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**Author:** Nieuwenhuijse, Marcus Johannes  
**Title:** Percutaneous vertebroplasty for painful long-standing osteoporotic vertebral compression fractures: benefits, risks and optimization  
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A clinical comparative study on low versus medium viscosity polymethylmethacrylate bone cement in percutaneous vertebroplasty

Viscosity associated with cement leakage

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Chapter 6

Abstract

**Background.** Viscosity is one of the characterizing parameters of PolyMethyl-MethAcrylate (PMMA) bone cement, currently the standard augmentation material in Percutaneous VertebroPlasty (PVP), and influences interdigitation and cement distribution inside the vertebral body, injected volume and occurrence of extravertebral leakage, and thereby affects the clinical outcome of PVP. Currently, low, medium and high viscosity PMMA bone cements are used interchangeably. However, the effect of viscosity on the clinical outcome after PVP in painful Osteoporotic Vertebral Compression Fractures (OVCFs) has not yet been explicitly evaluated.

**Objective.** Comparison of the clinical outcome after PVP between patients treated using low or medium viscosity PMMA bone cement.

**Methods.** Follow-up was conducted using a 0-10 pain intensity numerical rating scale and the Short-Form 36 (SF-36) quality of life questionnaire before PVP and at 7 days (pain only), 1, 3 and 12 months after PVP. Injected cement volume, degree of interdigitation and presence of cement leakage were analyzed on direct postoperative CT scans of the treated levels. At six and 52 weeks and at suspicion, patients were analyzed for the presence of new vertebral fractures.

**Results.** Thirty consecutive patients received PVP using low viscosity PMMA bone cement for 62 painful OVCFs, followed by 34 patients who received PVP using medium viscosity PMMA bone cement for 67 painful OVCFs. Results regarding postoperative back pain and SF-36 were comparable between both groups. Comparison of injected cement volume, degree of interdigitation, proportion of bipedicular procedures, incidence of new vertebral fractures and complications revealed no differences between both groups. Low viscosity was identified as a risk factor for occurrence of cement leakage (odds ratio 2.93, 95%CI: 1.07 – 7.98, p = 0.036).

**Conclusion.** No major differences in clinical outcome after PVP in OVCFs using low or medium viscosity PMMA bone cement were found. However, viscosity of PMMA bone cement was identified as an independent predictor of occurrence of cement leakage.
6.1 Introduction

Over the past two decades, Percutaneous VertebroPlasty (PVP) has gained popularity as a treatment modality for Osteoporotic Vertebral Compression Fractures (OVCFs). Promising results from large case series [1] and non-randomized controlled trials have been reported [2–4] and its position has been stated by professional societies [5]. Randomized controlled trials to establish the efficacy of PVP are currently being conducted [6–8].

However, the mechanism of pain relief through PVP is as intriguing as it is unknown. Possible mechanisms may include thermal or chemical effects on nerve endings or, more likely, a mechanical effect of stabilization of (micro)movements within the fracture [9, 10]. For this purpose multiple types of injectable bone cements, like PolyMethylMethAcrylate (PMMA), calcium phosphate and composite cements, are currently being used in PVP. So far PMMA is the most widely used cement type due to its good handling properties, strength, long time experience and low cost.

Viscosity, the most indicative parameter of the flowing capability of a liquid, is one of the main characterizing parameters of PMMA bone cement, and because of its effect on the interdigitation (penetration in cancellous bone), one of the factors particularly likely to influence this stabilization effect and the resulting mechanical properties of the treated vertebra [11, 12], and hence, outcome of PVP. Additionally, viscosity affects the spatial distribution of cement inside the vertebral body [12], which, when inadequate, could alter the pattern of load transfer and might thereby induce new (adjacent) VCFs [10, 13, 14].

Concomitantly, viscosity of bone cement is also an essential parameter regarding extravertebral bone cement leakage [10–13]. Cement leakage is one of the most common side effects of PVP and detected in up to 87.5% of treated vertebrae [15–17]. Although generally asymptomatic, occasionally severe results such as paraplegia [18], neurologic deficits [19, 20], pulmonary and cardiac cement embolisms [21–23] and cardiac perforation [24, 25] have been reported.
However, the degree in which PMMA bone cement viscosity affects the clinical outcome of PVP (through these various potential effectuations) is still unclear. In this study we evaluate the clinical outcome after PVP using either low or medium viscosity PMMA bone cement in painful OVCFs refractive to at least eight weeks of conservative treatment in terms of patient-reported outcome, i.e. pain and health-related quality of life, as well as procedural characteristics, interdigitation and incidence of cement leakage and complications.

