A Classification System for the Spread of Polymethyl Methacrylate in Vertebral Bodies Treated with Vertebral Augmentation

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ABSTRACT

In this study, we develop a classification system for describing polymethyl methacrylate (PMMA) spread in vertebral bodies after kyphoplasty or vertebroplasty for vertebral compression fractures (VCFs) and for assessing whether PMMA spread varies between operators, VCF etiology, or vertebral level. Intraoperative fluoroscopic images of 198 vertebral levels were reviewed in 137 patients (women, 84; men, 53; mean age, 75.8 ± 12.5; and those with a diagnosis of osteoporosis, 63%) treated with kyphoplasty between January 01, 2015 and May 31, 2015 at a single center to create a 5-class descriptive system. PMMA spread patterns in the same images were then classified by 2 board-certified radiologists, and a third board-certified radiologist resolved conflicts. A total of 2 primary PMMA spread patterns were identified, namely, acinar and globular, with subtypes of localized acinar, diffuse globular, and mixed, to describe an equal combination of patterns. Interrater reliability using the system was moderate ($\kappa = 0.47$). After resolving conflicts, the most common spread class was globular (n = 63), followed by mixed (n = 58), diffuse globular (n = 30), acinar (n = 27), and localized acinar (n = 20). The spread class after treatment by the 2 most frequent operators differed significantly ($n_1 = 63$, $n_2 = 70$; $P < .0001$). There was no difference in the spread class between VCF etiologies or vertebral levels. PMMA spread may, therefore, be a modifiable parameter that affects kyphoplasty and vertebroplasty efficacy and adverse events.

INTRODUCTION

Vertebral compression fractures (VCFs) can be asymptomatic or present with signs and symptoms such as height loss, kyphosis, and functional disability (1, 2). Balloon kyphoplasty (BKP) and percutaneous vertebroplasty (PVP) are commonly used procedures performed under fluoroscopic guidance to treat painful VCFs refractory to medical management or bracing, which remain the subject of investigation (3). Large open-label trials have shown earlier decreased pain, decreased pain at 1 year, more pain-free days over 1 year, and decreased analgesic use among patients treated with vertebral augmentation compared with conservative therapy for painful acute VCFs (4, 5). Serious adverse events are rarely caused by either BKP or PVP, and a considerable proportion of those that occur are due to cement embolism (6, 7). We also reported a case of vertebral refracture after asymmetric polymethyl methacrylate (PMMA) spread (8). Biomechanical studies have shown that distribution of PMMA in vertebral bodies is correlated with strength and stiffness parameters that may impact treatment efficacy (9, 10). Variability in how the procedures are performed presents an obstacle to effective analysis of adverse event frequency and pain-reducing efficacy (11). The absolute volume of injected PMMA has been shown to have a large variability (12). Cement viscosity has been shown to significantly impact PMMA spread; yet, there is no routine quantitative measurement of viscosity before injection (13). Finally, properties of vertebrae itself are associated with PMMA spread (14).

Multiple known and unknown factors result in an ultimate PMMA spread pattern that is visible on radiographs. Currently, there is no standardized language to describe the imaging appearance of PMMA spread within a vertebral body. This prevents retrospective and prospective analyses of a possible association between PMMA spread and either BKP or PVP outcomes. The purpose of this study was to develop a classification system to describe PMMA spread in vertebral bodies and assess whether PMMA spread varied between

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operators or because of the properties of the vertebrae that were injected.

METHODOLOGY

Approval for retrieval and analysis of electronic medical records (EpicCare EMR; Epic, Verona, Wisconsin) was obtained from the local institutional review board, and informed consent was waived. Accessed records included demographic and clinical data and intraoperative fluoroscopic images.

Patient Population

BKP was recommended for patients with acute VCFs refractory to conservative therapy, who exhibited edema on spinal magnetic resonance images (MAGNETOM Aera; Siemens, Munich, Germany) or active technetium-99m radiotracer (GE Healthcare, Little Chalfont, United Kingdom) uptake on single-photon emission computed tomography/computed tomography (Optima NM/CT 640; GE Healthcare) bone scans, and had localized tenderness over the fractured level. Conservative therapy included thoracolumbosacral orthosis bracing and/or pain medications.

A total of 198 VCFs (women, 84; men, 53; mean age, 75.8 ± 12.5; and those with a diagnosis of osteoporosis, 63%) were treated with BKP between January 01, 2015 and May 31, 2015 at a single center. Patient characteristics are described in Table 1. Radiofrequency ablation (SpineSTAR; DFine, San Jose, California) was performed in addition to BKP in 6 patients with either primary or metastatic osteolytic cancers at 9 total vertebral levels. A bone biopsy was collected in addition to BKP from 1 patient at 1 vertebral level.

