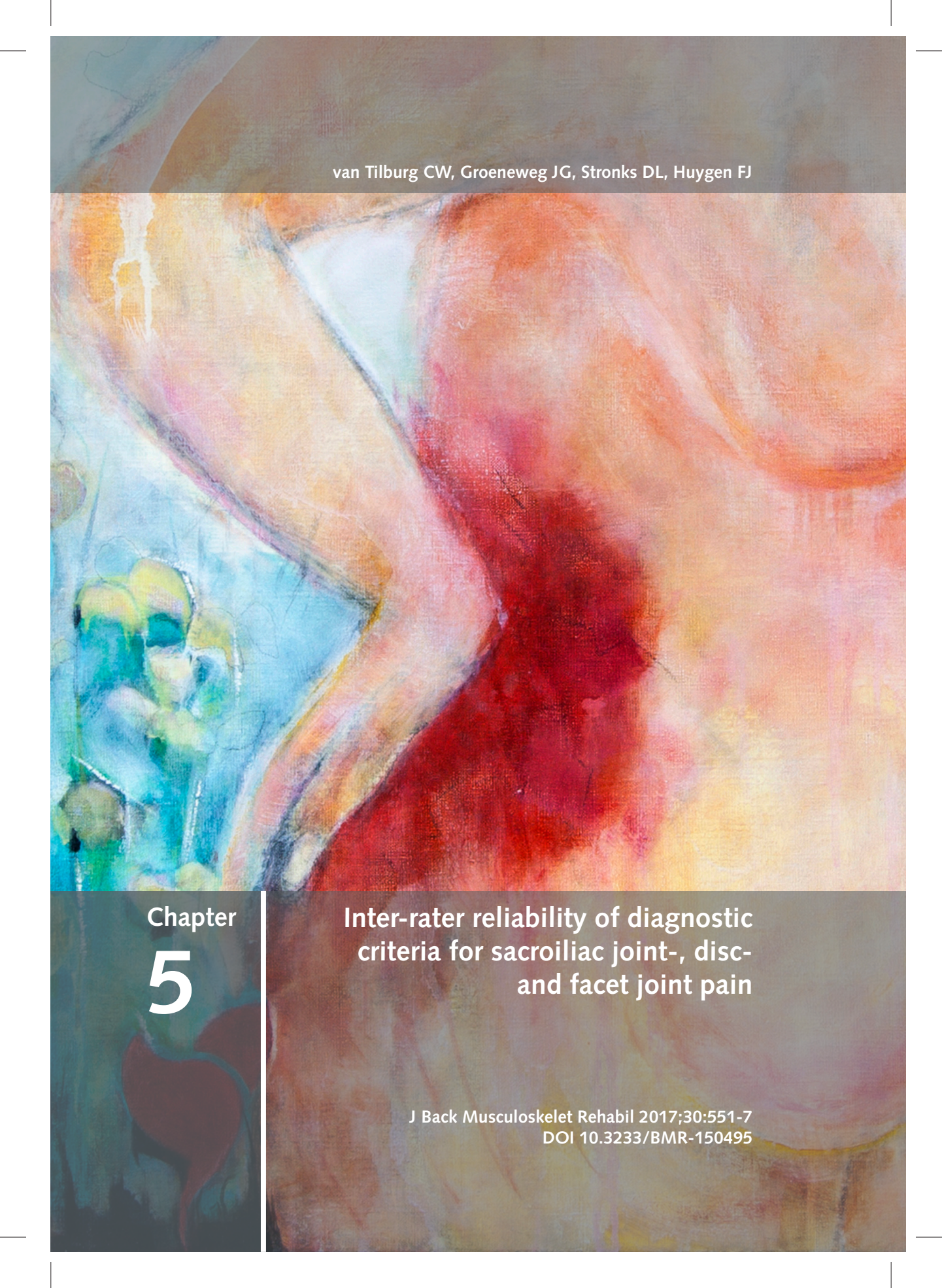2. **Pang WW, Mok MS, Lin ML, et al.** Application of spinal pain mapping in the diagnosis of low back pain - analysis of 104 cases. *Acta Anasthesiol Sin* 1998;36:71-4.
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Chapter

5

Inter-rater reliability of diagnostic criteria for sacroiliac joint-, disc- and facet joint pain

Abstract

Background / Objective

Several diagnostic criteria sets are described in the literature to identify low back pain subtypes, but very little is known about the inter-rater reliability of these criteria. We conducted a study to determine the reliability of diagnostic tests that point towards SI joint –, disc – or facet joint pain.

Methods

Inter-rater reliability study alongside three randomized clinical trials. Multidisciplinary pain center of general hospital. Patients aged 18 or more with medical history and physical examination suggestive of sacroiliac joint –, disc – and facet joint pain on lumbar level. Making use of nowadays most common used diagnostic criteria, a physical examination is taken independently by three physicians (two pain physicians and one orthopedic surgeon). Inter-rater reliability (Kappa (κ) measure of agreement) and significance (p) between raters are presented. Strengths of agreement, indicated with κ values above 0.20, are presented in order of agreement.

Results

One hundred patients were included. None of the parameters from the physical investigation had κ values of more than 0.21 (fair) in all pairs of raters. Between two raters (C and D), there was an almost perfect agreement on three parameters, more specifically "Abnormal sensory and motor examination, hyperactive or diminished reflexes", "Sitting exam shows no reflex, motor or sensory signs in the legs" and "Straight leg raising (Laségue) negative between 30 and 70 degrees of flexion". The "Drop test positive" parameters had moderate strength of agreement between raters A and D and fair strength between raters A and B. The "Digital interspinous pressure test positive" had moderate strength of agreement between raters C and D and fair strength of agreement between raters A and B as well as raters B and C. Three other parameters had a fair strength of agreement between two raters, all other parameters had a slight or poor strength of agreement. Inter-rater reliability, confidence intervals and significance of pooled items for SI joint -, disc – and facet joint pain are represented; κ values for the pooled parameters of the

physical examination suggestive of SI joint pain stayed below 0.20 between all raters. The same applies for the pooled parameters of the physical examination suggestive of facet joint – or disc pain.

Conclusions

The poor reliability of the diagnostic parameters seriously limits their predictive validity, and as such their use in patients with low back pain for more than 3 months.

Keywords

Reliability and validity, Reliability of results, Diagnostic equipment, Low back pain, Sacroiliac joint, Facet joint

Background

The assessment and interpretation of tests used to diagnose low back pain subtypes are often not standardized; however, this is necessary for the testing to be both valid and reliable[1]. Until now little is known about the inter-rater reliability of these diagnostic criteria. Regarding the diagnostic criteria, Young et al. demonstrated that pain when rising from sitting, as well as centralization of pain was associated with discogenic pain and that absence of pain when rising from sitting was associated with facet joint pain; sacroiliac (SI) joint pain was associated with three or more positive pain provocation tests, pain when rising from sitting, unilateral pain and absence of lumbar pain[2]. In a systematic review to determine the diagnostic accuracy of tests available to clinicians to identify the source of low back pain, Hancock et al. found that centralization was the only clinical feature to increase the likelihood of the disc as being the source of pain, while absence of degeneration on MRI decreased this likelihood. A combination of SI joint tests was informative, single tests not[3].

Methods

We conducted an inter-rater reliability study in patients aged 18 years or more with low back pain for more than 3 months, who were referred to the pain center of a general hospital. The guidelines for reporting of studies of reliability and agreement (GRRAS[4]) were followed.

Patients with a suspicion of having a spine related pain disorder on lumbar level who met the inclusion – (age ≥ 18 years, chronic (> 3 months) low back pain) and exclusion (presence of red flags, progressive neurological deficits, major psychiatric disorder (according to psychiatrists opinion), pain in other parts of the body that is more severe, pregnancy, active infection, communication (language) difficulties (according to physicians opinion)) criteria were eligible for inclusion. A total of three pain physicians and one orthopedic surgeon participated in the trial. The examination for each individual patient was performed by a combination of two pain physicians and one orthopedic surgeon. The consultations took place within a period of two weeks to decrease the chance for confounding and jointly determine the cause of the pain problem. A training session was held before the study to ensure as much consistency as possible of methods and standardization of test procedures, during which every item from the list with diagnostic criteria were judged on their presence or absence (Table 1). Before the physical examinations took place medical history was noted. The diagnostic criteria as well as the raters were applied in randomized order.

Physical examination	SI	Disc	Facet
Drop-test positive	✓		
Sitting exam shows no reflex, motor or sensory signs in the legs	✓		
Straight leg raising (Laségue) negative between 30 and 70 degrees of passive flexion	✓		
Distraction (Gapping) test positive	✓		
Posterior shear (thigh trust) test positive	✓		
Pelvic torsion (Gaenslen's) test positive	✓		
Patrick-Faber test positive	✓		
Compression test positive	✓		
Sacral thrust test positive	✓		
Cranial shear test positive	✓		
Bilateral internal rotation of the hip / Unilateral rotation of the hip painful at SI joint(s)	✓		
Yeoman's test positive	✓		
Gait deviation		✓	
Abnormal sensory and motor examination, hyperactive or diminished reflexes		✓	
Digital Interspinous Pressure (DIP) test positive		✓	
Straight leg raising (Laségue) positive between 30 and 70 degrees of passive flexion		✓	
Pain in extension			✓
Pain eased in flexion			✓
Pain when rising from forward flexion			✓
Schober test < 3-5 cm			✓
Pain in extension, lateral flexion or rotation manoeuvers to the ipsilateral side			✓
Replication or aggrevation of pain by unilateral pressure over the ipsilateral side			✓
Local unilateral passive movements show reduced range of motion or increased stiffness on the side of the involved facet joints			✓
Tight or facilitated muscles (psoas, hip adductors, gluteus medius muscles)			✓
Weak muscles (gluteus maximus, gluteus medius)			✓

Table 1: Findings from the physical examination suggestive of a SI[1-8] –, disc[2,3] – or facet joint[2,3] pain.

We conducted this study to determine the reliability of diagnostic tests that point towards SI joint –, disc – or facet joint pain. The diagnostic tests mentioned in the literature on this subject were used.

The first pain physician that questioned and examined the patient also took into account the results from spinal imaging. Each physician made a working diagnosis in each patient. If the working diagnoses from the three physicians were in agreement with each other, a general working diagnosis was made, after which a diagnostic test block was performed. The study flowchart is presented in Figure 1. The medical ethics committee from Erasmus University Medical Center approved the protocol. Written informed consent was obtained from all patients.
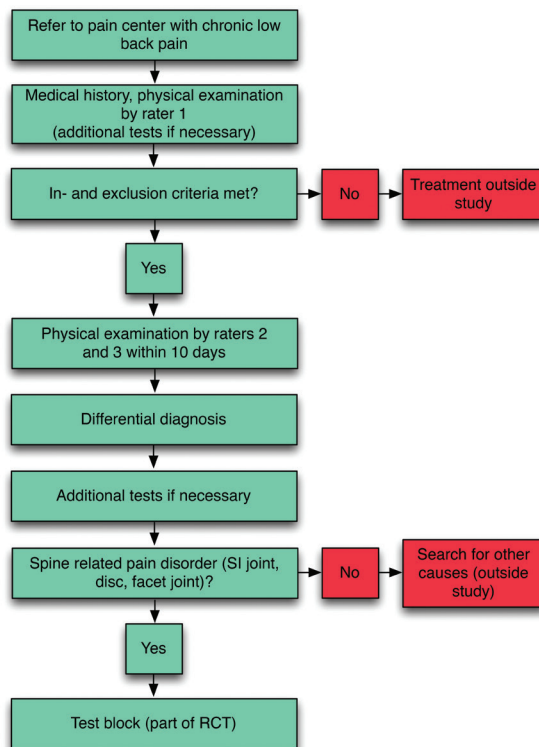
Figure 1: Study flowchart.

Data were analyzed using SPSS for Windows, version 22 (International Business Machines (IBM) Corporation, Software Group, Route 100, Somers, NY, 10589, United States of America). Inter-rater reliability of nowadays most common used diagnostic criteria was estimated using the Cohen Kappa (κ) index[10-13]. The significance level α was set to 0.05. Each variable was coded binary. The null hypothesis for agreement is a κ of 0.

Results

One hundred patients were included between January 2013 and April 2014. The progress through the fases of this inter-rater reliability study is presented in Figure 2. Demographic data of the patients were a median age of 55 (interquartile range (27,25) 65.75-44.25), a mean BMI of 26.8 (standard deviation 5.6), 66% female gender and 100% Caucasian race.

Figure 2: Flow diagram of the progress through the phases of the inter-rater reliability study.

Inter-rater reliability (Kappa (κ) measure of agreement) and significance (p) between raters (raters A, B and C are pain physicians (two physicians for each patient), rater D an orthopedic surgeon) are presented in Tables 2a-c.
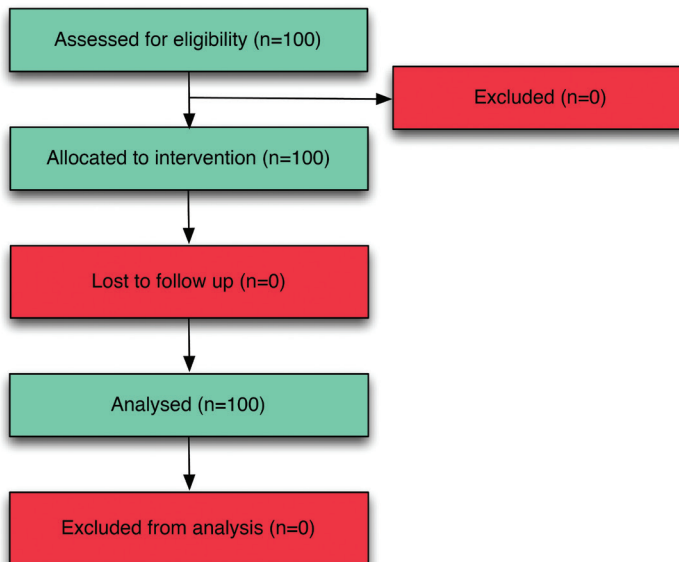
Nr.	A-B	A-C	A-D	B-C	B-D	C-D
1	0.23 (0.01)	-0.02 (0.45)	0.43 (0.03)	0.06 (0.31)	0.00 (1.00)	0.14 (0.10)
2	-0.40 (0.00)	-0.28 (0.00)	0.03 (0.00)	0.10 (0.01)	-0.22 (0.00)	0.86 (0.00)
3	-0.19 (0.04)	-0.02 (0.55)	0.21 (0.00)	0.00 (-)	-0.28 (0.00)	0.81 (0.00)
4	-0.02 (0.69)	-0.01 (0.50)	-0.04 (0.02)	0.00 (1.00)	0.03 (0.31)	-0.14 (0.07)
5	-0.02 (0.79)	-0.06 (0.08)	-0.03 (0.15)	-0.04 (0.49)	0.02 (0.55)	-0.02 (0.85)
6	-0.09 (0.29)	-0.03 (0.28)	-0.11 (0.00)	-0.02 (0.74)	0.07 (0.03)	-0.28 (0.00)
7	-0.07 (0.51)	-0.06 (0.10)	-0.09 (0.00)	-0.07 (0.20)	0.04 (0.21)	-0.21 (0.02)
8	0.02 (0.69)	-0.02 (0.36)	-0.03 (0.09)	0.06 (0.26)	0.06 (0.03)	0.00 (1.00)
9	-0.16 (0.12)	-0.04 (0.21)	0.01 (0.59)	0.02 (0.75)	-0.08 (0.02)	0.12 (0.17)
10	-0.02 (0.81)	0.02 (0.38)	-0.01 (0.59)	-0.10 (0.06)	-0.04 (0.18)	-0.10 (0.20)
11	0.07 (0.42)	0.01 (0.79)	0.04 (0.01)	0.04 (0.43)	-0.01 (0.80)	0.10 (0.15)
12	0.02 (0.81)	0.02 (0.63)	0.02 (0.50)	-0.09 (0.08)	0.02 (0.56)	-0.10 (0.21)

Table 2a: Inter–rater reliability (Kappa measure of agreement) and significance (p) between raters (raters A, B and C are pain physicians, rater D and orthopedic surgeon) of the physical examination suggestive of SI joint pain. 1: Drop–test positive; 2: Sitting exam shows no reflex, motor or sensory signs in the legs; 3: Straight leg raising (Laségue) negative between 30 and 70 degrees of passive flexion; 4: Distraction (Gapping) test positive; 5: Posterior shear (thigh trust) test positive; 6: Pelvic torsion (Gaenslen's) test positive; 7: Patrick–Faber test positive; 8: Compression test positive; 9: Sacral thrust test positive; 10: Cranial shear test positive; 11: Bilateral internal rotation of the hip / Unilateral rotation of the hip painful at SI joint(s); 12: Yeoman's test positive.

Nr.	A-B	A-C	A-D	B-C	B-D	C-D
1	0.09 (0.14)	-0.03 (0.09)	0.02 (0.09)	0.02 (0.31)	0.00 (1.00)	0.10 (0.01)
2	-0.09 (0.31)	-0.26 (0.00)	0.04 (0.00)	0.20 (0.00)	-0.12 (0.00)	0.91 (0.00)
3	0.30 (0.00)	-0.03 (0.48)	0.10 (0.00)	0.22 (0.00)	0.01 (0.78)	0.42 (0.00)

Table 2b: Inter–rater reliability (Kappa measure of agreement) and significance (p) between raters (raters A, B and C are pain physicians, rater D an orthopedic surgeon) of the physical examination suggestive of disc pain. 1: Gait deviation; 2: Abnormal sensory and motor examination, hyperactive or diminished reflexes; 3: Digital Interspinous Pressure (DIP) test positive.

Nr.	A-B	A-C	A-D	B-C	B-D	C-D
1	0.07 (0.29)	-0.01 (0.50)	0.02 (0.18)	0.00 (-)	0.00 (1.00)	0.04 (0.51)
2	-0.05 (0.66)	0.04 (0.34)	-0.10 (0.00)	0.00 (1.00)	0.08 (0.00)	-0.30 (0.00)
3	-0.07 (0.29)	-0.01 (0.69)	-0.14 (0.00)	0.09 (0.08)	0.17 (0.00)	-0.39 (0.00)
4	-0.09 (0.38)	-0.07 (0.02)	-0.09 (0.00)	0.00 (1.00)	0.00 (0.86)	-0.04 (0.71)
5	0.19 (0.02)	-0.04 (0.08)	-0.08 (0.00)	0.07 (0.15)	0.14 (0.00)	-0.18 (0.04)
6	0.07 (0.46)	0.02 (0.60)	-0.06 (0.01)	-0.04 (0.31)	0.07 (0.00)	-0.21 (0.01)
7	0.00 (1.00)	-0.12 (0.00)	-0.13 (0.00)	0.06 (0.20)	0.09 (0.00)	0.00 (1.00)
8	0.16 (0.09)	-0.03 (0.33)	-0.19 (0.00)	0.07 (0.18)	0.21 (0.00)	-0.37 (0.00)
9	0.12 (0.11)	0.02 (0.59)	0.05 (0.00)	0.07 (0.07)	0.01 (0.70)	0.10 (0.11)
10	-0.16 (0.10)	-0.01 (0.79)	0.06 (0.00)	-0.06 (0.21)	-0.15 (0.00)	0.21 (0.00)

Table 2c: Inter-rater reliability (Kappa measure of agreement) and significance (p) between raters (raters A, B and C are pain physicians, rater D an orthopedic surgeon) of the physical examination suggestive of facet joint pain. 1: Straight leg raising (Laségue) positive between 30 and 70 degrees of passive flexion; 2: Pain in extension; 3: Pain eased in flexion; 4: Pain when rising from forward flexion; 5: Schober test < 3–5 cm; 6: Pain in extension, lateral flexion or rotation manoeuvers to the ipsilateral side; 7: Replication or aggrevation of pain by unilateral pressure over the ipsilateral side; 8: Local unilateral passive movements show reduced range of motion or increased stiffness on the side of the involved facet joints; 9: Tight or facilitated muscles (psoas, hip adductors, gluteus medius muscles); 10: Weak muscles (gluteus maximus, gluteus medius).

Strengths of agreement are presented in order of agreement for values κ > 0,20 in Table 3.

k	Nr	Raters
0.91	Abnormal sensory and motor examination, hyperactive or diminished reflexes	C-D
0.86	Sitting exam shows no reflex, motor or sensory signs in the legs	C-D
0.81	Straight leg raising (Laségue) negative between 30 and 70 degress of passive flexion	C-D
0.43	Drop test positive	A-D
0.42	Digital interspinous pressure test positive	C-D
0.30	Digital interspinous pressure test positive	A-B
0.23	Drop test positive	A-B
0.22	Digital interspinous pressure test positive	B-C
0.21	Weak muscles (gluteus maximus, gluteus medius)	C-D
0.21	Local unilateral passive movements show reduced range of motion or increased stiffness on the side of the involved facet joints	B-D
0.21	Straight leg raising (Laségue) negative between 30 and 70 degrees of passive flexion	A-D

Table 3: Strength of agreement beyond chance, indicated with k values above 0.20 (< 0: poor; 0–0.20: slight; 0.21–0.40: fair; 0.41–0.60: moderate; 0.61–0.80: substantial; 0.81–1.00: almost perfect). The k values used are from Landis and Koch[12] and are in order in agreement.