6.2 Materials and methods

6.2.1 Patients

Between August 2002 and August 2007, sixty-four patients were prospectively recruited for participation in a follow-up study on the clinical significance of viscosity of injected bone cement in PVP in painful long-standing OVCFs at the Leiden University Medical Center (LUMC). Inclusion criteria were (I) Osteoporotic VCF, including very severe compression fractures [26], (II) focal back pain in the midline refractive to at least six weeks of appropriate conservative treatment, (III) back pain related to the location of the VCF on spinal radiographs, (IV) the presence of bone marrow edema on Magnetic Resonance Imaging (MRI) Short Tau Inversion Recovery (STIR) sequences in the collapsed Vertebral Body, (V) age over 40 years and (VI) written informed consent.

Exclusion criteria were (I) VCFs due to other causes than osteoporosis (II) spinal cord compression or stenosis of the vertebral canal > 30% of the local canal diameter, (III) neurological deficits, (IV) incorrectable bleeding disorders, (V) infections related to the vertebral column, (VI) inability to lie in prone position for two hours, (VI) an American Society of Anesthesiologists (ASA)-score [27] ≥ 4 and (VII) inability of the patient to complete questionnaires.
In the period August 2002 – August 2005, four men (13%) and 26 women (87%) with a mean age of 70.7 years (range 41.5 – 90.6) received PVP using low-viscosity PMMA bone cement (OsteoPal-V®, Hereaus Medical, Germany) in 62 OVCFs in 32 sessions. At the time of PVP, these 30 patients had a total of 139 preexisting VCFs, with a mean of 4.6 VCFs per patient (range 1 – 13). Of these 139 VCFs, sixty-two were painful, showed bone marrow edema on MRI scans and were treated with PVP.

Following august 2005 until august 2007, thirty-four patients, ten men (29%) and 24 (71%) women with a mean age of 74.3 years (range 48.5 – 90.8), received PVP using medium-viscosity PMMA bone cement (Disc-O-Tech®, Disc-O-Tech Medical Technologies Ltd. Israel) in 67 OVCFs in 34 sessions. One hundred and thirty-nine pre-existing VCFs were noted (4.1 per patient, range 1 – 10), whereas 67 VCFs were painful, showed bone marrow edema on MRI scans and were treated with PVP. Group characteristics were comparable (table 6.1).

### 6.2.2 Vertebroplasty work-up

When a patient presented with persistent pain after 6 weeks of conservative treatment, the complete clinical workup was conducted in two weeks ensuring that patients did not receive PVP within 8 weeks after onset of the VCF. In the work-up for PVP, anteroposterior and lateral radiographs and MRI scans, including fat suppression sequences, of the total spine were acquired. Fracture morphology was denominated according to the classification of Genant et al.[28] and was comparable between both groups, as was the fracture age (table 6.1). Fracture age was defined as the time between the onset of (new) back pain related to a radiographically confirmed fracture and the time of PVP.


6.2.3 Cement leakage, cement volume and interdigitation

Cement leakage, defined as the presence of any extravertebral cement, was assessed independent of the treating physician by two investigators (MJN, SPJM) on a Computed Tomographic (CT) scan made directly after PVP. Differences were re-examined until consensus was obtained. Patterns of cement leakage were described using the classification proposed by Yeom et al.[29], which discerns three types of leakage sites: 1) via the basivertebral vein (B-type), 2) via the segmental vein (S-type) and
3) through a cortical defect (C-type, figure 6.1). Intra- and extracorporal volumes were measured using Osirix®, an open source calibrated DICOM-viewer.

The degree of interdigitation of bone cement was scored on a semi-quantitative scale ranging from one (complete interdigitation throughout the injected volume with clearly visible bone trabecles) to four (no interdigitation at all with sharp boundaries along the cement clump, comparable to cleft filling) by two investigators (MJN, SPJM) (figure 6.2). In case of nonuniformity in scores, cases were re-examined until consensus was obtained.

### 6.2.4 Procedure

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

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

Pre- and postoperative clinical characteristics of each patient were obtained using a 0-10 pain intensity numerical rating scale for average and worst back pain and the SF-36 health survey [30–32]. Questionnaires were filled out before the procedure and at 7 days (pain only), 1 month, 3 months, and 12 months after the procedure.

Routine standing anteroposterior and lateral radiographs of the spine were made six weeks and one year after PVP and on indication, e.g. sudden new onset of back pain suspect for a new OVCF.

6.2.7 Statistical analysis

Raw SF-36 item scores were summarized and transformed to a 0-100 point scale, with a higher score representing a higher level of functioning or well-being.

