OSTEOPOROTIC VERTEBRAL COMPRESSION FRACTURES

ALEXANDER VENMANS

Thesis, University Utrecht

Cover
Design & Lay-out Frank Boesveld, cluster Multimedia, UMC Utrecht
Printed by Gildeprint drukkerijen, Enschede, The Netherlands

Osteoporotic Vertebral Compression Fractures

Osteoporotische Wervelfracturen

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan
ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op
dinsdag 18 oktober 2011 des middags te 2.30 uur

door

Alexander Venmans

Geboren op 24 juni 1978 te Tilburg, Nederland

Promotoren
Prof.dr. W.P.Th.M. Mali
Prof.dr. W.J.J. van Rooij

Co-promotor
Dr. P.N.M. Lohle

The research described in this thesis was supported by a grant from Stryker Nederland BV.

Contents

CHAPTER 1

GENERAL INTRODUCTION

Introduction

Natural course of osteoporotic vertebral compression fractures
Vertebral compression fractures (VCF's) are often seen in the elderly population with osteoporosis with an estimated 1.4 million clinically new fractures worldwide annually (1). Little is known about the natural course of conservatively treated VCF's. It is assumed that about two third of these patients heal more or less spontaneously and do not come to medical attention. Not all patients with osteoporotic vertebral fractures who are treated conservatively will show sufficient pain relief. It is assumed that about one in five of these patients eventually will develop chronic back pain as a direct result of the fracture (2,3). In a recent study (4), even a third of patients still had severe pain necessitating pain medication and physical therapy almost 2 years after an acute fracture. In this study no predictors for transition from acute to chronic pain could be identified. In Vertos II (4), an open label randomized controlled trial comparing vertebroplasty with conservative treatment in patients with osteoporotic vertebral fractures, we found that almost a quarter of conservatively treated patients had no significant pain relief after one year. In **Chapter 2**, we further analyzed the conservatively treated patients from Vertos II. We wanted to assess the proportion of patients that developed chronic back pain and assess possible risk factors for the transition from acute to chronic pain.

Percutaneous vertebroplasty and clinical results
Treatment of VCF's means treatment of pain. Until recently, bed rest, analgesia, casting and physical therapy were the therapeutic options. At present, percutaneous vertebroplasty (PV) is also frequently used to treat VCF's. This therapy was introduced in 1984 in France for the treatment of a painful aggressive vertebral angioma (5). After its introduction, indications for PV were expanded and include VCF's caused by osteoporosis, trauma, benign and malignant vertebral tumors and vertebral osteonecrosis.
The effectiveness of PV is currently under debate. Most results on the effectiveness of vertebroplasty are based on retrospective observational studies (6-9). Recently, three randomized controlled trials (4,10,11) concerning vertebroplasty have been published with conflicting results. Investigators in two trials (10,11) concluded that there is no benefit to vertebroplasty over a sham placebo procedure involving the injection of local anesthetic into the area adjacent to the fracture. Next to the lack of blinding in Vertos II, the most important differences between the two sham studies and Vertos II is patient selection. In the sham studies both acute and chronic fractures were included while in Vertos II only acute fractures were eligible. In addition, bone edema in the affected vertebra was not a consistent inclusion criterion in the sham

studies. The sham studies lacked a control group without intervention. The discordant results from the sham studies, on the one hand, and Vertos II, on the other hand, have incited much debate and the jury is still out. Apparently clinicians do still not know how to best treat their patients.
Meanwhile, the Vertos study group investigated other aspects of the PV procedure. We studied pain during the PV procedure, cement leakage during PV, pulmonary cement embolism, relation between cement volume and clinical response and new vertebral fractures during follow-up.

Percutaneous vertebroplasty technique
Pv is performed on a single or biplane angiographic unit under fluoroscopic guidance. Local infiltration analgesia is infiltrated from the skin to the periosteum of the targeted pedicle. Most patients seem to tolerate the procedure well and only in few cases additional intravenous Fentanyl is administered. We examined patients' subjective pain sensation during PV with our standard pain management protocol in **Chapter 6**. Polymethylmethacrylate (PMMA) bone cement is injected under continuous lateral fluoroscopy alternating both pedicles using 1cc syringes. Injection is stopped whenever perivertebral cement migration is observed. Venous PMMA migration towards the lungs visible on fluoroscopy during the procedure is described in **Chapter 3**. After a 15-20 second delay injection is resumed without changing needle position. Patients can be mobilized several hours after the PV.

Adverse effects of percutaneous vertebroplasty
Perivertebral leakage of cement during PV has been reported to occur frequently in up to 65% of treated osteoporotic VCF's (12,13). Most of these leakages cause no clinical symptoms but pulmonary embolism and neurological complications have occasionally been reported (14,15). In the Vertos II trial patients assigned to PV had a standard post-procedural CT scan of the treated VCF with the aim to assess the patterns of perivertebral cement leakage and its possible clinical impact. There is some concern that cement deposits may migrate to the lungs via the veins during follow-up. Although most pulmonary cement embolism remain asymptomatic, serious and even fatal sequelae have occasionally been reported (16,17). In addition, local damage to the adjacent anatomical structures by the leaked cement may cause symptoms like soft tissue hematoma or radiculopathy (18-21). Baseline and follow-up CT to assess the incidence, anatomical location and clinical impact of perivertebral cement leakage on short- and long-term in a large patient cohort are described in **Chapter 5**. Reported incidences of pulmonary cement embolism during PV vary, depending on sensitivity of used diagnostic tests. In **Chapter 4** we describe the true incidence of pulmonary cement embolism, after performing

native chest CT during follow-up in a large proportion of patients of the Vertos II trial.
Conflicting results exist regarding secondary fractures after PV. Some state that PV is associated with a higher incidence of secondary VCF's as a result of the augmented stiffness of the treated vertebra. Others consider the incidence of secondary VCF's is influenced by the presence and severity of osteoporosis. To elucidate this controversy, in **Chapter 8** we assessed the incidence of secondary VCF's during follow-up in patients with acute VCF's randomized to PV or conservative therapy in the Vertos II trial. In addition, we assessed further height loss of the treated vertebrae with both therapies.
There is considerable variance in technique among operators in performing vertebroplasty. A large point of procedural variability lies in the volume of injected cement into the compressed vertebra. Significant variability in injected cement volumes is even present in the same operator. It is generally believed that larger volumes of cement lead to better clinical response. Little is known about the relation between injected cement volume and vertebroplasty outcomes. In **Chapter 7**, we analyze the impact of cement volume on pain relief after percutaneous vertebroplasty in selected patients who participated in the Vertos II trial.
In the general discussion, **Chapter 9**, results of this thesis are placed in a larger perspective. A summary of the results of this thesis is presented in **Chapter 10**.

References

1. Johnell O, Kanis JA.
   An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporosis Int 2006;17(12):1726-1733.

2. Voormolen MH, Mali WP, Lohle PN, et al.
   Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol 2007;28:555-60

3. Ploeg WT, Veldhuizen AG, The B, Sietsma MS.
   Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: a systematic review. Eur Spine J 2006;15:1749-58

4. Klazen CA, Lohle PN, de Vries J, et al.
   Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. The Lancet 2010; 376:1085-1092

5. Galibert P, Deramond H, ROsat P.
   Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty. Neurochirurgie 1987;33(2):166-168.

6. Zoarski GH, Snow P, Olan WJ, et al.
   Percutaneous vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long-term outcomes. J Vasc Interv Radiol 2002;13:139-48

7. McGraw JK, Lippert JA, Minkus KD, Rami PM, Davis TM, Budzik RF.
   Prospective evaluation of pain relief in 100 patients undergoing percutaneous vertebroplasty: results and follow-up. J Vasc Interv Radiol 2002;13:883-6

8. Legroux-Gerot I, Lormeau C, Boutry N, Cotten A, Duquesnoy B, Cortet B.
   Long-term follow-up of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Clin Rheumatol 2004;23:310-7

9. Voormolen MH, Lohle PN, Lampmann LE, et al.
   Prospective clinical follow-up after percutaneous vertebroplasty in patients with painful osteoporotic vertebral compression fractures. J Vasc Interv Radiol 2006;17:1313-20

10. Kallmes DF, Comstock BA, Heagerty PJ, et al.
    A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79

11. Buchbinder R, Osborne RH, Ebeling PR, et al.
    A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557-68

12. Jensen ME, Evans AJ, Mathis JM et al.
    Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. AJNR Am J Neuroradiol 1997;18:1897-1904

13. Cortet B, Cotton A, Boutry N.
Percutaneous vertebroplasty in the treatment of osteoporotic vertebral compression fractures: an open prospective study. J Rheumatol 1999;26:2222-2228

14. Venmans A, Lohle PNM, van Rooij WJ et al.
Frequency and outcome of pulmonary polymethylmethacrylate embolism during percutaneous vertebroplasty. AJNR Am J Neuroradiol 2008;29:1983-1985

15. Nussbaum DA, Gailloud P, Murphy K.
A review of complications associated with vertebroplasty and kyphoplasty as reported to the food and drug administration medical device related web site. J Vasc Interv Radiol 2004:1185-1192

16. Chen HL, Wong CS, Ho ST et al.
A lethal pulmonary embolism during percutaneous vertebroplasty. Anesth Analg 2002; 95: 1060-1062

17. Monticelli F, Meyer HJ, Tutsch-Bauer E.
Fatal pulmonary cement embolism following percutaneous vertebroplasty (PVP). Forensic Science International 2005;149:35-38

18. Mathis JM.
Procedural techniques and materials: complication avoidance and tricks of the trade. AJNR Am J Neuroradiol 2002:119-120

19. Mathis JM.
Percutaneous vertebroplasty: complication avoidance and technique optimization. AJNR Am J Neuroradiol 2003:1687-1706

20. Hodler J, Peck D, Gilula LA.
Midterm outcome after vertebroplasty: predictive value of technical and patient-related factors. Radiology 2003:;227:662-668

21. Diamond TH, Bryant C, Browne L et al.
Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust 2006;184:113-7

CHAPTER 2

NATURAL HISTORY OF PAIN IN PATIENTS WITH CONSERVATIVELY TREATED OSTEOPOROTIC VERTEBRAL COMPRESSION FRACTURES

RESULTS FROM VERTOS 2

AJNR AM J NEURORADIOL PRINTED MARCH 2012

Abstract

Background and Purpose: We analyze the natural course of conservatively treated osteoporotic vertebral compression fractures from Vertos II, a randomized trial of vertebroplasty and conservative therapy in 202 patients with vertebral compression fractures. We want to assess the proportion of patients that developed chronic back pain and possible risk factors.

Materials and Methods: In Vertos II, VAS-score was assessed at regular intervals until 1 year follow-up. We followed 95 conservatively treated patients until sufficient pain relief, defined as a VAS-score ≤ 3. These patients were censored at the involved follow-up interval. In addition, baseline clinical, imaging data and class of pain medication used in patients with VAS-score ≤ 3 at any follow-up interval were compared with patients with a VAS-score › 3 at every follow-up using logistic regression analysis.

Results: During one year of follow-up, 57 of 95 patients (60%) had sufficient pain relief with VAS-scores ≤ 3. Thirty-eight patients (40%) still had pain with VAS-scores 4 or higher at last follow-up interval of 12 months despite use of higher class pain medication. Statistical analysis showed no risk factors.

Conclusion: In the Vertos II trial, most conservatively treated patients with acute osteoporotic compression fractures had sufficient pain relief during the first 3 months. However, after one year a substantial proportion of patients still had disabling pain despite higher class pain medication used. There were no predictors for the development of chronic pain. Patients with continuing pain 3 months or more after the fracture may be candidates for vertebroplasty.

Introduction

Little is known about the natural course of conservatively treated osteoporotic vertebral compression fractures (VCF). Not all patients with osteoporotic vertebral fractures will show sufficient pain relief. It is assumed that about one in five of these patients eventually will develop chronic back pain as a direct result of the fracture (1,2). In a recent study (3), even a third of patients still had severe pain necessitating pain medication and physical therapy almost 2 years after an acute fracture. In this study no predictors for transition from acute to chronic pain could be identified .
In Vertos II (4), an open label randomized controlled trial comparing vertebroplasty with conservative treatment in patients with osteoporotic vertebral fractures, we found that almost a quarter of conservatively treated patients had no significant pain relief after one year.
In the present study, we further analyze the conservatively treated patients from Vertos II. In particular, we want to assess the proportion of patients that developed chronic back pain. In addition, we want to assess possible risk factors for the transition from acute to chronic pain.

Materials and Methods

The patients for this study participated in the Vertos II trial (5). This trial was an open-label randomized controlled trial comparing vertebroplasty and conservative therapy for osteoporotic vertebral fractures in 202 patients. Between October 2005 and June 2008, 202 patients were randomized and 101 patients were assigned to conservative therapy. Informed consent was withdrawn after randomization by 6 patients. The remaining 95 patients form the subject of present study.
In Vertos II, VAS-score was assessed at 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year. For the purpose of this study, we followed these conservatively treated patients until sufficient pain relief, defined as a VAS-score ≤ 3. These patients were censored at the involved follow-up interval. Results were analyzed with Kaplan-Meier survival analysis.
In addition, patients with VAS-score ≤ 3 at any follow-up interval were compared with patients with a VAS-score › 3 at every follow-up interval using logistic regression analysis. The following factors were evaluated: mean age, gender, and baseline data (duration of back pain, VAS-score, Roland Morris Disability (RMD) score (5), bone mineral density, number of prevalent fractures, fracture severity and fracture type according to Genant (6). In addition, class of pain medication used at every follow-up interval was compared between patients with VAS › 3 and VAS ≤ using Pearson $\chi 2$ test. Pain medica-

tion was categorized according to WHO classification as (0) no medication, (1) non-opiates (paracetamol, non-steroidal anti-inflammatory agents), (2) weak opiate-derivatives, and (3) strong opiate-derivatives.

Results

During one year of follow-up, 57 of 95 patients (60%) had sufficient pain relief with VAS-scores ≤ 3. The time intervals until this significant clinical improvement is displayed in *Figure 1*. Most patients had sufficient pain relief during the first 3 months, after this interval the likelihood of good clinical outcome was very low. On the other hand, 38 patients (40%) still had pain with VAS-scores 4 or higher at last follow-up interval of 12 months.
The results of logistic regression analysis comparing patients with VAS-score ≤ 3 with patients VAS-score › 3 are displayed in *Table 1*. There were no significant differences in the evaluated clinical and imaging factors.
Patients with VAS › 3 used significant higher class of pain medication at 1, 6 and 12 months follow-up intervals. At the other intervals this difference was not significant.

