# Percutaneous vertebroplasty for painful long-standing osteoporotic vertebral compression fractures : benefits, risks and optimization

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# CHAPTER 9

## General discussion

*Relevance of thesis' findings in relation to the current status of the evidence for percutaneous vertebroplasty*

*Partially based on:*

*M.J. Nieuwenhuijse, A.R. van Erkel and P.D.S. Dijkstra*
*Vertebroplastiek nog niet afgeschreven.*
*Med Contact. 2010; 65(10):459-462.*

*and*

*M.J. Nieuwenhuijse and P.D.S. Dijkstra*
*Vertebroplasty: a treatment option for osteoporotic vertebral fractures.*
*Ned Tijdschr Geneeskd. 2010; 154:2199.*

## 9.1 Introduction

Before elaborating on the findings presented in this thesis, two aspects should be emphasized for a correct interpretation and implementation of its results.

First, all patients in all studies received Percutaneous VertebroPlasty (PVP) as treatment for one or more painful Osteoporotic Vertebral Compression Fractures (OVCFs) only after a stringent selection procedure. All patients had to fulfill a 'triad of indication' which maximizes the likelihood of pain originating from a vertebral fracture [1–7]: I) Focal back pain in the midline which is exacerbated by local pressure during physical examination; II) The location of the focal back pain corresponded to the location of a fracture on spinal radiographs; III) The fractured vertebral body showed bone marrow edema on Magnetic Resonance Imaging (MRI) scans.

Second, all patients had painful *long-standing* OVCFs, i.e. painful subacute and chronic OVCFs. All patients received at least two months of appropriate conservative treatment (analgesics, bracing, short-term bed rest) of the painful OVCF in order to await the possible onset of the favorable natural course of the (acute) OVCF. A favorable natural course occurs in 70-80% of the OVCFs and is characterized by a substantial decrease in pain and increase in function during the first two months after onset of symptoms [8–12]. It is our treatment philosophy that the possible onset of this favorable natural course should be awaited and that vertebral augmentation is a treatment option in those patients who do not exhibit this natural course and respond insufficiently to conservative treatment.

Consequently, due to these two aspects the results and conclusions from this thesis are only directly applicable in this selected group of patients and its generalizability to other patient groups cannot be guaranteed. However, since we consider this carefully selected group to represent the patients who are most likely to benefit optimally from PVP, the results and conclusions in this thesis are of importance to clinical practice.

## 9.2 Main finding and perspective

One important overall finding of the research presented in this thesis is the fact that patients with painful long-standing OVCFs benefit from PVP. An immediate, clinically relevant and durable decrease in back pain was found, combined with a relevant increase in health-related quality of life. Furthermore, the symptomatic complication rate was low (2.3%).

This result gains importance in light of the findings of the first three large randomized clinical trials published recently [13–15]. These trials were the natural next step in creation of the body of evidence for PVP as a treatment modality for painful OVCFs. The results of these trials were in some cases unexpected and all three trials will have a major impact on the position of PVP as a treatment modality for painful OVCFs. As such, the findings presented in this thesis cannot be fully appreciated without proper knowledge of these trials and therefore these three randomized trials are discussed briefly.

### 9.2.1 Placebo-controlled randomized trials

Two placebo-controlled randomized clinical trials, published in August 2009 in the prestigious *New England Journal of Medicine*, found no difference between treatment of painful OVCFs with PVP or with placebo-treatment [13, 14]. A substantially smaller benefit of either one of the procedures was found compared to values reported by large case series, systematic reviews and meta-analysis [16–23].

The study of Kallmes *et al.*[13] was a multicenter study in which 11 centers participated (5 United States, 5 United Kingdom, 1 Australia, primary center Mayo Clinics, Rochester, MN, USA). Primary outcome measures were the Roland-morris Disability Questionnaire (RDQ) and pain intensity 1 month postoperatively. Secondary outcome measures were other measures of pain, functional status and health-related quality of life (pain frequency index, pain bothersome index, SOF-ADL, EQ-5D, SF-

36) and opioid usage. After 1 month, patients were allowed to cross over to the other treatment group.

One-hunderd-and-thirty-one patients with one to three painful OVCFs were (stratified, block-) randomized to receive either PVP (68 patients) or the placebo-intervention (63 patients). The placebo-intervention consisted of infiltration of the skin and subcutaneous tissue with 1% lidocaine and infiltration of the pedicles, lamina and/or facet joint with 0.25% bupivacaine. Verbal and physical cues, such as pressure on the patient's back, were given to simulate the procedure and methacrylate monomer was opened to generate the odor associated with preparing PMMA bone cement. However, no needle was inserted in the vertebral body and cement was not injected.

