Percutaneous Vertebroplasty for Painful Long-Standing Osteoporotic Vertebral Compression Fractures

Indication, Clinical Outcome, Cement Leakage & Classification

Colophon

The studies described in this thesis were performed at the department of Orthopaedic Surgery of the Leiden University Medical Center, Leiden, The Netherlands.

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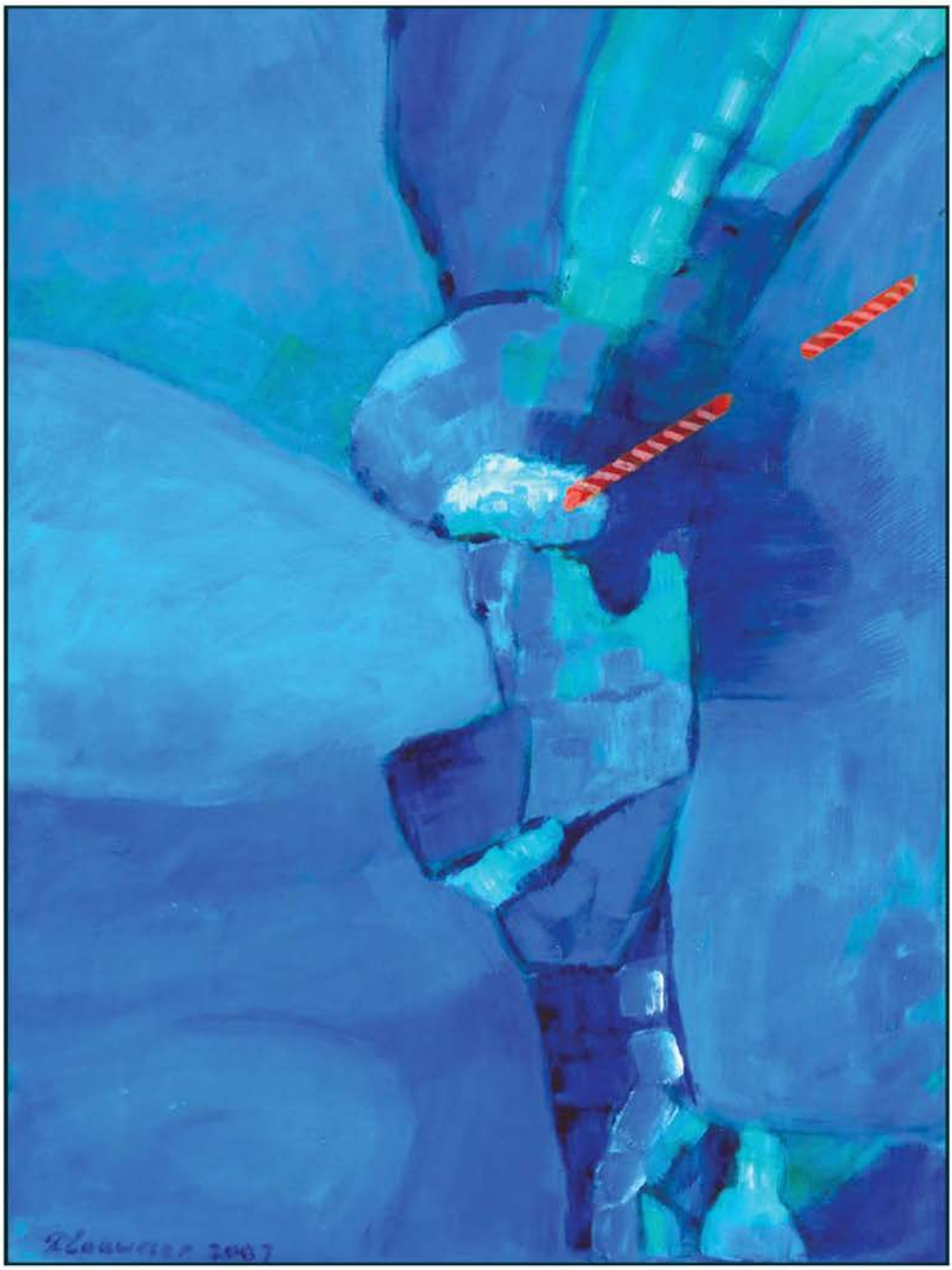

Patients artistic impression on vertebroplasty (Mw. T. Louwrier).

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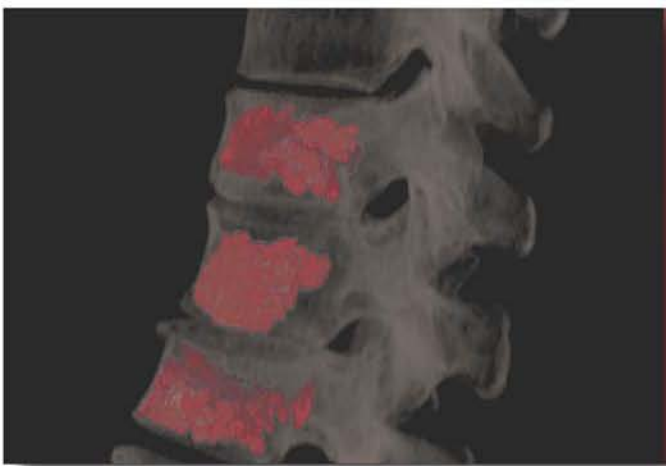

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General Introduction & Outline of the Thesis

General Introduction

The History of Percutaneous Vertebroplasty

Percutaneous VertebroPlasty (PVP) involves the percutaneous injection of liquid bone cement, usually PolyMethylMethAcrylate (PMMA) and an opacifier (barium or zirconium oxide) into the inter-trabecular marrow space of a vertebral body.

Vertebroplasty was initially developed to be used in combination with an open surgical procedure to fill large voids as a result of tumour resection. In 1984, Galibert and Deramond performed the first ever documented PVP at the University Hospital of Amiens, France.[1] The procedure was used in a patient with severe cervical pain, due to a large vertebral haemangioma encompassing the entire C2 vertebral body. A 15-gauge needle was inserted and acrylic cement was injected into the C2 vertebral body via an anterolateral approach. This case, as published in 1987, reports complete pain relief in this patient.[1]

A paper in the *American Journal of Neuroradiology* in November 1997,[2] describing a trial from the University of Virginia, which comprised 29 patients followed over a period of three-years, with promising outcomes of PVP in treatment of Osteoporotic Vertebral Compression Fractures (OVCFs), prompted a sudden and major increase in the number of PVP procedures being performed.

Next to the "traditional" PVP, a comparable procedure encompassing PVP in combination with an inflatable balloon tamp (often referred to as kyphoplasty (KP)), arose in the early 1990s and shows comparable clinical outcomes.[3] The evidence for performing kyphoplasty is however beyond the scope of this thesis and therefore will not be discussed.

Percutaneous Vertebroplasty: Performing the Procedure

PVP can be performed in multiple ways. In some institutions, the procedure is performed under general anaesthesia using a single C-arm in the operating room. In our institution however, the procedure is performed under conscious sedation using bi-plane fluoroscopy in a radiological intervention suite. Bellow the procedure, as performed in our institution (Leiden University Medical Center), is briefly described.

The patient is admitted at the day-care department and 30 minutes after oral pain medication (Symoron 5mg and Paracetamol 1000mg), transferred to the radiology department. The patient is placed in prone position on a standardized cushion, in such a way that the regions caudally and cranially from the fractured vertebra(e) are supported. The patient is prepared and draped in a sterile fashion. Conscious sedation is administered using injectable Fentanyl and Midazolam (doses depending on weight and procedure duration). During the procedure, saturation, blood pressure and heart rate are continuously monitored. Using Bi-plane fluoroscopy **(Figure 1)**, the fractured level is identified.

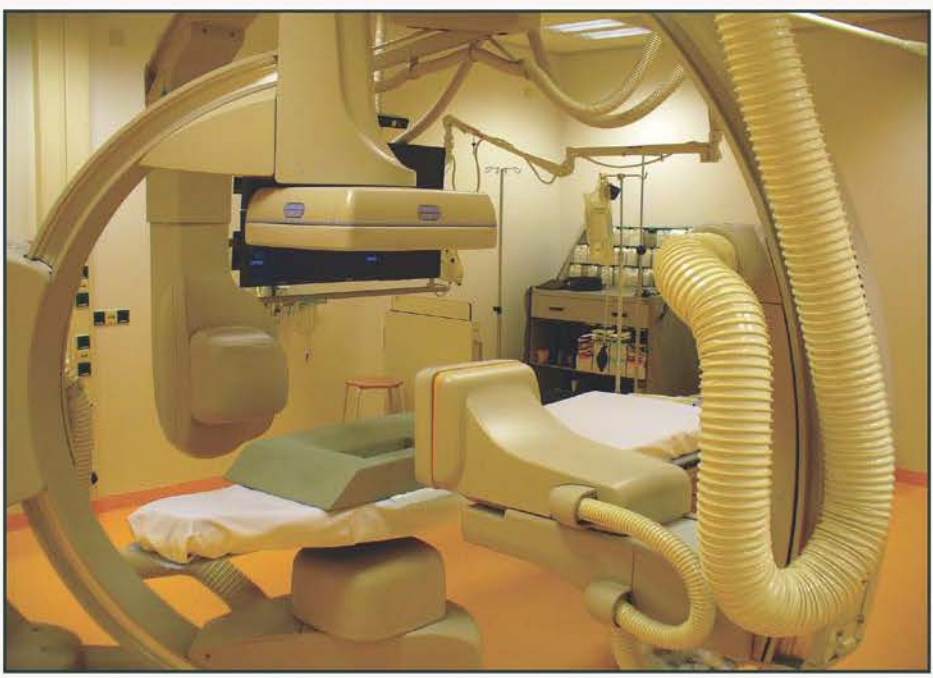

Figure 1. Bi-plane fluoroscopy set-up. Important advantage of this system is the possibility of direct manipulation of the position of the x-ray tubes by the specialist performing the intervention using the sterile dressed control panel.

High quality fluoroscopy is mandatory in order to safely perform PVP. First the lateral X-ray tube is positioned in such a way that the caudal pedicle arches are superimposed and the upper and lower endplate will project as parallel as possible on the fluoroscopy image (depending on the grade of vertebral collapse) **(Figure 2)**.

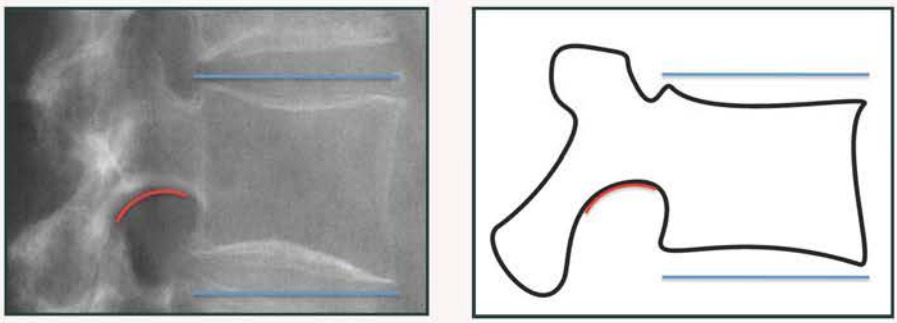

Figure 2. Superimposition of the pedicles (red lines) and parallel projection of the endplates (blue lines).

Next, in antero-posterior (AP) direction, the spinal processus are projected in the centre of the vertebral body and the pedicles should project over the upper third of the vertebral body. The projection of the "pedicle ring" results from projection of the isthmus of the pedicle **(Figure 3)**.

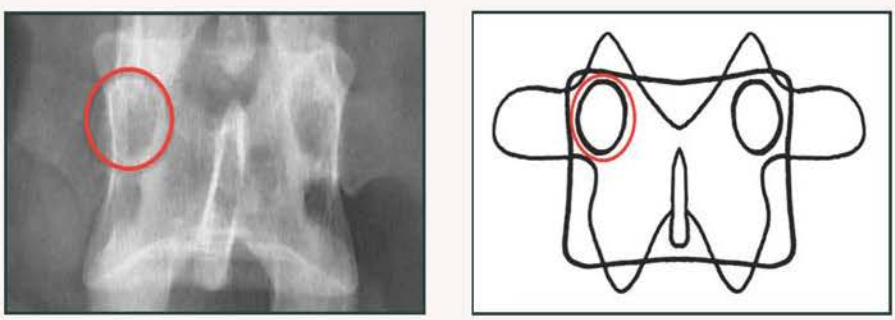

Figure 3. AP projection of the vertebral body (left), red circle: projection of the isthmus of the pedicle at the fluoroscopy image. Projection of the vertebral body (right), red circle: projection of the isthmus of the pedicle.

Local anaesthesia is achieved by injection of Lidocaine 1%. The position of the thin needle used for lidocaine injection determines the direction of the needle tract during fluoroscopy. This tract will be used for introduction of the large beveled PVP needle. Thus optimal introduction through the soft-tissues, without repeated placement of the large diameter (10G) PVP needle can be obtained. The preferred entrance is at ten-o-clock for the left pedicle, and two-o-clock for the right pedicle at the cranio-lateral border of the pedicle.

Under biplane fluoroscopy guidance and using a small mallet, one (preferred) or two needles are gently introduced into the vertebral body through a trans- or extra-pedicular route (depending on the level to be treated).

The trans-pedicular route is the easiest and safest route to the vertebral body in the lumbar spine. During the insertion of the needle into the vertebral body, the cortex of the pedicle surrounds the needle. However due to the position and angulation of the pedicles of the thoracic vertebral body and due to the fact that these (higher) thoracic vertebral bodies have a more pronounced apex, a trans-pedicular route is not advised for the (higher) thoracic vertebras. To access the (higher) thoracic spine, usually the extra-pedicular approach is used. For extra-pedicular approach the needle is inserted between the lateral margin of the pedicle of the thoracic vertebrae and the rib head.

During insertion of the needle, the beveled tip can be used to gain easy access to the pedicle by pointing the bevel laterally. When the needle has penetrated into the pedicle, prevention of perforation of the medial pedicle wall can be obtained by rotating the beveled side of the needle 180° to the medial pedicle wall **(Figure 4).**

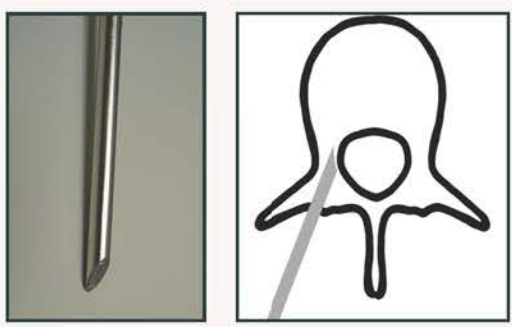

Figure 4. The beveled needle tip design facilitates easy and safe access to the vertebral body without penetration of the medial pedicle wall.

When lateral fluoroscopy shows that the tip of the needle has passed beyond 50% of the length of the pedicle, and PA projection shows a position of the needle lateral to the medial pedicle wall, a safe entrance into the vertebral body has been achieved.

At our institution, vertebral body bone biopsy and vertebroplasty are performed in one session using the following technique: the biopsy needle is inserted through the vertebroplasty needle just after penetration of the vertebral

body. The biopsy needle is withdrawn and the vertebroplasty needle is advanced through the same needle tract (see also, **Chapter 3** of *this thesis*). The preferred position of the needle is just lateral to the middle of the anterior one third of the vertebral body. If this position cannot be achieved, a second needle can be inserted through the contra-lateral pedicle. However placement of a second needle can also be done at a later stage during the procedure in case of inadequate cement interdigitation through the first needle.

The PMMA cement is prepared and transferred to an injector. The air is eliminated from the system. After 2-4 minutes after the start of cement mixing (depending on the viscosity of the cement and on the room temperature), the cement has reached its proper viscosity (toothpaste-like), and is ready to be injected. The cement is than injected slowly and carefully under constant bi-plane fluoroscopic imaging in order to achieve good filling of the intertrabecular space of the vertebral body and thus a minimal chance of major cement.

The injector is disconnected from the needle. Twelve to fourteen minutes after mixing, the needle is twisted to separate the tip from the cement. Then the needle(s) is (are) removed from the vertebral body. A post-procedural CT-scan is performed and the patient is placed in bed for transport to the ward. The post-procedural hospital stay is a minimum of 3 hours. Fast reactivation of the patient is started after the effect of the fentanyl and midazolam has ended, additional bed rest is not mandatory. When the overall clinical condition permits, the patient is discharged.

The Indications for Percutaneous Vertebroplasty

Although vertebroplasty was first used in spinal tumour surgery, the spectrum of indications for performing PVP has been increased since then. The procedure is also used for painful pathological compression fractures of other aetiologies, like trauma, aggressive vertebral haemangioma **(Figure 5)**, multiple myeloma **(Figure 6)** or bone metastasis.[4-8] PVP can offer mechanical stability to vertebral bodies, which are weakened by tumour invasion, and prevent further bone destruction when bone cement is injected between the trabeculae of the remaining unaffected bone.

Patients with disseminated disease and spinal metastasis and patients with primary vertebral malignant disease, who are non eligible candidates for extensive open surgery due to a combination of co-morbidity caused by malignant disease itself or due to (chemo)therapy, but are suitable candidates for a minimal

invasive procedure like PVP. Furthermore, the fact that PVP is performed in day-care and has a low morbidity rate and a quick potential pain relief, makes it an acceptable investment of time for patients with a short life expectancy.

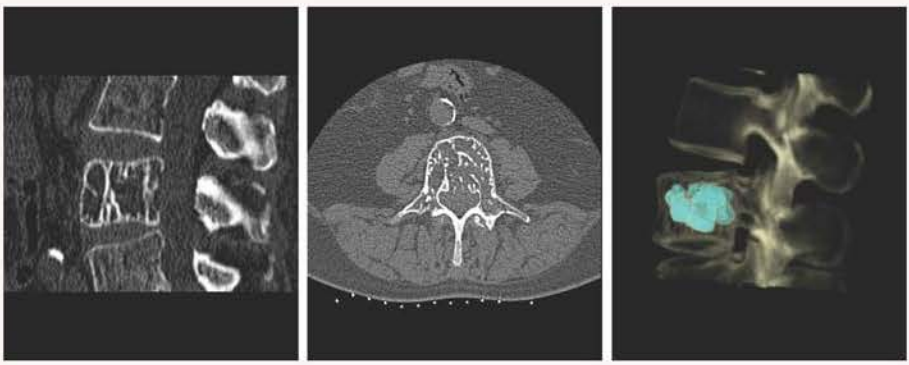

Figure 5. Painful pending vertebral collapse due to an aggressive haemangioma treated with PVP. From left to right: sagittal and axial CT-reconstruction both showing the specific trabecular destruction leading to a typical cement filling pattern as seen at a 3D CT-reconstruction (far right).

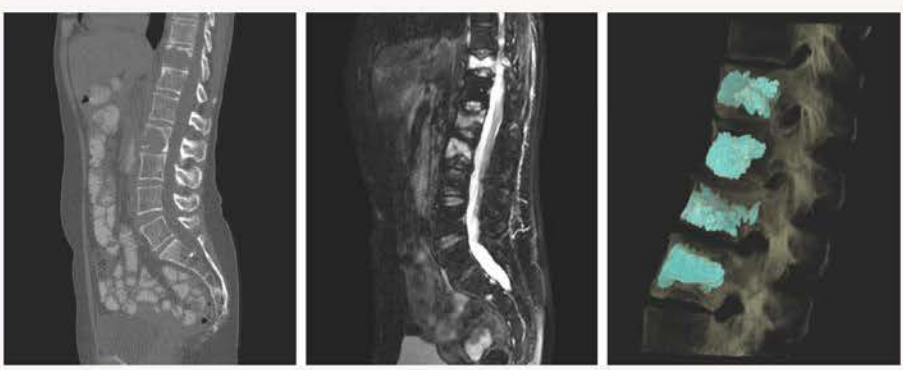

Figure 6. Vertebral destruction due to multiple myeloma, treated with PVP. From left to right: Sagittal CT-reconstruction showing extensive destruction of Th11 and L2. Sagittal reconstruction T2 MRI showing BME, most pronounced at Th11 and L2. Post-procedural 3D CT-reconstruction.

Due to its high incidence, compared to the above-mentioned indications, a painful compression fracture due to osteoporosis is the most common indication for PVP. The indication triad for PVP in OVCFs at our institution consists of I) incapacitating pain at the fractured level, with focal point tenderness, which increases when pressure is applied to the spinous process of the fractured vertebra,[10,11] II) unresponsiveness to at least 6-8 weeks of conservative treatment[9] and III) Bone Marrow Edema (BME) in the fractured vertebral body diagnosed at MR Imaging (see also, **Chapter 2** of *this thesis*).[12-14] **(Figure 7)**

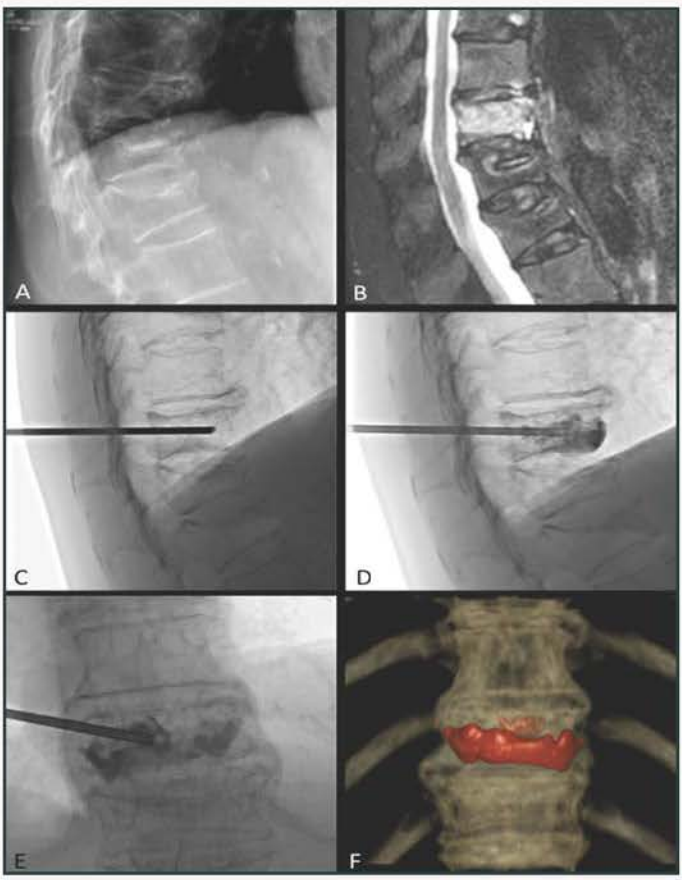

Figure 7. Example of a patient with multiple OVCFs as seen on the plain radiograph (A). On MR Imaging only one vertebra shows intravertebral BME (B). Lateral fluoroscopy images (C) and (D) show insertion of the needle and injection of the bone cement respectively. AP fluoroscopy image of cement injection (E) and 3D CT-reconstruction of the treated vertebra with cement (depicted in red).

Osteoporotic Vertebral Compression Fractures

The Osteoporotic Vertebral Compression Fracture (OVCF) is, with an estimated prevalence in the Netherlands of 18% for men and 22% for women above the age of 55 years, the most common complication of osteoporosis.[15-18]

In the year 2000, Dutch hospitals registered over 40.000 new vertebral fractures due to primary or secondary osteoporosis and with the ageing population it is expected that this number will increase throughout the upcoming years.[19] The Dutch population is expected to have the highest absolute increase of the number of OVCFs in the twenty-first century, compared to the other members of the European Union,[19]

Two thirds of the OVCFs have no clinical symptoms, they are "silent" fractures and are asymptomatic and as such there is no need for direct medical attention other than screening and treatment for osteoporosis in order to reduce the chance of new fractures.[20, 21]

In the group of patient with clinical symptoms due to an OVCF (one-third of all patients with a OVCF), pain is the most striking feature of the fracture. Next to pain, diminished mobilization is caused by progressive kyphosis, which in turn gives a decrease in lung capacity, with a subsequent decreased physical condition, which eventually results in an increase of bone loss, which is again the first step in a vicious circle leading to more OVCFs.[22, 23]

Treatment of Painful Osteoporotic Vertebral Compression Fractures

In 80-85% of the acute symptomatic patients, pain will disappear with conservative treatment within 6-8 weeks after initiation of treatment.[24-26] In the Netherlands, conservative treatment is therefore the preferred initial treatment in patients with an acute symptomatic OVCF without neurological symptoms. Conservative therapy involves a short period of bed rest (for a few days) and administration of oral analgesics and, optionally, short-term use of a thoraco-lumbar brace in order to achieve reduction of pain.[27] In case of neurological symptoms due to spinal stenosis, an open decompression combined with posterior stabilisation using pedicle screws, and vertebroplasty of the anterior vertebral column can be the treatment of choice.

Patients without neurological deficit, and no reduction of pain after 8 weeks of conservative treatment have a high chance of ending in a chronic circle of repeated pain attacks, with intermittent temporary pain relieve of a period for

up to two years.[24] For this group constituting 15-20% of the symptomatic OVCFs, i.e. patients with fractures refractive to conservative treatment, PVP can, after a careful workup, be the treatment of choice.

Outcome in Osteoporotic Vertebral Compression Fractures

Because of its reported fast analgesic effects, high effectiveness, low complication rate and relatively low cost, PVP has emerged as a widely used minimal invasive treatment of painful OVCFs over the past two decades.[28] The effect of PVP for OVCFs on pain is reported to be fast and reaches a plateau phase within a few days after the procedure.[29] After this period, the pain-scores do not change (see also, **Chapter 4** of *this thesis*).[30-33]

A meta-analysis of 60 studies reporting pre- and post-operative Visual Analogue Scale (VAS) scores (in which 10 represents excruciating pain) showed a mean pre-operative VAS of 8.36 (SD±0.78) and a mean post-operative VAS of 2.86 (SD±1.09). A mean and significant change in pain of 5.68 (SD±1.24)) on the VAS scale was found after PVP.[3]

Unfortunately, severe methodological problems exist in published studies so far. Most studies focus only on (often short term) pain outcome and do not report the use of any type of validated questionnaires reporting general Quality of Life, making it impossible to compare the PVP procedure with other (non- or minimal-invasive) procedures (see also, **Chapter 4** of *this thesis*). Furthermore, the majority of papers describe populations that are a case mix of "acute" (fracture age < 8 weeks) and "long-standing" (fracture age >8 weeks) OVCFs. The former having frequently a favourable natural course (there is a high chance that an acute OVCF will heal even without treatment).

Complications in Osteoporotic Vertebral Compression Fractures

The rate of clinically relevant complications after PVP for OVCFs is low. Complication rates reported range between 1.6% and 2.8%.[34] Most of these clinically relevant complications are due to leakage of bone cement (see also, **Chapter 5 & 6** of *this thesis*). Severe complications are rare and occur mainly in cases of high-volume cement leakage and are mainly reported in case reports.[35-38] Leakage of cement into the neural foramen or spinal canal can cause neurological injury.[39] Procedure related complications unrelated to cement leakage include; misplacement of the needle, rib fractures, pneumothorax, fracture of spinous process or pedicle, subcutaneous paravertebral haematoma and infection.[32, 40-45]

Aim and Outline of this Thesis

This thesis focuses on indications for and the clinical outcome of PVP for the treatment of long-standing OVCFs (i.e. after more than 8 weeks after onset of symptoms). Secondly, emphasis is made on the value of vertebral body biopsy during the vertebroplasty procedure in order to aid in early diagnosis of unexpected conditions. Thirdly, in line with the worldwide emerging registration and control of medical implants, emphasis is put on the need for careful registration of cement leakages, since these count for the largest number of clinically relevant complications of the vertebroplasty procedure.

Chapter Outline of this Thesis

The correlation between the amount of BME and the clinical outcome (pain) of PVP is discussed in **Chapter 2.** In **Chapter 3**, the outcome of a routine bone biopsy during PVP in treatment of "osteoporotic" vertebral fractures, was studied. A prospective follow-up study on the clinical outcome (Quality of Life as measured with the SF 36) up to 36 months after PVP for long-standing OVCFs, is discussed in **Chapter 4**. In **Chapter 5,** the clinical outcome of PVP in patients with long-standing OVCFs, treated with either low or medium viscosity PMMA bone cement, was evaluated in a prospective comparative follow-up study. In **Chapter 6,** a new system for **E**valuation and registration of e**X**tra vertebral cement leakage based on **A**natomy and **V**olume of the leakage using **CT**-scan analysis (the EXACT classification system), is proposed. Finally, in **Chapter 7** a review of the scientific evidence for PVP is presented.