None of the parameters from the physical investigation had k values of more than 0,21 (fair) in all pairs of raters. Between two raters (C and D), there was an almost perfect agreement on three parameters, more specifically "Abnormal sensory and motor examination, hyperactive or diminished reflexes", "Sitting exam shows no reflex, motor or sensory signs in the legs" and "Straight leg raising (Laségue) negative between 30 and 70 degrees of flexion". The "Drop test positive" parameters had moderate strength of agreement between raters A and D and fair strength between raters A and B. The "Digital interspinous pressure test positive" had moderate strength of agreement between raters C and D and fair strength of agreement between raters A and B as well as raters B and C. Three other parameters (Table 3) had a fair strength of agreement between two raters, all other parameters had a slight or poor strength of agreement.

Inter-rater reliability (including confidence intervals and significance) of pooled items for SI joint -, disc – and facet joint pain are represented in Tables 4a-c. Kappa values for the pooled parameters of the physical examination suggestive of SI joint pain stayed below 0.2 between all raters. The same applies for the pooled parameters of the physical examination suggestive of facet joint – or disc pain.

During the study we recorded no (serious) adverse events.

	Rater A κ; p; (95% CI κ)	Rater B κ; p; (95% CI κ)	Rater D κ; p; (95% CI κ)
Rater A			0.124; 0.006 (0.034;0.214)
Rater B	0.169; < 0.001 (0.085;0.252)		0.136; 0.001 (0.052;0.219)
Rater C	0.130; 0.004 (0.035;0.225)	0.166; < 0.001 (0.082;0.251)	0.036; 0.44 (0;0.129)

Table 4a: Inter-rater reliability (Kappa measure of agreement) (raters A, B and C are pain physicians, rater D an orthopedic surgeon), significance (p) and 95% confidence intervals (CI) of the pooled items of the physical examination parameters suggestive for SI joint pain.

	Rater A κ; p; (95% CI κ)	Rater B κ; p; (95% CI κ)	Rater D κ; p; (95% CI κ)
Rater A			0.194; 0.000 (0.075;0.313)
Rater B	N/A		0.191; 0.001 (0.009;0.373)
Rater C	0.205; 0.003 (0.070;0.341)	0.093; 0.145 (0;0.232)	0.129; 0.001 (0.051;0.207)

Table 4b: Inter-rater reliability (Kappa measure of agreement) (raters A, B and C are pain physicians, rater D an orthopedic surgeon), significance (p) and 95% confidence intervals (CI) of the pooled items of the physical examination parameters suggestive for disc pain (N/A: concordance is smaller than mean-chance).

	Rater A κ; p; (95% CI κ)	Rater B κ; p; (95% CI κ)	Rater D κ; p; (95% CI κ)
Rater A			0.313; 0.000 (0.255;0.372)
Rater B	0.258; 0.000 (0.173;0.343)		0.307; 0.000 (0.241;0.373)
Rater C	0.357; 0.000 (0.275;0.440)	0.232; 0.000 (0.111; 0.354)	0.276; 0.000 (0.205;0.346)

Table 4c: Inter-rater reliability (Kappa measure of agreement) (raters A, B and C are pain physicians, rater D an orthopedic surgeon), significance (p) and 95% confidence intervals (CI) of the pooled items of the physical examination parameters suggestive for facet joint pain.

Conclusion and discussion

We conducted this study to determine the reliability of diagnostic tests that point towards SI joint –, disc – or facet joint pain, using diagnostic tests mentioned in the literature on these subjects. The null hypothesis for agreement is a κ of 0. None of the diagnostic tests used in this study had k values of more than 0.21 (fair) in all pairs of raters. Also, the κ values in all pairs of raters of the pooled items of the physical examination parameters suggestive for SI joint -, disc – or facet joint pain stayed below 0.2. The poor reliability of the diagnostic parameters seriously limits their predictive validity, and as such their use in patients with low back pain for more than 3 months.

Kappa is an adequate measure for inter-rater agreement. Kappa has the advantage that it is corrected for agreement with statistical chance. The main disadvantage is that it is not free of dependence on disease prevalence or the number of rating categories. As a consequence it can be difficult to interpret the meaning of any absolute value, but is still useful if disease prevalence and number of categories are presented[12].

In correlating the clinical examination characteristics in 81 individuals (a total of 104 injection procedures were performed), both centralization of pain and pain when rising from sitting were significantly associated with a positive discogram[2], while not having pain when rising from sitting was strongly correlated with a positive facet joint injection. The presence of midline lumbar pain tends to exclude the SI joint as a potential pain generator. When there were three or more positive SI joint pain provocation tests, the presence of a SI joint source of pain is 28 times more likely. The physical examinations were performed by visiting physical therapists and the injections were performed if requested by the referring physician or deemed adequate by a radiologist, while in our study all parts of the trial were performed by the same physicians and on the basis of a general working diagnosis.

In a systematic review of tests to identify the source of low back pain, no available clinical test was found which could be used to increase or decrease the likelihoofd of the disc as the source of low back pain[3]. Also, the currently available tests have limited or no diagnostic validity regarding investigating the facet joint as the source of low back pain; our study is in accordance with this review in that we also found no useful diagnostic tests.
A combination of SI joint provocation tests appears to be useful to increase the likelihood of the SI joint as the source of pain. However, in a small study performed by physical therapists examining the intertester reliability of tests for SI joint dysfunction, the reliability was poor for all tests, except the iliac gapping and compression tests[14]. In our study, we found that no single parameter of the physical examination nor the pooling of these tests was useful to increase the likelihood of the SI joint as the source of pain; the same applies to the parameters of the physical examination suggestive for disc – or facet joint pain.

Only a small amount of investigation has been performed into the diagnostic accuracy of clinical tests. In our study we investigated the diagnostic accuracy of these tests in 100 patients referred to a pain center because of chronic low back pain and found a poor reliability of all diagnostic parameters.
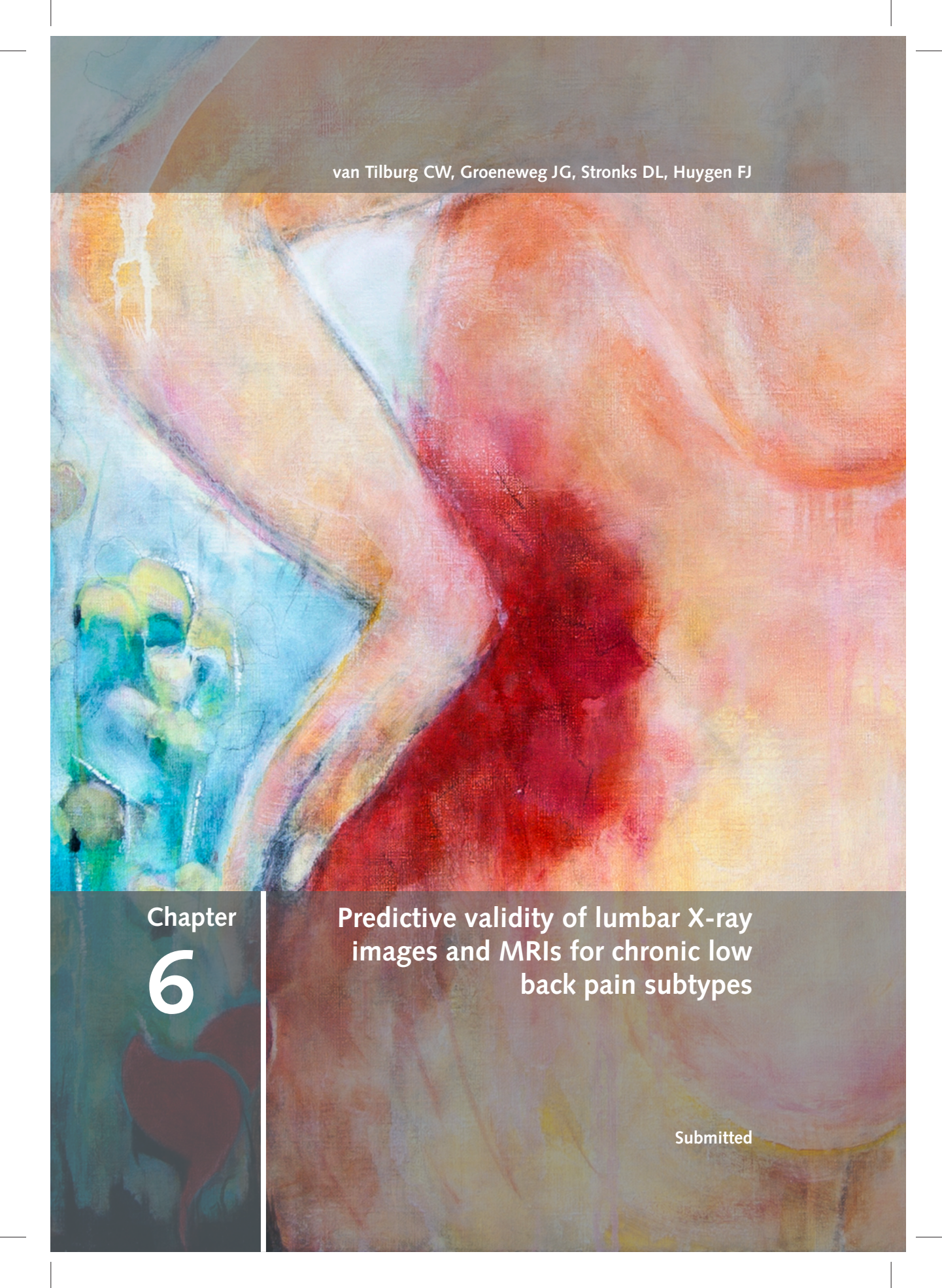
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Chapter

6

Predictive validity of lumbar X-ray images and MRIs for chronic low back pain subtypes

Abstract

The aim of this observational study is to investigate the accuracy of lumbar X-ray imaging and MRIs as diagnostic tools of low back pain (LBP) subtypes. Included were patients with medical history and physical examination suggestive of a chronic LBP subtype, followed by a diagnostic test block. One hundred patients were included. No general working diagnosis could be made in 17 patients. Facet joint pain was a general working diagnosis in 40 patients, disc pain in 8 patients and SI joint pain in 35 patients. The PPV of X-ray was 82.6% for facet joint pain, 66.7% for disc pain and 60% for SI joint pain; the NPV of X-ray was 50% for facet joint pain, 66.7% for disc pain and 7.7% for SI joint pain. The PPV of MRI was 81.8% for facet joint pain, 50% for disc pain and 0% for SI joint pain; the NPV of MRI was 55.6% for facet joint pain, 0% for disc pain and 13% for SI joint pain. In conclusion, the predictive validity of lumbar X-ray imaging and MRIs to distinguish between LBP subtypes in patients with chronic LBP is questionable.

Introduction

Low back pain (LBP) continues to be a very common problem globally and will increase in prevalence over the next years[1, 2]. Low back pain causes more disability than any other condition and ranks highest in terms of disability and sixth in terms of overall burden[2, 3]. Besides its negative impact on physical functioning and the quality of life, treatment of LBP is costly; 2% of all physician office visits are for low back pain complaints[4].
Ageing affects the spinal elements and causes a certain degree of degeneration, resulting in changes such as a reduction of disc height and altered load transmission across the vertebral endplates and paired facet joints (the three-joint spinal complex)[5]. Identification of the pain-producing structure is not easy in degenerative spinal disease. The intervertebral disc, facet joint and sacro-iliac (SI) joint can act as a major cause of chronic low back pain and referred pain. The prevalence of internal disc disruption, facet joint pain and SI joint pain was 39-42%[6, 7], 15-31%[7, 8] and 10-38%[7-9, 11], respectively; the younger the patient, the more likely LBP is discogenic in origin[7].

We recently have investigated the effect on pain reduction and global perceived effect (GPE) of a percutaneous radiofrequency (RF) heat lesion compared to a sham procedure, applied to the ramus communicans [12], the medial branch

of the primary dorsal ramus[13] and the dorsal ramus of L5 and lateral branches of the S1, S2, S3 and S4 nerve roots[14]. Based on the results of the sham-controlled trials the H0 hypothesis of no difference in pain reduction or in GPE between the treatment and the sham groups could not be rejected. We asked ourselves what is known about the diagnostic accuracy of the physical examination, X-ray imaging and MRIs in diagnosing chronic low back pain subtypes. The inter-rater reliability of diagnostic tests that point towards SI joint –, disc – or facet joint pain was investigated in a subsequent study[15].

Judging from spinal imaging tests whether the cause of chronic LBP is due to intervertebral disc degeneration, facet arthritis, or SI arthritis can be challenging[16]. When determining the association between deviations on spinal imaging and LBP, the research data yield conflicting results. Patients with disc herniations may have no symptoms[17-20], while patients with severe symptoms demonstrated no evidence on imaging of nerve root compression at all[21-23]. The severity of symptoms is not well correlated with the size of the herniation [24-27] and features on imaging may have little prognostic value towards outcome [28-32].

Routine imaging can be associated with radiation exposure, increased expenses and possibly unnecessary procedures[33]. Patient expectations and increasing satisfaction may play a role. Clinical practice guidelines for the diagnosis and treatment of LBP have been developed in the past[34]. Appropriateness criteria for LBP were issued by the American College of Radiology (1996, last revision 2011[35].

The aim of this study is to investigate the accuracy of lumbar X-ray images and MRIs as diagnostic tools of LBP subtypes (SI joint, disc and facet joint). Whether or not abnormalities were visible on the spinal imaging tests was judged by a radiologist and a pain physician.

Materials and Methods

We conducted an observational study alongside the inter-rater reliability trial (International Standard Randomised Controlled Trial Number Register (Current Controlled Trials) 43417727) to investigate the accuracy of lumbar X-ray images and MRIs as diagnostic tools of LBP subtypes. Patients who were referred because of their chronic LBP received three separate consultations (two from experienced pain physicians and one from an experienced orthopaedic surgeon) within a period of two weeks to decrease the chance for confounding and jointly determine the cause of the pain problem. Findings from the physical examination suggestive of a SI joint, disc or facet joint pain problem are presented in Table 1[36-40].

Physical examination	SI	Disc	Facet
Drop-test positive	✓		
Sitting exam shows no reflex, motor or sensory signs in the legs	✓		
Straight leg raising (Laségue) negative between 30 and 70 degrees of passive flexion	✓		
Distraction (Gapping) test positive	✓		
Posterior shear (thigh trust) test positive	✓		
Pelvic torsion (Gaenslen's) test positive	✓		
Patrick-Faber test positive	✓		
Compression test positive	✓		
Sacral thrust test positive	✓		
Cranial shear test positive	✓		
Bilateral internal rotation of the hip / Unilateral rotation of the hip painful at SI joint(s)	✓		
Yeoman's test positive	✓		
Gait deviation		✓	
Abnormal sensory and motor examination, hyperactive or diminished reflexes		✓	
Digital Interspinous Pressure (DIP) test positive		✓	
Straight leg raising (Laségue) positive between 30 and 70 degrees of passive flexion		✓	
Pain in extension			✓
Pain eased in flexion			✓
Pain when rising from forward flexion			✓
Schober test < 3-5 cm			✓
Pain in extension, lateral flexion or rotation manoeuvers to the ipsilateral side			✓
Replication or aggravation of pain by unilateral or bilateral pressure over the facet joints or transverse process			✓
Local unilateral or bilateral passive movements show reduced range of motion or increased stiffness on the side of the involved facet joints			✓
Tight or facilitated muscles (psoas, hip adductors, gluteus medius muscles)			✓
Weak muscles (gluteus maximus, gluteus medius)			✓

Table 1: Findings from the physical examination suggestive of a SI joint, disc or facet joint pain problem [36–40].

A training session was held before the study to ensure as much consistency as possible of methods and standardization of test procedures, during which every item from the list with diagnostic criteria were judged on their presence or absence. Medical history was noted, along with the results from spinal imaging. Patients suspected of a lumbar spine related pain disorder who met the inclusion - (age ≥ 18 years, chronic (> 3 months) LBP) and exclusion criteria (presence of red flags[41], progressive neurological deficits, major psychiatric disorder (according to psychiatrists opinion), pain in other parts of the body that is more severe, pregnancy, active infection, communication (language) difficulties (according to physicians opinion)) were eligible for inclusion. If the working diagnoses from the three physicians were in agreement with each other, a general working diagnosis was made, after which a diagnostic test block (gold standard) was performed:

1) Diagnostic SI joint test block
The injection was performed under fluoroscopy with a 10 cm Sluijter-Mehta Kit (SMK) needle (Cotop® via Neurotherm®, Wilmington, Massachusetts, United States). The patient lies in the prone position on the operating table with a pillow under the pelvis. From the anteroposterior (AP) view, the c-arm is rotated contralaterally until the medial cortical line of the posterior articulation is in focus. Local anesthesia with 1 mL lidocaine 2% was given for skin infiltration. Needle insertion is 1-2 cm cranially from the lower border of the SI joint at the level of the zone of maximal radiographic translucency. Introduction of the needle into the SI joint is characterized by a change in resistance. On a lateral view, the needle tip should appear anterior to the dorsal border of the sacrum. The SI joint was injected with a total of 3 mL lidocaine 2%.

2) Diagnostic test block at the ramus communicans
The injection was performed under fluoroscopy with 15 cm Sluijter-Mehta Kit (SMK) needles (Cotop® via Neurotherm®, Wilmington, Massachusetts, United States). The patient lies prone on the operating table with a pillow under the abdomen to flatten the lumbar lordosis. From the AP view, the c-arm is rotated obliquely to the ipsilateral side so that facet joints are projected away and the vertebral column is clearly visible. From the sagittal plane, the c-arm is rotated to let the transverse process change its location relative to the vertebral body and, as a result, the axis of the transverse process lies slightly above the middle of the vertebral body. The injection point is marked just caudally to the transverse process and somewhat medially to the lateral border of the vertebral body. Local anesthesia with 1 mL lidocaine 2%

was given for skin infiltration. The needle is advanced until contact is made with the vertebral body. On the lateral view, the tip of the needle should be somewhat ventral to the posterior side of the lateral body. After sensory (50 Hz) and motor (2 Hz) stimulation as an adjunct to confirm correct needle placement, the ramus communicans was surrounded with a total of 0.5 mL lidocaine 2%.

3) Diagnostic test block at the medial branch of the primary dorsal ramus
The injection was performed under fluoroscopy with three 10 cm Sluijter-Mehta Kit (SMK) needles (Cotop® via Neurotherm®, Wilmington, Massachusetts, United States of America) at the facet joint that was presumed to be the source of the pain and then at the two adjacent levels (in the case of the L5/S1 facet joint level, the adjacent L4/L5 facet joint level was also treated). The patient lay prone on the operating table with a pillow under the abdomen in order to flatten the lumbar lordosis. From the AP view, the c-arm was rotated obliquely to the ipsilateral side so that the junction between the superior articular process and the transverse process was more easily accessible. Local anesthesia with 1 mL lidocaine 2% per level was given for skin infiltration. Contact was made with the transverse process as close as possible to the superior articular process. After contacting bone, the needle was advanced slightly in a cranial direction so that its tip slides over the transverse process. In the lateral view the electrode tip lay at the base of the superior articular process at the lower aspect of the intervertebral foramen, approximately 1 mm dorsal to its posterior border. After sensory (50 Hz) - and motor (2 Hz) stimulation (contraction of the ipsilateral multifidus muscle and excluding a too close proximity to the segmental nerve), each medial branch was surrounded with a total of 0.5 mL lidocaine 2%.

