Treatment of osteoporotic vertebral compression fractures

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ISBN: 978-94-6108086-8

Cover Dr. M. Sluzewski
Lay-out Karin van Rijnbach
Printed by Gildeprint drukkerijen, Enschede, The Netherlands

Publication of this thesis was financially supported by:
COOK Medical
Raad van Bestuur Medisch Spectrum Twente
Maatschap Radiologie Medisch Spectrum Twente

Treatment of osteoporotic vertebral compression fractures

Behandeling van osteoporotische wervelfracturen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Utrecht
op gezag van de rector magnificus, prof. dr. J.C. Stoof
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen
op vrijdag 12 november 2010 des middags te 2.30 uur

door

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geboren op 7 april 1977 te Berkel-Enschot

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The research described in this thesis was supported by a grant from the Netherlands Organisation of Health Research and Development (ZonMW) and COOK Medical

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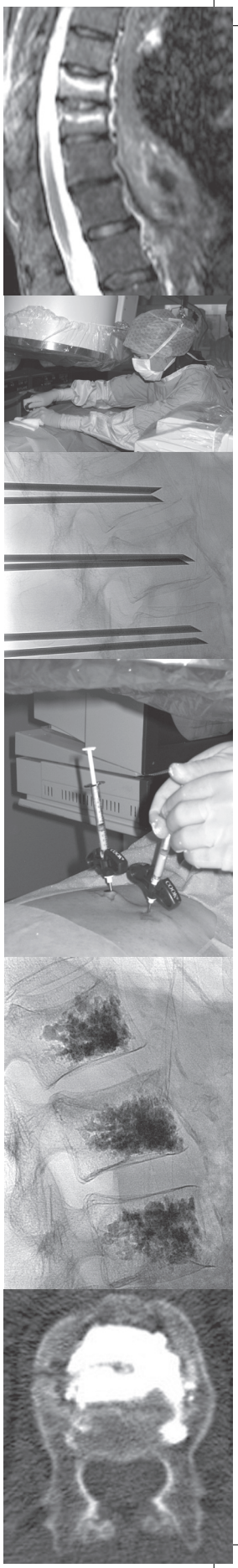
Chapter 1

Introduction



Introduction

Osteoporotic Vertebral Compression Fractures

Vertebral compression fractures (VCFs) following osteoporosis are common in the elderly population with an estimated 1.4 million clinically new VCFs worldwide annually [1]. About one third of new VCFs come to medical attention, suggesting that most VCFs are either asymptomatic or with tolerable symptoms [2]. Patients with an acute VCF can present with severe back pain that can last for weeks to months. The percentage of patients with chronic pain due to an osteoporotic VCF assumed in literature is 10%-20%[3, 4]. However, valid evidence is lacking. In **Chapter 2** we prospectively determined the natural course of pain in patients with conservatively treated acute osteoporotic vertebral compression fractures. Indications and timing of percutaneous vertebroplasty (PV) may depend on the natural course of an osteoporotic VCF

Treatment of Osteoporotic Vertebral Compression Fractures

Differential diagnosis of pain from an osteoporotic VCF includes myalgia, degenerative disease and a herniated disc. Anamnesis, physical examination and Magnetic Resonance Imaging (MRI) of the spine are needed to differentiate between these causes. Pain due to an osteoporotic VCF is mostly a focal, sharp pain at the level of the VCF and at adjacent regions, typical during movement and on physical exercise. A herniated disc typically presents with radiculair pain. A VCF can be simply diagnosed on a plain spine radiograph. However, MRI is needed to discriminate between old, healed VCFs and subacute, non-healed VCFs. In non-healed VCFs bone edema is present in the vertebral body [5]. When MRI is contraindicated, a bone scintigram should be performed to demonstrate activity in the vertebral body and the number of vertebral bodies that are involved[6]. Without a recent MRI or bone scintigram, it is impossible to demonstrate that the vertebral compression fracture is the cause of pain.

Treatment of osteoporotic VCFs is treatment of pain. Until recently, bed rest, analgesia, cast and physical support were the only treatment options for painful VCFs. Bed rest may result in loss of bone density and muscle mass, while braces are often poorly tolerated. In general, osteoporotic VCFs heal within 6-8 weeks. However, some patients develop invalidating chronic pain despite conservative treatment. For these patients, PV was introduced as an adjunct treatment of pain.

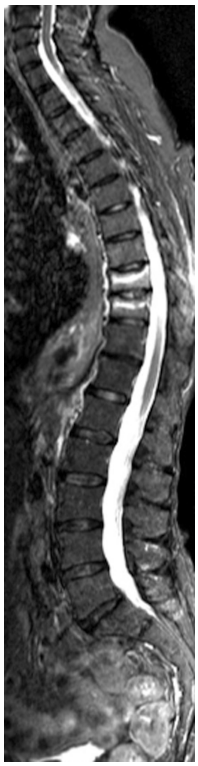


Figure 1. MRI with bone edema of Th10 and Th9.

The injected bone cement agglutinates the microfractures in the vertebral body and as such provides immediate and sustained pain relief.

To prevent new fractures in patients with osteoporosis, adjuvant biphosphonate medication is important. The risk of a second osteoporotic VCF within the first year after a VCF is about 20% [7]. This risk increases with the number and severity of pre-existing osteoporotic VCFs. Bisphosphonates reduce this proportion almost by half [8]

Percutaneous Vertebroplasty

In 1984 PV was developed in France for the treatment of painful aggressive vertebral angioma [9]. In the following years the indication for PV was expanded to vertebral fractures caused by osteoporosis, trauma, malignant or benign vertebral tumors and vertebral osteonecrosis. Presently, PV is most frequently performed to treat patients with painful osteoporotic VCFs.

PV is performed in an angiography suite on a single or biplane angiographic system (Figure 1). Local anaesthesia is infiltrated from the skin to the periosteum of the targeted pedicle. Some patients receive additional intravenous fentanyl during the procedure. Pain management during PV is discussed in **Chapter 8**. Two 11 or 13 Gauge bone biopsy needles are placed transpedicular in the fractured vertebral body. Polymethylmetacrylate bone cement is injected through the bone biopsy needles under continuous fluoroscopic monitoring to timely identify local cement leakage and cement migration into the venous system towards the lungs. Patients can be mobilized several hours after the procedure. Post procedural care consists of physiotherapy, osteoporosis medication and additional pain medication if necessary.

Clinical results of Percutaneous Vertebroplasty

Since its introduction, this minimally invasive technique has received widespread recognition with effective pain reduction both on short- and long-term [10-19].

A recent systematic literature review suggest effectiveness of PV in terms of pain relief [19]. However, the included prospective and retrospective follow-up studies do not comprise control groups to compare with. The VERTOS I study randomized a small group of patients with a subacute VCF and found immediate pain relief and improved mobility on short-term follow-up [20]. The study was terminated early due to many crossovers.

Recently, two randomized studies using a sham control intervention reported on clinical outcome one [21] and six [22] months after PV in patients with osteoporotic VCF up to one year old. Both studies seem to indicate that PV and sham treatment are equally effective. However, clinical interpretation of these studies is hampered by including also patients with subacute and chronic fractures instead of only acute fractures, lack of a control group without intervention, not using bone edema on MRI as a consistent inclusion criterion, lack of specific physical examination and some other methodological problems [23, 24].

We designed an open-label randomized controlled trial (VERTOS II) to clarify whether PV has additional value compared with optimal pain treatment in a well defined group of patients with acute VCFs. Study rationale, objectives and design are described in **Chapter 3**. In **Chapter 4** the main outcomes of the VERTOS II study are analysed: pain relief, cost-effectiveness, quality of life and function.

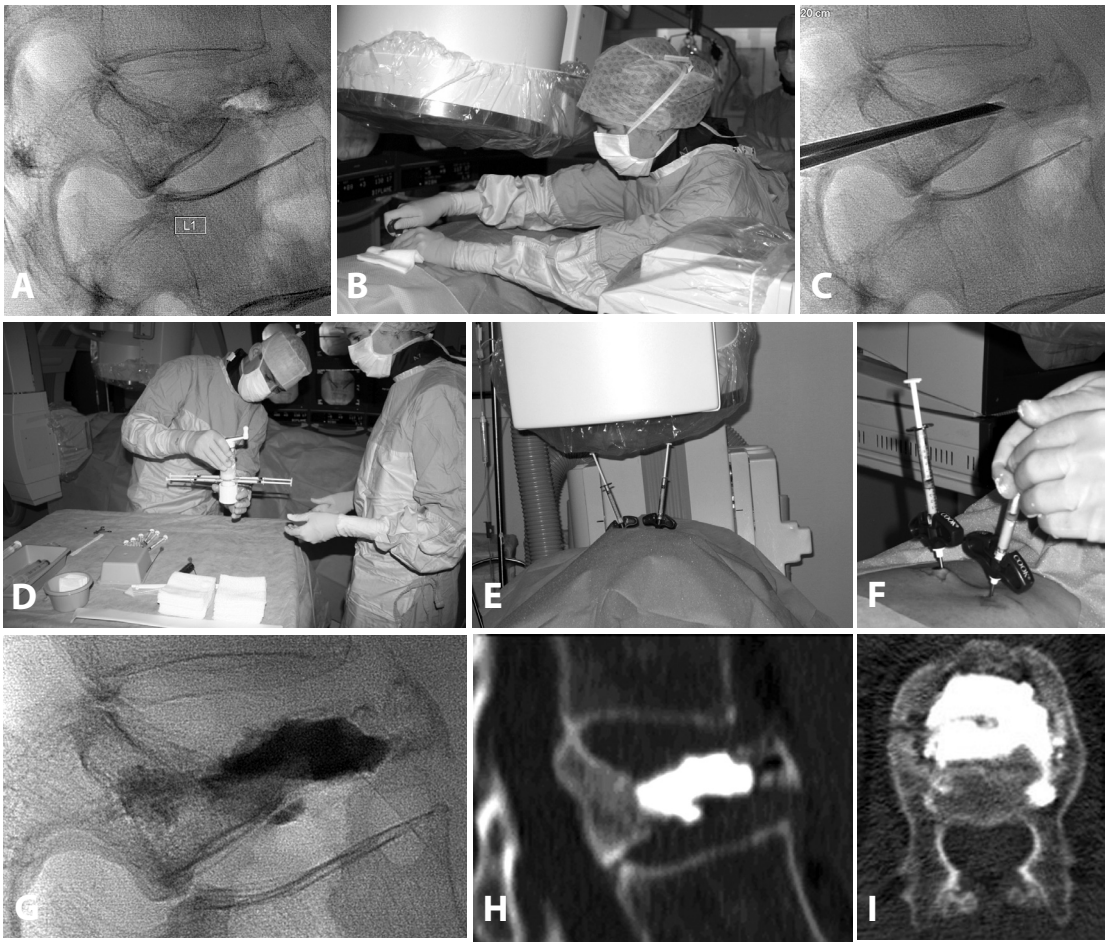


Figure 2. PV Procedure
a. vertebral fracture L1. **b**.needle placement under fluoroscopic guidance. **c**. two transpedicular needle are placed. **d**. mixing cement and filling 1cc syringes. **e**. syringes with cement are placed on the needle. **f**. cement injection. **g**. cement in the vertebral body. **h** and **i**. CT of the treated vertebral body.

Adverse effects of Percutaneous Vertebroplasty

Controversy exists as to whether PV increases the risk for new VCFs during follow-up. In **Chapter 5** we assessed the incidence of new VCFs in patients with acute VCFs randomized to PV and conservative therapy. In addition, we assessed further height loss of the treated vertebral bodies with both therapies.

Cement leakage after PV outside the vertebral body is frequently detected. Most leakages are into adjacent disks or segmental veins and most patients are asymptomatic. However, radiculopathy, myelopathy and pulmonary cement

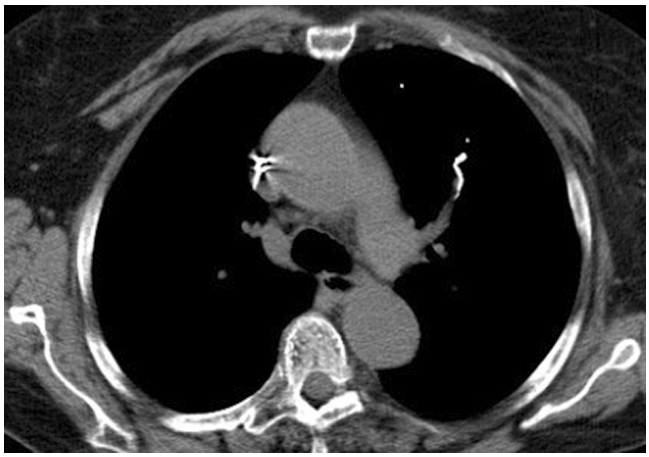


Figure 3. Pulmonary cement embolus in the left pulmonary artery.

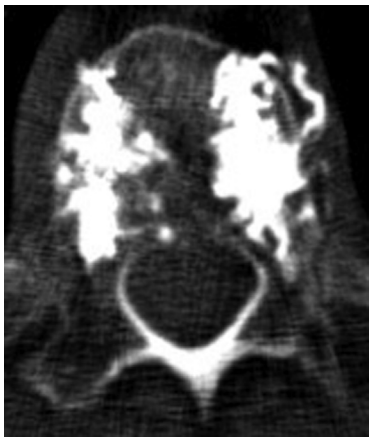


Figure 4. Cement leakage in a segmental vein

embolism (Figure 3) is occasionally reported [19]. In **Chapter 6** we assessed the true incidence of pulmonary cement embolism during follow-up in a large proportion of patients from the VERTOS II trial. We used baseline and follow-up CT to assess the incidence, anatomical location, and clinical impact of perivertebral cement leakage on short- and long-term in a large patient cohort; these results are described in **Chapter 7**.

In the general discussion, **Chapter 9**, the overall findings are placed in a larger perspective. A summary of the results of this thesis is presented in **Chapter 10**.

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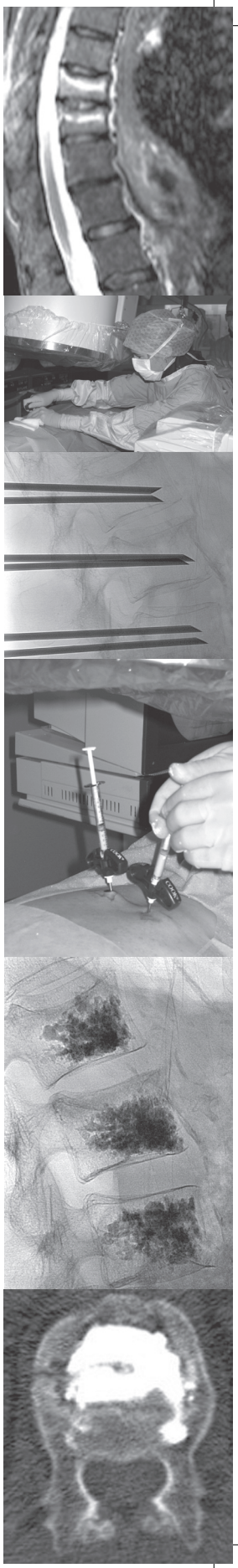
Chapter 2



Clinical course of pain in acute, osteoporotic vertebral compression fractures

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JVIR 2010;21:1405-1409

Abstract

Objective: The authors prospectively determined the natural course of pain in patients with conservatively treated acute osteoporotic vertebral compression fractures (VCF). In addition, the type of conservative therapy that these patients received was assessed.

Materials and Methods: Patients over 50-years-old, referred for spine radiography for acute back pain were asked to complete a baseline clinical questionnaire. Patients with an acute VCF were followed at 6 and 23 months with a questionnaire that included a Visual Analog Score (VAS) and type of pain medication and other conservative treatment. Significant pain relief was defined as a decrease in VAS-score of 50% or more.

Results: Forty-nine patients (mean age, 78 years; range 51-95) with acute VCF were followed up for almost 2 years. Significant pain relief was noted in 22 of 35 patients (63%) at 6 months and in 25 of 36 (69%) at 23 months. In patients with persisting pain at 23 months (mean VAS score 6.4), some decrease in VAS score was apparent at 6 months but not in the 6-23 months interval. No predictors for significant pain relief could be identified. Patients with significant pain relief used less pain medication and had less physical therapy.

Conclusions: In most patients with an acute VCF, pain decreases significantly with conservative therapy, predominantly in the first 6 months. However, almost 2 years after an acute VCF, a third of patients still had severe pain necessitating pain medication and physical therapy in the majority. No predictors for transition from acute to chronic pain could be identified.

Introduction

Due to the increasing age of the population, osteoporotic fractures are becoming an important health concern. Patients with osteoporosis more frequently fracture a vertebral body, proximal femur, distal radius or proximal humerus. The most common site is the vertebral body [1;2]. A vertebral compression fracture (VCF) is associated with an increased incidence of mortality, morbidity and a reduced health status [3]. Only about one third of the patients with a new VCF seeks medical attention [4;5].

The vast majority of patients with an osteoporotic VCF in the Netherlands is treated by the general practitioner with conservative therapy, also called standard care. This may include a range of therapies, such as bed rest, analgesics, physiotherapy, osteoporosis medication, and bracing. However, no information is available on the frequency of various therapies that are placed under the heading 'conservative therapy'.

Minimal invasive techniques, such as vertebroplasty and kyphoplasty are becoming increasingly accepted for a selected group of patients with an acute VCF. Indications for these minimal invasive techniques may depend on the natural course of an osteoporotic VCF. Although solid evidence is lacking, in some studies it is assumed that 10-20% of the symptomatic osteoporotic VCFs will eventually lead to chronic pain [6-8,9,10].

The primary aim of this prospective follow-up study was to determine the natural course of pain in acute osteoporotic VCFs. The secondary aim was to asses the type of conservative therapy given to these patients.

Materials and Methods

Patients

Patients were recruited in two large teaching hospitals (St. Elisabeth Hospital Tilburg and Diakonessenhuis Utrecht) in the Netherlands, between December 2004 and September 2005. Patients aged ≥ 50 years, referred by the general practitioner for a thoracic and/or lumbar spine radiograph, were asked to participate in this study. They received a clinical questionnaire at baseline. Patients with a radiographically diagnosed VCF and back pain for 2 weeks or less were included after written informed consent. Inclusion criteria were: (1) VCF on spine radiograph, (2) age of ≥ 50 years, (3) back pain for two weeks or less and (4) conservative therapy. Exclusion criteria were: (1) clinical and/or radiological suspicion of a pathological fracture (2) minimal invasive therapy (vertebroplasty, kyphoplasty).

Follow-up

At baseline patients reported a Visual Analog Score (VAS), and answered questions regarding the cause of the VCF, duration of symptoms, and use of pain medication. The VAS-score is ranging from 0 (no pain) to 10 (worst pain ever) [6]. The follow-up questionnaires at 6 and 23 months contained a VAS-score, and questions on the type of treatment during the previous period, including pain and osteoporosis medication. The use of pain medication was classified into an ordinal variable [7]: (0) no pain medication, (1) paracetamol (acetaminophen), (2) nonsteroidal anti-inflammatory agents (NSAID), and (3) opiate deratives.
The shape and grade of every VCF was scored using the visual semiquantitative system [8].

Statistical analysis

Changes in pain scores during follow-up were analysed with an ANOVA for repeated measures. Significant pain relief was defined as a decrease in VAS-score of 50% or more [9]. All potential predictors of the VAS-score and significant pain relief were examined using a (stepwise) multiple linear regression model. The possible predicting factors were: age, gender, number of VCFs at baseline, conservative therapy frequencies, grade of VCF, and pain medication.

A logistic regression analysis was performed to find predictors for significant pain relief at 23 months (yes or no). Spearman's rho correlations were calculated between the VAS-score at 6 months and 23 months, and the type of treatment prescribed. All data were analysed with SPSS, version 12.0.1.

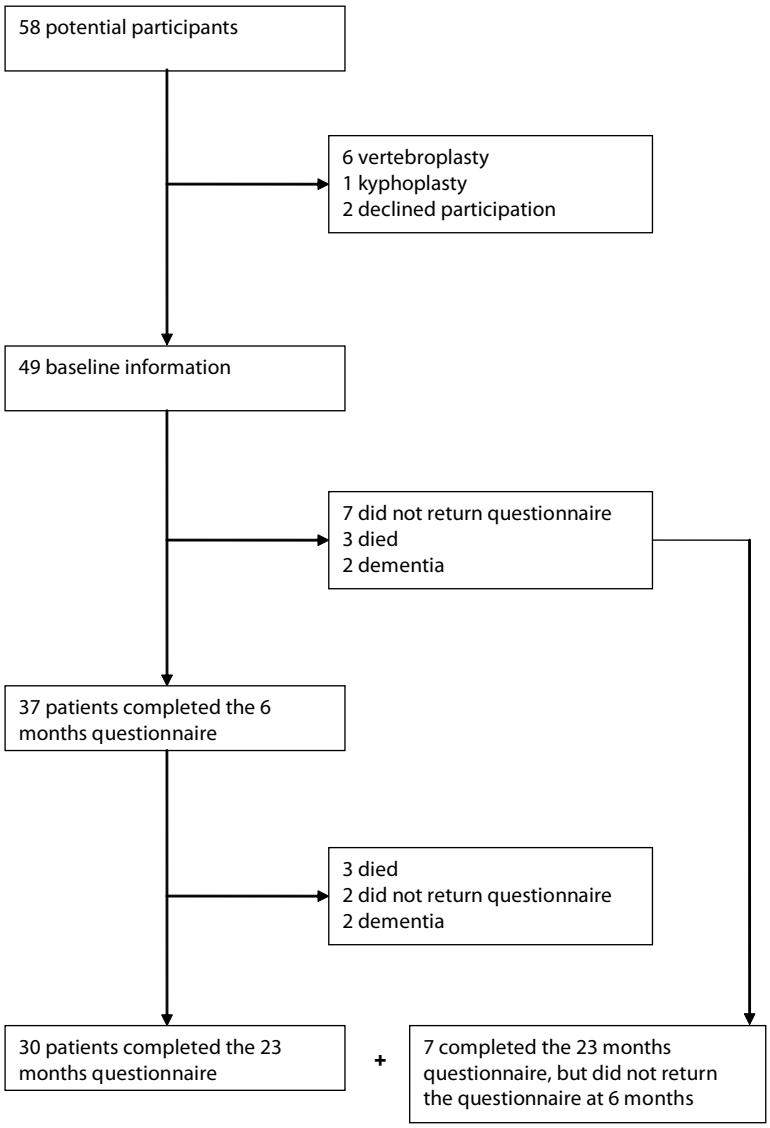

Figure 1. Patient flow diagram.

