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Recent advances in Vertebral Augmentation for the treatment of Vertebral body compression fractures

Dylan N. Wolman[1] · **Jeremy J. Heit**[1]

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Abstract
Purpose of Review Osteoporotic and pathologic vertebral compression fractures (VCFs) result in significant pain, reduced quality of life, and patient morbidity. Vertebral augmentation procedures (VAPs), which include vertebroplasty and kyphoplasty, have been extensively studied. Here, we review the evidence for the effectiveness of these techniques with an emphasis on recent clinical trials.
Recent Findings There has been controversy regarding the effectiveness of VAPs in the treatment of painful VCFs. Recent high-quality clinical trials have demonstrated that with proper patient selection, which includes identification of (1) pain referable to a fracture, (2) acute or subacute fracture (less than 6 weeks), and (3) evidence of bone edema or intravertebral clefts on magnetic resonance imaging or high radiotracer uptake on bone scintigraphy, patients are highly likely to achieve significant improvements in long-term pain control and reduced pain-related disability with low procedural risk. Both vertebroplasty and kyphoplasty are effective VAPs, and no high-quality, recent study has found a substantial difference in the relative effectiveness of these techniques.
Summary VAPs are safe and effective in the management of acute, painful osteoporotic, and pathologic VCFs given appropriate clinical and imaging-based patient selection. Developing evidence suggests a role for VAPs in the management of painful chronic osteoporotic fractures, and as part of a multimodal approach toward both pain and local tumor control in patients with pathologic VCFs.

Keywords Vertebral augmentation · Vertebroplasty · Kyphoplasty · Vertebral compression · Fracture

Introduction

Vertebral compression fractures (VCFs) result from a horizontal or nearly horizontal fracture within a vertebral body that is most commonly caused by osteoporosis, spinal metastatic disease, trauma, and osteoradionecrosis [1]. These increasingly common fractures affect at least 20% of patients over 50 years of age with a female predominance [2, 3]. Once a VCF has been sustained, most patients experience significant pain that is classically exacerbated by axial loading (standing), twisting of the thorax, and any activity that increases the force on the vertebral column. Pain secondary to VCFs often renders patients bedridden, which results in further deconditioning and worsening vertebral body osteoporosis. Thus, patients suffer from a permanent decline in health-related quality of life [4–6], an increased risk of subsequent fractures [1], and increased mortality [7–9]. The healthcare cost of VCFs is estimated at over $1 billion per year for osteoporotic and pathologic vertebral fractures [10, 11].

VCFs may be treated with conservative therapy, surgery, or vertebral augmentation procedures (VAPs). Standard conservative management of VCFs consists of bed rest, analgesic medication, back bracing, and rehabilitation. However, these conservative measures fail to control pain in at least half of the affected patients [12, 13], and physicians are increasingly referring patients for more aggressive surgical or VAP treatment. Surgical VCF treatment typically consists of spinal decompression and fusion, and surgery is often reserved for patients

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✉ Jeremy J. Heit
jheit@stanford.edu

[1] Department of Radiology, Neurointerventional Radiology, Stanford University Medical Center, 300 Pasteur Drive, Room S-047, Stanford, CA 94305, USA

with neurologic deficits secondary to burst-type vertebral fractures or bony retropulsion causing significant spinal canal stenosis [11, 14, 15].

VAPs are minimally invasive procedures designed to stabilize VCFs and are commonly performed by neurointerventional radiologists, interventional radiologists, neurosurgeons, orthopedic surgeons, physiatrists, and pain management physicians. These procedures are typically performed as outpatient procedures, with moderate conscious sedation for most patients. Although VAPs are common, there remains controversy in the literature surrounding the appropriate use and efficacy of VAPs. Here, we review the current literature governing the use of VAPs for the treatment of painful osteoporotic and pathologic VCFs.

Brief Overview of VAP Techniques

Percutaneous VAPs are minimally invasive, fluoroscopically, or computed tomography-guided procedures. The two most commonly performed VAPs are vertebroplasty and kyphoplasty [16]. Patients undergoing VAPs lie prone, and the operative field is sterilely prepared and draped. Real-time imaging is used to advance a 10- to 13-gauge needle through the skin into the fractured vertebral body by traversing the vertebral body pedicle or the soft tissues lateral to the pedicle. This transpedicular trajectory ensures that the spinal cord or spinal nerves are not traversed. Once the needle has been positioned within the fractured vertebral body, an inner stylet is removed from the needle, which provides a conduit through which to treat the VCF.

Vertebroplasty is the simplest VAP, which is performed by instilling polymethyl-methacrylate (PMMA) cement through the needle into the fractured vertebral body using real-time image guidance. The PMMA permeates the fractured bone and acts as an internal scaffold that stabilizes the fracture, with the goal of reducing pain and facilitating new bone growth between the fracture fragments.