The diagnostic test injection was evaluated using the Numerical Rating Scale (NRS, 0-10 point scale)[42-47] for pain. When employing the NRS for pain patients are asked to rate their pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including zero); if the decrease in NRS was equal to or greater than 2, the test was called positive[42].
Numbers of spinal imaging tests were noted for the entire sample and LBP subtypes. The presence of abnormalities on each lumbar spinal imaging test was judged by a radiologist as well as a pain physician; presence itself was assumed when at least one physician described it. The study flowchart is presented in Figure 1.
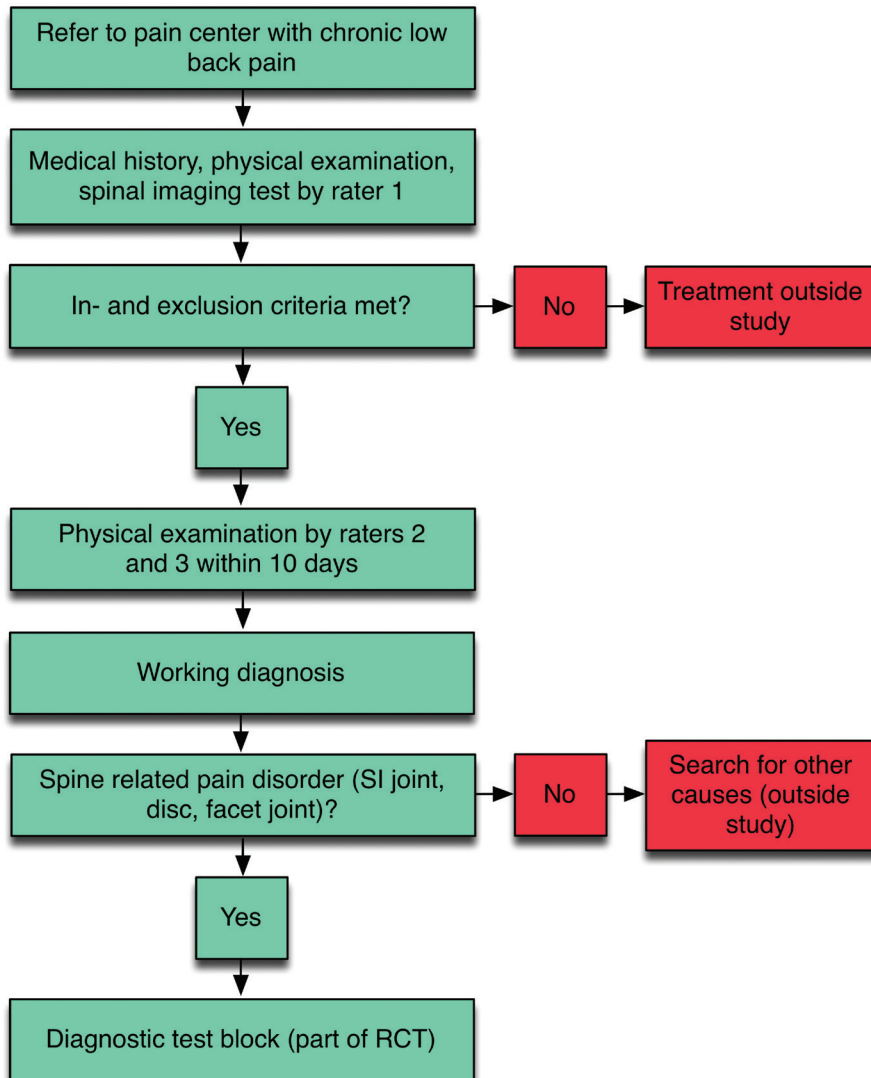
Figure 1. Study flowchart.

The medical ethics committee from the Erasmus MC University Medical Center approved the protocol (reference number MEC-2011-246). Written informed consent was obtained from all patients.

The predictive validity of X-ray images and MRIs in patients with a diagnosis of a LBP subtype (SI joint, disc and facet joint) was determined by assessing the sensitivity, specificity, positive – and negative predictive value. Data were analysed using SPSS for Mac, version 22 (International Business Machines

(IBM) Corporation, Software Group, Route 100, Somers, NY, 10589, United States of America).

Results

One hundred patients were included between January 2013 and April 2014. Demographic data of the patients were a median age of 55 (interquartile range (75,25) 65.75-44.25), a mean BMI of 26.8 (standard deviation 5.6), 66% female gender and 100% Caucasian race. The progress through the phases of the inter-rater reliability study is presented in Figure 2.
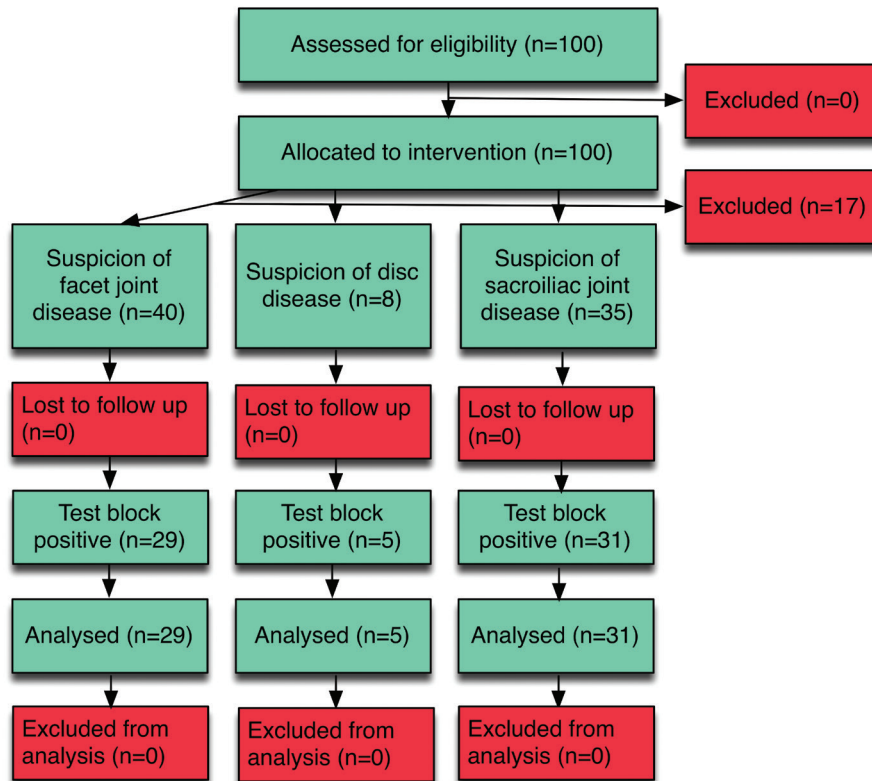

Figure 2: progress through the phases of the inter-rater reliability trial.

Demographic data of the patients were a median age of 55 (interquartile range (27,25) 65.75-44.25), a mean BMI of 26.8 (standard deviation 5.6), 66% female gender and 100% Caucasian race. Numbers of lumbar spinal imaging tests for the entire sample as well as for the LBP subtypes (before the diagnostic test block) are presented in Table 2.

Group (before test block)	Nr	X-ray made	CT made	MRI made
Total	100	90 (90%)	2 (2%)	61 (61%)
Facet joint	40	37 (92.5%)	2 (2%)	20 (50%)
Disc	8	6 (75%)	0 (0%)	6 (75%)
Sacroiliac joint	35	31 (88.6%)	0 (0%)	23 (65.7%)

Table 2: Total number of spinal imaging techniques, as well as for each subtype (differential diagnosis).

Lumbar X-ray imaging was used in 90% of the patients in the sample, MRI in 61%. No general working diagnosis could be made in 17 patients; these patients were excluded from the study.
Deviations present on lumbar X-ray imaging for each LBP subtype, and including the outcome of the diagnostic test block are presented in Table 3.

Group	Nr	X-ray made (%)	Facet joint pathology present (%)	Disc pathology present (%)	Sacroiliac joint pathology present (%)
Facet joint (test block positive)	29	26 (89.6)	19 (73.1)	23 (88.5)	1 (3.8)
Facet joint (test block negative)	11	11 (100)	4 (36.4)	9 (81.2)	0 (0)
Disc (test block positive)	5	3 (60)	1 (33.3)	2 (66.7)	0 (0)
Disc (test block negative)	3	3 (100)	1 (33.3)	1 (33.3)	0 (0)
Sacroiliac joint (test block positive)	31	27 (87.1)	16 (59.2)[1]	18 (66.7)[1]	3 (11.1)
Sacroiliac joint (test block negative)	4	4 (100)	4 (100)	4 (100)	2 (50)

Table 3: Pathology present on X-ray for each subtype of low back pain, depending on the outcome of the test block ([1]: 1 missing data entry).

When the facet joitnt was considered to be the primary source of pain and the diagnostic test block was positive (decrease in numerical rating scale for pain of 2 or more on a 0-10 point scale[42]), facet joint abnormalities were seen on X-ray imaging in 73.1%, disc abnormalities (in these same patients) in 88.5%.
Deviations present on lumbar MRI for each LBP subtype, and including the outcome of the diagnostic test block are presented in Table 4.

Group	Nr	MRI made	Facet joint pathology present (%)	Disc pathology present (%)	Sacroiliac joint pathology present (%)
Facet joint (test block positive)	29	13 (44.8)	9 (69.2)	13 (100)	N/A
Facet joint (test block negative)	11	7 (63.4)	2 (28.6)	6 (85.6)	N/A
Disc (test block positive)	5	3 (60)	2 (66.7)	3 (100)	N/A
Disc (test block negative)	3	3 (100)	0 (0)	3 (100)	N/A
Sacroiliac joint (test block positive)	31	20 (64.5)	9 (45)	20 (100)	0 (0)[1]
Sacroiliac joint (test block negative)	4	3 (75)	1 (33.3)	3 (100)	0 (0)[2]

Table 4: Pathology present on MRI for each subtype of low back pain, depending on the outcome of the test block ([1]: 17 missing data entries (MRI of lumbar spine); [2]: 3 missing data entries (MRI of lumbar spine).

Disc abnormalities were present in almost 100% of cases, irrespective of the results from the diagnostic test block and the general working diagnosis. The sensitivity, specificity, positive – and negative predictive value of X-ray imaging in the population with chronic LBP and in each LBP subtype is presented in Table 5, these of MRI in Table 6.

	X-ray			
	Sensitivity (%)	PPV (%)	Specificity (%)	NPV (%)
Facet joint	73.1	82.6	63.6	50
Disc	66.7	66.7	66.7	66.7
Sacro-iliac joint	11.1	60	50	7.69

Table 5: Sensitivity, specificity and predictive validity of lumbar spinal X-ray (PPV = Positive Predictive Value; NPV = Negative Predictive Value).

	MRI			
	Sensitivity (%)	PPV (%)	Specificity (%)	NPV (%)
Facet joint	69.2	81.8	71.4	55.6
Disc	100	50	0	0
Sacro-iliac joint	0	0	100	13

Table 6: Sensitivity, specificity and predictive validity of lumbar spinal MRI scan (PPV = Positive Predictive Value; NPV = Negative Predictive Value).

The positive predictive value of lumbar X-ray imaging for facet joint pain was 82.6%, the negative predictive value 50%. The positive predictive value of MRI for disc pain was 50%, the negative predictive value 0%. During the study we recorded no adverse events.

Discussion

This trial investigated the sensitivity, specificity and predictive value of X-ray and MRI in respect to the effectiveness of the diagnostic test block in patients in whom medical history and physical examination point towards a LBP subtype (SI joint, disc or facet joint). The results of this study show that the predictive validity of the lumbar spinal images in distinguishing between LBP subtypes is questionable.

Anatomic changes normally occur as a result from ageing and have the potential of producing mechanical and clinical symptoms. Loss of disc height alters the transmission of loads across structures like the facet joints, increasing further loading on adjacent structures. Establishing an accurate diagnosis of the specific source of low back pain will help in directing (or avoiding) treatment towards the source of the symptoms.

In the population without low back pain, the percentage of people with disc abnormalities varied between 31 and 64%[24, 25], while in this sample the prevalence of disc abnormalities in the patients with LBP was 100%, irrespective of the general working diagnosis. Furthermore, facet abnormalities were seen in 8% of people without LBP[24], but increased to 69.2% in the sample of patients with LBP when a working diagnosis of facet joint pain was established. From the MRI studies in people with and without low back pain we know that the high prevalence of disc abnormalities, combined with the high prevalence of back pain, bulging discs and protrusions of the disc may frequently be coincidental [13-16, 20-23] ; therefore, in chronic LBP, disc abnormalities cannot be used to distinguish one LBP type from the other.

A limitation of this study is that during the first consultation the pain physician took into account the results from lumbar spinal imaging, i.e. to exclude red flags. Perhaps this moment biased our results in moving more specifically towards a LBP subtype.

There were relatively few individuals under the age of 40 present in the study. This limits the interpretation and generalizability of the study findings.

Conclusions

We conducted this study to investigate the accuracy of lumbar X-ray imaging and MRIs as diagnostic tools of LBP subtypes (SI joint, disc and facet joint). Based on the results from this study, the predictive validity of lumbar X-ray imaging and MRIs to distinguish between LBP subtypes in patients with chronic LBP is questionable.
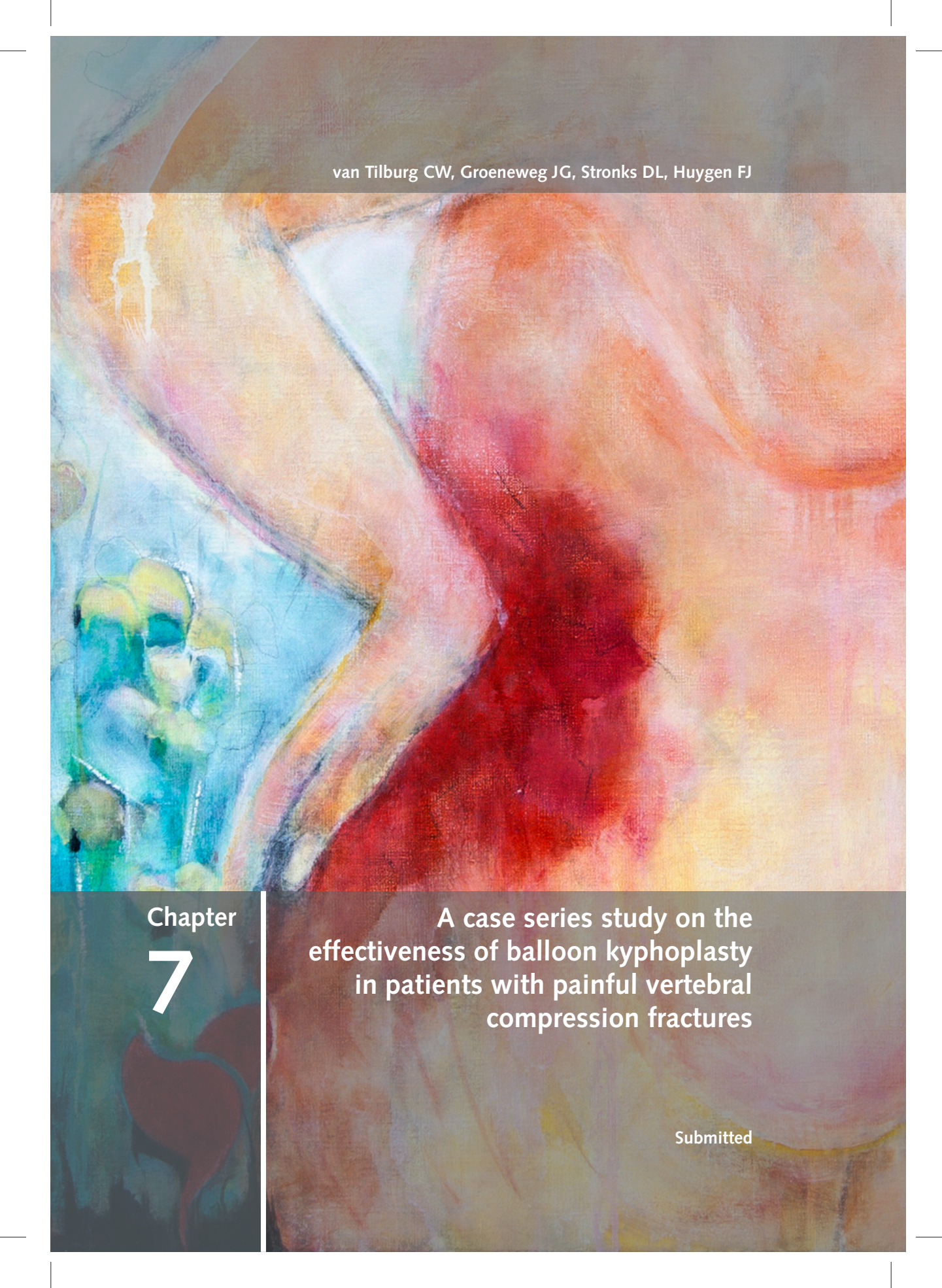
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Chapter

7

A case series study on the
effectiveness of balloon kyphoplasty
in patients with painful vertebral
compression fractures

Introduction

Vertebral fractures often are very painful and lead to reduced quality of life and disability[1]. Common causes of vertebral fractures are osteoporosis (postmenopausal, secondary), trauma, primary tumors of the spine and metastasis. The worldwide burden of osteoporotic fractures in the year 2000 was estimated to be 9 million, among them 1.4 million clinical vertebral fractures[2]; about a third come to medical attention[3,4]. The incidence of osteoporotic clinical vertebral fractures in The Netherlands was estimated to be 0.7% in women and 0.2% in men aged 55 years or older[5]. Traumatic spinal fractures occur in 11.8 to 16.4 per 100000 population (0.012-0.016%)[6,7]; the most common causes were a high-energy fall (39%, evenly distributed over the whole spine) and traffic accidents (26.5%, more fractures at the cervical and thoracic spine)[8]. The spine is also the most frequent site of bone metastasis. Spinal involvement may occur in up to 40% of patients with cancer and approximately 70% of patients with cancer have evidence of metastatic disease at the time of their deaths[9]. As many as 75% of vertebral metastases occur in patients with carcinoma of the breast, kidney, lung, prostate, thyroid and multiple myeloma[10,11]. Vertebral compression fractures occur in 55% to 70% of patients with multiple myeloma and is the initial clinical sign in 34% to 64% of these patients[4].

Usual treatment for vertebral osteoporotic compression fractures consists out of analgesics, bed rest, casting and physical support. Other modalities were introduced depending on the clinical presentation and spinal level, aiming at the vertebra itself (e.g. radiotherapy, surgical approaches and/or cement augmentation). Cement augmentation evolved into a percutaneous technique, injecting cement into the fractured vertebral body. Balloon kyphoplasty (BKP) seems to be a safe, minimally invasive procedure for the treatment of painful vertebral fractures, which is intended to reduce pain and disability and correct vertebral body deformity using balloons[12-18]. Studies have demonstrated that cement augmentation procedures provide better clinical outcome compared to non-surgical management[1,3,12,19]. When comparing BKP with vertebroplasty (VP), the first proved to have better results, which are maintained over long-term follow-up[20-23], with less side effects such as cement leakage[24]. In patients with cancer, BKP proved to be an effective and safe treatment that rapidly reduces pain and improves function[25-31]; a biopsy can routinely be performed[32].

Comparing to surgery, percutaneous cement treatment predicts significantly reduced costs as well as length of stay[33,34]. The use of BKP or VP in the management of vertebral compression fractures in patients with cancer may be a cost-effective strategy[35].

In 2009, two articles appeared in the New England Journal of Medicine, reporting that improvements made in pain (and pain related disability) by VP in patients with painful vertebral osteoporotic compression fractures were similar in the treatment group and the sham group[36,37]. The results of these trials seem to be in disagreement with the accumulated literature on this subject[38]. In one study[36], MRIs and/or bone scans were not required if the fracture was known and under one year of age. The targeted level was 250 patients, but only 131 subjects were enrolled. Eight patients (12%) in the vertebroplasty group crossed over to the sham group, while 43% (27) of patients from the sham group crossed over to the vertebroplasty group. In the other study[37], out of 219 eligible patients, only 78 (36%) were enrolled. While being a multicenter trial, more than 67% of the patients came from a single site. The mean volume injected into the vertebrae was (only) 2.8 mL. A meta-analysis of the individual patient data in the two randomised placebo controlled trials (RCTs) failed to show an advantage of VP over placebo[39]. More discussion regarding the differences between placebo efficacy and specific efficacy was provided in another article by Miller, Kallmes and Buchbinder[40].

Complications associated with BKP are attributed to the technique itself (e.g. cement leakage, infection) and/or cadiopulmonary events (e.g. cement, fat, bone marrow or air embolisation). These major complications are rarely seen, but may warrant a high level of suspicion and immediate action, e.g. early surgical intervention and/or pharmacological treatment[41-47].

This case series study reports on pain reduction after BKP in patients with painful vertebral compression fractures due to osteoporosis, trauma or cancer, who were referred to the pain center of a general hospital. All BKP procedures were performed by experienced interventional pain physicians.

Methods

Study design

We performed a case series study on the effectiveness of BKP for painful vertebral compression fractures in 60 patients with acute axial lumbar and/or thoracic spinal pain.