Results

Of 58 patients that were screened between December 2004 and September 2005, 51 met the inclusion criteria and 2 declined participation. The remaining 49 patients were included in the study (Figure 1). Baseline characteristics of the enrolled patients are summarized in Table 1.

Table 1: Characteristics of patients with pain at baseline for 2 weeks or less. Numbers are mean (range) or absolute (percentage if indicated by (%).

Number of patients	49
Age in years	77.6 (51-95)
Female sex (%)	39 (80%)
Mean duration of pain (days)	7.9 (0-14)
Initial VAS	7.2 (3-10)
Initial pain medication	0.88 (1-3)
Mean number of VCFs	1.8 (1-5)
Distribution of VCFs	Th6-L3
Shape VCF (%)	
- wedge	63 (77%)
- biconcave	19 (23%)
- crush	0
Grade VCF (%)	
- mild	48 (59%)
- moderate	27 (33%)
- severe	7 (9%)
Cause of VCF (%)	
- spontaneous	13 (27%)
- small trauma	31 (63%)
- trauma	5 (10%)

Changes in VAS- scores

At baseline the mean VAS-score was 7.2 ±2.5. Figure 2 shows a significant decrease in pain scores at 6 months ($F=24.48$, $p<0.001$). Between 6 and 23 months no significant decrease in pain scores occurred.

A multiple regression analysis was used to find factors that influence the VAS-score in the total group. None of the baseline factors predicted the VAS-score at 6 months. A high VAS-score at 6 months predicted a higher VAS-score at 23 months ($P<0.001$, $\beta=0.713$, adj. $R^2=0.418$). Also, female patients had a higher VAS-score at 23 months ($P=0.033$, $\beta=0.343$, adj. $R^2=0.098$). At 6 months, we found a correlation between the use of pain medication (yes or no) (rho= 0.579, $P<0.001$), and class of pain medication, with the VAS-score at 6 months (rho= 0.610, $P<0.001$). Patients with a high VAS-score at 6 months, used pain medication more often and they also used a higher class of pain medication. At 23 months, the same correlation was found between VAS-score and use of pain medication (rho= 0.685, $P<0.001$) and class of

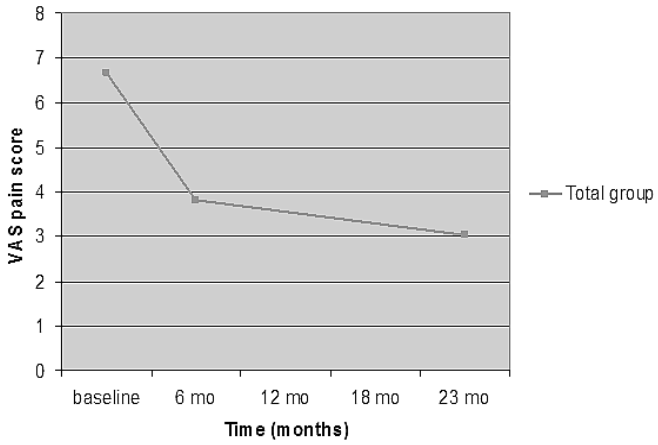

Figure 2. VAS-score in time for the total group.

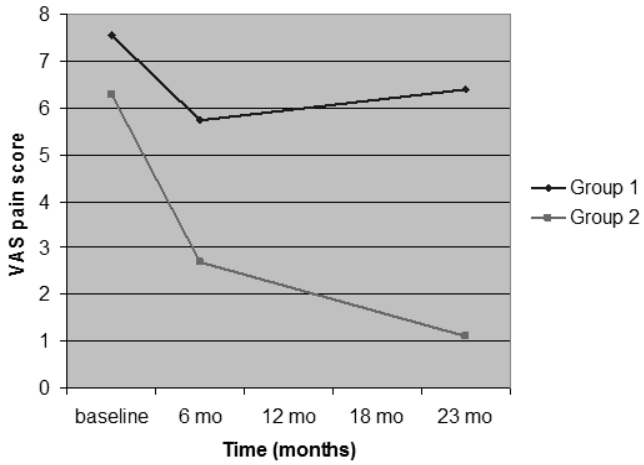

Figure 3. VAS-score in time. Group 1 had no significant pain relief at 23 months. Group 2 did have significant pain relief at 23 months.

pain medication (rho= 0.489, P=0.002). We also found a correlation between VAS-score at 23 months and physiotherapy (rho= 0.464, P=0.004). Physiotherapy was prescribed more often in patients with a high VAS-score.

Significant pain relief

After 6 months, 63% of patients with a VCF had significant pain relief (Figure 4). After 23 months, this percentage was 69%. So, almost two years after an acute VCF, 31% of the patients did not have significant pain relief.

Table 2: Total group: treatment of an acute, osteoporotic VCF in patients. Numbers are absolute or percentage if indicated by (%).

Treatment	Baseline	6 months	23 months
Pain medication	32 / 49 (65%)	11 / 35 (31%)	9 / 36 (25%)
Physiotherapy	9 / 49 (18%)	13 / 36 (36%)	4 / 37 (11%)
Brace	1 / 49 (2%)	3 / 36 (8%)	1 / 37 (3%)
Bed rest	2 / 49 (4%)	2 / 36 (6%)	0 / 37 (0%)
Osteoporosis medication			16 / 33 (48%)
Orthopedic surgeon		3 / 36 (8%)	0 / 36 (0%)
Neurologist		3 / 36 (8%)	0 / 36 (0%)
Anesthesiologist		0 / 36 (0%)	1 / 36 (3%)
Internist		3 / 36 (8%)	1 / 36 (3%)

None of the baseline factors predicted significant pain relief at 6 or 23 months.
A correlation was found between significant pain relief and pain medication. Patients with significant pain relief at 6 months, used pain medication less often (rho= -0.361, P=0.036) and a lower class (rho= -0.412, P=0.015). At 23 months, the same correlation was found (respectively, rho= -0.587, P<0.001 and rho= -0.640, P<0.001). Patients with no significant pain relief at 23 months were treated more often with physiotherapy (rho= 0.533, P=0.001).

Subsequently, we divided the patients in two groups, group 1 had no significant pain relief at 23 months, and group 2 had significant pain relief at 23 months. Figure 3 (F=25.36, P<0.001) shows a rapid decrease in VAS-score during the first 6 months in group 2 (n=25), and the decrease continues slower after 6 months. The osteoporotic VCF healed naturally with conservative treatment only. Group 1 (n=11) had a small decrease in VAS-score within the first 6 months, and thereafter there was even an increase in VAS-score. Group 1 contains patients suffering from chronic pain. The pattern of VAS-score in time was significantly different between both groups (F=8.84, P=0.001). None of the baseline factors predicted group membership. Only a high VAS-score at 6 months predicted no significant pain relief at 23 months with conservative therapy (OR=0.524, 95% CI= 0,293-0,938, P=0.030).

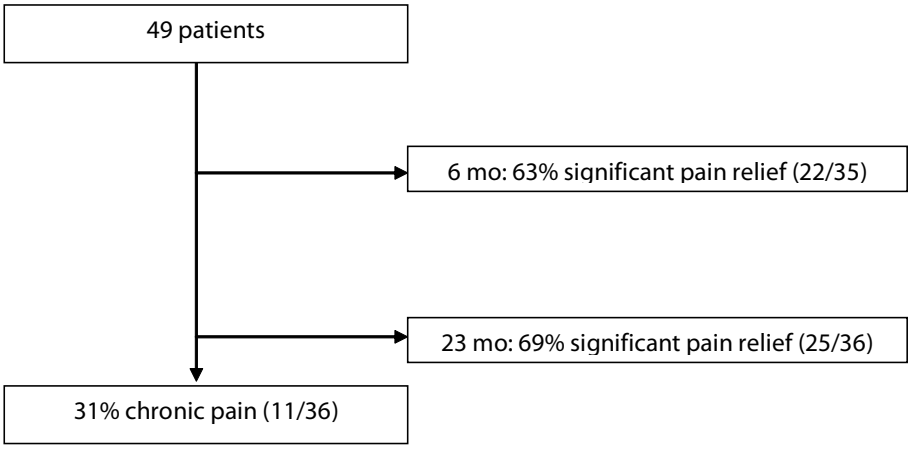

Figure 4. Significant pain relief (decrease in VAS pain score ≥ 50%) over time

Conservative therapy

All patients were treated by the general practitioner. Table 2 shows the type of treatment patients received from their general practitioner for the acute, osteoporotic VCF. Pain medication was the most frequent treatment of a painful, osteoporotic VCF. After 23 months, 25% of the patients still used pain medication (Table 2). Most of these patients belonged to group 1, 64% of patients in this group used pain medication at 23 months. Physiotherapy was prescribed in 36% of patients, also more often in patients in group 1. Bed rest and a brace were only prescribed in very few patients. Noteworthy was the low percentage of patients that received medication to treat the osteoporosis, only 48%. Remarkable is that most patients (73%) in group 1 received osteoporosis medication and only 38% in group 2.

A very limited number of patients (19%) was referred to a specialist (internist, orthopedic surgeon, neurologist). An overview of the specialists, these few patients were referred to, is shown in Table 2.

Discussion

The largest decrease in pain scores was within the first 6 months. After 6 months no significant decrease in pain scores was noted. A high VAS-score at 6 months predicted a high VAS-score at 23 months. In our study, 37% of the patients had no significant pain relief at 6 months.

The tendency of an osteoporotic VCF to heal within the time frame of six months was also described in an other study [10;11]. In this study, all patients presenting on the emergency department or admitted as inpatients, with an acute osteoporotic VCF, were offered a vertebroplasty. Patients, who declined, received conservative treatment and formed the control group. They showed a reduction in pain scores in the control group (n=38) of 80% after 6-12 months and 85% after 2 years. This percentage is a mean decrease in VAS-scores, with no information about the percentage of patients who experienced significant pain relief. A second study included patients who suffered from recent (<21 days), osteoporotic VCFs and randomized them to receive daily intravenous infusions of either placebo or 30 mg pamidronate for three consecutive days[12]. A decrease in VAS-scores of only 2.2 points (on a scale of 0-10) was reported within the first three days in the placebo group (n=16), and this remained stable during the total follow-up of 30 days. Thirty-eight percent of the patients reported significant pain relief after one month.

A third study divided patients with an acute, osteoporotic VCF and follow-up for 18 months in 2 types: type I had a fully collapsed vertebral body and type II had a mild VCF[13]. These two groups matched two different clinical types. Type I had pain for a rather short duration (4-8 weeks). Type II had less pain at baseline, but the pain lasted longer due to multiple attacks of acute pain. Unfortunately, the VAS-score in time was not exactly described and a group with chronic pain was not mentioned.

Almost a third of our patients had no significant pain relief after two years. This group may be considered to have chronic pain due to an osteoporotic VCF. This percentage is higher than the 10%-20% assumed in most other studies [14-16]. We could not find earlier studies that examined significant pain relief. We believe that the percentage of patients with chronic pain due to an acute VCF is higher than the assumed percentage in literature. However, a larger follow-up study is needed to assess this percentage more precisely. None of the baseline factors could predict the outcome, in terms of pain relief.

Conservative therapy by the general practitioner in patients with an acute, osteoporotic VCF mainly consisted of pain medication and, to a lesser extent, physiotherapy. Patients with no significant pain relief at 23 months used pain medication more often and a higher class. Also physiotherapy was prescribed more often in these patients. Bed rest and brace were only prescribed occasionally. Bed rest may result in loss of bone density and muscle mass, while braces are often

poorly tolerated. After almost two years, less than half of all the patients used medication for osteoporosis. In group 1, 73% of the patients received treatment for their osteoporosis, but in group 2 this percentage was only 38%. The difference in osteoporosis treatment between group 1 and 2 was almost significant (p=0.059) and could be explained by the difference in the course of pain. Patients with chronic pain might visit the general practitioner more often and therefore the general practitioner has more opportunity's to prescribe the medication. Osteoporosis medication is very important in preventing new vertebral fractures. The risk of a second osteoporotic VCF within the first year after a VCF is 20% [17]. The risk increases with the number and severity of pre-existing osteoporotic VCFs. Medication for osteoporosis (bisphosphonates) reduces this percentage almost by half [18]. In the Netherlands, the treatment of an acute osteoporotic VCF is in the hands of the general practitioner. Only a very limited number of patients are referred to a specialist. It seems that an important decision is taken on the moment of the spine radiograph, within two weeks after the start of the pain. None of the 49 patients we followed received a vertebroplasty or kyphoplasty during the 23 months follow-up.

There is no consensus in the literature about the best timing for minimal invasive techniques. Knowledge about the natural course of an osteoporotic VCF may help to estimate the best timing for these techniques. Based on the results of our study, it seems justified to perform a vertebroplasty or kyphoplasty if pain persists at six months after the onset of pain due to a VCF. However, we do not have information about the first six months. Waiting six months in all patients can cause unnecessary pain and lost days from work and normal activity, when treatment with vertebral augmentation can provide almost immediate pain relief.

Our study has some limitations. All patients were diagnosed with an osteoporotic VCF based on spine radiography. No physical examination, magnetic resonance imaging (MRI), or bone densitometry was performed to support the diagnosis. Sometimes, it is difficult to distinguish between other causes of back pain, such as degenerative disease, spinal stenosis, facet arthropathy, sacroiliac joint dysfunction, and muscular pain. To reduce the risk of including patients with other causes of back pain than a VCF, we only analysed patients with acute back pain, for two weeks or less. Another limitation was the lack of follow-up imaging, to detect new events. However, no clinical evident new events were reported during follow-up. The natural course could be described more precisely if we had more follow-up moments, especially within the first 6 months.

In conclusion, the natural fracture healing, in terms of pain relief, of an acute, osteoporotic VCF mainly took place within the first 6 months. In view of the high percentage (31%) of patients with chronic pain due to an acute VCF with conservative therapy only, minimal invasive techniques should be considered. In the Netherlands, conservative treatment mainly consists of pain medication and physiotherapy and is prescribed by the general practitioner.

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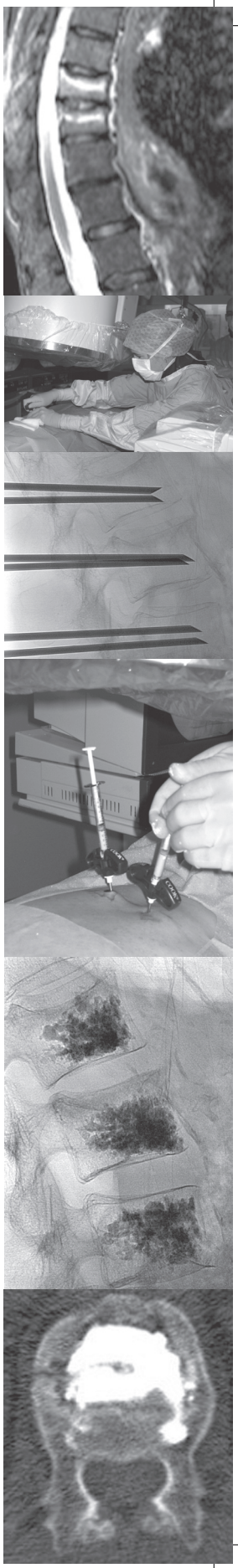
Chapter 3



VERTOS II: Percutaneous vertebroplasty versus conservative therapy in patients with painful osteoporotic vertebral compression fractures; rationale, objectives and design of a multicenter randomized controlled trial

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TRIALS 2007;8:33

Abstract

Background: The standard care in patients with a painful osteoporotic vertebral compression fracture (VCF) is conservative therapy. Percutaneous vertebroplasty (PV), a minimally invasive technique, is gaining popularity as a new treatment option. Many prospective and retrospective studies have reported on the effectiveness and safety of PV, but no large randomized controlled trial (RCT) has been published.

Objective: To estimate cost-effectiveness of PV compared to conservative therapy in terms of: pain reduction, quality of life, complications, secondary fractures and mortality.

Materials and methods: The VERTOS II study is designed as a prospective, multicenter RCT. Patients with a painful VCF with bone edema on MR imaging, local back pain for 6 weeks or less, osteopenia and aged 50 years or older, after obtaining informed consent are included and randomized for PV or conservative therapy. In total 200 patients will be enrolled. Follow-up is at regular intervals during a 1-year period with standard questionnaires, addressing: clinical symptoms, pain medication, Visual Analogue Scale (VAS) score, quality of life and cost-effectiveness. Secondary fractures, necessary additional therapies and complications are recorded.

Conclusion: The VERTOS II study is the first methodologically sound RCT designed to assess the cost-effectiveness of PV compared to conservative therapy in patients with an acute osteoporotic VCF.

Trial registration: ClinicalTrials.gov

Introduction

Because of an aging population osteoporosis and associated fractures are becoming an important health issue, especially in Western societies. The incidence of a new vertebral compression fracture (VCF) in Europe is, at age 50-79 years, 1% per year in women and 0,6% per year in men and at age 75-79 years the incidence is 2,9% per year in women and 1,4 % per year in men [1]. VCFs are associated with an increased incidence of mortality and morbidity, including back pain, loss of height, kyphotic deformity and a reduction in quality of life (QOL) [2].

Conservative therapy, bed rest, pain medication, physiotherapy and bracing, is considered the standard care in patients with symptomatic osteoporotic VCFs. Since the introduction of percutaneous vertebroplasty (PV) this minimal invasive therapy has gained popularity to stabilize osteoporotic VCFs and subsequently relief of associated local back pain. Despite the apparent lack of evidence, nowadays PV is considered an accepted therapy in many centres and acknowledged as a useful additional option in the care for these patients,

In 1984 PV was developed in France for the treatment of painful aggressive vertebral angioma [3]. In the following years the indications for PV were expanded to vertebral fractures caused by osteoporosis, trauma, malignant or benign vertebral tumors and vertebral osteonecrosis. Presently, PV is most frequently performed to treat patients with painful osteoporotic VCFs.

Numerous prospective and retrospective studies on PV have been published and described a high clinical success rate [4-12]. A recent systematic literature review demonstrated the effectiveness of PV in 87% of patients in terms of pain relief as well as a short- and long-term improvement of function [13]. However, these studies did not have a control group to compare with. In fact we do not know what would have been the natural course of pain in similar patients with a VCF. Only two non-randomised controlled trials have been published comparing PV with conservative therapy [14,15]. Both studies demonstrated a significant better improvement in pain scores after PV compared to conservative therapy on the short-term. However, after 6 months no differences could be demonstrated. Thus, the question on the balance between costs and effects becomes all the more pregnant.

VERTOS, the first randomized controlled trial (RCT) with a limited group of 34 patients reports only on short-term results [16]. Longer term results could not be obtained due to the cross-over of many patients from the optimal pain medication (OPM) group to the PV group already after two weeks follow-up. VERTOS confirmed immediate pain relief and improvement of mobility, function and stature after PV. The short-term results after PV were significantly better compared to OPM in these patients with sub-acute or chronic osteoporotic VCFs.

The development of new VCFs after PV in patients with osteoporosis is, in addition to pain relief and function, another important issue. It remains unclear whether PV is associated with a higher risk of secondary VCFs in adjacent vertebral bodies. Some authors believe in an increased risk of new VCFs after PV compared to the natural fracture incidence in osteoporosis, probably initiated by the increased stiffness of the cementated vertebral body [17-19]. The non-randomized study by Diamond reported no significant difference in the risk of new VCFs between PV and conservative therapy [14].

Even now, after decades of performing PV no large RCT with mid-term follow-up has been published. Therefore, the VERTOS II study, a new RCT, was initiated to compare PV with conservative therapy in patients with osteoporotic VCFs.

Material and methods

Objectives

To estimate cost-effectiveness of PV compared to conservative therapy in terms of: pain reduction, QOL, complications, secondary fractures and mortality.

Study design

VERTOS II is a multicenter RCT concerning the treatment of patients with a painful osteoporotic VCF. Patients are randomized to: (i) conservative therapy consisting of OPM, osteoporosis medication, physiotherapy or bracing; or (ii) PV with osteoporosis medication and analgesics, if necessary. Upon obtaining informed consent an independent central telephone operator completes the randomisation procedure, using a computer programme. The maximum allowed unbalance (block size) is six, with a maximum sample size of 84 for each participating centre. A total of 200 patients will be enrolled, 100 in each group. The enrolment of patients

takes place in five centres: four centres in The Netherlands (St. Elisabeth Hospital Tilburg, University Medical Centre Utrecht, Diakonessenhuis Utrecht / Zeist / Doorn, Catharina Hospital Eindhoven) and one in Belgium (AZ St. Lucas Hospital Gent). Randomization started November 2005 with an expected completion of enrolment by March 2008. There is a one-year follow-up, with the possibility of an extended follow-up at two years. At present a total number of 111 patients is included.

The overall Institutional Review Board approval was obtained at the St. Elisabeth Hospital in Tilburg. Each participating centre also obtained a local Institutional Review Board Approval. This study was registered in September 2005 at ClinicalTrials.gov [20].

Patients

All patients, 50 years of age or older, visiting the hospital for an X-ray of the thoracic and/or lumbar spine, receive a short clinical questionnaire. Patients diagnosed with a VCF (Th5-L5), pain for six weeks or less and a Visual Analogue Scale (VAS) score of five and higher are contacted to participate in the study.