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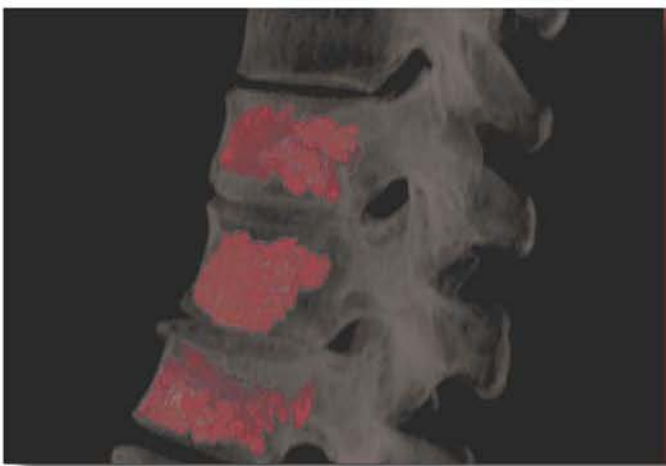
INDICATION

Chapter



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The Amount of Bone Marrow Edema Does Not Predict the Outcome in Single Level Percutaneous Vertebroplasty For Painful Osteoporotic Compression Fractures

Submitted

Abstract

In this study the influence of the pre-procedural intravertebral Bone Marrow Edema (BME) on post-operative pain relief in patients treated with single level Percutaneous VertebroPlasty (PVP) for non-acute osteoporotic vertebral compression fractures (OVCF) is investigated. Twenty-five patients with single level, BME containing OVCFs were included. BME volume and the percentage of the vertebral body filled with BME was volumetrically analyzed.

The mean BME volume was 11.4 mL (SD 8.2, range 2.6 – 29.3), which corresponded to a mean percentage of vertebral body volume of 46.0% (SD 19.5, range 10.0 – 71.4). During a 1-year follow-up, pain intensity was documented before PVP and 1, 4, 12 and 52 weeks after PVP.

A good clinical response to the PVP procedure was seen in all patients: pain decreased from 7.6 (SD 1.3) points before PVP to 5.3 (SD 2.6), 5.3 (SD 2.6), 3.7 (SD 2.3) and 2.9 (SD 2.2) points at 1, 4, 12 and 52 weeks follow-up. No association between the pain score and the percentage, ranging from 10%-70% BME, was found. The percentage of the vertebral body filled with BME on pre-procedural MRI does not predict the magnitude of pain reduction when performing PVP in single level non-acute OVCF.

Introduction

Percutaneous vertebroplasty, a procedure in which liquid bone cement is percutaneously injected into painful osteoporotic compressed vertebral bodies, is thought to relieve pain due to the stabilizing effect of the cured bone cement after polymerization. The precise mechanism (mechanical, or chemical) is still not completely known, but it has been shown that the bone cement halts movement within the fractured vertebral body and thus prevents further collapse.[1] Although recently some debate exists on the effect of this procedure, analysis of factors determining the clinical entity of Osteoporotic Vertebral Compression Fractures (OVCF) is of importance to evaluate the effectiveness of PVP.[2,3]

Subacute (>2 month old) and chronic (>6 month old) OVCFs are fractures which do not respond to at least 8 weeks of conservative treatment using analgesics, a short period of bed rest and a corset. Therefore, the indication triad for PVP in our institution consists of I) incapacitating pain at the fractured level,unresponsive to conservative treatment[4]; II) focal point tenderness, which increases when pressure is applied to the spinous process of the fractured vertebra[5,6]; and III) Bone Marrow Edema (BME) in the fractured vertebral body diagnosed at MR Imaging.[7-9]

In literature, it is stated that, intravertebral BME on MR Imaging is one of the indication criteria for treating painful OVCFs with PVP. A MR Imaging sequence with fat suppression, usually T2 Short Tau Inversion-Recovery (STIR) or Spectral Presaturation with Inversion Recovery (SPIR), leads to images in which structures with a high water content show a high signal and thereby visualize BME.

Intravertebral BME is seen in OVCFs that have not fully been healed. In these vertebra it is thought that persistent pain is caused by movement in unconsolidated (micro)fractures. The cause of persistent BME in chronic fractures might be explained by the altered healing cascade in these fractures compared to fractures in longbones.[10]

So far a small number of papers concerning BME in PVP have been published, however due to heterogeneous groups (acute vs chronic and multiple level vs single level), no conclusions regarding the influence of the volume of BME in chronic OVCFs can be made.[11-13] Furthermore there is no consensus about the percentage of the vertebral body that has to be filled with BME in order to be an indication for PVP nor on the relation to the clinical results after PVP.

The goal of our present study was to assess the influence of the pre-procedural intravertebral BME on the clinical outcome on pain in patients treated with PVP for single level non-acute OVCFs.

Patients and Methods

Patients were included from a consecutive series of 217 patients treated with PVP for painful OVCFs at our institution between August 2002 en January 2010. Inclusion criteria for PVP were: (I) An osteoporotic vertebral compression fracture including those with a severe compression deformity, (II) local mid-line back pain refractory to conservative treatment for at least 8 weeks, (III) back pain related to the site of the fracture on MR Imaging, (IV) the presence of intravertebral BME in the collapsed vertebral body on MR Imaging T2- weighted Short Tau Inversion Recovery (STIR) sequences, and (V) age over 40 years.

Exclusion criteria were (I) multiple OVCFs with intravertebral BME, (II) spinal cord compression or vertebral canal stenosis of >30% of the local canal diameter, (III) neurologic deficits, (IV) bleeding disorders, (V) infections related to the vertebral column, (VI) inability of the patient to lie in prone position for 2 hours, (VII) an American Society of Anesthesiologists-score ≥ 4 and (VIII) vertebral cleft fractures.

In this study, twenty-five patients (4 male, 21 female, mean age of 72.0 (SD 7.7) years) with a single level, intravertebral BME containing, OVCF with a mean time between onset of symptoms and PVP of 5.7 months (SD 2.6), were included for a prospective study.

All patients underwent a pre-operative radiograph of the spine (AP and lateral), a MR Imaging scan using a sequence with fat suppression, T2 Short Tau Inversion-Recovery (STIR) of the complete spine to visualize intravertebral BME with sagittal reconstructions using 5-millimeter slice thickness.

The levels of the treated chronically painful OVCFs were Th5(1), Th6(1), Th7(2), Th8(1), Th9(1), Th11(1), Th12(4), L1(1), L2(6), L3(3), L4(4). A mean of 2.5 (SD 2.5) old fractures without signs of intravertebral BME were present, mean spinal deformity index was 6.2 (SD 4.9).[14]

The volume of the intravertebral BME was measured by 2 independent observers (SPJM, LB) using a visual threshold (**Figure 1**). Excellent inter-observer agreement was found for measurement of the intravertebral BME volume (ICC 0.98, 95%CI: 0.96 – 0.99, $p < 0.001$). For calculation of the vertebral volume and intra-vertebral BME a DICOM viewer (Osirix 3.3, 64 bit, Kagi, Berkeley, California) was used.

The PVP procedure was performed as a uni-or bi-pedicular method using PMMA bone cement as described earlier, and during the PVP procedure in all cases a bone biopsy was performed, to rule out other causes than osteoporosis.[15,16]

During a 1- year follow-up all patients recorded a Pain Intensity Numerical Rating Scale (PI-NRS) before PVP and at 1, 4, 12 and 52 weeks after PVP. Patients underwent routine spinal radiographs at 6 and 52 weeks and at indication.

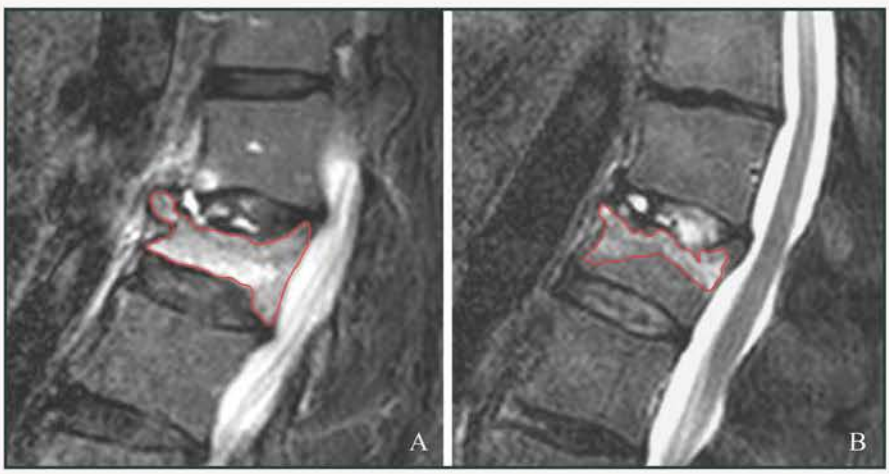

Figure 1. Measurement of intravertebral BME on T2 weighted STIR images (thickness 5 mm). Examples of BME containing vertebra of two patients. A: 64% and B: 27% of the total intravertebral volume is filled with BME. The border of the BME (high signal) is depicted by the red line.

Statistical analysis

The inter-observer agreement of the volume of intravertebral BME was assessed by calculation of the Intraclass Correlation Coefficient (ICC) (two-way mixed).

Measured values are reported as mean with Standard Deviation (SD) and range, estimates are reported as mean and 95% Confidence Interval (CI).

Patient-reported pain scores were analyzed using a linear mixed-model analysis, which takes the correlation between the repeated measurements within patients into account. Additional covariates in the analysis were patient age and gender, time since onset of symptoms, spinal deformity index and the occurrence of new OVCFs during follow-up.[17]

In all analyses, the model assumptions were assessed. A p-value of less than 0.05 was considered significant (SPSS statistical software 16.0, SPSS Inc, Chicago, IL).

Results

The mean pre-procedural PI-NRS score for back pain was 7.6 (SD 1.3) points, which decreased to 5.3 (SD 2.6), 5.3 (SD 2.6), 3.7 (SD 2.3) and 2.9 (SD 2.2) points after respectively one, four, 12 and 52 weeks post-procedurally ($p < 0.001$)(**Figure 2**). Six new OVCFs were noted in 5 patients after a mean of 8.0 months (SD 5.7). Three of these were adjacent fractures, which occurred after 1.3, 1.6 and 11.4 months. Two were symptomatic and one of these was treated with a second PVP procedure.

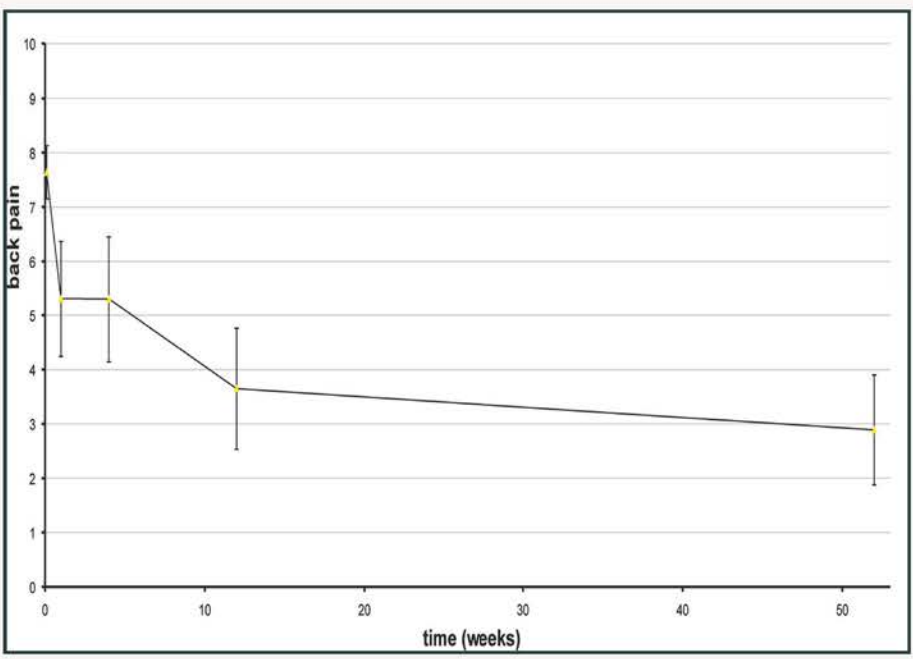

Figure 2. Mean back pain measured in pain intensity numeric rating scale score after one, four, 12 and 52 weeks post-operatively.

The mean intravertebral edema volume was 11.4 mL (SD 8.2, range 2.6 – 29.3), which corresponded to a mean percentage of vertebral body volume of 46.0% (SD 19.5, range 10.0 – 71.4)(**Figure 3**).

In multivariate repeated measures analysis, no association was found between the volume percentage of BME (in the range of 10% – 70%) and post-procedural back pain (0.04 per 10% vertebral body volume, 95%CI: -0.18 – 0.26, $p = 0.711$).

If the volume of BME was dichotomized in < 50% and ≥ 50%, intravertebral volume of BME (mean difference 0.27, 95%CI: -0.74 – 1.28, $p = 0.581$) or in <33% and ≥ 33% volume of intravertebral BME, no significant effect could be identified (mean difference 0.27, 95%CI: -0.74 – 1.28, $p = 0.581$ and 0.33, 95%CI: -0.61 – 1.28, $p = 0.466$).

Besides the positive effect of the PVP procedure itself, occurrence of a new OVCF during follow-up was consistently the only significant factor associated with the post-procedural outcome in terms of pain score (PI-NRS): occurrence of a new OVCF during follow-up was associated with a higher post-procedural pain score (mean increase 1.92, 95%CI: 0.86 – 2.92, $p = 0.001$).

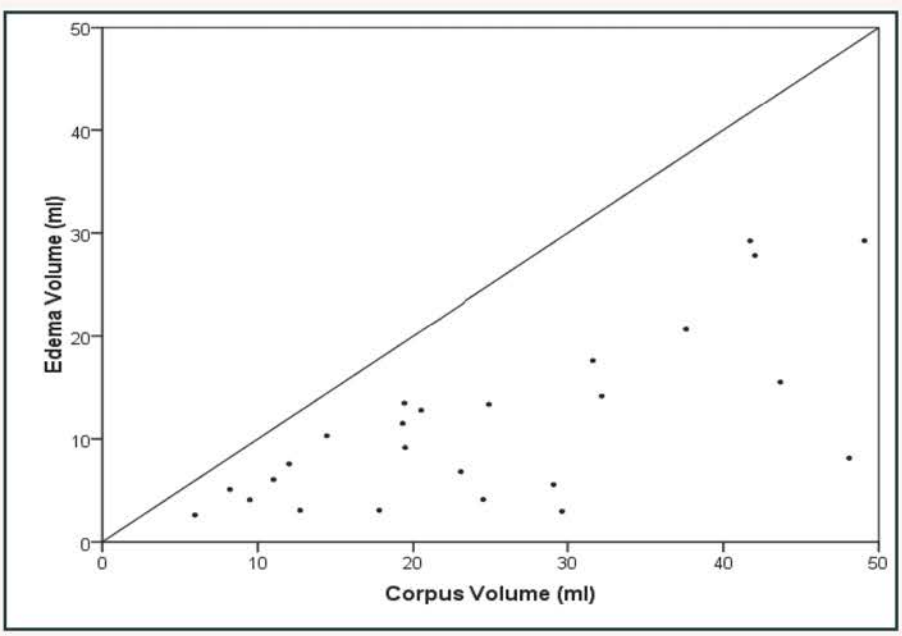

Figure 3. Shows the intravertebral BME volume (mL, y-axis) vs the intravertebral volume of the fractured vertebral body (mL, x-axis). The diagonal line depicts 100% filling with BME.

Discussion

Bone Marrow Edema (BME) due to unhealed (micro) fractures is seen in painful chronic osteoporotic vertebral compression fractures (OVCFs). Intravertebral BME persists in subacute and chronic painful OVCFs due to the altered healing cascade of the compression fracture caused by osteoporosis. The healing cascade of an OVCF is different compared to the well-organized healing cascade of a fractured long bone. The normal healing cascade in fractures of long bones consists of four stages. Resorption of necrotic bone is followed by matrix synthesis, bone formation and finally bone remodeling. In OVCFs with intravertebral BME on MR Imaging, these stages of bone healing are not seen as separate stages but show overlap.[10] The overlapping stages of the healing cascade seen in vertebral bodies containing BME may possibly be due to micro fractures due to slowly continuing collapse of the osteoporotic vertebral body.

In most clinics, intravertebral BME is one of the criteria for performing a PVP procedure. However, no guidelines on percentages of intravertebral BME in OVCF exists to be indicative as a threshold value for PVP. Moreover, the effect of BME in OVCF has not been quantitatively evaluated and studies are usually heterogeneous (multilevel versus single level OVCF). As such, the influence of the degree of intravertebral BME on the outcome of PVP remains unclear. In contrast to this lack of evidence, physicians often feel that a totally white vertebral body (100% vertebral body volume of intravertebral BME) at MR Imaging will have an excellent clinical outcome after PVP.

A review of the literature on intravertebral BME as (part of) the indication for PVP shows conflicting evidence. In 2005, Brown et al. showed no correlation between the outcome of PVP in chronic OVCFs and the presence of intravertebral BME at MR Imaging. However, they analysed BME in a dichotomous way (no BME (0%) vs. presence of any BME), patients had 1 to 5 OVCFs, and no pain score was used.[11] Contrary to this, 50-100% of intravertebral BME in OVCFs showed good pain reduction with PVP, compared to patients with less then 50% or no intravertebral BME.[8,13,18] All studies used either a dichotomy between no or presence of BME or between < 50% or more then 50% BME, while none of these studies used a volumetric analysis of the amount of BME on preoperative MR Imaging as was performed in the current study.

Debate exists on the use of a gadolinium enhanced T1 weighted MR I maging scan.[18,19] The current study shows no statistical difference in pain relief after PVP between patients with small or large percentages of intravertebral

BME. In order to prevent bias in the assessment of PVP, a strict inclusion protocol was used in the current study, these confounders are: first, pain generated by acute fractures (of which up to than 85% will resolve spontaneously within 8-12 weeks due to natural history).[20,21] Secondly, confounding due to pain from multiple fractures, and third exclusion of patients with intravertebral clefts, since these patients are a different entity and are merely a pseudo-arthrosis of the vertebral body due to necrosis.[22,23] Furthermore, these vertebral cleft fractures contain only a small area of very high signal on MR Imaging.[24]

Some limitations exist in the current study. First, the small size of the study cohort (25 patients), since only single level long-standing OVCFs were included and patients with vertebral cleft fractures were excluded. However, since repeated measurements during the first post-procedural year were obtained in all patients, the variability is highly reduced. Secondly, no control group - OVCF without intravertebral BME treated with PVP - was present. The latter, since presence of intravertebral BME was a prerequisite for treatment with PVP in our institution. Since data from literature is heterogeneous and includes multilevel and cleft fractures, no clear cut outcome scores etcetera were used and a control group from literature could not be used.

In conclusion, the amount of volumetric BME in long-standing single-level OVCF is not related to the post-procedural pain relief in the first year after PVP.

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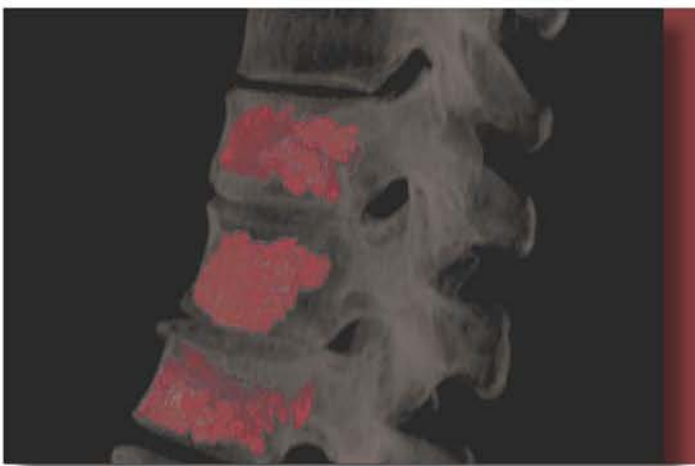
Chapter



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The Value of Routinely Performing a Bone Biopsy During Percutaneous Vertebroplasty in Treatment of Osteoporotic Vertebral Compression Fractures

Spine (Phila Pa 1976). 2009;34(22):2395-9

Abstract

Study Design. A retrospective histologic evaluation of biopsies obtained during percutaneous vertebroplasty (PVP) procedures as treatment for presumed osteoporotic vertebral compression fractures.

Objective. To determine the rate of unsuspected malignancy in bone biopsies of patients undergoing PVP for osteoporotic vertebral compression fractures.

Summary of Background Data. Most vertebral compression fractures, which result from minimal, or no trauma have osteoporosis as underlying cause. The diagnosis osteoporosis is based on clinical and radiologic findings. Even in patients with proven osteoporosis it is not always the true cause of the fractures. In literature, outcomes of bone-biopsies obtained during vertebroplasty have been described with inconsistent percentages of unexpected malignancy.

Methods. To determine the rate of unsuspected malignancy, 78 biopsies were obtained from 78 patients (18 male; 60 female; mean age, 73 years). The histologic diagnoses of vertebral body biopsy specimens were analyzed in a retrospective study.

Results. Seventy-one biopsies (91%) obtained from 71 patients, were suitable for histologic evaluation. Seven biopsies (9.0%) could not be interpreted as a result of suboptimal quality biopsy material. The population included 10 patients (13%) with a history of malignancy, in this group no malignancy was found in the bone biopsies. In 3 patients (3.8% of all biopsies) previously undiagnosed malignancies, 2 multiple myeloma stage IIa and 1 chondrosarcoma grade I, were found.

Conclusion. Obtaining bone biopsies during PVPs does not lead to increased morbidity and can verify the pathologic process underlying the vertebral compression fractures. Since this study showed an unsuspected malignancy rate of 3.8%, we recommend routine obtainment of a vertebral body bone biopsy, preferably using a biopsy needle with a diameter larger than 14 Gauge (>2.1 mm/0.083 inch), during every PVP procedure.

Introduction

The osteoporotic vertebral compression fracture (VCF) is, with an estimated prevalence of vertebral deformities in the Netherlands of 18% for men and 22% for women above the age of 55 years, the most common complication of osteoporosis.[1,2] The crude incidence of vertebral fractures in European man and woman aged 50 to 79 is 5.7/1000 and 9.9/1000 per year, respectively.[3] The demographic group in which the osteoporotic VCF mostly occurs is, due to the advanced age, however, also prone for malignant skeletal disease and compression fractures due to malignant disease.

Osteoporotic VCFs are a common cause of pain and disability. Twenty percent to 30% of these fractures are refractive to conservative treatment and become chronically painful.[1,4] Minimally invasive techniques such as percutaneous vertebroplasty (PVP) are increasingly used for the treatment of chronic pain and disability caused by osteoporotic VCFs.[5,6] PVP has been found to provide safe and effective means of pain control, diminishing disability, and accelerating return to function.[7–9]

The diagnosis osteoporosis is based on clinical and radiologic findings including DEXA examination. This, however, does not always reveal the true etiology of a VCF.[5,10–12]

In literature, outcomes of bone-biopsies obtained during PVPs have been described with inconsistent outcome in unexpected malignancy percentages.[5,10,13] A vertebral body biopsy acquired through the PVP needle during the procedure can identify unrecognized malignant bone tumors or metastasis, even in patients with normal results on laboratory studies.[5] The aim of this study was to determine the value of obtaining a routinely performed bone biopsy during PVP.

Materials and Methods

Patients

Between July 2003 and 2007, 78 consecutive patients, 18 male (23%) and 60 female (77%) with a mean age of 73 years (range, 48–93 years), with a total of 141 painful VCFs, were treated with PVP in the Leiden University Medical Center. During the PVP procedures 78 vertebral body biopsies were obtained through the vertebroplasty needle. The 78 biopsies included specimen from 30 thoracal, 30 thoracolumbar (Th12-L1) and 18 lumbar vertebrae (**Figure 1**). VCFs treated did not meet any of the radiologic criteria for possible malignancy and were since assumed to be the result of osteoporosis.[14] The population included 68 patients (87%) without any history of malignancy and 10 patients (13%) with history of malignancy. The group of patients with known history of malignancy consisted out of patients with carcinoma of the lung (n = 3), prostate (n = 1), mamma (n = 1), larynx (n = 2), and colon (n = 1) and furthermore 1 case of gastrointestinal stromal tumor and 1 malignant fibrous histiocytoma.

Inclusion criteria were (I) focal back pain in the midline refractive to at least 6 weeks of conservative treatment, (II) back pain related to the location of the VCF on magnetic resonance imaging (MR Imaging), (III) the presence of bone marrow edema on MRI short-[tau]-inversion-recovery sequences in the collapsed vertebral body, (IV) age over 40 years and (V) written informed consent.

Exclusion criteria were (I) spinal cord compression or stenosis of the vertebral canal >30% of the local canal diameter, (II) neurologic deficits, (III) bleeding disorders, (IV) infections related to the vertebral column, (V) inability of the patient to lie in prone position for 2 hours, and (VI) an American Society of Anesthesiologists-score equal to, or larger than 4. The medical history of all patients was checked for pre-existent malignancy and possible dissemination.

Imaging

Of all patients, AP and lateral conventional radiographs and short-[tau]-inversion-recovery MR images of the spinal column were acquired. All MR images were analyzed by a senior radiologist. Signs which were actively sought for and criteria for a suspected malignancy included: signal inhomogenicity, a major homogenous but nonlinear area with abnormal signal intensity, convex angulation of the posterior wall of the vertebral corpus without sharp angulations, multiple lesions in the vertebral column, especially at non adjacent levels, inhomogeneous spread in the lamina and disappearance of the basivertebral vein.[14]

Statistics

Results are presented as means ± SD (range). All analysis were performed using the Statistical Package for Social Studies version 14.0 (SPSS Inc., Chicago, IL).

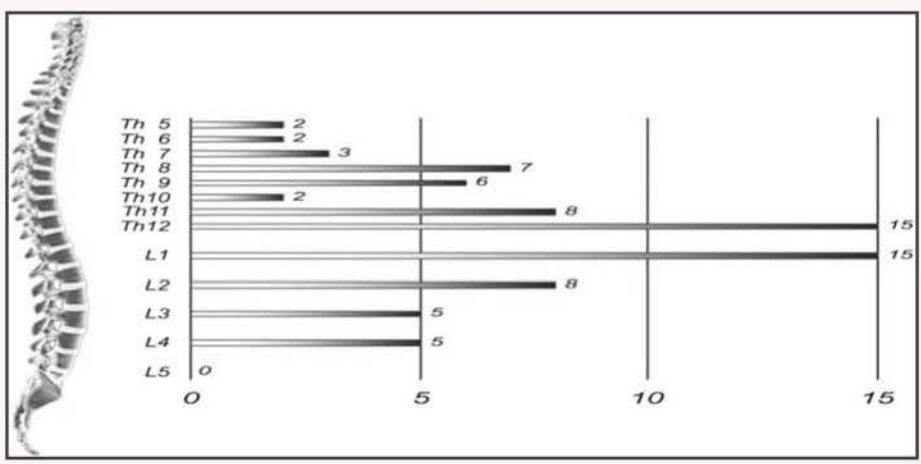

Figure 1. Vertebral levels of which 78 biopsies were obtained.

Procedure

PVP was performed under local anesthesia and conscious sedation using a biplane angiography unit with the patient placed in prone position. Preferably using a transpedicular approach, a 10G (3.4 mm) vertebroplasty needle (Optimed GmbH, Germany) was advanced into the pedicle and through the posterior wall of the VB using a small mallet.