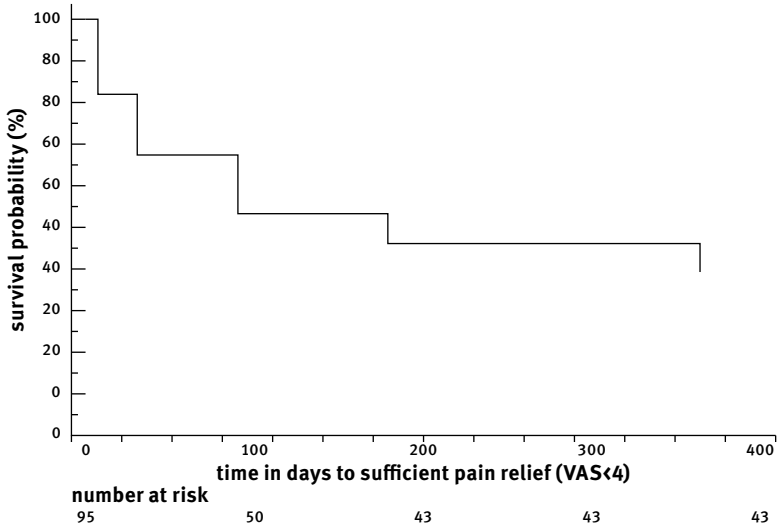


Figure 1. Kaplan-Meier curve showing time until significant clinical improvement.

Table 1. Baseline characteristics in relation to clinical outcome.

	VAS-score ≤ 3	VAS-score › 3	P-value
Number of patients	57	38	
Age	77.7 ± 8.0	80.6 ± 8.6	0.30
Female sex (%)	37 (57%)	28 (61%)	0.41
Duration of back pain (days)	29.3 ± 17.1	26.8 ± 16.0	0.46
VAS	7.4 ± 1.5	7.9 ± 1.4	0.08
RMD score	17.8 ± 3.7	16.9 ± 4.5	0.32
Number of VCF	2.1 ±1.5	2.2 ± 1.5	0.97
Genant (6)			
grade 1	24	12	0.87
grade 2	19	12	
grade 3	22	7	
wedge	46	29	0.48
biconcave	8	7	
crush	0	0	
Bone density (T-score)	-3.0 ± 1.17	-3.0 ± 1.02	0.44

Discussion

In this study, we found that 40% of conservatively treated patients with acute osteoporotic compression fractures still had disabling pain after one year despite higher class of pain medication used at various intervals. Optimal pain medication and supportive therapy was apparently not sufficient for pain relief in a large proportion of these conservatively treated patients. On the other hand, 60% of patients had sufficient pain relief with conservative therapy, almost all within 3 months after the acute fracture. We could not find any predictors for the development of chronic pain. In particular, baseline pain scores, number of fractures and degree or shape of vertebral compression had no influence on the development of chronic pain.

The proportion of patients with chronic pain after conservative treatment in the present study is higher than in previous studies. This can partly be explained by differences in definition of chronic pain: we defined chronic pain as VAS-scores 4 or higher while in other studies, including Vertos II, patients with insufficient decrease in VAS-scores were considered to have chronic pain. In these studies, patients with sufficient pain relief could have absolute VAS-scores at follow-up of 4 or higher.

In the natural history of pain after an acute vertebral compression fracture, the time point of 3 months may be of clinical significance. Patients with continuing pain at this time point, may be candidates for vertebroplasty.
The effectiveness of vertebroplasty is currently under debate. Most results on the effectiveness of vertebroplasty are based on retrospective observational studies (7-10). Recently, three randomized controlled trials concerning vertebroplasty have been published with conflicting results. Investigators in two trials (11,12) concluded that there is no benefit to vertebroplasty over a sham placebo procedure involving the injection of local anesthetic into the area adjacent to the fracture. In the study by Buchbinder et al (12), 78 patients with one or two painful osteoporotic VCF's were randomized to receive either vertebroplasty or a sham procedure, which included infiltration of anesthetic into the pedicular periosteum. The primary measured outcome was overall pain at 3 months. Despite significant reductions in overall pain in both groups, there was no significant advantage of vertebroplasty over the sham procedure. In the study by Kallmes et al (11), 131 patients with one to three painful osteoporotic VCF's were randomized to undergo either vertebroplasty or a simulated sham procedure, which included infiltration of anesthetic into the periosteum of the posterior lamina. The primary outcomes were RMD scores and average pain intensity during the preceding 24 hours at 1 month. Treatment group crossover was permitted at 1 month. At 1 month, there was no significant difference between the two groups in either the RMD score or the pain rating. In the third trial, Vertos II (5), vertebroplasty was compared to optimal conservative treatment in 202 patients with VCF's with bone edema on MRI, back pain for 6 weeks or less, and a VAS score for pain of 5 or more. The primary outcome was pain relief at 1 month and 1 year. The authors concluded that in a subgroup of patients with acute osteoporotic vertebral compression fractures and persistent pain, vertebroplasty is effective and safe. Pain relief after vertebroplasty is immediate, is sustained for at least a year, and is significantly greater than that achieved with conservative treatment, at an acceptable cost.
Next to the lack of blinding in Vertos II, the most important differences between the two sham studies and Vertos II is patient selection. In the sham studies both acute and chronic fractures were included while in Vertos II only acute fractures were eligible. In addition, bone edema in the affected vertebra was not a consistent inclusion criterion in the sham studies. The sham studies lacked a control group without intervention. The discordant results from the sham studies, on the one hand, and Vertos II, on the other hand, have incited much debate. Apparently clinicians do still not know how to best treat their patients. Medical societies understand the need for further randomized trials to support treatment decisions. Until then, based on our findings, we believe it

is justified to offer vertebroplasty to patients with compression fractures with insufficient pain relief after 3 months conservative treatment.

Conclusion

In the Vertos II trial, most conservatively treated patients with acute osteoporotic compression fractures had sufficient pain relief during the first 3 months. However, after one year a substantial proportion of patients still reported disabling pain. There were no predictors for the development of chronic pain. Patients with continuing pain 3 months or more after the fracture may be candidates for invasive therapy such as vertebroplasty.

References

1. Voormolen MH, Mali WP, Lohle PN, et al.
   Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol 2007;28:555-60

2. Ploeg WT, Veldhuizen AG, The B, Sietsma MS.
   Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: a systematic review. Eur Spine J 2006;15:1749-58

3. Klazen CA, Verhaar HJ, Lohle PN, et al.
   Clinical Course of Pain in Acute Osteoporotic Vertebral Compression Fractures.
   JVIR 2010;21:1405-1409

4. Klazen CA, Lohle PN, de Vries J, et al.
   Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. The Lancet 2010; 376:1085-1092

5. Roland M, Morris R.
   A study of the natural history of low-back pain. Part II: development of guidelines for trials of treatment in primary care. Spine 1983; 8:145-50

6. Genant HK, Wu CY, van KC, Nevitt MC.
   Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993 September;8:1137-48

7. Zoarski GH, Snow P, Olan WJ, et al.
   Percutaneous vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long-term outcomes. J Vasc Interv Radiol 2002;13:139-48

8. McGraw JK, Lippert JA, Minkus KD, Rami PM, Davis TM, Budzik RF.
   Prospective evaluation of pain relief in 100 patients undergoing percutaneous vertebroplasty: results and follow-up. J Vasc Interv Radiol 2002;13:883-6

9. Legroux-Gerot I, Lormeau C, Boutry N, Cotten A, Duquesnoy B, Cortet B.
   Long-term follow-up of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Clin Rheumatol 2004;23:310-7

10. Voormolen MH, Lohle PN, Lampmann LE, et al.
    Prospective clinical follow-up after percutaneous vertebroplasty in patients with painful osteoporotic vertebral compression fractures. J Vasc Interv Radiol 2006;17:1313-20

11. Kallmes DF, Comstock BA, Heagerty PJ, et al.
    A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79

12. Buchbinder R, Osborne RH, Ebeling PR, et al.
    A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557-68

CHAPTER 3

FREQUENCY AND OUTCOME OF PULMONARY POLYMETHYLMETHACRYLATE (PMMA) EMBOLISM DURING PERCUTANEOUS VERTEBROPLASTY

AJNR AM J NEURORADIOL 2008;29:1983-5

Abstract

Introduction: During Percutaneous Vertebroplasty (PV), PMMA cement may migrate into the venous system and subsequently transported to the pulmonary arteries. Frequency, outcome and imaging findings of PMMA pulmonary embolism are poorly understood. We retrospectively assessed frequency and outcome of PMMA embolism during PV in a large patient cohort and evaluated relationship of volume of injected PMMA with occurrence of pulmonary PMMA embolism.

Patients and Methods: Between 2001 and 2007, 502 osteoporotic compression fractures in 299 consecutive patients were treated with PV. PMMA embolism was defined as venous PMMA migration visible on biplane fluoroscopy during PV. CT scan was performed immediately and one year after PMMA migration. Mean volume of injected PMMA was assessed for all vertebrae and for T5-T10, T11-L2 and L3-L5.

Results: Venous PMMA migration occurred during 11 PV's in 11 patients (2.2%, 95% CI 1.2-3.9%). CT scan in 9 patients demonstrated small peripheral pulmonary PMMA emboli. All 11 patients remained asymptomatic during one year follow up. Repeat CT scan after one year in 6 patients demonstrated unchanged pulmonary PMMA deposits without late reactive changes. Mean cement volume in patients with and without PMMA embolism was not different: 3.6 ± 1.06 ml versus 3.3 ± 1.16 ml (P=0.43). Similar comparison for thoracic and thoracolumbar vertebrae yielded P values of 0.07 and 0.9.

Conclusion: Pulmonary PMMA embolism during PV is an infrequent complication without clinical sequelae. After one year, no pulmonary reaction is seen on CT. No definite relationship of PMMA emboli with injected cement volume could be established.

Introduction

Percutaneous vertebroplasty (PV) is increasingly used for pain relief in patients with symptomatic vertebral compression fractures. Since the introduction of PV in 1987, its safety and effectiveness has been confirmed in several studies (1-5). Complications of PV are rare and if they occur, are mostly related to polymethylmethacrylate (PMMA) leakage outside the treated vertebral body into adjacent anatomical structures. During PV, PMMA may migrate into the venous system and subsequently transported to the pulmonary arteries. Frequency, outcome and imaging findings of such PMMA pulmonary embolism are poorly understood.
In this study we retrospectively assessed frequency and clinical and imaging outcome of PMMA embolism during PV in a large patient cohort. In addition, we evaluated whether volume of injected PMMA is a risk factor for the occurrence of pulmonary PMMA embolism.

Patients and Methods

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

Patients
Between October 2001 and June 2007, PV was performed in 299 consecutive patients with osteoporotic vertebral compression fractures (OVCF). In 197 patients one vertebra was treated, in 102 patients 2 were treated and in 24 patients 3. During follow up, new fractures were treated with PV in 59 of 299 patients. Altogether, 502 OVCF's were treated. Of 299 patients, 60 were male and 239 were female with a mean age of 73 years (range 47-94). Location of treated vertebra is displayed in *Figure 1*.

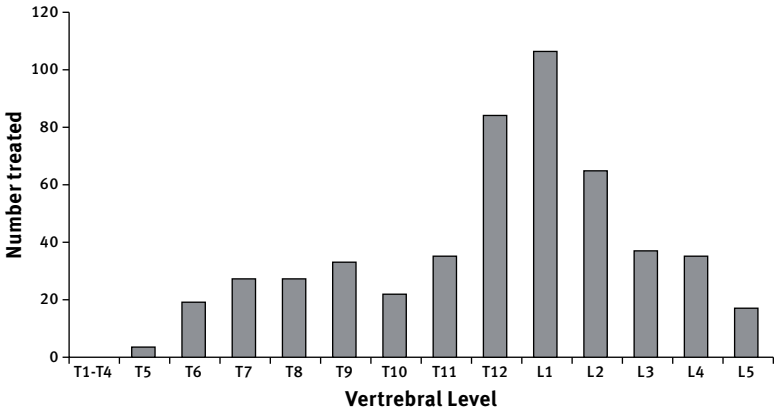


Figure 1. Distribution of treated osteoporotic compression fractures.

Vertebroplasty

PV was performed on a biplane angiographic unit (Integra BN 3000 Neuro, Philips Medical Systems, Best, The Netherlands). After local anaesthesia, two 11 or 13 gauge needles were bilaterally transpedicular inserted into the vertebral body. PMMA was injected under continuous biplane or lateral fluoroscopy alternating both pedicles using 1cc syringes. Injection was stopped whenever epidural or paravertebral migration was observed. When needed, the injection was resumed after a 15-20 second delay without changing needle position. Volume of injected cement in each treated vertebral body was recorded.

Definition of pulmonary PMMA embolism

Pulmonary PMMA embolism was defined as venous PMMA migration visible on fluoroscopy. If so, any clinical changes were recorded and a native chest CT scan was performed immediately after the procedure to detect location, number and distribution of PMMA and possible reactive changes of the lung parenchyma.

Follow-up of patients with pulmonary PMMA embolism

Medical records of patients with pulmonary PMMA embolism were reviewed for possible cardiovascular symptoms related to PMMA embolism. In October 2007, surviving patients were contacted and requested to fill out a short questionnaire regarding cardiovascular symptoms after PV. In addition, they were invited for repeat native chest CT for comparison with CT immediately after PV.

Statistical Analysis

Frequency of pulmonary PMMA embolism was assessed per treated vertebra as a proportion with 95% CI. Mean volume with standard deviation of injected PMMA per vertebra was assessed for all vertebrae and separately for thoracic (T5-T10), thoracolumbar (T11-L2) and lumbar vertebrae (L3-L5) both in patients with and without pulmonary PMMA embolism. T-test was used for comparison.

Results

In 502 PV's in 299 patients, pulmonary PMMA embolism occurred in 11 procedures (2.1%, 95% CI 1.2-3.9%) in 11 patients (*Table 1 and Figure 2*). Native chest CT scan in 9 patients demonstrated 1-3 small (2-6 mm) peripheral punctuate or tubular hyperdensities randomly distributed in one or two lobes without reactive pulmonary changes. No PMMA depositions were present in the heart or central pulmonary arteries. In none of 11 patients clinical symptoms developed during PV or afterwards during hospital admission. After a mean follow up of 12 months (range 5-22 months), two patients had died of metastatic cancer and one patient could not be traced. The remaining 8 patients reported no cardiopulmonary symptoms. All 8 patients agreed to native chest CT scan and in 6 of 8 results could be compared with previous CT (2 patients had no initial CT after PV). In all 8 patients, CT scans showed similar findings as on initial CT without reactive pulmonary changes. In 6 patients with initial and follow up CT, findings were unchanged.