After informed consent patients undergo a magnetic resonance imaging (MRI) scan of the spine, bone densitometry, blood sample screening and will visit the internist.

All patients enrolled in the study comply with the following inclusion criteria: (1) VCF on X-ray of the spine (minimal 15% loss of height), (2) level of VCF Th5 or lower, (3) back pain ≤ 6 weeks at time of X-ray, (4) ≥ 50 years of age, (5) bone edema on MRI of the fractured vertebral body, (6) focal tenderness on VCF level and (7) decreased bone density T-scores ≤ -1. The exclusion criteria are: (1) severe cardio-pulmonary condition, (2) untreatable coagulopathy, (3) systemic or local infection of the spine (osteomyelitis, spondylodiscitis), (4) indication of alternative underlying disease (malignancy) and (5) radicular and/or myelum compression syndrome. All patients contacted to participate in the study are registered in order to obtain an overview of the total patient population.

MRI protocol

MRI is performed in all patients prior to randomization using a 1 or 1,5 Tesla MRI scanner. The following MRI sequences are employed: sagittal T1 (TR 400 ms, TE 13 ms), T2 Turbo Spin Echo (TR 3500 ms, TE 120 ms) and STIR (TR 2500 ms, TE 70 ms)

and transverse T2 TSE (TR 2500 ms, TE 120 ms) at the level of the affected VCF. Bone edema in the VCF is defined as increased signal intensity at the STIR images and decreased signal intensity at the T1 weighted images. The shape and grade of every VCF is scored by two radiologists using the visual semiquantitative system according to Genant [21]. When there is disagreement between both observers a consensus meeting is held. The shape of the VCF is classified as wedge, biconcave or crush, depending on whether anterior, middle or posterior portion of vertebral body is most diminished in height. The grade of VCF is classified as a percentage of height reduction in mild (15-25%), moderate (25-40%) and severe (>40%).

Percutaneous vertebroplasty group

The pre-procedural work-up consists of: ECG, X-thorax and blood sampling. One hour prior to the procedure 2 g cefazolin is administered intravenously as prophylaxis.

All vertebroplasties are performed by experienced radiologists in the angio suite under optimal (anteroposterior and lateral) fluoroscopic guidance. The procedure takes place under sterile conditions. Local anaesthesia is administered from skin to the periosteum of the targeted pedicle. In two centres patients also receive fentanyl intravenously prior to the procedure. In one centre patients get propofol as intravenous anaesthetic.

Polymethylmetacrylate bone cement (Osteo-Firm®, COOK Medical, Bloomington, Indiana, USA) is injected under continuous fluoroscopic imaging guidance using 1,0 cc syringes and 11 or 13 Gauge bone biopsy needles. The amount of injected cement in each treated vertebral body and any cement leakage is recorded. After the procedure a computed tomography (CT) scan of the treated vertebral bodies is performed to identify cement leakage or other possible local complications.

All patients are put on osteoporosis medication, such as bisphosphonates together with supplemental calcium and vitamin D.

Conservative therapy group

Conservative therapy mainly consists of OPM. The internist optimizes the use of analgesics in ascending order: (1) Paracetamol (acetaminophen), (2) Tramadol, (3) Tramadol and Paracetamol, (4) Morphine. Non Steroid Anti Inflammatory Drugs (NSAID) are only prescribed if patients are intolerant for opiate-derivatives or in situations when already used. Corrections in dose and classification of pain

medication are made if necessary by the internist. In most cases physiotherapy is prescribed. All patients receive osteoporosis medication, such as bisphosphonates together with supplemental calcium and vitamin D.

Clinical follow-up

All patients are asked to fill out standard questionnaires before and at one day, one week, one month, three months, six months and twelve months after PV or when conservative treatment is started by the internist.

All standard questionnaires (except the questionnaire after one day) consist of the VAS score, QOL Questionnaire of the European Foundation for Osteoporosis (Qualeffo), EQ-5D, Roland Morris Disability (RMD) Questionnaire. Cost-effectiveness is assessed and questions concerning use of pain medication, pain location, pain type are included.

The VAS score is a pain score ranging from 0 (no pain) to 10 (worst pain ever) [22]. The Qualeffo is developed specifically for patients with osteoporosis [23]. This questionnaire consists of 41 questions about: pain, physical function, social function, general health perception and mental function. The Qualeffo score ranges from 0 (best quality of life) to 100 (worst quality of life).

The RMD questionnaire is a disability questionnaire that measures the functional status of patients with back pain [24,25].

EQ-5D is a standardized instrument utilized as a measure of health related quality of life outcome [26]. Furthermore, EQ-5D is one of a few measures recommended for use in cost-effectiveness analyses by the Washington Panel on Cost Effectiveness in Health & Medicine as well as in National guidelines in economic evaluation [27].

Procedural costs, other medical treatment and visits to alternative medical specialists, GP's and physical therapists are recorded and compared between groups. The questionnaire at day one post-procedural is a short questionnaire with a VAS score and questions about pain medication use, pain location, pain type and cost-effectiveness. All patients visit the internist at one and three months follow-up. All patients receive a pain diary. Patients are asked to fill out the VAS score and use of analgesics is recorded on a daily basis up until one month after randomization.

Imaging follow-up

At one, three and twelve months follow-up an X ray of the thoracic and lumbar

spine, including antero-posterior and lateral views, is performed and compared to the X-ray at baseline. Secondary fractures are recorded. The shape and grade of every VCF is scored by two radiologists using the visual semiquantitative system according to Genant [21]. When there is disagreement between both observers a consensus meeting is held.

Sample size considerations

Based on pilot data and literature we expect a difference of 25% in significant pain relief. If we assume that 20% withdraws from intervention we need approximately 100 patients in each group (α=0.05 and ß=0.20).

Statistical analysis

The data will be analysed according to the intention-to-treat principle. Standard statistical techniques will be used to describe characteristics of patients in both groups. We will compare base-line characteristics in the two treatment groups and if incomparability appears, we will in secondary analysis adjust for differences. The main outcome, significant pain relief will be compared with the Kaplan Meier survival analysis. Adjustment for possible baseline incomparability will be done with the Cox proportional hazards model.

A cost-effectiveness analysis will be performed at four weeks and one year. Medical costs, time without burdensome pain and quality adjusted survival time will be compared. Bootstrapping and in case long-term modelling is required for comprehensive evaluation multivariate probabilistic sensitivity analysis will be used to evaluate uncertainty in the cost-effectiveness ratios.

Conclusion

To the best of our knowledge the VERTOS II study is the first consistent RCT designed to assess the cost-effectiveness of PV compared to conservative therapy in patients with an acute osteoporotic VCF with mid-term follow-up.

Competing interests

The author(s) declare that they have no competing interests.

Acknowledgements

Participants of the VERTOS II study group are: The Netherlands: Tilburg: St. Elisabeth Hospital: P Lohle, L Lampmann, M Schoemaker, J Juttmann, M Voormolen

(presently in Antwerp, Belgium), J van de Laar, C Klazen. Utrecht: University Medical Centre: W Mali, H Verhaar, Y van der Graaf, E Buskens*, T Lo, G de Kort, M Versloot. Diakonessenhuis: K van Everdingen, A. Muller, M Deelen. Eindhoven: F Jansen, A Tielbeek, M Blonk, M Vos. Belgium: Gent: AZ St. Lucas Hospital; H Fransen, X Janssens, R de Meester.
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Financial support for this study was provided by the Netherlands Organisation for Health Research and Development (ZonMW, number: 945-06-351) and by a grant from COOK Inc.

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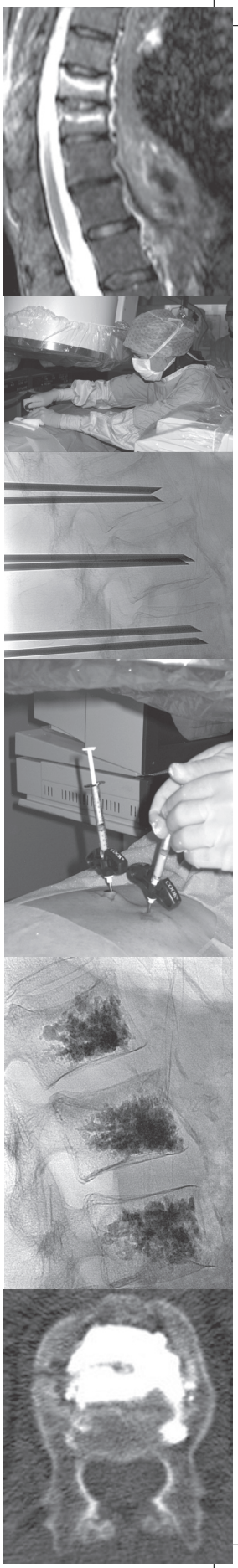
Chapter 4



Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (VERTOS II): an open-label randomised trial

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Lancet 2010;376:1085-1092

Summary

Background: Percutaneous vertebroplasty is increasingly used for treatment of pain in patients with osteoporotic vertebral compression fractures, but the efficacy, cost-effectiveness, and safety of the procedure remain uncertain. We aimed to clarify whether vertebroplasty has additional value compared with optimum pain treatment in patients with acute vertebral fractures.

Methods: Patients were recruited to this open-label prospective randomised trial from the radiology departments of six hospitals in the Netherlands and Belgium. Patients were aged 50 years or older, had vertebral compression fractures on spine radiograph (minimum 15% height loss; level of fracture at Th5 or lower; bone oedema on MRI), with back pain for 6 weeks or less, and a visual analogue scale (VAS) score of 5 or more. Patients were randomly allocated to percutaneous vertebroplasty or conservative treatment by computer-generated randomisation codes with a block size of six. Masking was not possible for participants, physicians, and outcome assessors. The primary outcome was pain relief at 1 month and 1 year as measured by VAS score. Analysis was by intention to treat. This study is registered at ClinicalTrials.gov number NCT00232466.

Findings: Between Oct 1, 2005, and June 30, 2008, we identified 431 patients who were eligible for randomisation. 229 (53%) patients had spontaneous pain relief during assessment, and 202 patients with persistent pain were randomly allocated to treatment (101 vertebroplasty, 101 conservative treatment). Vertebroplasty resulted in greater pain relief than did conservative treatment; difference in mean VAS score between baseline and 1 month was –5·2 (95% CI –5·88 to –4·72) after vertebroplasty and –2·7 (–3·22 to –1·98) after conservative treatment, and between baseline and 1 year was –5·7 (–6·22 to –4·98) after vertebroplasty and –3·7 (–4·35 to –3·05) after conservative treatment. The difference between groups in reduction of mean VAS score from baseline was 2·6 (95% CI 1·74–3·37, p<0·0001) at 1 month and 2·0 (1·13–2·80, p<0·0001) at 1 year. No serious complications or adverse events were reported.

Interpretation: In a subgroup of patients with acute osteoporotic vertebral compression fractures and persistent pain, percutaneous vertebroplasty is effective and safe. Pain relief after vertebroplasty is immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment, at an acceptable cost.

Introduction

Vertebral compression fractures in osteoporosis are common in the elderly population, with an estimated 1·4 million new fractures occurring every year worldwide.[1] About a third of new fractures come to medical attention, suggesting that most are either asymptomatic or have tolerable symptoms.[2] Patients with an acute vertebral fracture can present with severe back pain lasting for weeks to months. Until recently, bed rest, analgesia, and cast and physical support were the only treatment options. Vertebroplasty, involving percutaneous injection of bone cement into the fractured vertebral body, was introduced as an alternative option for treatment of pain. Since its introduction, this minimally invasive technique has gained widespread recognition, effectively reducing pain both in the short and long term.[3-12] Two randomised studies with a sham control intervention have reported clinical outcomes 1 month and 6 months after percutaneous vertebroplasty in patients with osteoporotic vertebral fractures up to a year old.[13,14] Results of both studies seem to show that vertebroplasty and sham treatment are equally effective. However, clinical interpretation of these studies is hampered by inclusion of patients with subacute and chronic fractures instead of acute fractures, absence of a control group without intervention, inconsistent use of bone oedema on MRI as an inclusion criterion, and other methodological issues.[15] We aimed to clarify whether percutaneous vertebroplasty has additional value compared with optimum pain treatment in a well defined group of patients with acute vertebral compression fractures.

Methods

Study design and patients

The methods of this study, including the protocol, patient selection, and clinical outcome measures, have been described in detail elsewhere;[16] in this Article, we mainly report on evolution of pain and cost-effectiveness of vertebroplasty. In short, we undertook an open-label randomised controlled trial in five large teaching hospitals in the Netherlands and one in Belgium. Patients were recruited at the radiology departments of the participating centres. All patients aged 50 years or older who were referred by their general practitioner for spine radiography because of back pain were asked to complete a short questionnaire about presence, severity, and duration of pain by a nurse practitioner. Inclusion criteria were: vertebral compression fracture on spine radiograph (minimum 15%

height loss); level of fracture at Th5 or lower; back pain for 6 weeks or less; visual analogue scale (VAS) score of 5 or more; bone oedema of vertebral fracture on MRI; focal tenderness at fracture level, as assessed by an internist on physical examination; and decreased bone density (T scores ≤–1). Exclusion criteria were: severe cardiopulmonary comorbidity; untreatable coagulopathy; systemic or local spine infection; suspected underlying malignant disease; radicular syndrome; spinal-cord compression syndrome; and contraindication for MRI. Eligible patients were contacted and requested to consider participation in the study. Patients who agreed to participate were referred to an internist who reassessed complaints, took an additional VAS score, and obtained written informed consent. The study protocol was approved by the institutional review board at each participating centre.

Procedures

Patients were randomly allocated to percutaneous vertebroplasty or conservative treatment by an independent central telephone operator using computer generated randomisation codes with a block size of six. Masking was not possible for participants, physicians, and outcome assessors. Percutaneous vertebroplasty was done on a single or biplane angiography system under fluoroscopic guidance. After local infiltration analgesia, two 11 or 13 gauge bone-biopsy needles were placed transpedicularly in the fractured vertebral body. Polymethylmetacrylate bone cement (Osteo-Firm, COOK Medical, Bloomington, IN, USA) was injected through bone-biopsy needles under continuous fluoroscopic monitoring to identify local cement leakage or migration into the venous system towards the lungs. When necessary, additional analgesia was used at the discretion of the treating physician. In patients who had more than one fracture with bone oedema on MRI, all vertebral bodies were treated in one or more procedures. After the procedure, a CT scan of the treated vertebral bodies was done with 2 mm slices to identify cement leakage outside the vertebral body or other possible local complications.

Patients were clinically assessed at baseline (the day of vertebroplasty or, in patients assigned to conservative treatment, the day of randomisation), and at 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year afterwards. Throughout follow-up, analgesia in both groups was individually tailored in a stepwise manner from non-opiates to weak opiate derivatives and strong opiate derivatives. Pain

treatment was categorised according to WHO classification as 0 (no drugs), 1 (non-opiates—eg, paracetamol, nonsteroidal anti-inflammatory agents), 2 (weak opiate derivatives), and 3 (strong opiate derivatives).[17] All patients were prescribed bisphosphonates, calcium supplementation, and vitamin D. Complications and adverse events were recorded. To identify new fractures during follow-up, spine radiographs were done at baseline, 1 month, 3 months, and 1 year. Two radiologists independently undertook morphometric measurements.[18] Disagreements were solved by consensus. A new vertebral fracture was defined as a decrease of at least 4 mm in vertical dimension.[2] Treatment of new vertebral fractures was according to the initial assigned protocol.

The primary outcome was pain relief at 1 month and 1 year, measured with a VAS score ranging from 0 (no pain) to 10 (worst pain ever).[19] We defined clinically significant pain relief as a decrease in VAS score from baseline of 3 points or more. Pain-free days were defined as days with a VAS score of 3 or lower. The secondary outcome was cost-effectiveness at 1 month and 1 year. Medical costs, time without burdensome pain, and quality-adjusted survival time were recorded. Costs were indexed to 2008 (webappendix) and derived from hospital billing systems and costing guidelines issued by the Dutch health insurance board.[20] Quality-adjusted life-years (QALYs) were estimated with the EuroQol-5 dimensions (EQ-5D) questionnaire.[21,22] We assessed uncertainty with respect to the incremental cost-effectiveness ratio using bootstrapping. The tertiary outcome was quality of life measured with the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO),[23] and physical function measured with the Roland Morris Disability (RMD) questionnaire.[24] Standard questionnaires including additional questions about pain treatment, hospital stay, outpatient visits, and medical aids were filled in with the help of a nurse practitioner.

Statistical analysis

On the assumption of a 25% difference in significant pain relief and 20% withdrawals from vertebroplasty, 100 patients were needed in each group (α=0·05 and β=0·20). Endpoints were compared by intention-to-treat analysis. We compared proportions of adverse events, drugs, and baseline fractures using χ^2 tests. p values are two-sided. Differences in mean VAS scores between baseline and 1 month and 1 year were assessed with the paired t test. We used analysis of variance for repeated measures to examine pain relief, quality of life, and physical function over time. Missing data for pain, EQ-5D, QUALEFFO, and RMD scores were imputed with

linear interpolation and last observation carried forward. Imputation of missing data increased the power, but did not affect the results. In concordance with the study protocol, we analysed significant pain relief over time using a Kaplan-Meier survival analysis. We estimated QALYs by calculating the individual area under the curve of the summary score. Imbalances at baseline were adjusted with linear regression analysis. We defined cost effectiveness as the ratio of difference in costs and difference in QALYs and the difference in pain-free days. SPSS (version 15.0.1) was used for all analyses. This trial is registered at ClinicalTrials.gov, number NCT00232466.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. The corresponding author had full access to the data and the final responsibility to submit for publication.

Results

Between Oct 1, 2005, and June 30, 2008, 934 patients were screened for eligibility, of whom 202 were randomly allocated to treatment (101 percutaneous vertebroplasty, 101 conservative treatment). Figure 1 shows the trial profile. Patients allocated to vertebroplasty were treated at a mean of 9·4 (SD 8·1) days after randomisation. Table 1 shows baseline characteristics of both groups. Informed consent was withdrawn after randomisation by six patients assigned to conservative treatment and by two patients assigned to vertebroplasty. Since these patients were not attended in any of the study centres, treatment choice was unknown and follow-up could not be obtained. Six patients assigned to vertebroplasty did not receive the procedure because their health deteriorated before treatment (n=3) or they had spontaneous pain relief (n=3). Follow-up information was obtained for five of these patients. Ten patients assigned to conservative treatment with ongoing invalidating pain requested and received vertebroplasty during follow-up. 163 (81%) participants completed 1 year of follow-up.

98 patients underwent vertebroplasty on 134 vertebrae in 103 procedures that took place a mean of 5·6 weeks (SD 2·9 weeks; range 4–92 days) after onset of symptoms. Mean volume of injected cement per vertebral body was 4·1 mL (SD 1·5; range 1–9). In one vertebral body, the second needle could not be placed properly and cement was injected at one side of the vertebra only. In 31 (30%) procedures,

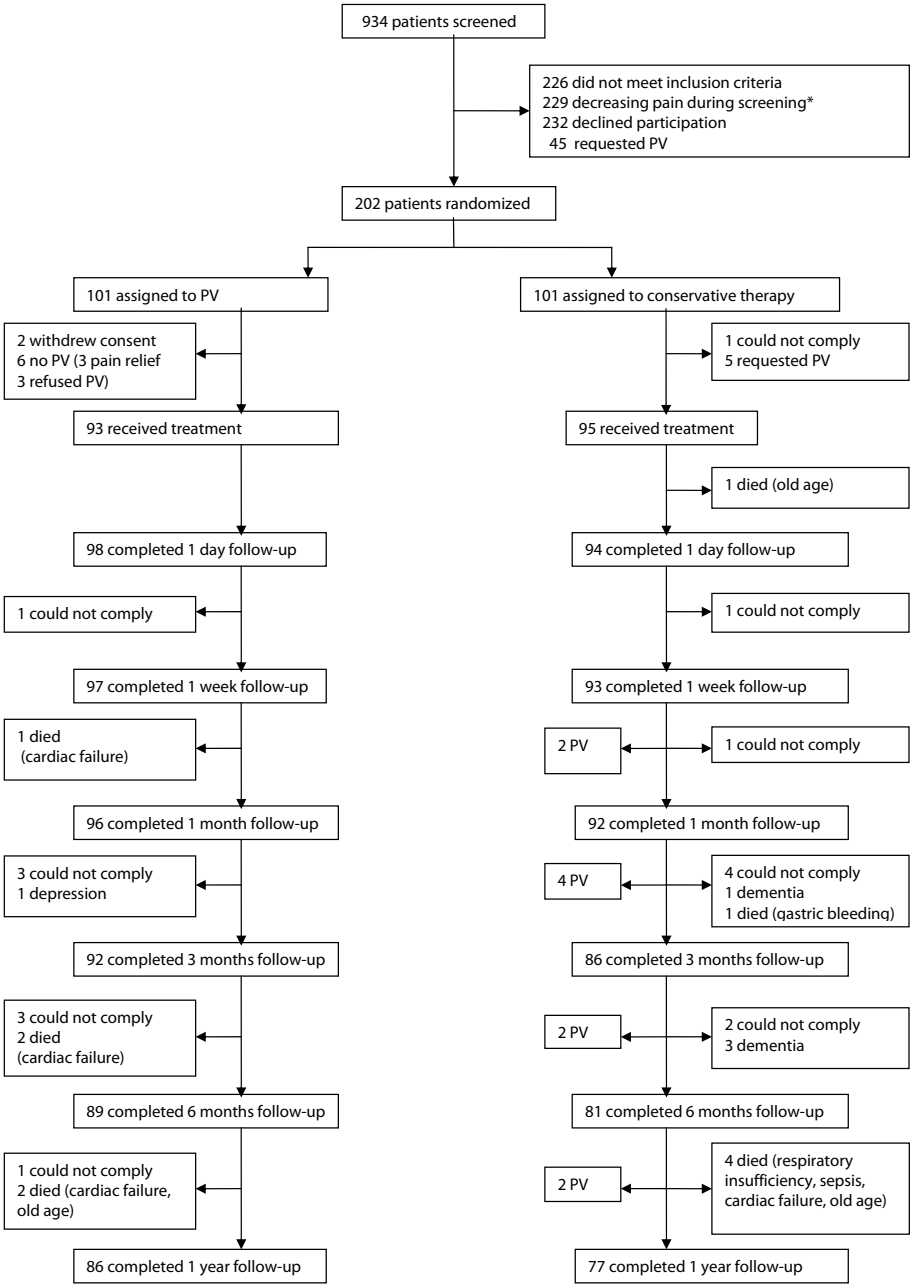

Figure 1. Trial profile.
PV=percutaneous vertebroplasty. *Visual analogue scale lower than 5 at consultation with internist, and thus no longer met inclusion criteria for randomisation.