Kyphoplasty and mechanical cavitation are more complex variations on the vertebrolasty technique, and these procedures are performed in an effort to instill a greater volume of cement (kyphoplasty and mechanical cavitation) or correct kyphotic angulation (kyphoplasty). During kyphoplasty, a balloon catheter is inserted through the introducer needle prior to PMMA instillation. The balloon is then inflated within the fractured vertebral body to create a cavity within it. The balloon is then deflated, and cement is instilled through the introducer needle in a manner identical to vertebroplasty. Mechanical cavitation is performed by introducing a steerable needle through the introducer needle, which carves a channel within the fractured vertebral body before cement instillation. PMMA is then instilled through the introducer needle as described above, and the cement distributes through the created channel and vertebral body. There are many variations of these VAP techniques, but the overall goal of all techniques is fracture stabilization and pain relief.

Risks of Vertebral Augmentation Procedures

A common concern following open surgical spinal fixation procedures is the development of adjacent segment disease, wherein abnormal loading forces or alignment secondary to spinal fusion lead to selective degenerative changes of the segments adjacent to the operative site. Similarly, there has been long-standing suspicion that treatment with VAPs may increase the risk of adjacent vertebral fractures. Early and primarily retrospective studies suggested that patients may be at an increased risk of subsequent fractures after vertebroplasty, and the majority of these fractures occurred in vertebrae adjacent to the treated fractures [17]. This concern even prompted suggestions that preventative vertebral augmentation should be performed in vertebrae adjacent to the fractured level [18]. However, long-term follow-up data from several randomized controlled trials and meta-analyses have failed to demonstrate an increased risk of subsequent VCFs at any location following either vertebroplasty or kyphoplasty [19–23••]. Patients who develop more than one fracture are likely at higher risk for VCFs due to lower bone mineral density and body mass index. Iatrogenic contributors to additional VCF after VAP include excessive vertebral height restoration or angular correction and cement leakage into the adjacent disk [21, 24, 25•].

Extravertebral cement leakage and embolization are a common complication of VAPs, and rates of cement leakage in several randomized controlled trials were reported to occur in 30–70% of patients following vertebroplasty and in 20–30% of patients following kyphoplasty [23••, 25•, 26••, 27•, 28•, 29•, 30•]. Cement leakage occurs most frequently at the vertebral body end plates and may extend into the paravertebral spaces, pre- and paravertebral veins, into the adjacent discs, or posteriorly into the spinal canal [31, 32]. Cement extension into the epidural space may result in severe neurologic symptoms that may require emergent surgical decompression [32]. Increased risk for extravertebral cement leakage or pulmonary cement embolism has been demonstrated with use of lower viscosity cement, greater total number of treated vertebral levels, and in patients with osteoporotic or malignancy-associated fractures, as opposed to trauma, or painful hemangiomas [32–34].

There is limited recognition of extra-vertebral cement leakage during the procedure, and 9–50% of such occurrences are only recognized upon review of procedural spot films or CT scans [31, 34]. Cement embolization to the lungs or paradoxical cerebral cement embolization events are extremely rare, and in the majority of cases with intravenous cement extension, the cement does not extend to the lungs [35–37]. Thus,

extra-vertebral cement leakage is common, but it is rarely symptomatic.

Early Waxing and Waning Enthusiasm Toward Vertebral Augmentation

Early enthusiasm for VAPs in the treatment of painful VCFs was driven by a series of positive, primarily observational studies in the early 2000s [38–40]. The positive trend of these data culminated in 2007 with the VERTOS I study, which was the first open-label randomized controlled trial comparing vertebroplasty to conservative treatments. VERTOS I showed that vertebroplasty improved short-term pain scores in patients with subacute and chronic osteoporotic compression fractures compared to conservative management [41•]. Following VERTOS I, there was enthusiastic support for VAPs among physicians and patients, and vertebroplasty procedure rates nearly doubled among the Medicare population from 2001 to 2008 [16, 42].

However, VERTOS I was followed in 2009 by back-to-back publication of two blinded, randomized, and sham procedure-controlled trials in the *New England Journal of Medicine* [43•, 44•]. Both trials failed to demonstrate the efficacy of vertebroplasty for treatment of osteoporotic VCFs relative to a sham procedure control group. Following these reports, enthusiasm for VAP began to wane as these studies concluded that the efficacy of VAPs was related primarily to a placebo effect [43•, 44•]. At most centers, referrals for VAPs sharply declined, and a subsequent reduction in the utilization of VAPs to levels close to those seen at the turn of the millennium was observed [42, 45]. At least two insurance providers also began to decline reimbursement for these procedures given the widely published negative results, although uncertainty remained about which populations, if any, might still benefit from treatment and warrant reimbursement [46, 47].

Given the divergence of these negative findings from previously established beliefs that VAPs were efficacious, the designs of the *NEJM* trials came under heavy scrutiny as potentially underpowered, lacking in patients with sufficiently high pre-procedural pain scores, and, crucially, for selecting patients with variable fracture acuity up to 1 year [48]. Additionally, neither trial required bone marrow edema on MRI or increased uptake on bone scan as an inclusion criteria (although one did require either a fracture line *or* marrow edema) [43•, 44•]. Doubt regarding the validity of these results was present even among one of the study authors, who wrote that despite a decrease in referrals for VAPs, they continued to offer the procedures to a large proportion of patients at their own institution [45]. In the following years, a series of additional trials were published (see below), which more convincingly demonstrated that VAPs are indeed effective given appropriate patient selection with demonstrably acute vertebral fractures.