No difference in both the primary and secondary outcome measures was found between the treatment groups after 1 month of follow-up (RDQ between group mean difference 0.7, 95%CI: -1.3 to 2.8, $p$ = 0.49, pain score between group mean difference 0.7, 95%CI: -0.3 to 1.7, $p$ = 0.19). There was some evidence towards more frequent clinically meaningful improvement in pain (improvement of 30% or more) in the PVP-group (64% versus 48%, $p$ = 0.06) and at 3 months postoperatively, a significantly higher proportion of patients in the placebo-group had crossed over to the PVP-group compared to the other way around (43% versus 12%, $p < 0.001$).

The study of Buchbinder *et al.*[14] was an Australian multicenter study in which 4 Australian centers participated (primary center Monash university hospital, Melbourne, Australia). Primary outcome of the study was overall pain on a 0-10 scale 3 months postoperatively, secondary outcome measures were measures of functional status and health-related quality of life (QUALEFFO, AQoL, EQ-5D, RDQ), pain aspects and usage of analgesics. Crossover was not allowed in this study.

Seventy-eight patients with one or two painful OVCFs were (block-)randomized: 38 received PVP and 40 received the placebo-intervention. The placebo-intervention consisted of the usual infiltration of the skin, subcutaneous tissue and periost of the lamina, pedicle and/or facet joint followed by gently tapping on a blunt stylet placed

on the lamina or pedicle to simulate PVP. In order to permeate the room with its distinctive smell, PMMA bone cement was prepared. There was no needle placed in the vertebral body and cement was not injected.

Three months after treatment, outcome regarding both primary and secondary outcome measures was comparable between both groups (overall pain between group mean difference 0.6, 95%CI: -0.7 to 1.8, $p > 0.05$).

### 9.2.2 Limitations of placebo-controlled trials

The results of both studies were worldwide news and were received with both surprise and disbelief. The results were in sharp contrast to all previously published studies and to the treatment response seen in clinical practice: immediate, dramatic pain relief combined with subsequent fast return of functioning and increased health-related quality of life [16–23]. These unexpected results and their perceived cognitive dissonance were reflected in various reports in the lay press and discussed in more than 50 editorials, letters and (spin-off) studies in (leading) specialist medical journals [24–89].

Reactions in the specialist journals were mainly due to concern regarding possibly overly rigorous and premature conclusions which may be based on the results of these trials. Both trials have several limitations which compromise their validity and generalizability; some even consider these trials not to represent evidence of level I, but instead should be considered as evidence of level II [35]. These limitations concern methodological, procedural and outcome aspects and can be summarized as follows.

A substantial methodological limitation is the fact that both trials included less than 30% of the patients considered suitable for inclusion in the trial and that no baseline characteristics from these patients were (routinely) obtained for comparison with the included patients. This is both surprising and disappointing considering the design and effort accompanying such trials. Also, after more than four years of

recruitment, the predetermined sample sizes from both trials were more than halved, even after the inclusion criteria had already been widened in an earlier stage. These aspects introduce a substantial risk of considerable selection bias, which also cannot be estimated due to the absence of baseline measurements in the non-participating patients. Furthermore, the multicentricity of both trials is questionable, since in none of the secondary centers more than five patients per year were included. This compromises generalizability and applicability of the results.

Due to an insufficiently stringent patient selection regimen, PVP or placebo-treatment may have been performed in patients in whom a relevant treatment effect could not be expected. In the included patients, it was unclear which underlying condition was treated since the standard triad of indication was not used in either one of the studies. This is a critical shortcoming. Findings from anamnesis and physical examination were not used in the evaluation whether treatment with PVP was appropriate and in the study of Kallmes *et al.* MRI was not used either. It is therefore unclear if the back pain experienced had its origin in a collapsed and painful vertebral body or was due to other frequently encountered causes, like degenerative disk disease or facet joint osteoarthritis, in the presence of an old – but consolidated and painless – vertebral fracture. Additionally, in the study of Kallmes *et al.* patients only had to have back pain scores of 3 or higher on a 0-10 visual-analogue scale. It is questionable if patients with pain scores less than 5 should actually be treated with PVP.

Debate regarding the procedures performed focused on the nature of the placebo-treatment. The placebo-treatment may have the nature of an alternative treatment. Infiltration of the facet joint is a common treatment for painful facet joint osteoarthritis and, in absence of thorough evaluation of the condition most likely to cause the experienced back pain, may explain part of the beneficial effect seen in the group receiving the placebo-treatment [90–94]. In addition, the adequacy of the performed PVP procedures has been called into question: It has been argued that in the study of Buchbinder *et al.* the injected cement volume may have been too low to achieve

sufficient augmentation of the fractured vertebral body [36–38]. This might explain the low treatment effect of PVP seen in this study, which is the lowest reported thus far and barely clinically relevant. In the study of Kallmes *et al.*, injected cement volumes were not reported and could not be recalled [13, 37].