Table 1: Baseline characteristics.

	Percutaneous vertebroplasty (n=101)	Conservative therapy (n=101)
Age (years)	75.2 (9.8)	75.4 (8.4)
Female sex (%)	70 (69%)	70 (69%)
Duration of back pain (days)	29.3 (17.1)	26.8 (16.0)
Initial VAS score	7.8 (1.5)	7.5 (1.6)
Mean number of VCF at baseline	2.4 (1.9)*	2.1 (1.5)*
Number and grading of VCF with bone edema †		
Mild (10%-20%)	57 (42%)	55 (46%)
Moderate (20%-40%)	58 (43%)	45 (38%)
Severe (> 40%)	21 (15%)	20 (17%)
Wedge	90 (66%)	97 (81%)
Biconcave	46 (34%)	23 (19%)
Crush	0 (0%)	0 (0%)
Initial pain medication		
None	5 (5%)	7 (8%)
Non-opiate drugs	40 (40%)	43 (43%)
Weak opiate derivatives	31 (31%)	22 (22%)
Strong opiate derivatives	19 (19%)	20 (20%)
Vertebral level with bone edema		
Th5-Th10	19 (14%)	32 (25%)
Th11-L2	91 (65%)	66 (52%)
L3-L5	29 (21%)	28 (22%)
Use of osteoporotic drugs	24 (24%)	26 (26%)
Bone density T-score	-3.0 (1.17)	-3.0 (1.05)
EQ-5D score	0.27 (0.03)	0.38 (0.03)
QUALEFFO score	58.7 (13.5)	54.7 (14.4)
Roland Morris Disability score	18.6 (3.6)	17.2 (4.2)

Data are mean (SD) or number (%). VAS=visual analogue scale. VCF=vertebral compression fracture. EQ-5D=EuroQol-5 dimensions. QUALEFFO=Quality of Life Questionnaire of the European Foundation for Osteoporosis. *Range 1-5. †Percentages are proportion of total number of VCFs (136 in percutaneous vertebroplasty group, 120 in conservative treatment group).

patients received additional intravenous analgesia. Two patients required atropine because of pain-induced vasovagal reaction. One patient developed an acute asthma exacerbation during vertebroplasty that led to stopping of the procedure. The procedure was successfully done 1 week later.

CT scanning of the 134 treated vertebral bodies showed cement leakage in 97 (72%). Most leakages were discal or into segmental veins; none were into the spinal canal. All patients remained asymptomatic. Fluoroscopy showed cement migration into the venous system towards the lungs in one patient (1%). This patient also remained asymptomatic and a follow-up chest CT after 1 year showed no perifocal inflammatory pulmonary changes.

After a mean follow-up of 11·4 months (median 12·0, range 1–24), 18 new fractures were reported in 15 of 91 patients treated with vertebroplasty and 30 new fractures in 21 of 85 conservatively treated patients. This difference was not significant (p=0·44). 12 patients refused follow-up radiographs.

Baseline VAS scores were similar in both groups (table 1). Figure 2 shows reduction in VAS score during follow-up in both groups. Decrease in VAS score after vertebroplasty was significantly higher than with conservative treatment at all time points (F=127·5; p<0·001; power 1·0). The improved pain relief after vertebroplasty was apparent from 1 day after the procedure (mean VAS score 3·7 [SD 2·4] vs 6·7 [2·1]; p<0·0001) and remained significant at 1 week (3·5 [2·5] vs 5·6 [2·5]; p<0·0001), 1 month (2·5 [2·5] vs 4·9 [2·6]; p<0·0001), 3 months (2·5 [2·7] vs 3·9 [2·8]; p=0·025), 6 months (2·3 [2·7] vs 3·9 [2·9]; p=0·014), and 1 year (2·2 [2·7] vs 3·8 [2·8]; p=0·014).

After vertebroplasty, the difference in mean VAS score between baseline and 1 month was –5·2 (95% CI –5·88 to –4·72), and between baseline and 1 year was –5·7 (–6·22 to –4·98). After conservative treatment, the difference in mean VAS score from baseline was –2·7 (–3·22 to –1·98) at 1 month and –3·7 (–4·35 to –3·05) at 1 year. The difference between groups in reduction of mean VAS score from baseline was 2·6 (1·74 to 3·37, p<0·0001) at 1 month, and 2·0 (1·13 to 2·80, p<0·0001) at 1 year. Survival analysis showed that significant pain relief (χ^2=55·6, p<0·0001) was achieved earlier and in more patients after vertebroplasty (29·7 days until significant pain relief, 95% CI 11·45–47·97) than with conservative treatment (115·6 days, 95% CI 85·87–145·40; figure 3).

At baseline, the class of drugs used for pain relief was similar in both groups. After vertebroplasty, use of drugs was significantly reduced compared with conservative treatment at 1 day (p<0·0001), 1 week (p=0·001), and 1 month (p=0·033). This difference was not significant at later stages of follow-up. At baseline, a significantly lower EQ-5D score was recorded in the vertebroplasty group than in the conservative treatment group (table 1). This difference had to have been caused by chance. After adjustment for baseline use with regression

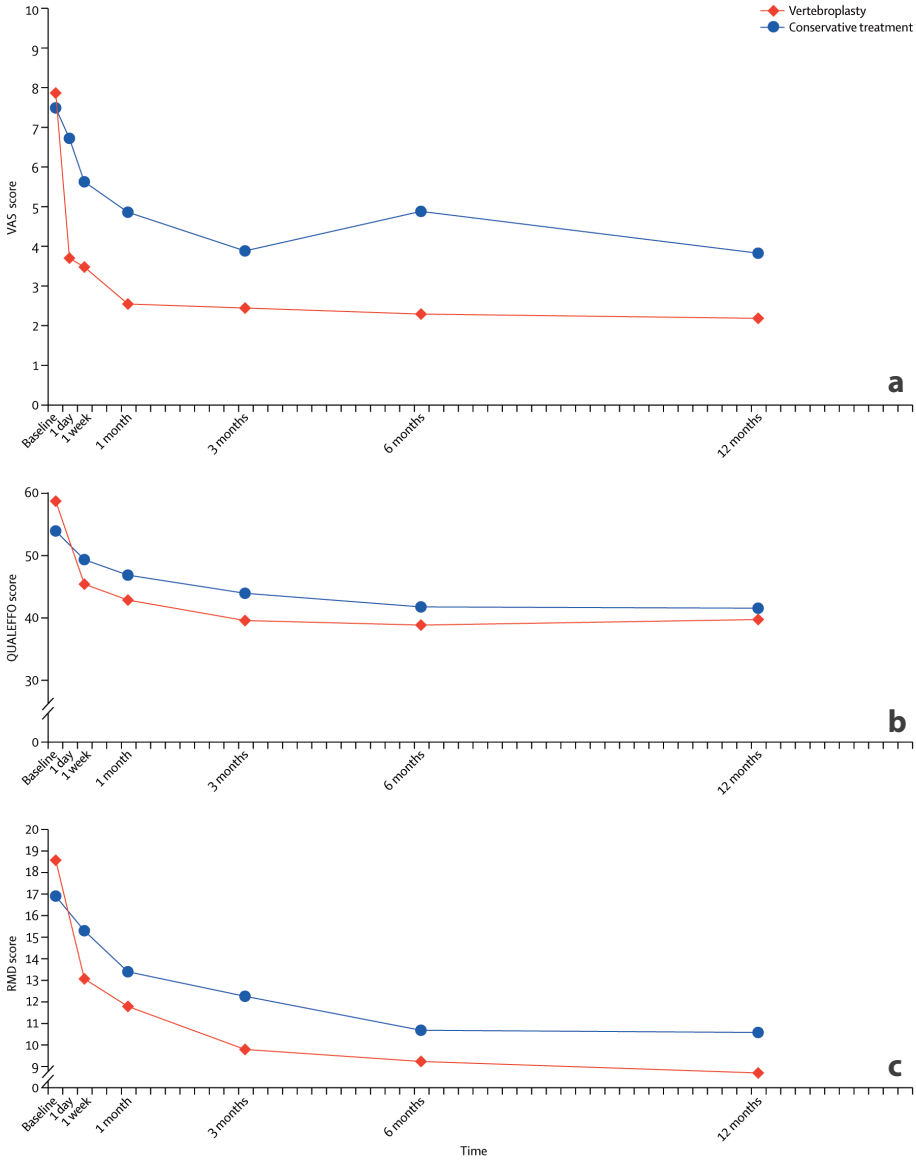

Figure 2. Analysis of variance models for VAS (**a**), QUALEFFO (**b**), and RMD scores (**c**) in vertebroplasty and conservative treatment groups during follow-up. VAS=visual analogue scale. QUALEFFO=Quality of Life Questionnaire of the European Foundation for Osteoporosis. RMD=Roland Morris Disability.

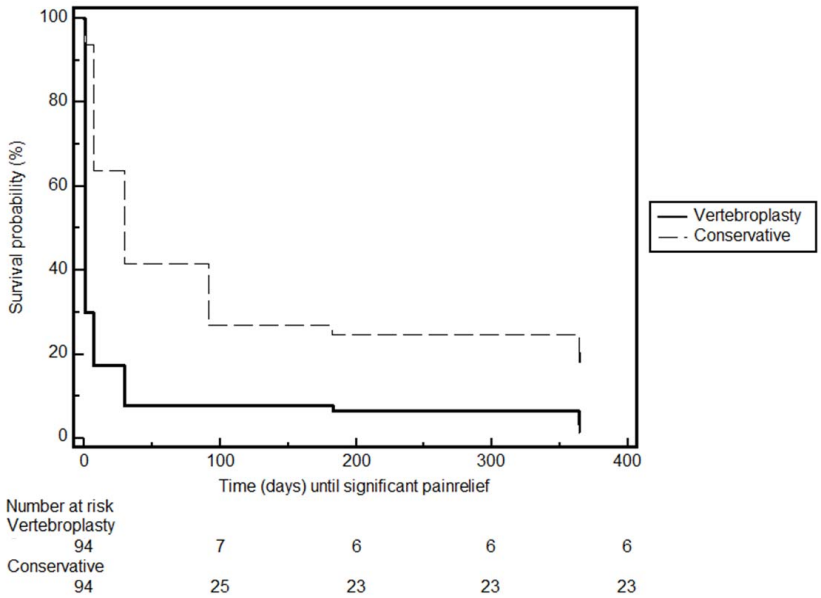

Figure 3. Kaplan-Meier survival curves for significant pain relief in vertebroplasty and conservative treatment groups

analysis, the difference in QALYs favouring the vertebroplasty group was 0·010 (95% CI 0·014–0·006) at 1 month and 0·108 (0·177–0·040) at 1 year. Both QUALEFFO and RMD scores at baseline were significantly worse for vertebroplasty than for conservative treatment (table 1). Improvement with time was significantly greater and quicker after vertebroplasty than with conservative treatment, for both QUALEFFO ($p<0·0001$) and RMD ($p<0·0001$) (figure 2).

The difference between treatments in mean total medical costs per patient was €2474 at 1 month and €2450 at 1 year, in favour of conservative treatment (table 2). The higher costs for vertebroplasty compared with conservative treatment at both intervals were roughly equivalent to the cost of the procedure (€2463). During the first year after vertebroplasty, an average 120·3 (95% CI 163·2–77·4) pain-free days were gained. The cost of one pain-free day gained was €20. The adjusted trial-based incremental cost-effectiveness ratio for vertebroplasty, as compared with conservative treatment, was €22.685 per QALY gained. Incremental costs and effects were adjusted for each bootstrap sample and the adjusted estimates were displayed in a cost-effectiveness plane (figure 4). These results were further processed to yield a cost-effectiveness acceptability curve (figure 4). The curve shows that if society were willing to spend €30 000 or more per QALY gained,

Table 2. Direct medical costs.

Mean Medical Costs	Percutane vertebroplastiek (n=94)	Conservative therapy (n=93)	*P*-value
Drugs, 1 month	€ 24.36 (33.61)	€ 43.51 (50.93)	0.003
Drugs, 1 year	€ 204.88 (368. 47)	€ 280.47 (352.89)	0.15
Family doctor, 1 month	€ 23.40 (49.16)	€ 14.13 (35.70)	0.14
Family doctor, 1 year	€ 970.30 (1167.49)	€ 900.11 (1386.70)	0.70
Medical specialist, 1 month	€ 46.08 (96.56)	€ 68.87 (169.53)	0.25
Medical specialist, 1 year	€ 2263.82 (3220.02)	€ 2138.99 (3558.86)	0.80
Physiotherapist, 1 month	€ 47.77 (71.71)	€ 16.68 (49.18)	0.001
Physiotherapist, 1 year	€ 694.72 (1249.80)	€ 640.69 (1331.45)	0.77
Hospital admission, 1 year	€ 2270.62 (9084.55)	€ 2006.44 (10081.68)	0.85
PV (including MRI spine, CT spine, day-care)	€ 2339.60 (542.34)	€ 233.43 (725.43)	<0.0001
Total costs 1 month	€ 2611.89 (148.07)	€ 383.78 (745.66)	<0.0001
Total costs 1 year	€ 9182.78 (10779.20)	€ 6327.45 (11872.79)	0.087

Data are mean (SD). All patients assigned to Percutaneous vertebroplasty (PV; who received the procedure or not) for whom information about costs were available were included in this analysis. *PV costs appear in both colums because several patients assigned to conservative treatment received PV.

Table 3. Medical costs in The Netherlands indexed to 2008.

	Medical costs (euro) indexed to 2008
MRI spine	€ 211.79
CT spine	€ 106.93
PV (including day-care)	€ 2145.33
Medical specialist consultation	€ 60.02
Family doctor consultation	€ 21.65
Physiotherapist	€ 24.38
Hospital admission	€ 361.20

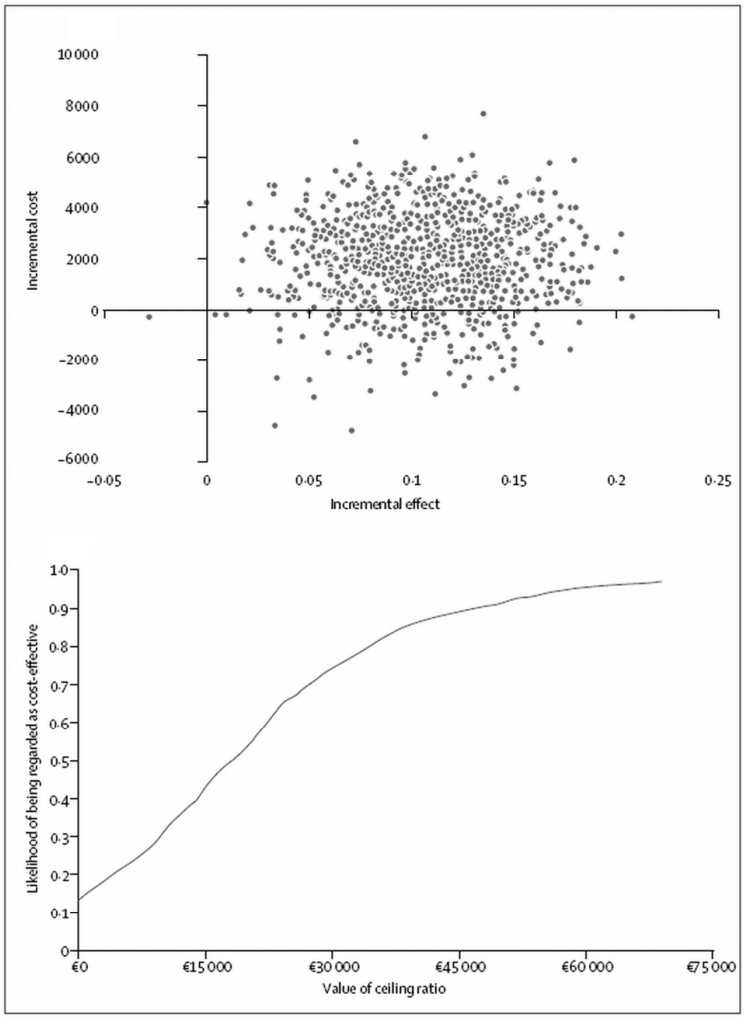

Figure 4. Cost-effectiveness of vertebroplasty compared with conservative treatment.
a. Scatterplot of adjusted point estimates of incremental cost-effectiveness ratios. **b.** Adjusted cost-effectiveness acceptability curve.

vertebroplasty is an acceptable treatment strategy, with more than 70% certainty.

One patient had urinary tract infection after vertebroplasty, and one patient had an asymptomatic cement deposition in a segmental pulmonary artery. 11 patients died of unrelated causes during follow-up: five in the vertebroplasty group and six in the conservative treatment group (figure 1). One patient in the conservative treatment group who died from gastrointestinal bleeding used morphine as their only pain drug.

Discussion

Our results show that in patients with acute osteoporotic vertebral fractures who have persistent severe pain, vertebroplasty done at a mean 5-6 weeks after onset of symptoms resulted in quicker and greater pain relief than did conservative treatment. Notably, in more than half of the patients who initially qualified for the study, pain spontaneously decreased to bearable levels, with a VAS score lower than 5 thereby precluding inclusion. After vertebroplasty, patients had significant pain relief and used a lower class of drugs than did those receiving conservative treatment, or no drugs at all. Pain relief was sustained throughout follow-up. With conservative treatment, pain relief was slower and less than with vertebroplasty, and pain treatment required tended to increase during the first month. Selection of optimum pain treatment and the psychological effect of care and daily attention accounted for the decrease in VAS score in the conservative treatment group during the first week. The Kaplan-Meier survival curve confirmed that significant pain relief was achieved earlier after vertebroplasty than with conservative treatment.

In all patients in both groups, use of analgesic drugs was individually tailored and corrections in dose and class of drugs were made on a day-to-day basis. This strategy implies that the improved pain relief after vertebroplasty compared with conservative treatment is due to the procedure itself, and not to differences in drugs used. The increased pain relief after vertebroplasty remained significant throughout a year of follow-up. This finding is remarkable, since fracture healing in the control group should be completed within several months. However, some patients in the control group developed chronic back pain, possibly because of non-healing of the fracture. Future research could be aimed at identification of these patients. With vertebroplasty, no serious complications occurred. This finding is in line with other studies.[3,12] Minor cement leakage was frequently noted on CT scan, but leakage was asymptomatic in all cases. During follow-up, the incidence of new fractures after vertebroplasty and after conservative treatment was similar. This finding is in concordance with results of some other studies.[3,25]

Incremental costs of vertebroplasty roughly equaled procedural costs, but because of substantial inter-individual variability with time, especially in the control group, the difference was no longer significant at 1 year. We did not include costs of care by family or professionals at home in our analysis. Since these resources are particularly used in case of continued pain and loss of function they will probably play a more important part in the conservative treatment group. Data for costs and cost effectiveness are only valid in the Netherlands and might differ

for other countries. The resulting incremental cost effectiveness suggests that vertebroplasty seemed warranted for the patients with vertebral fractures treated at a mean 5·6 weeks after start of symptoms.

Our study is the first open-label randomised controlled trial with mid-term follow-up to compare vertebroplasty with conservative treatment in patients with acute osteoporotic vertebral fracture. Results of a systematic literature review suggested that vertebroplasty effectively relieved pain;[12] however, the included prospective and retrospective follow-up studies did not include control groups for comparison. Improvements in VAS scores that have been reported previously were in concordance with our results. In the VERTOS I study, a small group of patients with subacute vertebral compression fractures who were randomly allocated to vertebroplasty had immediate pain relief and improved mobility during short-term follow-up.[26] The results were similar to ours, but the study was stopped early because of many crossovers. In our study, only 10% of patients assigned to conservative treatment crossed over to vertebroplasty.

Two randomised studies reported clinical outcomes after vertebroplasty compared with a sham procedure in patients with osteoporotic vertebral compression fractures.[13,14] Improvements in pain and pain-related disability were similar in both groups. The sham controlled studies differed in two important ways from our study. First, we focused on acute fractures, whereas the sham-controlled studies included subacute fractures up to a year old. Second, by contrast with our study, bone oedema on MRI was not a consistent inclusion criterion. These differences might account for the small mean gain in VAS score in the sham-controlled studies compared with both our study and the findings of the 2008 meta-analysis.[12] Apparently, vertebroplasty at a mean 5·6 weeks after onset of symptoms is more effective for pain relief than is treatment up to a year after onset. Finally, the sham-controlled studies did not have a control group without intervention, and the best treatment option remains unclear for the clinician. Our study compared vertebroplasty with the reference treatment and thus provides the clinician with directly applicable information about how to best treat the patient.