The Current State of Vertebral Augmentation

Perhaps the greatest criticism of the negative *NEJM* trials was that both trials failed to capture a cohort of patients with sufficiently acute and painful fractures, which are both considered indicators of active underlying bone inflammation [49]. In fact, a meta-analysis of these *NEJM* trials was underpowered to detect a treatment effect in patients with acute fractures, as only 25 vertebroplasty patients had fractures of less than 6 weeks of age [50, 51]. Predicated on the idea that early intervention could reduce pain in this specific subset of patients with acute or actively inflamed VCFs, several additional studies were published in the years following the contentious *NEJM* articles (Table 1). These newer trials focused on improved patient selection through stricter definitions of fracture acuity, typically less than 6 weeks, or positive radiographic evidence of ongoing local inflammation such as marrow edema on spinal MRI or bone scintigraphy, often with increased bone pain thresholds.

The VAPOUR trial is the most prominent and recent literature to support the efficacy of vertebroplasty in the early management of acute compression fractures. Like its predecessor *NEJM* trials, VAPOUR was a double-blind, randomized, and placebo-controlled trial. However, the VAPOUR trial differed crucially in its inclusion criteria: only patients with severe pain due to osteoporotic VCFs less than 6 weeks of age were included. Additionally, the primary outcome measure was success rate, defined as the proportion of subjects achieving a pain score < 4/10 (categorical data), which is the preferred statistical method of evaluating treatments of pain. Although the 95% confidence intervals overlapped slightly between the treatment and placebo groups at 14 days, 3 months, and 6 months, they did not overlap at 3 days (.19 to .43 in the treatment group compared to .01 to .17 in the placebo group) or at 1 month (.38 to .64 in the treatment group compared to .08 to .28 in the placebo group). While the overall success rates are somewhat disappointing (approximately 50% of patients treated with vertebroplasty did not achieve success), the non-overlapping 95% confidence intervals at 3 days and 1 month clearly demonstrate that the benefit from vertebroplasty is not due to placebo. In addition to the success rates, the authors found improved quality of life scores and reduced analgesic use in the treatment group [26••].

Two other large, open-label, randomized controlled trials that compared vertebroplasty to conservative management demonstrated similar findings among patients with acute osteoporotic VCFs of less than 6 weeks of age [23••, 52•]. Among these studies, the VERTOS II trial was notable in that it was the first to follow the *NEJM* reports, establishing that appropriate patient selection with acute VCFs was most important in demonstrating a treatment effect [23••]. Both studies showed similar significant improvements in pain and quality of life scores that persisted up to 1-year post-procedure and early reductions in analgesic use [23••, 52•].

Table 1 Comparison of vertebral augmentation trials

Article	*N*	Study type	Population type	Fracture acuity and characteristics	Comparison	Primary outcomes	Secondary outcomes	Primary outcome results	Secondary outcome results
Clark et al. [26••] (VAPO-UR)	120	Multicenter, double-blind, randomized, placebo--controlled trial	Osteoporotic patients	< 6 weeks with pain score ≥ 7 of 10 and MRI proven bone marrow edema or SPECT bone scintigraphy proven osteoblastic activity	Vertebroplasty to sham procedure	Numeric rated scale (NRS) pain score < 4 out of 10 at 14-days post-procedure.	Roland-Morris Disability Questionnaire (RDQ) score for back pain related disability, and quality of life questionnaires: Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) and the European Quality of Life-5 Dimensions (EQ-5D). Visual analog scale (VAS) pain score at baseline, 2 weeks and 6 months.	NRS pain score < 4 of 10 in 24/61 (44%) patients in treatment arm versus 12/59 (21%) in control arm (95% CI 6–39; $p = 0.011$).	Significantly reduced pain score at up to 6 months ($p = 0.027$), improved quality of life ($p = 0.032$), and reduced analgesic use between 3 and 6 months ($p = 0.028$–0.048). Reduced back pain related disability between 1 and 6 months ($p = 0.021$–0.002).
Leali et al. [52•]	400	Multinational, unblinded, prospective randomized controlled trial	Osteoporotic women	< 6 weeks with MRI proven bone marrow edema	Vertebroplasty to conservative management	VAS pain score at rest and with activities (0–5) and Oswestry Disability Index (ODI) at 6 months post-procedure.	Post-procedural analgesia use.	Mean pain score 4.8 pretreatment versus 2.3 post-treatment ($p \leq 0.023$); ODI 53.6% pretreatment to 31.7% post-treatment ($p \leq 0.012$), with similar results at 3 and 6 months. No significant benefit in the control arm.	65% of patients stopped all analgesics after 48 h post-procedure ($p \leq 0.0001$).
Blasco et al. [27•]	125	Single institution, unblinded, prospective randomized controlled trial	Osteoporotic patients	< 1 year with MRI proven bone marrow edema or bone scintigraphic evidence of osteoblastic activity and pain score ≥ 4 of 10 (mean fracture age 20 weeks)	Vertebroplasty to conservative management	VAS pain score and quality of life questionnaire (QUALEFFO) at 2 weeks, and 2, 6, and 12 months post-procedure.	Analgesia and antiosteoporotic medication utilization, post-procedural complications, and frequency of additional fractures with radiologic evidence.	Significantly improved pain scores in the vertebroplasty group up to 2 months ($p = 0.035$) and QUALEFFO scores throughout the study.	No difference in oral analgesic or antiosteoporotic medication use between groups. Significantly reduced necessity for intrathecal rescue analgesia in vertebroplasty group ($p = 0.0015$). Significantly increased risk of adjacent vertebral fracture after vertebroplasty (OR 2.78; $p = 0.0462$).
Farrokhi et al. [28•]	82	Single institution, single-blind, prospective randomized controlled trial	Osteoporotic patients	> 4 weeks and < 1 year refractory to analgesia (mean fracture age 28.5 weeks)	Vertebroplasty to conservative management	VAS pain score and ODI at 1 week, 2, 6, 12, 24 and 36 months.	Vertebral body height and kyphotic angle at 1, 2, and 3 years determined by plain radiography.	Reduced pain scores from 1 week ($p < 0.001$) to 6 months ($p < 0.021$) and improved ODI based quality of life from 1 week ($p < 0.028$) to 36 months ($p < 0.01$) as compared to conservative management.	Improved vertebral body height from 1 week to 36 months post-procedure ($p < 0.011$–0.01) and improved kyphotic angle from 1 week to 36 months ($p < 0.027$–0.011).
Berenson et al.	134	Multinational, unblinded,	Cancer patients	< 1 year with 1–3 pathologic	Kyphoplasty to conservative	RDQ score for back pain	RDQ score for back pain related disability,	Significantly improved RDQ and pain scores	Crossover and kyphoplasty groups had similar results at