Participants

Patients were referred to the pain center of a general hospital with complaints of acute axial pain on lumbar and/or thoracic level. These patients were managed according to the flowchart presented in Figure 1. When a painful vertebral compression fracture was suspected (Table 1) and patients satisfied to the indications and contra-indications (Table 2), they were eligible for BKP. Each patient received a brochure explaining the complete procedure. After obtaining written informed consent for the procedure patients were scheduled for BKP.
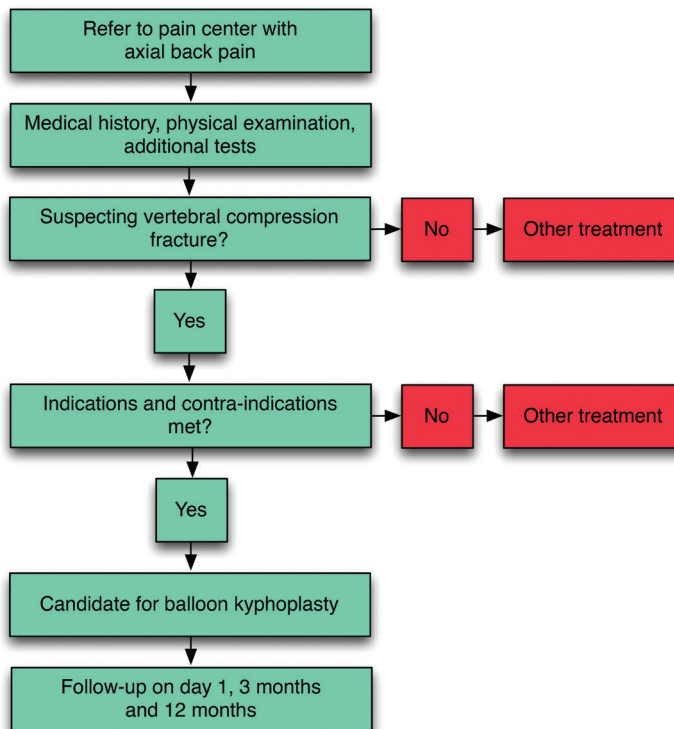

Figure 1: Procedure flowchart.

Medical history
1. Acute (deep) spinal pain episode
2. Trauma
3. Most comfortable when motionless
4. Osteoporosis
5. Cancer
6. Previous vertebral compression fracture(s)
7. Persistent pain after acute pain episode subsided
8. Abdominal symptoms (early satiety, abdominal bloating)
9. Anorexia and subsequent weight loss
10. Lower rib syndrome
11. Inactive, sedentary lifestyle
12. Fear of falling
13. Sleep pattern disturbed (due to pain and inactivity)
14. Depression
Physical examination
1. Tenderness to deep palpation and percussion over the affected vertebra
2. Para spinal muscle spasm
3. Short thoracic spine, kyphosis
4. Decreased pulmonary function (restrictive lung disease and reduced vital capacity)
Additional tests
1. Lateral X-ray of spine
2. MRI

Table 1: Medical history, physical examination and additional tests used in establishing the diagnosis of painful vertebral compression fractures.

Indications
1. Medical history, physical examination and additional tests suggestive of painful vertebral compression fracture on lumbar and/or thoracic level
2. Vertebral edema present on MRI
3. Numerical Rating tScale equal to or higher than 4/10
4. Preoperative anesthetic screening warrents the use of continuous IV sedation and analgesia
Contra-indications
1. Active infection
2. Progressive neurological deficits
3. Major psychiatric disorder (according to psychiatrists opinion)
4. Anticoagulation cannot be stopped
5. Allergies to any medication or cement
6. Pregnancy
7. Contra-indication for MRI

Table 2: indications and contra-indications for balloon kyphoplasty.

Intervention

Monitoring of vital parameters took place according to the American Society of Anesthesiologists House of Delegates Standards for Basic Anesthetic Monitoring (ASA)[48]. Antibiotic prophylaxis was provided with Cephazolin 2 g. Continuous Oxygen 15 L/min through a non-rebreather mask and bag was applied and patients were placed in the prone position using pillows under the chest and pelvic area. Continuous sedation with intravenous (IV) propofol Target Controlled Infusion (TCI) 0.5 μg/mL and continuous analgesia with IV remifentanyl 0.05 μg/kg/min was used.

Doses were titrated to a Ramsay score of 4 out of 6[49]. Continuous IV sedation and analgesia was provided to the patient by a nurse anaesthetist with subsequent training in sedation.

Skin – and periosteal infiltration was performed at each side with Lidocaine 2%. Under fluoroscopic guidance, a bilateral trans- or extrapedicular approach was used with introducer tools and inflatable balloon-like devices, polymethylmethacrylate (PMMA) bone cement and delivery devices (Kyphon inc. / Medtronic Spine LLC, 1221 Crossman Ave, Sunnyvale, CA 94089, United States of America). During each procedure, a biopsy was taken and a combination of Paracetamol 1 g IV, Dynastat 40 mg IV and Morphine 0.1 mg/kg IV was given for immediate postoperative pain management. Wound edges were infiltrated with Ropivacaine 0.2%.

Measurements

The main outcome parameter was pain reduction (Numerical Rating Scale (NRS) for pain)[50-54]. The 0–10 verbal NRS for pain is a tool that enjoys widespread clinical use due to its ease of administration. While using the NRS for pain, patients are asked to rate their pain on a scale from 0 to 10, where 0 represents "no pain" and 10 represents "the worst pain possible," using whole numbers (11 integers including zero). Often the value of "4" is used to confirm clinical nursing judgment as to the need for further intervention or documentation that the patient's goals for analgesia have been achieved. The NRS for pain was measured preoperatively (T0) and during follow-up.

Follow-up

Time periods for follow-up were on the first postoperative day (T1), at 3 months (T2) and at 12 months (T3).

Statistical considerations

Descriptive statistics were used to determine the frequencies of the demographic and the outcome parameters. Using the Kolmogorov-Smirnov test, the distributions of these parameters appeared to be skewed. Therefore, central tendency and dispersion of the distributions are reported as median and interquartile range (IQR).

Differences in pain level between baseline (preoperative, T0) and postoperative

(T1, T2 and T3) time periods were analyzed using the related-samples Friedman's Two-Way Analysis of Variance by Ranks. Post-hoc pairwise comparisons were performed with the Related Samples Wilcoxon Signed Rank Test, using a Bonferoni correction to counteract the problem of multiple comparisons.

The independent-samples Mann-Whitney U test was used to study the hypothesis that the distribution of the NRS for pain scores (T0-T1) is the same in the patients with osteoporosis and those with cancer.

Data were analyzed using SPSS for Mac, version 22 (International Business Machines (IBM) Corporation, Software Group, Route 100, Somers, NY, 10589, United States of America).

Results

Sixty patients were treated with BKP for painful vertebral compression fractures and had follow-up for 1 year. The procedure is presented in Figure 2. Demographic data are presented in Table 3. Vertebral fracture levels are presented in Figure 3. Most fractures occurred at the Th12-L1 region. The pain intensity levels appeared to be statistically significant different between the pain level at baseline (T0) and the three moments of measurement after the procedure, p<.001 (Figure 4). No statistically significant difference was found between the three moments of measurement after the procedure. Results of the pairwise comparisons are presented in table 4.
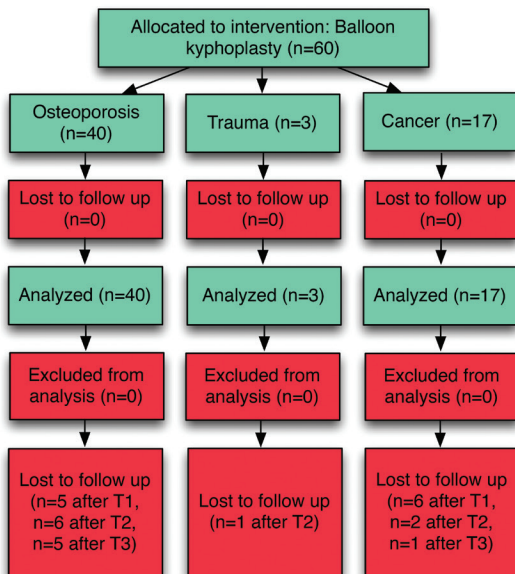

Figure 2: Progress through the phases of the procedure.

Group	N (F, %)	Age		BMI	
		Median	IQR (Q3-Q1)	Median	IQR (Q3-Q1)
Osteoporosis	40 (28, 70)	77	16	26	7.3
Trauma	3 (2, 66.7)	59	N/A	27.9	N/A
Cancer	17 (10, 58.8)	71	11	22.8	10.3

Table 3: demographic data of the patients (100% Caucasian) in the study (IQR: Interquartile range; N: number of patients; F: Female).
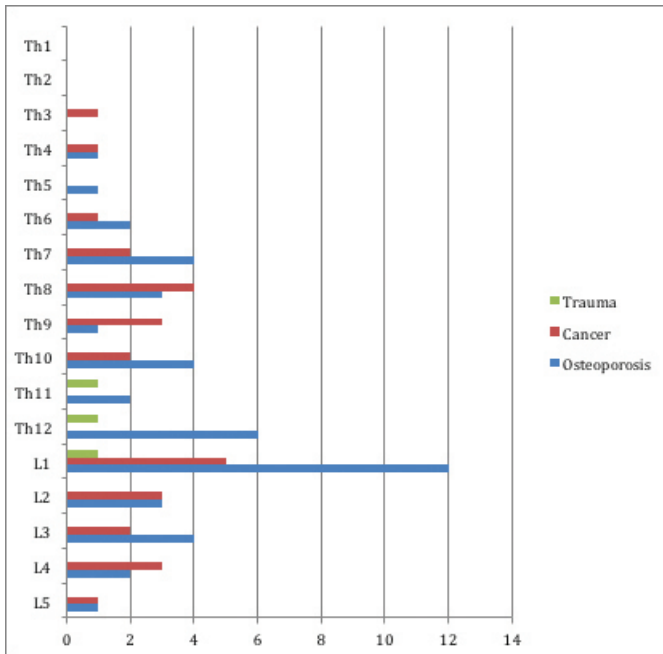

Figure 3: Vertebral fracture levels (Y-axis) and number of patients (X-axis) with vertebral compression fractures due to osteoporosis, trauma and cancer.

	T0	T1	T2
T0			
T1	< .001		
T2	< .001	.41	
T3	< .001	.12	.43

Table 4: results (p-value) of the pairwise comparisons between the moments of measurement, using a Bonferroni correction ($\alpha = 0.08$) (T0: before the BKP procedure; T1: first postoperative day; T2: 3 months after treatment; T3: 12 months after treatment).
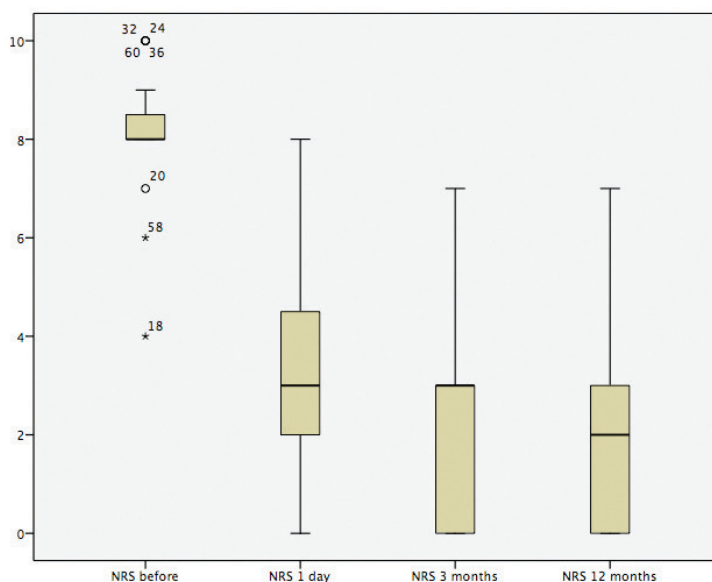
Figure 4: Boxplot of the pain intensity before vertebral augmentation (NRS before), first postoperative day (NRS 1 day), at 3 months (NRS 3 months) and at 12 months (NRS 12 months) in patients with painful vertebral compression fractures due to osteoporosis, trauma or cancer.

In 40 patients, a painful vertebral compression fracture was present due to osteoporosis, in three patients due to trauma and in 17 patients due to cancer (five patients with multiple myeloma, six with metastatic lung cancer, two with metastatic breast cancer, two with metastatic prostate cancer, one with metastatic ovary cancer and one with metastatic cervix cancer). No statistically significant difference in NRS for pain was found between the patients with osteoporosis and those with cancer between T0 and T1 (p=.48).

In the patients with cancer, one patient died after one day, another ten within one month and another two within three months. In the patients with osteoporosis, one patient died within one month and another one within three months. In the patients with traumatic vertebral compression fracture, no one died within the follow-up period of 1 year. No major complications occurred as a direct result from the BKP procedure.

Discussion

In this case series study, we measured the pre- and postoperative (until at least one year after operation) pain levels in 60 patients with painful vertebral compression fractures on lumbar and/or thoracic level due to osteoporosis, trauma or cancer, who were treated with BKP. The pain intensity levels

appeared to be statistically significant different between the pain level at baseline and the three moments of measurement after the procedure. No statistically significant difference was found between the three moments of measurement after the procedure. No statistically significant difference in pain intensity was found between the patients with osteoporosis and those with cancer between baseline and the first postoperative day.

One patient with cancer died within 1 day after the BKP procedure; the exact cause of death is unknown, more specifically a possible contribution to this death from the BKP procedure and/or the IV sedation.

In support of the recently published papers advocating the use of BKP for painful vertebral compression fractures in recent years, and contrary to two papers reporting no statistically significant difference of vertebroplasty compared to a sham control group, our case series study indicates that BKP can result in a statistically significant and sustained pain reduction during 1 year follow-up.

This case series study has several limitations: 1) we didn't include experimental control, and therefore cannot compare the treatment results with a control group, e.g. a placebo procedure; 2) pain scores were measured during specific moments in time; we don't know if using pain scores reflecting certain periods of time might lead to a different result; 3) due to morbidity and mortality predominantly occurring in the group of patients with cancer, the number of missing data increased as time progressed.

In conclusion, in patients with painful (non)malignant vertebral compression fractures, BKP can result in a statistically – and clinically significant pain reduction lasting at least one year. Being a spine related pain disorder, patients with painful vertebral compression fractures can be referred to pain centers having interventional pain physicians performing BKP.

Acknowledgements

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A CASE SERIES STUDY ON THE EFFECTIVENESS OF BALLOON KYPHOPLASTY IN PATIENTS WITH PAINFUL VERTEBRAL COMPRESSION FRACTURES
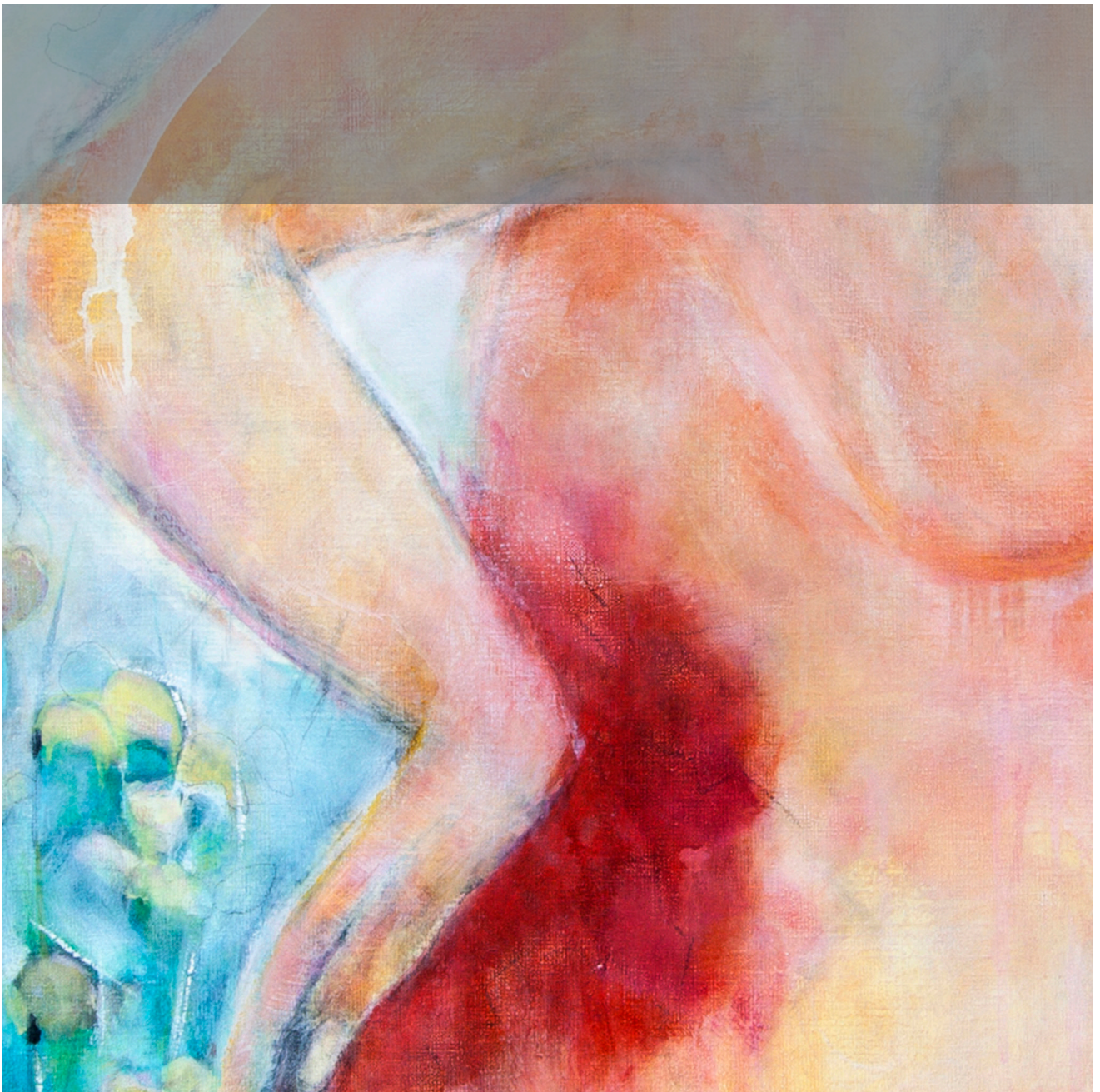
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"There are hunters and there are victims. By your discipline, cunning, obedience and alertness, you will decide if you are a hunter or a victim"

James Mattis (1950-)

Chapter

8

General discussion

The aim of the work presented in this thesis was to study the effectiveness of radiofrequency (RF) treatments for mechanical low back pain.
Several techniques can be used. We have chosen treatments that resemble the common practice in The Netherlands on the moment that we designed the studies, namely: RF lesioning with the Simplicity© III tool for SI joint pain (*Chapter 2*), RF lesioning of the ramus dorsalis of the segmental nerve root for facet joint pain (*Chapter 3*) and RF lesioning of the ramus communicans for discogenic pain (*Chapter 4*). Patient selection could be an important prognostic factor in treatment success. That is why we studied the inter-rater reliability on the diagnostic parameters of the physical examination (*Chapter 5*) and the predictive validity of lumbar X-ray images and MRIs (*Chapter 6*). Finally, we studied the effectiveness of balloon kyphoplasty (BKP) in patients with painful vertebral compression fractures due to cancer – and non-cancer etiology *(Chapter 7)*.
In this chapter we will present the main findings from our studies in relation to existing evidence and we will address some methodological challenges. The chapter closes by presenting implications for daily practice and implications for further research.

Main findings

Question 1: What is the effectiveness of the RF heat lesion employed for treatment of chronic low back pain originating from the SI joint, the facet joint or the intervertebral disc?

In *Chapter 2*, the effect on pain reduction and the global perceived effect (GPE, a 7 point Likert scale) were investigated of a percutaneous RF heat lesion compared to a sham procedure, applied to the dorsal ramus of L5 and the lateral branches of the S1, S2, S3 and S4 nerve roots. There was no statistically significant difference in pain level (measured by means of a Numerical Rating Scale (NRS) for pain) over time (measurements at baseline, one month and three months after the procedure). The same applies to satisfaction and recovery, no statistically significant effect was found.
In *Chapter 3*, the effect on pain reduction and the GPE were investigated of a percutaneous RF heat lesion compared to a sham procedure, applied to the medial branch of the primary dorsal ramus of the lumbar facet joints. There was a statistically significant effect on the level of pain in the factor period (baseline pain level versus the pain level one month after the procedure). However, there was no statistically significant difference with the passage of time between the treatment and sham groups. Also, there was no statistically significant difference in satisfaction or recovery.

In *Chapter 4*, the effect on pain reduction and GPE were investigated of a percutaneous RF heat lesion compared to a sham procedure, applied to the ramus communicans of the lumbar discs. No statistically significant difference in pain level over time (measurements at baseline, one month and three months after the procedure) between the treatment and sham groups were found. Also, no statistically significant difference in satisfaction or recovery was found between the treatment and sham groups.
Based on the results of the sham-controlled trials the H0 hypothesis of no difference in pain reduction (NRS) or in GPE between the treatment and the sham groups could not be rejected in these three RCTs.

