Although over 300 articles have been published annually on vertebral augmentation in the last 5 years, there remains much debate about a fundamental question — is vertebral augmentation a safe and effective treatment to achieve analgesia, reduce disability, and improve quality of life in patients with a vertebral fracture? In this modern era of evidence-based clinical practice and public health care policy and funding, an evidentiary basis is needed to continue to perform vertebral augmentation.

The aim of this narrative review is to summarize the latest and highest quality evidence for efficacy, safety, cost effectiveness, and potential survival benefit after vertebroplasty and kyphoplasty. The design, major inclusion criteria, primary outcome measures, relevant primary baseline characteristics, primary outcomes, relevant secondary outcomes, and limitations of prospective multicenter randomized sham-controlled and conservative management-controlled trials are summarized. Recently published meta-analyses or systematic reviews of efficacy that include these recent prospective studies of vertebral augmentation are examined. The highest quality procedural safety data relating to medical complications, cement leaks, and subsequent vertebral fracture are reviewed. Publications from national databases analyzing potential reduction in length of hospital stay and reduction in mortality after vertebral augmentation are presented. Finally, emerging literature assessing the potential cost-effectiveness of vertebral augmentation is considered.

This narrative review will provide interventional pain physicians a summary of the latest and highest quality data published on vertebral augmentation. This will allow integration of the best available evidence with clinical expertise and patient wishes to make the most appropriate evidence-based clinical decisions for patients with symptomatic vertebral fracture.

Key words: Vertebroplasty, kyphoplasty, spinal fracture, osteoporosis, cancer

Most osteoporotic vertebral compression fractures are asymptomatic or result in minimal pain. It is estimated that only one third of vertebral fractures result in medical attention, and 10 – 20% result in hospitalization (2,4). In the vast majority of patients, acute back pain symptoms are mild and subside over 6 – 8 weeks as the fracture heals. Conservative medical therapy is thus appropriate for the vast majority of vertebral compression fractures. Vertebral augmentation is typically considered for patients presenting with a symptomatic vertebral fracture that results in severe disabling back pain, marked reduction in mobility, and quality of life. These patients typically represent a small fraction of patients who are hospitalized for a symptomatic vertebral fracture. Open surgical decompression and fusion is generally reserved for patients with associated neurological deficit; only 5% of those seeking medical attention receive open surgical intervention (5). Hybrid techniques such as short-segment spinal fusion combined with vertebroplasty are also typically limited to patients with associated neurological deficit (6).

**Burden of Disease — Neoplasia**

Vertebral fractures in cancer patients may be secondary to osteoporosis, primary neoplasm, metastasis, osteopenic effects of drug therapy, or effects of radiation therapy. Reduced bone mineral density is found in nearly half of all patients diagnosed with cancer and osteoporosis is more common when compared to the general population (7). Spinal metastases occur in up to 70% of patients with breast and prostate cancer (8). These weaken bony integrity which can be further compromised by the effects of therapy — aromatase inhibitors in breast carcinoma and androgen deprivation in prostate cancer markedly increase the rate of bone loss (9) and consequent fracture risk. Radiation treatment for spinal metastases also increases the risk of vertebral fracture from radiation necrosis of both tumor and bone (10-12).

Most spinal metastases are asymptomatic at time of radiographic discovery (13). As the spinal tumor progresses, stretching or invasion of the periosteum causes local somatic pain. Foraminal or epidural extension resulting in nerve root or cord compression causes neuropathic pain. Between 10 – 20% of patients experience symptomatic cord compression (14); 90% of these patients experience pain (15). The prevalence of malignant vertebral fractures is unknown. Even in patients with known history of malignancy and vertebral fracture, malignancy is only identified in about half of...
patients undergoing biopsy of the fractured vertebra (16). Regardless of the etiology, fractures in patients with cancer cause significant exacerbation of local pain, and can be disabling.