Table 1 (continued)

Article	*N*	Study type	Population type	Fracture acuity and characteristics	Comparison	Primary outcomes	Secondary outcomes	Primary outcome results	Secondary outcome results
[25•] (CAFE)		prospective randomized controlled trial	with pathologic fractures	vertebral fractures with pain score ≥ 4 of 10 (mean fracture age 3.4–3.5 months)	management with crossover design at 1 month	related disability at 1 month.	Karnofsky performance status score, back pain NRS, analgesic use, number of reduced activity days caused by back pain, bed rest days caused by back pain, adverse events, and proportion of subsequent radiographic compression fractures assessed at 1, 3, 6 and 12 months.	in the kyphoplasty group over the control at 1 month ($p < 0.0001$).	6 and 12 months, with significantly improved RDQ, and functionality scores at 6 months, and pain scores at 1 month.
Klazen et al. [23••] (VERT-OS II)	202	Multinational, unblinded, prospective randomized controlled trial	Osteoporotic patients	< 6 weeks with pain score ≥ 5 of 10 and MRI proven bone marrow edema	Vertebroplasty to conservative management	VAS pain score at 1 month and 1 year, with clinically significant pain relief defined as a decrease of 3+ points.	Cost-effectiveness at 1 month and 1 year based on pain-free days, medical costs, and quality-adjusted survival time, estimated using the EQ-5D, QUALEFFO and RDQ questionnaires.	Significantly improved pain scores in the vertebroplasty group at 1 month and 1 year ($p < 0.0001$).	Significantly reduced analgesic use from 1 day to 1 month ($p < 0.0001$) with an average gain of 120.3 pain-free days. Vertebroplasty determined to be a cost-effective strategy with a set value of €30,000/quality-adjusted life-year.
Rousing et al. [29••] and [53•]	50	Single institution, unblinded, prospective randomized controlled trial	Osteoporotic patients	< 2 weeks or ≥ 2 but < 8 weeks refractory to analgesia	Vertebroplasty to conservative management	VAS pain score at 12–24 h and at 3 and 12 months.	Physical and quality of life assessments with the Short-Form physical component summary scale (SF-36), EQ-5D, and Dallas Pain Questionnaries (DPQ), and the Barthel Index for pain-related functionality and quality of life, performed at 3+ months.	Significantly improved pain scores in the vertebroplasty group at 12–24 h ($p < 0.001$) but no difference at 3 or 12 months between groups.	No significant difference between groups at 3 months and 12 months regarding quality of life or functionality scores, but initial pain and functionality scores differed significantly at inclusion.
Wardlaw et al. [30•] (FREE)	300	Multinational, unblinded, prospective randomized controlled trial	Osteoporotic or cancer patients with pathologic fractures	< 3 months with pain score ≥ 4 of 10 and MRI proven bone marrow edema	Kyphoplasty to conservative management	Short-form physical component summary scale (SF-36) from baseline to 1 month, measuring physical ability weighted quality of life.	SF-36 and EQ-5D scores at 1, 2, 6, and 12 months, VAS pain score, and analgesic utilization. Quantitative morphometric and semiquantitative assessments for new or worsening vertebral fractures assessed by plain radiography at baseline, 3 months and 12 months.	Significantly improved SF-36 scores at 1 month ($p < 0.0001$) in the kyphoplasty group, which remained significant to 6 months ($p = 0.0064$).	Significantly improved EQ-5D quality of life scores at 1 month ($p = 0.0003$) and 12 months ($p = 0.0252$), with 1.5 fewer activity restricted days per week ($p = 0.0004$) at 1 month, and improved pain scores from 1 week to 1 year ($p < 0.0001$ to $p = 0.0034$). Reduced