Mean cement volume in 462 vertebrae in patients without PMMA embolism was 3.3 ± 1.16 ml (range 0.5-9) and in 11 vertebrae in patients with PMMA embolism this was 3.6 ± 1.06 ml (range 2.6-5.5). This difference was not significant (P=0.43).

Similar comparison was done for thoracic (116 versus 5, P=0.07), thoracolumbar (272 versus 5, P=0.9) and lumbar (74 versus 1, P=invalid) vertebrae. Although there was a trend towards more injected cement volume in patients with pulmonary PMMA during PV of thoracic vertebrae, this just was not significant.

Table 1. CT findings in patients with pulmonary PMMA embolism during PV.

Pt #	Gender Age	vertebra	PMMA volume (ml)	Native chest CT after PV
1	F/68	T8	5	No
2	F/72	T7	4	Multiple small punctuate opacities in LLL
3	F/85	L2	4	1 small tubular and 1 punctuate opacity in LUL
4	M/91	T6	2	2 small punctuate opacities in LUL
5	F/66	T11	4	2 tubular opacities in RUL and 3 small punctuate opacities in LUL
6	F/68	T11	2,8	No
7	F/83	T12	4	Small punctuate opacities in RUL and lingula
8	F/52	T11	3	2 very small punctuate opacities in RUL
9	F/74	T9	2,8	Small punctuate opacity in LUL and a small tubular opacity in RUL
10	F/60	L3	5,5	No
11	F/60	T10	2,6	1 small tubular and 1 punctuate opacity RUL

Abbreviations: T=thoracic; L=lumbar; LLL= left lower lobe; LUL=left upper lobe; RUL=right upper lobe

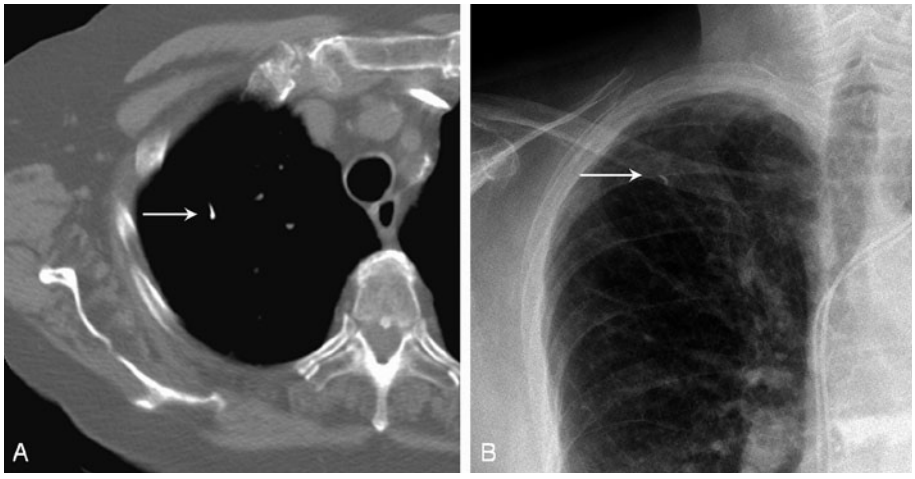


Figure 2. Small pulmonary PMMA embolus in right upper lobe visible on a native chest CT scan (a) and on a chest radiograph (b).

Discussion

Pulmonary PMMA embolization during VP for compression fractures is rare with an incidence of 2.1%. CT scan demonstrated small PMMA deposits in segmental or subsegmental pulmonary arteries without early or late reactive pulmonary changes. No PMMA depositions were present in the heart or central pulmonary arteries. In none of the patients clinical symptoms developed during follow up of one year.

The low frequency of pulmonary PMMA embolism is confirmed in other observational studies with frequencies of 0-4.8% (6-10). Combined data of 791 VP's indicate a frequency of 1.9% with a narrow confidence interval (*Table 1*). We could not establish a definite relation of injected cement volume with the occurrence of PMMA embolism, although there was a trend towards more injected cement volume in patients with pulmonary PMMA during PV of thoracic vertebrae. In all cited studies patients with PMMA embolism remained asymptomatic. However, in several case reports severe or fatal clinical complications of PMMA embolism are reported (11-16) (*Table 2*). In all cases there was evidence of a large injected total PMMA volume (9-15 ml) or a large amount of PMMA in the heart or central pulmonary arteries. This suggests that in these cases, venous cement migration was not timely fluoroscopically detected.

In our opinion, supported by others, with proper use of fluoroscopy and limited volume of PMMA injected in repeated small quantities, pulmonary PMMA embolism will rarely occur and if so, only very small quantities of PMMA will be transported to the pulmonary arteries without clinical sequelae. Therefore, standard chest radiographs or CT after PV is not warranted.

Next to PMMA embolism, intramedullary fatty bone marrow embolism may occur, a well-recognized phenomenon in orthopedic surgery (17). Injection of bone cement may force fatty bone marrow into disrupted medullary veins and migrate to the pulmonary vessels. This may cause increased pulmonary resistance, hypoxemia and thus decreased cardiac output (11, 18). In an experimental study of PV in a sheep model (19), PV provoked an initial reflexive decrease in heart rate and arterial blood pressure followed by fat and bone marrow emboli passing through the heart into the pulmonary vasculature. This indicates that fat embolism also may occur during PV in humans. Apparently, these fat emboli are well tolerated in patients without associated cardiopulmonary disease. However, especially in patients with compromised cardiopulmonary reserve, it seems sensible to limit the levels treated per session and injected PMMA volumes per vertebra.

Conclusion

Pulmonary PMMA embolism during PV is an infrequent complication and has no short- and mid-term clinical sequelae. After one year, no pulmonary reaction is seen on CT. Although there was a trend towards more injected cement volume in patients with pulmonary PMMA during PV of thoracic vertebrae, this just was not significant.

References

1. Galibert P, Deramond H, Rosat P et al.
   Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty (in French). Neurochirurgie 1987;33:166-168

2. Mathis JM, Barr JD, Belkoff SM et al.
   Percutaneous vertebroplasty: a developing standard of care for vertebral compression fractures. AJNR Am J Neuroradiol 2001;22:373-381

3. Cotton A, Dewatre F, Cortet B et al.
   Percutaneous vertebroplasty for osteolytic metastasis and myelomas: effects of the percentage of lesion filling and the leakage of methyl methacrylate at clinical follow-up. Radiology 1996;200:525-530

4. Weill A, Chiras J, Simon JM.
   Spinal metastases: indications for and results of percutaneous injection of acrylic surgical cement. Radiology 1996;99:241-247

5. Cotton A, Boutry N, Cortet B et al.
   Percutaneous vertebroplasty: state of the art. Radiographics 1998;18:311-320

6. Jensen ME, Evans AJ, Mathis JM et al.
   Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. AJNR Am J Neuroradiol 1997;18:1897-1904

7. Grados F, Depriester C, Cayrolle G et al.
   Long-term observations of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Rheumatology (Oxford) 2000;39:1410-1414

8. Zoarski GH, Paige Snow PA, Olan WJ et al.
   Percutaneous vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long-term outcomes. J Vasc Interv Radiol 2002;13: 39-148

9. Legroux-Gerot I, Lormeau C, Boutry N et al.
   Long-term follow-up of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Clin Rheumatol 2004;23:310-7

10. Diamond TH, Bryant C, Browne L et al.
    Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust 2006;184:113-7

11. Chen HL, Wong CS, Ho ST et al.
    A lethal pulmonary embolism during percutaneous vertebroplasty. Anesth Analg 2002; 95: 1060-1062

12. Francois K, Taemans Y, Poffyn B et al.
    Successful management of a large pulmonary cement embolus after percutaneous vertebroplasty. Spine 2003;28; E424-425

13. Stricker K, Orler R, Yen K et al.
Severe hypercapnia due to pulmonary embolism of polymethylmathacrylate during vertebroplasty. Anesth Analg 2004;98:1184-1186

14. Yoo KY, Jeong SW, Yoon W et al.
Acute respiratory distress syndrome associated with pulmonary cement embolism following percutaneous vertebroplasty with polymethylmethacrylate. Spine 2004;29:E294-297

15. Monticelli F, Meyer HJ, Tutsch-Bauer E.
Fatal pulmonary cement embolism following percutaneous vertebroplasty (PVP).
Forensic Science International 2005;149:35-38

16. Freitag M, Gotschalk A, Schuster M et al.
Pulmonary embolism caused by polymethylmethacrylate during percutaneous vertebroplasty in orthopaedic surgery. Acta Anaesthesiol Scand 2006;50:248-251

17. Parisi D, Koval K, Egol K.
Fat embolism syndrome. Am J Orthop 2002;31:507-512

18. Syed MI, Jan S, Patel NA et al.
Fatal fat embolism after vertebroplasty: identification of the high-risk patient.
AJNR Am J Neuroradiol 2006;27:343-345

19. Aebli N, Krebs J, Davis G et al.
Fat embolism and acute hypotension during vertebroplasty: an experimental study in sheep.
Spine 2002;27:460-466

CHAPTER 4

PERCUTANEOUS VERTEBROPLASTY AND PULMONARY CEMENT EMBOLISM

RESULTS FROM VERTOS 2

AJNR AM J NEURORADIOL 2010;31:1451-53

Abstract

Background and Purpose: Reported incidences of PCE during PV vary, depending on sensitivity of used diagnostic tests. To assess the true incidence of PCE, we performed native chest CT during follow-up in a large proportion of patients of the Vertos II trial.

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

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

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

Introduction

Cement leakage commonly occurs during PV with incidences in observational studies varying from 0-23% (1-6). Occasionally, cement that has been leaked into the veins may migrate into the lungs causing PCE. Although most PCE's remain asymptomatic, serious and even fatal sequelae have occasionally been reported (7,8). In most studies with low incidence of PCE, the occurrence of PCE is defined as cement migration towards the lungs observed during fluoroscopy (9). In studies with standard post-procedural chest radiographs the observed incidences are higher (10,11,12); apparently a substantial proportion of PCE remains undetected during fluoroscopy. As for now, the long-term effects of pulmonary cement deposits on the surrounding lung parenchyma are largely unknown.
In this study, we use follow-up chest CT to assess the true incidence of the occurrence of PCE during fluoroscopy in a large patient cohort with osteoporotic vertebral compression fractures treated with PV. In addition, we evaluate possible inflammatory response of cement deposits on the lung parenchyma.

Materials and Methods

Patients
The Vertos II trial (13) was a pragmatic randomized controlled trial comparing PV and conservative therapy for OVCF's in 202 patients. The study protocol has been described in detail elsewhere (13). In short, Vertos II was a randomized controlled trial in five large teaching hospitals in the Netherlands and one in Belgium. The protocols of Vertos II including the present study were approved by the institutional review boards at each participating centre. Between October 2005 and June 2008, 202 patients were randomized for PV and conservative therapy. Ultimately, in 98 patients PV was performed without clinical procedural complications. These 98 patients form the bases of the present study. During a mean follow-up of 22 months (median 21, range 6-42 months), 10 patients died and 6 refused to complete the protocol of Vertos II. The remaining 82 patients were invited by telephone for a native CT of the treated vertebra and chest to detect peri-vertebral cement leakage and PCE. Of these 82 patients, 24 declined participation and four patients could not be reached. Thus, 54 of 82 patients (69%) had follow-up CT. In these 54 patients no cement migration had been visible on fluoroscopy during the procedure. There were 36 women (67%) and 18 men (33%) with a mean age of 74 years (median 77; range 53-88 years). These 54 patients had 80 OVCF's and were treated in 60 sessions. Thirty-nine patients were treated for one OVCF, 11 patients for two, and four patients for three OVCF's in one session. During

follow-up, 4 patients presented with a new OVCF and were treated again. One of these 4 patients had 2 additional PV's, for one OVCF each time. Location of treated osteoporotic compression fractures in relation to pulmonary cement embolism is displayed in *figure 1*.

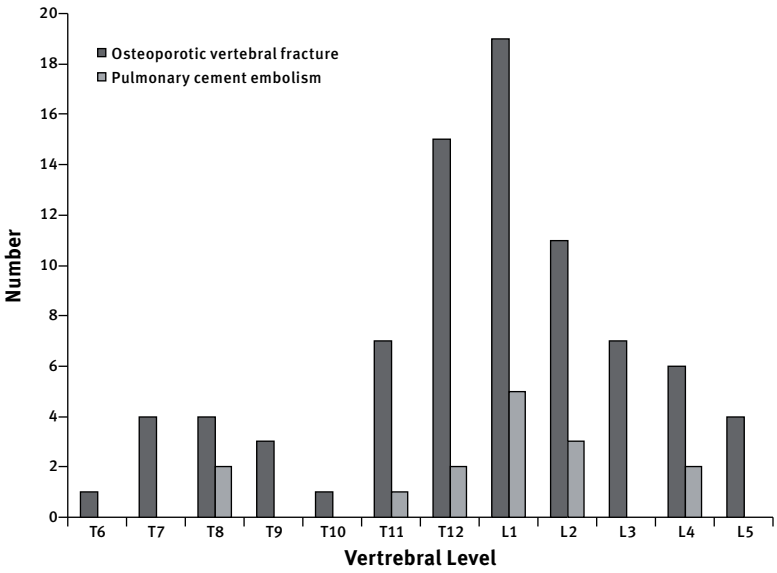


Figure 1. Location of treated osteoporotic compression fractures in relation to pulmonary cement embolism.

PV technique

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

Perivertebral cement leakage on post-procedural and follow-up CT scan

Treated vertebrae were assigned into 3 location categories: T5-T10, T11-L2 and L3-L5. Perivertebral venous cement leakage was assessed from direct post-procedural CT scan and categorized as limited to the anterior external venous

plexus, azygos vein, or inferior vena cava. PCE was defined as any high density lesion in the lungs, heart or large vessels. In patients with PCE and multiple levels treated, we assumed the level with the most leakage to be the origin of PCE.

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

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

Results

Incidence and characteristics of PCE on native follow-up chest CT scan
After median 21 months of follow-up, PCE was detected in 14 of 54 patients (26%, 95% CI, 16-39%). All patients were asymptomatic. An example of a PCE is presented in *figure 2*.

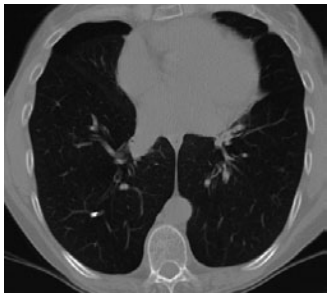


Figure 2. Native chest CT scan demonstrating a cement embolus in a peripheral right lower lobe pulmonary artery.