In cancer patients, palliative treatments that provide rapid pain relief with improved functional status and quality of life are important. Conservative medical therapy with appropriate narcotic and non-narcotic pharmacologic pain management is the mainstay. Palliative radiotherapy for pain relief from painful spinal metastasis results in complete and partial pain relief in 20% and 50% of patients by 3 months (17). However median time to response is approximately 3 weeks (18). Moreover new or worsening vertebral fractures occur in 10 – 40% of patients after spinal radiotherapy (10-12). This typically occurs at a median of 3 months, and in larger lytic metastases of the lower spine (11,12).

Vertebral augmentation is another option for cancer patients presenting with a symptomatic fracture that results in severe disabling back pain and marked reduction in quality of life; patients with significant epidural tumoral extension or neural compression are typically excluded. Open surgical decompression and fixation is typically reserved for patients with symptomatic focal cord compression, good baseline performance status, and reasonable life expectancy (19).

Efficacy

Evidence based medicine involves the integration of the best available evidence with clinical expertise and patient values. The best evidence arises from prospective randomized trials and meta-analysis of these trials, as their design overcomes many biases in observational studies. Multicenter studies increase the generalizability of the trial result. The design, major inclusion criteria, primary outcome measures, relevant primary baseline characteristics, primary outcomes, relevant secondary outcomes, and limitations of prospective multicenter randomized sham-controlled and conservative management-controlled trials are summarized.

Prospective Randomized Sham-controlled Studies

The Investigational Vertebroplasty Safety and Efficacy Trial (INVEST) was an international prospective multicenter blinded randomized sham-controlled trial of vertebroplasty for osteoporotic fracture published in 2009 (20). A total of 131 patients were randomized to vertebroplasty (n = 68) and sham procedure arms (n = 63).

Major Inclusion Criteria

This included back pain intensity of 3 or more (scale 0 – 10) of less than 12-month duration with inadequate pain relief with standard medical therapy; one to 3 painful osteoporotic vertebral compression fractures between vertebral levels T4 and L5. For fractures of uncertain age, an additional requirement was increased uptake on bone scan or marrow edema on MRI.

Primary Outcome Measures

The primary outcome measure was back-pain intensity scores during the preceding 24 hours (on a scale of 0 to 10, with higher scores indicating more severe pain) and scores on the modified Roland–Morris Disability Questionnaire (RDQ), both at one month.

Relevant Primary Baseline Characteristics

Average back pain intensity in last 24 hours was 7 in both arms. Mean back pain duration was 16 weeks in the vertebroplasty arm and 18 weeks in the control arm. Pain for greater than 6-months duration was present in one-third of patients in both arms. Mean RDQ score was 17 in the vertebroplasty arm and 18 in the control arm.

Primary Outcome

There was no significant difference in back pain intensity or modified RDQ score at one month (P = 0.19 and P = 0.49 at one month, respectively).

Relevant Secondary Outcomes

There were no differences in further measures of pain, disability, and quality of life between the 2 groups at one month. In a post hoc analysis, there was a trend toward a higher rate of clinically meaningful improvement in pain (a 30% decrease from baseline) in the vertebroplasty group compared to the control group (64% vs. 48%, P = 0.06).

Relevant Limitations

A major limitation of the INVEST trial was the inclusion of fractures up to 12 months old and the lack of a physical examination component. Marrow edema on magnetic resonance imaging (MRI) or uptake on bone scan was only required for those fractures of indeterminate clinical age; however, the rate of usage of MRI or bone scan was not initially published. Importantly, the lack of MRI or bone scan correlation could mean that a radiographically occult adjacent level vertebral fracture responsible for the back pain was not treated.
in the vertebroplasty arm. Furthermore, in the sham procedure arm, infiltration of local anesthetic to the periosteum may have resolved pain that primarily arose from facet joints, pedicle, or paravertebral soft tissues that were unrelated to the vertebral fracture. Moreover, there was no standardization or report of the additional medical treatments that the patient received during the follow-up period. In addition, by 3 months, 27 patients (43%) in the control arm had crossed over to the intervention arm and no longer-term comparisons were possible.

Similarly, an Australian prospective multicenter blinded randomized sham-controlled trial of vertebroplasty for osteoporotic fracture was published in 2009 (21,22). A total of 78 patients were randomized to vertebroplasty (n = 38) and sham procedure (n = 40) arms.