The FREE study[25] compared kyphoplasty with nonsurgical care in 300 patients with acute vertebral compression fractures. Instead of direct cement injection into the vertebral body, as in vertebroplasty, kyphoplasty involves use of an inflatable bone tamp that forms a space in the vertebral body into which cement can be injected. This method is regarded to be in competition with percutaneous vertebroplasty. The design of the FREE study was similar to that of our study, with kyphoplasty

used instead of vertebroplasty. Kyphoplasty had a similar favourable effect on pain relief as did vertebroplasty in our study, with rapid and sustained improvement. Also, pain relief in conservatively treated patients was in the same range. An advantage of vertebroplasty is that the procedure can be done on an outpatient basis with local analgesia, whereas kyphoplasty requires general anaesthesia and hospital admission.[27] Additionally, kyphoplasty can generate procedural costs that are up to 20 times higher than those of vertebroplasty.[28]

The main drawback of our study was that treatment could not be masked. Knowledge of the treatment assignment might have affected patient responses to questions or radiologist assessments. Time needed for planning of vertebroplasty resulted in mean delay of 9 days until start of treatment compared with conservative treatment. We believe that this small difference in natural course was unlikely to have affected outcomes at 1 month and 1 year.

In conclusion, in a selected subgroup of patients with acute osteoporotic vertebral fractures and persistent pain, vertebroplasty is effective and safe. Pain relief after the procedure is immediate, sustained for 1 year, and is significantly better than that achieved with conservative treatment and at acceptable costs, on the assumption of a societal willingness to pay €30,000 per QALY gained.

Contributors

THL, FHJ, AVT, MCB, MCS, AV, JRJ, KJVE, AFM, HF, XJ, DRH, and OEE contributed to study design, literature search, and data collection. YVDG contributed to study design and data analysis. JDV contributed to data analysis, data interpretation, and writing. EB contributed to study design, data interpretation, data analysis, writing, and figures. WJJVR contributed to data interpretation and writing. WPM, HJV, PNML, and CAHK contributed to study design, data collection, literature search, data analysis, data interpretation, and writing.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

This study was sponsored by ZonMw (Dutch organisation for health care research and innovation of care), project number 945-06-351 and an unrestricted grant from COOK Medical (Bloomington, IN, USA).

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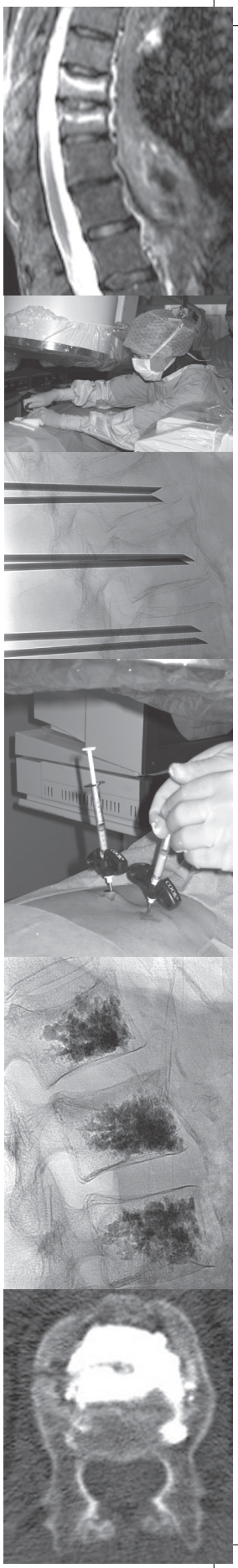
Chapter 5



Percutaneous vertebroplasty is not a risk factor for new osteoporotic compression fractures-results from VERTOS II

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AJNR Am J Neuroradiol 2010; 31:1447–50

Abstract

Background and Purpose: Percutaneous vertebroplasty (PV) is increasingly used as treatment for osteoporotic vertebral compression fractures (VCFs). However, controversy exists whether PV increases the risk for new VCFs during follow-up.

Materials and Methods: VERTOS II is a prospective multicenter randomized controlled trial comparing PV with conservative therapy in 202 patients. Incidence, distribution and timing of new VCFs during follow-up were assessed from spine radiographs. In addition, further height loss during follow-up of treated VCFs was measured.

Results: After a mean follow-up of 11.4 months (median 12.0, range 1-24 months), 18 new VCFs occurred in 15 of 91 patients after PV and 30 new VCFs in 21 of 85 patients after conservative therapy. This difference was not significant ($p=0.44$). There was no higher fracture risk for adjacent versus distant vertebrae. Mean time to new VCF was 16.2 months after PV and 17.8 months after conservative treatment (log rank $p=0.45$).

The baseline number of VCFs was the only risk factor for occurrence (OR 1.43; 95%CI 1.05-1.95) and number ($p=0.01$) of new VCFs. After conservative therapy, further height loss of treated vertebrae occurred more frequently (35 of 85 versus 11 of 91 patients, $p<0.001$) and was more severe ($p<0.001$) than after PV.

Conclusion: Incidence of new VCFs was not different after PV compared with conservative therapy after mean 11.4 months follow-up. The only risk factor for new VCFs was the number of VCFs at baseline. PV contributed to preservation of stature by decreasing both the incidence and severity of further height loss in treated vertebra. (ClinicalTrials.gov NCT00232466)

Introduction

Vertebral compression fractures (VCFs) are the most common fractures associated with osteoporosis (1). In the elderly population with osteoporosis, VCFs may lead to morbidity and even mortality due to incapacitating back pain, decreased daily activity and increased days of bed rest (2;3). In addition, deterioration of stature such as severe thoracic kyphosis may contribute to morbidity by decreased pulmonary function or higher risk of falling. Fortunately, only a minority of VCFs cause such a severe pain that patients seek medical attention (4). When pain response to analgesics is insufficient during several weeks, Percutaneous Vertebroplasty (PV) is increasingly used as a minimally invasive technique to induce durable pain relief. However, some authors believe that PV is associated with a higher incidence of future new VCFs as a result of the augmented stiffness of the treated vertebra, related to the amount of injected cement or by cement leakage in the adjacent vertebral disc space (5-8). Others dispute this assumption and consider the incidence of new VCFs dependant on the presence and severity of osteoporosis (9-13). To elucidate this controversy, we assessed the incidence of new VCFs during follow-up in 202 patients with acute VCFs randomized to PV and conservative therapy from VERTOS II (14). In addition, we assessed further height loss of the treated vertebrae with both therapies.

Materials and methods

Patients

The detailed study design has previously been published (14). In short, we performed a randomized controlled trial comparing PV with conservative therapy in selected patients with acute VCF in five large teaching hospitals in the Netherlands and one in Belgium. Inclusion criteria were: (1) VCF on spine radiograph (minimal 15% loss of height), (2) level of VCF Th5 or lower, (3) back pain ≤ 6 weeks, (4) VAS-score ≥ 5 on a 0-10 scale, (5) bone edema of the fractured vertebral body on MR imaging, (6) focal tenderness on VCF level and (7) decreased bone density with T-scores ≤ -1. Exclusion criteria were: (1) severe cardio-pulmonary co-morbidity, (2) untreatable coagulopathy, (3) infection, (4) suspected alternative underlying malignancy, (5) radicular syndrome, (6) myelum compression syndrome, and (7) contraindication for MRI. The study protocol was approved by the institutional review board at each participating centre.

Table 1: Baseline characteristics of 202 randomized patients.

	PV	Conservative therapy	*P*-value
Number of patients	101	101	
Age	75.2+/- 9.8	75.4+/- 8.4	0.90
Female sex (%)	70 (69%)	70 (69%)	1.0
Duration of back pain (days)	29.3 +/- 17.1	26.8 +/- 16.0	0.46
Initial VAS	7.8 +/- 1.5	7.5 +/- 1.6	0.12
Mean number of VCF at baseline	2.4 +/- 1.9 (1-5)	2.1 +/- 1.5 (1-5)	0.24
Number and grading of VCF with bone edema	136	120	
- mild	57	55	0.59
- moderate	58	45	
- severe	21	20	
- wedge	90	97	
- biconcave	46	23	0.18
- crush	0	0	
Vertebral level with bone edema			
- Th5-Th10	19	32	0.16
- Th11-L2	91	66	
- L3-L5	29	28	
Bone density (T-score)	-3.0 +/- 1.17	-3.0 +/- 1.05	0.78

Procedures

Participants were randomly assigned to PV or conservative therapy. PV was performed under biplane fluoroscopy with bilateral transpedicular injection of bone cement. Native computed tomography (CT) scan of the spine was performed to detect possible cement leakage. Conservative therapy consisted of analgesics optimized in classification and dose by an internist on a daily basis. Patients in both treatment groups received bisphosphonates, calcium suppletion and vitamin D. Symptomatic new VCFs were treated according to the originally allocated treatment strategy.

Imaging

At baseline, radiography and MR imaging of the spine was performed. Spine radiographs were repeated at 1-, 3- and 12- months follow-up. Two radiologists

independently performed semiquantitative and quantitative morphometric assessments at baseline and follow-up imaging (15;16). A `new VCF´ was defined as a decrease of at least 4 mm in vertical dimension (17). Height loss in new VCFs was categorized as mild, moderate and severe. Distribution of new VCFs were classified as adjacent to a treated level, between treated levels and distant to a treated level (18). `Further height loss´ during follow-up of treated baseline VCFs with bone edema was defined as height loss of 4 mm and more and categorized as moderate (4-7 mm) and severe (>8mm). Disagreement between observers was resolved in a consensus meeting. Because bone cement is radio-opaque, treatment assignment could not be blinded.

Statistical analysis

Patient characteristics were compared. A t-test was used for means and Chi-square test for proportions. The incidence and timing of new VCFs was analysed using survival analysis. The cumulative incidence was calculated using Kaplan-Meier estimates. Logistic regression analysis was used to assess a possible relation between the incidence of new VCFs and the following factors: age, gender, randomization, baseline VAS-score, bone mineral density, number of prevalent fractures, fracture severity, number of vertebral levels treated, mean amount of bone cement injected per vertebra, cement leakage into the disk, cement leakage into the soft tissue around the vertebra, and cement leakage into the veins. Linear regression analysis was used to determine risk factors for the number of new VCFs. Analysis was by intention-to-treat.

Statistical analysis were performed with the Statistical Package for the Social Sciences, Version 15.0.1. (SPSS, Chicago, Illinois). The VERTOS II study is registered with ClinicalTrials.gov, with the number NCT00232466.

Results

Of 934 patients that were screened between October 2005 and June 2008, 202 met the inclusion criteria and agreed to participate in the study. Of the 202 participating patients, 101 were assigned to PV and 101 to conservative therapy. Baseline characteristics were similar (Table 1). Informed consent was withdrawn after randomization by 6 patients assigned to conservative therapy and 2 patients assigned to PV. These patients had no therapy and follow-up could not be obtained. Six patients assigned to PV did not receive this treatment because of poor health

Table 2: Distribution of new VCFs.

Distribution of new VCFs	PV (*n*=91)	Conservative therapy (*n*=85)	*P*-value
Adjacent	7	11	
Between	4	3	0.23
Distant	7	16	

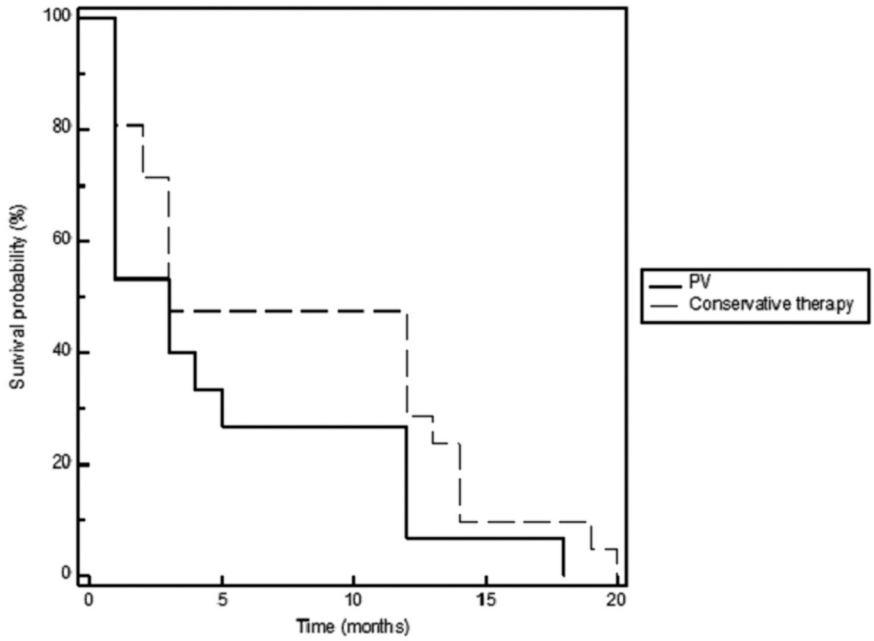

Fig 1. Kaplan-Meier survival curve for the timing of new VCFs after PV and conservative therapy.

(n=3) and spontaneous pain relief (n=3). Follow-up was obtained in 5 of these 6 patients. Ten patients assigned to conservative therapy with ongoing invalidating pain requested and received PV during follow-up. Five of these ten patients withdrew informed consent, so the PV procedure could not be documented and analyzed. Finally, 81% of the participants completed the follow-up at 1 year.

PV was performed in 98 patients on 134 vertebras in 103 procedures. The mean volume of injected cement per vertebral body was 4.10 cc (range 1 - 9 cc). CT scan of the 134 treated vertebral bodies showed cement leakage in 97 (72%). Most leakages were into adjacent discs or segmental veins, there was no leakage into the spinal canal. All patients remained asymptomatic.

Table 3: Height loss of the treated VCF between baseline and last follow-up.

Further height loss of treated vertebrae	**PV** 136 vertebrae	**Conservative therapy** 120 vertebrae	***P*-value**
None (0-3 mm)	118	74	
Moderate (4-7mm)	7	28	<0.001
Severe (≥8mm)	4	11	

New VCFs during Follow-Up

After a mean follow-up of 11.4 months (median 12.0, range 1-24 months) 18 new fractures were observed in 15 of 91 patients treated with PV and 30 new vertebral fractures were apparent in 21 of 85 patients with conservative therapy. This difference in incidence was not significant (p=0.44). New VCFs occurred at 4.6+/-5.4 months after PV and 6.1+/-5.9 months after conservative therapy (p=0.48).

The distribution of new VCFs is shown in Table 2. Distribution of location was not significantly different (p=0.23). There was no higher fracture risk for adjacent versus distant vertebrae.

Time to new VCF is graphically displayed in Figure 1. The Kaplan-Meier estimate of the mean time to incident was 16.2 months after PV and 17.8 months after conservative treatment. This difference was not significant (log rank p=0.45).

The baseline number of vertebral fractures was the only risk factor for the occurrence of new VCFs (OR 1.43; 95% CI 1.05-1.95) and also for the number of new VCFs (p=0.01).

Further height loss during follow-up of treated baseline VCFs with bone edema was observed in 11 vertebrae in 11 of 91 patients after PV and in 39 vertebrae in 35 of 85 patients after conservative therapy. Further height loss occurred more frequently in patients after conservative therapy (35 of 85 versus 11 of 91 patients, p<0.001). Severity grading of further height loss is displayed in Table 3. After conservative therapy, further height loss was significantly more severe than after PV (p<0.001)

Discussion

We found that PV does not increase the risk of new vertebral fractures in the first year. The incidence and distribution of new VCFs were similar after PV and conservative therapy. After PV, there was no higher fracture risk for adjacent - versus - distant vertebrae. After both PV and conservative therapy, the only risk

factor for the occurrence of new VCFs was the number of VCFs at baseline. This number of baseline VCFs in turn is associated with the severity of osteoporosis. Thus, the occurrence of new VCFs is due to the ongoing osteoporosis only and not to the type of therapy.

Our study shows that PV prevented further height loss of the treated fractured vertebral bodies in most patients. Apparently, the injected cement strengthened the fractured vertebral body. This is an important advantage in the prevention of morbidity associated with deterioration of stature such as severe kyphosis with decreased pulmonary function. PV not only decreased the incidence but also the severity of further height loss in affected vertebrae, thus further contributing to preservation of stature.

Our study is the first randomized controlled trial evaluating the risk of new VCFs in the first year after PV in a large patient cohort. The only limitation of our study is the inability to blind treatment assignment due to the radio-opacity of the bone cement used in PV. A study with a comparable design is the FREE study that compared kyphoplasty with conservative treatment in 300 patients with acute VCFs(19). Kyphoplasty involves an inflatable bone tamp to preform a space for the bone cement instead of a direct cement injection into the vertebral body as in PV. In this FREE study, an equal incidence of new VCFs was found after kyphoplasty and conservative treatment but risk factors for new VCFs, distribution of new VCFs and further height loss of treated VCFs at baseline were not analyzed.

The findings of our study and the FREE study are in concordance with other studies (9-13;20). On the other hand, some studies have reported an increased risk of new VCFs after PV (5;6;8;20;21). However, most of these studies are small non-randomized follow-up only studies, lacking a control group without intervention.

Some non-controlled follow-up studies after PV reported new VCFs to be more often located adjacent to the vertebroplasty level, allegedly contributed to the increased dimensional stability of the cemented vertebral body (6;8;22;23). However, in our randomized study, no difference in location distribution of new VCFs was found after PV and conservative therapy. In addition, after PV the risk for a new VCF adjacent to the cemented level was equal to the risk of a new VCF at a distant level.

In our study cement leakage after PV outside the vertebral body was frequently detected with CT. Most leakages were into adjacent discs or segmental veins, none into the spinal canal. All patients remained asymptomatic. Cement leakage was not associated with occurrence of new VCFs during follow-up, in contradiction to some

other studies in which leakage into an adjacent disk was considered a risk factor for new VCFs (5;24). Post-procedural CT imaging is not needed in routine daily practice, only in cases with clinical symptoms or significant volumes of cement leakage.

Conclusions

The incidence of new VCFs in patients with an acute, osteoporotic VCF was not different after PV compared with conservative therapy in the first year of follow-up. The only risk factor for the occurrence of new VCFs was the number of VCFs at baseline. PV contributed to preservation of stature by decreasing the incidence and severity of further height loss in treated vertebrae.

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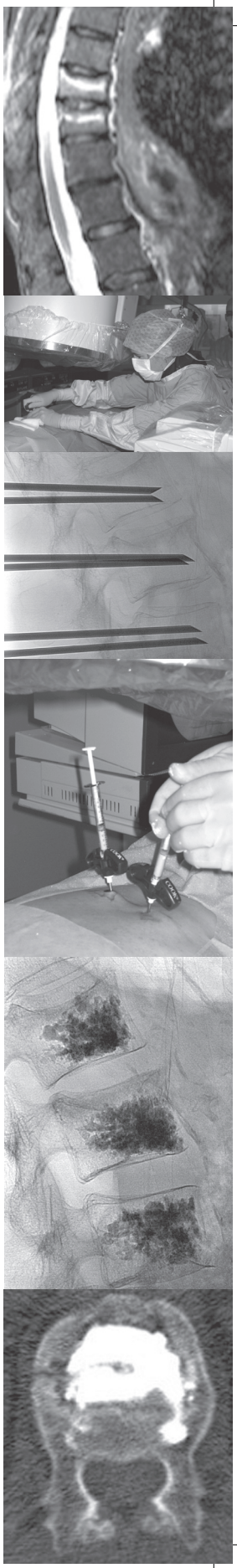
Chapter 6



Percutaneous Vertebroplasty and Pulmonary Cement Embolism-results from VERTOS II

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H.J.J. Verhaar, J. de Vries, W.P.Th.M. Mali

AJNR Am J Neuroradiol 2010; 31:1451–53

Abstract

Background and Purpose: The reported incidence of pulmonary cement embolism (PCE) during PV varites, depending on the sensitivity of diagnostic tests used. To assess the true incidence of PCE, we performed native chest CT during follow-up in a large proportion of patients of the VERTOS II trial.

Materials and Methods: VERTOS II is a prospective multicenter randomized controlled trial comparing PV with conservative therapy in 202 patients. After a mean follow-up of 22 months (median 21, range 6-42 months), 54 of 78 patients (69%) with 80 vertebrae treated with PV underwent native chest CT to detect possible PCE. The presence, location, number, and size of PCE were recorded. In addition, the presence of pulmonary parenchymal changes adjacent to PCE was noted. Possible risk factors for PCE such as age, sex, number of treated vertebrae, cement volume per vertebra and presence and location of perivertebral cement leakage, were evaluated.

Results: PCE was detected in 14 of 54 patients (26%, 95% CI, 16-39%). All patients were asymptomatic. Cement emboli were small and randomly distributed in peripheral small vessels. There were no reactive pulmonary changes. Cement leakage in the azygos vein was the only risk factor for the occurrence of PCE (OR 43, 95% CI 5-396).

Conclusion: Small and clinically silent PCE occurred in a quarter of patients treated with PV. Cement leakage into the azygos vein was the only risk factor. Over time, these small cement emboli remained inert, without inflammatory pulmonary response. Standard postprocedural CT or chest radiographs are not necessary.

Introduction

Cement leakage commonly occurs during PV with occurrance in observational studies varying from 0% to 23% (1-6). Occasionally, cement that has been leaked into the veins may migrate into the lungs causing pulmonary cement embolism (PCE). Although most PCEs remain asymptomatic, serious and even fatal sequelae have occasionally been reported (7,8). In most studies with low incidence of PCE, 'the occurrence of PCE' is defined as cement migration towards the lungs observed during fluoroscopy (9). In studies with standard post-procedural chest radiographs, the observed incidence is higher (10,11); apparently a substantial proportion of PCE remains undetected during fluoroscopy. In 1 study the long-term effects of pulmonary cement deposits on the surrounding lung parenchyma are largely unknown. In this study, we use follow-up chest CT to assess the true incidence of the occurrence of PCE during fluoroscopy in a large patient cohort with osteoporotic vertebral compression fractures treated with PV. In addition, we evaluate possible inflammatory response of cement deposits on the lung parenchyma.