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

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

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

Discussion

This study showed that during PV for OVCF's, clinically silent PCE occur in a quarter of patients. Cement emboli were small and scattered in peripheral portions of the lungs without specific lobar distribution. There were no cement deposits in the heart and large vessels. Cement leakage in the azygos vein was the only risk factor for PCE. Remarkably, the volume of injected cement was not correlated with the occurrence of PCE. After a mean follow-up of almost 2 years, the cement emboli caused no inflammatory reactive pulmonary changes.
In a comparable study with use of CT to detect PCE, Kim et al (10) found a similar incidence in 75 patients undergoing PV for OVCF's with cement leakage to the inferior caval vein as only relevant risk factor. In studies that only used post-procedural chest radiographs for detection of PCE, the observed incidences were substantially lower (11,12). This is not surprising since small pulmonary cement deposits easily remain undetected on chest radiographs while these are readily apparent on CT scanning. In one study (12) an incidence of 4.6% was reported after retrospectively reviewing post-procedural chest radiographs in 69 VP sessions. In that study, all patients with cement emboli had multiple myeloma and remained asymptomatic. An association was found between pulmonary cement embolism and paravertebral venous cement leakage but not between pulmonary cement embolism and the number of

vertebral bodies treated or whether kyphoplasty or vertebroplasty was performed. Another study (11) also retrospectively reviewed post-procedural chest radiographs, and when pulmonary cement embolism was detected, they confirmed it with CT. In that study, 5 of 73 patients (6.8%) had pulmonary cement embolism. Four of these patients had osteoporotic compression fractures and one had multiple myeloma. Venous leakage was not recognized during fluoroscopy in patients with pulmonary cement embolism.
In the Vertos II trial (13) fluoroscopic venous cement migration to the lungs was detected and reported by the operator in only one patient (CA Klazen, unpublished data, 2010). This patient remained asymptomatic and was censored 3 months later because of unrelated comorbidity. In no patients that were included in the present follow-up study fluoroscopically visible cement migration towards the lungs was reported by the operators. The findings of our study imply that with fluoroscopy virtually all migration of small cement quantities remain undetected. Thus, when the operator notices cement leakage into anterior venous structures, careful observation of pulmonary symptoms is mandatory. Conversely, when a patient complains of pulmonary symptoms after PV, PCE should be excluded, even though venous cement migration was not seen.
Like in previous studies (9,11,12), our study showed that cement emboli were scattered in peripheral portions of the lung without specific lobar distribution and no acute inflammatory pulmonary reaction. Our study indicates that also on the long-term, cement emboli do not cause inflammatory changes in the pulmonary parenchyma.
In our study, cement in the azygos vein on the post-procedural CT of the treated vertebra was the only risk factor for PCE. Analogously, other studies (10,14) showed a statistically significant relation between PCE and cement leakage into the inferior caval vein.
Our study has several limitations. Our patient group was relatively small and not all patients agreed to participate. Results were expressed on a per patient base while some patients had multiple levels treated. Thus, in patients with PCE and multiple treated vertebrae, the level of leakage remained uncertain. However, we used post-procedural CT of the treated levels to indicate the most likely level of origin of leakage. On the other hand, strong points of the study were the use of CT for the detection of PCE and the long follow-up interval that allowed a reliable assessment of clinical consequences of PCE over time.
Based on our findings and other studies, in our opinion standard CT or chest radiograph after PV is not warranted in asymptomatic patients, even not when small quantities of cement have been observed to migrate towards the lungs. Only in symptomatic patients, CT should be performed to guide the appropriate therapy. Since cement emboli remain inert over time, follow-up CT is not necessary.

Conclusion

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

References

1. Krueger A, Bliemel C, Zettl R et al.
   Management of pulmonary cement embolism after percutaneous vertebroplasty and kyphoplasty: a systematic review of the literature. Eur Spine J 2009;18:1257-1265

2. Jensen ME, Evans AJ, Mathis JM et al.
   Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. AJNR Am J Neuroradiol 1997;18:1897-1904

3. Grados F, Depriester C, Cayrolle G et al.
   Long-term observations of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Rheumatology (Oxford) 2000;39:1410-1414

4. Zoarski GH, Paige Snow PA, Olan WJ et al.
   Percutaneous vertebroplasty for osteoporotic compression fractures: quantitative prospective evaluation of long-term outcomes. J Vasc Interv Radiol 2002;13: 39-148

5. Legroux-Gerot I, Lormeau C, Boutry N et al.
   Long-term follow-up of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Clin Rheumatol 2004;23:310-7

6. Diamond TH, Bryant C, Browne L et al.
   Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust 2006;184:113-7

7. Chen HL, Wong CS, Ho ST et al.
   A lethal pulmonary embolism during percutaneous vertebroplasty. Anesth Analg 2002; 95: 1060-1062

8. Monticelli F, Meyer HJ, Tutsch-Bauer E.
   Fatal pulmonary cement embolism following percutaneous vertebroplasty (PVP). Forensic Science International 2005;149:35-38

9. Venmans A, Lohle PNM, van Rooij WJ et al.
   Frequency and outcome of pulmonary polymethylmethacrylate embolism during percutaneous vertebroplasty. AJNR Am J Neuroradiol 2008;29:1983-1985

10. Kim JY, Lee JW, Park KW et al.
    Pulmonary cement embolism after percutaneous vertebroplasty in osteoporotic vertebral compression fractures: incidence, characteristics, and risk factors. Radiology 2009;251:250-259

11. Duran C, Sirvanci M, Aydooan M et al.
    Pulmonary cement embolism: a complication of percutaneous vertebroplasty. Acta radiol 2007;48:854-859

12. Choe DH, Marom EM, Ahrar K et al.
    Pulmonary embolism of polymethyl methacrylate during percutaneous vertebroplasty and kyphoplasty. AJR Am J Roentgenol 2004;183:1097-1102

13. Klazen CA, Verhaar HJ, Lampmann LE et al.
Percutaneous vertebroplasty versus conservative therapy in patients with painful osteoporotic vertebral compression fractures; rationale, objectives and design of a multicenter randomized controlled trial. Trials 2007;8:33

14. Barragán-Campos HM, Vallée JN, Lo D et al.
Percutaneous vertebroplasty for spinal metastases: complications. Radiology 2006;238:354-362

CHAPTER 5

POSTPROCEDURAL CT FOR PERIVERTEBRAL CEMENT LEAKAGE IN PERCUTANEOUS VERTEBROPLASTY IS NOT NECESSARY

RESULTS FROM VERTOS 2

NEURORADIOLOGY 2010;53:19-22

Abstract

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

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

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

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

Introduction

Perivertebral leakage of cement during percutaneous vertebroplasty (PV) has been reported to occur frequently in up to 65% of treated osteoporotic vertebral compression fractures (OVCF's) (1,2). Most of these leakages cause no clinical symptoms but pulmonary embolism and neurological complications have occasionally been reported (3,4).
Vertos II is a randomized controlled trial comparing PV and conservative therapy for OVCF's in 202 patients. In this trial patients assigned to PV had a standard post-procedural CT scan of the treated OVCF with the aim to assess the patterns of perivertebral cement leakage and its possible clinical impact. There is some concern that cement deposits may migrate to the lungs via the veins during follow-up; sharp and elongated spike-like cement fragments might cause perforation of vessels or heart. In addition, local damage to the adjacent anatomical structures by the leaked cement may cause symptoms like soft tissue hematoma or radiculopathy (5-8). In this study, we used baseline and follow-up CT to assess the incidence, anatomical location and clinical impact of perivertebral cement leakage on short- and long-term in a large patient cohort.

Methods

Patients
The study protocol of the Vertos II trial has been described in detail elsewhere (9). In short, Vertos II was an unmasked randomized controlled trial in five large teaching hospitals in the Netherlands and one in Belgium. The protocols of Vertos II and the present study were approved by the institutional review board at each participating centre. Between October 2005 and June 2008, 202 patients were randomized for PV and conservative therapy. All patients assigned to PV had baseline post-procedural CT scans of the treated vertebral bodies. Ultimately, in 98 patients PV was performed without clinical procedural related complications. These 98 patients form the bases of the present study. During a mean follow-up of 22 months (median 21 months; range 6-42 months), 10 patients died and 6 refused to complete the protocol of Vertos II. The remaining 82 patients were invited by telephone for a native CT scan of the treated vertebra to detect possible migration of the perivertebral cement leakages and evaluation of possible local pathology related to the cement leakage.
Twenty-four patients declined participation and four patients could not be reached. Thus, 54 of 82 patients (69%) had follow-up CT. There were 36 women (67%) and 18 men (33%) with a mean age of 74 years (median 77;

range 53-88 years). These 54 patients had 80 OVCF's and were treated in 60 sessions. Thirty-nine patients were treated for one OVCF, 11 patients for two, and four patients for three OVCF's in one session. During follow-up, 4 patients presented with a new OVCF and were treated again. One of these 4 patients had 2 additional PV's, for one OVCF each time. Location of treated vertebra is displayed in *figure 1*.

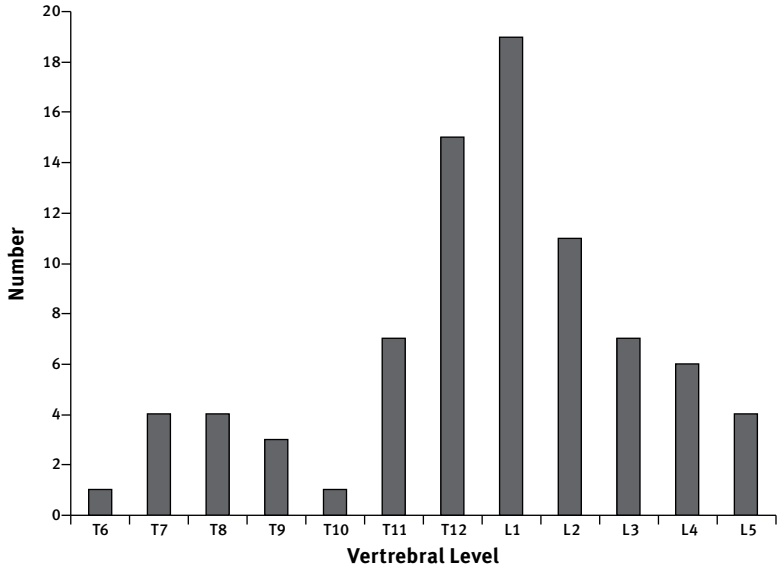


Figure 1. Distribution of 54 treated osteoporotic compression fractures.

PV technique

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

Perivertebral cement leakage on postprocedural and follow-up CT scan

Treated vertebrae were assigned into 3 location categories: T5-T10, T11-L2 and L3-L5. The anatomical location of perivertebral venous cement leakage was

recorded according to the plexus venosus vertebralis , a venous network that extends along the entire length of the vertebral column (*figure 2*). In addition to the venous location, discal and soft tissue leakages were recorded.

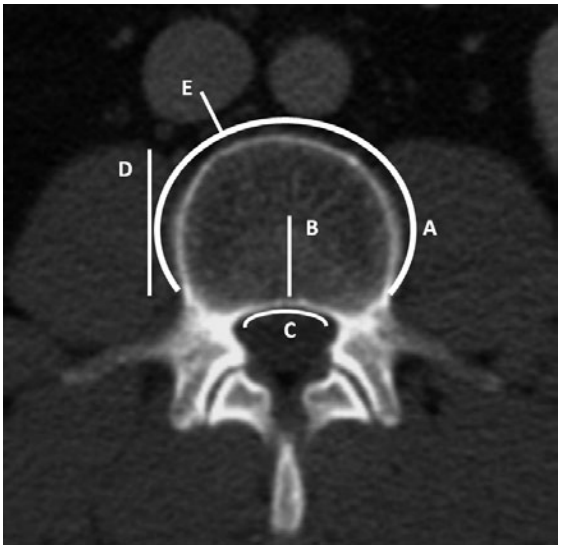


Figure 2. Schematic representation of patterns of perivertebral venous cement leakage. Leakage into the anterior external venous plexus (A), basivertebral vein (B), anterior internal venous plexus (C), segmental vein (D), inferior caval vein or (hemi) azygos vein (E)

Data analysis

Chi-square test was used to correlate perivertebral cement leakage with the location of treated OVCF's into 3 categories. Mean volume of injected cement in vertebrae with leakage was compared to mean volume of cement in vertebrae without leakage using the t-test. Statistics were performed with SPSS version 15.0.1. The Vertos II study is registered with ClinicalTrials.gov, with the number NCT00232466.

Results

Perivertebral cement leakage on postprocedural and follow-up CT scan

Any perivertebral cement leakage was observed in 64 of 80 treated vertebrae (80%, 95% CI 70 to 87%). Discal leakage was present in 22 vertebrae (34%), in 8 vertebrae (13%) in combination with venous leakage. Perivertebral soft tissue leakage occurred in 2 vertebrae (4%). Altogether, 56 of 64 vertebrae (88%) had cement leakage into the perivertebral venous system. Cement in

the anterior external venous plexus was observed in 46 of 56 vertebrae (82%), in 32 vertebrae (57%) in combination with cement in a segmental vein. Five vertebrae (9%) had cement in the inferior caval vein and 6 (11%) in the azygos vein, all in combination with cement in a segmental vein and the anterior external venous plexus. Cement in the basivertebral vein was present in 30 of 56 vertebrae (54%), in the anterior internal venous plexus in 33 (59%) and both in the basivertebral vein and anterior internal venous plexus in 26 (46%). Three vertebrae (5%) had cement in the intervertebral vein, all in combination with cement in the anterior external venous plexus, basivertebral vein and anterior internal venous plexus. No cement leaks were seen in the posterior internal and external venous plexus.
Comparison of follow-up CT scan (mean 22 months, median 21 months, range 6-42 months) of treated vertebrae with baseline CT showed unchanged anatomical location of the perivertebral cement leakages in all vertebrae without late cement migration.

Data analysis
Chi-square test showed no statistical relation between location of the treated vertebra and the occurrence of perivertebral cement leakage (p=0.64).
Mean volume of injected cement in 47 vertebrae with leakage was 4.5 ± 1.8 cc and in 33 vertebrae without leakage this was 3.7 ± 1.6 cc. This difference was significant (p=0.04, 95% CI -1,58 to -0,02%).

Discussion

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

major intercommunicating networks (10,11): the internal and the external venous plexus and the basivertebral system. The basivertebral system is oriented horizontally in the centre of the upper half of the vertebral body. The basivertebral veins originate in the ventral third of the vertebral body, and converge posteriorly to drain into the ventral part of the internal venous plexus, sometimes as a single vein, and sometimes as two separate tributaries. Anteriorly, the basivertebral veins join the external plexus. The exiting point of the basivertebral vein on the dorsal surface of the vertebral body is located in the middle between the pedicles. The anterior internal venous plexus drains into the segmental veins that exit the spinal canal through the foramen, between the nerve root and the medial wall of the pedicles. This means there is a direct venous connection between the bone marrow and the foraminal space.