**Major Inclusion Criteria**
This included back pain of less than 12-month duration and the presence of one or 2 recent vertebral fractures, defined as vertebral collapse and MRI bone marrow edema, a fracture line or both.

**Primary Outcome Measure**
The primary outcome measure was the score for overall back pain (over the course of the previous week) as measured on a scale of 0 to 10 (with 0 indicating no pain, 10 indicating the maximum imaginable pain) at 3 months.

**Relevant Primary Baseline Characteristics**
Baseline mean VAS scores were 7.1 and 7.6 in the vertebroplasty and conservative arms, respectively. Mean duration of back pain was almost 3 months.

**Primary Outcomes**
There was no significant difference in overall back pain intensity at 3 months. In the vertebroplasty arm there was a reduction in overall back pain intensity by 2.6+/-2.9 compared to 1.9+/-3.3; the absolute adjusted between-group mean difference was 0.6 in favor of vertebroplasty (95% confidence interval [CI]; -0.8 to 1.8).

**Relevant Secondary Outcomes**
There was no significant difference in back pain scores at one week, one month, or at 6 months. Additional measures of pain, disability, and quality of life also did not differ between the 2 groups.

**Relevant Limitations**
Major limitations of this trial are the inclusion of fractures up to 12 months old, the lack of a minimum back pain intensity score, the lack of a physical examination component, and small patient numbers. In addition, the outcomes may have been weighted to the treatment effect at a single center — 70% of patients were recruited at one of the 4 recruiting centers; 2 of the recruiting sites enrolled only 5 patients.

**Prospective Multicenter Randomized Conservative Management-controlled Studies**
The VERTOS trial was a multicenter open label randomized conservative management controlled trial of vertebroplasty for osteoporotic fracture published in 2007 (23). A total of 34 patients were randomized to vertebroplasty (n = 18) and medical management (n = 16).

**Major Inclusion Criteria**
This included invalidating back pain that was refractory to medical therapy for at least 6 weeks but not longer than 6 months, focal tenderness on physical examination at the fractured level, and bone marrow edema on MRI scan (defined as a decreased signal intensity on T1-weighted images and increased signal intensity on short tau inversion recovery [STIR] images).

**Primary Outcome Measure**
The primary outcome measure was the score for overall back pain (using the Visual Analogue Scale [VAS] [24]) as measured on a scale of 0 to 10 (with 0 indicating no pain, 10 indicating the maximum imaginable pain) at 2 weeks.

**Relevant Primary Baseline Characteristics**
Baseline mean VAS scores were 7.1 and 7.6 in the vertebroplasty and conservative arms, respectively. Mean duration of back pain was almost 3 months.

**Primary Outcomes**
By day one post vertebroplasty, the mean VAS scores were 4.7 and 7.1 in the vertebroplasty and medical arms, respectively, with a significant difference between the 2 arms of -2.4 (95% CI; -3.7 to -1.0) in favor of vertebroplasty. By 2 weeks, the difference in the VAS scores was no longer significant (difference between the 2 arms of -1.5 (95% CI; -3.2 to 0.2).
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Relevant Secondary Outcomes

Analgesic use was also reduced in the vertebroplasty arm (-1.4; 95% CI; -2.1 to -0.8). There were significant improvements in disability and quality of life in the vertebroplasty arm over conservative management at 2 weeks. The mean difference in the RDQ scores between the 2 groups at 2 weeks was -5 points (95% CI; -8.4 to -1.2); the mean difference in the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO) scores between the 2 groups at 2 weeks was -14 points (95% CI; -24.7 to -3.4).

Relevant Limitations

The major limitation of the VERTOS trial was the small size and lack of blinding. Moreover, as crossover was allowed after 2 weeks, no long-term follow-up was possible. Notably, 14 of the 16 patients in the conservative arm requested vertebroplasty after 2 weeks.