When very small pedicles in the thoracic region were encountered, a 12G (2.8 mm) vertebroplasty needle was used. Subsequently, a bone biopsy was taken using a 14G (2.1 mm) bone biopsy needle (Cöok Medical, Limerick, Ireland), which was advanced through the PVP needle. The bone biopsy needle used was 5 cm longer than the vertebroplasty needle, and facilitated the opportunity to advance the biopsy needle beyond the tip of the vertebroplasty needle into the corpus. The placement of the biopsy needle was monitored by continuous fluoroscopic guidance to prevent endplate or cortex damage. When the biopsy needle was optimally placed, a luer-lock syringe was connected to the biopsy needle. By pulling the plunger a vacuum was created and after rotating the needle 5 times, the biopsy needle was retracted. After progression of the PVP needle into the anteromedial third of the vertebral body, PMMA bone cement was injected. The specimens were kept moist using sterile saline, placed in a sterile container and sent to the Pathology department. The specimens were fixated in paraformaldehyde, decalcified in formic acid for 4 hours, and embedded in paraffin. The histologic specimen were stained with a hemotoxylin and eosin and interpreted by a pathologist. If during this analysis signs of a malignancy were found, additional stainings, including specific immunohistochemic testing for CD-138, the presence of monoclonal IgA and kappa expression were conducted. These specimens were interpreted by a senior pathologist to diagnose or rule out multiple myeloma.

Results

Seventy-one biopsies (91%) obtained from 71 patients were suitable for histologic evaluation. The specimen with a diameter of 1.6 mm had a mean length of 5.9 mm (SD, 3.00; range, 1–15 mm). Seven biopsies (9.0%) with a mean length of 5.5 mm (range, 0.5–8 mm), consisted of too little or scant material (N = 5, 6.4%), or crushed material (N = 2, 2.6%), which could not be indisputably interpreted.

Out of 71 biopsies, 3 cases (3.8%) showed malignancy, which was not suspected on preoperative imaging or clinical symptoms. The 3 diagnosed unsuspected malignancies included 2 male patients (age 71 and 76 years) with cases of multiple myeloma stage IIa (**Figure 1A**) and a female (age 83 years) with chondrosarcoma grade I (**Figure 1B**).

In 38 of 71 (53.5%) of the biopsies, reactive changes due to bone regeneration, growth, and remodeling was seen. In the group of 8 patients with a history of malignancy and no radiological suspicion of malignancy causing the fracture, and since were treated for assumed osteoporotic VCFs, no signs of malignant disease were found in the biopsies.

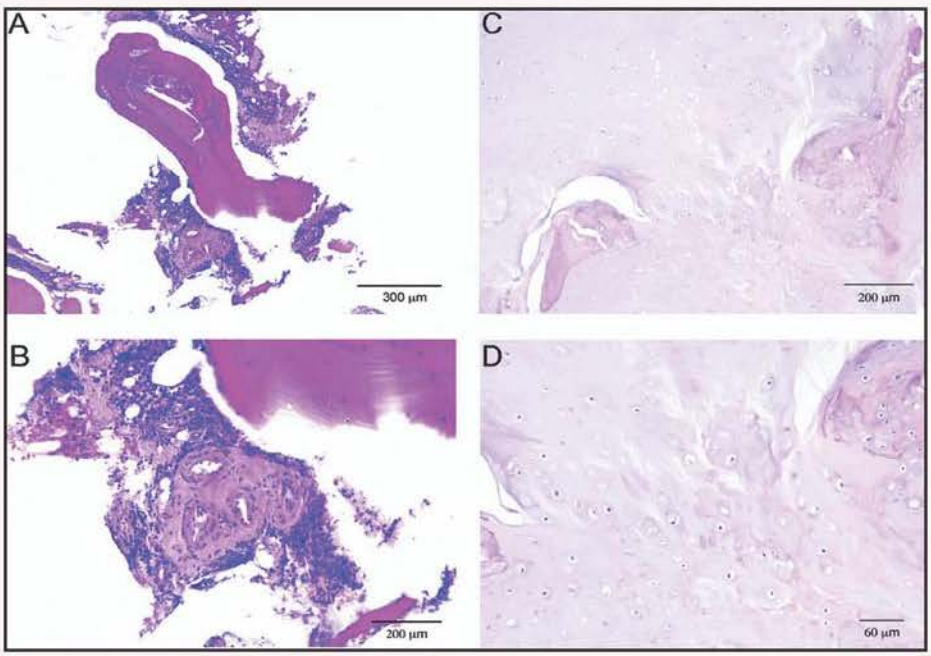

Figure 1. Histologic findings of unsuspected malignancy. A, Low-power photomicrograph with hematoxylin and eosin staining, showing hypercellularity due to interstitial infiltration of plasma cells. B, Magnification of the plasmacel-rich areas in Figure A containing clustered plasma cells with round nuclei, sporadically containing a nucleolus. This specimen combined with a positive CD 138 staining and monoclonal expression of IgA and Kappa are consistent with the diagnosis of multiple myeloma. C, Low-power photomicrograph with hematoxylin and eosin staining, showing pre-existent laminar bone entrapped by chondroid matrix. D, Magnification of Figure C showing chondrocytes with hyperchromatic nuclei surrounded by an inconsistent amount of eosinophil cytoplasm. Multinucleated cells are more than sporadically present, consistent with a chondrosarcoma grade I.

Discussion

Given the prevalence of osteoporosis, in the population of patients with VCFs, most patients are presumed to have osteoporosis as the ultimate etiology causing their compression fractures. The diagnosis of OVCF before PVP is based on clinical and radiologic findings. These preoperative investigations do not always provide a correct diagnosis as shown in other studies.[5,10,11,12] Lymphoma, multiple myeloma, and metastatic carcinomas are also prevalent in the same age-group as osteoporosis and pathologic compression fractures often can not be reliably diagnosed based on radiographic (including MRI) interpretation alone.

In the current study, 3 patients (3.8%) were diagnosed with a previously unknown malignancy, which was diagnosed by biopsy, obtained during a PVP for an assumed osteoporotic VCF. The nature of the underlying pathology related to vertebral collapse is important regarding prognosis, assessing response to therapy, and long-term patient care.[5]

Outcomes of bone-biopsies obtained during PVPs have been described with inconsistent outcome in unexpected malignancy percentages varying from 0.7% to 7.3%, the 3.8% unsuspected malignancy rate in patients treated with PVP reported in the current study is higher than percentages reported by several other authors.[5,10,13] Shindle et al.[10] found 1.3% (3/238) previously unsuspected malignancy (lymphoma) in their population whereas Togawa et al.[5] found a 0.7% incidence (1/142) of unsuspected cases of multiple myeloma in their population. Recently, Schoenfeld et al.[13] reported a considerably higher percentage of unsuspected malignancies in their population. In this study, a 7.3% (3/41) incidence of previously unsuspected malignancy including metastatic adenocarcinoma, lymphoma and multiple myeloma in patients treated for osteoporotic VCFs, was reported (**Table 1**).

Schoenfeld et al.[13] and Shindle et al.[10] recommended that vertebral body biopsies should be performed before every vertebral augmentation procedure. In contrast, Togawa et al.[5] recommended that a vertebral body biopsy should only be performed during each first-time vertebral augmentation procedure. The difference in percentages of unsuspected malignancy between Schoenfeld et al.[13] and the current study might be explained by the size of the cohorts or differences in radiologic preoperative work-up.

Table 1. Unsuspected Malignancy in VCFs Assumed to Have an Osteoporotic Etiology

Study	Unsuspected Malignancy (Malignancies/Total No. Patients)
Current study	3.8% (3/78 patients)
Schoenfeld *et al*[13]	7.3% (3/41 patients)
Shindle *et al*[10]	1.3% (3/238 patients)
Togawa *et al*[5]	0.7% (1/142 patient)

Table 1. Unsuspected malignancy in VCFs assumed to have an osteoporotic etiology

We found a relatively high number of biopsies (9%) not suitable for histologic examination. In other studies, this finding is, however, not mentioned. The diagnostic accuracy of percutaneous vertebral body biopsy has been reported to be 89% in the normal population and this has been found to increase to higher than 90% in patients with radiologic abnormalities, diagnosis or clinical suspicion of a malignancy, or if the biopsy involved a lytic lesion.[15–17] Because of the fact that the PVP needle facilitates easy access to the vertebral body, a biopsy can be acquired without increased morbidity and can verify the underlying pathologic process. In this study, a 14G biopsy needle was used to grant continuous usage of the same biopsy needle, independent of the usage of a 10 or 12G vertebroplasty needle. In clinical studies concerning vertebral bone biopsies during PVP, the diameter of the biopsy needle is only rarely mentioned. Although the use of a biopsy needle with a bigger diameter does not per se increase the chance of a correct histologic diagnosis, it is also found that the diagnosis rate was significantly poorer and the probability of crush artifacts increased with a needle diameter of less than 2 mm.18–20 In our study, crush artifacts were limited due to an aspiration procedure conducted by using a syringe to create a vacuum, this technique is also successfully conducted in other studies.[18] The authors, however, feel that the use of a biopsy needle with the maximal possible diameter for the vertebroplasty needle can be advocated since the size of access route (the inner diameter of the vertebroplasty needle) is not altered while more material for histologic evaluation will be obtained. To the author's knowledge, no

complications of conducting a biopsy during PVP have been published. However, complications due to procedures conducted solitary for the purpose of obtaining vertebral biopsy material, including neurologic injury, pneumothorax, fracture, puncture of thecal sac and bleeding, have been published.[16,21]

Undoubtedly most VCFs have an underlying osteoporotic etiology, nonetheless a variety of malignant conditions such as multiple myeloma and metastatic disease are also present in this elderly patient group.[5] Phekoo et al. reported that the crude incidence rates of multiple myeloma increases with age from <5 per 100,000 at 45 to 54 years of age, to >30 per 100,000 in the group aged over 75 years.[22] In 70% of patients with multiple myeloma or metastatic disease the spine will be involved during the course of their disease.[23] Moreover, both osteoporosis and malignancy can present in the same patient.[13]

The preoperative work-up in this patient group should include a thorough history and physical examination not only aimed on the spinal pain complaints, but also on possible signs of malignancy, in case of any doubt extra laboratory or radiologic/nuclear testing should be conducted.

In literature, recommendations concerning obtainment of biopsy material during PVP procedures have been inconsistent in timing and frequency. We feel that the possible advantages of early detection of malignant disease outweighs the risks when the biopsy is taken through the PVP needle. Therefore we advise that not only during the first-time a patient is treated with PVP, material for histologic evaluation is obtained, but also in case of new VCFs for which PVP is indicated.

To obtain the best clinical outcome and to limit both morbidity and mortality in patients with spinal tumors, which present themselves by a VCF, it is important to carefully match the treatment modality to the pathologic process.[23] We recommend routine obtainment of a vertebral body bone biopsy, preferably using a biopsy needle with a diameter over 2.1 mm (0.083 inch/14 Gauge), during every PVP procedure.

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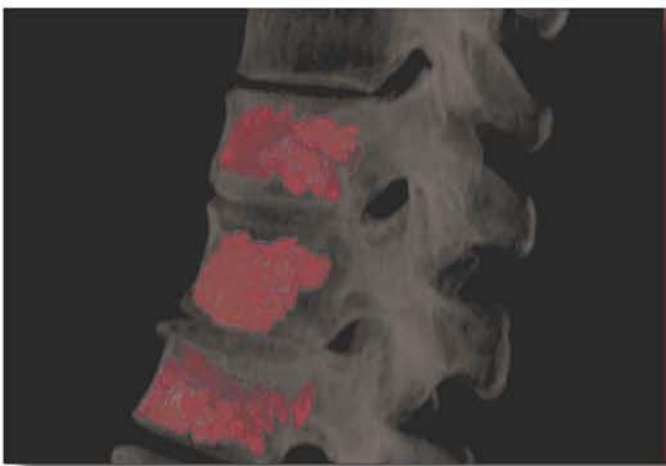
CLINICAL OUTCOME

Chapter



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Percutaneous Vertebroplasty for the Treatment of Osteoporotic Vertebral Compression Fractures:

Evaluation after 36 Months

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Abstract

In a prospective study between August 2002 and August 2005, we studied the quantitative clinical and radiological outcome 36 months after percutaneous vertebroplasty for intractable type-II osteoporotic vertebral compression fractures, which had been unresponsive to conservative treatment for at least eight weeks. We also examined the quality of life (QoL). The clinical follow-up involved the use of a pain intensity numerical rating scale (PI-NRS, 0 to 10), the Short-Form 36 (SF-36) QoL questionnaire and an anamnestic questionnaire before and at seven days (PI-NRS only), and one, three, 12 and 36 months post-operatively.

A total of 30 consecutive patients received percutaneous vertebroplasty for 62 vertebral compression fractures with a mean time between fracture and treatment of 7.7 months (2.2 to 39). An immediate, significant and lasting reduction in the average and worst back pain was found, represented by a decrease of 3.1 and 2.7 points after seven days and 3.1 and 2.8 points after 36 months, respectively ($p < 0.00$). Comparison of the pre- and postvertebroplasty scores on the various SF-36 domains showed an ultimate significant increase in six of eight domains and both summary scores. Asymptomatic leakage of cement was found in 47 of 58 (81%) of treated vertebrae. Two minor complications occurred, an asymptomatic pulmonary cement embolism and a cement spur along the needle track.

Percutaneous vertebroplasty in the treatment of chronic vertebral compression fractures results in an immediate, significant and lasting reduction in back pain, and overall improvement in physical and mental health.

Introduction

Vertebral compression fractures are the most common complication of osteoporosis[1,2] and often go unnoticed. However, one-third of patients present with extreme pain and limited activities of daily life, resulting in a decrease in the quality of life.[3,4] The initial treatment of a painful osteoporotic vertebral compression fracture is non-operative, using a combination of analgesia, bed rest and bracing. Fractures resistant to such treatment are an indication for percutaneous vertebroplasty in which the fractured vertebra is stabilised by an injection of acrylic bone cement into the vertebral body.

Percutaneous vertebroplasty is shown to result in significant and lasting relief from pain in 80% to 100% of patients with only a few related complications.[5-8] Notwithstanding these results, the long-term effect of percutaneous vertebroplasty on the quality of life has yet to be determined. The optimal balance between the timing of percutaneous vertebroplasty in relation to the age of the fracture and the risk to the patient has not been fully established and varies widely.[9-12]

As described by Lyritis et al.[13] two types of osteoporotic vertebral compression fracture can be distinguished, the more common being acute (type I) and characterised by a single attack of intense back pain of short duration. Type II is chronic and consists of sequential attacks of pain over a longer period (45 to 60 weeks). Since natural healing of a type-I fracture occurs within four to eight weeks, percutaneous vertebroplasty within this time may not provide maximum benefit and may possibly introduce unnecessary risk.

Our aim was to evaluate the short- ($\leq$ 12 months) and long-term (36 months) outcome, in terms of the quality of life, function, pain and radiological outcomes after percutaneous vertebroplasty using low-viscosity polymethylmethacrylate (PMMA) bone cement in type-II vertebral compression fractures.

Patients and Methods

Between August 2002 and August 2005, 30 consecutive patients with type-II vertebral compression fracture were prospectively recruited at Leiden University Medical Centre. Four men and 26 women with a mean age of 70.7 years (41.5 to 90.6) had a total of 139 pre-existing vertebral compression fractures, with a mean of 4.6 per patient (1 to 13). Of these 139 fractures, 62 were painful and showed bone-marrow oedema on MR Imaging. They were treated by percutaneous vertebroplasty over 32 sessions. Approximately 50% of the procedures were in the thoracolumbar region (**Figure 1**).

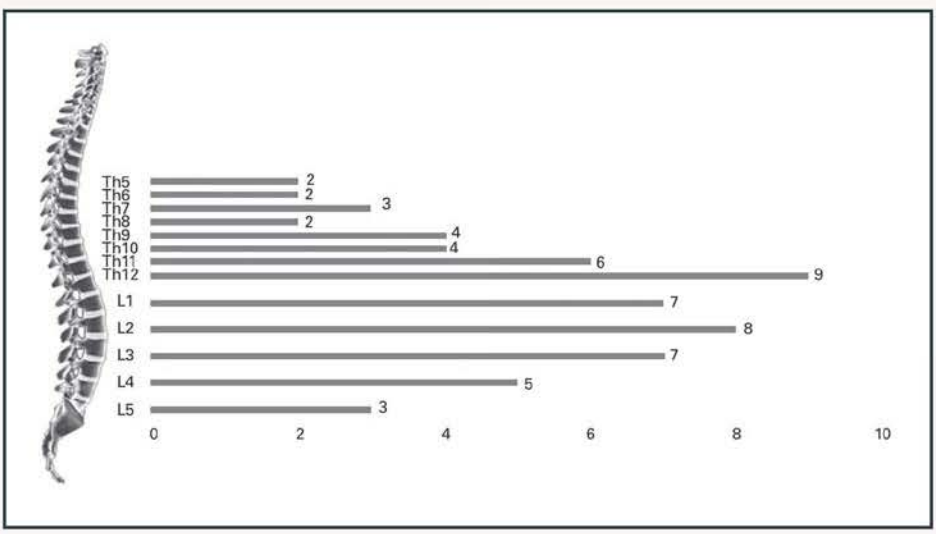

Figure 1. Diagram showing the distribution of treated vertebra. The most commonly treated was Th12, followed by the first three lumbar levels.

The inclusion criteria were an osteoporotic vertebral compression fracture including that with a severe compression deformity,[14] local mid-line back pain refractory to conservative treatment for at least six weeks, back pain related to the site of the fracture on MR Imaging, the presence of bonemarrow oedema in the collapsed vertebral body on MR Imaging T2-weighted short tau inversion recovery (STIR) sequences, age over 40 years and written informed consent.

Exclusion criteria were vertebral compression fractures due to causes other than osteoporosis, compression of the spinal cord or stenosis of the vertebral canal by > 30% of the local diameter, neurological deficits, an uncorrectable bleeding disorder, infection of the vertebral column, inability to lie prone for two hours, an American Society of Anesthesiologists score ≥ 4[15] and inability to complete a questionnaire.

When a patient presented with pain after conservative treatment for six weeks, the complete clinical procedure was carried out in two weeks. This protocol ensured that patients were not treated by percutaneous vertebroplasty within eight weeks after the onset after the fracture.

The mean length of follow-up was for 29.2 months (1 to 48). The 36-month follow-up was completed by 80% of the patients. Four died from causes unrelated to the treatment, two were unable to complete the follow-up because of severe cognitive problems, and one was unwilling to participate further. One patient had a history of leukaemia and three had metastasised carcinoma. However, all biopsies during the vertebroplasty confirmed osteoporosis and showed no signs of malignancy. The mean age of the fracture as established by the time between the onset of new back pain related to a radiologically confirmed fracture and the time of vertebroplasty was 7.7 months (2.2 to 3.9). Pre-operative anteroposterior and lateral radiographs and MR scans including fat-suppression sequences of the total spine were taken. Single-level percutaneous vertebroplasty was performed in ten patients (33.3%), two levels in 13 (43.4%), three levels in three (10.0%), four levels in three (10%) and five levels (in two sessions) in one patient (3.3%). The approach was unipedicular in 32 vertebral bodies (52%) and bipedicular in 30 (48%).

Percutaneous vertebroplasty was performed using a biplane angiography unit, under sedation and with the patient prone. A 10G vertebroplasty needle (Optimed GmbH, Ehingen, Germany) was advanced into the pedicle and through the posterior wall of the vertebral body using a small mallet. A bone biopsy was taken through the percutaneous vertebroplasty needle using a 13G Cook bone biopsy needle (Cook Medical, Limerick, Ireland) and, after progression into the anteromedial third of the vertebral body, low-viscosity PMMA bone cement (Osteopal-V; Heraeus Medical GmbH, Hanau, Germany) was injected using an Optimed Cemento gun (OptiMed Medizinische Instrumente GmbH, Ettlingen, Germany). If distribution of the cement in the vertebral body was unsatisfactory, a second needle was inserted through the contralateral pedicle, followed by injection of cement.

The aim of the procedure was to symmetrically fill the central and anterior parts of the vertebral body. An immediate post-operative CT scan was taken to reconfirm the correct positioning of the cement and to detect any leakage.

For each patient, the pre- and post-operative clinical characteristics were obtained, including the SF-36 health survey, a 0 to 10 Pain Intensity Numerical Rating Scale (PINRS) [16] for average and worst back pain and a 0 to 10 Satisfaction Numerical Rating Scale (S-NRS).[17,18] Health state was estimated by the SF-6D,[19] a preference-based measure of health derived from the SF-36. A back-pain-specific anamnestic vertebroplasty questionnaire (**Figure 2**) was used to record the clinical outcome. This contained specific questions about the influence of back pain on the activities of daily life. Questionnaires were completed before and at seven days (PI-NRS, S-NRS) and one, three, 12 and 36 months after the procedure.

Statistical analysis.

Raw SF-36 scores were summarised and converted to a 100-point scale, a high score representing a high level of function or well-being. Normality of the data was checked using the Kolmogorov-Smirnov test. The significance of changes in the PI-NRS, S-NRS, SF-36 and the anamnestic questionnaire was assessed by the paired

Student's *t*-test or, when the assumption of normality was not justified, the Wilcoxon signed-rank test using SPSS version 14.0 software (SPSS Inc., Chicago, Illinois). A p-value of less than 0.05 was considered to be significant.

Anamnestic Questionnaire – Overview

Did you experience back pain in the past 4 weeks? **Yes** **No**

How much back pain did you experience in the past 4 weeks?
Very lightly **Lightly** **Moderate** **Much** **Very much**

How often did you experience back pain in the past 4 weeks?
Once or twice **A few times** **Often** **Very often** **Almost every day**

On average, how long lasted back pain experienced in the past 4 weeks?
A few minutes **Up to one hour** **Several hours** **One or two days** **Longer than two days**

Did you need to reduce your activities of daily life because of back pain in the past 4 weeks? **Yes** **No**

If so, on how many days (of 28)? **..... Days**

How many days (of 28) did you experience limitation, caused by back pain, in carrying out your activities of daily life?
.....Days

In the past 4 weeks, did you have difficulty with the following activities because of back pain?

	No	**Yes, quite a bit**	**Yes, very much**	**Yes cannot do it**
Bending or bowing down				
Lifting 5 kg				
Grasping above one's own head				
Putting on one's socks				
Standing or being busy for 1 hour				
Sitting in a chair for 30 minutes				
Standing up out of a chair				

In the past 4 weeks, how much has back pain influenced your:

	Not at all	**A bit**	**Moderate**	**Quite a bit**	**Very much**
Mood					
Gait					
Sleep					
Daily Activities					
Relaxing					
Joy in life					

Figure 2. The questions and format of the verteboplasty questionnaire.

Results

The mean pre-operative average and worst back pain scores were 7.9 and 8.8 (5.0 to 10.0), respectively. Post-operatively the decrease in the mean average back pain score was 3.1 points at seven days and at 36 months ($p < 0.005$, paired sample *t*-test) and the decrease in the mean worst back pain score was 2.7 points at seven days and 2.8 points at 36 months ($p < 0.005$, Wilcoxon signed ranks test). At that time six patients (25%) had no back pain (**Table 1**).

At seven days post-operatively and throughout the follow-up the mean patient satisfaction, using the S-NRS, deviated from indifference (score 5) and ranged from 8.0 to 8.5.

Comparison of pre- and post-vertebroplasty scores on the various SF-36 domains showed a final and significant increase in six of eight domains and in both summary scores, thereby indicating a significant overall increase in the quality of life. During the first month after percutaneous vertebroplasty, significant improvement was seen only in the domains of physical function ($p = 0.003$), bodily pain ($p < 0.001$) and in the physical component score ($p < 0.001$) (**Table 2, Figure 3**).

The health state utility, using SF-6D, showed a statistically significant increase from 0.50 pre-operatively to 0.59 ($p = 0.03$), 0.58 ($p = 0.021$) and 0.59 ($p = 0.032$) at three, 12 and 36 months, respectively (paired sample *t*-test).

The vertebroplasty questionnaire showed significant improvement (McNermar's test) in the activities of daily life after percutaneous vertebroplasty and the back-painrelated limitation in activities of daily life also decreased significantly (Wilcoxon signed ranks test) (**Table 3A**). Moreover, the intensity, frequency and duration of back pain decreased significantly after vertebroplasty (**Table 3B**). In those who did not experience complete relief this decrease was also significant, except at the long-term follow-up for the duration of episodes of back pain.

In performing specified movements, only difficulty standing from a chair had immediate and durable significant improvement (Wilcoxon signal ranks test). However, the joy of life improved three months after percutaneous vertebroplasty (**Table 3C**).

The mean injected volume of cement per vertebral body was 5.3 ml (0.6 to 11.7). The immediate post-operative CT scans were examined for extra-vertebral leakage of cement. Of 58 treated vertebrae examined 67 sites of leakage were found in 47 vertebrae (81.0%).

Minor complications occurred in two patients. In one, leakage of cement during treatment of a thoracic vertebral body caused an asymptomatic cement embolism in the pulmonary vasculature, detected on the post-operative CT-scan. In the other, a spur of cement was present which followed the track of the needle from the pedicle to the subcutaneous tissues. This was removed immediately, resulting in a post-operative haematoma and low pain, which resolved within two days.

	Screening			Difference screening - 7 days				Difference screening - 1 month				Difference screening - 3 months				Difference screening - 12 months				Difference screening - 36 months			
	Mean	SD	Number	Change	SD	Number	p- value	Change	SD	Number	p-value	Change	SD	Number	p-value	Change	SD	Number	p-value	Change	SD	Number	p-value
ABP*	7.87	1.85	30	3.12	3.00	25	<0.001	2.88	3.24	25	<0.001	3.42	3.39	19	<0.001	3.32	3.77	19	0.001	3.13	3.82	23	0.001
WBP*	8.80	1.45	30	2.72	3.40	25	0.001	2.84	3.68	25	0.001	2.95	3.58	19	0.002	3.42	3.81	19	0.001	2.82	3.86	22	0.003

* ABP, average back pain; WBP, worst back pain

Table 1. PI-NRS screening scores and differences between scores at the respective follow-up points and the screening scores.

	Screening			Change screening - 1 month				Change screening -3 months				Change screening - 12 months				Change screening - 36 months			
Score*	Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
PF	25.33	24.03	30	11.91	17.08	23	0.003	13.18	21.02	22	0.008	16.11	24.77	18	0.013	18.54	28.72	24	0.004
RP	5.00	15.25	30	-1.09	23.21	23	0.785	22.73	37.73	22	0.017	23.61	37.84	18	0.016	15.97	36.11	24	0.039
BP	18.67	14.69	30	21.65	21.52	23	<0.001	26.41	27.06	22	<0.001	28.11	31.61	18	0.002	25.33	29.62	24	<0.001
GH	46.73	22.35	30	2.55	21.07	23	0.567	-0.86	21.92	22	0.855	4.11	28.69	18	0.551	-5.02	25.22	24	0.340
VT	35.17	18.12	30	2.83	16.98	23	0.433	11.59	17.89	22	0.006	8.06	23.15	18	0.158	11.46	24.07	24	0.029
SF	41.67	26.12	30	6.52	28.92	23	0.291	20.45	28.23	22	0.003	18.75	28.84	18	0.013	16.67	29.18	24	0.010
RE	34.44	43.31	30	-14.49	62.62	23	0.224	3.03	38.36	22	0.777	18.52	41.57	18	0.083	22.22	42.47	24	0.021
MH	53.37	23.97	30	-0.74	24.17	23	0.885	10.36	17.87	22	0.013	6.83	21.04	18	0.186	9.00	23.03	24	0.068
PCS	26.53	5.37	30	7.46	8.59	23	<0.001	7.19	8.48	22	0.001	7.93	12.00	18	0.012	5.68	10.52	24	0.015
MCS	39.59	11.74	30	-4.35	11.50	23	0.083	3.35	7.93	22	0.061	3.49	9.41	18	0.134	5.07	10.89	24	0.032

* PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health perceptions; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health; PCS, physical component score; MCS, mental component score

Table 2. SF-36 screening scores and differences between scores at the respective follow-up points and the screening scores.