Materials and Methods

Patients

The VERTOS II trial (12) was a pragmatic randomized controlled trial comparing PV and conservative therapy for osteoporotic vertebral compression fractures (OVCF) in 202 patients. The study protocol has been described in detail elsewhere (12). In short, VERTOS II was conducted in 5 large teaching hospitals in the Netherlands and 1 in Belgium. The protocols of VERTOS II including the present study, were approved by the institutional review boards at each participating centre. Between October 2005 and June 2008, 202 patients were randomized for PV and conservative therapy. Ultimately, in 98 patients PV was performed without clinical procedural complications. These 98 patients form the basis of the present study. During a mean follow-up of 22 months (median 21, range 6-42 months), 10 patients died and 6 refused to complete the protocol of VERTOS II. The remaining 82 patients were invited by telephone for a native CT of the treated vertebrae and chest to detect peri-vertebral cement leakage and PCE. Of these 82 patients, 24 declined participation and four patients could not be reached. Thus, 54 of 82 patients (69%) had follow-up CT. CT was performed after a mean follow-up of 22 months (median 21, range 6-42 months). In these 54 patients no cement migration had been visible on fluoroscopy during the procedure. There were 36 women (67%) and 18 men (33%) with a mean age of 74 years (median 77; range 53-88 years). These 54 patients

had 80 OVCFs and were treated in 60 sessions. Thirty-nine patients were treated for 1 OVCF, 11 patients for 2, and 4 patients for 3 OVCFs in one session. During follow-up, 4 patients presented with a new OVCF and were treated again. One of these 4 patients had 2 additional PVs, for 1 OVCF each time. The location of treated osteoporotic compression fractures in relation to PCE is displayed in figure 1.

PV Technique

PV was performed on a single or biplane angiographic unit under fluoroscopic guidance. After local infiltration analgesia (Lidocain 1%), needles were bilaterally transpedicular inserted into the vertebral body. Polymethylmethacrylate bone cement (Osteo-firm®, COOK Medical, Bloomington, Indiana, USA) was injected under continuous lateral fluoroscopy alternating both pedicles using 1cc syringes. Injection was stopped whenever perivertebral cement migration was observed. Injection was resumed after a 15-20 second delay without changing needle position. The volume of injected cement in each treated vertebral body was recorded. Immediately after the procedure, a CT scan of the treated OVCF was obtained to evaluate perivertebral cement leakage.

Follow-up CT

Follow-up CT was performed in 5 different hospitals with a multidetector spiral CT scanner with 16- or 64- detector arrays. Native CT of the chest and treated vertebrae was performed with a slice thickness of 2 mm. Two radiologists reviewed the follow-up CT-scans. Differences were resolved by consensus. Cement-embolus detection was performed at bone window (window width, 2400 HU; window level, 350 HU) and lung window (window width, 1500 HU; window level, -700 HU). PCE should be located in the expected course of a pulmonary vessel with an attenuation of > 500 HU. To distinguish between a calcified granuloma and a PCE, we made a comparison with an old chest radiograph or chest CT scan if possible.

Perivertebral cement leakage on postprocedural and follow-up CT

Treated vertebrae were assigned into 3 location categories: T5-T10, T11-L2 and L3-L5. Perivertebral venous cement leakage was assessed from direct postprocedural CT and categorized as limited to the anterior external venous plexus, azygos vein, or inferior vena cava. 'PCE' was defined as any high attenuation lesion in the lungs, heart or large vessels. In patients with PCE and multiple levels treated, we assumed the level with the most leakage to be the origin of PCE.

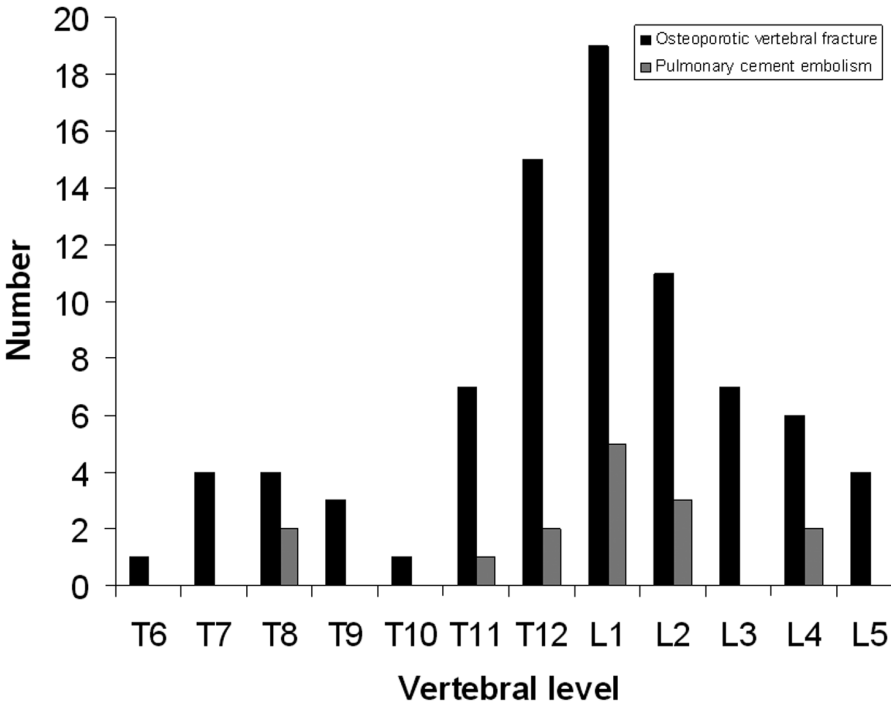

Figure 1. Location of treated osteoporotic compression fractures in relation to PCE.

Data analysis

The frequency of PCE was assessed per patient as a proportion with 95% CI Univariate logistic regression analysis was performed for the following possible risk factors for the occurrence of PCE: age, sex, number of treated vertebrae, cement volume injected per vertebra higher than median, and presence and location of perivertebral venous cement leakage. Chi-square test was used to correlate PCE with location of treated vertebrae. Statistics were performed with SPSS version 15.0.1. The VERTOS II trial is registered with ClinicalTrials.gov, number NCT00232466.

Results

Incidence and characteristics of PCE on native follow-up chest CT

After median 21 months of follow-up, PCE was detected in 14 of 54 patients (26%, 95% CI, 16-39%). All patients were asymptomatic. An example of a PCE is presented in figure 2.

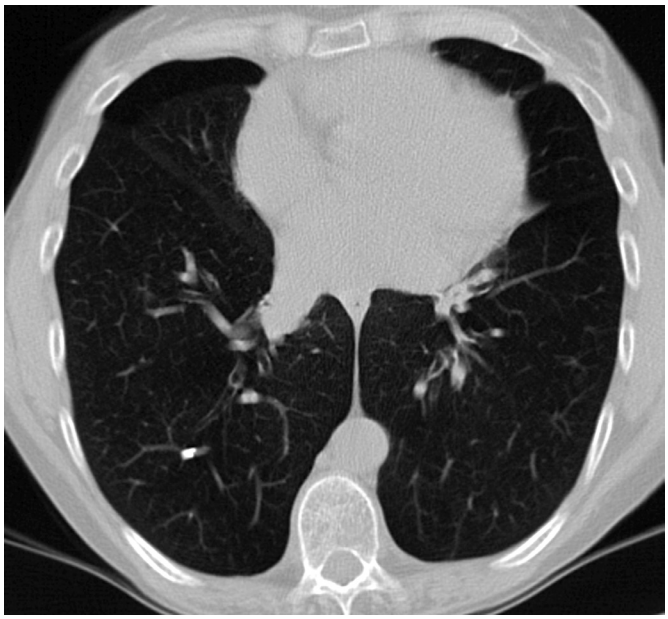

Figure 2. Native chest CT scan demonstrating a cement embolus in a peripheral right lower lobe pulmonary artery.

The emboli varied in size between 1-12 mm and were randomly distributed in the periphery of the lungs. No cement depositions were observed in the heart and central pulmonary vessels. In the 14 patients with PCE, 6 (43%) had a single cement embolus and 8 (57%) had 2-35 cement depositions. With multiple PCEs, these were randomly scattered in peripheral portions of both lungs. No patients showed reactive pulmonary parenchymal change associated with cement embolism.

Cement leakage after PV

Venous cement leakage immediately after PV was observed on CT in 34 of 80 treated vertebra (43%); 23 cement deposits were into the anterior external venous plexus, 7 into the azygos vein and 4 into the inferior caval vein.

Statistical analysis

Cement leakage in the azygos vein was the only risk factor for the occurrence of PCE (OR 43, 95% CI 5-396). Age, sex, number and location of treated vertebra and injected cement volume were not correlated with the occurrence of PCE.

Discussion

This study showed that during PV for OVCFs, clinically silent PCE occur in a quarter of patients. Cement emboli were small and scattered in peripheral portions of the lungs without specific lobar distribution. There were no cement deposits in the heart and large vessels. Cement leakage in the azygos vein was the only risk factor for PCE. Remarkably, the volume of injected cement was not correlated with the occurrence of PCE. After a mean follow-up of almost 2 years, the cement emboli caused no structural parenchymal changes.

In a comparable study with use of CT to detect PCE, Kim et al (13) found a similar incidence in 75 patients undergoing PV for OVCFs, with cement leakage to the inferior caval vein as only relevant risk factor. In studies that only used post-procedural chest radiographs for detection of PCE, the observed incidences were substantially lower (10,11). This is not surprising since small pulmonary cement deposits easily remain undetected on chest radiographs while these are readily apparent on CT. In 1 study (11) an incidence of 4.6% was reported after retrospectively reviewing postprocedural chest radiographs in 69 PV sessions. In that study, all patients with cement emboli had multiple myeloma and remained asymptomatic. An association was found between PCE and paravertebral venous cement leakage but not between PCE and the number of vertebral bodies treated or the performance of kyphoplasty or vertebroplasty. In another study (10), the anthors also retrospectively reviewed postprocedural chest radiographs, and when PCE was detected, they confirmed it with CT. In that study, 5 of 73 patients (6.8%) had PCE. Four of these patients had osteoporotic compression fractures and one had multiple myeloma. Venous leakage was not recognized during fluoroscopy in patients with PCE.

In the VERTOS II Trial (12) fluoroscopic venous cement migration to the lungs was detected and reported by the operator in only 1 patient (C.A.H. Klazen, unpublished data, 2010). This patient remained asymptomatic and stopped the trial 3 months later because of unrelated comorbidity. In no patients who were included in the present follow-up study fluoroscopically visible cement migration towards the lungs was reported by the operators. The findings of our study imply that with fluoroscopy virtually all migration of small cement quantities remain undetected. Thus, when the operator notices cement leakage into anterior venous structures, careful observation of pulmonary symptoms is mandatory. Conversely, when a patient complains of pulmonary symptoms after PV, PCE should be excluded, even though venous cement migration was not seen.

Like in previous studies (9-11), our study showed that cement emboli were scattered in peripheral portions of the lung without specific lobar distribution and no acute inflammatory pulmonary reaction. Our study indicates that also on the long-term, cement emboli do not cause structural changes of the pulmonary parenchyma. A previous study showed that PCE occurred infrequently and caused no pulmonary reaction on CT after 1 year (9).

In our study, cement in the azygos vein on the postprocedural CT of the treated vertebrae was the only risk factor for PCE. Analogously, other studies (13,14) showed a statistically significant relation between PCE and cement leakage into the inferior caval vein.

Our study has several limitations. Our patient group was relatively small and not all patients agreed to participate. Results were expressed on a per-patient basis while some patients had multiple levels treated. Thus, in patients with PCE and multiple treated vertebrae, the level of leakage remained uncertain. However, we used post-procedural CT of the treated levels to indicate the most likely level of origin of leakage. Another limitation is that post-procedural chest CT was not routinely performed. Therefore, it is possible that small cement emboli might have been resolved or changed over time or have been migrated. In addition, earlier but transient pulmonary changes cannot be excluded. On the other hand, strong points of the study were the use of CT for the detection of PCE and the long follow-up interval, which allowed a reliable assessment of PCE with time.

On the basis of our findings and other studies, in our opinion standard CT or chest radiograph after PV is not warranted in asymptomatic patients, even not when small quantities of cement have been observed migrating towards the lungs. Only in symptomatic patients, should CT be performed to guide the appropriate therapy. Because cement emboli remain inert over time, follow-up CT is not necessary.

Conclusions

In the VERTOS II trial, small and clinically silent PCE occurred in a quarter of patients treated with PV. Cement leakage into the azygos vein was the only risk factor. With time, these small cement emboli remained inert without inflammatory pulmonary response. Standard post-procedural CT or chest radiographs are not necessary.

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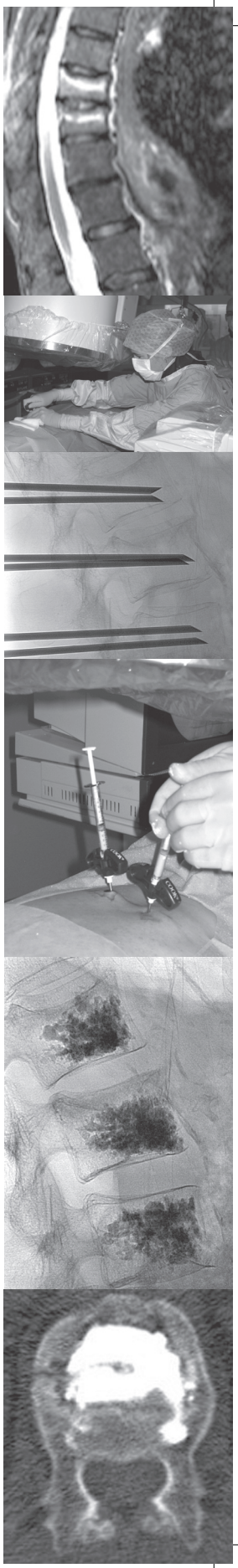
Chapter 7



Postprocedural CT for perivertebral cement leakage in percutaneous vertebroplasty is not necessary – results from VERTOS II

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Neuroradiology 2010 May 5 (Epub ahead of print)

Abstract

Introduction During percutaneous vertebroplasty (PV) perivertebral cement leakage frequently occurs. There is some concern that cement deposits may migrate towards the lungs via the veins during follow-up. We used baseline and follow-up Computed Tomography (CT) to assess the incidence and extend of late cement migration in a large consecutive patient cohort.

Methods VERTOS II is a prospective multicenter randomized controlled trial comparing PV with conservative therapy for osteoporotic vertebral compression fractures (OVCFs). Patients assigned to PV had baseline postprocedural CT scans of the treated vertebral bodies. After a mean follow-up of 22 months, 54 of 78 patients (69%) had follow-up CT. CT scans were analyzed and compared for perivertebral venous, discal and soft tissue leakage.

Results Perivertebral cement leakage occurred in 64 of 80 treated vertebrae (80%, 95% CI 70 to 87%). All patients remained asymptomatic. Perivertebral venous leakage was present in 56 vertebrae (88%), mostly in the anterior external venous plexus (46 of 56, 82%). Discal leakage occurred in 22 of 64 vertebrae (34%) and soft tissue leakage in 2 of 64 (4%). Mean injected cement volume in vertebrae with leakage was higher (4.5 versus 3.7 cc, p=0.04). Follow-up CT scan showed unchanged perivertebral cement leakages without late cement migration.

Conclusion Perivertebral cement leaks during PV for OVCFs occurred frequently in the VERTOS II trial. Cement leakage occurred more frequently with higher injected volumes. However, all patients remained asymptomatic and late cement migration during follow-up did not occur. Standard post-procedural CT of the treated vertebral body in PV is not necessary.

Introduction

Perivertebral leakage of cement during percutaneous vertebroplasty (PV) has been reported to occur frequently in up to 65% of treated osteoporotic vertebral compression fractures (OVCFs) (1,2). Most of these leakages cause no clinical symptoms, but pulmonary embolism and neurological complications have occasionally been reported (3,4).

VERTOS II is a randomized controlled trial comparing PV and conservative therapy for OVCFs in 202 patients. In this trial patients assigned to PV had a standard postprocedural Computed Tomography (CT) scan of the treated OVCF with the aim to assess the patterns of perivertebral cement leakage and its possible clinical impact. There is some concern that cement deposits may migrate to the lungs via the veins during follow-up; sharp and elongated spike-like cement fragments might cause perforation of vessels or heart. In addition, local damage to the adjacent anatomical structures by the leaked cement may cause symptoms like soft tissue hematoma or radiculopathy (5-8). In this study, we used baseline and follow-up CT to assess the incidence, anatomical location and clinical impact of perivertebral cement leakage on short- and long-term in a large patient cohort.

Methods

Patients

The study protocol of the VERTOS II trial has been described in detail elsewhere (9). In short, VERTOS II was an unmasked randomized controlled trial in five large teaching hospitals in the Netherlands and one in Belgium. The protocols of VERTOS II and the present study were approved by the institutional review board at each participating centre. Between October 2005 and June 2008, 202 patients were randomized for PV and conservative therapy. All patients assigned to PV had baseline post-procedural CT scans of the treated vertebral bodies. Ultimately, in 98 patients PV was performed without clinical procedural related complications. These 98 patients form the bases of the present study. During a mean follow-up of 22 months (median 21 months; range 6–42 months), ten patients died and six refused to complete the protocol of VERTOS II. The remaining 82 patients were invited by telephone for a native CT scan of the treated vertebra to detect possible migration of the perivertebral cement leakages and evaluation of possible local pathology related to the cement leakage.

Twenty-four patients declined participation and four patients could not be

reached. Thus, 54 of 82 patients (69%) had follow-up CT. There were 36 women (67%) and 18 men (33%) with a mean age of 74 years (median 77; range 53-88 years). These 54 patients had 80 OVCFs and were treated in 60 sessions. Thirty-nine patients were treated for one OVCF, 11 patients for two, and four patients for three OVCFs in one session. During follow-up, four patients presented with a new OVCF and were treated again. One of these four patients had 2 additional PVs, for one OVCF each time. Location of treated vertebra is displayed in figure 1.

PV technique

PV was performed on a single or biplane angiographic unit under fluoroscopic guidance. After local infiltration analgesia (Lidocain 1%, Braun, Melsungen, Germany), needles were bilaterally transpedicular inserted into the vertebral body. Polymethylmethacrylate bone cement (Osteo-firm®, COOK Medical, Bloomington, Indiana, USA) was injected under continuous lateral fluoroscopy alternating both pedicles using 1cc syringes. Injection was stopped whenever perivertebral cement migration was observed. Injection was resumed after a 15-20 second delay without changing needle position. Volume of injected cement in each treated vertebral body was recorded. Immediately after the procedure a CT scan of the treated OVCF was performed to evaluate perivertebral cement leakage.

Perivertebral cement leakage on postprocedural and follow-up CT scan

Treated vertebrae were assigned into 3 location categories: T5-T10, T11-L2 and L3-L5. The anatomical location of perivertebral venous cement leakage was recorded according to the plexus venosus vertebralis , a venous network that extends along the entire length of the vertebral column (figure 2). In addition to the venous location, discal and soft tissue leakages were recorded.

Data analysis

Chi-square test was used to correlate perivertebral cement leakage with the location of treated OVCFs into 3 categories. Mean volume of injected cement in vertebrae with leakage was compared to mean volume of cement in vertebrae without leakage using the t-test. Statistics were performed with SPSS version 15.0.1. The VERTOS II study is registered with ClinicalTrials.gov, with the number NCT00232466.

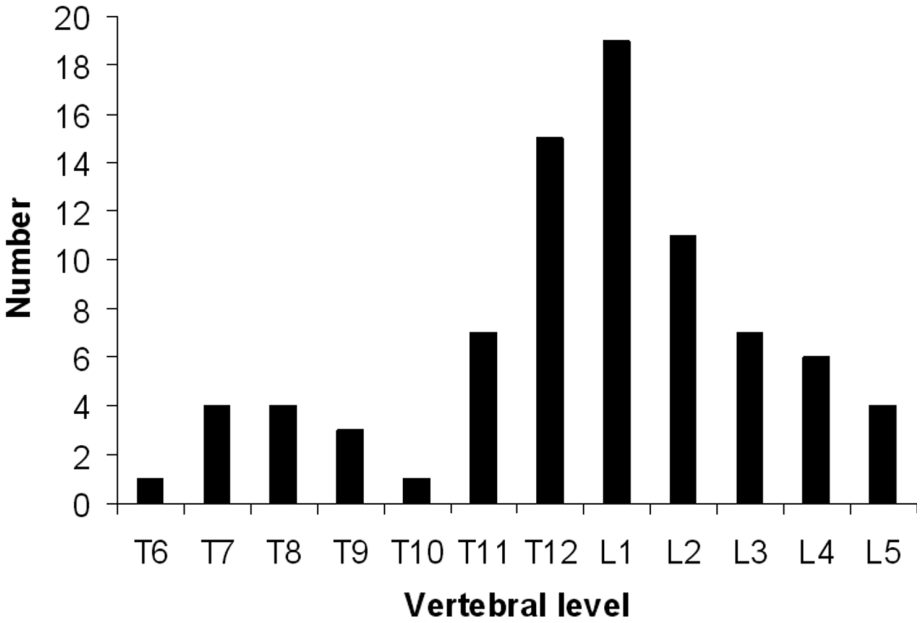

Figure 1. Distribution of 54 treated osteoporotic compression fractures.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report or the decision to submit the paper for publication.