Distribution and skewness of the data were assessed and normality was tested using the Kolmogorov-Smirnov test. Where appropriate, the (paired) Student’s t-test, the Mann-Whitney U test, the chi-square test, Fisher’s exact test and the logrank test were used.

Longitudinal analysis of back pain score and SF-36 was performed using mixed-model analysis based on maximum likelihood estimation. A multiple logistic regression analysis was carried out in order to identify factors associated with the occurrence of cement leakage. Using multiple linear regression analysis, factors independently associated with the volume of cement leakage volume were assessed.

A p-value of less than 0.05 was considered significant (SPSS statistical software 14.0, SPSS Inc, Chicago, IL).
Table 6.2: Preoperative SF-36 physical and mental summary scores and mean difference with follow-up scores

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Mean increase at 1 month</th>
<th>Mean increase at 3 months</th>
<th>Mean increase at 12 months</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>PCS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVC</td>
<td>26.53</td>
<td>5.37</td>
<td>30</td>
<td>7.46</td>
<td>8.59</td>
</tr>
<tr>
<td>MVC</td>
<td>26.02</td>
<td>8.23</td>
<td>34</td>
<td>2.46</td>
<td>8.05</td>
</tr>
<tr>
<td></td>
<td>p = 0.773</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| MCS   |     |     |     |      |     |     |      |     |     |      |     |     |         |
| LVC   | 39.59| 11.7| 30  | -4.35| 11.5| 23  | 3.35 | 7.93| 22  | 3.49 | 9.41| 22  | 0.058  |
| MVC   | 40.75| 13.0| 34  | 3.68 | 9.52| 27  | 1.18 | 10.1| 25  | 5.06 | 14.5| 28  |         |
|       | p = 0.712 |     |     |      |     |     |      |     |     | Overall effect of viscosity: p = 0.271 |

PCS = SF-36 Physical Component Score, MCS = SF-36 Mental Component Score, LVC = Low Viscosity Cement, MVC = Medium Viscosity Cement

### 6.3 Results

#### 6.3.1 Patient-reported outcome

Preprocedurally obtained back pain and SF-36 scores were comparable between both groups (figure 6.3, table 6.2). Mean average and worst back pain scores were respectively 7.9 and 8.8 for the group treated with Low Viscosity Cement (LVC-group) and 7.5 and 8.5 for the group treated with Medium Viscosity Cement (MVC-group) and showed a significant decrease of 3.1 and 2.7 (LVC-group, \( p < 0.001 \)) and 2.6 and 2.8 (MVC-group, \( p < 0.001 \)) points seven days after PVP, which was durable and comparable between both groups throughout the remaining follow-up period (\( p = 0.142 \) and \( p = 0.337 \)).

Comparison of one month post-vertebroplasty scores on the eight domains and both component (summary) measures of the SF-36 showed a significantly higher increase of the ‘Physical Component Score’ (PCS) in the LVC-group compared to the MVC-group, while the ‘Role Physical’ and ‘Role Emotional’ domain scores and the ‘Mental Component Score’ (MCS) were significantly higher in the MVC-group.
compared to the LVC-group. At the three and 12 month follow-up moments, scores on all eight domains and both summary measures were comparable. The PCS was significantly increased at both follow-up moments in both groups, whereas the MCS was not (table 6.2, figure 6.4).

Figure 6.3: Average (upper) and worst (lower) back pain in the first postoperative year of patients treated with low or medium viscosity bone cement (mean and 95%CI).
Figure 6.4: Scores on all eight SF-36 domains at baseline and various follow-up moments of patients treated with PVP using low or medium viscosity bone cement. Baseline domain scores were comparable between both groups. At 1 month postoperatively, $RP$ and $RE$ were significantly higher in the group treated with medium viscosity cement ($p = 0.03$ and $p = 0.01$ respectively). $PF$, physical functioning; $RP$, role physical; $BP$, bodily pain; $GH$, general health perception, $VT$, vitality; $SF$, social functioning; $RE$, role emotional; $MH$, mental health.
6.3.2 Procedural characteristics

Of the 58 OVCFs in the LVC group with a CT scan suitable for assessment, PVP was unipedicular in 33 (56.9%) and bipedicular in 25 (43.1%) procedures whereas the procedure was unipedicular in 45 (68.2%) and bipedicular in 22 (31.8%) of 67 OVCFs in the MVC-group ($p = 0.194$).