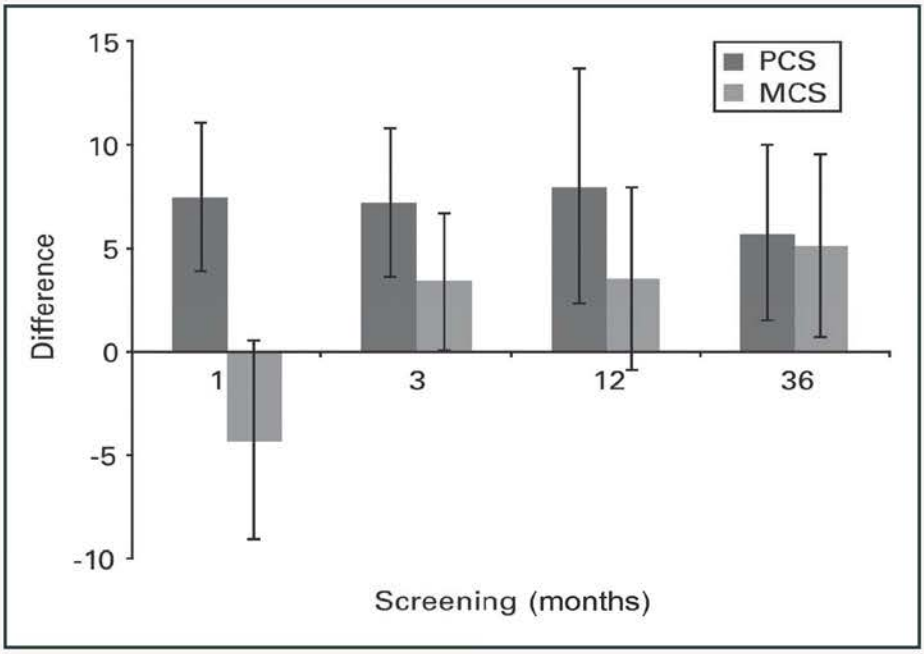

Figure 3. Bar chart showing the SF-36 difference in physical component and mental component scores between screening and the respective follow-up points (MCS, mental component score; PCS, physical component score).

Reduction in activities of daily life in the last four weeks because of back pain (yes/no)

Screening		1 month			3 months			12 months			36 months		
Yes	No	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
30	0	15	8	0.008	9	9	0.004	12	6	0.031	11	10	0.002

Number of days (0 to 28) reduction in daily activities because of back pain

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
22.63	10.77	30	12.52	13.08	23	0.010	7.22	11.07	18	0.002	5.78	9.12	18	0.001	8.57	12.27	21	0.002

Number of days (0 to 28) limitation experienced in executing activities of daily life because of back pain

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
26.76	5.36	29	23.67	7.62	18	0.027	17.53	11.98	15	0.011	15.19	12.37	16	0.007	21.50	9.78	18	0.018

Table 3A. Outcome of the vertebroplasty questionnaire relating to ADL

Presence of back pain in the last 4 weeks (yes/no)

Screening		1 month			3 months			12 months			36 months		
Yes	No	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value	Yes	No	p-value
29	0	18	5	0.125	15	4	0.125	16	2	0.500	18	6	0.031

Intensity of back pain in the last 4 weeks (0, none; 1, very lightly; 2, lightly; 3, moderate; 4, yes, much; 5, yes, very much)

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
4.31	0.76	29	2.87	1.49	23	0.001	2.63	1.58	19	<0.001	3.06	1.43	18	0.003	2.71	1.76	24	0.001

Intensity of back pain in the last 4 weeks (1, very lightly; 2, lightly; 3, moderate; 4, yes, much; 5, yes, very much)

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
4.31	0.76	29	3.47	0.70	19	0.002	3.33	0.82	15	0.001	3.44	0.96	16	0.007	3.61	0.85	18	0.028

Frequency of back pain experienced in the last 4 weeks (0, never; 1, once or twice; 2, a few times; 3, often; 4, very often; 5, almost every day)

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
4.90	0.31	29	3.57	1.83	23	0.003	3.32	2.00	19	0.004	3.39	1.79	18	0.007	3.25	2.07	24	0.002

Frequency of back pain experienced in the last 4 weeks (1, once or twice; 2, a few times; 3, often; 4, very often; 5, almost every day)
Only people who confirmed having experienced back pain in the last 4 weeks

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
4.90	0.31	29	4.32	0.82	19	0.013	4.20	1.08	15	0.039	3.81	1.38	16	0.018	4.33	0.91	18	0.047

Average duration of episodes of back pain experienced in the last 4 weeks (0, never; 1, a few minutes; 2, up to one hour; 3, several hours; 4, one or two days; 5, longer than two days)

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
4.55	0.91	29	3.35	1.90	23	0.010	2.50	1.92	18	0.003	3.17	1.79	18	0.003	3.00	2.13	23	0.006

Average duration of episodes of back pain experienced in the last 4 weeks (1, a few minutes; 2, up to one hour; 3, several hours; 4, one or two days; 5, longer than two days)
Only people who confirmed having experienced back pain in the last 4 weeks

Screening			1 month				3 months				12 months				36 months			
Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
4.55	0.91	29	4.05	1.18	19	0.034	3.21	1.53	14	0.017	3.56	1.46	16	0.007	4.06	1.30	17	0.176

Table 3B. Outcome of the vertebroplasty questionnaire relating to back pain characteristics.

Difficulty with the following activities because of back pain (1, no; 2, yes, quite a bit; 3, yes, very much; 4, yes cannot do it)

	Screening			1 month				3 months				12 months				36 months			
	Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
Bending or bowing down	2.38	0.98	29	1.82	0.91	22	0.066	1.65	0.93	17	0.039	2.00	1.07	15	0.114	1.86	0.99	22	0.087
Lifting 5 kg	3.08	0.86	25	2.77	1.15	22	0.358	2.39	1.24	18	0.135	2.47	1.30	15	0.231	2.42	1.22	19	0.210
Grasping above one's hand	2.56	1.12	27	1.91	1.02	22	0.125	1.89	1.10	19	0.056	1.65	1.06	17	0.034	1.80	1.01	20	0.184
Putting on one's socks	2.20	1.04	25	1.52	0.75	21	0.038	1.61	0.92	18	0.035	2.18	1.07	17	0.579	1.90	1.02	20	0.395
Getting in and out of car	2.31	0.84	26	1.68	0.72	23	0.046	1.68	0.75	19	0.011	1.88	0.89	16	0.053	1.87	0.92	23	0.107
Standing or being busy for 1 hour	3.22	0.89	27	2.85	0.99	20	0.117	2.65	1.17	17	0.075	2.69	1.03	13	0.102	2.48	1.20	23	0.050
Sitting in a chair for 30 minutes	2.07	0.96	27	1.90	1.09	21	0.218	1.39	0.78	18	0.005	1.59	0.80	17	0.132	1.92	0.97	24	0.537
Standing up out of a chair	2.61	0.78	23	1.62	0.74	21	0.012	1.61	0.70	18	0.004	1.88	0.86	17	0.020	1.79	0.78	24	0.002

Influence of back pain experienced in the last 4 weeks on miscellaneous characteristics (1, not at all; 2, a bit; 3, moderate; 4, quite a bit; 5, very much)

*** Only people who confirmed having experienced back pain in the last 4 weeks**

	Screening			1 month				3 months				12 months				36 months			
	Mean	SD	Number	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value	Mean	SD	Number	p-value
Mood	3.34	1.14	29	2.79	1.18	19	0.067	2.36	1.28	14	0.006	2.56	0.81	16	0.011	2.65	1.12	17	0.035
Gait	4.38	0.56	29	3.79	0.79	19	0.013	3.36	0.93	14	0.004	3.38	1.20	16	0.009	3.82	0.88	17	0.104
Sleep	3.17	1.17	29	2.37	1.21	19	0.010	2.14	1.29	14	0.010	2.31	1.20	16	0.002	2.24	0.97	17	0.050
Normal daily activities	4.29	0.81	28	4.00	0.82	19	0.029	3.50	1.16	14	0.013	3.50	1.10	16	0.034	3.53	1.13	17	0.061
Relaxing	3.90	1.08	29	3.58	1.17	19	0.249	3.43	1.28	14	0.200	3.31	1.25	16	0.057	3.24	1.20	17	0.141
Joy in life	3.69	1.29	29	3.32	1.25	19	0.107	2.57	1.34	14	0.026	2.75	1.39	14	0.005	3.06	1.20	17	0.046

Table 3C. Outcome of the vertebroplasty questionnaire relating to specific activities and miscellaneous characteristics.

Discussion

The benefits of percutaneous vertebroplasty depend on the selection of the patient, surgical skill, complication rates and procedural characteristics such as the viscosity of the cement, the filling volume and distribution. Hitherto, there have been no definite criteria for the selection of patients for percutaneous vertebroplasty.[9-12] It is known that 80% of all symptomatic osteoporotic vertebral compression fractures are acute (type I) and heal naturally within four to eight weeks, whereas the remaining 20% are chronic (type II) and heal spontaneously after 45 to 60 weeks.[13,20-22] Since the introduction of percutaneous vertebroplasty, both types have been treated by this technique.[12,23,24]

Treatment of acute vertebral compression fracture results in an immediate and significant decrease in pain in most cases. This is the only true benefit compared with conservative management[24-27] and may be one of the key factors in the success of percutaneous vertebroplasty. However, because this technique is not without risk,[28-33] the decision as to whether to undertake it before eight weeks from the onset of symptoms should be made according to careful riskbenefit analysis and the experience of the surgeon.

Our mean decreases in the average and worst back pain are in accordance with figures reported in meta-analyses,[33,34] and from several other prospective studies investigating the effect of percutaneous vertebroplasty on patients with type-II osteoporosis.[35-38]

Although the severity of pain is generally used as the primary outcome measure, the change in quality of life reflects the overall effect of treatment. Despite the successful use of the SF-36 in evaluation of the quality of life in patients with osteoporotic vertebral compression fractures,[3,4] back pain[39,40] and spinal surgery,[41,42] there are only three prospective studies specifically examining the effect of percutaneous vertebroplasty on the quality of life using the SF-36[22,43,44] and these are characterised by poor response rates, limited follow-up ($\leq$ 12 months) and the use of different types of bone cement. To our knowledge, our study is the first analysis of prospectively collected data on the quality of life three years after percutaneous vertebroplasty with one type of cement and with a response rate of 80%.

A comparison of the pre- and post-vertebroplasty scores in the various SF-36 domains has shown a significant and clinically relevant[45] increase in six of eight domains and both summary scores, thereby indicating a significant overall

increase in the quality of life. Pre-operative SF-36 scores were substantially lower than for gender-corrected scores of the average Dutch population of 65 to 74 years and above,[46,47] and comparable with those in patients with osteoporotic vertebral compression fractures who are suitable for vertebral augmentation.[23,43,44,48-50]

During the first month after operation significant improvement was seen only in the domains of physical function, which is known to have the highest correlation with physical ability,[18,51] and bodily pain, reflecting the results of the numerical pain score. The role physical and role emotional domains showed an obvious, albeit nonsignificant decrease in the first month, probably due to general post-treatment role-inhibiting behaviour. There was a significant improvement in six of eight SF-36 domains at follow-up at three and 36 months in our series. This contrasts with the study of Do et al,[23] in which a significant improvement in seven of eight domains had already occurred during the first month after percutaneous vertebroplasty. The general health domain perceptions showed no improvement throughout the follow-up period, which is in accordance with other similar studies.[23,43] Our role emotional domain results agree with others[48,49] and show no long-term significant improvement. The physical component score showed an immediate, significant and lasting increase, whereas the mental component score had a gradual, but eventually significant increase after more than 12 months (**Figure 3**). The only two studies which have reported SF-36 summary scores showed a significant increase in both summary scores as early as one month after percutaneous vertebroplasty.[23,44] The delayed response in improvement in scores may be because our study included only patients with type-II osteoporotic vertebral compression fractures, whereas other studies enrolled patients with acute and possibly type-I osteoporotic vertebral compression fractures.[24,44] Because of the longer period patients had more severe pain and disability and therefore recovery might have been prolonged. However, despite working against the natural decrease in quality of life with ageing,[46,47] the amount of improvement was comparable.[22,43,44]

Health state utility, using the SF-6D, showed a statistically significant increase from 0.50 pre-operatively to 0.59 at three and 36 months after percutaneous vertebroplasty, indicating a post-operative health state, which was 18% higher.

The vertebroplasty questionnaire used in our study has not yet been formally validated, but resembles the questionnaire of Evans, Kip and Boutin.[52] When our prospective study began, neither their questionnaire nor any other validated vertebroplasty specific questionnaire was available. The back-pain-

related limitation in activities of daily life also decreased significantly after percutaneous vertebroplasty. Moreover, the intensity, frequency and duration of back pain decreased significantly. These outcomes are in line with those of the SF-36 and indicate that the improvement in the SF-36 scores is due to a decrease in the problems which are prevalent in patients with an osteoporotic vertebral compression fracture.

The rate of asymptomatic leakage of cement was comparable with that of other studies,[6,38,53] as was our minor complication rate (6.7%).[24,38]

The limitations of our study were the small sample size, the lack of specific recording of the use of analgesics during follow-up and the absence of a control group. Another limitation was that the SF-36 is a generic healthrelated instrument, which might be influenced by ageing and co-morbidity.

We have shown an immediate, significant and lasting improvement in pain and overall physical and mental health after percutaneous vertebroplasty. However, the decision as to whether to perform percutaneous vertebroplasty should be made carefully and according to risks and potential benefits for each patient.

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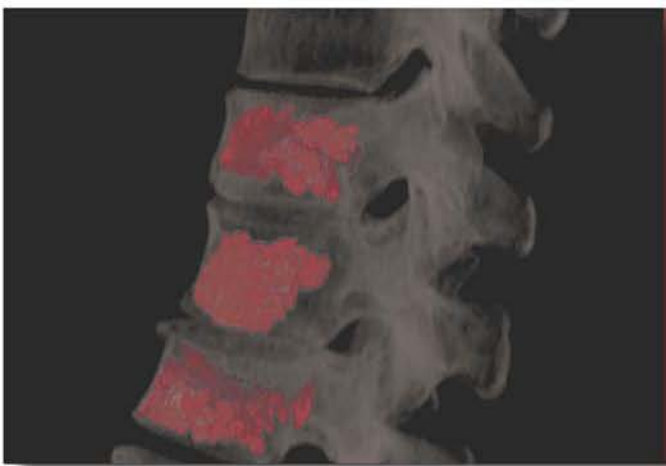
CEMENT LEAKAGE & CLASSIFICATION

Chapter



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A Clinical Comparative Study on Low Versus Medium Viscosity PolyMethylMetAcrylate Bone Cement in Percutaneous Vertebroplasty: Viscosity Associated With Cement Leakage

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Abstract

Study Design. Comparative, prospective follow-up study.

Objective. Comparison of outcome between patients treated with Percutaneous VertebroPlasty (PVP) using low and medium viscosity PolyMethylMetAcrylate (PMMA) bone cement.

Summary of Background Data. Viscosity is the characterizing parameter of PMMA bone cement, currently the standard augmentation material in PVP, and influences interdigitation, cement distribution inside the vertebral body, injected volume and extravasation, thereby affecting the clinical outcome of PVP. Currently, low, medium, and high viscosity PMMA bone cements are used interchangeably. However, effect of viscosity on clinical outcome in patients with Osteoporotic Vertebral Compression Fractures (OVCFs) has not yet been explicit subject of investigation.

Methods. Follow-up was conducted using a 0 to 10 Pain Intensity Numerical Rating Scale (PI-NRS) and the Short Form 36 (SF-36) Quality of Life questionnaire before PVP and at 7 days (PI-NRS only), 1, 3, and 12 months after PVP. Injected cement volume, degree of interdigitation, and cement leakage were analyzed on direct postoperative computed tomography scanning. At 6 and 52 weeks and at suspicion, patients were analyzed for new fractures.

Results. A total of 30 consecutive patients received PVP using low viscosity PMMA bone cement (OsteoPal-V) for 62 OVCFs, followed by 34 patients who received PVP using medium viscosity PMMA bone cement (Disc-O-Tech) for 67 OVCFs. Results regarding PI-NRS and SF-36 were comparable between both groups. Postoperative comparison of injected cement volume, degree of interdigitation, proportion of bipedicular procedures, incidence of new vertebral fractures and complications revealed no differences between both groups. Viscosity was identified as a risk factor for the occurrence of cement leakage (yes/no, OR: 2.925, 95% confidence interval: [1.072-7.984], P = 0.036).

Conclusion. No major differences in clinical outcome after PVP in OVCFs using low and medium viscosity PMMA bone cement were found. Viscosity of PMMA bone cement was identified as an independent predictor of cement leakage.

Introduction

Over the past 2 decades, percutaneous vertebroplasty (PVP) has gained popularity as a treatment modality for osteoporotic vertebral compression fractures (OVCFs). Promising results from large case series[1] and nonrandomized controlled trails have been reported,[2-4] and its position has been stated by professional societies.[5] Randomized controlled trails to establish the efficacy of PVP are currently being conducted.[6-8]

However, the mechanism of pain relief with PVP is as intriguing as it is unknown. Possible mechanisms may include thermal or chemical effects on nerve endings and more likely a mechanical effect of stabilization of (micro) movement within the fracture.[9,10]

For this purpose, multiple types of injectable bone cements like PolyMethylMetAcrylate (PMMA), calcium phosphate, and composite cements are currently being used in PVP. Polymethylmetacrylate is the most widely used cement type due to its good handling properties, strength, long time experience, and low costs.

Viscosity, the most indicative parameter of the flowing capability of a liquid, is one of the main characterizing parameters of PMMA bone cement, and because of its effect on the interdigitation (penetration in cancellous bone), one of the factors particularly likely to influence this stabilization effect and the resulting mechanical properties of the treated vertebra,[11,12] and hence, outcome of PVP.

Additionally, viscosity affects the spatial distribution of cement in the vertebral body (VB),[12] which, when inadequate, could alter the pattern of load transfer and might thereby induce new (adjacent) VCFs.[10,13,14]

Concomitantly, viscosity of bone cement is also an essential parameter regarding extravertebral bone cement leakage,[11-13] one of the most common side effects of PVP and detected in up to 87.5% of treated vertebra [15-17] with, although generally asymptomatic, occasionally severe results as paraplegia,[18] neurologic deficits,[19,20] pulmonary and cardiac cement embolisms,[21-23] and cardiac perforation.[24,25]

However, the degree to which these various manifestations of bone cement viscosity affect the clinical outcome of PVP is still unclear. In this study, we aimed to evaluate the clinical outcome of PVP in patients with OVCFs refractive to at least 8 weeks of conservative treatment in terms of patient clinical outcome, i.e., pain and quality of life (QoL), as well as cement leakage, interdigitation, and complications in patients treated with either low or medium viscosity PMMA bone cement.

Materials and Methods

Between August 2002 and August 2007, 64 patients were prospectively recruited for participation in a follow-up study on the clinical significance of viscosity of injected bone cement in PVP in chronic OVCFs at the Leiden University Medical Centre.

Inclusion criteria were (I) Osteoporotic VCF, including severe compression fractures,[26] (II) focal back pain in the midline refractive to at least 6 weeks of appropriate conservative treatment, (III) back pain related to the location of the VCF on Magnetic resonance imaging (MRI), (IV) the presence of bone marrow edema (BME) on MRI T2-weighted short tau inversion recovery sequences in the collapsed VB, (V) age over 40 years, and (VI) written informed consent.

Exclusion criteria were (I) VCFs due to other causes than osteoporosis, (II) spinal cord compression or stenosis of the vertebral canal >30% of the local canal diameter, (III) neurologic deficits, (IV) incorrectable bleeding disorders, (V) infections related to the vertebral column, (VI) inability to lie in prone position for 2 hours, (VI) an American Society of Anesthesiologists score 27 >=4, and (VII) inability of the patient to complete questionnaires.

In the period August 2002 to August 2005, 4 men (13%) and 26 women (87%) with a mean age of 70.7 years (range, 41.5-90.6) received PVP using low-viscosity PMMA bone cement (OsteoPal-V, Heraeus Medical, Germany) for 62 OVCFs in 32 sessions. At the time of the PVP procedure, 30 patients had a total of 139 preexisting VCFs, with a mean of 4.6 VCFs per patient (range, 1-13). Of these 139 VCFs, 62 were painful, showed BME on MRI and were treated with PVP.

Following August 2005 until August 2007, 34 patients, 10 men (29%) and 24 (71%) women with a mean age of 74.3 years (range, 48.5-90.8) received PVP, using medium-viscosity PMMA bone cement (Disc-O-Tech, Disc-O-Tech Medical Technologies Ltd., Israel) for 67 OVCFs in 34 sessions. A total of 139 pre-existing VCFs were noted (4.1 per patient; range, 1-10), whereas 67 VCFs were painful and showed BME on MRI and were treated with PVP. Group characteristics were comparable (**Table 1**).

When a patient presented with persistent pain after 6 weeks of conservative treatment, the complete clinical workup was conducted in 2 weeks ensuring that patients did not receive PVP within 8 weeks after commencement of the VCF.

Table 1. Characteristics of Both Patient Groups

Patient Characteristics	Cement		
	Group 1: LVC OsteoPal-V	Group 2: MVC Disc-O-Tech	*P*
No. patients	30	34	
Male (%)	4 (13)	10 (29)	0.142
Female (%)	26 (87)	24 (71)	
Mean age (range)	70.7 (41.5–90.6)	74.3 (48.5–90.8)	0.150
Fractures			
Pre-existing (range, mean per patient)	139 (1–13, 4.6)	140 (1–10, 4.1)	0.331
Treated (range, mean per patient)	62 (1–5, 2.1)	67 (1–5, 2.0)	0.690
Type according to Genant et al			
Wedge			
Grade 1	10	4	0.131
Grade 2	14	21	
Grade 3	10	19	
Biconcave			
Grade 1	5	4	
Grade 2	14	12	
Grade 3	7	5	
Complete			
Grade 1	0	0	
Grade 2	0	0	
Grade 3	0	2	
Mean fracture age (mo)	8.2 (2.4–35.0)	6.4 (2.2–17.4)	0.660
Corrected for 2 outliers in group 1 (32.2 and 35.0)	6.0 (2.4–11.6)	6.4 (2.2–17.4)	0.656

LVC indicates low viscosity cement; MVC, medium viscosity cement.

Table 1. Characteristics of both patient groups.

In the work-up for PVP, anteroposterior and lateral radiographs and MRI, including fat suppression sequences, of the total spine were acquired. Fracture morphology was denominated according to the classification from Genant et al,[28] and was comparable between both groups, as was fracture age (**Table 1**). Fracture age was defined as the time between the onset of new back pain related to a radiologic confirmed fracture and the time of PVP.

Cement leakage, defined as the presence of any extravertebral cement, was assessed independent of the treating physician by 2 investigators (S.P.J.M. and M.J.N.) using a computed tomography (CT) scan made directly after PVP. Differences were re-examined until consensus was obtained. Patterns of cement leakage are described using the classification proposed by Yeom et al,[29] identifying 3 types of leakage sites: (1) via the basivertebral vein (B-type), (2) via the segmental vein (S-type), and (3) through a cortical defect (C-type, **Figure 1**). Intra- and extracorporal volumes were measured using OsiriX, an open source calibrated Digital Imaging and Communications in Medicine (DICOM)-viewer.

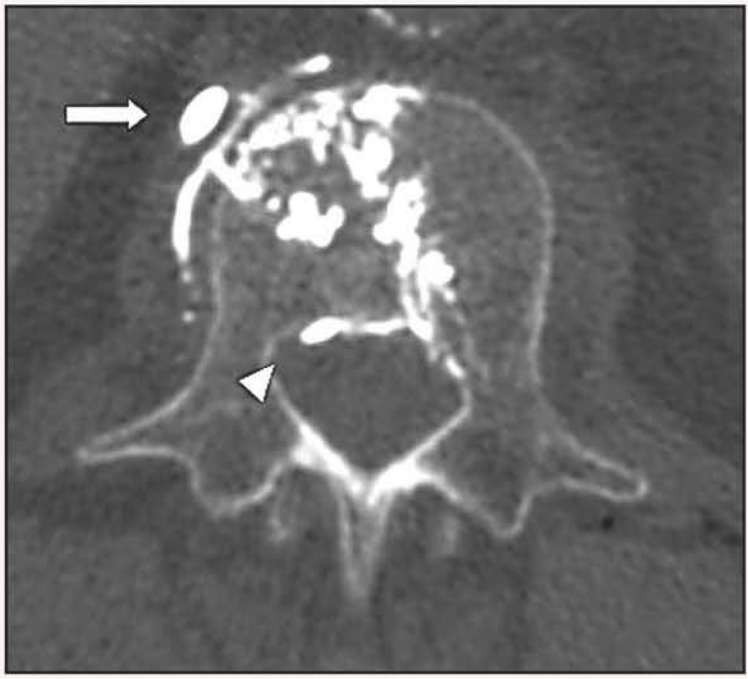

Figure 1. Computed tomography-scan of a vertebra after PVP. Two leakage patterns are clearly visible: 1 S-type leakage site (arrow) and 1 B-type leakage site (arrowhead).

In addition, the degree of interdigitation of bone cement was scored on a semiquantitative scale ranging from 1 (complete interdigitation throughout the injected volume with clearly visible bone trabecles) to 4 (no interdigitation at all with sharp boundaries along the cement clump, comparable to cleft filling) by 2 investigators (S.P.J.M. and M.J.N.) (**Figure 2**). In case of nonuniformity in scores, cases were re-examined until consensus was obtained.

The PVP procedure in detail has been described previously.[17] In short, PVP was performed on a biplane angiography unit using conscious sedation. After advancement of a 10-G vertebroplasty needle (Optimed GmbH, Germany) into the VB, a bone biopsy was obtained and PMMA bone cement was injected using an Optimed Cemento gun (Optimed GmbH, Germany) until satisfactory distribution of the cement, i.e., symmetrical filling of the central and anterior parts of the VB, was achieved. When necessary, a second needle was advanced into the VB through the contralateral pedicle, followed by injection of cement.

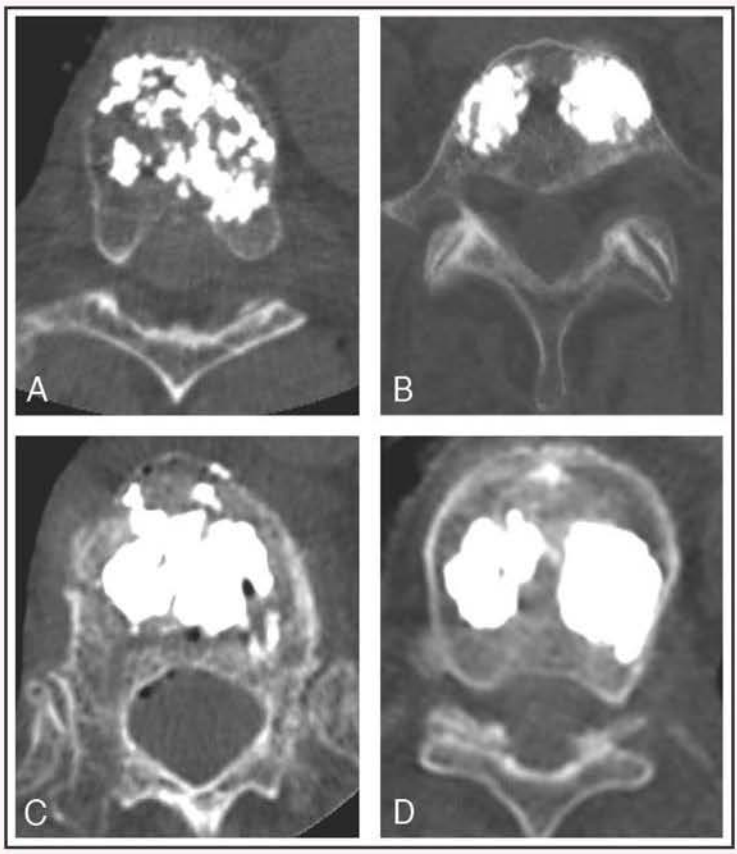

Figure 2. Interdigitation score. A, Grade 1, complete interdigitation between bone trabecles; B, Grade 2, considerable interdigitation along the boundaries of a clearly recognizable cement deposit; C, Grade 3, a clump like filling pattern with sparsely gross interdigitation; D, Grade 4, a sharply demarcated cement clump with no interdigitation at all.

The PMMA bone cement is a 2-component liquid methyl methacrylate and polymer powder mixture which, after mixture, cures from a liquid to a solid phase. During the curing phase, viscosity increases with time and temperature. Bone cement was prepared as stated by the respective manufacturers in order to obtain the specified cement properties. The PVP procedure was tailored at optimal filling of the VB and patient safety and was not altered due to the type of cement used. Qualification of cement viscosity is cited here as stated by the manufacturer.