Procedure

BKP, which has been previously described (15), was performed at all treated vertebral levels. In brief, a bone tamp was inserted into the vertebral body under fluoroscopic guidance, the inner stylet removed leaving the trocar, and a kyphoplasty balloon inserted through the trocar (Kyphon; Medtronic, Dublin, Ireland). The balloon was inflated with radiocontrast medium, which allows for visualization, compacts cancellous bone, and re-expands the vertebral body. Last, the balloon was deflated and removed, and PMMA from the Kyphon kit was injected through the trocar under fluoroscopic guidance. The method of vertebral body access was recorded for BKP at 160 levels. A unipedicular approach was used at 111 (69.4%) vertebral levels, and a bipedicular approach at 49 (39.6%) vertebral levels. Fluoroscopy time was recorded during 96 procedures for treatment of 137 vertebral levels, and mean time was 10.2 ± 5.9 minutes per procedure or 8.3 ± 4.1 minutes per vertebral level.

Table 1. Patient Characteristics

	Male	Female	Combined
Number of treated patients	53	84	137
Number of treated levels	75	123	198
Age (years)	74.4 ± 13.6	76.6 ± 11.7	75.8 ± 12.5
Etiology by patient[a]	21/11/7/2	49/7/14/0	70/18/21/2
Etiology by level[a]	35/19/7/2	73/14/17/0	108/33/24/2

[a] Fracture etiology was recorded for 111 patients treated at 167 levels. Counts are listed as osteoporosis/cancer/trauma/other.

PMMA Spread Classification

We developed a 5-class system to describe PMMA spread after a review of anterior–posterior and lateral intraoperative fluoroscopic images from all procedures. A preliminary classification system was developed while viewing the complete image set for the first time. The system was refined during a subsequent review of the images by the same viewers. The same intraoperative fluoroscopic images were then reviewed by 2 additional board-certified radiologists who classified PMMA spread at each level according to the system. A third board-certified radiologist resolved conflicts.

Statistics

Continuous variables were expressed as mean ± standard deviation. Interrater reliability was assessed using Cohen's kappa coefficient. Associations between PMMA spread characteristics and categorical variables were assessed using Pearson's χ^2 tests. The 5th–8th and 9th–11th thoracic vertebrae, 12th thoracic vertebra through the 2nd lumbar vertebra, and the 3rd–5th lumbar vertebrae were binned together to meet expected cell-count assumptions of the χ^2 tests. All analyses were performed using SAS 9.3 and SAS Enterprise Guide 5.1.

RESULTS

Description of the 5-Class System

We identified 2 primary patterns of PMMA spread that were visible on the intraoperative fluoroscopic images. Subclassification of these patterns considering the number of the vertebral bodies infiltrated with PMMA, and a pattern admixture yielded a total of 5 PMMA spread classes: acinar and globular, with subtypes of localized acinar, diffuse globular, and mixed, to describe an equal combination of patterns within the vertebral body. Prototypes are shown in Figure 1.

The acinar pattern of spread was defined as expected when filling complex cortical bone with a low-viscosity fluid. Characteristics commonly associated with the acinar pattern spread included numerous small dot-like collections of PMMA interrupted by a web of trabecular bone. The globular pattern was defined by much larger, potentially solitary accumulations of PMMA showing lobular smooth margins and homogeneous texture. The prototypical globular pattern was a circular cannonball without extension across the vertebral body midline. However, globular pattern variants also included more lobulated amorphous shapes. Vertebral bodies showing a mixture of at least 40% of both acinar and globular spread pattern components on at least 1 imaging angle were classified as having a mixed spread.

A substantial proportion of treated vertebral bodies showed near-complete PMMA filling in at least 1 viewing angle. Diffuse spread was defined by >90% of the anterior–posterior or medial–lateral axis of the vertebral body making up the border of PMMA spread on at least 1 viewing angle with spread height and pattern homogeneity throughout. Globular pattern spread was most often localized and not diffuse. Therefore, diffuse