In order to correct for eventual geometrical, anatomical or weight bearing induced differences, injected cement volume and interdigitation score were analyzed separately for the thoracic and lumbar spine. Neither the injected cement volume nor the interdigitation score per region differed significantly between the LVC- and the MVC-group (table 6.3).
6.3.3 Cement leakage

The proportion of treated fractures with detected cement leakage was significantly higher in the LVC-group (87.9% versus 71.6%, $p = 0.029$). The distribution of leakage types was similar in both groups (table 6.4). A subsequent multiple logistic analysis identified cement viscosity to be independently associated with occurrence of cement leakage (adjusted odds ratio 2.93, 95%CI: 1.07 - 7.98, $p = 0.036$, table 6.5). A multiple linear regression analysis revealed fracture severity, the number of leakage sites and the injected volume to be independently associated with the volume of cement leakage (table 6.6).

### Table 6.4: Leakage specifications

<table>
<thead>
<tr>
<th></th>
<th>Low viscosity cement (OsteoPal-V$^\circ$)</th>
<th>Medium viscosity cement (Disc-O-Tech$^\circ$)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated fractures with cement leakage</td>
<td>51 of 58 (87.9%)</td>
<td>48 of 67 (71.6%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Leakage type acc. to Yeom et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-type</td>
<td>21 (28.8%)</td>
<td>19 (22.4%)</td>
<td>0.567</td>
</tr>
<tr>
<td>S-type</td>
<td>18 (24.7%)</td>
<td>26 (30.6%)</td>
<td></td>
</tr>
<tr>
<td>C-type</td>
<td>34 (46.6%)</td>
<td>40 (46.8%)</td>
<td></td>
</tr>
<tr>
<td>(into discus)</td>
<td>(32, 43.8%)</td>
<td>(38, 44.7%)</td>
<td>(0.762)</td>
</tr>
</tbody>
</table>

B-type: via the basivertebral vein, S-type via the segmental veins, C-type through a cortical defect

### Table 6.5: Results of multiple logistic regression analysis

<table>
<thead>
<tr>
<th>Multiple logistic regression for occurrence of cement leakage</th>
<th>Odds ratio [95% CI]</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity grade acc. to Genant et al. (1 – 3)</td>
<td>1.37 [0.70 – 2.67]</td>
<td>0.355</td>
</tr>
<tr>
<td>Fracture type acc. to Genant et al.</td>
<td>0.68 [0.24 – 1.95]</td>
<td>0.474</td>
</tr>
<tr>
<td>Injected volume</td>
<td>1.03 [0.79 – 1.33]</td>
<td>0.843</td>
</tr>
<tr>
<td>Spinal region (thoracic / lumbar)</td>
<td>0.48 [0.54 – 3.74]</td>
<td>0.476</td>
</tr>
<tr>
<td>Cement viscosity (low / medium)</td>
<td>2.93 [1.07 – 7.98]</td>
<td>0.036</td>
</tr>
</tbody>
</table>
6.3.4 New fractures

In the LVC-group, 14 new fractures, of which 9 adjacent to treated levels, occurred in 10 patients (33.3%) after a mean of 6.8 months (range 1.3 – 13.6), whereas in the MVC-group 17 new fractures, of which 10 adjacent, occurred in 9 patients (26.5%) after a mean of 4.2 months (range 0.03 – 11.9). One VCF occurred one day after PVP. In two patients in the LVC-group and four patients in the MVC-group, these new fractures were treated using PVP. The proportion of patients with new OVCFs, the proportion of adjacent fractures, the time distribution and the mean time to occurrence of new fracture were comparable between both groups ($p = 0.380$, $p = 0.097$, $p = 0.080$ and $p = 0.071$ respectively).

6.3.5 Complications

Two minor complications occurred in the LVC-group: one asymptomatic pulmonary cement embolism was detected and one cement spur following the needle tract through the pedicle into the subcutaneous tissue was present, which was removed immediately. In the MVC-group, in two patients a similar cement spur through the pedicle but not into the subcutaneous tissue was noted postoperatively. Proving to be asymptomatic, these spurs were not removed.
6.4 Discussion

6.4.1 Role of bone cement viscosity

Besides injection technique and bone- and fracture-related parameters, the material properties of the PMMA bone cement used in PVP influence cement flow, distribution and volume inside the vertebral body, and thereby ultimately the outcome of PVP. Viscosity of bone cement used in PVP is hypothesized to influence the outcome of the procedure in various ways. One way is by determining or affecting the potential of the cement to interdigitate with the trabecular bone, which relates to the stabilization of (micro)movements in the fractured vertebra and possibly subsequent pain relief and preservation or restoration of mechanical strength [11, 12, 33].