Pre- and postoperative clinical characteristics of each patient were obtained using the Short Form (SF)-36 health survey[30-32] and a 0 to 10 Pain Intensity Numerical Rating Scale (PI-NRS) for mean and worst back pain.[33] Questionnaires were filled out before the procedure and at 7 days (PI-NRS only), 1 month, 3 months, and 12 months after the procedure. Routine standing anteroposterior and lateral radiographs of the spine were made 6 weeks and 1 year after PVP and on indication, e.g., sudden new onset of back pain suspect for a new OVCF.

Statistical Analysis

Raw SF-36 item scores were summarized and transformed to a 100-points scale, with a higher score representing a higher level of function or well-being. Longitudinal analysis of PI-NRS and SF-36 was performed using mixed model analysis based on maximum likelihood estimation. Distribution and skewness of data were assessed, as was normality using the Kolmogorov-Smirnov test. Where appropriate, the (paired) Student t test, the Mann-Whitney U test, the [chi]2 test, Fisher exact test, and the log-rank test were used. A multiple logistic regression analysis was carried out to identify predictive factors for the occurrence of cement leakage. Using multiple linear regression analysis, factors independently associated with the volume of cement leakage were assessed.

Results

Preprocedurally obtained PI-NRS and SF-36 scores were comparable between both groups (**Figure 3, Table 2**). Mean average and worst back pain scores were respectively 7.9 and 8.8 for the group treated with low viscosity cement (LVC-group) and 7.5 and 8.5 for the group treated with medium viscosity cement (MVC-group), and showed 7 days after PVP a significant decrease of 3.1 and 2.7 (LVC-group, P = 0.142 and P = 0.337).

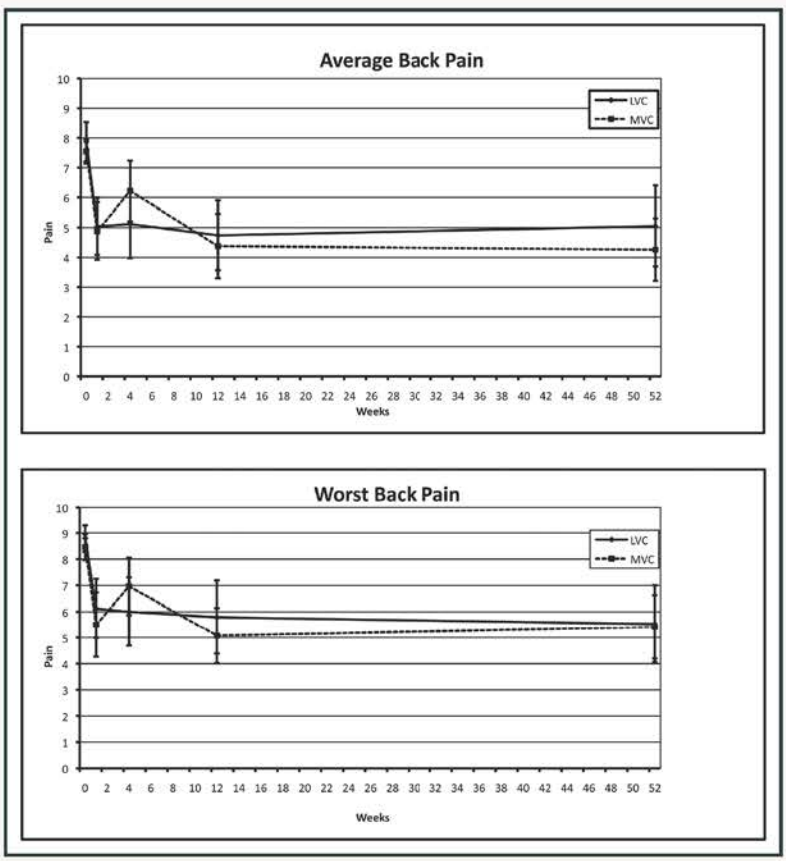

Figure 3. Average (A) and worst (B) back pain. Both were found to be significantly and consistently lower after PVP (P = 0.142 and P = 0.337 respectively).

Table 2. SF-36 Screening Scores and Differences Between Scores at the Respective Follow-Up Points and the Screening Scores

	Screening			Change Screening—1 Month			Charge Screening—3 Month			Change Screening—12 Month			
	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	*P*
PCS													
LVC	26.53	5.37	30	7.46	8.59	23	7.19	8.48	22	7.93	12.00	18	<0.001
MVC	26.02	8.23	34	2.46	8.05	27	6.12	9.36	25	5.11	9.14	28	
	P = 0.773												Over all effect of viscosity: *P* = 0.559
MCS													
LVC	39.59	11.74	30	-4.35	11.50	23	3.35	7.93	22	3.49	9.41	18	0.058
MVC	40.75	13.01	34	3.68	9.52	27	1.18	10.14	25	5.06	14.46	28	
	P = 0.712												Over all effect of viscosity: *P* = 0.271

No effect of bone cement viscosity was identified for PCS (*P* = 0.559). For MCS, no effect of time or viscosity was found (*P* = 0.058 and *P* = 0.271, respectively). PCS indicates physical component score; MCS, mental component score; LVC, low viscosity cement; MVC, medium viscosity cement; SD, standard deviation.

Table 2. SF-36 screening scores and differences between scores at the respective follow-up points and the screening scores.

Comparison of 1 month postvertebroplasty scores on the 8 domains and both component (summary) measures of the SF-36 showed a significantly higher increase on the domain "Physical Functioning" and the "Physical Component Score" for the LVC group compared to the MVC-group, while scoring on the domain "Role Physical" and the "Mental Component Score" was significantly higher for the MVC-group compared to the LVC-group). At 3- and 12-months follow-up, SF-36 scores on all domains and both summary measures were comparable. The Physical Component Score was significantly increased at both follow-up points, whereas the Mental Component Score was not (**Table 2, Figure 4**).

Of 62 vertebrae in the LVC group, PVP was unipedicular in 36 (58.1%) cases and bipedicular in 26 (41.9%), whereas the procedure was unipedicular in 45 (62.8%) and bipedicular in 22 (32.8%) of 66 vertebrae in the MVC-group (P = 0.285).

In order to correct for eventual geometrical, anatomic, or weight-bearing induced differences, injected cement volume, and interdigitation score were analyzed separately for the thoracic and lumbar spine. Neither the injected cement volume nor the interdigitation score per region differed significantly between the LVC- and the MVC-group (**Table 3**).

The proportion of vertebrae with detected cement extravasation was significantly higher in the LVC-group (87.9% vs. 71.6%, P = 0.029, **Table 4**). A subsequent multiple logistic analyses identified cement viscosity to be associated with the occurrence of leakage (yes/no), P = 0.036, **Table 5**). The distribution of leakage types was similar in both groups (**Table 4**).

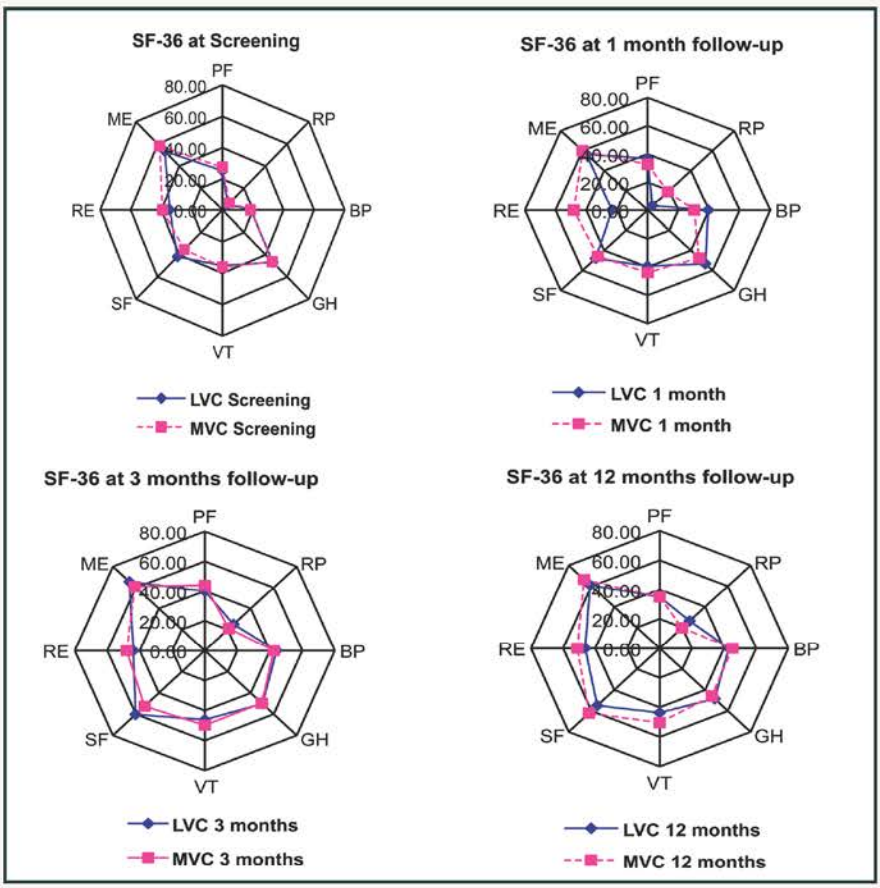

Figure 4. SF-36 Domain scores at various follow-up points. Baseline domain scores were comparable between both groups. At 1 month PF was significantly higher in the LVC-group (P = 0.03), whereas RP was significantly higher in the MVC-group (P = 0.01). At 3 and 12 months, all domain scores were similar in both groups. PF indicates physical functioning; RP, role physical; BP, bodily pain; GH, general health perceptions; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Table 3. Comparison of Vertebrae Treated, Average Cement Volume, and Interdigitation Score per Region Between Both Groups

Level	LVC	MVC	Region
Th5	2	2	32/43
Th6	2	3	
Th7	3	3	
Th8	2	7	
Th9	4	5	
Th10	4	5	
Th11	6	6	
Th12	9	12	
L1	7	9	30/24
L2	8	8	
L3	7	4	
L4	5	3	
L5	3	0	
			$P = 0.148$

	Injected Cement Volume (mL)		Interdigitation Score (I–IV)	
	LVC	MVC	(LVC/MVC)	
Thoracic	4.66 (n = 31)	4.27 (n = 43)	I: 12/10 II: 11/19	III: 6/12 IV: 2/2
	$P = 0.372$		$P = 0.487$	
Lumbar	6.02 (n = 29)	4.91 (n = 24)	I: 11/12 II: 8/4	III: 9/8 IV: 1/0
	$P = 0.081$		$P = 0.576$	

LVC indicates low viscosity cement; MVC, medium viscosity cement, Th, thoracic; L, lumbar.

Table 3. Comparison of vertebrae treated, average cement volume, and interdigitation score per region between both groups.

A multiple linear regression revealed fracture severity, the number of extravasation sites, and the injected volumes to be independently associated with leakage volume (**Table 5**). In the LVC-group, 14 new fractures, of which 9 adjacent to treated levels, occurred in 10 patients (33.3%) after a mean of 6.8 months (1.3-13.6), whereas in the MVC-Group 17 new fractures, of which 10 adjacent, occurred in 9 patients (26.5%) after a mean of 4.2 months (0.03-11.9). One VCF occurred 1 day after PVP. In 2 patients in the LVC-group and 4 patients in the MVC-group, these fractures were treated using PVP. Proportion of patients with new OVCFs, proportion of adjacent fractures, time distribution, and mean time to occurrence of new fracture were comparable between both groups (P = 0.380, P = 0.756, P = 0.080, and P = 0.071, respectively).

Two minor complications, 1 asymptomatic pulmonary cement embolism and 1 cement spur following the needle tract from the pedicle to the subcutaneous tissue, which was removed immediately, occurred in the LVC-group. In the MVC-group, in 2 patients a similar cement spur was noted after surgery. Proving asymptomatic, the spurs were not removed.

Table 4. Leakage Specifications

	Cement		
	Group 1: LVC OsteoPal-V	Group 2: MVC Disc-O-Tech	*P*
Vertebrae with leakage	51 of 58 (87.9%)	48 of 67 (71.6%)	0.029
Type according to Yeom *et al*			
B	21 (28.8%)	19 (22.4%)	
S	18 (24.7%)	26 (30.6%)	0.567
C	34 (46.6%)	40 (46.8%)	
Into discus	32, (43.8%)	38, (44.7%)	0.762

LVC indicates low viscosity cement; MVC, medium viscosity cement; B, *via* the basivertebral vein; S, *via* the segmental vein; C, through a cortical defect.

Table 4. Leakage Specifications.

Table 5. Results of Regression Analysis

		P
Multiple logistic regression for presence of cement leakage (yes/no)	Odds Ratio (95% CI)	
Severity according to Genant *et al*	1.37 (0.70–2.67)	0.355
Fracture type according to Genant *et al*	0.68 (0.24–1.95)	0.474
Injected volume	1.03 (0.79–1.33)	0.843
Spinal region	0.48 (0.54–3.74)	0.476
Cement viscosity	2.93 (1.07–7.98)	0.036
Multiple linear regression for log total volume of cement leakage	Coefficient (95% CI)	
Severity acc. to Genant *et al*	0.35 (0.17–0.53)	0.001
Fracture type acc. to Genant *et al*	0.04 (−0.20–0.28)	0.763
Injected volume	0.08 (0.00–0.15)	0.045
Spinal region	0.04 (−0.12–0.21)	0.595
Cement viscosity	−0.05 (−0.30–0.20)	0.702
No. leakage sites	0.30 (0.13–0.46)	0.001

CI indicates confidence interval.

Table 5. Results of regression analysis.

Discussion

Besides injection technique and bone- and fracture-related parameters, cement properties influence cement flow, distribution, and volume inside the VB, and thereby ultimately the outcome of PVP.

Viscosity of bone cement used in PVP is hypothesized to influence the outcome of the procedure in various ways. One way is by determining or affecting the potential of the cement to interdigitate with the trabecular bone, and thereby its potential to stabilize (micro)movements in the fractured vertebra and relief pain, as well as preserve its mechanical strength.[11,12,34] In addition, it is unclear whether spatial distribution of the cement, also influenced by cement viscosity,[12,35] affects the outcome of PVP and the risk of subsequent (adjacent) vertebral fractures by alteration of the distribution of load and its transfer over the VB.[10,13,14,36,37] Hence, placement of a second needle through the contralateral pedicle, and thereby introducing substantial additional risks and costs, is frequently opted for when the distribution of cement is unsatisfactory or asymmetrical. Hemivertebral filling through a unipedicular approach appears as effective as using a bipedicular approach though.[38-40]

Regarding the procedure itself, more viscous cement has better handling properties, especially in controlling the amount and speed of injection. Downside of the higher viscosity is the higher injection pressures required[12,41] and the volume of injectable cement can therefore be limited, necessitating conversion from a uni- to a bipedicular approach.

Above all, however, viscosity of cement is a crucial parameter regarding the main cause of (severe) complications of PVP, being extravastion of cement outside the VB.[11-13,41] Despite its proven superiority over radiography for detection of cement leakage,[16,29] CT-scanning after PVP is infrequently executed for this purpose, rendering most reported cement leakage incidences invaluable. Reported in up to 87.5% of treated vertebrae on postoperative CT-scanning[15-17] and generally asymptomatic, extravasation of cement inside the spinal foramen or the venous circulation can result in neurologic deficits, paraplegia, pulmonary and cardiac embolisms, or cardiac perforation.[18-25]

In PVP, low, medium, and high viscosity PMMA bone cements are used interchangeably. Effects of viscosity, (optimal) injected volume and distribution of cement in relation to cement leakage and restoration of biomechanical properties of fractured vertebra have been investigated in experimental or cadaver studies or using finite element analysis.[9-12,36-38,40,41] However, patient clinical significance

has not yet been explicit subject of investigation and an in vivo direct comparison of clinical outcome between groups treated with PVP using identical injections methods, but bone cements with different viscosities has, to the authors' best knowledge, not been reported thus far. This study focused on the effect of bone cement viscosity on the clinical outcome of PVP using periprocedurally and prospectively acquired (follow-up) data from 2 patient groups which have been treated with PVP for OVCFs using low and medium viscosity PMMA bone cement.

For the LVC- and the MVC-group, our results showed a clinically relevant,[33] significant, immediate, and durable reduction in average back pain, respectively 3.1 and 2.6 at 7 days and 3.3 and 3.2 at 1 year, and worst back pain respectively 2.7 and 2.8 at 7 days and 3.4 and 3.0 at 1 year, which was comparable between both groups. Increase in QoL, measured using the SF-36, was similar in both groups.

Comparison of mean injected cement volume per vertebra per region revealed no significant difference, although a tendency was seen toward injecting less cement in the MVC-group. The degree of interdigitation of bone cement was also found to be similar in both groups, thereby contrasting the expectation of more pronounced interdigitation or uniform filling facilitated by higher viscosity cement.[11,12] This is supported by the similar proportion of bipedicular procedures in both groups, being an indication of the similar spatial distribution of cement inside the VB and the comparable number of and mean time to development of new OVCFs after PVP in both groups.

In the MVC-group, a significantly smaller proportion of treated vertebrae exhibited cement leakage (71.6% vs. 87.9%, P = 0.029). In order to correct for eventual confounders, a multiple logistic analysis was carried out and revealed cement viscosity to be significantly associated with the occurrence of cement leakage (yes/no, P = 0.036), the risk of occurrence of cement extravasation using LVC being nearly 3-fold compared to when using MVC (OR, 2.925; 95% confidence interval, [1.072-7.984]). Despite its intuitive nature, this is actually the first study proving this hypothesis in vivo and confirming experimental results.[11,12]

The amount of cement extravasation was found to be independently associated with the volume of injected cement, the number of leakage sites, and the semiquantitatively graded severity of the fracture. No independent association with viscosity was found. Trivially, when intraoperative cement leakage is noted, further injection of cement should be done with great care and the number of leakage sites as well as the fracture severity should be kept in

mind, predisposing for a greater amount of cement leakage with potentially more severe sequelae. Whether or not the severe leakage described with low-viscosity cement,[20] due to its predisposition for taking the "path of least resistance," resulting from intravertebral irregularities,[11,12] will be reduced using high viscosity bone cement remains unconfirmed.

A limitation of our study was the subsequent treatment using low and MVCs in study cohorts instead of randomized usage of both cements, thereby unable to cancel out effects of an operator learning curve and increased expectations of patients as a result of the gradual general awareness of the procedure and its results. Other limitations are the lack of measurement of injected cement viscosity and degree of osteoporosis.

In conclusion, in experienced hands, viscosity of PMMA bone cement used in PVP for OVCFs did not influence clinical outcome. The immediate and durable reduction in pain and improvement in QoL was comparable between both groups, as was the injected cement volume, degree of interdigitation, proportion of bipedicular procedures, incidence of new vertebral fractures and complications. Cement viscosity, however, was identified as an independent predictive factor for the occurrence of cement leakage. In the presence of cement extravasation, leakage volume is associated with injected cement volume, number of leakage sites and fracture severity.

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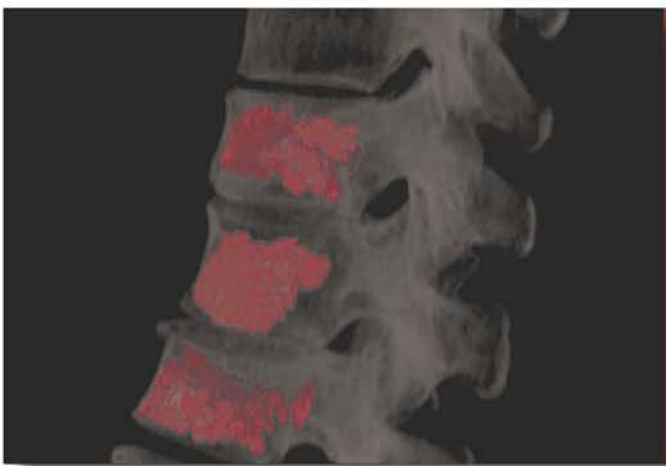
Chapter



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A system for Evaluation of eXtra vertebral cement leakage in vertebroplasty based on Anatomy and volume in CT-scan analysis; The EXACT classification

Submitted

Abstract

Purpose. The majority of clinically relevant complications after Percutaneous VertebroPlasty (PVP) are due to cement leakage. A radiological classification of these cement leakages should be reproducible precise and logical. The currently used classification systems, provide no information on the anatomical location and volume of the cement leakage, making it impossible to determine which leakages lead to clinically relevant complications.

Aim. The aim of this study is to test a new system for Evaluation of eXtra vertebral cement leakage in vertebroplasty based on Anatomy and volume of the leakage using CT-scan analysis (the EXACT classification system) with superior discrimination potential. This system describes spatial distribution and anatomical structures of the leakage in addition to the Cement Leakage Volume.

Materials and methods. The direct postoperative CT-data of 106 vertebral bodies from 53 patients, treated with PVP were analyzed. Leakages were analyzed according to the system published by Yeom et al., and using the new anatomy based classification system.

Results. The inter-observer variability, using the new scoring system was 0.94 ($p<0.001$), which is comparable to the inter-observer variability of 0.97 ($P<0.001$) found when using the system of Yeom et al. In addition to the leakage volume, the new system identified leakage sites more specific in terms of anatomical and spatial distribution compared to the classification system according to Yeom et al.

Conclusions. The new system facilitates research, investigating divergence in leakage patterns of different cement types available on the market and to register specific cement leakages and possible clinical sequelae.

Introduction

Since Percutaneous VertebroPlasty (PVP) was introduced in 1989 as a minimal invasive procedure for the treatment of painful Osteoporotic Vertebral Compression Fractures (OVCFs), the procedure gained popularity because of its high effectiveness in fast pain reduction.[1] Fast, significant and clinically relevant relief of symptoms and restoration of mobility, is achieved in more than 80% of patients in multiple large studies.[2-4] Moreover, PVP has many advantages compared to extensive surgery due to its minimal invasiveness, and relatively low costs.

Due to two recent randomized blinded controlled trials, which showed no beneficial effect of vertebroplasty compared to a sham procedure, specialists became more alert on possible negative side effects of the procedure.[5,6] The new insights called for more accurate registration of possible negative side effects and complications of the PVP procedure.

The rate of complications with a clinical sequel of PVP is low and is reported to range from 1.6% to 2.8%.[7] The reported complications with PVP in OVCFs however range from apparently clinically silent unanticipated advents to catastrophic clinical outcome and death.[8-11] The vast majority of the clinically relevant complications of PVP are due to leakage of bone-cement. Severe complications are rare and mainly occur in case of high volume cement leakage.

Reported complications include cement entering the nerve root foramen or spinal canal, resulting in radiculopathy or spinal cord compression, embolic events due to marrow fat or cement entering the circulation, malplacement of the needle, rib fractures, pneumothorax, fracture of processus spinosus or pedicle, subcutaneous paravertebral hematoma and infection.[12-18]

In PVP, PolyMethylMethAcrylate (PMMA) bone cement is the most widely used type of cement. There's a wide variety of PMMA cements types with different viscosity available. The viscosity is often categorized as low-viscosity (comparable to yoghurt), medium viscosity (comparable to toothpaste) and high viscosity (comparable to dough). These types of cement are clinically used interchangeably, despite of the fact that literature suggests that there are differences in frequency volume and leakage types between the cement types used.[19,20] Currently, still new types of PMMA cement are introduced to the market without certainty concerning its potential leakage behavior.

So far, accurate and comparable data concerning the risk of clinically relevant complications due to specific cement leakage types are unavailable. This is partly due to a lack of radiological (i.e. CT) follow-up and the lack of a clinically applicable classification system for cement leakages.

The only paper specifically describing and testing a leakage classification system is by Yeom et al in 2003.[18] This classification system, divides cement leakages in Basivertebral (B), Segmental (S) and Cortical (C) but gives no information on the anatomical location and volume of the cement leakage and may therefore lack clinical relevance.

Papers concerning cement leakage describe a variety systems, which are based on the system published by Yeom et al. and show resemblances but are however not similar enough to compare the outcomes in a detailed meta-analysis.[21-26] In order to facilitate more accurate registration of cement leakages, a logical, accurate, and reproducible cement leakage classification system is mandatory.

The aim of the current study was therefore to develop and test a new system for Evaluation of eXtra vertebral cement leakage in vertebroplasty based on Anatomy and volume of the leakages using CT-scan analysis (EXACT system). This system describes spatial distribution (anterior (A.x.x), medial (B.x.x) or posterior (C.x.x)) and anatomical structures (venous system (x.1.x), cortical defect (x.2.x)) of the leakage and specific sites (e.g. vein or discus) in addition to the cement leakage volume (x.x.0.5cc)(**Figure 1**). For venous leakages (x1x), 5 types are recognized by their anatomical location (anterior external plexus, the basivertebral vein, the segmental vein, the anterior internal plexus and the posterior internal plexus (**Figure 2**), a comprehensive description of the vertebral venous structures has previously been published by Groen et al.[27]

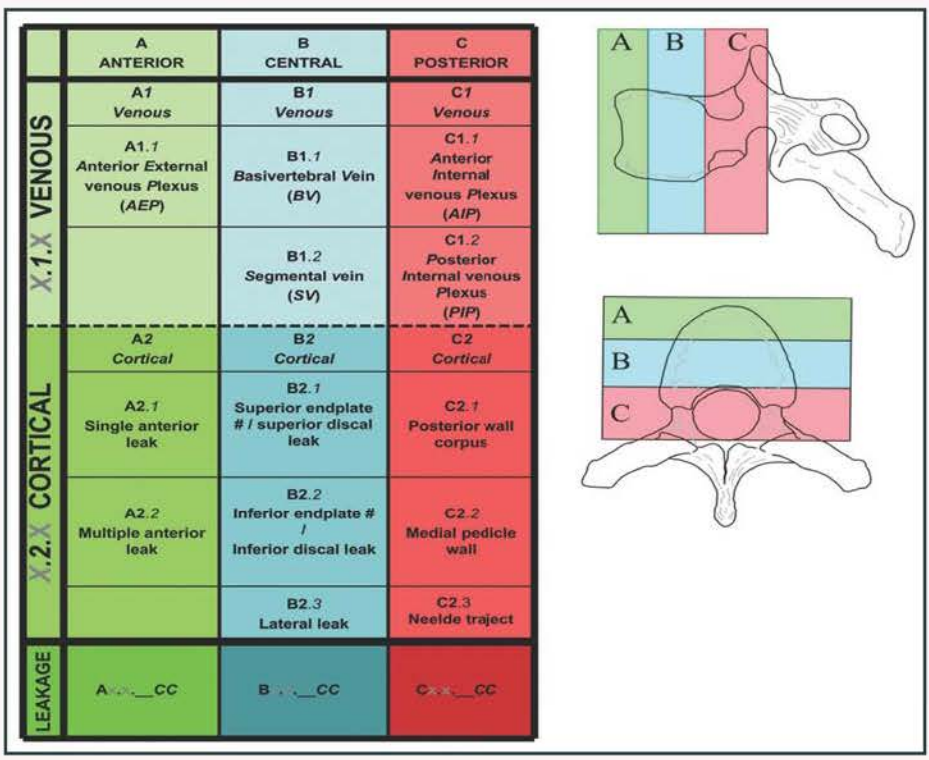

Figure 1. Overview of the EXACT anatomy based scoring system.

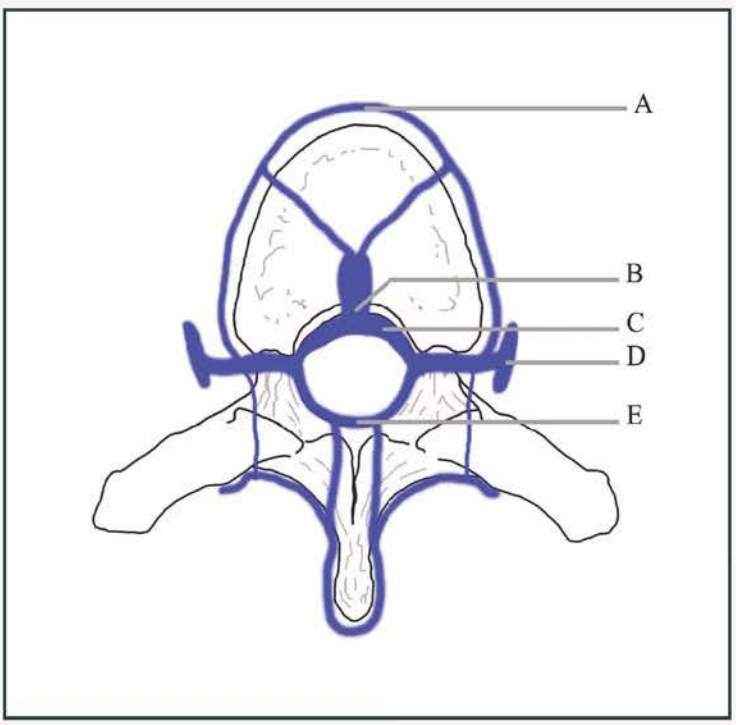

Figure 2. Shows a schematic drawing of the anatomy of the vertebral venous system. A; Anterior External Plexus (AEP), B: Basivertebral Vein (BV), C: Anterior Internal Venous Plexus (AIP), D: Segmental Vein (SV), E: Posterior Internal Venous Plexus (PIP).