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

Cement leakage during PV seems to be largely inevitable according to the high reported rates in this study and in the literature. Small leakages are without clinical consequences. With proper use of technique and fluoroscopy, clinical relevant cement leakage should be avoided.

Conclusion

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

References

1. Jensen ME, Evans AJ, Mathis JM et al.
   Percutaneous polymethylmethacrylate vertebroplasty in the treatment of osteoporotic vertebral body compression fractures: technical aspects. AJNR Am J Neuroradiol 1997;18:1897-1904

2. Cortet B, Cotton A, Boutry N.
   Percutaneous vertebroplasty in the treatment of osteoporotic vertebral compression fractures: an open prospective study. J Rheumatol 1999;26:2222-2228

3. Venmans A, Lohle PNM, van Rooij WJ et al.
   Frequency and outcome of pulmonary polymethylmethacrylate embolism during percutaneous vertebroplasty. AJNR Am J Neuroradiol 2008;29:1983-1985

4. Nussbaum DA, Gailloud P, Murphy K.
   A review of complications associated with vertebroplasty and kyphoplasty as reported to the food and drug administration medical device related web site. J Vasc Interv Radiol 2004:1185-1192

5. Mathis JM.
   Procedural techniques and materials: complication avoidance and tricks of the trade. AJNR Am J Neuroradiol 2002:119-120

6. Mathis JM.
   Percutaneous vertebroplasty: complication avoidance and technique optimization. AJNR Am J Neuroradiol 2003:1687-1706

7. Hodler J, Peck D, Gilula LA.
   Midterm outcome after vertebroplasty: predictive value of technical and patient-related factors. Radiology 2003:;227:662-668

8. Diamond TH, Bryant C, Browne L et al.
   Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy. Med J Aust 2006;184:113-7

9. Klazen CA, Verhaar HJ, Lampmann LE et al.
   Percutaneous vertebroplasty versus conservative therapy in patients with painful osteoporotic vertebral compression fractures; rationale, objectives and design of a multicenter randomized controlled trial. Trials 2007;8(1):33.

10. Groen RJM, Toit du DF, Philips FM.
    Anatomical and pathological considerations in percutaneous vertebroplasty and kuphoplasty: a reappraisal of the vertebral venous system. Spine 2004;29(13):1465-1471

11. Kasó G, Horváth Z, Szenohradszky K.
    Comparison of CT characteristics of extravertebral cement leakages after vertebroplasty performed by different navigation and injection techniques. Acta Neurochir 2008;150:677-683

12. Yeom JS, Kim WJ, Choy WS.
Leakage of cement in percutaneous transpedicular vertebroplasty for painful osteoporotic compression fractures. J Bone Joint Surg Br 85:83-89

13. Schmidt R, Cakir B, Mattes T.
Cement leakage during vertebroplasty: an underestimated problem? Eur Spine J 2005;14:466-473

CHAPTER 6

PERCUTANEOUS VERTEBROPLASTY AND PROCEDURAL PAIN

AJNR AM J NEURORADIOL 2010;31:830-1

Abstract

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

Methods: In 44 consecutive patients with symptomatic osteoporotic vertebral compression fractures (OVCF's) local infiltration anesthesia was used during PV. After the PV patients indicated pain sensation on a visual analog score (VAS). In addition, patients indicated the most painful moment during the procedure; lidocaine infiltration, placing the needles or cement injection. In addition, patients were asked whether pain medication during the procedure was sufficient or not. After the procedure the operator was asked what the expected VAS score of the patient would be.

Results: From September 2008 to March 2009, 44 consecutive patients with symptomatic OVCF's were included in the study. There were 35 women and 9 men with a mean age of 74 years (median 75, range 45-89 years). Mean VAS score was 5.7 (median 6, range 1-10). Seventeen patients (39%), with a mean VAS score of 7.3 (range 5-10), indicated lidocaine infiltration was insufficient. Placing the needles was specified as the most painful moment in 29 patients (66%), lidocaine infiltration in 11 patients (25%) and cement injection in 4 patients (9%). Operators' expectations of patients' VAS scores were mean 3.3 (median 3, range 1-6).

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

Introduction

Percutaneous vertebroplasty (PV) is increasingly used for management of pain associated with osteoporotic vertebral compression fractures (OVCF's), vertebral haemangiomas and osteolytic vertebral lesions (1).
Pain management during PV is subject to variation among operators: from local infiltration anesthesia only to general anesthesia supplied in the operating room. In a recent study (2), a protocol of titrated intravenous sedation with fentanyl and propofol, local infiltration anesthesia and monitoring of vital parameters resulted in good tolerance for the procedure.
In our hospital, we use local infiltration anesthesia as the only pain medication in patients undergoing PV for OVCF's. Most patients seem to tolerate the procedure well and only in few cases additional intravenous fentanyl is administered. In this study, we examined patients' subjective pain sensation during PV with our standard pain management protocol.

Methods

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

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

Percutaneous Vertebroplasty technique
One day before PV, patients were informed about the procedure by the attending radiology resident on the ward. During this consultation, the possibility to ask for additional pain medication during the procedure was emphasized.
PV's were performed by one of two experienced radiologists on a biplane angiographic system (Integris BN 3000 Neuro, Philips Healthcare, Best, The Netherlands). Ten mL of Lidocain 1% (Braun, Melsungen, Germany) was infiltrated from skin to periost of the targeted vertebral pedicles. Oxygen saturation and electrocardiogram was monitored by pulse oximetry. Via a bilateral transpedicular approach using 11- or 13-gauge needles, bone cement was alternating injected under continuous fluoroscopy using 1.0 mL syringes.

Pain evaluation

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

After the procedure the operator was asked what he or she expected what the VAS score of the patient would be.

Results

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

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

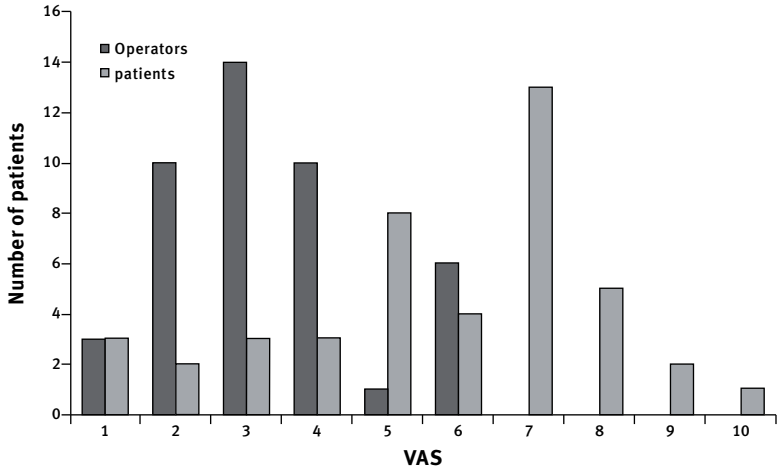


Figure. Patients' VAS and operators' expectation of patients' VAS of 44 patients during percutaneous vertebroplasty.

Discussion

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

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

Pain management during PV is subject to variation among operators and varies from local infiltration anesthesia only to general anesthesia in the operating room. Until now, two authors (2,5) concentrated on this subject. In a study of 20 patients (2), a protocol of fentanyl and titrated intravenous propofol allowed for a pain free procedure. No adverse advents were registered. Such a protocol might meet the criteria of a targeted analgosedative procedure that ensures comfort during PV without, as with general anesthesia, the need for longer hospitalization.

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

Conclusion

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

References

1. Voormolen MH, Mali WP, Lohle PN et al.
   Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR Am J Neuroradiol 2007; 28: 555-560

2. Della Puppa A, Andreula C, Frass M.
   Assisted sedation: a safe and easy method for pain-free percutaneous vertebroplasty. Minerva Anestesiol 2008;74:57-62

3. Haefeli M, Elfering A.
   Pain assessment. Eur Spine J 2006;15:S17-S24

4. Huskisson EC.
   Measurement of pain. Lancet 1974;2:1127-31

5. Sesay M, Tauzin-Fin P, Jeannin A et al.
   Median effective dose (ED50) of alfentanil for monitored anesthesia care of percutaneous vertebroplasty of osteoporotic fractures. J Neurosurg Anesthesiol 2009;21:165-169

CHAPTER 7

EFFECT OF CEMENT VOLUME ON CLINICAL RESPONSE OF PERCUTANEOUS VERTEBROPLASTY

RESULTS FROM VERTOS 2

NEURORADIOLOGY (AWAITING SUBMISSION)

Abstract

Background and Purpose: In Vertos II, an open label randomized controlled trial comparing vertebroplasty with conservative treatment in 202 patients with osteoporotic vertebral fractures, we analyzed the impact of cement volume on pain relief after percutaneous vertebroplasty.

Materials and Methods: Of 101 patients assigned to vertebroplasty in Vertos II, 43 patients had percutaneous vertebroplasty at a single vertebral level. Median and mean cement volume used for vertebroplasty was assessed. Relationship between injected cement volume and fracture location, fracture severity and type of treated vertebra were analyzed using Pearson $\chi 2$ test. The relation between injected cement volume and VAS at follow-up intervals was analysed for various volume cut-off points and displayed in a VAS versus time graph.

Results: Median and mean injected cement volumes were 3.4 and 3.6 ± 1.4 ml respectively, with a range of 1-9 ml. There was no correlation between injected cement volume and clinical response over time. Also fracture location, fracture severity and type of treated vertebra were not correlated with injected cement volume (respectively P=0.56, P=0.70 and P=0.34).

Conclusion: Clinical response of percutaneous vertebroplasty is not affected by differences in injected cement volume. There is also no correlation between injected cement volume and fracture location, fracture severity and type of treated vertebra.

Introduction

Percutaneous vertebroplasty is increasingly used in the treatment of painful osteoporotic vertebral compression fractures. There is considerable variance in technique among operators in performing vertebroplasty. An obvious variance is the uni- or bipedicular approach. Apart from that a large point of procedural variability lies in the volume of injected cement into the compressed vertebra. Significant variability in injected cement volumes is even present in the same operator. This may be related to several factors such as vertebral body size, ease of filling, the occurrence of cement leakage and the perception of sufficient filling. It is generally believed that larger volumes of cement lead to better clinical response through increased filling, increased strength and stiffness, and improved internal casting and immobilization of the fractured vertebra.
Little is known about the relation between injected cement volume and vertebroplasty outcomes. In this study, we analyze the impact of cement volume on pain relief after percutaneous vertebroplasty in selected patients who participated in the Vertos II trial, an open label randomized controlled trial comparing vertebroplasty with conservative treatment in 202 patients with osteoporotic vertebral fractures.

Materials and Methods

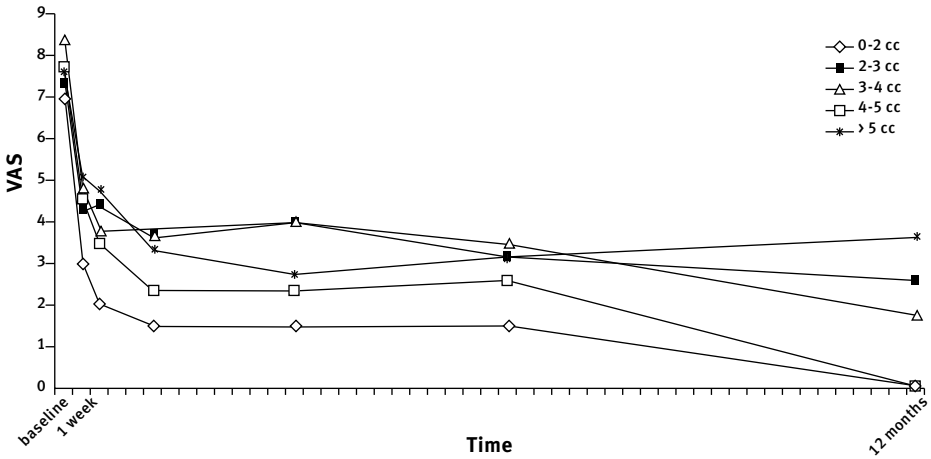
The patients for this study participated in the Vertos II trial (3), an open-label randomized controlled trial comparing vertebroplasty and conservative therapy for osteoporotic vertebral fractures. Between October 2005 and June 2008, 202 patients were randomized and 101 patients were assigned to percutaneous vertebroplasty. Informed consent was withdrawn after randomization by 6 patients. To reduce the confounding of outcome measures that would be introduced by including patients with multiple treated vertebral fractures, we included only those 43 patients with vertebroplasty at a single vertebral level.
In Vertos II, a visual-analog score for pain (VAS-score) was assessed at 1 day, 1 week, 1 month, 3 months, 6 months, and 1 year.
Median and mean injected cement volume used for vertebroplasty was assessed. We first analyzed a possible relation between injected cement volume and location of treated vertebra categorized as thoracic (T5-T10), thoracolumbar (T11-L2) and lumbar vertebrae (L3-L5) and fracture severity and fracture type according to Genant (4) by using Pearson $\chi 2$ test.

The relation between injected cement volume and VAS at the various follow-up intervals were analyzed with a general linear model for repeated measures and displayed in a VAS versus time graph for various volume cut-off points.

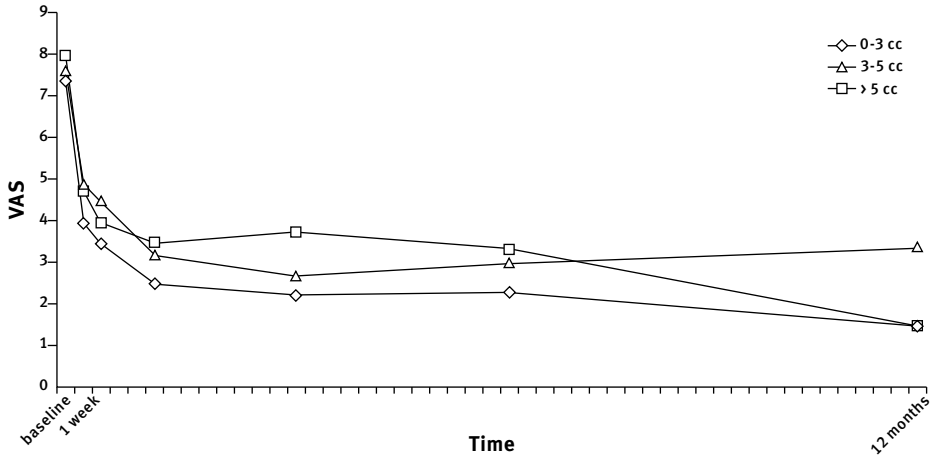
Results

Location of the treated vertebrae in the 43 patients with vertebroplasty at a single level was as follows: 5 thoracic, 32 thoracolumbar and 6 lumbar vertebrae. Median and mean injected cement volumes were 3.4 and 3.6 ± 1.4 ml respectively, with a range of 1-9 ml. Location, fracture severity and fracture type of treated vertebra were not correlated with injected cement volume (respectively P=0.56, P=0.70 and P=0.34).
The relation between injected cement volume for several volume cut-off points and VAS at various follow-up intervals is displayed in *Figure 1*. From these graphs it is apparent that there is no correlation between injected cement volume and clinical response over time.

a.



b.



c.