Question 2: What is known about the diagnostic accuracy of the physical examination, X-ray imaging and MRIs in diagnosing chronic low back pain subtypes?

In *Chapter 5*, the reliability of diagnostic tests that point towards SI joint –, disc – or facet joint pain was investigated. None of the parameters from the physical investigation had Kappa (κ) values of more than .21 (fair) in all pairs of raters. Also, κ values for the pooled parameters of the physical examination suggestive of SI joint pain stayed below .20 between all raters. The same applies for the pooled parameters of the physical examination suggestive of facet joint – or disc pain.
In *Chapter 6*, the diagnostic accuracy of lumbar X-ray imaging and MRIs as diagnostic tools of low back pain subtypes was investigated. The positive predictive value of X-ray was 82.6% for facet joint pain, 66.7% for disc pain and 60% for SI joint pain; the negative predictive value of X-ray was 50% for facet joint pain, 66.7% for disc pain and 7.7% for SI joint pain. The positive predictive value of MRI was 81.8% for facet joint pain, 50% for disc pain and 0% for SI joint pain; the negative predictive value of MRI was 55.6% for facet joint pain, 0% for disc pain and 13% for SI joint pain. The predictive validity of imaging tools investigated to distinguish between low back pain subtypes in patients with chronic low back pain is questionable.
Based on the results of the inter-rater reliability study on the diagnostic parameters of the physical examination, as well as of the predictive validity of lumbar X-ray images and MRIs, patient selection remains a challenge in the treatment of chronic low back pain.

Question 3: What is the effectiveness of balloon kyphoplasty employed for the treatment of patients with painful vertebral compression fractures?

Sixty patients were treated with balloon kyphoplasty (BKP) for painful vertebral compression fractures and had follow-up for 1 year. The pain intensity levels appeared to be statistically significant different between the pain level at baseline (T0) and the three moments of measurement after the procedure, p<.001. No statistically significant difference was found between the three moments of measurement after the procedure. No statistically significant difference in NRS for pain was found between the patients with osteoporosis and those with cancer between T0 and T1 (p=.48).
In support of the recently published papers advocating the use of BKP for painful vertebral compression fractures in recent years, and contrary to two papers reporting no statistically significant difference of vertebroplasty compared to a sham control group, our case series study indicates that BKP can result in a statistically significant and sustained pain reduction during 1 year follow-up.

Considerations

Could the results from our studies be explained by 1) patient selection, i.e. the results from the diagnostic test block, or 2) by the way how the RF treatments were performed and 3) by the choice of the outcome parameters, i.e. the results from the diagnostic test block and the RF treatments themselves?

1) On patient selection

Question 4: What is the diagnostic value of the test block?

The percentage of positive diagnostic test blocks was 86.1 in SI joint trial, 77.8 in the facet joint trial and 64.5 in the ramus communicans trial. Compared to earlier studies this is high. The question raises whether a relatively high percentage of false positive patients entered the study. Possible explanations for these high proportions may be the use of local anaesthetics only, the possible spread of the local anaesthetics to pain generating structures other than those targeted, the use of only one diagnostic test block instead of two, the use of sedation, the combination of multidisciplinary treatment and the criteria chosen for the diagnostic test to be called positive[1-5]. The use of one instead of two diagnostic test blocks was chosen because it reflects the Dutch pain management practice[6-8].

When used as prognostic tools before lumbar facet RF lesioning, medial branch blocks may be associated with a higher success rate than intra-articular injections[9]. No significant differences were noted between single versus multiple blocks. Reducing the volume during cervical medial branch blocks may improve precision and accuracy[10]. The use of intraarticular diagnostic facet joint blocks cannot be recommended anymore[11]. But what is the value of diagnostic medial branch blocks in clinical practice?

Most RCTs evaluating lumbar facet RF lesioning used single diagnostic test blocks as prognostic tools. Cohen et al. studied the chance on a successful outcome of no, one or two diagnostic medial branch blocks in patients having lumbar RF facet joint lesioning[12]. In the group of patients without a diagnostic medial branch block performed 33% obtained a successful outcome at 3 months versus 16% in the group of patients having had one diagnostic medial branch block and 22% in the group having had two diagnostic medial branch blocks. Based on these results as well as taking into account its cost-effectiveness, the question may be whether any blocks should be done before lumbar facet joint denervation. However, until now diagnostic blocks are the only reliable approach to identify the facet joints as the source of pain[13]. In the absence of a reference standard, medial branch blocks serve more of a prognostic than a diagnostic role, enabling the selection of patients who might respond to RF denervation treatment. Using double blocks reduces the false positive rate of medial branch blocks, but will invariably reduce the overall treatment success rate. By increasing the number of diagnostic blocks, the false positive rate will be reduced but the false negative rate will increase, thus increasing the risk of withholding an active treatment from patients[11]. And what about the balance of the burden of multiple interventions versus the potential benefit?

There were no statistically significant differences in RF outcomes based on any medial branch block with a pain relief cutoff over 50%[14]. No optimal threshold for designating a diagnostic block as positive, above 50% pain relief, could be calculated. Employing more stringent selection criteria is likely to result in withholding a beneficial procedure from a substantial number of patients, without improving success rates.

When the RF treatment after a positive diagnostic test block does not lead to a statistically (and clinically) significant pain reduction, does that mean that the diagnostic test block was an invalid predictor of the effect of a RF treatment (i.e. led to false positives)? Does this mean that the diagnostic test block is a different treatment as compared to the RF treatment and, therefore, is it a poor predictor of the treatment outcome? As suggested by Maas et al., the diagnostic accuracy of the test block should be studied[15].

Question 5: What is the contribution of other parameters than RF treatment to the prediction of pain relief?

In order to evaluate the possible contribution of other parameters than the RF treatment to the prediction of pain relief, we analysed multiple parameters (gender, body mass index, duration of symptoms, the level of pain at baseline, age and the interaction between group and age) and found that – in the facet joint RCT – age and the level of pain at baseline contributed to the prediction of a statistically significant decrease in lumbar facet joint pain; i.e. the younger the patient and the higher the pain at baseline, the higher the contribution to the prediction of this decrease in pain. However, in the disc RCT we found that none of the parameters investigated contributed to the prediction of a statistically significant decrease in disc pain.

2) On the way studies were performed

Several studies that have investigated the use of percutaneous RF current to diminish SI joint pain describe a success ratio between 64% and 80%[16-18]. The application of RF current can be provided in several ways (pulsed or continuous, side of the lesion, number of lesions, cooled versus non-cooled)[19-24]. Several devices are commercially available, e.g. (P)RF single needles, cooled RF single needles, and multi-electrode RF probes. We have used a multi-electrode RF probe that has a unique design that allows for positioning using a single percutaneous entry point. With this procedure the lateral branches of S1, S2, S3 and S4 are targeted at the same time (a L5 dorsal root ramus radiofrequency lesioning is performed separately with a single RF needle). There were no RCTs available on the efficacy of a multi-electrode RF probe in the treatment of SI joint pain. We performed a RCT with the aim to study the efficacy of this device. More recently evidence emerged about the use of cooled RF current in providing a significant and long lasting pain relief[25-30].
We observed several limitations. First, due to the construction of the RF probe and the anatomy of the sacrum, we sometimes couldn't reach the S4 branch. However, we don't know what the exact contribution of the S4 branch holds towards SI joint pain. Second, the size of the heat lesion by the RF probe with three independent active electrodes might be smaller than the one from the cooled RF treatment variant[30]. Third, the presence of pain distal to the knee in patients with SI joint pain is described but not often found.
Age was not normally (bimodally) distributed. This might reflect differences in disease type in younger and older people, encompassing different structures (diastasis from pregnancy and childbirth, anatomical changes and disorders of

the capsuloligamentous structures, and disorders from the vascular plexus or complex neural network) and operative procedures[31,33]. These differences should be investigated further in studies on the treatment of SI joint pain.

Recent systematic reviews[13,33,34] regarding RF treatment for facet joint pain have identified six RCTs investigating the efficacy of the radiofrequency lesion on the medial branch of the primary dorsal ramus. Three small studies[35-37] were positive, two were equivocally positive[13,34], and one was negative[38]. The overall quality of the evidence of the studies was low to moderate. Lack of concealment of allocation and failure to blind patients was reported in several trials, and the risk of selective reporting in all trials. For this reason, we developed a new RCT.
Depending on the median duration of the symptoms, decrease in pain is unlikely to be due to spontaneous recovery in our RCT. In addition, the regression analysis revealed no statistically significant effect of the interaction of group and age. Therefore, a possible overall effect of treatment due to the imbalance in age between the two groups is unlikely.
We did not test the patients for the success of blinding. However, since the results of the crossover, when the patients knew that they would receive the real radiofrequency heat lesion, were comparable, we do not think this compromised the results.
Age distribution was skewed but other parameters were normally distributed. Regression analysis revealed no statistically significant effect of the interaction of group and age. Therefore, a possible overall effect of treatment due to the imbalance in age between the two groups is unlikely.

To evaluate the efficacy of a percutaneous RF treatment at the ramus communicans, two studies[36,37] were performed. Methodological differences exist in these studies concerning the inclusion criteria, outcome parameters and follow-up. In a systematic review[33] addressing RF treatment for low back pain subtypes, differences between the studies were observed regarding RF technique, duration of low back pain before entering the study, the exclusion criteria and the number of participants. In the study from Kapural et al.[38], the sham procedure was not the same as the actual RF treatment. Kapural et al. made use of a positive response to diagnostic discography instead of a decrease in NRS of 2 or more from a diagnostic test block at the ramus communicans as an inclusion parameter, like we did in our study.
A comprehensive understanding of spinal innervation is needed to increase to effectiveness of pain treatment[39,40]. The sinuvertebral nerves that innervate the lumbar discs are formed by a somatic root from a ventral ramus and

an autonomic root from a grey ramus communicans; an ascending branch passes as far as the next higher intervertebral disc, while a descending branch supplies the disc at the level of entry[41]. Two types of rami communicantes are observed, a superior oblique ramus and a deep transverse ramus; sinuvertebral nerves originate from the deep transverse rami[42]. These deep transverse rami run close to the vertebral bodies and along the lumbar arteries and veins; they run along the lateral side of each lumbar vertebral body and connect to the corresponding lumbar spinal nerve and sympathetic trunk in a segmental manner. All superficial oblique rami run upon the surface of the aponeurosis, while the deep transverse rami run beneath the aponeurosis. In this way, using fluoroscopic guidance, together with sensory – and motor stimulation, we have tried to interrupt the pain impulses with high frequency energy at the site of origin. We have targeted the deep transverse ramus (and a root from the ventral ramus), while the superior oblique ramus (running upon the surface of the aponeurosis) ascends to the next higher intervertebral disc. Due to the complexity (and convergence) of lumbar spinal innervation, perhaps treatment should be aimed at different structures than we nowadays routinely use?

In support of the recently published papers advocating the use of BKP for painful vertebral compression fractures in recent years, and contrary to two papers reporting no statistically significant difference of vertebroplasty compared to a sham control group, our case series study indicates that BKP can result in a statistically significant and sustained pain reduction during 1 year follow-up.
This case series study has several limitations: 1) we didn't include experimental control, and therefore cannot compare the treatment results with a control group, e.g. a placebo procedure; 2) pain scores were measured during specific moments in time; we don't know if using pain scores reflecting certain periods of time might lead to a different result; 3) due to morbidity and mortality predominantly occurring in the group of patients with cancer, the number of missing data increased as time progressed.

Randomisation was performed using sealed envelopes, which the patients chose randomly. In this way, patients as well as their pain physicians were completely unaware of the content of the envelope during any stage of the investigation. The pain research nurse was the only one aware of the contents and performed the treatment accordingly.
Regarding the radiofrequency generator, all sound indicators were turned off and the generator itself was visually hidden from the patient by means of a linen cloth, hung between two metal infusion poles. The pain physician left the

operating theatre when the actual treatment (RF current or sham) took place. The same time period was taken for an actual – or a sham treatment.
A limitation is that we did not test the patients for the success of blinding. However, since the results of the crossover studies performed - when the patients knew that they would receive the real RF heat lesion - were comparable, we do not think this compromised the results.
All patients received graded activity physiotherapy, but not at one single center. Perhaps there were differences in the frequency and way patients were treated at the different centers. It was difficult for us to gain evidence on equal quality of physiotherapy accompaniment. However, there were no differences in the way patients from the actual treatment and sham groups were referred. Hence, we cannot assume a systematically different treatment between the groups.

3) On the choice of the outcome parameters

In the RCT on the efficacy of percutaneous RF current to diminish facet joint pain we analysed a possible association between the amount of pain reduction after the diagnostic test block and after the intervention and found no statistically significant correlation between these parameters. Could the amount of pain reduction after the diagnostic test block possibly not to be related to the amount of the pain reduction after the intervention? Further studies should confirm this observation.
A patient was considered to have a successful outcome in case of a reduction equal to or greater than the minimal clinically important change for pain. The minimal clinically important change is the least improvement that patients rate as rendering them better than they were. For back pain, it is an NRS of 2 out of 10 points[43]. These patients nevertheless continue to have pain. What patients consider as an improvement might be different from this minimal important change in pain, e.g. 50% or 80%[44]. Inquiring about patients' expectations of reduction in pain is important in establishing realistic treatment goals. Minimal clinically important changes might fall short.
Recommendations on outcome measures for chronic pain trials were described in 2005[45]. Besides outcome measures on pain, global improvement and satisfaction, other outcome measures include physical and emotional functioning, symptoms and adverse events, and participant disposition. Core outcome sets for research and clinical practice in various domains have been introduced[46].

Implications for clinical practice and future research

This thesis shows that although percutaneous RF treatment for chronic mechanical low back pain is frequently used, evidence for the effect of this treatment in the way we performed the RF procedures is not supported. The results of the inter-rater reliability study on the parameters of the physical examination and the diagnostic accuracy study of lumbar X-ray imaging and MRIs leaves us faced with the challenges that come with patient selection in the case of chronic low back pain trials.

Future studies should establish: i) the diagnostic accuracy of the test block; ii) the identification of subgroups of patients with low back pain that may benefit from RF treatment; iii) unification of anatomical sites targeted for RF treatment; iv) targeting new anatomical sites based on a comprehensive understanding of anatomy; v) and unification of outcome parameters in (low back) pain trials.

The aim of all the studies is to further improve the diagnosis and treatment of patients with chronic spine related pain disorders.

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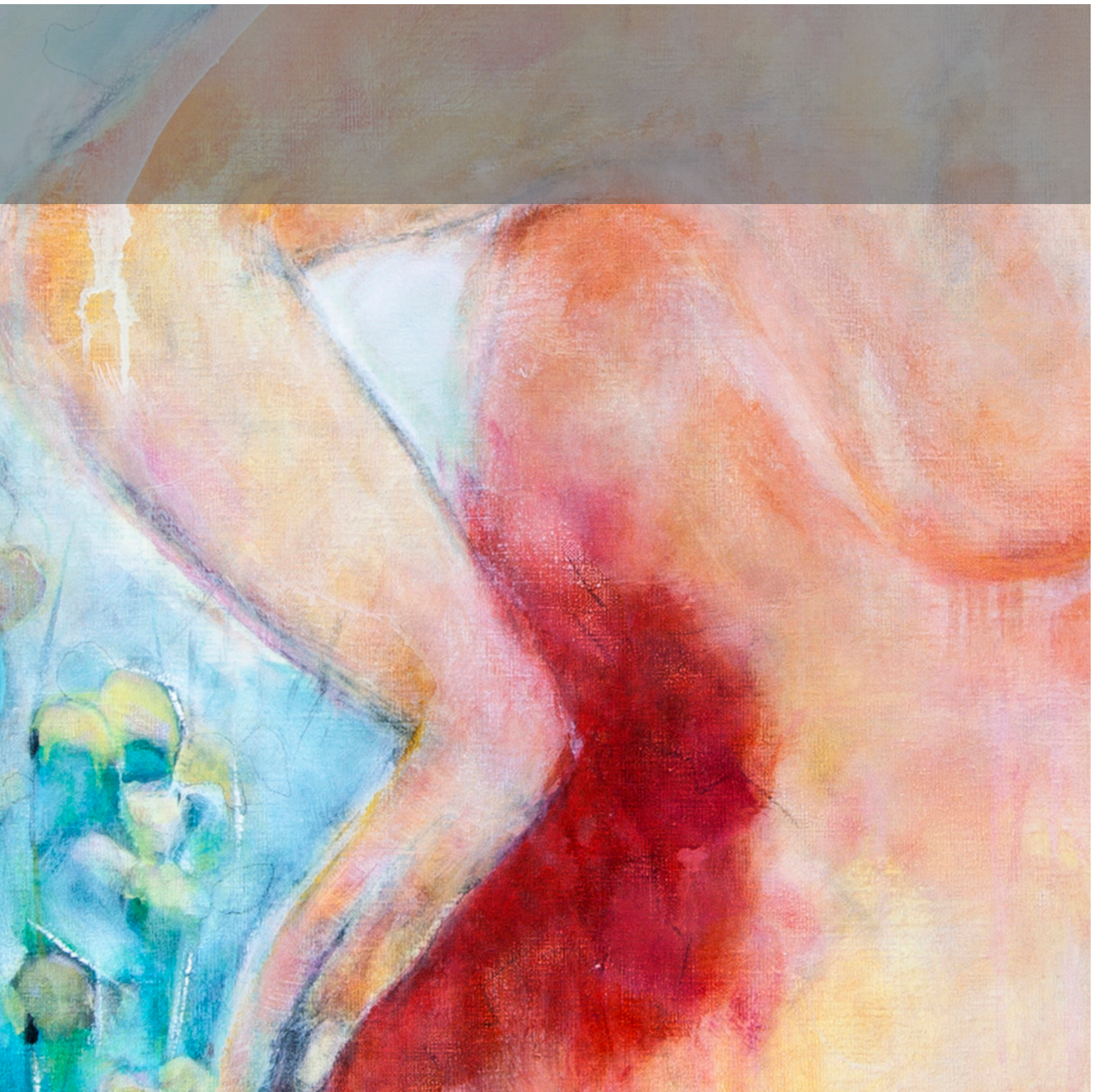
Chapter

9

Summary

This dissertation on the effectiveness of minimally invasive treatment for chronic lumbar spine related pain disorders is divided into eight chapters. After the introduction on low back pain and its management, followed by the outline of the thesis and the problem formulation, chapter two describes the randomised sham-controlled double blind multicentre trial to ascertain the effect of percutaneous radiofrequency (RF) treatment for SI joint pain. Chapter three describes the randomised sham-controlled double blind multicentre clinical trial to ascertain the effect of percutaneous RF treatment for lumbar facet joint pain. The randomised sham-controlled double blind multicentre clinical trial to ascertain the effect of percutaneous RF treatment at the ramus communicans for lumbar disc pain is described in chapter four. Chapter five describes the inter-rater reliability of the diagnostic criteria for SI joint –, disc – and facet joint pain, chapter six the predictive validity of X-ray images and MRIs of the lumbar spine. The effectiveness of balloon kyphoplasty in patients with painful vertebral compression fractures is described in chapter seven. Chapter eight is a general discussion of the main findings, strengths and limitations of all studies in this thesis.

The introductory chapter describes (prevalence rates for) chronic low back pain and the evaluation of the pain producing structures. I review the available evidence on treatment possibilities and specifically address the question of lack of sound evidence on the effectiveness of minimally invasive treatment, leading to the rationale of this thesis.

The reports on the results of the three sham-controlled RCTs on the effectiveness in terms of pain relief of percutaneous RF for chronic low back pain are described in chapters two, three and four. Each RCT included 60 patients who were randomised to receive the actual (RF) or sham treatment. The main study parameter was pain reduction (NRS) with the secondary study parameter being global perceived effect (GPE). In all RCTs the pooled data from both groups showed a statistically significant pain reduction between T0 (before the treatment) and T1 (1 month after the treatment). However, the hypothesis (H0) of no differences in terms of pain relief or in GPE between the groups could not be rejected. In other words, percutaneous RF when comparing to a sham intervention does not lead to a statistically significant more substantial pain reduction, nor to a more substantial GPE.