Patients and Methods

Data were collected from 53 patients treated for 106 painful OVCFs between January 2008 and January 2009. All patients underwent a post-intervention CT-scan using a standardized protocol and a standard multi-slice CT-scanner (Thoshiba Aquilion 64 slice, slice thickness: 1.0mm, Gantry-tilt: 0 degrees, X-ray tube kilovoltage (KVP) 135, X-ray tube current 250, Exposure time 500)

The 106 vertebral bodies (VB) from 53 patients were divided into three regions. 1) Thoracic region, in which T5-T10 were grouped, (37 VB (34.9%)), 2) Thoraco-lumbar region, in which T11-L2 were grouped, (50 VB (47.2%)), and 3) Lumbar region in which L3-L5 were grouped (19 VB (17.9%)).

Calibration

The direct postoperative CT-data of the 106 vertebral bodies (VB) treated with PVP were analyzed using a calibrated DICOM viewer (Osirix 3.3, 64 bit, Kagi, Berkeley, California). The Osirix DICOM viewer was calibrated by CT-analysis of cement volumes injected in 8 cadaveric pig vertebrae, which were hermetically sealed in a container of gelatin and scanned on the same CT-scanner, which was used during the clinical experiment. The analyzed vertebral bone was dissolved in hydrochloric acid and the volume of the remaining PMMA-cement was determined by water-displacement volumetry. After measurement of the actual, in vitro, cement-volume, 3D growing region segmentation was calibrated using a fixed lower pixel threshold of 100, and a fixed upper threshold of 10.000. This wide window could be used due to the high difference in opacity of the opacified bone-cement compared to the surrounding vertebral bone. All specimens were tested and all volumes were calculated 4 times. After calibration, the CT-analysis was found to be accurate up to 0.01mL of PMMA cement.

Analysis of CT-data

Analysis of the CT-data acquired from the treated patients in our cohort included: 1) vertebral level; 2) Cement Leakage Volume, defined as the total cement volume outside of the cortical border of a treated vertebral body and is acquired by adding the volume of all solitair cement leakages in a single treated vertebral body; 3) Total Cement Volume , defined as the total volume of cement within the vertebral body (including the volume trabecular bone captured within the injected cement) and outside the cortical boundaries of the vertebral

body; 4) cement leakage classification according to Yeom et al.; and 5) cement leakage classification acc. to the new classification system. All vertebral levels were graded by 3 independent observers experienced in assessing skeletal CT-scans, using both the classification system according to Yeom et al. and the new classification system.

Statistical Analysis

A probability value of <0.05 (two-tailed) was considered statistically significant. The intra-class correlation coefficient for leakage category scoring was tested for absolute agreement using a two-way mixed model where people effects are random and measures effects are fixed in SPSS statistical software 16.0, (SPSS Inc, Chicago, IL).

Results

Classification according to the EXACT system showed a total of 124 leakages. In the thoracic region, 46 leakages were detected (1.24 leakage sites/VB). Mean cement leakage volume in the thoracic region was 0.33 mL and ranged from 0.02 to 1.76 mL. In the thoraco-lumbar, region 61 leakages were detected (1.24 leakage sites/VB). Mean cement leakage volume in the thoraco-lumbar region was 0,47 mL (range 0.02-5.59 mL). In the lumbar region 17 leakages were detected (0.89 leakage sites/VB). Mean cement leakage volume the lumbar region was 0,32 (range 0.02-3,61 mL). Of all leakages, 53 (43%) consisted out of a cement volume ≥ 0.25 mL and 28 (23%) out of ≥ 0.5 mL. Of these larger leakages, 38 (72%) were located through the superior and inferior endplates B2.1 and B2.2, and 9 (17%) into the anterior internal plexus C1.1 *(***Table1, Figure 3***)*. Mean total cement volume was: 3.82 ±1.45 mL in the thoracic region, 5.26 ±2.04 mL in the thoraco-lumbar region and 6.57±2.15 mL in the lumbar region.

Classification of the leakages according to the classification system of Yeom et al. also showed 124 leakage sites of which 30 type B (Basivertebral vein leakage), 29 type S (segmental vein leakage) and 65 type C (Cortical defect). **Table 2** demonstrates the subdivision of cortical and venous leakages in relation to the system of Yeom et al.

The inter-observer variability (intra-class observer correlation) of 3 independent observers for the EXACT classification system, was 0.94, the inter-observer variability when using the classification system according to Yeom et al. was 0.97 (P<0.001).

	Yeom et al.			Current study											
	B	S	C	A 1.1	A 2.1	A 2.2	B 1.1	B 1.2	B2.1	B2.2	C1.1	C1.2	C2.1	C2.2	C2.3
T	11	9	26	6	1	1	1	4	13	10	9	1	0	0	0
TL	15	14	32	7	3	1	0	6	15	13	14	0	0	0	0
L	4	6	7	2	1	0	0	3	1	4	4	1	0	0	2
	30 (24%)	29 (23%)	65 (52%)	16 (13%)	5 (4%)	2 (2%)	1 (1%)	13 (10%)	29 (24%)	27 (22%)	29 (22%)	0 (2%)	0 (0%)	0 (0%)	2 (2%)

Table 1. Cement leakage per region according to Yeom et al. and the EXACT classification system. (T=thoracic region,TL= thoracolumbar region, L= lumbar region).

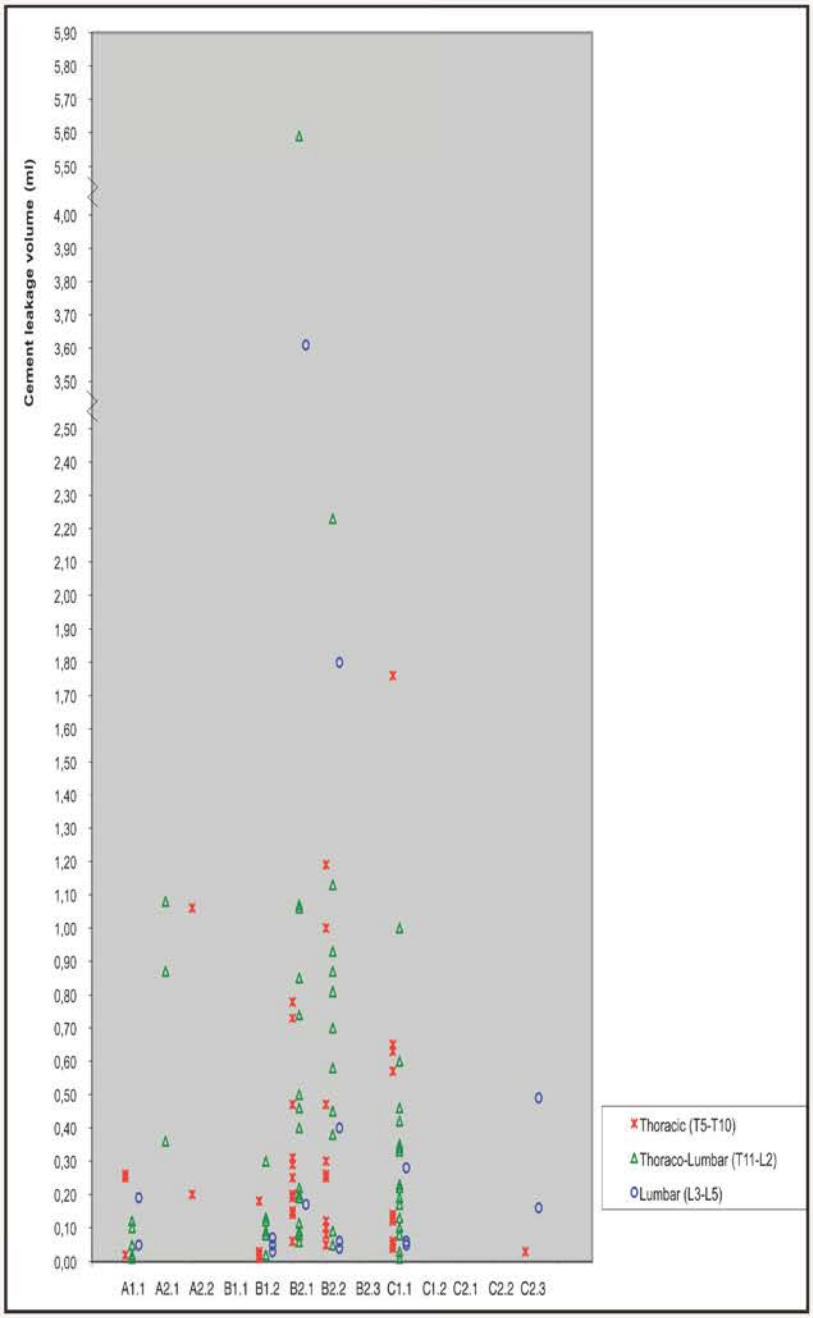

Figure 3. Cement leakage volume (mL) per anatomical class according to the EXACT system.

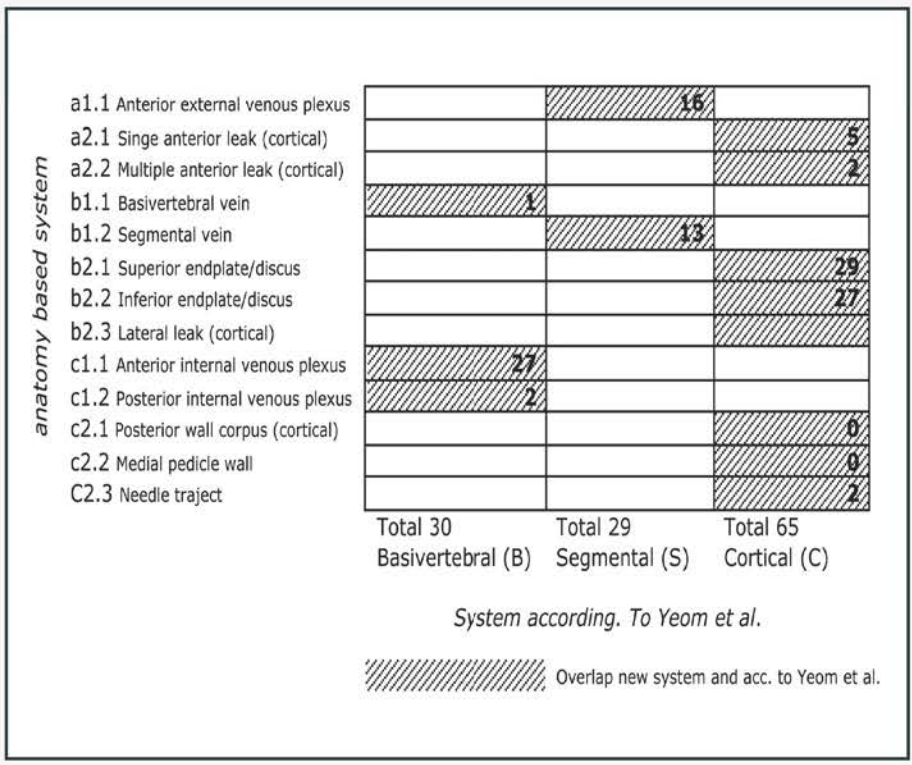

Table 2. Comparison overview of the number and distribution of leakages in the EXACT classification system versus the classification system according to Yeom et al.

Discussion

In 2009, two randomized, blinded, controlled trials, have been published.[5,6] Both trials showed no beneficial effect of vertebroplasty compared to a sham procedure among patients with painful osteoporotic vertebral fractures. An even more recent randomized study however showed that vertebroplasty is superior compared to conservative treatment. The outcome of the former two trials, which showed no beneficial effect of vertebroplasty, made specialists more alert on possible negative side effects of the procedure.[28,29] Because both papers were simultaneously published in the prestigious New England Journal of Medicine, the results had a major effect on physicians, media and public. The new insights called for accurate registration of possible negative side effects and complications of the PVP procedure.

In light of the renewed emphasis on critical judging of complications and possible side-effects of the PVP procedure, research should be conducted using understandable, reproducible and precise outcome measures.

As cement leakage is reported to account for the majority of complications of PVP, and is found in up to 88% of the PVP procedures, the leakages and their sequeale should be registered.[30,31] Cement leakage is dependent on the injected cement volume and is best detected using post-operative CT-scanning.[32] The use of CT scanning versus plain X-ray results in a increase of more than 50% leakage detection.[30] Fluoroscopic or plain radiography imaging, which are often used for assessing cement leakage, are insufficient to collect enough information concerning the effects of the leakages. Both the exact anatomical position as well as the volume of the leakage is very difficult to assess. Schmidt et al. found in their study that the agreement rate between fluoroscopy and CT scans ranged from 66% to 74%, while inter-observer reliability showed only fair agreement. Especially leakages in the basivertebral veins were frequently misinterpreted.[30]

To objectivate the clinical outcome after PVP or other procedures, numerous well-tested questionnaires have been developed over the years (Short-Form 36 (SF36), Roland-Morris disability score, visual analogue score (VAS)).[33-35] However, when investigating the complication rate in PVP, in which the most prevalent complication is cement leakage, there is no classification system to evaluate the clinical consequences of cement leakage.

In vertebroplasty the complication rate is low (1.6% - 2.8%), but mainly due to cement leakage.[7] So far, the "common" cement leakage in PVP, is said to be without clinical consequences in the majority of cases. Clinical relevance of cement leakages is highly dependant on the site of the leakage. Leakage to the neuro-foramen or the spinal canal might result in neurologic complications.[10] Furthermore, leakage to the intervertebral disc could lead to altered biomechanical stress to the adjacent vertebral body and could possibly cause an increased risk of new fractures.[36] Leakages to arterial or venous structures are reported to cause pulmonary embolism, and have been reported to be present in up to 18% of patients after a PVP procedure.[12] Even cardiac perforation and cerebral cement embolism have been reported.[9,12,37] Without a precise system to measure cement leakage in order to correlate these outcomes to possible clinical consequences of these leakages, a good insight in the dangers of cement leakages during PVP can not be made.

When using the classification system published by Yeom et al., leakages of cement are classified into three types: 1) Type B - leakages via the basivertebral vein - these leakages involve leakage of cement into the spinal canal. They proceed via the vascular foramen and in the spinal canal they follow the epidural venous plexus, 2) Type-S - leakages via the segmental vein - these leaks often proceed horizontally, in line of the segmental veins. They therefore often mimic a small paravertebral leak on anteroposterior radiographs. They are, however, often long leaks, and may reach the neural foramina and finally Type-C - through a cortical defect around a vertebral body, including the spinal canal. Leaks into the spinal canal for example therefore may be scored as a type-B or type-C leakage, when using the system according to Yeom et al.[18] No information concerning the anatomical position or the volume of the leakage is provided using the aforementioned system. Moreover, cortical leakage (C) in the system of Yeom et al. are grouped in one category, hereby discarding all information concerning structures which could be at risk at specific sites.

When using the EXACT system, in which not only insight concerning the specific anatomical position of a leakage is added to the classification but also the leakage volume. All information about spatial distribution (anterior (A.x.x), medial (B.x.x) or posterior (C.x.x)) and anatomical structures (venous system (x.1.x), cortical defect (x.2.x)) of the leakage and specific sites (e.g. vein or discus) and the cement leakage volume (x.x.0.5 mL) are combined into one classification. Due to the anatomical description of the leakage combined with a spatial classification, a more accurate registration of leakages is possible (**Figure 4**).

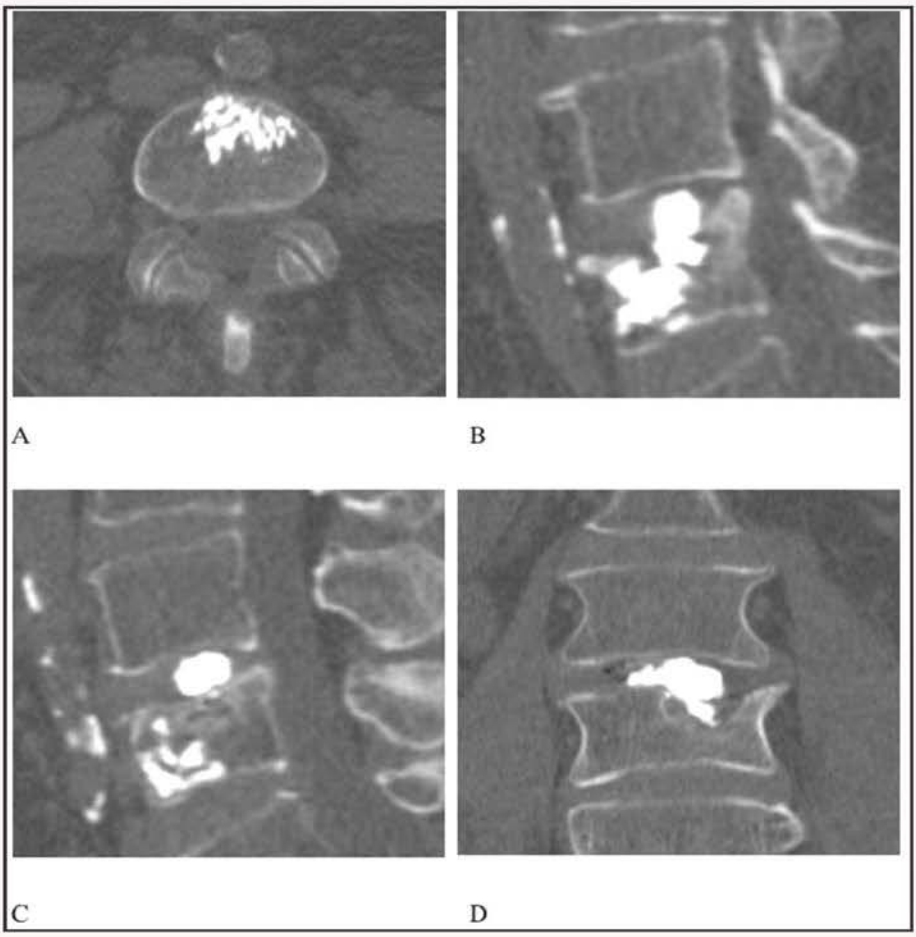

Figure 4. Shows the practical implementation of the new classification system. **A**: axial image of the treated corpus shows no venous leakage and no leakage through the anterior, lateral or posterior cortex. **B** and **C**: sagittal images show a leakage through the superior endplate into the discus (3.6 mL). **D**: coronal reconstruction shows the leakage centrally through the superior endplate. When using the system of Yeom et al. and thus neglecting were the leak penetrates through the cortical bone, the fact that it concerns a high-volume discus leakage, this leakage would be a type C. According to the EXACT classification this leakage would be a B-2-1-3.6 mL.

The current study showed that, when using the EXACT system, the majority of larger leakages (≥0.5 mL) occur through the endplates into the intervertebral disc, which will lead to altered forces applied to the adjacent levels and possibly even to new vertebral fractures.[38,39] Furthermore in 17% of the leakages ≥0.5 mL, the anterior internal plexus is involved, a structure which is situated within the spinal canal.

As with every classification system, inter-observer variability should be as low as possible. When categories are too much alike, the interobserver variability will rise making the classification system less reliable. The proposed system has, due to its high precision in describing the anatomical and spatial distribution, more categories in which the observer could place a certain cement leakage than in the system published by Yeom et al. The intra-class correlations of the EXACT system (0.94, $p<0.001$) was comparable to the interobserver variability of 0.97 ($P<0.001$) found when using the classification system acc. to Yeom et al.

While this study provides a logical, precise and reproducible new classification system for cement leakages during PVP, some limitations should be noted. This system is only applicable when postoperative CT scans are routinely performed. Some categories (C1.1 and C2.2) in the new system, were not encountered during this study, the authors however feel that if leakages at these sites do occur, a high chance of clinical consequences is to be expected.

Considering that the PVP procedure is being scrutinized due to the publications in NJEM in 2009, combined with the knowledge that there is a lack of adequate data concerning leakage frequency and patterns, the growing evidence on the role of viscosity, and the fact that still new types of PMMA cement are introduced to the market, calls for a reliable registration as is currently done in other types of prosthesis.

When using the EXACT system, leakage sites can be more specifically identified as compared to the classification according to Yeom et al. The EXACT system has an obvious value in research of the PVP procedure and the types of cement used during the procedure. The authors furthermore expect the EXACT classification system to be of greater clinical value. Implementation of the EXACT system and registration of leakages on large scale data facilitates pooling data from different centers and offers the possibility to gain important new insight into which leakages are to be expected to lead to clinically relevant complications and which viscosity types of cement are more likely to result in clinically relevant cement leakages.

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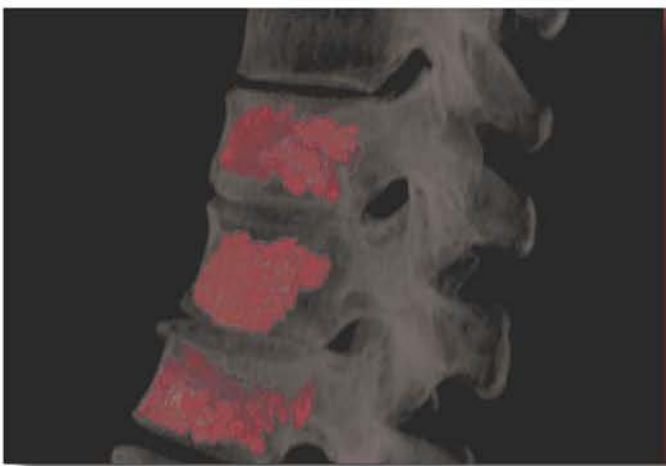
REVIEW OF LITERATURE

Chapter 7



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Treatment of Painful Osteoporotic Vertebral Compression Fractures: a Brief Review of the Evidence for Percutaneous Vertebroplasty

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Abstract

Vertebral compression fractures are the most prevalent complication of osteoporosis and percutaneous vertebroplasty (PVP) has emerged as a promising addition to the methods of treating the debilitating pain they may cause.

Since PVP was first reported in the literature in 1987, more than 600 clinical papers have been published on the subject. Most report excellent improvements in pain relief and quality of life. However, these papers have been based mostly on uncontrolled cohort studies with a wide variety of inclusion and exclusion criteria. In 2009, two high-profile randomised controlled trials were published in the *New England Journal of Medicine,* which led care providers throughout the world to question the value of PVP. After more than two decades a number of important questions about the mechanism and the effectiveness of this procedure remain unanswered.

Osteoporotic Vertebral Compression Fractures

Osteoporosis is the most frequent cause of vertebral compression fractures (VCFs) in the elderly.[1] In 2000, over 40.000 new vertebral fractures due to primary or secondary osteoporosis were registered in The Netherlands.[2] With an ageing population it is expected that this number will only increase with time. The generally preferred initial treatment of patients with a symptomatic stable osteoporotic VCF without attendant neurological symptoms is conservative.[3] In 85% of symptomatic patients, pain caused by these 'acute' osteoporotic fractures will settle within 12 weeks of starting conservative treatment.[4–6] The remaining 15% with 'chronic' osteoporotic compression fractures, can fail to respond to conservative treatment, and there may be an indication for percutaneous vertebroplasty (PVP).

The effect of PVP on pain is reported to be rapid and to reach a plateau within a few days of the procedure,[7] after which the pain scores do not change significantly over the following two years.[8–11] A meta-analysis of 60 studies by Eck et al[12] reported a change in the visual analogue scale (VAS) score. After PVP patients improved from a mean pre-operative VAS of 8.36 (SD 0.78) to a mean post-operative VAS of 2.86 (SD 1.09), with a mean statistically significant change in the level of pain of 5.68 (SD 1.24). After two high-profile randomised controlled trials, by Buchbinder et al[13] and Kallmes et al,[14] were published in the *New England Journal of Medicine* in 2009, care providers began to question the value of injecting cement into fractured vertebral bodies and revived discussion about the evidence for, the mechanism of and the risks involved in PVP.

Percutaneous Vertebroplasty

PVP is a procedure used to stabilise fractured vertebrae in order to relieve pain. It involves the injection of bone cement, usually polymethylmethacrylate (PMMA), and an opacifier into the inter-trabecular marrow space of a fractured vertebra. The procedure may be used for pathological compression fractures caused by osteoporosis, avascular necrosis, multiple myeloma or bone metastases.[15–17] In general, patients are selected on the basis of the following: incapacitating pain at the level of the fracture which is unresponsive to conservative treatment;[18] focal point tenderness, which increases when pressure is applied to the spinous process of the fractured vertebra;[19–21] and bone marrow oedema in the fractured vertebral body on MR Imaging with fat suppression.[22–25]

The first PVP was performed by Deramond in 1984 and reported in the literature in 1987.[26] A paper in the *American Journal of Neuroradiology* in November 1997[27] describing a trial from the University of Virginia which comprised[29] patients followed over a period of three-years, with promising short-term outcomes, prompted a sudden increase in the number of procedures being performed.

PVP may be performed under general anaesthesia, although more commonly the patient is given a local anaesthetic at the injection site and conscious sedation. The procedure takes between 1 and 2 hours, depending on the number of vertebrae requiring treatment. After its injection into the vertebra, the cement hardens and prevents further collapse of the vertebral body, and is thought to support the micro fractures in the trabeculae.

As well as 'traditional' PVP, there is a similar procedure in which it is used in combination with an inflatable balloon tamp often referred to as kyphoplasty. This was developed in the early 1990s and gives comparable clinical outcomes.[12] The evidence for performing kyphoplasty is, however, beyond the scope of this review and therefore will not be discussed further.

According to a number of large studies, relief of symptoms and restoration of mobility are rapidly achieved in more than 80% of patients after PVP. Most of these studies are, however, of evidence level IIIB or IV.[15,17,25,28] The rate of complications after PVP is reported to range between 1.6% and 2.8%.[29] The reported complications with PVP in osteoporotic VCFs, however, range from unanticipated and apparently clinically silent events to catastrophic complications and even death.[12,30–32] Most of the clinically relevant complications are due to leakage of bone cement. Severe complications are rare and occur mainly in cases of high-volume cement leakage. Complications include cement penetration of the nerve root foramen or spinal canal resulting in radiculopathy or spinal cord compression, embolic events due to marrow fat or cement entering the circulation, misplacement of the needle, rib fractures, pneumothorax, fracture of spinous process or pedicle, subcutaneous paravertebral haematoma and infection.[10,33–38]

Leakage of cement into the neural foramen or spinal canal can cause neurological injury.[32] Furthermore, leakage, especially into the intervertebral disc, may lead to altered biomechanical stresses on the adjacent vertebral body and an increased risk of new fractures.[39] Leakage into the arterial or venous system has been reported to cause pulmonary embolism, cardiac perforation and cerebral cement embolism.[40,41] Alongside these reported complications, it appears that the prevalence of new fractures in PVP-treated patients is between 12% and

more than 50%.[39,42–48] Research on the development of new compression fractures after PVP has been conducted in biomechanical models and clinical trials.[48–50] Up to 70% of new fractures after PVP are adjacent to a previously treated level.[47,51] The main difficulty in conducting clinical trials to answer the question 'Does PVP increase the risk of subsequent fracture of the adjacent vertebral body?' is that in a patient who has already sustained one compression fracture the risk of developing a new fracture is increased, whether the previous fracture has been treated or not.[52–54] Biomechanical testing may explain why secondary adjacent fractures occur in patients with a wedge compression fracture, as the mechanical load on the endplate changes from perpendicular to a shearing off-axis load.[55]

The exact mechanism of pain relief by cement augmentation of the vertebral body is still debated; it has been suggested that bone cement stops vertebral micro- or macromovement and is consequently responsible for the analgesic effect of the procedure.[56] However, there appears to be no correlation, in terms of pain relief or the use of medication, between the degree of cement filling of the fractured vertebral body and the clinical outcome.[57] Due to its rapid analgesic effects, high effectiveness, low complication rate and relatively low cost, over the past two decades PVP has become a widely used, minimally invasive treatment for painful vertebral compression fractures, despite the unknown mechanism of pain relief and the lack of studies with a high level of evidence.