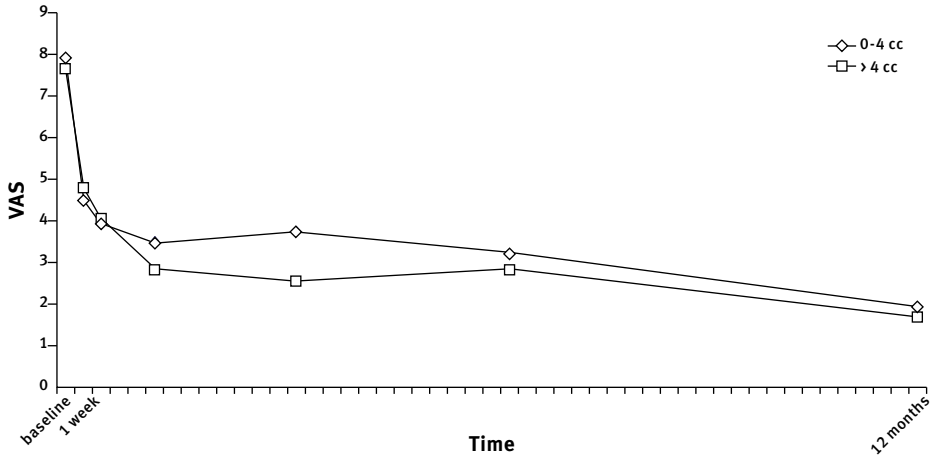


Figure 1. Relation between injected cement volume and VAS at various follow-up intervals.

a. 5 different subgroups of cement volumina

b. 3 different subgroups of cement volumina

c. 2 different subgroups of cement volumina

Conclusion

Clinical outcome of percutaneous vertebroplasty is not affected by differences in cement volume injected. There is no correlation between injected cement volume and fracture location, severity and type of treated vertebra.

Discussion

In this study, we found that there is no correlation between injected cement volume and clinical response over time. Injected cement volume was also not correlated with fracture location, fracture severity and type of treated vertebra.

The results of our study are consistent with the findings of other studies about technical issues of vertebroplasty. One should intuitively expect some type of dose response if cement is the active agent for pain reduction with more pain relief with injection of more cement. However, several previous studies were unable to find such a relation (1,5). Even little amounts of cement yielded good outcomes in some patients while some other patients with large injected volumes developed chronic pain. Apart from a lack of correlation on clinical response of injected cement volume, several other factors were also not related to outcome in previous studies (6-11) including operator experience, presence of marrow edema, pain at palpation, duration of the fracture, the use of one versus two needles or the use of a balloon (6–11).

Among these studies that commented on cement volumes used in vertebroplasty, only Kaufmann et al (5) limited the analysis to those patients who were treated at a single vertebral level. Also in our opinion each vertebral fracture probably plays a separate role in the symptoms of the patient. Failure of pain relief after vertebroplasty in patients who were treated at multiple levels may potentially represent failure of treatment at 1, 2 or all of these levels. To prevent confounding, we limited our analysis to those patients who were treated at a single vertebral level and thus yielded a relatively small study group.

It has been suggested from ex vivo studies of vertebral body strength and stiffness (12) that the amount of cement needed to relieve pain clinically may approximate the amount of cement needed to restore the vertebral body's pre-fracture mechanical properties. Our findings suggest that this is not necessarily the case and that fracture stabilization and, presumably, associated improvement in clinical outcome can occur without full restoration of pre-fracture properties of strength and stiffness of the vertebral body.

Our study confirms that operators need not feel compelled to achieve particular volumes of cement injected but should be guided by their clinical sense of what constitutes an adequate and safe fill of a compressed vertebral body.

References

1. Kaufmann TJ, Trout AT, Kallmes DF.
   The effects of cement volume on clinical outcomes of percutaneous vertebroplasty.
   AJNR Am J Neuroradiol 2006;27:1933-37

2. Hodler J, Peck D, Gilula LA.
   Midterm results after vertebroplasty: predictive value of technical and patient-related factors. Radiology 2003;227:662-68.

3. CAH Klazen, PNM Lohle, J de Vries et al.
   Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (Vertos II): an open-label randomised trial. Lancet 2010; 376:1085-1092

4. Genant HK, Wu CY, van KC, Nevitt MC.
   Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48

5. Al-Ali F, Barrow T, Luke K.
   Vertebroplasty: what is important and what is not. AJNR Am J Neuroradiol 2009;30:1835-183

6. McDonald RJ, Gray LA, Cloft H, Thielen KR, Kallmes DF.
   The effect of operator variability and experience in vertebroplasty outcomes. Radiology 2009;253:478-485

7. Brown DB, Glaiberman CB, Gilula LA, Shimony JS.
   Correlation between preprocedural MRI findings and clinical outcomes in the treatment of chronic symptomatic vertebral compression fractures with percutaneous vertebroplasty.
   AJR Am J Roentgenol 2005;184:1951-1955

8. Gaughen JR Jr, Jensen ME, Schweickert PA, Kaufmann TJ, Marx WF, Kallmes DF.
   Lack of preoperative spinous process tenderness does not affect clinical success of percutaneous vertebroplasty. J Vasc Interv Radiol 2002;13:1135-1138

9. Kaufmann TJ, Jensen ME, Schweickert PA, Marx WF, Kallmes DF.
   Age of fracture and clinical outcomes of percutaneous vertebroplasty. AJNR Am J Neuroradiol 2001; 22:1860-1863

10. Eck JC, Nachtigall D, Humphreys SC, Hodges SD.
    Comparison of vertebroplasty and balloon kyphoplasty for treatment of vertebral compression fractures: a meta-analysis of the literature. Spine J 2008;8:488-497

11. Kim AK, Jensen ME, Dion JE, Schweickert PA, Kaufmann TJ, Kallmes DF.
    Unilateral transpedicular percutaneous vertebroplasty: initial experience.
    Radiology 2002;222:737-741

12. Belkoff SM, Mathis JM, Jasper LE et al.
    The biomechanics of vertebroplasty: the effect of cement volume on mechanical behaviour.
    Spine 2003;28:1549-54.

CHAPTER 8

PERCUTANEOUS VERTEBROPLASTY IS NOT A RISK FACTOR FOR NEW OSTEOPOROTIC COMPRESSION FRACTURES

RESULTS FROM VERTOS II

AJNR AM J NEURORADIOL 2010;31:1447-50

Abstract

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

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

Results: After a mean follow-up of 11.4 months (median 12.0, range 1-24 months), 18 new VCF's occurred in 15 of 91 patients after PV and 30 new VCF's in 21 of 85 patients after conservative therapy. This difference was not significant ($p=0.44$). There was no higher fracture risk for adjacent versus distant vertebrae. Mean time to new VCF was 16.2 months after PV and 17.8 months after conservative treatment (log rank $p=0.45$). The baseline number of VCF's was the only risk factor for occurrence (OR 1.43; 95%CI 1.05-1.95) and number ($p=0.01$) of new VCF's. After conservative therapy, further height loss of treated vertebrae occurred more frequently (35 of 85 versus 11 of 91 patients, $p<0.001$) and was more severe ($p<0.001$) than after PV.

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

Introduction

Vertebral compression fractures (VCF's) are the most common fractures associated with osteoporosis (1). In the elderly population with osteoporosis, VCF's may lead to morbidity and even mortality due to invalidating back pain, decreased daily activity and increased days of bed rest (2;3). In addition, deterioration of stature such as severe thoracic kyphosis may contribute to morbidity by decreased pulmonary function or higher risk of falling. Fortunately, only a minority of VCF's cause such a severe pain that patients seek medical attention (4). When pain response to analgesics is insufficient during several weeks, Percutaneous Vertebroplasty (PV) is increasingly used as a minimally invasive technique to induce durable pain relief. However, some authors believe that PV is associated with a higher incidence of future new VCF's as a result of the augmented stiffness of the treated vertebra, related to the amount of injected cement or by cement leakage in the adjacent vertebral disc space (5-8). Others dispute this assumption and consider the incidence of new VCF's dependant on the presence and severity of osteoporosis (9-11). To elucidate this controversy, we assessed the incidence of new VCF's during follow-up in 202 patients with acute VCF's randomized to PV and conservative therapy from Vertos II. In addition, we assessed further height loss of the treated vertebrae with both therapies.

Methods

Patients

The detailed study design has previously been published (12). In short, we performed a randomized controlled trial comparing PV with conservative therapy in selected patients with acute VCF in five large teaching hospitals in the Netherlands and one in Belgium. Inclusion criteria were: (1) VCF on spine radiograph (minimal 15% loss of height), (2) level of VCF Th5 or lower, (3) back pain ≤ 6 weeks, (4) VAS-score ≥ 5 on a 0-10 scale, (5) bone edema of the fractured vertebral body on MRI, (6) focal tenderness on VCF level and (7) decreased bone density with T-scores ≤ -1. Exclusion criteria were: (1) severe cardio-pulmonary co-morbidity, (2) untreatable coagulopathy, (3) infection, (4) suspected alternative underlying malignancy, (5) radicular syndrome, (6) myelum compression syndrome, and (7) contraindication for MRI. The study protocol was approved by the institutional review board at each participating centre.

Procedures

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

Imaging

At baseline, radiography and Magnetic Resonance Imaging (MRI) of the spine was performed. Spine radiographs were repeated at one, three and twelve months follow-up. Two radiologists independently performed semi-quantitative and quantitative morphometric assessments at baseline and follow-up imaging (13;14). A new VCF was defined as a decrease of at least 4 mm in vertical dimension (15). Height loss in new VCF's was categorized as mild, moderate and severe. Distribution of new VCF's were classified as adjacent to a treated level, between treated levels and distant to a treated level (16). Further height loss during follow-up of treated baseline VCF's with bone edema was defined as height loss of 4 mm and more and categorized as moderate (4-7 mm) and severe (›8mm). Disagreement between observers was resolved in a consensus meeting. Because bone cement is radio-opaque, treatment assignment could not be blinded.

Statistical analysis

Patient characteristics were compared. T-test was used for means and Chi-square test for proportions. The incidence and timing of new VCF's was analysed using survival analysis. The cumulative incidence was calculated using Kaplan-Meier estimates. Logistic regression analysis was used to assess a possible relation between the incidence of new VCF's and the following factors: age, gender, randomization, baseline VAS-score, bone mineral density, number of prevalent fractures, fracture severity, number of vertebral levels treated, mean amount of bone cement injected per vertebra, cement leakage into the disk, cement leakage into the soft tissue around the vertebra, and cement leakage into the veins. Linear regression analysis was used to determine risk factors for the number of new VCF's. Analysis was by intention-to-treat.

Statistics were performed with SPSS, version 15.0.1. The Vertos II study is registered with ClinicalTrials.gov, with the number NCT00232466.

Results

Of 934 patients that were screened between October 2005 and June 2008, 202 met the inclusion criteria and agreed to participate in the study. Of the 202 participating patients, 101 were assigned to PV and 101 to conservative therapy. Baseline characteristics were similar (*Table 1*). Informed consent was withdrawn after randomization by six patients assigned to conservative therapy and two patients assigned to PV. These patients had no therapy and follow-up could not be obtained. Six patients assigned to PV did not receive this treatment because of poor health (n=3) and spontaneous pain relief (n=3). Follow-up was obtained in 5 of these 6 patients. Ten patients assigned to conservative therapy with ongoing invalidating pain requested and received PV during follow-up. Finally, 81% of the participants completed the follow-up at 1 year.

Table 1: Baseline characteristics of 202 randomized patients.

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

PV was performed in 98 patients on 134 vertebras in 103 procedures. The mean volume of injected cement per vertebral body was 4.10 cc (range 1-9 cc). CT scan of the 134 treated vertebral bodies showed cement leakage in 97

(72%). Most leakages were into adjacent discs or segmental veins, none into the spinal canal. All patients remained asymptomatic.

New VCFs during follow-up

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

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

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

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

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

Table 2. Distribution of new VCFs.

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

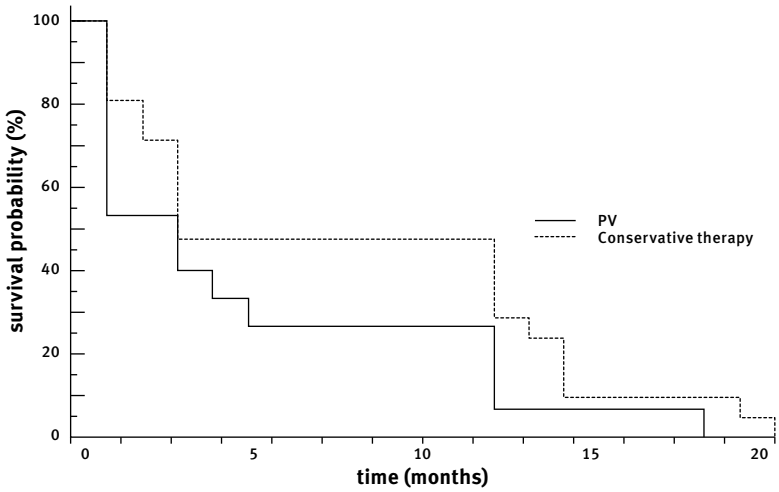


Figure 1. Kaplan-Meier survival curve for timing of new VCFs after PV and conservative therapy.