Very little is known about the inter-rater reliability of the diagnostic criteria to identify low back pain subtypes. The study to determine the reliability of diagnostic tests that should indicate SI joint –, disc – or facet joint pain

represents the contents of chapter five. One hundred patients were included. The inter-rater reliability was estimated using Cohen's Kappa (κ) index. The null hypothesis was an agreement of not bigger than coincidence (Kappa = 0). There was no Kappa value of more than .21 (fair) for each individual physical test in all raters together. The Kappa values for the pooled items for SI joint –, disc – and facet joint pain were less than .20 in all raters together. The inter-rater reliability of the diagnostic tests appeared to be small and this fact seriously limits their predictive validity. The practical value of the tests investigated in patients with low back pain for more than three months thereby seems to be doubtful.
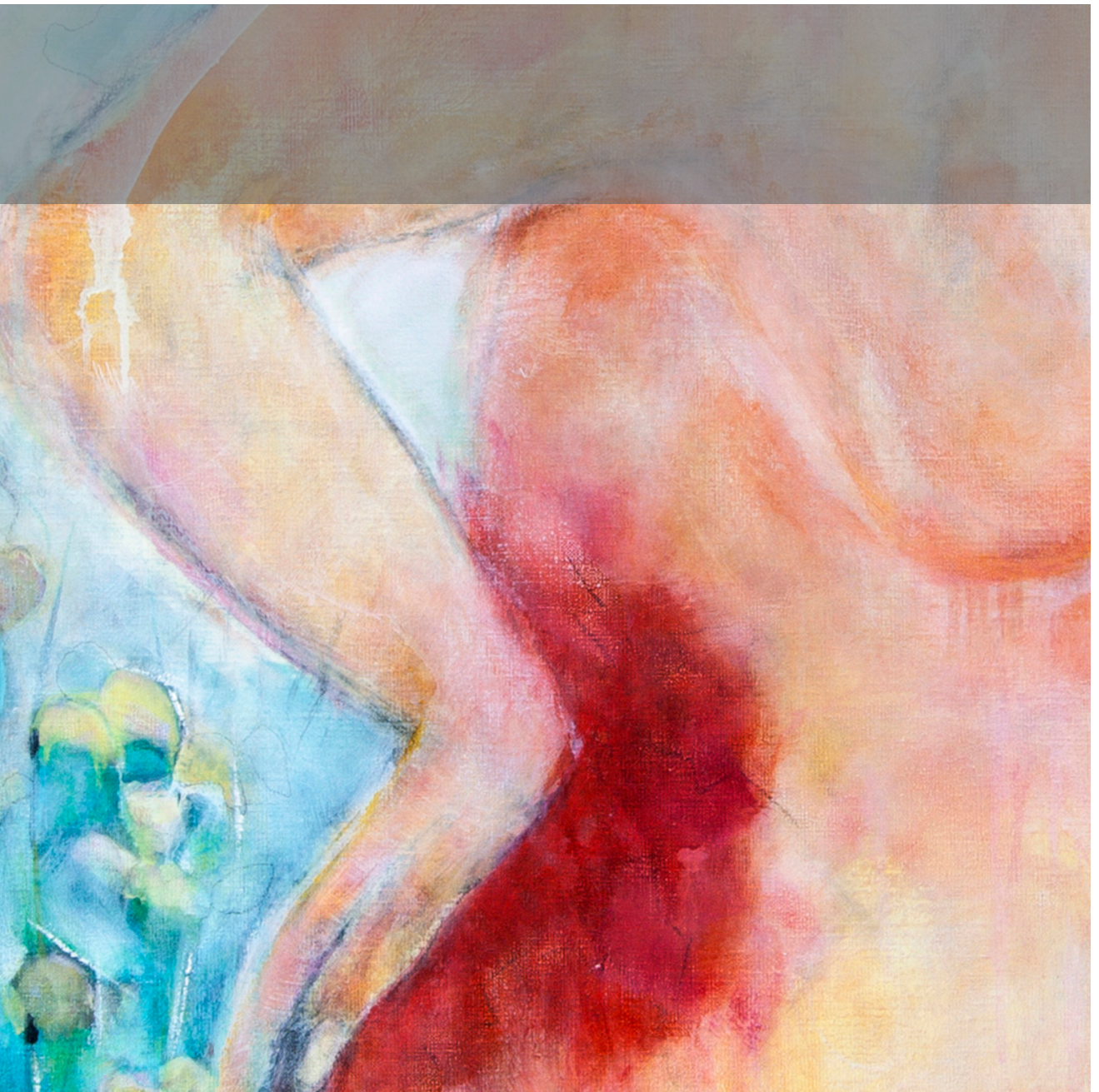
The current evidence regarding the predictive validity of imaging tests of the lumbar spine to identify the source of low back pain is inconsistent and does not help to determine their role. The predictive validity of X-ray images and MRIs of the lumbar spine is written down in chapter six. One hundred patients were included. The positive predictive value of X-ray was 82.6% for facet joint pain, 66.7% for disc pain and 60% for SI joint pain; the negative predictive value of X-ray was 50% for facet joint pain, 66.7% for disc pain and 7.7% for SI joint pain. The positive predictive value of MRI was 81.8% for facet joint pain, 50% for disc pain and 0% for SI joint pain; the negative predictive value of MRI was 55.6% for facet joint pain, 0% for disc pain and 13% for SI joint pain. The predictive validity (and as such their practical value) of X-ray images and MRIs of the lumbar spine to identify the source of low back pain appears to be doubtful.

Several studies report that cement augmentation provides better clinical outcome compared to non-surgical management in patients with painful vertebral compression fractures due to cancer and non-cancer etiology, although in two RCTs the treatment and sham groups demonstrated similar results. In our case series study of 60 patients treated with BKP a statistically significant effect (p<.001) was demonstrated between the pain level at baseline and the three moments of measurement after the procedure. No statistically significant effect was found (p=.48) in the pain level at baseline and the first postoperative day between the patients with vertebral compression fractures due to osteoporosis and those with vertebral compression fractures due to cancer. In patients with painful (non)malignant vertebral compression fractures, BKP can result in a statistically – and clinically significant pain reduction lasting at least one year.

Samenvatting

Deze dissertatie over de effectiviteit van minimaal invasieve behandeling van chronische wervelkolomgerelateerde pijnklachten van de lage rug is onderverdeeld in zeven hoofdstukken. Na de inleiding over de last van lage rugklachten en haar behandeling, gevolgd door de uiteenzetting van de thesis en formulering van de problematiek beschrijft hoofdstuk twee de gerandomiseerde, sham-gecontroleerde, dubbelblinde multicenter studie naar het effect van percutane radiofrequente (RF) behandeling voor SI gewrichtsklachten. Hoofdstuk drie beschrijft de gerandomiseerde, sham-gecontroleerde, dubbelblinde multicenter studie naar het effect van percutane RF behandeling voor lumbale facetgewricht pijnklachten. De gerandomiseerde, sham-gecontroleerde, dubbelblinde multicenter studie naar het effect van percutane RF behandeling ter hoogte van de ramus communicans voor pijnklachten afkomstig van de lumbale tussenwervelschijf wordt beschreven in hoofdstuk vier. Hoofdstuk vijf beschrijft de inter-beoordelaar betrouwbaarheid van de diagnostische criteria voor SI gewricht –, tussenwervelschijf – en facetgewricht pijnklachten tussen de beoordelaars, hoofdstuk zes predictieve validiteit van röntgenfoto's en MRI's van de lendenwervels. Hoofdstuk zeven is een algemene discussie over de voornaamste bevindingen, sterktes en beperkingen van alle studies in deze thesis.

Het inleidende hoofdstuk is beschrijft de (prevalentie cijfers voor) chronische lage rugklachten en de evaluatie van weefsels welke pijn genereren. Ik blik terug op het beschikbare bewijs omtrent behandelingsmogelijkheden en ga specifiek in op het gebrek aan sterke bewijsvoering betreffende de effectiviteit van minimaal invasieve behandeling, leidend tot de rationale van deze thesis.

De rapportage over de resultaten van drie sham-gecontroleerde RCT's betreffende de effectiviteit in termen van pijnverlichting van percutane RF voor chronische lage rugklachten staan beschreven in de hoofdstukken twee, drie en vier. In iedere RCT werden 60 patiënten geïncludeerd welke werden gerandomiseerd om ofwel de werkelijke (RF) of sham behandeling te ontvangen. De belangrijkste studie parameter was pijnvermindering (NRS) en de tweede studie parameter was globaal ervaren effect (Global Perceived Effect, GPE). Voor alle RCT's geldt dat de data van beide groepen gepooled een statistisch significante pijnreductie laten zien tussen T0 (voorafgaande aan de behandeling) en T1 (één maand na de behandeling). Echter, de hypothese (H0) van geen verschil in vermindering van pijnklachten of in GPE tussen de groepen kon niet worden verworpen. Met andere woorden, percutane RF in vergelijking met de sham interventie leidt niet tot een statistisch significant grotere pijnverlichting, evenmin tot een groter globaal ervaren effect.

Er is weinig bekend over de inter-beoordelaar betrouwbaarheid van de diagnostische criteria voor subtypering van chronische lage rugklachten. De studie betreffende de inter-beoordelaar betrouwbaarheid van diagnostische fysieke tests die zouden indiceren of het SI gewricht –, de tussenwervelschijf – of het facetgewricht de pijnklachten geeft wordt beschreven in hoofdstuk vijf. Honderd patiënten werden geïncludeerd. De inter-beoordelaar betrouwbaarheid werd geschat met behulp van Cohen's Kappa (κ) index. De nul hypothese was dat er geen grotere overeenstemming is tussen de beoordelaars dan op grond van toeval kan worden verwacht (Kappa = 0). Er werd geen Kappa waarde gevonden van meer dan .21 (redelijk) voor de individuele fysieke tests tussen alle beoordelaars. De Kappa waarden voor de samengevoegde onderdelen voor SI gewricht –, tussenwervelschijf – of facetgewricht pijnklachten waren kleiner dan .20 tussen alle beoordelaars. De inter-beoordelaar betrouwbaarheid van de diagnostische tests bleek dus gering en dit feit beperkt hun predictieve waarde in hoge mate. Daarmee lijkt de praktische waarde van de onderzochte tests bij gebruik in patiënten met lage rugklachten welke langer dan drie maanden aanwezig zijn twijfelachtig.

De huidige bewijsvoering van de predictieve validiteit van beeldvormend onderzoek van de lendenwervels voor het identificeren van de bron van lage rugpijn is onsamenhangend, waardoor de rol van dit onderzoek onduidelijk was. In hoofdstuk zes wordt het onderzoek naar de predictieve validiteit van röntgenfoto's en MRI's van de lendenwervels beschreven. Honderd patiënten werden geïncludeerd. De positieve predictieve waarde van röntgenfoto's was 82.6% voor facetgewricht pijnklachten, 66.7% voor discogene pijnklachten en 60% van SI pijnklachten; de negatieve predictieve waarde was 50% voor facetgewricht pijnklachten, 66.7% voor discogene pijnklachten en 7.7% voor SI pijnklachten. De positieve predictieve waarde van MRI was 81.8% voor facetgewricht pijnklachten, 50% voor discogene pijnklachten en 0% voor SI pijnklachten; de negatieve predictieve waarde was 55.6% voor facetgewricht pijnklachten, 0% voor discogene pijnklachten en 13% voor SI pijnklachten. De predicitieve validiteit (en daarmee de praktische waarde) van röntgenfoto's en MRI's van de lendenwervels voor het identificeren van de bron van lage rugpijn bleek dus twijfelachtig te zijn.

Diverse onderzoeken beschrijven dat wervelcementering betere klinische resultaten oplevert in vergelijking met niet-chirurgische behandeling bij patiënten met pijnlijke wervelinzakkingen door oncologische – en niet-oncologische oorzaken, hoewel in twee RCT's resultaten gelijkaardig waren in de behandel– en placebo groep. In onze case series studie werden 60 patiënten behandeld met BKP en werd een statistisch significant effect (p<.001) aangetoond tussen het pijn niveau voorafgaande aan de behandeling en deze op de drie meetmomenten na de behandeling. Er kon geen statistisch significant effect (p=.48) worden aangetoond tussen het pijn niveau voorafgaande aan de behandeling en deze op de eerste postoperatieve dag bij patiënten met wervelinzakkingen door osteoporose en bij hen met met wervelinzakkingen door kanker. Bij patiënten met pijnlijke (niet-)oncologische wervelinzakkingen kan BKP een statistisch – en klinisch significante pijnvermindering opleveren welke gedurende tenminste één jaar aanhoudt.
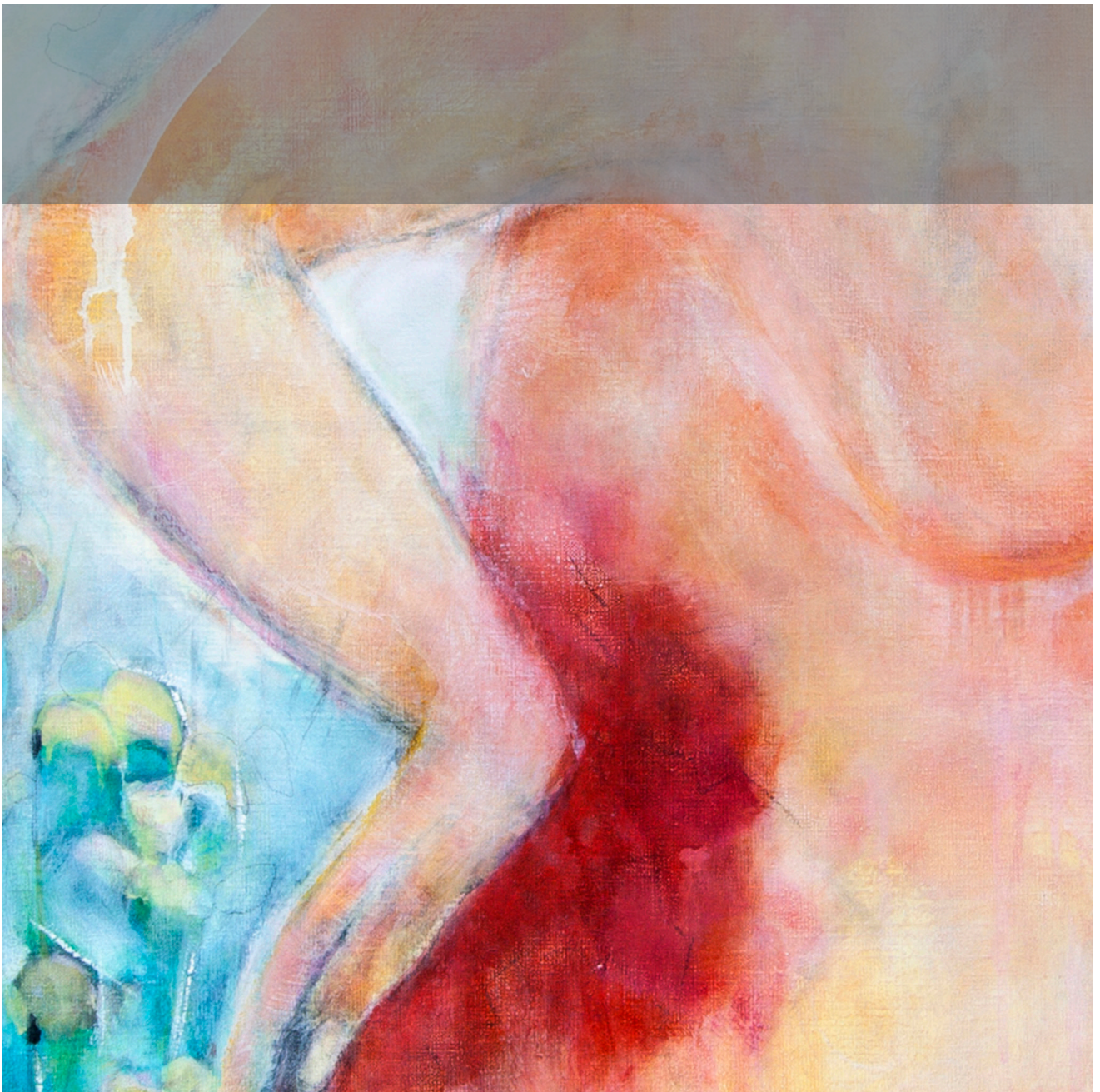
"There are three kinds of Budoka: one that tries to look strong, one that tries to perfect the technique and one that tries to gain a good heart."

Masaaki Hatsumi (1931-)

Chapter

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Acknowledgements

After an intensive period of seven years, today is the day: writing this note of thanks is the finishing touch on my disseration. It has been a period of intense learning for me, not only in the scientific arena, but also on a personal level. Writing this disseration has had a big impact on me. I would like to reflect on the people who have supported and helped me so much throughout this period.

First I would like to express the deepest appreciation to my promotor and committee chair prof.dr. Frank Huygen, who has the substance of a genius, however acting as a normal man. He continually and convincingly conveyed a spirit of adventure in regard to research, and an excitement in regard to teaching. Without his guidance and persistent help this dissertation would not have been possible.
In addition, I would like to thank mrs. Anita van Toor, secretary to prof. dr. Frank Huygen, for all her help in establishing the meetings and all communication regarding this dissertation.

Second, I would like to express my deepest apprecation to my copromotor dr. George Groeneweg for his wonderful collaboration. He supported me greatly and was always willing to help me. I want to thank him for all of the opportunities I was given to conduct my research and further my disseration. In addition, I would like to thank the other members of the pain research group for their valuable guidance, especially dr. Dirk Stronks who helped me with all of the statistics involved. They provided me with the tools that I needed to choose the right direction and succesfully complete my dissertation.

Third, I would like to thank the committee members for reading this dissertation and deciding that it was worth the while to continu with the PhD trajectory: prof.dr. Frank Huygen, dr. J. George Groeneweg, prof.dr. Jan Verhaar, prof.dr. Bart Koes, prof.dr. Maarten Moens, prof.dr. André Wolff, prof.dr. Barend J. van Royen, and dr. B. Sanjay Harhanghi.

Many thanks go out to the pain team from Lievensberg hospital (now Bravis hospital) for all the years that we worked together and succeeded in building a pain centre with an almost full range of treatment options: David, Fleur, Ingrid, Jacqueline, Jinny[†], Lieneke, Marion, Miranda, Nicole, Reinier, Sonja, and Sylvia. When we started with our work in 2007, the hospital had almost

no pain treatment available. During the years we grew up and became strong, and perhaps too strong for some people.
A special word of thanks goes out to David, Fleur and Reinier. David was not only my colleague but also my friend and we've accomplished many things together. Fleur helped me with the scientific research and was part of the team organising all kinds of pain related events throughout the years. At that time, Reinier was manager of the pain centre and helped me tremendously with many things that were directly or indirectly related to this thesis.
To Annemieke I would also like to say thanks, being the nurse practitioner (in training) from Franciscus hospital Roosendaal who was involved in the scientific research.

To the OR team from Lievensberg hospital I would like to express my gratitude for all the help that I received with the procedures in the research patients, and also for the numerous procedures outside the field of this thesis: Hans, Hélène, Irene, Jacqueline, Rian, and all the other team members that helped me. We have done many treatments together. The same goes for the anaesthesia team involved: Alex, Anneke, Jurgen, Sabien, Sigrid, and all the other team members. Also, I will not forget all the help that I received from the X-ray department: Maarten, Marlies, Miranda, and all other team members.

A special word of thanks goes out to my colleagues and friends dr. Teo Goroszeniuk and Ciaran Wazir. We have known each other for more than ten years now. Throughout the years we discussed many scientific and non-scientific subjects and organised many pain related events. Thank you for both your wisdom and guidance. Thank you for the new patterns of thought as well as new treatment possibilities. I always love to come over to "the office" for talks with a small or large Polish film on top. To the daughter of Teo, Julia, a special word of thanks for grammar check.