Table 1 (continued)

Article	*N*	Study type	Population type	Fracture acuity and characteristics	Comparison	Primary outcomes	Secondary outcomes	Primary outcome results	Secondary outcome results
									narcotic analgesic use between 1 and 6 months.
Kallmes et al. [43•] (INVES-T)	131	Multinational, double-blind, prospective randomized controlled trial	Osteoporotic patients	< 1 year with pain score ≥ 3 of 10 and MRI proven bone marrow edema if uncertain fracture age (mean fracture age 16–20 weeks)	Vertebroplasty to sham procedure (including periosteal bupivicaine injection) with crossover design at 1 month	Modified RDQ score for back pain related disability at 1 month.	Pain Frequency Index, Pain Bothersomeness Index, Study of Osteoporotic Fractures-Activities of Daily Living (SOF-ADL) scale, SF-36, and EQ-5D scale scores at 3, 14, 30, and 90 days, and modified RDQ score at 3, 14, and 90 days. Analgesic medication use was also assessed at 3, 14, 30 and 90 days.	Significant improvement from baseline without significant intergroup difference in modified RDQ or VAS pain scores at 1 month, however results trended toward a clinically significant improvement in pain in the vertebroplasty group (30% reduction from baseline; $p = 0.06$).	Higher crossover rate in the control group than in the vertebroplasty group at 3 months ($P < 0.001$). Similar significant improvement in back-related disability, quality of life scores, and analgesia in both groups from 3 days to 1 month.
Buchbinder et al. [44•]	78	Multicenter, double-blind, randomized, placebo--controlled trial	Osteoporotic patients	< 1 year with MRI proven bone marrow edema (median fracture age 9–9.5 weeks)	Vertebroplasty to sham procedure	VAS pain score at 1 week, and 1, 3, and 6 months.	QUALEFFO, Assessment of Qality of Life (AQoL), and EQ-5D questionnaires as quality of life measures, modified RDQ scale for pain-related disability, and pain scores at rest and in bed, assessed at 1 week, and at 1, 3, and 6 months.	Significant improvement from baseline without significant intergroup difference in VAS pain scores at any time point from 1 week to 6 months.	Significant improvement from baseline without significant intergroup differences in any quality of life, disability or pain-related measures at any time point from 1 week to 6 months.

Several other randomized controlled trials utilized less stringent inclusion criteria. These studies included patients with subacute or chronic vertebral fractures based upon time of symptom onset, or pain refractory to analgesia, with variable use of imaging indicators of inflammation, such as bone marrow edema on MRI. Likely due to their heterogeneous patient populations, these trials demonstrated less consistent results for the efficacy of VAPs, with pain score improvements in the treatment arms demonstrating variably over time. Some patients showed pain score improvement only in the immediate postoperative period [29•, 53•], whereas others benefited 2 or 6 months after treatment with an associated improvement in quality of life scores [27•, 28•]. Furthermore, a post hoc analysis of patients from one of the original 2009 *NEJM* trials demonstrated a modest improvement in pain score 1 year after treatment by vertebroplasty, which also likely reflects the heterogeneous patient population initially enrolled in this study [54•].

Evidence for VAP Effectiveness Summary

The body of evidence for VAPs in the treatment of painful VCFs is developing in a fashion analogous to that for endovascular thrombectomy in patients with stroke secondary to large vessel intracranial occlusions [63]. In the stroke literature, several trials initially failed to demonstrate safety and efficacy of endovascular therapy due primarily to inappropriate patient selection and underdeveloped tools until in 2015, five landmark trials definitively demonstrated the efficacy of the procedure [64–66]. With several promising trials pending, particularly VERTOS IV, a randomized, placebo-controlled trial designed to further test the efficacy of vertebroplasty in the management of acute osteoporotic fractures, and two additional trials regarding the efficacy of VAPs for chronic vertebral fractures (VERTOS V and OSTEO + 6), the VAP literature may soon parallel that for endovascular stroke therapy [67–69].

Pathologic Compression Fractures and Vertebral Augmentation

Pathologic vertebral fractures are common in patients with bony metastases, large vertebral hemangiomas, multiple myeloma, and primary bone tumors. These fractures may occur from chemotherapy-, malignancy-, or radiation-induced osteopenia or osteonecrosis, which together comprise the second most common cause of VCFs [11, 55]. However, most major trials to evaluate the efficacy of VAPs focus on the more prevalent osteoporotic population, which leaves less data to guide physicians in the treatment of pathologic VCFs with VAP [56]. Nevertheless, VAPs for the treatment of pathologic VCFs is commonly performed and recommended [57].