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

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

Discussion

We found that PV does not increase the risk of new vertebral fractures in the first year. Not only was the incidence of new VCF's similar after PV and conservative therapy, but also the distribution of the new VCF's. After PV, there was no higher fracture risk for adjacent versus distant vertebrae. Both after PV and conservative therapy, the only risk factor for the occurrence of new VCF's was the number of VCF's at baseline. This number of baseline VCF's in turn is associated with the severity of osteoporosis. Thus, the occurrence of new VCF's is due to the ongoing osteoporosis only and not to the type of therapy. Our study shows that PV prevented further height loss of the treated fractured vertebral bodies in most patients. Apparently, the injected cement strengthened the fractured vertebral body. This is an important advantage in the

prevention of morbidity associated with deterioration of stature such as severe kyphosis with decreased pulmonary function. PV not only decreased the incidence but also the severity of further height loss in affected vertebra thus further contributing to preservation of stature.
Our study is the first randomized controlled trial evaluating the risk of new VCF's in the first year after PV in a large patient cohort. The only limitation of our study is the inability to blind treatment assignment due to the radio-opacity of the bone cement used in PV. A study with a comparable design is the FREE study that compared kyphoplasty with conservative treatment in 300 patients with acute VCF's (17). Kyphoplasty involves an inflatable bone tamp to preform a space for the bone cement instead of a direct cement injection into the vertebral body as in PV. In this FREE study also an equal incidence of new VCF's was found after kyphoplasty and conservative treatment but risk factors for new VCF's, distribution of new VCF's and further height loss of treated VCF's at baseline were not analyzed.
The findings of our study and the FREE study are in concordance with other studies (9-11). On the other hand, some studies have reported an increased risk of new VCF's after PV (5;6;8;18). However, most of these studies are small non-randomized follow-up only studies, lacking a control group without intervention.
Some non-controlled follow-up studies after PV reported new VCF's to be more often located adjacent to the vertebroplasty level, allegedly contributed to the increased dimensional stability of the cemented vertebral body (6;8;19;20). However, in our randomized study no difference in location distribution of new VCF's was found after PV and conservative therapy. In addition, after PV the risk for a new VCF adjacent to the cemented level was equal to the risk of a new VCF at a distant level.
In our study cement leakage after PV outside the vertebral body was frequently detected with CT. Most leakages were into adjacent discs or segmental veins, none into the spinal canal. All patients remained asymptomatic. Cement leakage was not associated with occurrence of new VCF's during follow-up, in contradiction to some other studies were leakage into an adjacent disk was considered a risk factor for new VCF's (5;21).

Conclusion

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

References

1. Johnell O, Kanis JA.
   An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int 2006;17:1726-1733

2. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR.
   Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med 1999;159:1215-12203

3. Hasserius R, Karlsson MK, Jonsson B, Redlund-Johnell I, Johnell O.
   Long-term morbidity and mortality after a clinically diagnosed vertebral fracture in the elderly--a 12- and 22-year follow-up of 257 patients. Calcif Tissue Int 2005;76:235-2424

4. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ, III.
   Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. J Bone Miner Res 1992;7:221-227

5. Lin EP, Ekholm S, Hiwatashi A, Westesson PL.
   Vertebroplasty: cement leakage into the disc increases the risk of new fracture of adjacent vertebral body. AJNR Am J Neuroradiol 2004;25:175-180

6. Grados F, Depriester C, Cayrolle G, Hardy N, Deramond H, Fardellone P.
   Long-term observations of vertebral osteoporotic fractures treated by percutaneous vertebroplasty. Rheumatology (Oxford) 2000;39:1410-1414

7. Baroud G, Heini P, Nemes J, Bohner M, Ferguson S, Steffen T.
   Biomechanical explanation of adjacent fractures following vertebroplasty.
   Radiology 2003;229:606-607

8 Mudano AS, Bian J, Cope JU, et al.
   Vertebroplasty and kyphoplasty are associated with an increased risk of secondary vertebral compression fractures: a population-based cohort study. Osteoporos Int 2009;20:819-826

9. Al-Ali F, Barrow T, Luke K.
   Vertebroplasty: what is important and what is not. AJNR Am J Neuroradiol 2009;30:1835-1839

10. Hierholzer J, Fuchs H, Westphalen K, Baumann C, Slotosch C, Schulz R.
    Incidence of symptomatic vertebral fractures in patients after percutaneous vertebroplasty. Cardiovasc Intervent Radiol 2008;31:1178-1183

11. Diamond TH, Bryant C, Browne L, Clark WA.
    Clinical outcomes after acute osteoporotic vertebral fractures: a 2-year non-randomised trial comparing percutaneous vertebroplasty with conservative therapy.
    Med J Aust 2006;184:113-117

12. Klazen CA, Verhaar HJ, Lampmann LE, et al.
    VERTOS II: percutaneous vertebroplasty versus conservative therapy in patients with painful osteoporotic vertebral compression fractures; rationale, objectives and design of a multicenter randomized controlled trial. Trials 2007;8:33

13. Genant HK, Wu CY, van KC, Nevitt MC.
Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-1148

14. Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton LJ, III.
Classification of vertebral fractures. J Bone Miner Res 1991;6:207-215

15. Black DM, Cummings SR, Karpf DB, et al.
Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-1541

16. Pitton MB, Herber S, Bletz C, et al.
CT-guided vertebroplasty in osteoprotic vertebral fractures: incidence of secondary fractures and impact of intradiscal cement leakages during follow-up. Eur Radiol 2008;18:43-50

17. Wardlaw D, Cummings SR, Van MJ, et al.
Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet 2009;373:1016-1024

18. Syed MI, Patel NA, Jan S, Harron MS, Morar K, Shaikh A.
New symptomatic vertebral compression fractures within a year following vertebroplasty in osteoporotic women. AJNR Am J Neuroradiol 2005;26:1601-1604

19. Trout AT, Kallmes DF, Kaufmann TJ.
New fractures after vertebroplasty: adjacent fractures occur significantly sooner. AJNR Am J Neuroradiol 2006;27:217-223

20. Uppin AA, Hirsch JA, Centenera LV, Pfiefer BA, Pazianos AG, Choi IS.
Occurrence of new vertebral body fracture after percutaneous vertebroplasty in patients with osteoporosis. Radiology 2003;226:119-124

21. Komemushi A, Tanigawa N, Kariya S, et al.
Percutaneous vertebroplasty for osteoporotic compression fracture: multivariate study of predictors of new vertebral body fracture. Cardiovasc Intervent Radiol 2006;29:580-585

CHAPTER 9

GENERAL DISCUSSION

General discussion

Natural course of osteoporotic vertebral compression fractures
We found that 40% of conservatively treated patients with acute osteoporotic vertebral compression fractures (VCF's) still had disabling pain after one year. Optimal pain medication and supportive therapy was apparently not sufficient for pain relief in a large proportion of these conservatively treated patients. On the other hand, 60% of patients had sufficient pain relief with conservative therapy, almost all within 3 months after the acute fracture. We could not find any predictors for the development of chronic pain. In particular, baseline pain scores, number of fractures and degree or shape of vertebral compression had no influence on the development of chronic pain. The proportion of patients with chronic pain after conservative treatment in the present study is higher than in previous studies. This can partly be explained by differences in definition of chronic pain: we defined chronic pain as VAS-scores 4 or higher while in other studies, including Vertos 2, patients with insufficient decrease in VAS-scores were considered to have chronic pain. In these studies, patients with sufficient pain relief could have absolute VAS-scores at follow-up of 4 or higher. In the natural history of pain after an acute vertebral compression fracture, the time point of 3 months may be of clinical significance.

Percutaneous vertebroplasty technique
Pain management during percutaneous vertebroplasty (PV) is subject to variation among operators. We found that during the PV procedure from the patients perspective the use of infiltration analgesia as single pain medication is mostly not sufficient to make the procedure tolerable in the perspective of the patient: three quarters of patients indicated a VAS score of 5 or more. Despite this high VAS score, patients did not request for additional medication during the procedure. The operators who performed the PV's did not have the impression that pain was apparently unbearable: in many cases they were surprised by the patients' high VAS scores after the procedure. Apparently, there is a discrepancy between pain as perceived by the patient and the impression of pain perception by the operator. We believe the patients' relatively high mean VAS score in our study is a good representative of the experienced pain during PV, and the operators impression of pain experienced by the patient is of little importance. The results of this study has made us realize that lidocaine infiltration only is for most patients not sufficient for pain reduction during the procedure. We adjusted our pain medication protocol and now administer Fentanyl in all patients.

Percutaneous vertebroplasty and CT for perivertebral cement leakage
Cement leakage during PV seems to be largely inevitable according to this thesis and in the literature (1,2). Comparison of frequency of cement leakage between studies is hampered by differences in methods used. In the Vertos 2 perivertebral cement leakage occurred in more than half of the treated vertebrae. Most leakages were in perivertebral venous structures, leakage into the disk or perivertebral soft tissues was infrequent. Cement leakage occurred more frequent with higher volumes of injected cement. Follow-up CT after almost 2 years showed that late migration of leaked cement deposits did not occur. Clinically, patients remained asymptomatic. Our findings suggest that standard post-procedural CT scan of the treated vertebra is not warranted and should be confined to symptomatic patients only. Omitting CT from the PV protocol is cost-effective and reduces radiation burden. With proper use of technique and fluoroscopy, clinical relevant cement leakage should be avoided.

Percutaneous vertebroplasty and pulmonary cement embolism
Fluoroscopic venous cement migration to the lungs is seen infrequently. On the other hand, clinically silent pulmonary cement embolism as seen on native chest CT scan occurred frequently. These findings suggest that with fluoroscopy virtually all migration of small cement quantities remain undetected. Pulmonary cement emboli were small and scattered in peripheral portions of the lungs and caused no reactive pulmonary changes after 2 years. There were no cement deposits in the heart and large pulmonary vessels. Cement leakage in the azygos vein was the only risk factor for pulmonary cement embolism. Remarkably, the volume of injected cement was not correlated with the occurrence of pulmonary cement embolism. With proper use of fluoroscopy and limited volume of PMMA injected in repeated small quantities, pulmonary cement embolism can occur and if so, only very small quantities of PMMA will be transported to the pulmonary arteries without clinical sequelae. Therefore, standard chest radiographs or CT after PV is not warranted.

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

Percutaneous vertebroplasty and cement volume
In our study, clinical response of percutaneous vertebroplasty was not affected by differences in injected cement volume. There was also no correla-

tion between injected cement volume and fracture location, fracture severity and type of treated vertebra. Our study confirms that operators need not feel compelled to achieve particular volumes of cement injected. There have been case reports of severe or fatal clinical complications of pulmonary cement embolism (3-8). In all of these cases there was evidence of large injected total cement volume (9-15 ml) or a large amount of cement in the heart or central pulmonary arteries. We think the operators should be guided by their clinical sense of what constitutes an adequate and safe fill of a compressed vertebral body with proper use of fluoroscopy and limited volume of cement injected in repeated small quantities.

References

1. Yeom JS, Kim WJ, Choy WS.
   Leakage of cement in percutaneous transpedicular vertebroplasty for painful osteoporotic compression fractures. J Bone Joint Surg Br 85:83-89

2. Schmidt R, Cakir B, Mattes T.
   Cement leakage during vertebroplasty: an underestimated problem? Eur Spine J 2005;14:466-473

3. Chen HL, Wong CS, Ho ST et al.
   A lethal pulmonary embolism during percutaneous vertebroplasty. Anesth Analg 2002; 95: 1060-1062

4. Francois K, Taemans Y, Poffyn B et al.
   Successful management of a large pulmonary cement embolus after percutaneous vertebroplasty. Spine 2003;28; E424-425

5. Stricker K, Orler R, Yen K et al.
   Severe hypercapnia due to pulmonary embolism of polymethylmathacrylate during vertebroplasty. Anesth Analg 2004;98:1184-1186

6. Yoo KY, Jeong SW, Yoon W et al.
   Acute respiratory distress syndrome associated with pulmonary cement embolism following percutaneous vertebroplasty with polymethylmethacrylate. Spine 2004;29:E294-297

7. Monticelli F, Meyer HJ, Tutsch-Bauer E.
   Fatal pulmonary cement embolism following percutaneous vertebroplasty (PVP). Forensic Science International 2005;149:35-38

8. Freitag M, Gotschalk A, Schuster M et al.
   Pulmonary embolism caused by polymethylmethacrylate during percutaneous vertebroplasty in orthopaedic surgery. Acta Anaesthesiol Scand 2006;50:248-251

CHAPTER 10

SUMMARY

Summary

In **Chapter 1**, an outline of this thesis is given.

In **Chapter 2** we analyzed the natural course of conservatively treated osteoporotic vertebral compression fractures from Vertos II. We assessed the proportion of patients that developed chronic back pain and possible risk factors. We followed 95 conservatively treated patients until sufficient pain relief, defined as a VAS-score ≤ 3. During one year of follow-up, 57 of 95 patients (60%) had sufficient pain relief. Thirty-eight patients (40%) still had pain with VAS-scores 4 or higher at last follow-up interval of 12 months despite use of higher class pain medication. Statistical analysis showed no risk factors.
We concluded that most conservatively treated patients with acute osteoporotic vertebral compression fractures had sufficient pain relief during the first 3 months. However, after one year a substantial proportion of patients still had disabling pain despite higher class pain medication used. There were no predictors for the development of chronic pain. Patients with continuing pain 3 months or more after the fracture may be candidates for vertebroplasty.

In **Chapter 3** we retrospectively assessed frequency and outcome of pulmonary polymethylmethacrylate (PMMA) embolism during PV in a large patient cohort and evaluated relationship of volume of injected PMMA with occurrence of pulmonary PMMA embolism. Between 2001 and 2007, 502 osteoporotic compression fractures in 299 consecutive patients were treated with PV. PMMA embolism was defined as venous PMMA migration visible on biplane fluoroscopy during PV. CT scan was performed immediately and one year after PMMA migration. Venous PMMA migration occurred during 11 PV's in 11 patients (2.2%, 95% CI 1.2-3.9%). CT scan in 9 patients demonstrated small peripheral pulmonary PMMA emboli. All 11 patients remained asymptomatic during one year follow up. Repeat CT scan after one year in 6 patients demonstrated unchanged pulmonary PMMA deposits without late reactive changes. Mean cement volume in patients with and without PMMA embolism was not different: 3.6 ± 1.06 ml versus 3.3 ± 1.16 ml (P=0.43). Similar comparison for thoracic and thoracolumbar vertebrae yielded P values of 0.07 and 0.9.
We concluded that pulmonary PMMA embolism during PV is an infrequent complication without clinical sequelae. After one year, no pulmonary reaction is seen on CT. No definite relationship of PMMA emboli with injected cement volume could be established.

In **Chapter 4** we assessed the true incidence of pulmonary cement embolism (PCE) by performing native chest CT during follow-up in a large proportion of

patients of the Vertos II trial. After a mean follow-up of 22 months (median 21, range 6-42 months), 54 of 78 patients (69%) with 80 vertebrae treated with PV had native chest CT to detect possible PCE. Possible risk factors for PCE were evaluated. PCE was detected in 14 of 54 patients (26%, 95% CI, 16-39%). All patients were asymptomatic. Cement emboli were small and randomly distributed in peripheral small vessels. There were no reactive pulmonary changes. Cement leakage in the azygos vein was the only risk factor for the occurrence of PCE (OR 43, 95% CI 5-396).
We concluded that small and clinically silent PCE occurred in a quarter of patients treated with PV. Cement leakage into the azygos vein was the only risk factor. Over time, these small cement emboli remained inert without inflammatory pulmonary response. Standard post-procedural CT or chest radiographs are not necessary.