Results

Perivertebral cement leakage on postprocedural and follow-up CT scan

Any perivertebral cement leakage was observed in 64 of 80 treated vertebrae (80%, 95% CI 70 to 87%). Discal leakage was present in 22 vertebrae (34%), in 8 vertebrae (13%) in combination with venous leakage. Perivertebral soft tissue leakage occurred in 2 vertebrae (4%). Altogether, 56 of 64 vertebrae (88%) had cement leakage into the perivertebral venous system. Cement in the anterior external venous plexus was observed in 46 of 56 vertebrae (82%), in 32 vertebrae (57%) in combination with cement in a segmental vein. Five vertebrae (9%) had cement in the inferior caval vein and 6 (11%) in the azygos vein, all in combination with cement in a segmental vein and the anterior external venous plexus. Cement in the basivertebral vein was present in 30 of 56 vertebrae (54%), in the anterior

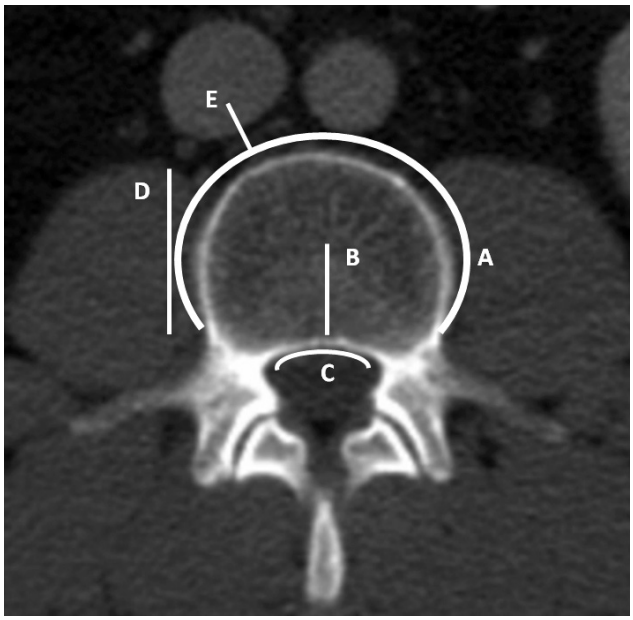

Figure 2. Schematic representation of patterns of perivertebral venous cement leakage. Leakage into the anterior external venous plexus (A), basivertebral vein (B), anterior internal venous plexus (C), segmental vein (D), inferior caval vein or (hemi)azygos vein (E)

internal venous plexus in 33 (59%) and both in the basivertebral vein and anterior internal venous plexus in 26 (46%). Three vertebrae (5%) had cement in the intervertebral vein, all in combination with cement in the anterior external venous plexus, basivertebral vein and anterior internal venous plexus. No cement leaks were seen in the posterior internal and external venous plexus.

Comparison of follow-up CT scan (mean 22 months, median 21 months, range 6–42 months) of treated vertebrae with baseline CT showed unchanged anatomical location of the perivertebral cement leakages in all vertebrae without late cement migration.

Data analysis

Chi-square test showed no statistical relation between location of the treated vertebra and the occurrence of perivertebral cement leakage (p=0.64).

Mean volume of injected cement in 47 vertebrae with leakage was 4.5 ± 1.8 cc and in 33 vertebrae without leakage this was 3.7 ± 1.6 cc. This difference was significant (p=0.04, 95% CI -1,58 to -0,02%).

Discussion

In this well-defined and large patient cohort from VERTOS II, we found that during PV, perivertebral cement leakage occurred in more than half of the treated vertebrae. Most leakages were in perivertebral venous structures, leakage into the disk or perivertebral soft tissues was infrequent. Cement leakage occurred more frequent with higher volumes of injected cement. Follow-up CT after almost 2 years showed that late migration of leaked cement deposits did not occur. Clinically, patients remained asymptomatic; there were no symptomatic pulmonary emboli and radiculopathy or soft tissue hematoma did not occur. Our findings suggest that standard post-procedural CT scan after PV is not warranted and should be confined to symptomatic patients only. Omitting CT from the PV protocol is cost-effective and reduces radiation burden.

Knowledge of the anatomy of the perivertebral veins is helpful in understanding the venous leakage patterns on CT. Leakage more often occurs in the perivertebral venous plexus than in adjacent disks or perivertebral soft tissues. The venous complex along the vertebral column consists of three major intercommunicating networks (10,11): the internal and the external venous plexus and the basivertebral system. The basivertebral system is oriented horizontally in the centre of the upper half of the vertebral body. The basivertebral veins originate in the ventral third of the vertebral body, and converge posteriorly to drain into the ventral part of the internal venous plexus, sometimes as a single vein, and sometimes as two separate tributaries. Anteriorly, the basivertebral veins join the external plexus. The exiting point of the basivertebral vein on the dorsal surface of the vertebral body is located in the middle between the pedicles. The anterior internal venous plexus drains into the segmental veins that exit the spinal canal through the foramen, between the nerve root and the medial wall of the pedicles. This means there is a direct venous connection between the bone marrow and the foraminal space.

Comparison of frequency of cement leakage between studies is hampered by differences in methods used. Detection rates in studies using intraoperative fluoroscopy only instead of CT will be substantially lower since sensitivity of CT is much higher. In 2 studies about frequency of local cement leakage that used post-procedural CT for detection, rates of 63% and 81% were found, comparable to our 80% (12,13).

Cement leakage during PV seems to be largely inevitable according to the high reported rates in this study and in the literature. Small leakages are without clinical

consequences. With proper use of technique and fluoroscopy, clinical relevant cement leakage should be avoided.

Conclusion

Perivertebral cement leaks during PV for OVCFs occurred frequently in the VERTOS II trial. Cement leakage occurred more frequently with higher injected volumes. However, all patients remained asymptomatic and late cement migration during follow-up did not occur. Standard post-procedural CT of the treated vertebral body in PV is not necessary.

Conflict of Interest Statement

We declare that we have no conflict of interest.

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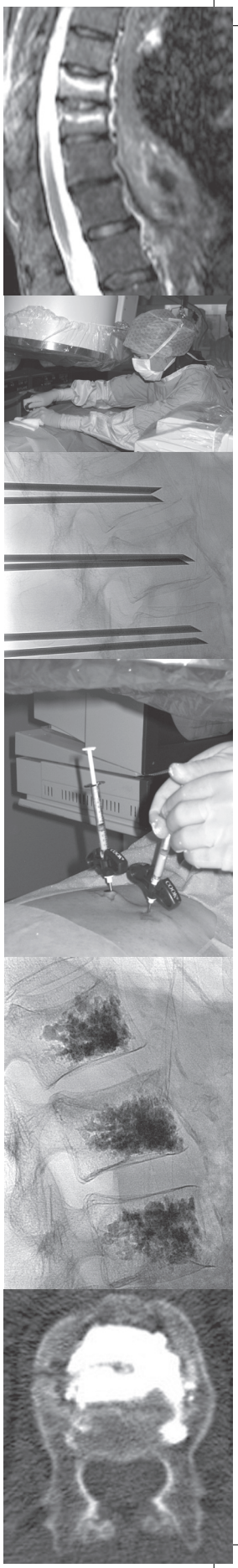
Chapter 8



Percutaneous vertebroplasty and procedural pain

A. Venmans, C.A. Klazen, P.N. Lohle, W-J. van Rooij

AJNR Am J Neuroradiol 2010;31:830-1

Abstract

Background and Purpose: No consensus exists regarding pain management during percutaneous vertebroplasty (PV). In this study we evaluated the effectiveness of local infiltration anesthesia as the only pain medication.

Materials and Methods: From September 2008 to March 2009, 44 consecutive patients (35 women and 9 men, mean age 74 years) with symptomatic vertebral compression fractures (OVCFs) were included in the study. Lidocaine was infiltrated to the skin and the periosteum of the pedicle. After PV patients indicated pain sensation on a visual analog score (VAS). In addition, patients indicated the most painful moment during the procedure; lidocaine infiltration, placing the needles or cement injection. In addition, patients were asked whether pain medication during the procedure was sufficient or not. After the procedure the operator was asked what the expected VAS score of the patient would be.

Results: Mean VAS score was 5.7 (median 6, range 1 – 10). Seventeen of 44 patients (39%) indicated lidocaine infiltration was insufficient for procedural pain reduction. The mean VAS score of these patients was 7.3 (range 5 - 10). Placing the needles was specified as most painful moment in 29 patients (66%), lidocaine infiltration in 11 (25%) and cement injection in 4 (9%). Operators' expectations of patients' VAS scores were mean 3.3 (median 3, range 1 – 6).

Conclusion: For a substantial proportion of patients local infiltration anesthesia was not sufficient for pain reduction during PV. The severity of pain experienced by the patient is mostly not valued correctly by the operator.

Introduction

Percutaneous vertebroplasty (PV) is increasingly used for management of pain associated with osteoporotic vertebral compression fractures (OVCFs), vertebral hemangiomas and osteolytic vertebral lesions (1).

Pain management during PV is subject to variation among operators: from local infiltration anesthesia to general anesthesia supplied in the operating room. In a recent study (2), a protocol of titrated intravenous sedation with fentanyl and propofol, local infiltration anesthesia and monitoring of vital parameters resulted in good tolerance for the procedure.

Since the introduction of PV for OVCFs in our hospital in 2001, we use local infiltration anesthesia as the only pain medication. In our experience most patients seem to tolerate the procedure rather well and only in a minority of patients additional intravenous fentanyl is requested. In order to objectify our assumption of patients' tolerability of the procedure, we quantified patients' subjective pain sensation during PV with our standard pain management protocol.

Materials and Methods

This prospective study was approved by the Institutional Review Board and patient informed consent was obtained.

Patients

From September 2008 to March 2009, 44 consecutive patients with OVCFs were included in the study. There were 35 women and 9 men with a mean age of 74 years (median 75, range 45-89 years).

Percutaneous Vertebroplasty technique

One day before PV, patients were informed about the procedure by the attending radiology resident on the ward. During this consultation, the possibility to ask for additional pain medication during the procedure was emphasized.

PVs were performed by one of two experienced radiologists on a biplane angiographic system (Integris BN 3000 Neuro, Philips Healthcare, Best, The Netherlands). Ten mL of Lidocain 1% (Braun, Melsungen, Germany) was infiltrated from skin to periosteum of the targeted vertebral pedicles. Oxygen saturation and electrocardiogram was monitored by pulse oximetry. Via a bilateral transpedicular approach using 11- or 13-gauge needles, bone cement was alternating injected

under continuous fluoroscopy using 1.0 cc syringes.

During the procedure, patients were informed about the progress with notification of local infiltration anesthesia, needle placement and cement injection.

Pain evaluation

Immediately after the procedure patients filled out a questionnaire to indicate pain sensation on a Visual Analog Score (VAS) ranging from 0 (no pain) to 10 (worst pain ever) (3). In addition, patients were asked to specify the most painful moment during the procedure as lidocaine infiltration, placing the needles or cement injection. Finally, patients were asked whether pain medication during the procedure was sufficient or not.

After the procedure the operator was asked to estimate the patients' expected VAS score.

Results

Patients' VAS scores and operators' expectation of patients' VAS scores are displayed in figure 1. Mean patients' VAS score was 5.7 (median 6, range 1 – 10). Seventeen patients (39%) indicated that lidocaine infiltration was insufficient. These 17 patients had a mean VAS score of 7.3 (range 5 - 10). For 27 patients (61%) lidocaine infiltration was sufficient. These patients had a mean VAS score of 4.7 (range 1 - 8).

The most painful moment was placement of the needles in 29 patients (66%), lidocaine infiltration in 11 patients (25%) and cement injection in 4 patients (9%). None of the patients requested additional medication.

Discussion

In the performance of PV, the use of infiltration anaesthesia as the only pain medication is usually not sufficient to make the procedure tolerable in the perspective of the patient: Three-quarters of patients indicated a VAS score of ≥5. Despite this high VAS score, patients did not request for additional medication during the procedure. The operators who performed the PVs did not have the impression that pain was apparently unbearable: in many cases they were surprised by the patients' high VAS scores after the procedure. Apparently, there is a discrepancy between pain as perceived by the patient and the impression of pain perception by the operator.

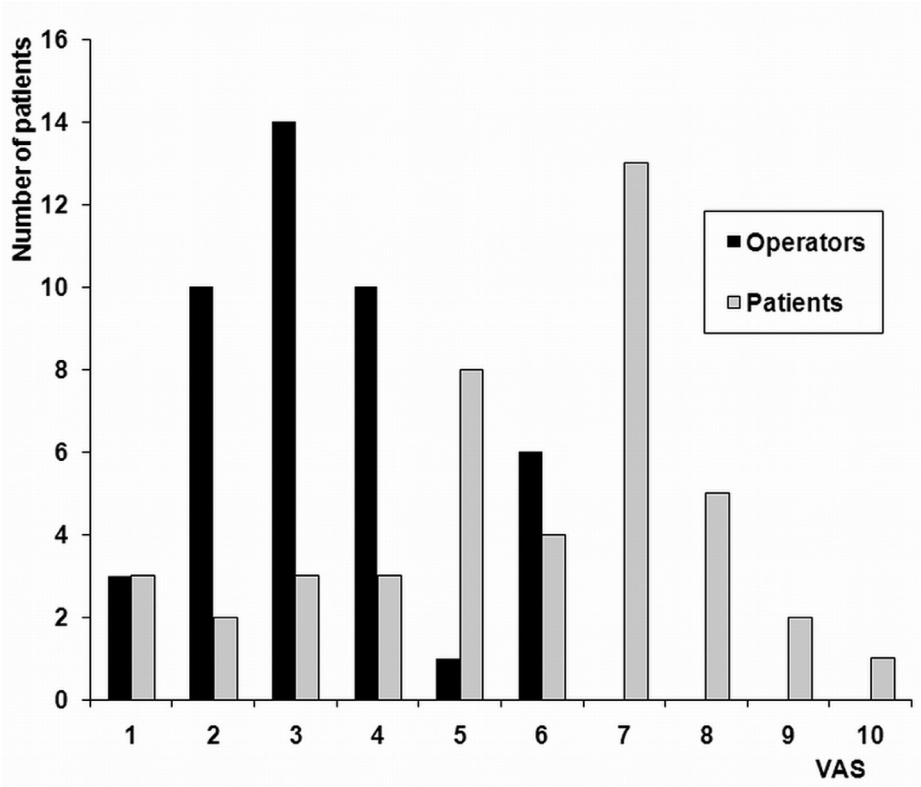


Figure 1. Patients' VAS and operators' expectation in patients' VAS of 44 patients during PV.

There are several aspects that define pain. It has been shown that pain intensity can be measured by several methods that show high intercorrelation (3). The VAS appears to be a sensitive instrument for assessing pain-intensity and is the most frequently used method. There is some difference of opinion as to whether pain should be measured by the subject or by an observer. Some patients find it difficult to express their pain severity within the descriptive limits of a particular scale or exaggerate the severity of their pain. On the other hand, the opinion of others is that the severity of pain is known only to the patient and not to an observer who measures another person's pain. Pain is a psychological experience, and an observer can play no legitimate part in its measurement (3, 4).

Pain management during PV is subject to variation among operators and varies from local infiltration anesthesia only to general anesthesia in the operating room. Until now, two authors (2,5) concentrated on this subject. In a study of 20 patients (2), a protocol of fentanyl and titrated intravenous propofol allowed for a pain free

procedure. No adverse advents were registered. Such a protocol might meet the criteria of a targeted analgosedative procedure that ensures comfort during PV without, as with general anesthesia, the need for longer hospitalization.

There was a remarkable discrepancy between the patients' VAS scores and the expectation of the operators, with far more pain experienced by the patients than expected by the operators. We believe the patients' relatively high mean VAS score in this study is a good representative of the experienced pain during PV, and the operators' impression of pain experienced by the patient is of little importance. The results of this study have made us realize that lidocaine infiltration only is, for most patients, not sufficient for pain reduction during the procedure. We adjusted our pain medication protocol and now administer fentanyl in all patients.

Conclusion

For a substantial proportion of patients, local anesthesia was not sufficient for pain reduction during PV. The severity of pain experienced by the patient is mostly not valued correctly by the operator.

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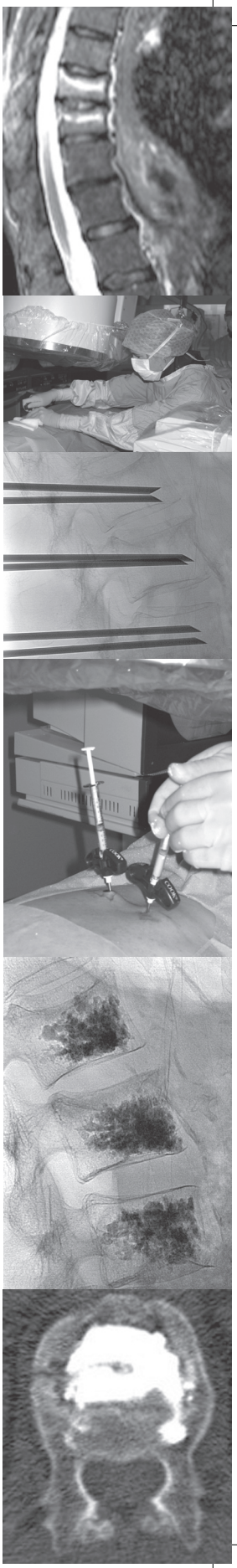
Chapter 9

General Discussion



General Discussion

In 1984 Percutaneous Vertebroplasty (PV), involving transpedicular bone cement injection in the vertebral body, was developed in France for the treatment of painful and aggressive vertebral angioma[1]. Bone cement injection was found to have a favourable effect on pain from the damaged vertebral body, both on short and long-term. The favourable clinical results led to a gradual expanding indication for PV. Presently, PV is most frequently performed to treat patients with painful osteoporotic vertebral compression fractures (VCFs).

Since its introduction for the treatment of painful VCFs, this minimally invasive technique has received widespread recognition with effective pain reduction at short and long-term. Many observational clinical cohort studies confirmed the good clinical results [2-12]. However, until recently, studies with the highest level of evidence were lacking. This made us decide in 2005 to design a multicenter randomized controlled trial comparing PV with conservative treatment in selected patients with VCFs, VERTOS II. Masking therapies for patients was judged impossible since PV is performed in the angiosuite by percutaneous transpedicular placement of needles while conservative therapy only involves pain medication and physiotherapy. This lack of masking was an important drawback of the trial, since a potential bias was introduced. For many reasons, VERTOS II took longer than anticipated and just before the end of data accumulation in 2009, two sham studies about PV with the highest level of evidence were published in the same issue of The New England Journal of Medicine. To the surprise of many clinicians, both studies showed no difference between PV and the sham treatment for the treatment of pain.

The two sham studies: the end of PV?

The publication of these studies has incited great debate about the merits of PV: both sham studies demonstrated no additional pain relief from PV. Since PV is a rather costly procedure, hospital administrators and health insurance companies all over the world took their responsibility and announced to abandon this type of therapy and stopped reimbursement. The results of the sham studies and the immediate clinical consequences caused a shock in the medical community. From their own experience, many clinicians could not believe the results of the sham studies and a lively debate in medical journals and congresses started. Methodological weaknesses were found in the two randomized studies using a

sham control intervention. One of the studies reported on clinical outcome one [13] and six [14] months after PV in patients with osteoporotic VCF up to one year old. Both studies seem to indicate that PV and sham treatment are equally effective. However, clinical interpretation of these studies is hampered by including patients with sub acute and chronic fractures instead of acute fractures. Unlike in VERTOS II, there was no control group without intervention. Bone edema in the fractured vertebral body on MRI was not used as a consistent inclusion criterion. Patients were not physically examined before inclusion. In the sham intervention, the use of a local anaesthetic may have resolved secondary soft tissue and facet joint pain unlikely to be affected by PV. [15, 16].

Since the design of the sham studies differs in many ways from VERTOS II, the results may differ as well. VERTOS II is designed as a randomized controlled but unmasked trial to clarify whether PV has additional value compared with optimal pain treatment in a selected and well defined group of patients with acute VCFs. Patient selection in VERTOS II is the most important difference from the sham studies.

VERTOS II: Patient selection for PV

During the past years we empirically learned that proper patient selection for PV is necessary to warrant clinical success. Patients with osteoporosis should at least meet the following 3 criteria: (1) painful VCF, (2) bone edema on MRI and (3) focal tenderness at fracture level, as assessed by a clinician on physical examination. Proper patient selection ensures that only patients with back pain due to the VCF are treated with PV. This was done in VERTOS II. However, in the two sham studies that were recently published these criteria were not used for inclusion. Thus, according to the criteria of VERTOS II, a proportion of patients in the sham studies had no indication for PV. This difference in patient selection largely explains the very limited decrease in pain after PV found in these sham studies.

VERTOS II: General results

We found that in patients with acute VCFs with persistent severe pain, PV performed at 6 weeks after onset of symptoms resulted in quicker and greater pain relief than did conservative treatment. After PV, patients had significant pain relief and used a lower class of drugs than did those receiving conservative treatment, or no drugs at all. Pain relief was sustained throughout follow-up. With conservative treatment, pain relief was slower and less than with PV, and pain medication required tended

to increase during the first month. Selection of optimal pain treatment and the psychological effect of care and daily attention accounted for the decrease in VAS score in the conservative treatment group during the first week.

The increased pain relief after PV remained significant throughout a year of follow-up. This finding is remarkable, since fracture healing in the control group should be completed within several months. However, some patients in the control group developed chronic back pain, possibly because of non-healing of the fracture. Future research should be aimed at identification of these patients.

For both quality of life (QUALEFFO) and function (RMD), improvement with time was significantly greater and quicker after PV than with conservative treatment.

Natural course of osteoporotic VCFs

In more than half of the patients with an acute VCF, pain spontaneously decreases to bearable levels (VAS-score ≤ 5) within several weeks. Timing of PV is under debate: treating all patients immediately after the onset of pain is optimal pain treatment at relatively high direct costs. A waiting period of about 6 weeks will exclude about half of the patients from PV. However, with acute PV patients can be mobilized immediately and complications of inactivity with inherent indirect costs can be avoided.

Cost-effectiveness of PV

Incremental costs of PV roughly equalled procedural costs, but because of substantial inter-individual variability with time, especially in the control group, the difference was no longer significant at 1 year. Data for costs and cost-effectiveness are only valid in the Netherlands and might differ for other countries. The resulting incremental cost-effectiveness suggests that PV seemed warranted for the patients with VCFs treated at a mean 5.6 weeks after start of symptoms.