Two major unblinded randomized controlled trials compared kyphoplasty to conservative management of patients with variably acute, subacute, or chronic pathologic vertebral fractures, and these studies demonstrated significantly improved pain, quality of life, and functionality scores at 1 month [25•, 30•]. These differences lessened, however, with longer follow-up to 1-year post-procedure in the vertebroplasty arm, which may be related to the heterogeneity of fracture acuity among enrolled patients [25•, 30•]. Several additional non-randomized prospective studies support VAPs in the management of painful pathologic fractures, and these studies show excellent procedural safety and improved post-procedural pain, functionality, and mobility scores at 12–24 months [58–61]. Additionally, VAPs reduced lengths of stay and improved safety and cost-efficiency profile relative to open surgery [62].

Patient Selection for Vertebral Augmentation

Appropriate patient selection is critical to maximize the efficacy of VAPs. Once a patient with a VCF is identified, the evidence best supports treatment of those with acute fractures (less than 6 weeks of age) with severe pain referable to the fracture (Table 1; [23••, 26••, 52•]). Definition of a reliable pain threshold to warrant intervention remains difficult due to variability in the specific pain scales and thresholds employed by several trials, and a lack of standardization in the administration of pain questionnaires may skew patient responses [70].

Vertebral augmentation is additionally commonly recommended for patients with persistently painful subacute or chronic fractures, or those with painful pathologic fractures of any age, although the evidence is less decisive for these subpopulations [57, 71, 72]. Several trials demonstrated significantly improved analgesia and quality-of-life scores following VAPs in a heterogeneous population with VCFs under 1 year of age [25•, 27•, 28•, 30•], though few have focused on these patients specifically [41•, 73, 74]. While more definitive trials regarding the treatment of non-acute VCFs are pending [68, 69], the following radiologic signs of active fracture inflammation remain most predictive of therapeutic success across fractures of any age.

Reliable radiographic predictors of successful therapy include vertebral marrow short-tau inversion recovery (STIR) sequence hyperintensity on MRI and increased radiotracer uptake on bone scintigraphy, which are indicators of bone marrow edema and osteoblastic activity, respectively. These imaging findings are radiologic biomarkers for fracture acuity or evidence of otherwise occult fractures that may be amenable to treatment. These criteria are of particular importance in patients with severe osteoporosis, in whom visualization of vertebral fractures on plain radiography or computed tomography is often limited. Identification of such occult fractures

by MRI with a STIR sequence may change or increase the number of therapeutic vertebral targets [49, 75] while also providing additional procedural planning information in patients with metastatic or primary bony tumors [76]. Beyond STIR imaging, contrast-enhanced MRI has been demonstrated to be more sensitive than unenhanced MRI for the detection of intravertebral clefts, which represent fracture cavities within a compressed vertebral body [77]. Intravertebral clefts are associated with a more painful or non-healing compression fracture subtype and are therefore likely to be most amenable to treatment by VAP [77]. Figure 1 demonstrates an example of both osteoporotic and pathologic acute VCFs identified by MRI with a STIR sequence, which were subsequently successfully treated with vertebroplasty.

Bone scintigraphy with technetium 99m-methyl diphosphonate (MDP) is the most sensitive indicator of osteoblastic activity, which is a sign of active bone turnover and inflammation seen in acute or subacute fractures and a reliable predictor of response to treatment with a VAP [78–80]. Particularly when used with SPECT-CT imaging for improved anatomic localization, scintigraphy is at least as sensitive as MRI, and this technique should be strongly considered in patients in whom MRI is contraindicated [81]. There is some evidence to suggest that bone scintigraphy may be more sensitive than MRI in the detection of acute to subacute vertebral fractures [82]. However, this study did not compare the sensitivity of bone scintigraphy to MRI with STIR [82]. Another small retrospective study found that scintigraphy was more sensitive in the detection of chronic fractures than MRI, but that the two techniques were complimentary [83].

Dynamic plain radiography that demonstrates vertebral mobility may be another indicator of positive response to VAP treatment. Patients with a mobile pseudoarthrosis within the fractured vertebral body may experience pain relief following cement stabilization of the mobile bony elements, which is one potential mechanism for the long-acting analgesic effect of VAPs [84, 85]. However, these findings do not necessarily explain the analgesia demonstrated by VAPs in the articles summarized in Table 1 and may only represent one facet of the poorly understood mechanisms by which VAPs treat pain.