I would like to thank my parents Sjaak and Corry van Tilburg-Kostermans for their wise council and sympathetic ear. They are always there for me. They have encouraged my (academic) interests from day one, even if my curiosity led to incidents that were kind of hard to explain.
Without the love, encouragement and endurance of my wife Miranda, this thesis would not have been possible. The support that she gave me is tremendous and remarkable. Now that this thesis is complete, she and I and our son Jelte have many more hours to spend together during the evenings and weekends.
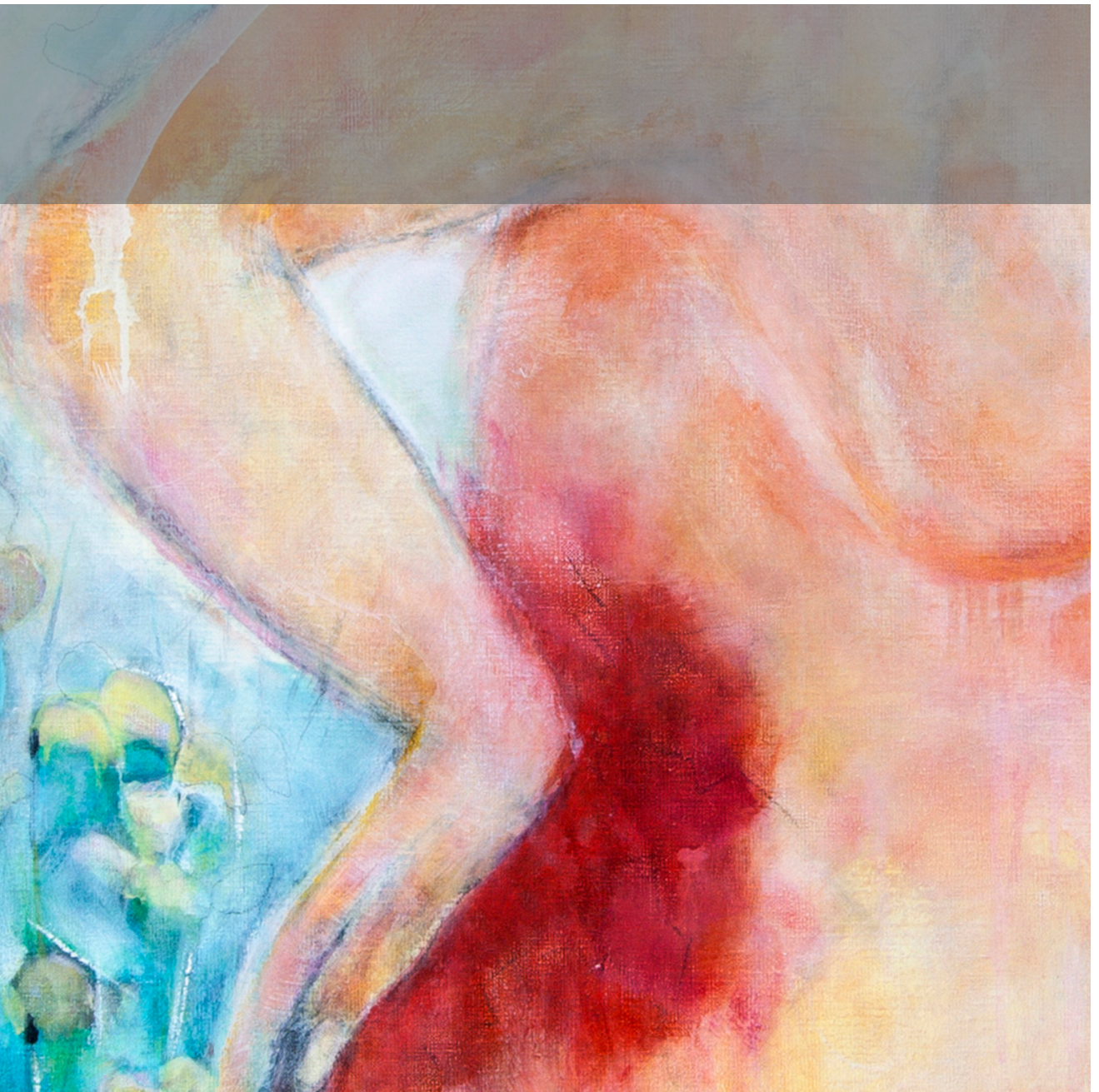
To my friends I would like to say that you were not only able to support me by deliberating over the problems and findings, but also happily by talking about things other than just this thesis. A special word of thanks towards my paranymphs Lyando and Janneke. I am blessed with such sweet and strong friends.

To anyone that I may have forgotten. I apologize. Thank you as well.

With the accomplishment of this thesis, conducting scientific research receives a new boost at our own private hospital for pain medicine Pain - and Neuromodulation Centre Excellent Klinieken. Quite a large part of our daily work at the hospital is reserved for conducting scientific research and exploring new ways to help the patient with chronic (low back) pain. I want to thank my colleagues, friends and business partners dr. Jehad Shaikhani and Lena Macleane for all their help and support.

Chapter

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Dankwoord

Na een intensieve periode van zeven jaar is vandaag de dag: het schrijven van dit dankwoord is het finale stuk van mijn thesis. Het is een periode van intensief leren voor mij geweest, niet alleen in de wetenschappelijke arena, maar tevens op een persoonlijk niveau. Het schrijven van dit proefschrift heeft een grote impact op mij gehad. Ik wil graag de personen benoemen die mij hebben ondersteund en veel hebben geholpen gedurende deze periode.

Allereerst wil ik graag mijn diepste waardering uiten voor mijn promotor en voorzitter van het comité prof.dr. Frank Huygen, welke de inhoud heeft van een genie, zich echter uitend als een gewone man. Hij stelde continue en op overtuigende wijze een avontuurlijke en opwindende geest ten tonele met betrekking tot onderzoek en onderwijs. Zonder zijn richting en blijvende hulp zou deze thesis niet mogelijk zijn geweest.
Bovendien wil ik graag mevr. Anita van Toor bedanken, secretaresse van prof. dr. Frank Huygen, voor al haar hulp in het plannen van de bijeenkomsten en alle communicatie met betrekking tot deze dissertatie.

Ten tweede wil ik graag mijn diepste waardering uiten voor mijn copromotor dr. George Groeneweg en zijn fantastische manier van samenwerking. Hij heeft me enorm ondersteund en was altijd bereid om mij te helpen. Ik wil hem graag bedanken voor alle mogelijkheden die mij werden geboden om mijn onderzoek te plegen en mijn dissertatie rond te krijgen.
Bovendien wil ik graag de andere leden van de onderzoeksgroep pijngeneeskunde bedanken voor hun waardevolle begeleiding, met name dr. Dirk Stronks welke mij heeft geholpen met alle benodigde statistiek. De onderzoeksgroep voorzag in de hulpmiddelen welke ik nodig had om de juiste richting te kiezen en deze dissertatie met succes te completeren.

Ten derde wil ik de leden van het comité bedanken welke deze dissertatie hebben gelezen en besloten hebben dat het de moeite waard was om het PhD traject te continueren: prof.dr. Frank Huygen, dr. J. George Groeneweg, prof.dr. Jan Verhaar, prof.dr. Bart Koes, prof.dr. Maarten Moens, prof.dr. André Wolff, prof.dr. Barend J. van Royen, and dr. B. Sanjay Harhanghi.

Veel dank gaat uit naar het pijnteam van ziekenhuis Lievensberg te Bergen op Zoom (tegenwoordig Bravis ziekenhuis) voor alle jaren dat we hebben samengewerkt en slaagden in het bouwen van een pijncentrum met een bijna compleet pakket aan behandelmogelijkheden: David, Fleur, Ingrid, Jacqueline, Jinny[†], Lieneke, Marion, Miranda, Nicole, Reinier, Sonja, en Sylvia.
Bij het starten van onze werkzaamheden in 2007 bestonden er in het

ziekenhuis bijna geen pijnbehandelingsmogelijkheden. Met het vorderen van de jaren groeiden we op en werden we sterk, voor sommige personen wellicht tè sterk.

Een speciaal woord van dank gaat uit richting David, Fleur en Reinier. David was niet alleen mijn collega maar ook mijn vriend en we hebben we vele zaken samen verwezenlijkt. Fleur heeft me geholpen met het wetenschappelijk onderzoek en was deelgenote van het team dat allerlei vormen van pijngerelateerde evenementen organiseerde in de afgelopen jaren. Reinier was destijds manager van het pijncentrum en heeft me geholpen met vele zaken wel direct of indirect verbonden waren met deze thesis.

Ook naar Annemieke wil graag mijn dank uitspreken. Zij werkt als verpleegkundig specialist in opleiding in het Franciscus ziekenhuis Roosendaal en was betrokken bij het wetenschappelijk onderzoek.

Naar het OK team van ziekenhuis Lievensberg wil ik mijn dankbaarheid uiten voor alle hulp welke ik heb ontvangen met de procedures bij de onderzoekspatiënten en eveneens met de talloze procedures buiten het veld van deze thesis: Hans, Hélène, Irene, Jacqueline, Rian en alle andere teamleden welke mij behulpzaam zijn geweest. We hebben vele behandelingen samen uitgevoerd. Hetzelfde geldt voor het betrokken anesthesiologie team: Alex, Anneke, Jurgen, Sabien, Sigrid en alle andere teamleden. Ik zal eveneens de hulp niet vergeten welke ik heb ontvangen van de röntgenafdeling: Maarten, Marlies, Miranda en alle andere teamleden.

Een speciaal dankwoord gaat uit naar mijn collegae en vrienden dr. Teo Goroszeniuk en Ciaran Wazir. We kennen elkaar al meer dan tien jaar. Gedurende de jaren we hebben vele wetenschappelijke en niet-wetenschappelijke zaken bediscussieerd en vele pijngeregelateerde evenementen georganiseerd. Dank aan beiden voor jullie wijsheid en richting. Dank aan beiden voor de nieuwe gedachtenpatronen evenals de nieuwe behandelmogelijkheden. Ik hou er iedere keer weer van om naar "het kantoor" te komen voor gesprekken met een klein of groter Pools laagje er op. Aan de dochter van Teo, Julia, hartelijk dank voor grammatica controle.

Ik wil graag mijn ouders Sjaak en Corry van Tilburg-Kostermans bedanken voor hun wijze raad en luisterend oor. Ze zijn er altijd voor me. Zij hebben mijn (academische) interesses vanaf de eerste dag aangemoedigd, zelfs wanneer mijn nieuwsgierigheid tot incidenten leidde welke min of meer moeilijk vielen uit te leggen.

Zonder de liefde, aanmoediging en volhardendheid van mijn vrouw Miranda zou deze thesis niet mogelijk zijn geweest. De ondersteuning die ze me gaf is overweldigend en bijzonder. Nu dat mijn thesis af is zal zij, onze zoon Jelte en ik veel meer uren samen kunnen spenderen in de avonden en weekends. Tegen mijn vrienden wil ik zeggen dat jullie er niet alleen voor me waren met ondersteuning betreffende de gerezen problemen en bevindingen, maar gelukkig ook door te praten over dingen buiten deze thesis. Een bijzonder woord van dank richting mijn paranimfen Lyando en Janneke. Ik ben gezegend met zulke lieve en sterke vrienden.

Aan iedereen die ik vergeten ben. Mijn excuses. Eveneens hartelijk dank.

Met de vervulling van deze thesis ontvangt het uitvoeren van wetenschappelijk onderzoek een nieuwe boost in ons privé ziekenhuis voor pijngeneeskunde Pijn- en Neuromodulatiecentrum Excellent Klinieken. Een relatief groot gedeelte van de dagelijkse werkzaamheden staan gereserveerd voor het uitvoeren van wetenschappelijk onderzoek en het ontdekken van nieuwe wegen om de patiënt met chronische (lage rug) klachten helpen. Ik wil mijn collegae, vrienden en zakenpartners dr. Jehad Shaikhani en Lena Macleane bedanken van al hun help en ondersteuning.
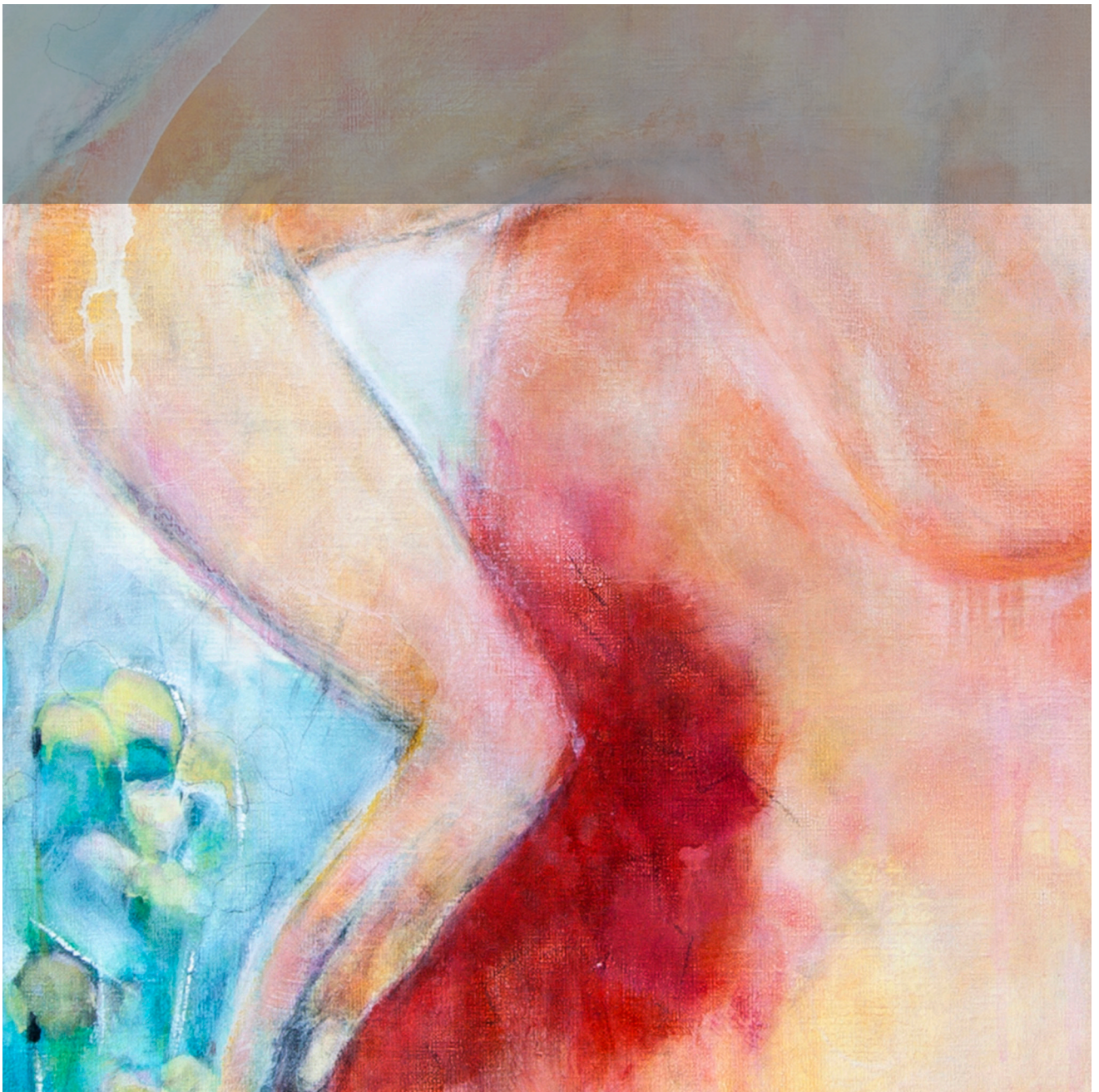
Chapter

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About the author

Kenneth van Tilburg was born on July 30, 1971 at Lievensberg hospital, Bergen op Zoom, The Netherlands as a son of a bricklayer and a housewife. He grew up in the city of Steenbergen, The Netherlands and had a very happy childhood. Already in puberty, Kenneth courted Miranda, grew up together and moved in together. In June 2010, their son Jelte was born. They were married on 1 July 2017.
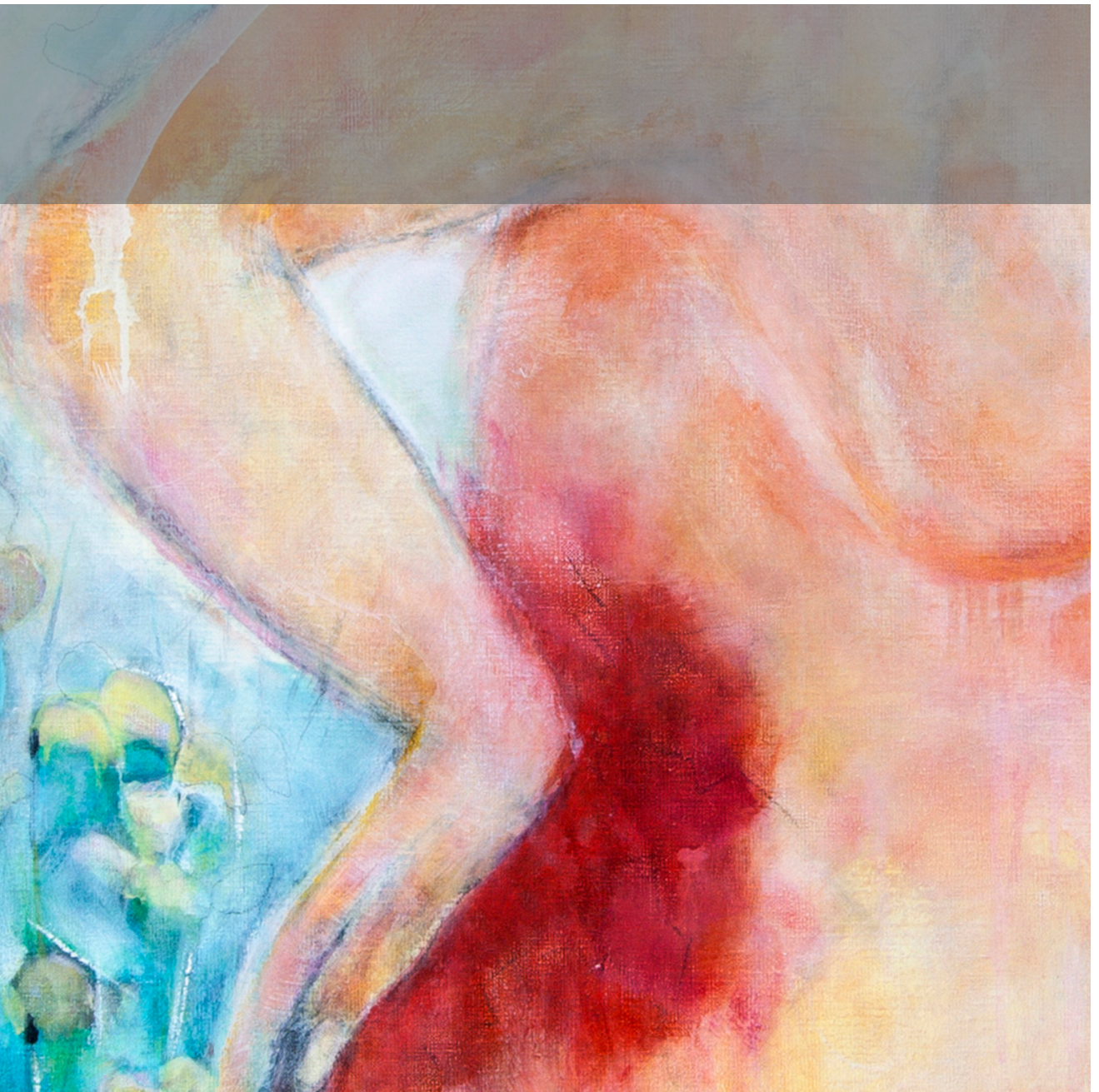
After graduating from secondary school and higher education in 1992, Kenneth started his academic career at the University of Antwerp, Belgium. Parallel to his career in health care, he saw chance to develop his other passion being ninjutsu (ninpo), a Japanese martial arts, led by sensei Hans Hesselmann from Utrecht, The Netherlands.

After obtaining his medical degree, he worked as a physician at the emergency departments and intensive care units of several hospitals in The Netherlands. In 2001, he started his anaesthesia training at the University of Antwerp, spending the last one and a half years of this training at Radboud University, Nijmegen, The Netherlands. At several moments during his academic training in both countries, he developed a passion for pain medicine. Shortly after his graduation, he started to work as an anaesthetist with an interest in pain medicine at Lievensberg hospital. Together with his colleague David van den Tol, he developed a pain centre with an almost full range of treatment options for patients with chronic pain. In 2010 he became a consultant in pain medicine and his PhD trajectory was set in motion.

Kenneth is passionate about organising pain conferences all over the world and a series of very successful events were organised as of 2009. As of 2014, he spent time and energy on the realisation of Nerfact, being an electronic patient record system for pain medicine, and an event management bureau for pain related conferences. As of September 2016, he changed his career in being a consultant in pain medicine working at DC Klinieken, The Netherlands and Pain – and Neuromodulation centre Excellent Klinieken, The Netherlands, two centers that focus on pain medicine.

Chapter

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Over de auteur

Kenneth van Tilburg werd geboren op 30 juli 1971 in het Lievensberg ziekenhuis te Bergen op Zoom als zoon van een metselaar en huisvrouw. Hij groeide op in Steenbergen en had daar een zeer gelukkige jeugd. Al in de pubertijd kreeg hij verkering met Miranda, samen groeiden zij op tot volwassenen en gingen samenwonen. In juni 2010 werd hun zoon Jelte geboren. Op 1 juli 2017 zijn ze getrouwd.

Na zijn diploma's voor M.A.V.O., M.L.O. en H.L.O. te hebben behaald, startte Kenneth in 1992 met zijn academische carrière aan de Universiteit Antwerpen.

Parallel aan zijn carrière in de gezondheidszorg zag hij kans om zijn andere passie ninjutsu (ninpo) te ontwikkelen, een Japanse krijgskunst, onder leiding van sensei Hans Hesselmann te Utrecht.