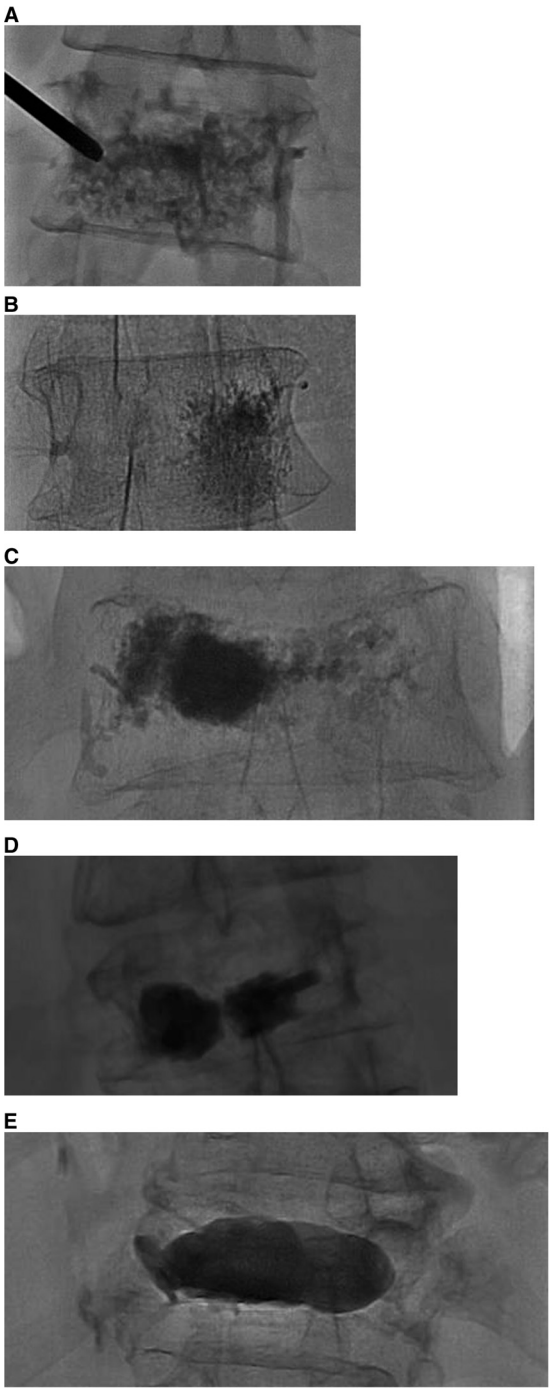

Figure 1. Intraoperatoive medial–lateral fluoroscopic images of prototypical PMMA spread patterns. Acinar (A) and localized acinar (B) spread both appear pockmarked with areas of lucency. Mixed spread (C) has >40% acinar and globular components. Globular (D) and diffuse globular (E) spread both have a homogenous smooth texture.

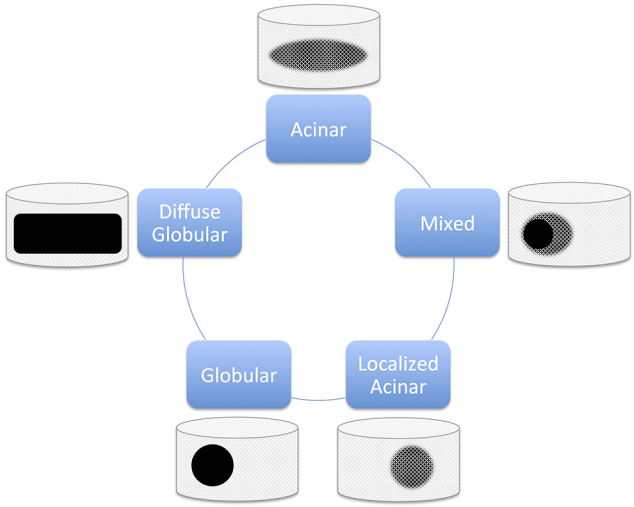

Figure 2. Schematic of relationships between spread patterns. Each pattern is most similar to adjacent patterns and most distinct from nonadjacent patterns.

globular spread was considered as a subtype. The acinar pattern spread was most often diffuse. Similarly, the localized acinar spread was considered as another subtype. In theory, a diffuse mixed spread would appear as layers of globular and acinar spread extending across the vertebral body, although this was not observed in our sample.

Interrater reliability using the entire system was moderate ($\kappa = 0.47$). Similarly, interrater reliability was moderate for assessing PMMA infiltration ($\kappa = 0.49$) and pattern ($\kappa = 0.48$). A total of 51.2% of the levels were classified as having the same spread class by the first 2 raters. Of the vertebral levels not assigned the same spread class by the first 2 raters, 68.8% were assigned spread classes that were considered to be the most similar (Figure 2). Raters assigned 78.3% of the levels as having the same degree of PMMA infiltration (localized vs diffuse) and 60.1% of the levels as having the same spread pattern (acinar vs globular vs mixed). Examples of difficult-to-classify images are in Figure 3.