Vertebroplasty Versus Kyphoplasty

Vertebroplasty and kyphoplasty are similar VAPs, but kyphoplasty purports to provide superior pain relief through partial vertebral body height restoration using a balloon positioned within the collapsed vertebral body prior to the instillation of PMMA cement. Several trials have attempted to

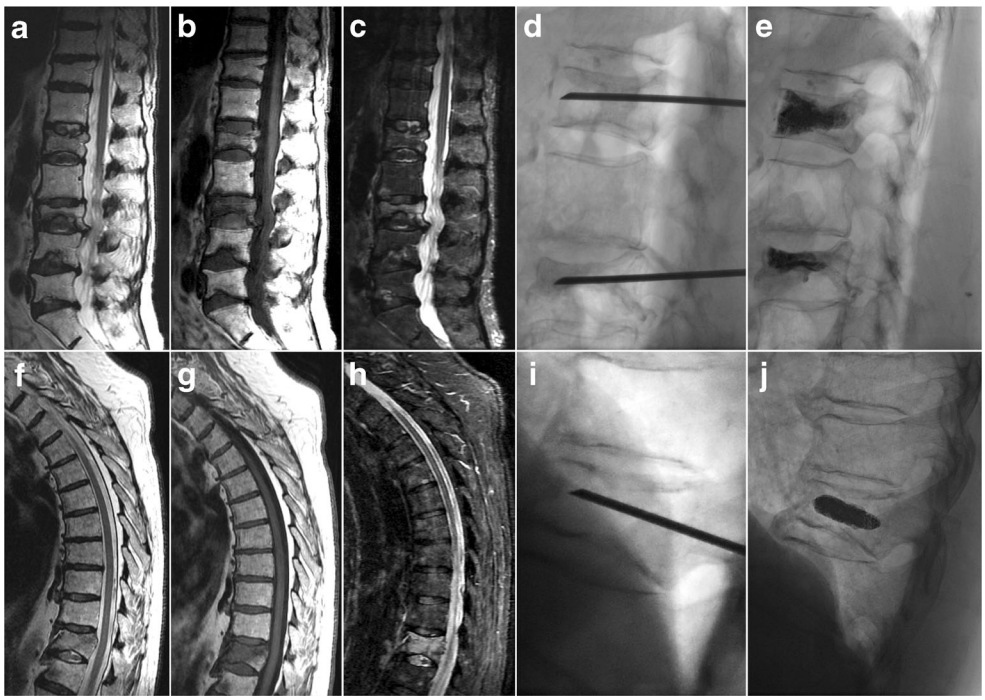

Fig. 1 Osteoporotic and pathologic vertebral compression fractures before and after treatment. **a**–**e** Magnetic resonance and procedural fluoroscopic images of the lumbar spine in an 80-year-old female patient with osteoporosis, demonstrating acute compression fractures of the L1 and L3 vertebral bodies. **f**–**f** Magnetic resonance and procedural fluoroscopic images of the thoracic spine in a 73-year-old male patient with multiple myeloma, demonstrating an acute pathologic fracture of the T12 vertebral body. Significant bone marrow edema is seen within the fractured vertebral bodies as decreased T1-weighted signal intensity (**b**, **g**) and increased T2-weighted and STIR signal intensity (**a**, **f** and **c**, **h**). Procedural fluoroscopic images during (**d**, **i**) and after (**e**, **j**) successful vertebroplasty of the vertebral compression fractures, which provided excellent pain relief for both patients.

determine if outcomes or complications in patients with VCFs treated by vertebroplasty differ from those treated by kyphoplasty. In patients with osteoporotic fractures present for less than 12 months, two large randomized controlled trials failed to demonstrate a difference in pain or disability scores from 1 to 5 years following treatment; one of these trials was stopped after an interim analysis failed to demonstrate a significant difference between the two techniques [24, 86, 87]. Kyphoplasty provided a significant improvement in abnormal kyphotic angle, but this improvement did not result in reduced pain or disability. Furthermore, there was a small increase in the number of subsequent adjacent vertebral fractures 5 years after treatment follow-up, which was suggested to be etiologically related to excessive angular correction [24]. The equivalency of vertebroplasty and kyphoplasty in improving pain, quality of life, and disability reduction was further supported by two meta-analyses [88, 89]. These studies, among others, indicate that there was no difference in risk of additional fractures up to 1 year following treatment [88–90]. However, kyphoplasty may result in reduced recurrent fractures of the treated vertebrae [88, 89].

All VAP procedures performed with PMMA incur a small risk of extravertebral cement leakage, which may impinge upon adjacent nerves, the spinal cord, or vascular structures. Interestingly, many studies have shown an approximately three-fold higher rate of extra-vertebral cement leakage with vertebroplasty compared to kyphoplasty [24, 86–89], although the clinical significance of this leakage has not been well described. The cause of the higher rate of cement leakage seen in vertebroplasty is not completely understood. The risk of cement leakage is thought to be increased by high pressure infusion and low cement viscosity, and kyphoplasty is thought to result in lower pressure cement infusion following balloon dilation of the vertebral body. In one prospective study, the use of a high viscosity cement during vertebroplasty resulted in less extra-vertebral cement leakage relative to kyphoplasty performed with cement of standard viscosity [33]. However, there were no differences in the frequency of clinically significant cement embolization between vertebroplasty and kyphoplasty [33].