Uncontrolled Clinical Vertebroplasty Trials (Level IV Evidence)

Since 1987 more than 600 clinical papers about PVP have been published. The largest trials to date are those conducted by McGraw et al[15] (100 patients), Evans et al[58] (245 patients), Kobayashi et al[28] (175 patients), Alvarez et al[25] (278 patients), Layton et al[10] (552 patients) and Masala et al[11] (624 patients), which were mostly non-randomised and retrospective. They report markedly different patient selection criteria, duration of follow-up and outcome measures, but uniformly encouraging results for short-term pain relief in the vast majority of patients. The study by Masala et al[11] also showed that the significant mean reduction in pain achieved (6.5 points on a VAS) four hours after the procedure was unchanged one year later. However, without any form of concurrent or historical control group it is impossible to be confident of the true benefits of PVP. Some or all of the improvement might be caused by the favourable natural course of an osteoporotic VCF,[6] or by a placebo effect.[59]

Non-Randomised Controlled Clinical Vertebroplasty Trials (Level III B Evidence)

In 2003, Diamond, Champion and Clark[60] conducted the first non-randomised controlled trial of PVP against conservative treatment in 79 patients. This study showed a significant and immediate effect on pain relief, with improved function and reduced use of analgesics after 24 hours. However, it also showed that the effect might be short-lived. Substantial improvements seen in the conservatively treated group resulted in there being no clinically important differences between the two treatment groups in pain or function at six weeks or between six and 12 months.[54,60] The lack of randomisation in this study raised the possibility of selection bias, although both groups of patients had similar characteristics before treatment. Furthermore, without blinding the patient to the treatment received, it is impossible to disentangle the treatment effect from the placebo effect.

Randomised Controlled Clinical Vertebroplasty Trials (Level IIB Evidence)

In 2002, Do et al[61] randomly assigned 31 patients with acute VCFs to PVP or continued medical treatment. This study suggested improvements in pain, activity and analgesic use six weeks after intervention.

In 2007, Voormolen et al[9] compared PVP with optimal pain medication (OPM) in the VERTOS I study. They reviewed 34 patients who had suffered from painful osteoporotic VCFs for more than six weeks but no longer than six months, and randomised them to PVP or OPM. As nearly all of the patients randomised to the OPM group requested to cross over after two weeks, the study was stopped early. This suggested that pain relief, improved mobility, function and stature after PVP are immediate and significantly better in the short term than following OPM treatment.[9] To gain more insight into the cost-effectiveness of PVP, a second trial (VERTOS II) was conducted by Klazen et al[62,63]: the results were published in *The Lancet* in 2010. In this trial, 202 patients with back pain lasting for six weeks or less as a result of an osteoporotic VCF were randomly allocated to PVP or conservative treatment. Inclusion criteria included focal tenderness over a compression fracture with a minimum of 15% loss of vertebral height, osteoporosis, and bone marrow oedema on MR Imaging. The primary outcome was the relief of pain after one month and one year using a VAS. This showed that vertebroplasty resulted in greater pain relief than conservative treatment. The authors concluded that pain relief after vertebroplasty is

immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment.[62]

Randomised Controlled Blinded Vertebroplasty Trials (Level IB Evidence)

A number of authors have emphasised the importance of randomised blinded controlled trials of PVP in order to obtain level I evidence.[56,59,60,64,65] So far, three such trials have been conducted. In 2002, Kallmes at al[66] conducted a small, single-blinded, randomised crossover study in which five patients with subacute vertebral fractures were included. The control procedure involved the injection of local anaesthetic next to the vertebral body, without introducing cement. Three patients initially underwent the control procedure and two underwent PVP. All patients in both groups had minimal relief of symptoms and chose to cross over to the other procedure. All patients guessed that they had received the control procedure first.[66] However, this pilot study demonstrated the feasibility of enrolling patients into a sham-controlled trial of PVP.[65]

In 2009, two randomised, blinded controlled trials were published. The INvestigational Vertebroplasty Efficacy and Safety Trial (INVEST) conducted by Kallmes et al[14] randomised patients to PVP versus a control intervention in which local anaesthetic was injected without cement.[67] Both the patients and the clinical coordinators who performed the follow-up remained blinded to the type of procedure. The primary outcomes were pain relief and Roland Morris Disability Scale score[68] at 30 days. Patients were followed clinically for one year.

The second randomised blinded trial by Buchbinder et al[13] offers some potential advantages over the INVEST trial. First, in control patients a PVP needle was placed into the bone, but without the injection of cement, whereas in the INVEST trial a PVP needle was not placed in bone. This difference in design might have made it easier to blind patients to the type of procedure. Secondly, crossover was not allowed in the trial by Buchbinder, which allowed longer-term follow-up than was possible in the INVEST trial.

Both the INVEST trial and the trial conducted by Buchbinder found that pain was significantly reduced after PVP, but that the improvement was not clinically more significant than that in the control groups. The overall conclusion of the INVEST trial was that at one month the clinical improvement in patients with painful osteoporotic VCFs was similar in those treated with PVP and those treated with a simulated procedure. The overall conclusion of the trial

by Buchbinder also showed no beneficial effect of PVP over a sham procedure after one week, or at one, three or six months, among patients with painful osteoporotic VCFs.

Because both papers were published simultaneously in the *New England Journal of Medicine*,[13,14] the results had a major effect on physicians, the media and the public, and a procedure which had shown very promising results in numerous large cohort studies was instantly discarded by many. The high-profile nature of the articles makes this rigorous step understandable but not necessarily justifiable. Even though these studies may be the only two blinded randomised controlled trials of reasonable size, some important considerations should be considered when reading these papers.

In both studies the inclusion criteria were not the generally accepted indications for PVP, which are focal back pain on palpation corresponding to a fracture, and bone marrow oedema on MRI.[8,24,25] In both studies physical examination was disregarded, potentially leading to the inclusion of other causes of back pain. Furthermore, the study by Kallmes[14] lacks the standard inclusion criteria of bone marrow oedema, and in both studies only one-third of eligible patients without contraindications were included, and with these numbers a selection bias is highly likely.

In the study populations of both the INVEST[14] and in the study by Buchbinder[13] a high percentage of patients suffered from acute fractures (less than six weeks old). In the INVEST study 32% of the fractures were acute. In the Buchbinder study 44% of the fractures were of mixed age, ranging from one to 14 weeks old. Subgroup analysis did not demonstrate statistically significant differences between chronic and subchronic fractures because of the small numbers available. In the study populations described by Buchbinder[13] and Kallmes,[14] patients with pseudoarthroses after an osteoporotic VCF, which are known to not respond well to conservative treatment,[69] were entirely missing. A reduction in VAS of 3 to 6 points one week after PVP is common in the literature.[12] The INVEST study showed values close to this range, with 2.3 points at day three to 2.9 points at day 14. Remarkably, the opposite results are shown by the trial by Buchbinder, a 1.5 reduction in VAS after PVP being among the smallest in literature and barely clinically relevant.[70]

Furthermore, by presenting short-term results in both studies, the natural course is not taken into account,[4] which results in a lack of statistical power to draw any long-term conclusions.

Conclusions

Indisputable level 1 evidence in favour for or against the effectiveness PVP is still lacking. The most probable explanation for the positive effects observed in prospective cohort studies still seems to be the mechanical impact of the bone cement. Until proven, however, this will continue to be a hypothesis. The randomised, but effectively unblinded, trials conducted by Voormolen et al[9] and Klazen et al[62] are well designed and use clear, widely used inclusion criteria, such as focal tenderness on physical examination and bone marrow oedema on MRI scan. The studies give some answers to the question 'Is PVP better than continuing conservative treatment for a longer period?' and suggest that pain relief after PVP is immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment.

The randomised, double-blind controlled INVEST[14] trial and the trial by Buchbinder[13] were conducted with far less clear inclusion criteria, in which physical examination and MRI had a limited or no role in the standard work-up. We feel that the trials by Buchbinder[13] and Kallmes[14] have made it easier to discuss placebo-controlled vertebroplasty trials with medical ethical committees. Because of these publications it is clear that a well-designed double-blinded randomised controlled trial using the right indications and inclusion criteria is feasible and should be performed in the near future.

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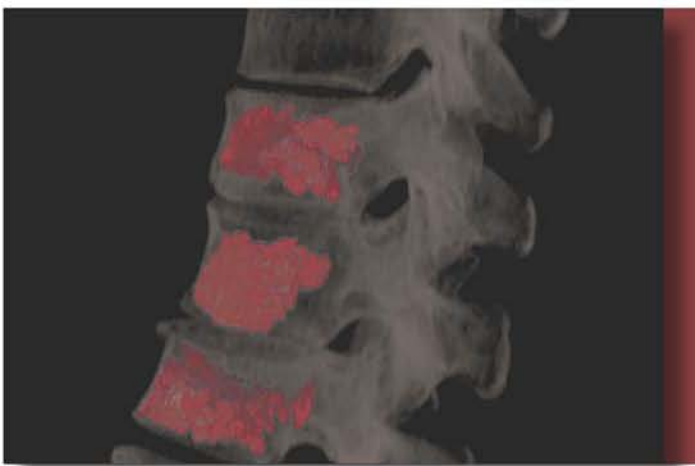
DISCUSSION
&
SUMMARY

Chapter



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General Discussion

The (R)evolution of Percutaneous VertebroPlasty

Since 1984, in which Deramond performed the first PVP, vertebroplasty gained enormous popularity due to the encouraging outcomes of numerous follow-up studies.[1-5] Sometimes, vertebroplasty was considered, a "magic intervention" by patients (and some doctors too), that could cure all types of chronic back pain.

Due to two widely discussed papers in the *New England Journal of Medicine*, this highly positive perspective made a 180 degree turn and promptly PVP was believed to be a worthless procedure by many healthcare providers.[6-9]

As a result, today PVP for OVCFs is no longer part of the standard insured medical costs in the Netherlands. Although questions concerning the effectiveness of PVP in specific patient groups and the precise working mechanism of the procedure remain, the current research presented in this thesis (which was initiated before other "critics" appeared), does however not support this acute discarding of the PVP procedure, which is based on rather awkward methodology of that research.[10, 11]

Patient Selection and Indications

Not unlike other medical interventions, the outcome of PVP is highly dependent on selecting the correct indications for a specific medical problem. As such, in general, patient selection is the keystone of a successful treatment outcome.

In acute OVCFs, patients should be confined to a period of at least 6-8 weeks of conservative treatment (in which up to 85% of the OVCFs will spontaneously heal), whilst strict inclusion criteria for PVP should be met - including a thorough physical examination, plain radiography and MR Imaging - before PVP should be considered (see also, **Chapter 7**, *this thesis*).

The triad of indication criteria for painful long-standing OVCFs includes: I) incapacitating pain at the fractured level, with focal point tenderness, which increases if pressure is applied to the spinous process of the fractured vertebra,[12, 13] II) unresponsiveness to at least 6-8 weeks of conservative treatment[14] and III) intravertebral BME on MR Imaging.

The research presented in the current thesis, showed no correlation between the volume of intravertebral BME and the outcome of PVP for long-standing OVCFs (see also, **Chapter 2**, *this thesis*). Other authors showed, that when treating patients without any signs of intravertebral BME, the outcome is significantly worse.[15, 16] Thus, these studies suggest that the mere presence of and not the volume of intravertebral BME should be used as part of the indication criteria strategy. Pathophysiologically this might be explained by the fact that the presence of intravertebal BME shows that part of the fractured vertebral body still is in the early phase of the fracture healing cascade, with subsequent micro-movement in the unconsolidated vertebral body.[17]

Next to VCFs due to osteoporosis (aetiology of the majority VCFs), painful (pending) compression fractures due to aggressive haemangioma, multiple myeloma or bone metastasis and trauma are included in the indication spectrum for PVP.[18-20] These patients with disseminated or primary vertebral malignant disease have generally a poor general health condition (i.e. co-morbidity, chemotherapy), which makes them non-eligible for extensive spinal (resection) surgery. But, since PVP is performed under local anaesthesia and is performed in day-care, PVP provides a treatment modality with an acceptable cost effectiveness for the patient and an immediate improvement of Quality of Life, mainly due to pain relief.[21,22] The PVP procedure in metastatic bone destruction may be performed in combination with radio frequency ablation using CT-fluoroscopy guidance.[23-26]

The value of routine bone biopsy during every PVP for any presumed osteoporotic VCF, shows an unsuspected malignancy rate of 3.8% in our population, with no signs of malignancy at MR Imaging. Thus we advocate a vertebral body bone biopsy during every PVP procedure, in order to early diagnose an unexpected malignancy, which can be treated, like multiple myeloma (see also, **Chapter 3** of *this thesis*).

Clinical Outcome in Long-Standing OVCFs

In literature, the clinical outcome of a PVP is usually presented in pain rating scales i.e. the visual analogue scale (VAS). Next to pain, other possible improvements in daily functioning can be as important as a decrease in pain, for example increased mobility despite presence of (less) pain, which will improve the overall Quality of Life.

In order to make the PVP procedure more easily comparable to other (surgical) interventions and to potentially calculate effect sizes, **Chapter 4** of *this thesis*, evaluates the short-form 36 (SF 36) Quality of Life questionnaire in a prospective three year follow-up study on patients treated for long-standing OVCFs.[27] This study showed a durable and significant improvement in both the domains of physical function, bodily pain and the physical component score and in both summary SF 36 scores, thus indicating a significant and durable overall increase in the Quality of Life after a PVP.

Registration and Complications

During the last decade, registration of medical implants in order to facilitate monitoring of implant survival and (long-term) complications, has become more important despite it's presence for hip prostheses since 1979.[28] Registration of implants is a powerful tool to evaluate both the quality of an implant and the possible (long-term) complications. An important advantage, if such registration relates practice descriptive statistics and performance to the overall national level (i.e. " mirror information), is that quality at local levels will be improved.[28] In essence, the injection of non-absorbable bone cement into a vertebral body, which will stay in-situ for life, can also be seen as an implant. Therefore at least the type and volume of the injected cement and the vertebral levels should be registered.

Although cement leakage as a complication is present in up to 88%, severe complications are rare. The latter underscoring the importance of a registry, which enables to identify rare complications earlier. Severe complications occur mainly in cases of high-volume cement leakage. Leakage of cement into the neural foramen or spinal canal can cause neurological injury.[32,29-32] Next to a massive leakage, leakage into the intervertebral disc, may alter biomechanical stresses around adjacent vertebral bodies and may even pose an increased risk for new fractures.[33] Due to the fact that new OVCFs tend to form adjacent to an old fracture (even in patients who are not previously treated with PVP), large series (i.e. registries) are needed to proof if PVP is a potential thread to adjacent vertebrae.

In our institution, a post-procedural CT-scan is part of the standard treatment protocol. On the necessity of the standard post-procedural CT-scan some debate exists in literature. Some authors feel that there is no need for a standard postoperative CT-scan due to the fact that the (acute) complication rate in PVP is low.[33] The radiation dose of a CT-scan of the spine is also a point of concern, since the patient is exposed to more than 5 times the effective radiation dose compared to an AP and lateral plain radiograph of the spine.[34,35] If the worldwide registration of cement leakages is found to be important, a post-operative CT-scan will be mandatory.

Leakages are best detected using post-procedural CT-scan.[32] The use of CT-scan versus a plain X-ray results in an increased detection rate of more than 50% of cement leakages.[29] The exact anatomical position, the volume of the leakage as well as leakages in the basivertebral venous system can be more easily assessed with CT.[29] In this thesis, the development of a new CT-based leakage classification system was described (see also, **Chapter 6**, *this thesis*). So far, no anatomical based classification system for cement leakage had been published, making it impossible to conduct uniform registration of the most common complication of PVP.

The use of a low-viscosity PMMA-cement showed to triple the risk of cement leakage when compared to a medium viscosity PMMA cement (see also, **Chapter 5**, *this thesis).* Still new types of PVP cement with different viscosities and an unknown outcome in terms of cement leakage and possible complications are being introduced to the market and used in the clinical setting without any phased introduction to the market with good clinical control to prevent (long-term) complications.[28,36] The latter underscores the need for a cement leakage classification system with good validity in order to offer the best patient care possible: primum non nocere.

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Editorial - Further Opinion

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The battle over the treatment of patients with a painful osteoporotic vertebral fracture is hotting up nicely. On one side, the protagonists of vertebroplasty are carrying out a considerable number of these procedures and claiming significant, prolonged pain relief for their patients: on the other, the evidencebased medicine brigade can find no evidence that the procedure has anything other than a placebo effect. In their instructional review, Muijs, van Erkel and Dijkstra consider the place of percutaneous vertebroplasty in the 15% of patients who fail to respond to 12 weeks of conservative treatment. In its favour, they cite Eck et al[1] who, in 2008, reported a meta-analysis of the literature to date and found a mean, statistically significant, improvement of 5.68 (SD+/-1.24) in post-operative VAS level. More recently, however, two randomised controlled studies were published in the New England Journal of Medicine (the Australian[2] and INVEST[3] studies) which cast doubt on its efficacy.

In the midst of this debate, the potential for causing harm should not be overlooked. Eck et al reported a 17.9% risk of new fracture, usually at an adjacent level, after vertebroplasty and a 19.7% risk of cement leak. Complications may be catastrophic and are usually related to leakage of large volumes of cement.

The indications for the procedure, whether effective or not, are now fairly clear. Patients with an osteoporotic fracture with more than 15% loss of anterior vertebral height, severe pain which is unresponsive to all reasonable modalities of conservative treatment, tenderness over spinous process of the fractured vertebra and bone marrow oedema on MRI imaging with fat suppression may be considered for treatment. It is the timing of this treatment that raises a number of issues. In the literature to date patients have been treated as early as one week after their fracture and as late as 12 months. Of the major randomised studies, The Vertos ll study[5] only included patients with back pain for six weeks or less, the Australian[2] and INVEST[3] studies included patients with back pain for up to a year. The Vertos ll study showed that vertebroplasty gave greater pain relief than conservative treatment and concluded that the pain relief is immediate, sustained for at least a year, and is significantly greater than that achieved with conservative treatment. The Australian and INVEST studies concluded that vertebroplasty conferred no additional benefit over placebo or sham treatment.

These studies are not really comparable as they clearly study different populations. Given that the pain of an osteoporotic vertebral fracture will probably settle within 12 weeks in 85% of patients, it seems paradoxical to study a group in which the pain has been present for less than six weeks. Similarly, is it reasonable to study groups of patients who have been in pain for anything between a few weeks and a year?

One further piece of evidence should be considered. Since the article by Muijs et al was accepted for publication, the authors of the Australian and INVEST studies have combined their findings in a meta-analysis to try to identify any subgroups which would benefit from vertebroplasty[6]. They have concentrated on patients with fractures of recent onset (<6 weeks) and patients in severe pain and have still failed to show any benefit from vertebroplasty over placebo.

Muijs et al are certainly correct in concluding that indisputable evidence in favour or against the effectiveness of percutaneous vertebroplasty is still lacking and that further studies are needed. When these are planned, not only should the inclusion and exclusion criteria be crystal clear but the investigators should undoubtedly narrow down the population studied by duration of symptoms: perhaps 3 to 6 months would be sensible in the first instance. Otherwise, how are we to know if we should advise vertebroplasty, and if so, who to treat and when?

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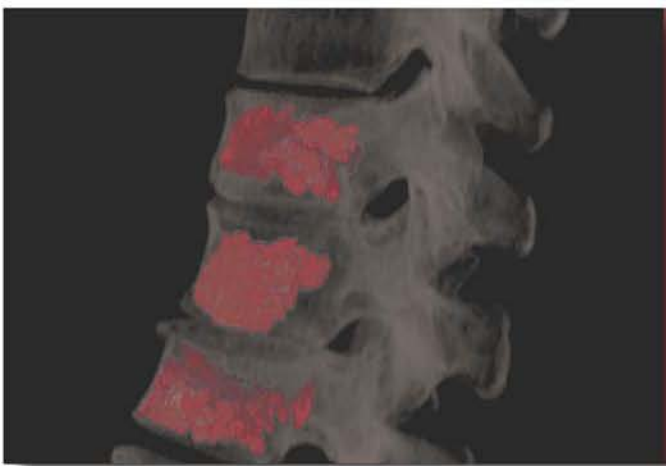
Chapter



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Summary, Conclusions & Future Perspectives

Samenvatting, Conclusies & Toekomstperspectieven

Summary, Conclusions & Future Perspectives

Summary

The General Introduction in Chapter 1 of this thesis provided an overview of the history of PVP, the PVP procedure, the indications, the outcome and the complications.

In Chapter 2, the influence of the pre-procedural volume of intravertebral Bone Marrow Edema (BME) on post-procedural pain relief in patients treated with single level PVP for long-standing OVCFs was studied. Intravertebral BME persists in subacute and chronic painful OVCFs due to the altered healing cascade of the VCF caused by osteoporosis. In most clinics, intravertebral BME is one of the criteria for performing a PVP procedure. Until now, intravertebral BME has been assessed only by semi-quantitative grading and not by volumetric analysis. In this study, 25 patients (4 male, 21 female, mean age of 72.0 (SD 7.7) years) with a single level OVCF, with mean time between onset of symptoms and PVP of 5.7 months (SD 2.6), were included for a prospective study. All patients underwent a preoperative radiograph (AP and lateral of the spine) and MR-sequence with fat suppression, T2 Short Tau Inversion-Recovery (STIR), of the complete spine to visualize intravertebral BME with sagittal reconstructions using a 5 millimeter slice thickness. Volumetric assessment of the intravertebral BME was conducted by 2 independent observers using a visual threshold. During a 1- year follow-up, a Pain Intensity Numerical Rating Scale (PI-NRS) was recorded in all patients. In multivariate repeated measures analysis, no association was found between the volume percentage of BME (in the range of 10% – 70%) and post-procedural back pain (0.04 per 10% vertebral body volume, 95%CI: -0.18 – 0.26, p = 0.711). In conclusion, no relation between the amount of BME on preoperative MR imaging, quantified using volumetric analysis, and post-procedural pain relief in the first year after PVP was found in patients with single-level long-standing OVCFs.

Chapter 3, describes a study on the rate of unsuspected malignancy in bone biopsies of patients undergoing PVP for OVCFs. Undoubtedly, most VCFs have an underlying osteoporotic aetiology, nonetheless a variety of malignant conditions such as multipele myeloma or metastatic disease are also present in this elderly patient group. A vertebral body biopsy acquired through the PVP needle during the procedure can identify unrecognized primary malignant bone tumors or metastasis even in patients without any signs for malignancy on pre-procedural MR Imaging. Furthermore, the nature of the underlying pathology causing the vertebral collapse is important regarding prognosis, therapy and long-term outcome for those patients. In this study, the histology of vertebral body biopsy specimens was studied in a cohort of 78 patients (mean age 73 years). In 3 patients (3.8% of all biopsies), previously undiagnosed malignancies - 2 multiple myeloma stage IIa and 1 chondrosarcoma grade I,- were found. A routine vertebral body bone biopsy during every PVP procedure is recommended.

In **Chapter 4**, the outcome of PVP in patients with intractable OVCFs, which had been unresponsive to conservative treatment for at least eight weeks (i.e. long-standing OVCF), was prospectively studied by analyzing the quantitative clinical and radiological outcome up to three years post-procedurally. Additionally, the Quality of Life (QoL) was studied by using a Pain Intensity Numerical Rating Scale (PI-NRS, 0 to 10), the Short-Form 36 (SF-36) QoL questionnaire and a PVP-specific questionnaire. An immediate and lasting reduction in average back pain, but also in the worst back pain, was found at seven days and at 36 months follow-up. Furthermore, this study showed a clinically relevant increase in six of eight SF-36 domains and both summary SF-36 scores, indicating a significant overall increase in QoL. In summary, results from this study demonstrated an immediate, significant and lasting reduction in back pain and overall improvement in both physical and mental health after PVP in the treatment of long standing OVCFs.

Chapter 5, describes the influence of cement viscosity on the occurrence of cement leakage. Cement viscosity was shown to be significantly associated with the occurrence of cement leakage. The risk of occurrence of cement leakage using low viscosity cement was found to be nearly 3-fold compared to using medium viscosity cement.

The clinical outcome after PVP or other procedures can reliably be objectivised by using one of the numerous well-tested questionnaires that have been developed over the years, as was also shown in **Chapter 4** by using the PI-NRS and SF-36 questionnaires. However, when evaluating the complication rate in PVP (most prevalent is cement leakage), there is no classification system available to evaluate the clinical consequences of cement leakage. So far, cement leakages are described according to the classification system by Yeom et al. (2003), dividing cement leakages in Basivertebral (B), Segmental (S) and Cortical (C). This system however does not provide information on the anatomical location and volume of the cement leakage and may therefore lack clinical relevance. **Chapter 6,** describes the development of a new system for Evaluation of eXtra vertebral cement leakage in vertebroplasty based on Anatomy and volume of the leakage using CT-scan analysis (the EXACT classification system). This new classification system combines information about spatial distribution (anterior (A.x.x.), medial (B.x.x) or posterior (C.x.x.)), anatomical structures (venous system (x.1.x.), cortical defects (x.2.x.) of the leakage and specific sites (e.g. vein or discus) in addition to the cement leakage volume (x.x.0.5cc). Due to the anatomical description of the leakage combined with a spatial classification, a more accurate registration of leakages is possible. In this study, the direct post-procedural CT-data of 106 vertebral bodies from 53 patients treated with PVP was analyzed according to the classification system of Yeom et al. and according to the new EXACT classification system by three independent observers. The inter-observer variability was comparable between the Yeom et al. classification system (0.97, $p<0.001$) and the EXACT classification system (0.94, $p<0.001$). This study demonstrated that the EXACT classification system provides a logical, precise and reproducible classification system for cement leakages in PVP and has an obvious value in research of the PVP procedure and the different types of cement used in PVP and is therefore expected to be of high clinical value.

Finally, **Chapter 7**, provided a review of the scientific evidence for performing PVP. Since PVP was first reported in literature in 1987, more than 600 clinical papers have been published on the subject. Most reports demonstrate excellent improvements in pain relief and Quality of Life, mostly based on uncontrolled control studies with a wide variety of inclusion and exclusion criteria. In 2009, two randomised controlled trials were published in *The New England Journal of Medicine*, which led care providers all over the world to question the value of PVP over conservative treatment. In the presented review, the most important clinical papers are discussed in perspective to their level of evidence. After more than two decades, multiple important questions about the mechanism and effectiveness of this procedure still remain unanswered.

Conclusions

- The percentage of the vertebral body filled with BME on pre-procedural MR Imaging, does not predict the magnitude of pain reduction when performing PVP in long-standing single level OVCFs.

- While undoubtedly, most VCFs have an underlying osteoporotic aetiology, a routine vertebral body bone biopsy during every PVP procedure is recommended, since previously undiagnosed malignancies can be found in up to 4% of these bone biopsies.

- The Quality of Life analysis of PVP in the treatment of long-standing VCFs results in an immediate, significant and lasting reduction of back pain and overall improvement in both the perceived physical and mental health of the patient.

- The occurence of cement leakage is significantly associated with PMMA cement viscosity.

- The newly proposed EXACT classification system provides a logical, precise and reproducible classification system for cement leakages in PVP and therefore has an obvious value in research of the PVP procedure and the different types of cement used in PVP and is expected to be of great clinical value.

Future Perspectives

Indisputable evidence in favour for or against the effectiveness of PVP is still lacking. Prospective cohort studies support the hypothesis that the positive effect of PVP derives from the mechanical impact of the bone cement. Several recent randomised (controlled) trials have given some answers to the question 'Is PVP better than continuing conservative treatment for a longer period?' and suggest that pain relief after PVP is immediate, is sustained for at least a year and is significantly greater than achieved with conservative treatment. A well-designed double-blinded randomised controlled trial using the correct indications and strict inclusion criteria comparing PVP for long-standing OVCFs to a placebo treatment is however still lacking, but seems feasible and should be performed in the near future.