Finally, the substantial difference in crossover rate seen at 3 months postoperatively in the study of Kallmes *et al.* suggests dissatisfaction with the placebo-treatment which is not covered by the evaluated outcome measures and cannot be explained.

Nevertheless, the initiation, management and execution of placebo-controlled randomized trials like these two trials takes great effort and it is commendable that the investigators undertook the challenge of obtaining the highest level of evidence. No consensus regarding the strength of their conclusion has been reached and it is premature to dismiss PVP as a treatment modality for painful OVCFs. The results of these trials, however, emphasize the importance of adequate patient selection and demonstrate the fallaciousness of performing PVP in every patient with an OVCF.

It is important that the findings of these studies should be interpreted with proper knowledge of their limitations and of routine clinical practice regarding patient selection and execution of PVP. In order to inform the Dutch practitioners, the author of this thesis discussed the position of PVP as a treatment modality for painful OVCFs after the publication of these trials in the two most widely read Dutch medical journals [87–89].

### 9.2.3 Vertebroplasty compared to conservative treatment

Since placebo-treatment provides no realistic treatment alternative to PVP, its value needs to be compared to realistic alternative treatments. In August 2010, the first high quality randomized clinical trial comparing PVP to optimal conservative treatment for painful acute OVCFs (fractures less than 6 weeks old) was published in another prestigious, high-impact journal, the *Lancet* [15]. This study was a multicenter study

conducted in five centers in the Netherlands and one in Belgium (primary center: st. Elisabeth Hopital, Tilburg, the Netherlands). Patients were included only when they fulfilled the aforementioned triad of indication.

Two-hundred-and-two patients were randomized to receive either PVP or optimal conservative treatment. During the entire first year after PVP, a statistically significant and clinically relevant benefit of PVP over conservative treatment was seen in both the primary outcome measure (pain on a 0-10 scale, between group mean difference 2.6, 95%CI: 1.74 – 3.37, $p < 0.001$ at 1 month and 2.0, 95%CI: 1.13 – 2.80, $p < 0.001$ at 1 year after treatment) and all secondary outcome measures, which assessed functional status and health-related quality of life (EQ-5D, QUALEFFO, RDQ). No symptomatic complications were reported in both groups and the incidence of new vertebral fractures was comparable [15, 95, 96].

Two interesting additional aspects should be noted. First, already in the inclusion phase of this trial 229 of 431 patients (53%) who were eligible for inclusion improved dramatically in the few weeks between randomization and initiation of the assigned treatment. Consequently, these patients no longer met the inclusion criterion of a preoperative pain score of 5 or higher and were excluded [15]. Second, in the group of conservatively managed patients, substantial benefit was found in the majority of the patients during the first months after initiation of treatment. However, around 30% of the patients who received conservative treatment continued to experience substantial back pain and gained no quality of life after several months of optimal conservative treatment (i.e. they were insufficiently responsive to conservative management) [9, 12]. These findings demonstrate the relatively benign natural course of the painful acute OVCF, which occurs in the majority of the cases and is characterized by fast collapse of the vertebral body accompanied by invalidating back pain followed by subsequent consolidation and dramatic reduction of pain and disability over the first 6-8 weeks after onset of symptoms [8–12]. Recently, the authors of this study recommended usage of PVP after a trial of several months of conservative management [12].

## 9.3 Relevance of thesis' findings

The definitive conclusion regarding the position of PVP as a treatment modality for painful OVCFs remains subject of debate and needs to be evaluated in further randomized trials. Especially since percutaneous cement augmentation may be the only interventional treatment option available in the frail and elderly and is associated with fast pain relief and return of function [16–23], increased patient survival [97–99] and a low complication rate [22, 23, 100], PVP remains a viable treatment option in patients with invalidating back pain due to an OVCF.

However, these trials undeniably demonstrate the importance of application of PVP only after stringent patient selection *and* after optimal conservative management has been attempted for at least at 8 weeks. Since it was exactly this philosophy which served as the basis for the treatment regimen in the center at which the research for this thesis was performed, the results of this thesis apply particularly well to the status of PVP in the era after the findings of these important randomized trials.