Multiple studies demonstrated a significant reduction in kyphotic angle following kyphoplasty, although the absence of kyphotic correction was not associated with differences in pain, disability, or quality of life scores. Additionally, compression ratios and vertebral body heights were not significantly improved with kyphoplasty, suggesting a failure to adequately expand a compressed vertebral body in practice [89]. Among patients with intravertebral clefts, vertebroplasty was demonstrated to significantly reduce pain scores without a difference in disability scores at 1 year when compared against kyphoplasty, constituting the only patient population for whom there is evidence of analgesic superiority of one procedure over the other [91].

Overall, vertebroplasty and kyphoplasty appear broadly equivalent in the improvement of pain scores, quality of life scores, and disability rates, and these two techniques have similar risk profiles. Kyphoplasty improves kyphotic angulation and slightly reduces the risk of vertebral re-fracture, but these benefits are of uncertain clinical significance. Given a relative lack of comparisons between the procedures in patients with acute vertebral fractures or among those with spinal metastatic disease, further studies are warranted to determine if these subpopulations may benefit from a particular VAP.

Novel Utilization of Vertebral Augmentation and Future Directions

Spinal Metastatic Disease Advances

There are emerging data that vertebral augmentation may be a beneficial component of a multimodal approach to the treatment of malignant spinal metastases. Early evidence suggests that the analgesic effects of VAPs are complimentary to those of external beam radiation in the treatment of pathologic spinal fractures, and VAPs may achieve high rates of complete pain control when performed before or after external beam radiation [92]. Additional studies are warranted to determine more definitively whether VAPs may be more broadly used to treat pathologic fractures in oncology patients.

While external beam radiation is the standard of care for spinal metastases, some tumors are relatively radio-resistant, which limits the effectiveness of radiation therapy. Trials are underway to determine whether radiofrequency-ablation or cryo-ablation of spinal metastatic disease followed by VAPs result in local tumor control and pain relief [93]. The effectiveness of radiofrequency- and cryo-ablation in the treatment of localized bone tumors, such as osteoid osteomas, osteoblastomas, and chondroblastomas, offers hope that these techniques may prove effective in the treatment of spinal metastatic disease [94].

VAPs for the treatment of spinal metastatic disease may be bolstered by the recent approval of radium-223 dichloride (^{223}Ra), which is an alpha particle radiation emitter approved for the treatment of metastatic prostate cancer. ^{223}Ra is a calcium mimetic that is delivered systemically and incorporated into the hydroxyapatite bone matrix at sites of high bony turnover (characteristic of osteoblastic metastases) where it releases short-range, high-energy ionizing particles that ablate adjacent tumor cells [95, 96]. Vertebral augmentation following systemic ^{223}Ra therapy or VAPs performed using cement that encapsulates an alpha-emitting agent may provide improved local tumor control and pain management. It will be of interest to see whether these techniques are of benefit in the treatment of spinal metastatic disease.

Osteoporotic Compression Fracture Advances

The effectiveness of VAPs for the treatment of acute and subacute VCFs has prompted speculation as to whether VAPs may benefit some patients with chronic VCF. Two prospective trials found that patients with persistently painful, chronic (aged greater than 3 months), osteoporotic vertebral fractures experienced significant pain relief and reduced disability following VAPs compared to conservative management [73, 74]. These results suggest that vertebral augmentation may stabilize a pseudoarthrosis within a chronic non-healed VCF, although other mechanisms are possible. An upcoming randomized, placebo-controlled clinical trial, VERTOS V, promises to provide a more definitive evaluation of the efficacy of VAPs in the treatment of chronic fractures [68].

Just as kyphoplasty was developed as a technological evolution of vertebroplasty, several new methods of vertebral augmentation are under exploration. Novel cements, including calcium phosphate, calcium sulfate, and elastic silicon polymer cements, may reduce the risk of extra-vertebral cement extension and adjacent nerve damage from the exothermic curing reaction of PMMA. The emerging elastoplasty technique is performed by injection of a non-exothermic silicon polymer cement that has a longer working time than PMMA cement, higher elasticity, and a higher adherence to bone. This technique has been shown to be non-inferior to standard kyphoplasty in an initial trial [97]. Several new percutaneous endoprostheses are being developed for intravertebral insertion. Two of these expandable nitinol endoprostheses have demonstrated improved vertebral height restoration, lower rates of extravertebral cement extrusion, and comparable analgesic effects for both osteoporotic and malignancy-associated fractures [98–100]. It will be of interest to determine if these endoprostheses are clinically superior and cost-effective relative to standard VAPs.

Conclusions

VAPs are a safe and effective first-line treatment for VCFs, and these procedures result in significantly improved rates of pain relief and quality of life as well as reduced disability. The effectiveness of VAP requires appropriate patient selection, and patients most likely to benefit include those with painful acute fractures (less than 6 weeks of age) with associated high radiotracer uptake on bone scintigraphy, STIR hyperintensity on MRI, or evidence of intravertebral clefts. There is currently no strong evidence that one VAP technique is superior to another, and vertebroplaty and kyphoplasty should be considered equivalent techniques. New devices and cement in concert with well-designed clinical trials are expected to expand the role of vertebral augmentation in the treatment of VCF and spinal metastatic disease in the near future.

Compliance with Ethics Standards

Conflict of Interest The authors declare that they have no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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