Na het behalen van zijn artsendiploma werkte hij op de spoedeisende hulp en intensive care unit afdelingen van verschillende ziekenhuizen. In 2001 begon hij met zijn opleiding anesthesiologie aan de Universiteit Antwerpen, waarvan de laatste anderhalf jaar werden doorlopen aan de Radboud Universiteit te Nijmegen. Op diverse momenten tijdens zijn academische training ontwikkelde hij een passie voor pijngeneeskunde.

Kort na het behalen van zijn diploma ging hij aan de slag als anesthesioloog met interesse in pijngeneeskunde in het Lievensberg ziekenhuis. Samen met zijn collega David van den Tol ontwikkelde hij een pijncentrum met een nagenoeg volledig pallet aan behandelmogelijkheden voor patiënten met chronische pijn. In 2010 werd hij anesthesioloog-pijnspecialist en startte hij met zijn promotietraject.

Kenneth is een gepassioneerde organisator van pijngerelateerde congressen over de gehele wereld en vanaf 2009 werden een serie van succesvolle evenementen georganiseerd. Vanaf 2014 spendeerde hij tijd en energie aan de realisatie van Nerfact, een electronisch patiënten dossier voor pijngeneeskunde en een evenementenbureau voor pijngerelateerde congressen. Vanaf september 2016 veranderde hij zijn carrière naar anesthesioloog-pijnspecialist bij DC Klinieken en Pijn – en Neuromodulatie centrum Excellent Klinieken, twee centra met een focus op pijngeneeskunde.

Chapter

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PhD portfolio

General

First name: Cornelis
Middle initials: W. J.
Surname: van Tilburg
Given name: Kenneth
Titles: MD, FIPP, EDRA
Date of birth: July 30, 1971
Address: Kapitein Frensstraat 6
Zip code: 4661 ZH
Town: Halsteren
Country: The Netherlands
Nationality: Dutch

Profession:	Consultant in Pain Medicine and Anaesthesia, Medical events organiser, Entrepreneur
Practicing since:	2006
Medical registration number:	39050352201
Subspecialties:	pain management

Telephone number (private):	0031612057127
E-mail address (private):	vtilburg@ziggo.nl
E-mail address (work):	kvantilburg@dcklinieken.nl, kvtilburg@excellentklinieken.nl

Education

1983-1987
M.A.V.O. "Petrus Canisius", Steenbergen, The Netherlands
Diploma: June 10, 1987

1987-1991
M.L.O. "Spectrum College Breda", Etten-Leur, The Netherlands
Differentiation: cyto-, histo- and pathology
Diploma: July 12, 1991

1991-1992
H.L.O. "Hogeschool West-Brabant", Etten-Leur, The Netherlands
Getuigschrift propedeuse H.B.O.
Getuigschrift: July 17, 1992

1992-1995
Universiteit Antwerpen, Rijks Universitair Centrum Antwerpen,
Antwerp, Belgium
Geneeskunde 1e cyclus
Diploma: September 21, 1995

1995-1999
Universiteit Antwerpen, Universitaire Instelling Antwerpen,
Antwerp, Belgium
Geneeskunde 2e cyclus
Diploma: June 21, 1999

1999-2000
Arts-assistent SEH, Ziekenhuis Walcheren,
Vlissingen, The Netherlands

2000-2000
Arts-assistent ICU, Erasmus UMC & University Hospital,
Rotterdam, The Netherlands

2001-2001
Arts-assistent SEH, Franciscus ziekenhuis,
Roosendaal, The Netherlands

2001-2003
Arts-assistent Anesthesiologie, AZ Middelheim & Koningin Paola
Kinderziekenhuis, Antwerp, Belgium

2003-2005
Arts-assistent Anesthesiologie, Universiteit & Universitair Ziekenhuis,
Antwerp, Belgium

2005-2006
Arts-assistent Anesthesiologie, Universiteit & St. Radboud Ziekenhuis,
Nijmegen, The Netherlands

2006-2007
Anesthesioloog, IJsselland Ziekenhuis,
Capelle aan den IJssel, The Netherlands

2007-2016
Anesthesioloog(-pijnspecialist), Bravis Ziekenhuis,
Bergen op Zoom, The Netherlands

2016-
Anesthesioloog-pijnspecialist, DC Klinieken,
Breda and Rotterdam, The Netherlands

Anesthesioloog-pijnspecialist, Pain - and Neuromodulation centre Villa Delta,
Dordrecht, The Netherlands

Memberships

National

Nederlandse Vereniging voor Anesthesiologie (NVA), section on pain medicine
Vereniging voor Neuromodulatie Nederland (VvNN)

International

International Association for the Study of Pain (IASP)
World Institute of Pain (WIP)
European Society of Regional Anaesthesia & Pain Therapy (ESRA)
International Neuromodulation Society (INS)

Courses & meetings

2000

Advanced Trauma Life Support Course,
Stichting ATLS, Tilburg, The Netherlands

2001

Beademingscursus,
NVIC, Ede, The Netherlands

Advanced Life Support Provider Course,
ERC, Antwerp, Belgium

2002

Pediatric Advanced Life Support Course,
Stichting SHK, Tilburg, The Netherlands

Advanced Pediatric Life Support Course,
Stichting SHK, Tilburg, The Netherlands

2003

Demonstration of regional techniques on cadavers,
BARA, Brussels, Belgium

2004

Cadaver workshop: demonstration of peripheral nerve blocks,
BARA, Brussels, Belgium

5th Christmas echo; international course of perioperative echocardiography,
SARB / NVA, Brussels, Belgium

Advanced Trauma Life Support refresher course,
Stichting ATLS, Tilburg, The Netherlands

Mechanische beademingsdagen,
NIVC, Arnhem, The Netherlands

Nederland zone symposium,
ESRA, Heeze, The Netherlands

2005

Echo-geleide perifere zenuwblokkades,
Nijmegen, The Netherlands

Nederland zone symposium,
ESRA, Heeze, The Netherlands

5th Annual meeting,
BARA, Brussels, Belgium

2006

Echo geleide perifere zenuwblokkades,
Nijmegen, The Netherlands

Nederland zone symposium,
ESRA, Heeze, The Netherlands

6th Annual meeting,
BARA, Affligem, Belgium

8e congres sectie pijnbestrijding,
NVA/VAVP, Eindhoven, The Netherlands

Workshop loco-regionale technieken
Rotterdam, The Netherlands

2007

Nederland zone symposium
ESRA/DARA, Heeze, The Netherlands

CRPS-symposium,
Nijmegen, The Netherlands

ASRA 32nd annual regional anesthesia meeting and workshops,
Vancouver, British Columbia, Canada

ESRA Scandinavian zone meeting
Oslo, Norway

Workshop percutaneous discectomy
Amphia ziekehuis, Breda, The Netherlands

NYSORA 1st annual europe symposium
London, United Kingdom

De anesthesioloog als pijnbestrijder
9e congres NVA/VAVP, Antwerp, Belgium

Registratie en terminologie in de pijnbestrijding
UMC Utrecht, The Netherlands

2008

Epiduroscopy workshop,
Alysis zorggroep, Arnhem, The Netherlands

DARA/ESRA Nederland Zone symposium 2008,
Heeze, The Netherlands

XI cadaver workshop - Neural blockades on cadavers,
Innsbruck, Austria

Nucleoplasty & Vertebroplasty cadaver training course
Paracelcus Medical University, Salzburg, Austria

Dutch Society of Anesthesiologists (NVA) annual meeting,
Maastricht, The Netherlands

XXVII annual ESRA congress,
Genoa, Italy

Basiscursus stralingsbescherming deskundigheidsniveau 4A/M,
Green Park Hotel, Leidschendam, The Netherlands

3rd Interventional pain management workshop,
Guy's & St. Thomas' Hospital, London, United Kingdom

2nd Annual NYSORA Europe symposium,
Royal college of physicians, London, United Kingdom

Zevende onderwijsprogramma, 10e congres sectie pijnbestrijding NVA,
NH Koningskof, Veldhoven, The Netherlands

Nationaal Medisch Specialisten Forum
Utrecht, The Netherlands

2009

7th half day external neuromodulation workshop,
Guy's & St. Thomas' Hospital, London, United Kingdom

Fellow of Interventional Pain Practice (FIPP),
Lectures, workshops and examination,
World Institute of Pain (WIP), New York, USA

Eerste regionale congres rondom de zorg voor de patiënt met pijnklachten,
Lievensberg ziekenhuis, Bergen op Zoom, The Netherlands

Basiscursus operatieve technieken voor anesthesiologen,
UMC Nijmegen, The Netherlands

XXVIII annual ESRA congress,
Salzburg, Austria

ECMT - Neuromodulation for chronic pain,
Morges, Switzerland

Congres zorglogistiek en zorgpaden "Hoe organiseer ik een zorgpad",
Erasmus MC, Rotterdam, The Netherlands

Dutch Society of Anesthesiologists (NVA) annual meeting
Maastricht, The Netherlands

4th Hands-on interventional workshop - pain relief & neuromodulation,
London, UK

Cadaver workshop: Aperius® PercLid® system,
Leids Universitair Medisch Centrum, Leiden, The Netherlands

11e congres "De Anesthesioloog als pijnbestrijder"
VAVP/NVA, Antwerp, Belgium

Cadaver workshop: Balloonkyphoplasty,
Leids Universitair Medisch Centrum, Leiden, The Netherlands

2010

Introductory Ultrasound Workshop,
Toronto Western Hospital, University of Toronto, Toronto, Canada

Tweede internationale pijncongres: de zorg rondom pijnklachten,
Bergen op Zoom, The Netherlands

Dutch Society of Anesthesiologists (NVA) annual meeting,
Maastricht, The Netherlands

ICU update on intoxication,
Bergen op Zoom, The Netherlands

2011

Symposium "Twee handen op één hart",
Eindhoven, The Netherlands

Imperial Spine Course,
London, UK

Ultrasound for Pain Medicine,
Toronto, Canada

II Peripheral neuromodulation masterclass,
London, UK

2012

ESRA cadaver workshop - Neural blockades on cadavers,
Innsbruck, Austria

26th workshop "Ultrasound in Regional Anaesthesia and Pain Therapy"
Vienna, Switzerland

Third biannual international pain congress
Middelburg, The Netherlands

4th International Educational Meeting "Pain from head to toe"
Venice, Italy

Three-day course on Obstetric Anaesthesia and Analgesia
London, United Kingdom

Third international peripheral neuromodulation masterclass
London, United Kingdom

2013

Newborn Life Support Provider Course
Riel, The Netherlands

Dutch Pain Society - van multi naar meer
Ede, The Netherlands

USRA introductory workshop for ultrasound guided nerve blocks
Toronto, Canada

USRA advanced workshop for ultrasound guided nerve blocks
Toronto, Canada

Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)
Rotterdam, The Netherlands

2014

SI-BONE iFuse Implant System – Surgeon training
Bergen op Zoom, The Netherlands

Flowonix Prometra system (training)
Bergen op Zoom, The Netherlands

Statistical Package for the Social Sciences (SPSS) intermediate course
The Hague, The Netherlands

Toegepaste statistiek en data-analyse
The Hague, The Netherlands

NVA Anesthesiologendagen 2014
Maastricht, The Netherlands

Annual London Spine Course
London, United Kingdom

Fourth biannual International Multidisciplinary Pain Congress
Eindhoven, The Netherlands

2015

XIII meeting of the London Pain Forum
London, United Kingdom

Interprofessional Pain Care Symposium
Amsterdam, The Netherlands

Interprofessional Pain Care Symposium
London, United Kingdom

ISURA 2015
Rotterdam, The Netherlands

2016

1st International Spinal Analgesic Drug Delivery symposium
Dublin, Ireland

NVA Pijndagen
's-Hertogenbosch, The Netherlands

2017

Advances in Pain Medicine, Winter Symposium
Tignes, France

Lectures & presentations

2007

Sandwichdagen Werkgroep Deskundigheidsbevordering Huisartsen,
Golden Tulip hotel, Bergen op Zoom, The Netherlands

Locoregionale anesthesie voor carotischirurgie,
IJsselland ziekenhuis, The Netherlands

2008

 "Pijnbestrijding bij patiënten met kanker"
Bergen op Zoom, The Netherlands

2009

Pijnbestrijding in de palliatieve zorg
Werkgroep Deskundigheidsbevordering Huisartsen,
Hotel "Green & White", Serooskerke, The Netherlands

Kennis en Kunde over Palliatie (KOP-cursus)
Golden Tulip hotel, Bergen op Zoom, The Netherlands

 "Pijnbestrijding bij patiënten met kanker"
Bergen op Zoom, The Netherlands

2010

Kennis en Kunde over Palliatie (KOP-cursus)
Meeting point Braakmanzicht, Biervliet, The Netherlands

 "Pijnbestrijding bij patiënten met kanker"
Bergen op Zoom, The Netherlands

2011

"Pijnbestrijding bij patiënten met kanker"
Bergen op Zoom, The Netherlands

Bedside teaching for general physicians
Bergen op Zoom, The Netherlands

2012

Making a diagnosis (Low Back Pain workshop)
3rd biannual International Pain Congress
Middelburg, The Netherlands

Training session "Pijnbestrijding bij patiënten met kanker" (oncology training)
Bergen op Zoom, The Netherlands

Minimal interventional & invasive treatment: expectations & facts
4th International Educational Meeting "Pain from head to toe"
Venice, Italy

2013

Bedside teaching for general physicians
Bergen op Zoom, The Netherlands

Neuromodulation in the case of multiple sclerosis ("neuromodulatie bij MS")
"Landelijke dag MS verpleegkundigen"
Apeldoorn, The Netherlands

Pain medicine at the annual meeting of medical officers
Bergen op Zoom, The Netherlands

2014

Multidisciplinary treatment for low back pain
"Fysiovakcongres"
Hoevelaken, The Netherlands

2015

Spinal analgesic drug delivery
Interprofessional Pain Care symposium
Amsterdam, The Netherlands

Evidence based interventional pain management
Interprofessional Pain Care symposium
London, United Kingdom

The case for intrathecal drug delivery in pain management
Interprofessional Pain Care symposium
London, United Kingdom

2016

Presentation "Pijngeneeskunde" at Rotary
Etten-Leur, The Netherlands

Presentation "Minimally invasive treatment of lumbar spine related pain disorders" at the Dutch Society of Anesthesiology annual scientific meeting
Rotterdam, The Netherlands

Presentation "Pijnklachten bij Whiplash" at the Dutch Whiplash Foundation
Houten, The Netherlands

2017

Evidence based low back pain management
Advances in Pain Medicine, Winter Symposium
Tignes, France

Management of pain after Whiplash injury
Advances in Pain Medicine, Winter Symposium
Tignes, France

Intrathecal analgesic drug delivery
Advances in Pain Medicine, Winter Symposium
Tignes, France

Scientific output

ORCID ID 0000-0002-6689-9499

2000

van Tilburg CWJ, Schoonderbeek J, van der Hoven B. Relaparotomie bij intra-abdominale sepsis op de intensive care afdeling: indicaties en prognose. *NTvIC* 2000;15:270-7.

2001

van Tilburg CWJ, van der Hoven B. Intrapleurale fibrinolyse op de intensive care afdeling. *NTvIC* 2001;16:21-8.

2005

van Tilburg CWJ, De Jongh K, Vercauteren M, Hoffmann V. A comparison of the posterior and lateral approach to the sciatic nerve in the popliteal fossa. Best free paper, *XXIV annual ESRA congress*, Berlin.

2016

van Tilburg CW, Schuurmans FA, Stronks DL, Groeneweg JG, Huygen FJ. Randomised sham-controlled double-blind multicenter clinical trial to ascertain the effect of percutaneous radiofrequency treatment for sacroiliac joint pain: three month results. *Clin J Pain* 2016;32:921-6.

van Tilburg CW. Spinal analgesic drug delivery for Ehlers-Danlos hypermobility type chronic pain treatment: a case report. *J Pain Relief* 2016;5:235.

van Tilburg CW, Stronks DL, Groeneweg JG, Huygen FJPM. Randomised sham-controlled double blind multicenter clinical trial to ascertain the effect of percutaneous radiofrequency treatment for lumbar facet joint pain. *Bone Joint J* 2016;98-B:1526-33.

van Tilburg CW, Stronks DL, Groeneweg JG, Huygen FJPM. Predictive validity of lumbar X-ray images and MRI's for chronic low back pain subtypes. *Submitted*.

van Tilburg CW. Intrathecal Analgesic Drug Delivery is Effective for Analgesia in a Patient with Post-Poliomyelitis Syndrome: A Case Report. *Am J Case Rep* 2016;17:957-62.

2017

van Tilburg CW, Stronks DL, Groeneweg JG, Huygen FJ. Randomized sham-controlled double blind multicenter clinical trial on the effect of percutaneous radiofrequency at the ramus communicans for lumbar disc pain. *Eur J Pain* 2017;21:520-9.

van Tilburg CW, Stronks DL, Groeneweg JG, Huygen FJPM. Inter-rater reliability of diagnostic criteria for sacroiliac joint -, disc - and facet joint pain. *J Back Musculoskelet Rehabil* 2017;30:551-7.

van Tilburg CW, Groeneweg JG, Stronks DL, Huygen FJPM. A case series study of the effectiveness of balloon kyphoplasty in patients with painful vertebral compression fractures. *Submitted.*

Diploma's and certificates

2002

Leraar Martial Arts A
Federatie Oosterse Gevechtskunsten
Amsterdam, The Netherlands

2008

Diploma stralingsbescherming deskundigheidsniveau 4A/M
Leidschendam, The Netherlands

2009

Fellow of Interventional Pain Practice (FIPP)
World Institute of Pain (WIP)
New York, United States of America

ESRA European Diploma in Regional Anaesthesia & Acute Pain
Management (EDRA)
Genoa, Italy & Salzburg, Austria

2010

Dutch Society of Anesthesiologists (NVA) certificate Anesthesioloog-pijnspecialist
Utrecht, The Netherlands

2013

Basiscursus Regelgeving en Organisatie voor Klinisch onderzoekers (BROK)
Rotterdam, The Netherlands

Organisational (non-)hospital work and management

2007–2013

Building an integrated pain medicine service
Bergen op Zoom, The Netherlands

2009

Regional congress "De zorg voor de patiënt met pijnklachten",
Bergen op Zoom, The Netherlands

2010

Second international congress "De zorg rondom pijnklachten",
Bergen op Zoom, The Netherlands

2011

World Institute of Pain - Excellence in Pain Practice (EPP) award
Bergen op Zoom, The Netherlands

ISO 9001:2008 certification – multidisciplinary pain centre
Bergen op Zoom, The Netherlands

2012

Third biannual International Pain Congress,
Middelburg, The Netherlands

2013

Optimising the Preoperative Screening Unit
Bergen op Zoom, The Netherlands

Designing Nerfact (initial stage) – expert electronic system for
multidisciplinary pain management
Halsteren, The Netherlands

2014

ISO 9001:2008 recertification – multidisciplinary pain centre
Bergen op Zoom, The Netherlands

Fourth biannual International Multidisciplinary Pain Congress
Eindhoven, The Netherlands

Designing Nerfact (final stage) – expert electronic system for multidisciplinary
pain management
Halsteren, The Netherlands

2015

Organising the Interprofessional Pain Care symposium
Amsterdam, The Netherlands

Organising the Interprofessional Pain Care symposium
London, United Kingdom

Organising ISURA 2015
Rotterdam, The Netherlands

2016

Organising the 1st International Intrathecal Analgesic Drug Delivery
symposium

Dublin, Ireland

Designing and constructing Pain – and neuromodulation centre Excellent
Klinieken
Dordrecht & Meierijstad, The Netherlands

Organising the ultrasound workshop at the NVA Pijndagen
's-Hertogenbosch, The Netherlands

2017

Organising the Evolution of Pulsed Radiofrequency (PRF) symposium
Amsterdam, The Netherlands

Companies

van Tilburg Holding BV / Kokoro Anaesthesia BV (fiscal unity)
Chamber of commerce: 20160279 / 20160285

Kokoro Pain Management BV
Chamber of commerce: 66511305

Nervita Holding BV / Nerfact BV (fiscal unity)
Chamber of commerce: 58010475 / 58010785

Stichting Excellent Klinieken
Chamber of commerce: 67176771

Excellent Klinieken BV
Chamber of commerce: 68719655

Stichting Wetenschappelijk Onderzoek Excellent Klinieken
Chamber of commerce: 68717628

Painways Medical Events BV
Chamber of commerce: 68728352

Miscellaneous

2001

van Tilburg CWJ: Ninpo, een leidraad. Uitgeverij van Tilburg, Steenbergen, februari 2001, ISBN 90-806269-1-0.

2002

Leraar Martial Arts A,
F.O.G., Amsterdam, The Netherlands