All patients with a painful OVCF described in this thesis had to fulfil the triad of indication and had to experience insufficient pain relief after a trial of at least 8 weeks of optimal conservative management. Consequently, only a minority of the patients with painful OVCFs were suitable candidates for treatment with PVP since only 20-30% of all patients with painful OVCFs are insufficiently responsive to several months of optimal conservative management. As such, recruitment of a sufficient number of patients to allow sound conclusions took a substantial amount of time.

In this thesis, the study sample size varies from 64 to 115 patients with painful long-standing OVCFs treated with PVP, which is sufficiently large to draw meaningful conclusions regarding several relevant aspects of PVP in this patient group. All patients received at least one year of prospective follow-up using measurement of patient-reported outcomes and routine spinal radiographs. This unique cohort of carefully selected patients is one of the largest currently available which focuses exclusively on treatment of painful long-standing OVCFs and is representative of both

our current clinical practice and probable future *general* clinical practice.

Concomitantly to suggesting a more restricted use of PVP in patients with painful OVCFs, the results of the randomized trials dictate a careful evaluation of the expected benefits and risks for each patient individually. In order to be able to do so, efficacy and safety in specific patient groups should be established, a preoperative estimation of the risks of the procedure should be possible and the procedure should be optimized for achievement of a maximum likelihood for accomplishment of patient benefit. This thesis is aimed at facilitating this evaluation and investigates these aspects.

## 9.4 Conclusion

The findings in this thesis support usage of PVP as a beneficial treatment modality for painful long-standing OVCFs in carefully and stringently selected patients. Moreover, it was found that even patients with very severely collapsed fractures and with fractures with an intravertebral cleft benefit from PVP, although the complication risk was higher and treatment benefit may be obtained more gradually. Risk factors for occurrence of cement leakage were identified in order to reduce the risk of cement leakage-related complications. Viscosity of PMMA bone cement was found to be a notable means for this purpose. New vertebral fractures occurred frequently after PVP and vertebral survival estimates, which depended heavily on the presence or absence of the identified patient- and vertebra-specific risk factors, were provided in order to facilitate patient selection and follow-up. Intradiscal cement leakage was the only identified risk factor specifically related to the procedure and should be avoided. Furthermore, it was shown that PVP may safely be timed at an appropriate moment in the first year after onset of symptoms without compromising its efficacy or increasing the risk of relevant complications and that (at least) 24% of the fractured vertebral body should be cemented in order to obtain a high likelihood for accomplishment of pain relief.

## 9.5 Recommendations for future research

In this thesis it was shown that viscosity of PMMA bone cement is a crucial parameter regarding occurrence of cement leakage. Cement leakage occurs frequently, is the most common cause of symptomatic complications and is also related to the occurrence of subsequent new OVCFs. However, cement viscosity may also be related to the benefit of PVP: viscosity influences interdigitation and interdigitation may affect the degree of bone-interlocking and fracture stabilization. Although no difference in clinical outcome or interdigitation was found between usage of low or medium viscosity PMMA bone cement, augmentation of painful OVCFs with an intravertebral cleft resulted in substantially less interdigitation and a more gradual and possibly smaller benefit from PVP.

This phenomenon can only be fully attributed to cement viscosity, and not to the presence of an intravertebral cleft as a distinct entity or other relevant variables, in a well-designed randomized trial. Consequently, a double-blind, randomized clinical trial comparing the usage of high or low viscosity PMMA bone cement in PVP for painful long-standing OVCFs was designed and initiated by the author of this thesis (Dutch Trial Register 3282). This trial is currently recruiting patients and investigates the effect of usage of either high or low viscosity PMMA bone cement on occurrence of cement leakage, pulmonary cement emboli, procedural characteristics, treatment efficacy and occurrence of new OVCFs in the first postoperative year.

A related interesting research topic may be the nature of the filler material. Polymethylmethacrylate is an inert material which can never fully be incorporated by the human body and which is much stiffer than intact vertebrae. Osteoconductive biocompatible materials which provide sufficient initial stability but which eventually would resolve and be replaced by (trabecular) bone could further improve the procedure.

In light of the aforementioned recent changes in the position of PVP as a treatment modality for painful OVCFs, further assessment of its clinical value by well-designed,

(large, blinded) randomized trials is necessary. Inclusion criteria for these trials should be tailored at stringent selection of clinically representative patients who are expected to benefit from PVP. As such, fulfilment of the triad of indication should be required and it may be argued that only patients with painful long-standing OVCFs should be considered, since these patients may benefit particularly from treatment with PVP. Additionally, injected cement volumes should be recorded and appropriateness of the cemented vertebral body fraction should be verified. Worldwide, and also by our study group, such trials have been designed and initiation is being attempted.

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