In **Chapter 5** we assessed the incidence and extend of late cement migration in a large consecutive patient cohort. We used baseline and follow-up CT scans. Patients assigned to PV had baseline post-procedural CT scans of the treated vertebral bodies. After a mean follow-up of 22 months, 54 of 78 patients (69%) had follow-up CT. Perivertebral cement leakage occurred in 64 of 80 treated vertebrae (80%, 95% CI 70 to 87%). All patients remained asymptomatic. Perivertebral venous leakage was present in 56 vertebrae (88%), mostly in the anterior external venous plexus (46 of 56, 82%). Discal leakage occurred in 22 of 64 vertebrae (34%) and soft tissue leakage in 2 of 64 (4%). Mean injected cement volume in vertebrae with leakage was higher (4.5 versus 3.7 cc, p=0.04). Follow-up CT scan showed unchanged perivertebral cement leakages without late cement migration.
We concluded that perivertebral cement leaks during PV for osteoporotic vertebral compression fractures occurred frequently in the Vertos II trial. Cement leakage occurred more frequently with higher injected volumes. However, all patients remained asymptomatic and late cement migration during follow-up did not occur. Standard post-procedural CT of the treated vertebral body in PV is not necessary.

In **Chapter 6** we evaluated the effectiveness of local infiltration anesthesia as the only pain medication. From September 2008 to March 2009, 44 consecutive patients with symptomatic osteoporotic vertebral compression fractures were included in the study. Mean VAS score was 5.7 (median 6, range 1-10). Seventeen patients (39%), with a mean VAS score of 7.3 (range 5-10), indicated lidocaïne infiltration was insufficient. Placing the needles was specified as the most painful moment in 29 patients (66%), lidocaïne infiltration in 11 patients (25%) and cement injection in 4 patients (9%). Operators' expectations of patients' VAS scores were mean 3.3 (median 3, range 1-6).

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

In **Chapter 7** we analyzed the impact of cement volume on pain relief after PV in the Vertos II trial. Of 101 patients assigned to vertebroplasty in Vertos II, 43 patients had PV at a single vertebral level. Median and mean injected cement volumes were 3.4 and 3.6 ± 1.4 ml respectively, with a range of 1-9 ml. There was no correlation between injected cement volume and clinical response over time. Also fracture location, fracture severity and type of treated vertebra were not correlated with injected cement volume (respectively P=0.56, P=0.70 and P=0.34).
We concluded that clinical response of percutaneous vertebroplasty is not affected by differences in injected cement volume. There is also no correlation between injected cement volume and fracture location, fracture severity and type of treated vertebra.

In **Chapter 8** we assessed new vertebral compression fractures after PV during follow-up in the Vertos II trial. Incidence, distribution and timing of new vertebral compression fractures during follow-up were assessed from spine radiographs. In addition, further height loss during follow-up of treated vertebral compression fractures was measured. After a mean follow-up of 11.4 months (median 12.0, range 1-24 months), 18 new VCF's occurred in 15 of 91 patients after PV and 30 new VCF's in 21 of 85 patients after conservative therapy. This difference was not significant (P=0.44). There was no higher fracture risk for adjacent versus distant vertebrae. Mean time to new VCF was 16.2 months after PV and 17.8 months after conservative treatment. Baseline number of VCF's was the only risk factor for occurrence (OR 1.43; 95%CI 1.05-1.95) and number (P=0.01) of new vertebral compression fractures. After conservative therapy, further height loss of treated vertebrae occurred more frequently (35 of 85 versus 11 of 91 patients, P<0.001) and was more severe (P<0.001) than after PV.
We concluded that the incidence of new vertebral compression fractures was not different after PV compared with conservative therapy after a mean of 11.4 months follow-up. The only risk factor for new vertebral compression fractures was the number of vertebral compression fractures at baseline. PV contributed to preservation of stature by decreasing both incidence and severity of further height loss in treated vertebra.

In **Chapter 9** the results of the different aspects of percutaneous vertebroplasty are interpreted and discussed.

CHAPTER 10

SAMENVATTING IN HET NEDERLANDS

Samenvatting in het Nederlands

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

In **Hoofdstuk 2** hebben we het natuurlijk beloop van de conservatief behandelde patiënten met osteoporotische wervelfracturen uit de Vertos II trial geanalyseerd. We hebben het aantal patiënten vastgesteld dat chronische rugpijn ontwikkelde en de risicofactoren hiervoor. We volgden 95 conservatief behandelde patiënten in de tijd tot het moment dat voldoende pijnafname optrad, gedefinieerd als VAS-score ≤ 3. Tijdens 1 jaar follow-up toonden 57 van de 95 patiënten (60%) voldoende pijnafname. Na 12 maanden follow-up hadden 38 patiënten (40%) nog VAS-scores van 4 of hoger ondanks een hogere klasse pijnmedicatie. Er werden geen risicofactoren gevonden.
We concludeerden dat de meeste conservatief behandelde patiënten met acute osteoporotische wervelfracturen voldoende pijnafname hadden gedurende de eerste 3 maanden follow-up. Echter, een substantiële groep patiënten had nog pijnklachten na 1 jaar ondanks een hogere klasse pijnmedicatie. Er werden geen risicofactoren voor chronische pijn aangetoond. Patiënten met persisterende pijn 3 maanden of meer na het moment van de wervelfractuur kunnen een kandidaat zijn voor percutane vertebroplastiek.

In **Hoofdstuk 3** hebben we bij een grote groep patiënten retrospectief de frequentie en klinische uitkomst bepaald van pulmonale polymethylmethacrylaat (PMMA) emboli tijdens PV. Relatie tussen volume geïnjecteerde PMMA en optreden van pulmonale PMMA emboli werd onderzocht. Tussen 2001 en 2007, werden 502 osteoporotische wervelinzakkingen bij 299 opeenvolgende patiënten behandeld met PV. PMMA embolus werd gedefinieerd als veneuze PMMA migratie zichtbaar tijdens biplane fluoroscopie tijdens PV. Een CT scan werd gemaakt direct na de procedure alsmede 1 jaar na PMMA migratie. Veneuze PMMA migratie trad op tijdens 11 PV's bij 11 patiënten (2.2%, 95% CI 1.2-3.9%). De CT scan bij 9 patiënten toonde kleine perifere PMMA emboli. Alle patiënten bleven asymptomatisch gedurende 1 jaar follow-up. Controle CT scan na 1 jaar bij 6 patiënten toonde onveranderde PMMA deposities zonder late reactieve pulmonale veranderingen. Gemiddelde cement volume bij patiënten met en zonder PMMA emboli was niet significant: 3.6 ± 1.06 ml versus 3.3 ± 1.16 ml (P=0.43). Een zelfde vergelijking voor thoracale en thoracolumbale wervelfracturen resulteerde in P-waarden van 0.07 and 0.9. We concludeerden dat pulmonale PMMA emboli tijdens PV een niet frequente complicatie is en zonder klinische consequenties. Na 1 jaar is geen pulmonale reactie te zien op een CT scan. Er bestaat geen relatie tussen PMMA emboli en volume geïnjecteerde PMMA.

In **Hoofdstuk 4** hebben we de werkelijke incidentie van pulmonale cement emboli bepaald door een blanco CT thorax te verrichten tijdens follow-up bij een grote groep patiënten van de Vertos II trial. Na een gemiddelde follow-up van 22 maanden (mediaan 21, range 6-42 maanden), kregen 54 van de 78 patiënten (69%) met 80 wervelfracturen en behandeld met PV een blanco CT thorax voor het detecteren van mogelijke pulmonale cement emboli. Mogelijke risicofactoren werden geëvalueerd. Pulmonale cement emboli werden ontdekt bij 14 van de 54 patiënten (26%, 95% CI, 16-39%). Alle patiënten waren asymptomatisch. Het waren kleine willekeurig verspreide cement emboli in perifere kleine vaten. Er waren geen reactieve pulmonale veranderingen. Cement lekkage in de vena azygos was de enige risicofactor voor het optreden van pulmonale cement emboli (OR 43, 95% CI 5-396).
We concludeerden dat kleine en asymptomatische pulmonale cement emboli optraden bij een kwart van de met PV behandelde patiënten. Cement lekkage in de vena azygos was de enige risicofactor. Deze kleine cement emboli zijn inert en veroorzaakten geen pulmonale reactie. Het standaard verrichten van postprocedurele CT of conventionele röntgenfoto van de thorax is niet noodzakelijk.

In **Hoofdstuk 5** hebben we gekeken naar de incidentie van late cement migratie bij een grote groep met opeenvolgende patiënten. We gebruikten baseline en follow-up CT scans. PV patiënten hadden een postprocedurele CT scan van de behandelde wervelfractuur. Na een gemiddelde van 22 maanden hadden 54 van de 78 patiënten (69%) een follow-up CT. Perivertebrale cement lekkage trad op bij 64 van de 80 behandelde wervelfracturen (80%, 95% CI 70-87%). Alle patiënten waren asymptomatisch. Perivertebrale veneuze lekkage was aanwezig in 56 wervels (88%), het meest in de anterieure externe veneuze plexus (46 van de 56, 82%). Lekkage naar de discus intervertebralis werd gezien bij 22 van de 64 wervels (34%) en lekkage naar de weke delen bij 2 van de 64 (4%). Gemiddeld geïnjecteerde cement volume in wervels met lekkage was hoger (4.5 versus 3.8 cc, P=0.04). Follow-up CT scan toonde onveranderde perivertebrale cement lekkage zonder late cement migratie.
We concludeerden dat perivertebrale cement lekkage tijdens PV voor osteoporotische wervelfracturen frequent optrad in de Vertos II trial. Cement lekkage trad meer op bij hogere geïnjecteerde cement volumina. Alle patiënten waren asymptomatisch en late cement migratie trad niet op tijdens follow-up. Standaard postprocedurele CT scan van de behandelde wervelfractuur is niet noodzakelijk.

In **Hoofdstuk 6** hebben we de effectiviteit van locale anaesthesie geëvalueerd. Van september 2008 tot maart 2009 werden 44 opeenvolgende patiënten geïncludeerd met symptomatische osteoporotische wervelfracturen. Gemid-

delde VAS score was 5.7 (mediaan 6, range 1–10). Zeventien patiënten (39%), met een gemiddelde VAS score van 7.3 (range 5-10), vonden locale anaesthesie insufficiënt. Het plaatsen van de naalden werd gespecificeerd als meest pijnlijke moment bij 29 patiënten (66%), lidocaïne infiltratie bij 11 patiënten (25%) en cement injectie bij 4 patiënten (9%). De verwachte VAS score van de patiënt, gescoord door de operateur, was 3.3 (mediaan 3, range 1-6).
We concludeerden dat lokale anaesthesie tijdens PV door een substantiële groep patiënten als insufficiënt werd ervaren. De pijnsensatie van de patiënt werd niet correct geïnterpreteerd door de operateur.

In **Hoofdstuk 7** hebben we de relatie tussen cementvolume en pijnafname na PV geanalyseerd in de Vertos II trial. Van de 101 met PV behandelde patiënten kregen er 43 PV voor 1 wervelfractuur. De mediane en gemiddelde cement volumina waren respectievelijk 3.4 en 3.6 ± 1.4 ml, met een range van 1-9 ml. Er bestond geen correlatie tussen geïnjecteerde cement volume en klinische respons in tijd. Fractuur locatie, gradering van de wervelfractuur en type wervelfractuur waren niet gecorreleerd aan cementvolume (respectievelijk P=0.56, P=0.70 and P=0.34).
We concludeerden dat klinische respons van PV niet beïnvloed werd door cementvolume. Er bestaat geen correlatie tussen verschillend geïnjecteerde cement volumina en fractuur locatie, gradering van wervelfractuur of type wervelfractuur.

In **Hoofdstuk 8** beschrijven we de incidenties van nieuwe wervelfracturen na PV gedurende follow-up in de Vertos II trial. Incidentie, distributie en timing van nieuwe wervelfracturen tijdens follow-up werden verkregen door conventionele opnamen van de wervelkolom. Progressief hoogteverlies van een wervelfractuur werd gemeten. Na een gemiddelde follow-up van 11.4 maanden (mediaan 12.0, range 1-24 maanden), traden 18 nieuwe wervelinzakkingen op bij 15 van de 91 patiënten na PV en 30 nieuwe wervelfracturen bij 21 van de 85 patiënten na conservatieve therapie. Dit verschil is niet significant (P=0.44). Er is geen hoger fractuurrisico voor aanliggende wervels in vergelijking met wervels op afstand. Gemiddelde tijd tot een nieuwe wervelfractuur is 16.2 maanden na PV en 17.8 maanden na conservatieve therapie. Aantal wervelfracturen op baseline was de enige risicofactor voor het optreden van (OR 1.43; 95%CI 1.05-1.95) en aantal (P=0.01) nieuwe wervelfracturen. Progressief hoogteverlies van de behandelde wervelfractuur trad vaker (35 of 85 versus 11 of 91 patiënten, P<0.001) op na conservatieve therapie en was ook ernstiger (P<0.001) dan na PV.
We concludeerden dat ten aanzien van incidentie van nieuwe wervelfracturen na een gemiddelde follow-up van 11.4 maanden er geen verschil bestaat tussen PV en conservatieve therapie. De enige risicofactor voor een nieuwe

wervelfractuur is het aantal wervelfracturen op baseline. Pv draagt bij tot preservatie van de houding door vermindering van verder hoogteverlies van de behandelde wervel.

In **Hoofdstuk 9** worden de resultaten van de verschillende aspecten van de PV geïnterpreteerd en bediscussieerd.

CHAPTER 10

DANKWOORD

Dankwoord

CHAPTER 10

CURRICULUM VITAE

Curriculum vitae

Alexander Venmans was born on the 24st of June, 1978 in Tilburg, The Netherlands. After graduating high school in 1996 at Theresia Lyceum in Tilburg, he studied pharmacy for one year at the University of Utrecht. From 1997 he studied medicine at the Academic Medical Centre in Amsterdam and obtained his medical degree in 2004. In 2004 he started his radiology residence at the St. Elisabeth Hospital in Tilburg and his PhD in 2007 under supervision of Prof. Dr. W.P.Th.M. Mali, Prof.Dr. W.J.J. van Rooij and Dr. P.N.M. Lohle. He completed his residency in 2009.