Samenvatting, Conclusies & Toekomstperspectieven

Samenvatting

In de algemene inleiding in **Hoofdstuk 1** van dit proefschrift werd een overzicht gegeven van de historie van de PVP (percutane vertebroplastiek) procedure, de indicaties, de uitkomsten en de complicaties.

In **Hoofdstuk 2,** werd de invloed van het pre-procedureel intravertebraal beenmergoedeem (BMO) op de post-procedurele pijnreductie bij patiënten behandeld met een 'single-level' PVP voor osteoporotische vertebrale compressie fracturen (OVCFs) van oudere datum, bestudeerd. Intravertebraal BMO is aanwezig in subacute en chronische pijnlijke OVCFs als gevolg van een door osteoporose veranderde consolidatie cascade van de compressiefractuur. In de meeste klinieken is intravertebraal BMO een van de criteria voor de indicatiestelling voor een PVP. Tot op heden is BMO in de literatuur alleen nog bestudeerd met semikwantitatieve (indirecte) scoringssystemen en (nog) niet door gebruik te maken van een kwantitatieve volumetrische analyse. In de studie beschreven in dit hoofdstuk werden 25 patiënten (4 mannen, 21 vrouwen, gemiddelde leeftijd 72.0 (SD 7.7) jaar met een 'single level' OVCF, met een gemiddelde tijd tussen het begin van symptomen tot het ondergaan van een PVP procedure van 5.7 maanden (SD 2.6), geïncludeerd in een prospectieve studie. Alle patiënten werden gediagnosticeerd met een pre-operatief conventioneel röntgenonderzoek (zowel AP als laterale opname van de wervelkolom) en een MR-scan met vetsuppressie, T2 Short Tau Inversion-Recovery (STIR), van de gehele wervelkolom teneinde intravertebral BMO met sagittale reconstructies met een 5 millimeter coupe dikte te visualiseren. Volumetrische analyse van het intravertebrale BMO werd vervolgens door twee onafhankelijke beoordelaars d.m.v. een visuele drempel bepaald. Gedurende een follow-up periode van 1 jaar, werd de Pain Intensity Numerical Scale (PI-NRS) afgenomen bij alle patiënten. In een multivariate repeated measures analyse, werd geen associatie gevonden tussen het volumepercentage BMO (van 10% tot 70%) en post-procedurele rugpijn (0.04 per 10% vertebra volume, 95% CI: -0.18-0.26, p=0.711). Concluderend lijkt er geen relatie te bestaan tussen de hoeveelheid BMO op de pre-procedurele MR-

scan, en de post-procedurele vermindering in rugpijn in het eerste jaar na een PVP procedure bij patiënten met 'single level' chronische OVCFs.

Hoofdstuk 3 beschrijft een retrospectieve studie ter bepaling van de prevalentie van onverwachte maligniteiten in botbiopten van patiënten die een PVP procedure ondergaan voor een veronderstelde OVCFs. De meeste VCFs hebben een osteoporotische etiologie, daarnaast komt in deze oudere patiëntenpopulatie een variëteit aan maligniteiten zoals multipele myeloom of gemetastaseerde ziekte aan het licht. Het verrichten van een botbiopsie uit het wervellichaam via de PVP naald, kan een nog onbekende maligne bottumor of metastasen aan het licht brengen bij patiënten zonder klinische symptomen en normale laboratoriumuitslagen. Daarnaast is kennis omtrent de aard van de onderliggende pathologie die geleid heeft tot de wervelinzakking, belangrijk voor zowel de prognose, het beoordelen van het effect van therapie als voor de lange-termijn behandeling van de individuele patiënt. De histologie van de botbiopten in dit cohort van 78 patiënten (gemiddelde leeftijd 73 jaar), liet bij 3 patiënten (3.8% van alle botbiopten), een eerder ongediagnosticeerde maligniteit zien, waarvan 2x een multipele myeloom stadium IIa en 1x een chondrosarcoom stadium I. Het routinematig verkrijgen van een botbiopt uit het wervellichaam tijdens elke PVP procedure, is daarom aanbevolen.

In **Hoofdstuk 4** werd een prospectieve studie van PVP bij patiënten met hardnekkige type-II OVCFs (gedurende minimaal 8 weken niet succesvol conservatief behandeld), beschreven. Hierin werden kwantitatieve klinische en radiologische resultaten, gedurende een follow-up periode van 1 tot 3 jaar, bestudeerd. Daarnaast werd de kwaliteit van leven (QoL) geanalyseerd met een 'Pain Intensity Numerical Rating Scale' (PI-NRS, 0 to 10), de 'Short-Form-36 (SF-36) QoL' vragenlijst en anamnese gegevens. Tijdens de follow-up periode werd een directe, en blijvende afname van de gemiddelde en ergste rugpijn gevonden na een follow-up van zeven dagen en na 36 maanden postoperatief. Tevens werd een significante en klinisch relevante toename van de SF-36 score op zes van de acht SF-36 domeinen en de beide 'summary SF-36 scores' gevonden. Dit laatste betekent een algehele toename in de QoL in de perceptie van de patiënt. Samenvattend bestaat er een blijvende pijnverlichting en een algehele verbetering in zowel de fysieke als psychische gezondheid in de perceptie van de patiënt gedurende een follow-up periode van 3 jaar na PVP voor chronische OVCFs.

Hoofdstuk 5, beschrijft de invloed van cement viscositeit op de kans op cement lekkage. De viscositeit van het cement bleek significant geassocieerd te zijn met de kans op cement lekkage. Wanneer cement met een lage viscositeit gebruikt werd, bleek er sprake te zijn van een bijna drie-voudige kans op cement lekkage in vergelijking met het gebruik van cement met een medium viscositeit. De klinische resultaten van PVP en andere procedures kunnen, zoals beschreven in **Hoofdstuk 4** (PI-NRS en SF-36 vragenlijsten), betrouwbaar worden geobjectiveerd door gebruik te maken van een van de vele in de literatuur beschreven gevalideerde vragenlijsten, die de afgelopen jaren zijn ontwikkeld. Wanneer men echter het complicatiepercentage bij PVP wil onderzoeken, waarbij de meest voorkomende complicatie cement lekkage is, blijkt er geen classificatiesysteem voorhanden te zijn waarmee de klinische consequenties van cement lekkage betrouwbaar kunnen worden geobjectiveerd. Cement lekkages worden geclassificeerd volgens het classificatiesysteem van Yeom et al. (2003), waarin cement lekkages worden onderverdeeld in Basivertebraal (B), Segmentaal (S) en Corticaal (C). Dit classificatiesysteem geeft echter geen informatie over de anatomische locatie en het volume van de cement lekkage en lijkt hierdoor klinische relevantie te missen.

In **Hoofdstuk 6** is een nieuw classificatiesysteem ontwikkeld voor de Evaluatie van eXtra vertebrale cement lekkage bij PVP, gebaseerd op de Anatomie en het volume van de lekkage door gebruik te maken van CT-scan analyse (ofwel het EXACT-classificatiesysteem). Dit nieuwe classificatiesysteem combineert informatie betreffende de spatiële distributie (anterior (A.x.x.), medial (B.x.x) or posterior (C.x.x.)), de anatomische structuren (venous system (x.1.x.), cortical defects (x.2.x.) van de lekkage, de specifieke locaties (e.g. vein or discus) en het cement lekkage volume (x.x.0.5cc). Door de combinatie van de anatomische beschrijving en de spatiële classificatie van de lekkage, is een meer valide registratie van cement lekkages mogelijk. In deze studie werden de direct postoperatieve CT-data van 106 vertebra van 53 patiënten behandeld met PVP geanalyseerd door drie onafhankelijke beoordelaars volgens zowel het bekende classificatiesysteem van Yeom et al. als het nieuwe EXACT classificatiesysteem. De inter-observer variabiliteit was vergelijkbaar tussen het classificatiesysteem van Yeom et al. (0.97, $p<0.001$) en het EXACT classificatiesysteem (0.94, $p<0.001$). Deze studie heeft laten zien dat het EXACT classificatiesysteem een logisch, accuraat en reproduceerbaar classificatiesysteem voor cement lekkages is en heeft daarmee een duidelijke meerwaarde voor wetenschappelijk onderzoek

naar de PVP procedure en de verschillende types cement die gebruikt worden bij PVP en heeft daarmee ook een verwachte grotere klinische waarde.

In **Hoofdstuk 7** werd tenslotte een review gegeven van het wetenschappelijke bewijs over de uitkomsten van een PVP procedure versus conservatieve behandeling voor een OVCF. Sinds de introductie van de PVP procedure in 1987, zijn meer dan 600 klinische artikelen in de literatuur verschenen. De meeste studies beschrijven een aanzienlijke pijnverlichting en verbetering van de kwaliteit van leven, wat voornamelijk gebaseerd is op resultaten van onderzoek zonder controle groep (i.e. geen PVP) met bovendien een grote variëteit aan inclusie- en exclusie criteria. In 2009 werden twee gerandomiseerde gecontroleerde trials gepubliceerd in het prestigieuze *New England Journal of Medicine (NEJM)*, welke ertoe hebben geleid dat medici over de hele wereld de waarde van PVP boven conservatieve behandeling van OVCFs in twijfel trokken. Echter, ondanks publicatie in de NEJM bestonden er ook methodologische problemen in deze studies. In het review beschreven in dit hoofdstuk, werden de belangrijkste klinische artikelen beoordeeld op "level of evidence." Na meer dan 20 jaar na de introductie van PVP, blijven er veel belangrijke vragen betreffende het mechanisme en de effectiviteit van de procedure nog onbeantwoord.

Conclusies

- Het percentage van het wervellichaam gevuld met BMO, gezien op een pre-PVP MR-scan, heeft geen voorspellende waarde voor de uitkomst van een PVP voor pijnlijke OVCFs van oudere datum (> 8 weken).

- Alhoewel het overgrote deel van de VCFs een osteoporotische etiologie kent, blijkt er in 4% van de behandelde patiënten een onverwachte maligniteit aanwezig te zijn. Dit pleit voor het routinematig uitvoeren van een botbiopsie tijdens elke PVP procedure.

- Kwaliteit van leven analyse bij PVP voor de behandeling van OVCFs van oudere datum, resulteert in een onmiddellijke, significante en blijvende vermindering van rugpijnklachten en een algemene verbetering in de perceptie van de patiënt van zowel de fysieke als de mentale gezondheid.

- De kans op botcement lekkage blijkt significant geassocieerd te zijn met de PMMA botcement viscositeit.

- Het EXACT classificatie systeem maakt het mogelijk om op logische, precieze en reproduceerbare wijze, cement lekkages bij PVP procedures te classificeren en heeft hiermee naast klinische waarde, een duidelijke plaats in onderzoek naar de PVP procedure en de verschillende typen cement die gebruikt worden bij PVP.

Toekomstperspectieven

Onomstotelijk bewijs ten faveure of ten nadele van de effectiviteit van PVP is tot op heden niet geleverd. Prospectieve cohort studies ondersteunen de hypothese dat het positieve effect van PVP ontleend wordt aan de mechanische effecten van het botcement op het wervellichaam. Verschillende recent verschenen gerandomiseerde (gecontroleerde) trials, hebben enkele antwoorden gegeven op de vraag of PVP superieur is aan het continueren van conservatieve behandeling gedurende een langere periode en suggereren dat pijnverlichting na PVP direct en blijvend is gedurende ten minste één jaar en dat de pijnverlichting daarbij significant groter is dan die verkregen wordt bij conservatieve behandeling. Een goed opgezette, dubbel-blinde gerandomiseerde gecontroleerde studie met heldere indicaties voor PVP en duidelijk omschreven inclusie- en exclusiecriteria, waarin OVCFs van ouder datum afgezet worden tegen een placebobehandeling, is vooralsnog echter niet verricht, maar lijkt zeker haalbaar en zou in de nabije toekomst uitgevoerd moeten gaan worden.

List of Publications

Full Papers

Muijs SP, Dijkstra PD, Bos CF. Clinical outcome after anatomical reconstruction of the lateral ankle ligaments using the Duquennoy technique in chronic lateral instability of the ankle: a long-term follow-up study. **J Bone Joint Surg Br. 2008; 90(1): 50-6.**

Muijs SP, Dijkstra PD, van Erkel AR. Percutaneous vertebroplasty for vertebral fractures caused by multiple myeloma, an aggressive vertebral haemangioma and in a traumatic burst fracture. **Ned Tijdschr Geneeskd. 2008; 152(30): 1686-93. [Article in Dutch]**

Muijs SP, Nieuwenhuijse MJ, Van Erkel AR, Dijkstra PD. Percutaneous vertebroplasty for the treatment of osteoporotic vertebral compression fractures: evaluation after 36 months. **J Bone Joint Surg Br. 2009 Mar; 91(3): 379-84** (see also, **Chapter 4**, *this thesis*)

Muijs SP, Akkermans PA, van Erkel AR, Dijkstra PD. The value of routinely performing a bone biopsy during percutaneous vertebroplasty in treatment of osteoporotic vertebral compression fractures. **Spine (Phila Pa 1976). 2009; 34(22): 2395-9.** (see also, **Chapter 3**, *this thesis*)

Nieuwenhuijse MJ, Muijs SP, van Erkel AR, Dijkstra SP. A clinical comparative study on low versus medium viscosity polymethylmetacrylate bone cement in percutaneous vertebroplasty: viscosity associated with cement leakage. **Spine (Phila Pa 1976). 2010; 35(20): E1037-44.** (see also, **Chapter 5**, *this thesis*)

Muijs SP, van Erkel AR, Dijkstra PD. Treatment of painful osteoporotic vertebral compression fractures: a brief review of the evidence for percutaneous vertebroplasty. **J Bone Joint Surg Br. 2011; 93(9): 1149-53.** (see also, **Chapter 7**, *this thesis*)

Muijs SP, Dijkstra PD, van Rijswijk CS, van Erkel AR. Breakage of a Needle During a Vertebroplasty Procedure, a Rare Complication: Report of a Case and Options when Facing a Stuck Needle. (**Submitted**)

Muijs SP, Dijkstra PD, van Erkel AR. A system for Evaluation of eXtra Vertebral cement leakage in vertebroplasty based on Anatomy and volume in CT-scan analysis: the EXACT classification. (**Submitted**) (see also, **Chapter 6**, *this thesis*)

Muijs SP, Nieuwenhuijse MJ, Bollen L, van Erkel AR, Dijkstra PD, Nelissen RG. The Amount of Bone Marrow Edema Does Not Predict the Outcome in Single Level Percutaneous Vertebroplasty For Painful Osteoporotic Compression Fractures. (**Submitted**) (see also, **Chapter 2**, *this thesis*)

Book Chapters

Muijs SPJ. Inversietrauma van de enkel en instabiliteit. In: Boerhaave cursus Orthopedie II voor (verpleeg)huisarts: De onderste extremiteit en het bekken. **ISBN 978-90-6767-624-3**

Peer-Reviewed Abstracts

Muijs SPJ, Dijkstra PDS. Vertebroplasty in treatment of osteoporotic vertebral compression fractures: prospective evaluation of short-term outcomes. *The annual autumn meeting of the NOV (Netherlands society of Orthopaedic Surgery), Leiden University Medical Center, Leiden, The Netherlands.* **Acta Orthop Scand. 2004**

Dijkstra PDS, Muijs SPJ, van der Linden E, Taminiau AHM. Radiofrequency heat ablation in combination with vertebroplasty, a novel treatment in spinal metastases with osteolytic defects. Preliminary results. Dept. of Orthopaedics and Radiology, Leiden University Medical Center, Leiden, the Netherlands. *The 18th annual EMSOS (European Musculoskeletal Oncology Society) meeting, Trieste, Italy, May 2005.*

Muijs SPJ, Dijkstra PDS, Bos CFA. Outcome after the anatomical reconstruction of the lateral ankle ligaments as described by Duquennoy in chronic lateral ankle instability. *The 8th EFORT (European Federation of National Associations of Orthopedics and Traumatology) conference, Florence, Italy, May 2007.* **J Bone Joint Surg Br. 2009; 91-B: Supp I**

Muijs SPJ, Nieuwenhuijse MJ, Dijkstra PDS, van Erkel AR. Percutane vertebroplastiek als behandeling van chronische osteoporotische compressiefracturen: prospectieve middellange termijnresultaten. *The annual autumn meeting of the NOV (Netherlands society of Orthopaedic Surgery), Veldhoven, The Netherlands, November 2007.* **Acta Orthop Scand. 2007**

Muijs SPJ, Nieuwenhuijse MJ, Dijkstra PDS, van Erkel AR. Is there a difference in clinical outcome between usage of low and medium viscosity PMMA bone cement in percutaneous vertebroplasty? *The EUROSPINE conference, Geneve, Switzerland. May 2008*

Muijs SPJ, Nieuwenhuijse MJ, Dijkstra PDS, van Erkel AR. Percutaneous vertebroplasty in advanced fractures age: Prospectively acquired results after a follow-up of more than two years. *The 9th EFORT (European Federation of National Associations of Orthopedics and Traumatology) conference, Nice, France, June 2008.* **J Bone Joint Surg Br. 2010; 92-B: Supp II**

Muijs SPJ, Akkermans PA, Dijkstra PDS, van Erkel AR. Bone biopsy during percutaneous vertebroplasty for osteoporotic vertebral compression fractures, a necessity? *The 9th EFORT (European Federation of National Associations of Orthopedics and Traumatology) conference, Nice, France, June 2008 (Nominated for the 10 best Free papers at the conference).* **J Bone Joint Surg Br. 2010; 92-B: Supp II**

Muijs SPJ, Nieuwenhuijse MJ, Dijkstra PDS, van Erkel AR. Does the viscosity of PMMA bone cement used during vertebroplasty influence the clinical outcome? A one year prospective follow-up comparison between a low and a medium viscosity bone cement. *The 54th NOF (Nordic Orthopaedic Federation) conference in Amsterdam, The Netherlands, June 2008.*

Muijs SPJ, Oostenrijk A, Dijkstra PDS, van Erkel AR. Vertebroplasty: sustained vertebral wedge angle and heights in a one-year follow-up of type II osteoporotic vertebral compression fractures. *The 10th EFORT (European Federation of National Associations of Orthopedics and Traumatology) conference, Vienna, Austria, June 2009.* **J Bone Joint Surg Br. 2010; 92-B: Supp IV**

Curriculum Vitae

De auteur van dit proefschrift werd geboren op 20 februari 1981 te Haren (Groningen). In 2000 behaalde hij zijn Atheneumdiploma aan het Zernicke College te Haren. Hierna startte hij met zijn opleiding Geneeskunde aan de Universiteit Leiden. In 2004 startte hij met een klinisch wetenschappelijk doctoraal afstudeeronderzoek naar de lange termijn resultaten van anatomische recontructie van de laterale enkel ligamenten volgens Duquennoy bij chronische laterale enkelinstabiliteit onder begeleiding van Dr. P.D.S. Dijkstra en Dr. C.F.A. Bos (Orthopaedische Chirurgie, LUMC). In augustus 2004 behaalde hij zijn doctoraalexamen en hij startte tijdens de co-schappenfase van zijn studie met wetenschappelijk onderzoek naar minimaal invasieve behandelingstechnieken (vertebroplastiek) bij osteoporotische wervelinzakkingen. Eind 2006 behaalde hij zijn artsexamen en startte in 2007 met zijn promotietraject onder begeleiding van Prof. dr. R.G.H.H. Nelissen (orthopaedie), Dr. P.D.S. Dijkstra (orthopaedie) en Dr. A.R. van Erkel (radiologie) naar vertebroplastiek bij osteoporotische wervelinzakkingen, resulterend in dit proefschrift.

Op 1 januari 2009 startte hij met de opleiding Orthopaedie vanuit het Leids Universitair Medisch Centrum (LUMC) (opleider Prof. dr. R.G.H.H. Nelissen), welke werd aangevangen met de vooropleiding algemene Chirurgie (opleider Dr. A. Da Costa) in het Rijnland Ziekenhuis te Leiderdorp. In 2011 keerde hij terug naar het LUMC voor een academisch opleidingsjaar Orthopaedie, waarna hij in 2012 zijn perifere opleidingsjaren vervolgde in het Medisch Centrum Haaglanden (Westeinde Ziekenhuis) te Den Haag (opleider Dr. E.R.A. van Arkel) en hij zal medio 2013 zijn opleiding voortzetten in het HAGA Ziekenhuis te Den Haag en vervolgens medio 2014 terugkeren naar het LUMC en zijn opleiding afronden in 2015. Naast het vervolgen van zijn klinische opleiding Orthopaedie, hoopt hij zich in de toekomst bezig te blijven houden met wetenschappelijk onderzoek.

Curriculum Vitae

The author of this thesis was born February 20th 1981 in Haren (Groningen), The Netherlands. In 2000, he graduated and received his Atheneum diploma from the Zernicke College in Haren (Groningen), whereafter he started studying Medicine at the University of Leiden. In 2004 he started a clinically oriented research project concerning the long-term clinical outcome after the anatomical reconstruction of the lateral ankle ligaments as described by Duquennoy in chronic lateral ankle instability under supervision of Dr. P.D.S. Dijkstra en Dr. C.F.A. Bos (Orthopaedic surgery, LUMC) to complete the Bachelor part of his study in August 2004. During his internships, he started his research on vertebroplasty for treatment of osteoporotic vertebral compression fractures under supervision of Prof. dr. R.G.H.H. Nelissen, Dr. P.D.S. Dijkstra and Dr. A.R. van Erkel. After his medical degree in 2006, he continued his research as a PhD-project, of which this thesis is the result.

As of January 1st 2009, he started his Orthopaedic Surgery training at the Leiden University Medical Center (LUMC) (Prof. Dr. R.G.H.H. Nelissen), which commenced with by the pre-Orthopaedics phase of General Surgery at the Rijnland Hospital in Leiderdorp (Dr. A. Da Costa), after which he returned to the LUMC in 2011 for an academic training year. In 2012 he continued his training at the Medisch Centrum Haaglanden (Westeinde Hospital) in The Hague (Dr. E.R.A. van Arkel) and will proceed at the HAGA Hospital in The Hague in June 2013. Thereafter he will complete the last part of this training in the LUMC in 2015. Besides completing his Orthopaedic Surgery training, he hopes to remain active in scientific work.

Dankwoord

De studies beschreven in dit proefschrift zijn uitgevoerd op de afdelingen Orthopaedie en Radiologie van het Leids Universitair Medisch Centrum (LUMC). Graag wil ik iedereen bedanken die heeft bijgedragen aan de totstandkoming van dit proefschrift en met wie ik de afgelopen jaren heb samengewerkt.

Aan de wieg van dit proefschrift staan, naast mijn ouders, Dr. P.D.S. Dijkstra en Dr. C.F.A. Bos bij wie ik mijn wetenschapsstage naar de langetermijnresultaten van enkelbandreconstructie volgens Duquennoy, heb mogen doen. Door gelukkige samenloop van omstandigheden hadden de, sinds ik begon in 2005 geen dag ouder geworden meisjes van de balie, enkele patiënten van Sander Dijkstra op het spreekuur van Sander Muijs gepland. Onder deze patiënten bevonden zich enkele patiënten die een Percutane VertebroPlastiek (PVP) hadden ondergaan en hier enthousiast over waren. Hieruit is mijn interesse in de PVP ontstaan, waaruit uiteindelijk mijn promotieonderzoek is voortgekomen.

Tijdens mijn promotietijd hebben vervolgens meerdere studenten en arts-onderzoekers (Alexander, Narada, Paul en Laurens) mij tijdens hun wetenschapsstage bijgestaan in het onderzoek. Marc Nieuwenhuijse bleek hierbij dusdanig veel enthousiasme en interesse voor het onderwerp te hebben dat hij de PVP naald van mij heeft overgenomen en nu ook promoveert op Percutane VertebroPlastiek.

Apart wil ik mijn dank betuigen aan mijn co-promotoren Dr. P.D.S. Dijkstra en Dr. A.R. van Erkel en mijn promotor Prof. Dr. R.G.H.H. Nelissen. Beste Sander, door jouw begeleiding bij mijn wetenschapsstage kon ik mijn promotieonderzoek beginnen. Ook tijdens de rest van mijn onderzoek heb ik je betrokkenheid, nachtelijke brainstorm sessies (sorry voor de nachtelijke telefoontjes familie Dijkstra), vrijwel onmogelijke 'last minute' presentatie voorbereidingen en hulp en steun bij zowel praktische als "politieke" zaken, zeer op prijs gesteld. Ook heb ik het erg gewaardeerd dat ik gedurende mijn gehele promotietijd een werkplek heb gehad met jou als kamergenoot. Arian, jou wil ik danken voor je persoonlijke interesse en geduldige houding (rust en bezinning wanneer de 'manie' van Dijkstra zelfs mij even te veel werd) en ook voor je, meestal door mij ter harte genomen, soms wat vaderlijke adviezen. Jouw grondige correcties van onze artikelen maakten van Engels English. Beste Rob, ik ben zeker niet de eerste die het opvalt dat je voor tenminste 40 jaar fulltime onderzoek ideeën in anderhalf uur met ongekend enthousiasme weet te produceren. Het is niet altijd even gemakkelijk om hier het voor de promovendus haalbare uit te destilleren. Wel laat het je ongetemde enthousiasme voor wetenschappelijk onderzoek binnen (en ook buiten) de Orthopaedie zien en werkt het voor vele mensen, waaronder mij zelf, aanstekelijk. Met name tijdens de afronding van dit proefschrift heb je je erg ingezet voor het hier geleverde eindresultaat, mijn dank hiervoor.

Beste (voormalige en huidige) collegae onderzoekers van zowel de "TU Delft groep" als de arts-onderzoekers van de afdeling Orthopaedie. Ik wil jullie bedanken voor de laagdrempelige hulp en overlegmomenten en de gezellige congresbezoeken. Speciaal zou ik hierbij mijn dank willen betuigen aan Dr. Ir. P.W. de Bruin, voor zijn tijd en hulp bij computergeassisteerde 3-dimensionale volume reconstructies en metingen van CT-data en de 24/7 'first-aid' bij de vele computer crashes, die mijn promotietijd gekend heeft.

Ook wil ik mijn dank betuigen aan de medewerkers van de afdeling Radiologie, aan de secretaresses voor hun hulp en voor het buiten werktijd belangeloos scannen van mijn preparaten door enthousiaste laboranten. Mijn dank gaat verder uit naar de medewerkers van het 'oude' Cardio-biochemie laboratorium, die mij met groot enthousiasme, rustig zo nu en dan een middagje varkens wervels lieten oplossen in kokend zoutzuur. Ook wil ik hierbij mijn huidige collegae en opleiders in het Medisch Centrum Haaglanden bedanken voor de fijne werksfeer en flexibiliteit omtrent mijn laatste promotie-regeldingen.

Familie, schoonfamilie, vrienden en kennissen, dank voor jullie interesse en mentale steun. Beste schoonouders, Roos en Humphrey, bedankt voor het altijd klaarstaan om te helpen, onder andere bij het oppassen op onze zoon (wat voor jullie geen straf is), zodat ik weer een stukje verder kon met het schrijven van dit proefschrift. Broers, zwager en schoonzusjes, de reproductieve capaciteiten van onze familie zijn goed benut, zouden ze al uitgeput zijn ? Het is een gezellig groepje baby's, peuters en kleuters. Wouter, ik vind het leuk dat jij mijn paranimf wilt zijn.

Pa en Ma, echt enthousiast over mijn keuze om geneeskunde te gaan studeren waren jullie niet, ik herinner mij termen als: "dure hobby" en "als je later te veel uren wilt maken voor te weinig geld, moet je het niet laten." Jullie hebben mijn keuze echter volledig gesteund en het mogelijk gemaakt om op comfortabele wijze mijn studie af te ronden. De vergaande verdieping in allerlei medische onderwerpen van Pa en de continue bezorgdheid over te hard werken en te weinig slapen en eten van Ma zal ik nooit vergeten.

Lieve Denise, jouw onvoorwaardelijke interesse, motivering en hulp bij alle aspecten van mijn promotieonderzoek was groter dan die van wie dan ook. Voor jou is het een welkome invulling geweest van ál die vrije tijd die je over had naast: zelf promoveren, de opleiding tot Cardiologe volgen, ons huis renoveren, en de beste moeder die Floris-Jan zich zou kunnen wensen zijn, enz. enz. Doe alsjeblieft even een beetje rustig aan en zorg dat je geniet van onze snel verwachte volgende telg.

Sander