The most common spread class after resolving conflicts was globular (n = 63), followed by mixed (n = 58), diffuse globular (n = 30), acinar (n = 27), and localized acinar (n = 20). Therefore, 80.1% of levels were considered as localized and 19.9% as diffuse. The distribution of levels that were assigned various spread patterns was 23.7% acinar, 47.0% globular, and 29.3% mixed.

Spread Pattern Varies by Operator

There was a significant difference in the spread class of vertebral bodies treated by the 2 most frequent operators ($n_1 = 63$, $n_2 = 70$; $P < .0001$). PMMA infiltration also differed by operator ($P < .0001$), and there was a marginal difference in the spread pattern between operators ($P = .07$). The 2 most common spread patterns for operator 1 were mixed and globular, whereas the 2 most common spread patterns for operator 2 were diffuse globular and acinar.

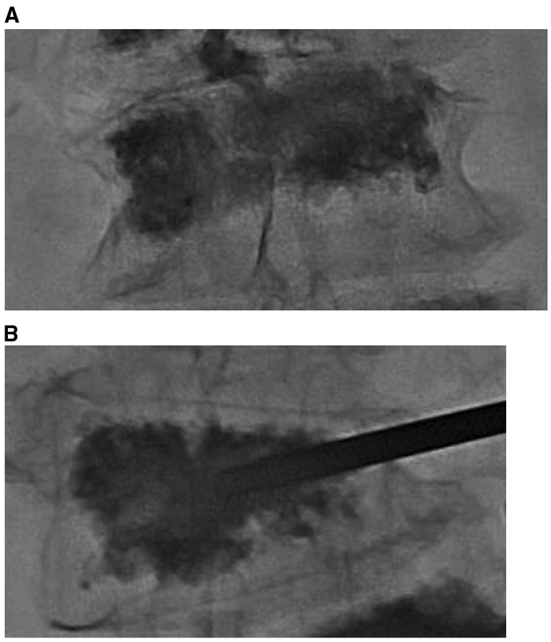

Figure 3. Images with a heterogeneous spread, but few entirely lucent areas presented difficulties to raters. This image was ultimately classified as mixed (A). Images with considerable obstruction and poorer quality were also more likely to receive discordant ratings from raters. This image was ultimately classified as mixed (B).

No Association Between Spread Pattern and Vertebral Parameters

There was no difference in spread class ($P = .55$), PMMA infiltration ($P = .72$), or spread pattern ($P = .28$) in treated osteoporotic VCFs compared with VCFs of other etiologies. In addition, there was no difference in the spread class ($P = .80$), PMMA infiltration ($P = .28$), or spread pattern ($P = .52$) between different vertebral levels.

DISCUSSION

We reviewed 198 vertebral levels treated with BKP in 137 patients at a single institution to develop a classification system for PMMA spread after BKP or PVP. We then applied the classification system to all treated vertebral levels to assess the interrater reliability and whether PMMA spread differs significantly by operator or because of the properties of the VCF. A 5-class system was developed that had moderate interrater reliability. PMMA spread was found to differ significantly between operators, but not between VCF etiologies or by the vertebral level.

Descriptions of the various appearances of PMMA spread have varied between reports. To remedy this, we created a classification system that can be used with minimal training. Examples of previous descriptions of PMMA spread include Anselmetti et al.'s contrasting "spherical" to "diffuse and irregular" spread patterns, which correspond to our globular and acinar types (13). In another clinical trial, no description of PMMA spread was provided despite an analysis of the radiographic outcomes such as height and kyphotic angle restoration (16). Baroud et al. stated that an appearance similar to a "single, uniformly expanding cloud" was preferable to that like the "fingers of a glove," which again correspond with our globular and acinar types without distinguishing localized from diffuse spread or describing mixed spread (17). A case report attributed lateral wedging after BKP to "abnormal spatial distribution of PMMA cement . . . [with] insufficient filling of PMMA cement . . . on the right side" (18). Radiopacity was highlighted as a major imaging difference between 2 cements used in an ex vivo biomechanical study (19). In another ex vivo study, Loeffel et al. made the sole quantification of PMMA spread by calculating circularity (a ratio of the actual distribution perimeter to the perimeter of a circle with equal area) and mean cement-spreading distance (14). However, these measurements did not assess the pattern within the filled area, which may reflect the PMMA concentration. Our classification system required an assessment of the spread pattern within the filled area, as well as an assessment of the degree of PMMA infiltration into the vertebral body. Interrater agreement was considered moderate on the basis of a frequently cited scale (20, 21), which is similar to the agreement found using the current protocols for prostate cancer (22), pancreatic cancer (23), and pulmonary nodule (24). Our system's categories are related, and image interpretation disagreement was most often found between closely related categories (Figure 2). This gives the classification system utility in outcomes' trials beyond what its moderate interrater reliability suggests because the effect of related classes on outcomes is likely similar and the effect of less-related classes is divergent. Raters agreed more frequently on the spread pattern (acinar vs globular vs mixed) and PMMA infiltration (localized vs diffuse) than on the spread class. However, interrater reliability was similar between all 3 measures, indicating that reducing the number of spread classes would not make the system more robust.