Incidence of new VCFs after PV

The incidence of new VCFs in patients with an acute osteoporotic VCF was not different after PV compared with conservative therapy in the first year of follow-up. The only risk factor for the occurrence of new VCFs was the number of VCFs at baseline. PV contributed to preservation of stature by decreasing the incidence and severity of further height loss in treated vertebral bodies.

Cement leakage and pulmonary cement embolism

Minor cement leakage was frequently noted on CT, but leakage was asymptomatic in all cases. Cement leakage occurred more frequently with higher injected volumes. Late cement migration during follow-up did not occur. Standard post-procedural CT of the treated vertebral body in PV is therefore not necessary.

Chest CT showed that small and clinically silent pulmonary cement embolisms occurred in a quarter of patients treated with PV. Cement leakage into the azygos vein was the only risk factor. With time, these small cement emboli remained inert on follow-up CT without inflammatory pulmonary response.

PV versus kyphoplasty

The design of the FREE[17] study was similar to that of our study, with kyphoplasty used instead of PV. The FREE study compared kyphoplasty with nonsurgical care in 300 patients with acute VCFs. Instead of direct cement injection into the vertebral body, as in PV, kyphoplasty involves use of an inflatable bone tamp that forms a space in the vertebral body into which cement can be injected. This method is regarded to be in competition with PV. Kyphoplasty had a similar favourable effect on pain relief as did PV in our study, with rapid and sustained improvement. Also, pain relief in conservatively treated patients was in the same range. Some studies suggest that kyphoplasty is superior to PV in restoring vertebral body height[18]. Other studies indicate that PV also restores vertebral height to approximately the same extent[19]. However, the presumed difference in height restoration between the two techniques, if any, is small, with unclear clinical significance[19]. An advantage of PV is that the procedure can be done on an outpatient basis with local analgesia, whereas kyphoplasty requires general anaesthesia and hospital admission[20]. Additionally, kyphoplasty can generate procedural costs that are up to 20 times higher than those of vertebroplasty[21].

Critical gloss

The decrease in VAS score after conservative therapy from 7.5 to 5.6 during the first week might be the result of optimization of pain medication by the internist on a daily basis. Consequently, also family doctors can improve the standard pain treatment by tailoring the medication to the specific needs of the individual patient. In addition to the optimal pain medication, the psychological effect of care and daily attention also may have lowered the VAS score.

Analogous to conservative therapy, the psychological effect of receiving a PV

may to some extent have been responsible for the favourable results. On the other hand, the difference in VAS score favoring PV was still significant after 1 year. A placebo-effect is very unlikely to last that long. With conservative therapy, 24% of patients develop chronic back pain versus 6% after PV. This difference largely explains the better results of PV at one year follow-up.

The time needed for planning PV resulted in a mean 9 days delay in start treatment compared to conservative treatment. It is unlikely that this small difference in natural course affected outcomes at 1 month and 1 year. However, it could have influenced the results at 1 day and 1 week.

Clinical implications of VERTOS II: new life for PV

VERTOS II demonstrated that in a selected group of patients with acute osteoporotic vertebral fractures and persistent pain, vertebroplasty is effective and safe. Pain relief after the procedure is immediate, sustained for 1 year, and is significantly better than that achieved with conservative treatment and at acceptable costs. In the two sham studies, poor patient selection prevented to demonstrate the favourable effect of PV on pain. Publication of VERTOS II will provide clinicians with solid evidence that PV helps against pain in selected patients with VCFs. In the future, the sham studies should be repeated, now with better patient selection and probably with a third arm without intervention.

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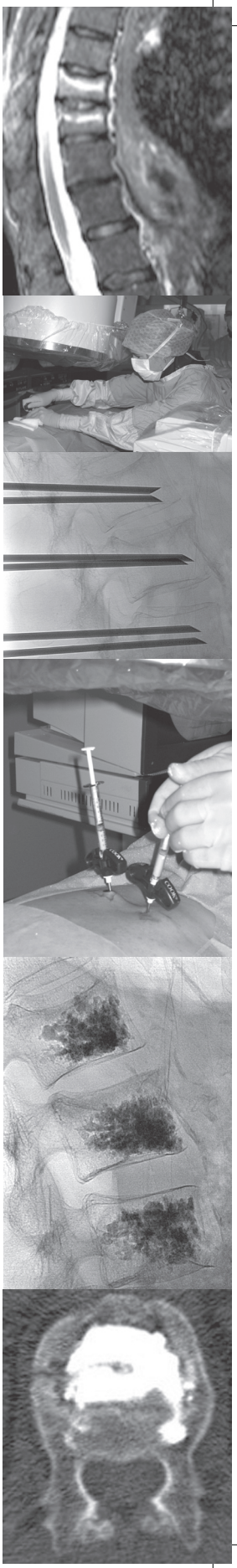
Cement bij ingezakte wervels verlicht pijn
MAAR NEEN MIJNHEER DEVRIES .. DAT IS VOOR HET BOUWEN VAN DE NIEUWE VLEUGEL
RRRRRR
CANARY PETE

Chapter 10

Summary en Samenvatting in het Nederlands



Summary

In **Chapter I**, an outline of this thesis is given.

In **Chapter 2** we prospectively determined the natural course of pain in patients with conservatively treated acute osteoporotic vertebral compression fractures (VCF). In addition, we assessed the type of conservative therapy that these patients received. The natural fracture healing, in terms of pain relief, of an acute, osteoporotic VCF mainly took place within the first 6 months. In view of the high percentage (31%) of patients with chronic pain due to an acute VCF with conservative therapy only, minimal invasive techniques should be considered. In the Netherlands, conservative treatment mainly consists of pain medication and physiotherapy and is prescribed by the general practitioner.

In **Chapter 3** rationale, objectives and design of the VERTOS II study are described. VERTOS II is an open-label randomized controlled trial comparing percutaneous vertebroplasty (PV) with optimal conservative pain management.

In **Chapter 4** the main outcomes of the VERTOS II study are analyzed en discussed. Our results show that in patients with acute osteoporotic VCFs who have persistent severe pain, PV done at a mean 5.6 weeks after onset of symptoms resulted in quicker and greater pain relief than conservative treatment did. Pain relief was sustained throughout a year of follow-up. After PV, patients used a lower class of drugs than did those receiving conservative treatment, or no drugs at all. With conservative treatment, pain relief was slower and less than with PV, and pain treatment required tended to increase during the first month. Some patients (24%) in the control group developed chronic back pain, possibly because of non-healing of the fracture. For both quality of life and function, improvement with time was significantly greater and quicker after PV than with conservative treatment.

Incremental costs of PV roughly equaled procedural costs. The cost of one pain-free day gained was €20. The trial-based incremental cost-effectiveness ratio for PV, as compared with conservative treatment, was €22,685 per quality adjusted life year gained. The resulting incremental cost-effectiveness suggests that PV seemed warranted for the patients with VCFs treated at a mean 5.6 weeks after start of symptoms.

In **Chapter 5** we found that the incidence of new VCFs in patients with an acute osteoporotic VCF was not different after PV compared with conservative therapy in the first year of follow-up. The only risk factor for the occurrence of new VCFs was the number of VCFs at baseline indicating the severity of osteoporosis. PV contributed to preservation of stature by decreasing the incidence and severity of further height loss in treated vertebral bodies.

In **Chapter 6** we assessed the incidence of pulmonary cement embolism by performing native chest CT during follow-up in a large proportion of patients from the VERTOS II trial. Small and clinically silent pulmonary cement embolism occurred in a quarter of patients treated with PV. Cement leakage into the azygos vein was the only risk factor. With time, these small cement emboli remained inert on follow-up CT, without inflammatory pulmonary response. Standard post-procedural CT or chest radiographs are not necessary.

In **Chapter 7** we assessed the incidence, anatomical location, and clinical impact of perivertebral cement leakage on short- and long-term in a large patient cohort. Cement leakage after PV outside the vertebral body was frequently detected on CT. Most leakages are into adjacent disks or segmental veins and all patients were asymptomatic. Cement leakage occurred more frequently with higher injected volumes. Late cement migration during follow-up did not occur. Standard post-procedural CT of the treated vertebral body in PV is not necessary.

In **Chapter 8** pain management during PV is evaluated. In a substantial proportion of patients, local anaesthesia was not sufficient for pain reduction during PV. The severity of pain experienced by the patient is usually not appreciated correctly by the operator.

In **Chapter 9** the results of the VERTOS II study are interpreted and the clinical implications are discussed.

Samenvatting in het Nederlands

In **Hoofdstuk 1** wordt een algemene inleiding gegeven.

In **Hoofdstuk 2** hebben we prospectief het natuurlijk beloop van pijn veroorzaakt door een conservatief behandelde, acute wervelfractuur in kaart gebracht. Daarbij hebben we onderzocht welke conservatieve behandeling in Nederland wordt gegeven. De fractuur genezing (en dus pijn afname) van een acute osteoporotische wervelfractuur vond voornamelijk plaats gedurende de eerste 6 maanden. Het hoge percentage (31%) patiënten dat chronisch pijn ontwikkelt na alleen conservatieve therapie rechtvaardigt de overweging van minimaal invasieve technieken voor de bestrijding van pijn. Conservatieve therapie bestaat in Nederland voornamelijk uit pijnmedicatie and fysiotherapie en wordt voorgeschreven door de huisarts.

In **Hoofdstuk 3** zijn de studie opzet en eindpunten van de VERTOS II studie beschreven. VERTOS II is een open-label gerandomiseerde gecontroleerde trial waarin percutane vertebroplastiek (PV) wordt vergeleken met optimale conservatieve therapie.

In **Hoofdstuk 4** zijn de belangrijkste uitkomsten van de VERTOS II studie geanalyseerd en beschreven. Onze resultaten laten zien dat patiënten met ernstige persisterende pijn door een acute wervelfractuur (gemiddeld 5,6 weken na start pijn) een snellere en betere pijnafname hebben na PV dan na conservatieve therapie. Zelfs 1 jaar nadien hadden patiënten met PV nog minder pijn dan met conservatieve therapie. Na PV gebruikten patiënten ook een lagere klasse pijnmedicatie dan na conservatieve therapie, of helemaal geen pijnmedicatie meer. Met conservatieve therapie nam de pijn niet alleen langzamer, maar ook in mindere mate af. Bijna een kwart van de patiënten met conservatieve therapie ontwikkelde zelfs chronische rugpijn, waarschijnlijk op basis van onvolledige consolidatie van de wervelfractuur.

Ook verbetering in kwaliteit van leven en functie was significant beter en sneller na PV dan na conservatieve therapie.

De additionele kosten van PV komen overeen met de kosten van de procedure. De kosten per gewonnen pijnvrije dag bedragen €20. De kosteneffectiviteit ratio voor PV vergeleken met conservatieve therapie bedroeg €22.685 per gewonnen

jaar rekening houdend met de kwaliteit van leven. De kosteneffectiviteit ratio suggereert dat PV kosteneffectief is voor patiënten met een osteoporotische wervelfractuur van gemiddeld 5,6 weken oud.

In **Hoofdstuk 5** beschrijven we dat de incidentie van nieuwe wervelfracturen in patiënten met een acute osteoporotische wervelfractuur gedurende 1 jaar follow-up gelijk is na PV vergeleken met conservatieve therapie. De enige risicofactor voor het ontstaan van een nieuwe wervelfractuur was het aantal wervelfracturen op baseline, als een maat voor de ernst van de osteoporose. PV beschermt zelfs tegen verdere inzakking van de behandelde wervels en draagt daarmee bij aan het behoud van houding en longfunctie.

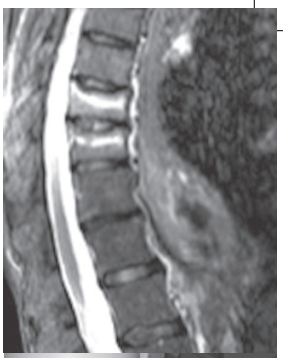
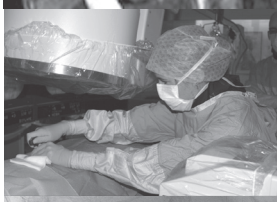
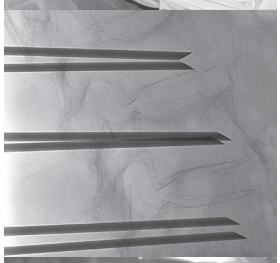
In **Hoofdstuk 6** hebben we met CT de incidentie van cement embolieën in de longen geanalyseerd in een groot deel van de patiënten uit de VERTOS II studie. Kleine, asymptomatische cement embolieën zagen we op CT in ongeveer een kwart van de patiënten na PV. Cement lekkage in de vena azygos was de enige risicofactor. De cement embolieën bleken inert en gaven geen ontstekingsreactie is het omliggende longweefsel op vervolg CT. Het standaard vervaardigen van een vervolg thorax foto of CT na PV is dan ook niet nodig.

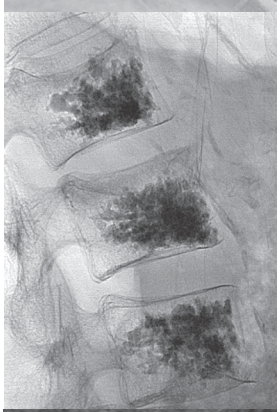
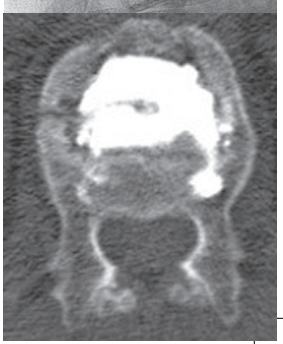
In **Hoofdstuk 7** hebben we de incidentie, anatomische locatie en klinische impact van perivertebrale cementlekkage op de korte en lange termijn in een grote groep patiënten geëvalueerd. Cementlekkage na PV buiten het wervellichaam werd frequent gedetecteerd op CT. De meeste cementlekkages waren in de aangrenzende tussenwervelschijven of segmentale venen en alle patiënten bleven asymptomatisch. Injectie van meer cement vergrootte het risico op lekkage. Latere cementmigratie werd niet gezien. Een standaard CT-scan van de behandelde wervel hoeft niet vervaardigd te worden.

In **Hoofdstuk 8** wordt pijnbestrijding tijdens de PV procedure besproken. Locale verdoving is niet voor alle patiënten afdoende. De subjectieve pijnbeleving ervaren door de patiënt gedurende de procedure wordt veelal onderschat door de uitvoerend radioloog.

In **Hoofdstuk 9** worden de resultaten van de VERTOS II studie geïnterpreteerd en de implicaties ervan bediscussieerd.

Dankwoord

Dit proefschrift is tot stand gekomen met hulp, vertrouwen en inzet van velen. Graag wil ik iedereen bedanken die zijn/haar steentje heeft bijgedragen.
Een aantal mensen wil ik in het bijzonder bedanken.

Allereerst wil ik mijn promotoren en co-promotoren bedanken.
Professor Mali, in het eerste gesprek over de VERTOS II studie vroeg u, weet je wel waar je aan begint om zo'n studie op te zetten tijdens je opleiding? Dat wist ik inderdaad niet en dat was maar goed ook. Bedankt voor de goede en prettige begeleiding, heldere inzichten en constructieve commentaar.
Professor de Vries, beste Jolanda, je bent iemand waar je energie van krijgt. Onze besprekingen waren altijd kort, krachtig en gezellig.
Dr. Lohle, beste Paul, als pionier van de vertebroplastiek in Nederland heb je de studie bedacht. Bedankt voor het vertrouwen dat ik dit mocht gaan doen. Op moeilijke momenten in de studie stond je vierkant achter me. Bedankt voor je steun, begeleiding en praktische inzichten.
Dr. Verhaar, beste Harald, je internistische benadering bracht balans in de besprekingen. Bedankt voor je waardevolle commentaar.

Bij het tot stand komen en de uitvoering van de VERTOS II studie is een cruciale rol vervuld door de leden van de VERTOS II studie groep: Drs. Jansen, Dr. Tielbeek, Dr. Blonk, Monique Vos, Riekie van Beers, Drs. Schoemaker, Dr. Juttmann, Janny van der Laar, Dr. Elgersma, Drs. Halkema, Dr. Valk, Femmy Meenhorst, Dr. van Everdingen, Dr. Muller, Marianne Deelen, Drs Lo, Drs. Fransen, Drs. Janssens, Ruth de Meester. Bedankt voor jullie enorme inzet om patiënten te selecteren, randomiseren, behandelen en begeleiden.
Professor Buskens, beste Erik, bedankt voor het begeleiden van de kosteneffectiviteit analyse en waardevolle commentaar.
Marianne Versloot, bedankt voor je geweldige inzet voor de studie. Je hebt niet alleen patiënten geselecteerd en begeleid, maar ook meegedacht over de vragenlijsten en patiënten flow, de database ingevoerd en gezorgd dat alle data compleet waren. Het was heerlijk om regelmatig onder het genot van een kopje choco de ins en outs van de studie te bespreken.

Professor van Rooij, beste Willem-Jan, afgelopen jaar hebben we dagen lang samen artikelen verbeterd en commentaren beantwoord. Jij kunt ongelofelijk goed schrijven en hier heb ik veel van geleerd. Je beste advies: een artikel moet lezen als een spannend jongensboek. Bedankt voor je steun en geweldige (altijd snelle) inzet.

Alexander Venmans, toen je de VERTOS 3 studie opstartte zaten we in het zelfde schuitje. We hebben samen onderwerpen voor artikelen bedacht en 100den foto's gescoord. Het is erg prettig samenwerken met iemand die zo integer is als jij. Gelukkig staat ons volgende gezamenlijke artikel al weer op stapel.

Dr. Sluzewski, beste Menno, bedankt voor het ontwerpen van de omslag.

De maatschap radiologie van het St. Elisabeth Ziekenhuis Tilburg, bedankt dat jullie mij de mogelijkheid hebben gegeven om de opleiding te combineren met wetenschappelijk onderzoek.

De maatschap radiologie van het Medisch Spectrum Twente, bedankt voor jullie steun, interesse en enthousiasme. De eerste vertebroplastieken hebben we nu gedaan, dat er nog velen mogen volgen.

Cees en Anneke, jullie hebben een geweldig trialbureau. Bedankt voor jullie inzet en het bouwen van de database.

Karin, bedankt voor de lay-out. Je geeft de deadlines goed aan en werkt heel secuur.

Lieve Joris en Nicole, bedankt voor jullie niet-aflatende belangstelling en gezelligheid. Familie is voor altijd.

Lieve Juul en Eef, ik ben blij met zulke lieve vriendinnen.

Lieve Patricia, Paatje, wat fijn dat jij mijn paranimf wil zijn. Al bijna 20 jaar een van mijn beste vriendinnen. Samen alles doorlopen: middelbare school, studeren en opleiding in het EZ. Ik verwacht je eigenlijk komend jaar ook in Enschede! Dank voor je fantastische humor, gezelligheid en relativeringsvermogen.

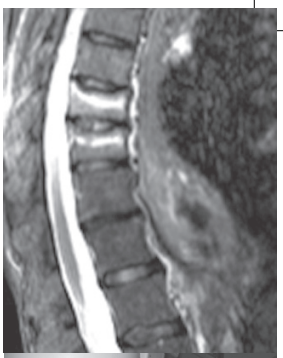
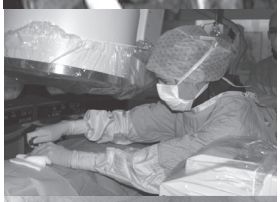
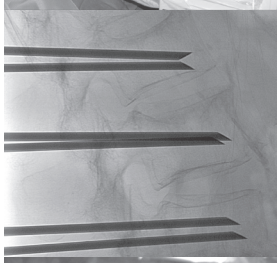
Lieve Anjob, Anjobski, met jou naast me als paranimf durf ik het wel aan. Sinds we samen hockeyden bij Kampong ben je een van mijn beste vriendinnen geworden. Samen hebben we de opleiding doorlopen. Op jouw vriendschap kun je echt bouwen! Dank voor alle gezelligheid en steun afgelopen jaren.

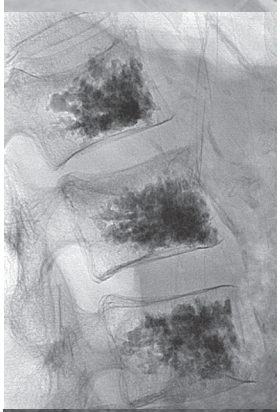
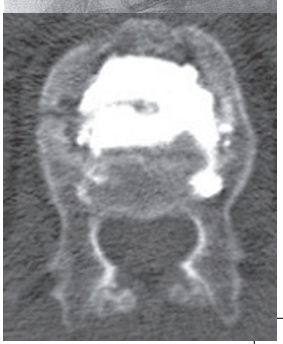
Lieve pap en mam, jullie onvoorwaardelijke liefde en steun hebben mij gemaakt tot wie ik ben. Jullie betrokkenheid is ongelofelijk. Dank voor alles.

Lieve Annemijn en Fréderique, mijn kleine meisjes, jullie zijn waar het echt om draait. Jullie lieve vrolijkheid en ondeugendheid maken alles mooier.

Lieve Bram, de Moor I see you, the more I want you.

Curriculum Vitae

Curriculum Vitae

Caroline Anne Henriette Klazen was born on April 7th, 1977 in Berkel-Enschot, The Netherlands. She started her medical training at the University of Utrecht in 1995 and obtained her medical degree in 2002. After one year as a resident at the emergency room at Mesos Medisch Centrum, she started her radiology residence in October 2003 at the St. Elisabeth Hospital Tilburg (Dr. K.H. Schuur and Dr. P.N.M. Lohle). In 2005 she started the VERTOS II study under supervision of Prof. W.P.Th.M. Mali and Dr. P.N.M. Lohle. She completed her residency in Radiology in November 2009. Since February 2010 she is attached to Medisch Spectrum Twente as a radiologist.