Besides interdigitation, it is unclear whether the spatial distribution of the cement, also influenced by cement viscosity [12, 34], affects the outcome of PVP and the risk of subsequent (adjacent) vertebral fractures by alteration of the load distribution and its transfer over the vertebral body [10, 13, 14, 35, 36]. Hence, placement of a second needle through the contralateral pedicle, and thereby introducing additional risks and costs, is frequently opted for when the distribution of cement is unsatisfactory or asymmetrical. Hemivertebral filling through a unipedicular approach may be as effective as using a bipedicular approach though [37–39].

Regarding the procedure itself, more viscous cement has better handling properties, especially in controlling the volume and speed of injection. Downside of higher viscosity is the higher injection pressure required [12, 40] and the volume of injectable cement can therefore be limited, necessitating conversion from a uni- to a bipedicular procedure.

Above all, however, viscosity of PMMA bone cement is a crucial parameter regarding the main cause of (severe) complications of PVP: leakage of cement outside the vertebral body [10–13, 40]. Despite its proven superiority over radiography for detection of cement leakage [16, 29], CT scanning after PVP is infrequently
executed for this purpose, rendering most reported cement leakage incidences a substantial underestimation. Reported to occur in up to 87.5% of the treated OVCFs on postoperative CT scans [15–17] and although generally asymptomatic, leakage of cement inside the spinal foramen or the venous circulation can result in neurological deficits, paraplegia, pulmonary and cardiac embolisms or cardiac perforation [18–25].

6.4.2 Current practice regarding cement viscosity

In PVP, low, medium and high viscosity PMMA bone cements are used interchangeably. The effect of viscosity, injected volume and distribution of cement in relation to cement leakage and restoration of biomechanical properties of fractured vertebrae have been investigated in experimental and cadaver studies, and using finite element analysis [9–11, 13, 35–37, 39, 40]. However, (patient) clinical significance has not yet been explicit subject of investigation and an in vivo direct comparison of clinical outcome between groups treated with PVP using identical injection methods but bone cements with different viscosities has, to the authors' best knowledge, not been reported thus far. The current study focused on the effect of PMMA bone cement viscosity on clinical outcome of PVP using periprocedurally and prospectively acquired (follow-up) data from two patient groups which have been treated with PVP for painful OVCFs using low and medium viscosity PMMA bone cement.

6.4.3 Study findings

For the LVC- and the MVC-group our results showed a clinically relevant [41] significant, immediate and durable reduction in average and worst back pain, which was comparable between both groups. Increase in health-related quality of life, measured using the SF-36, was similar in both groups.
Comparison of the mean injected cement volume per vertebra per region revealed no significant difference, although a tendency was seen towards injecting less cement in the MVC-group. The degree of interdigitation of bone cement was also found to be similar in both groups, thereby contrasting the expectation of more pronounced interdigitation or uniform filling facilitated by a higher viscosity cement [11, 12]. This is supported by the similar proportion of bipedicular procedures in both groups, which is an indication of an intraoperatively perceived similar spatial distribution of cement inside the vertebral body, and the comparable number of and mean time to development of new OVCFs after PVP in both groups.

In the MVC-group, a significantly smaller proportion of treated vertebrae exhibited cement leakage (71.6% versus 87.9%). In order to correct for eventual confounders, a multiple logistic analysis was carried out and revealed cement viscosity to be significantly associated with the occurrence of cement leakage: the odds of occurrence of cement leakage using LVC being nearly threefold compared to when using MVC. Despite its intuitive nature, this is actually the first study proving this hypothesis in vivo and confirming experimental results [11, 12].

The volume of cement leakage was found to be independently associated with the volume of injected cement, the number of leakage sites and the semi-quantitative severity grade of the fracture. No independent association with viscosity was found. Trivially, when intra-operative cement leakage is noted, further injection of cement should be performed with great care and the number of leakage sites as well as the fracture severity should be kept in mind, predisposing for a larger volume of cement leakage with potentially more severe sequelae. Whether or not the severe leakage described with usage of low viscosity cement [20], due to its predisposition for taking the ‘path of least resistance’ resulting from intravertebral irregularities [11, 12], will be reduced using high viscosity bone cement remains unconfirmed.
### 6.4.4 Study limitations

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

### 6.5 Conclusion

In experienced hands, viscosity of PMMA bone cement used in PVP for painful OVCFs did not influence clinical outcome. The immediate and durable reduction in back pain and improvement in health-related quality of life was comparable between both groups, as was the injected cement volume, degree of cement interdigitation, proportion of bipedicular procedures, incidence of new vertebral fractures and incidence of complications. Low cement viscosity, however, was identified as an independent predictor of occurrence of cement leakage. In the presence of cement leakage, larger cement leakage volumes were associated with a larger injected cement volume, more different leakage sites and an increased fracture severity.

### References


References


Chapter 6