We used the newly created classification system to first assess differences in PMMA spread between operators. It is paramount to understand interoperator variability in BKP and PVP, as the largest clinical trials, to date, have been conducted at multiple sites and have not adjusted for potential heterogeneity between operators (4, 5, 25, 26). McDonald et al. showed, in a sample of 2 operators experienced in PVP and 5 novice operators, that several procedural measures and short-term clinical outcomes significantly change as novice operators gain experience (27). Other studies have found that the volume of PMMA injected is an important operator-dependent variable in BKP and PVP (28, 29). In addition, the time between PMMA mixing and delivery modifies viscosity, which may impact the risk of adverse events (13, 17). We showed that the 2 experienced operators achieved significantly different PMMA spreads. The first most often created a localized PMMA infiltration with a trend toward a globular pattern, whereas the other most often created a diffuse spread without a trend toward either an acinar or a globular pattern. This indicates that there is a significant heterogeneity even between experienced operators. Clinical outcomes could differ between approaches.

There are several mechanisms through which PMMA spread could affect either BKP or PVP outcomes. Liu et al. found that

PMMA distribution in the inferior portion of the vertebral body or along the endplate increases the risk of adjacent-level refracture (30). Biomechanical and finite-element analysis studies have shown that limited distribution of PMMA after unipedicular BKP or PVP potentially result in biomechanical imbalance, which could lead to lateral wedge deformities or painful toggling (9, 10). Intraosseous nerve damage has been hypothesized as a potential mechanism for pain relief after BKP or PVP (31). PMMA spread could therefore impact which nerves and how many nerves are damaged within the vertebral body. Operators may use the classification system presented in this study to quickly evaluate cement spread after procedures. Although clear recommendations do not currently exist, previous reports suggest that globular diffuse spread provides maximal biomechanical support to treated vertebral bodies with minimal risk of cement extravasation (9, 10, 17).

The next step in our study was to assess whether VCF etiology or vertebral level were associated with PMMA spread class. Loeffel et al. found that artificial media with smaller pores aided in creating denser, more circular PMMA spread (14). They interpreted this to indicate that PMMA will spread widely and unevenly in osteoporotic bone. There are few in vivo comparisons of spread between VCFs of different etiologies. In 1 study without a systematic approach for assessing spread, PMMA spread appearance was interpreted as different in VCFs because of osteoporosis compared with metastatic lesions (13). However, other studies that included patients with VCFs secondary to osteoporosis and osteolytic lesions did not compare appearance (4, 32-34). There have been no in vivo comparisons of PMMA spread within the vertebrae from different levels. In contrast to previous reports, we found no difference in PMMA spread class between fracture etiologies. We also did not observe a difference between the vertebral levels.

The limitations of our study must be acknowledged. First, the sample was drawn from a single center and only 2 operators performed a sufficient number of procedures to be compared. However, 198 total vertebral levels were treated, and finding differences in a small sample of operators may indicate that heterogeneity is prevalent. Second, VCF etiology was not uniformly reported. Despite this, an adequate number were available for comparison. Our analysis was limited to fluoroscopic images during BKP, but the classification system encompasses PMMA distributions expected after PVP. Last, a standardized follow-up was not obtained from patients, which prevents the analysis of a potential association between PMMA spread class with adverse events and pain reduction in this sample. However, the classification scheme we developed will enable future assessment of this.

We created a standardized language with which to describe PMMA spread after either BKP or PVP. PMMA spread is primarily operator-dependent, and therefore, may be a modifiable parameter that affects BKP and PVP outcomes. Future research is needed to determine if PMMA spread classes are associated with clinical outcomes after either BKP or PVP.

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