The Fracture Reduction Evaluation trial (FREE) trial was an international multicenter open label randomized conservative management controlled trial of kyphoplasty for osteoporotic fractures published in 2009 (25,26). A total of 300 patients were randomized and divided into kyphoplasty (n = 149) and conservative medical management arms (n = 151).

Major Inclusion Criteria

This included severe back pain with intensity score of 4 or more (on 10 point scale) that was present for less than 3 months, bone marrow edema or pseudoarthrosis on MRI scans, and fracture level of T5 or lower. Fractures from primary or secondary osteoporosis, multiple myeloma, or osteolytic metastatic tumors were included. Patients with osteoblastic tumors and radicular or spinal cord compression pain syndromes were excluded.

Primary Outcome Measure

The primary outcome measure was the difference in a global quality of life measure weighted on physical abilities, using the short-form-36 physical component summary (SF36-PCS) scale between the kyphoplasty and control groups.

Relevant Primary Baseline Characteristics

Mean duration of back pain was approximately 6 weeks. Mean time between randomization and kyphoplasty was 7 days. SF-36 PCS scores were approximately 25 in both groups.

Primary Outcomes

Kyphoplasty resulted in significantly improved quality of life over conservative treatment at one month. The improvement in mean SF-36 PCS score from baseline to one month was 5.2 points (95% CI; 2.9 – 7.4) more in the kyphoplasty group than in the conservatively managed arm (P < 0.0001). The minimum clinically important difference (MCID) is a quantitative assessment of clinical relevance for a given magnitude of health related quality of life or disability score change. Scores above the MCID are indicative of a potentially important change. The MCID threshold proposed for SF-36 PCS scores after lumbar spine surgery is 4.9 (27).

Relevant Secondary Outcomes

Secondary outcome measures were SF-36 PCS and other quality of life scores, back pain and disability scores at one, 3, 6, and 12 months. There remained significant improvements in the SF-36 PCS scores in favor of kyphoplasty at 3 and 6 months (P = 0.0008 and P = 0.0064) but not at 12 months (P = 0.208). Back pain scores were significantly reduced at one week (P < 0.0001) and 12 months (P = 0.0034). Reductions in the RDQ disability scores in favor of kyphoplasty were significant at one month (P < 0.0001) and 12 months (P = 0.0012). Kyphoplasty patients were less likely to be using narcotic analgesia between one and 6 months; patients in the kyphoplasty arm reported 3 fewer days of restricted activity per fortnight (1.3 – 4.6; P = 0.0004) because of back pain at one month. This was no longer significant at 12 months (1.6 days, -0.1 to 3.3; P = 0.0678). There remained a significant reduction in back pain scores for patients in the kyphoplasty arm compared to conservative therapy at 24 months (P = 0.009), there were no significant differences in the SF-36 PCS or RDQ scores at 24 months (25).

Relevant Limitations

A major limitation to the FREE trial was the lack of blinding, which can overestimate treatment benefit (28). Furthermore, cancer related fractures were also included; however, only 4 of the 300 patients randomized had pathological fractures.

The VERTOS II trial was an international multicenter open label randomized conservative management controlled trial of vertebroplasty for osteoporotic fracture published in 2010 (29). A total of 202 patients were equally randomized into vertebroplasty (n = 101) and conservative medical management (n = 101) arms.
Major Inclusion Criteria
This included severe back pain with VAS intensity score of 5 or more that was present for 6 weeks or less, focal tenderness on physical examination at the fractured level, bone marrow edema on MRI scan, and fracture level of T5 or lower.

Primary Outcome Measure
The primary outcome measure was pain relief at one month and one year, measured with a VAS score.

Relevant Primary Baseline Characteristics
Baseline mean VAS scores were 7.8 and 7.5 in the vertebroplasty and conservative arms, respectively. Mean duration of back pain was approximately 30 days. Vertebroplasty was performed at a mean of 5.6 weeks post symptom onset.

Primary Outcomes
Vertebroplasty resulted in significantly greater pain relief at one month than did conservative treatment. The mean reduction of VAS score from baseline was 2.6 (95% CI; 1.74 – 3.37, \( P < 0.0001 \)) greater in the vertebroplasty arm at one month. This was a durable effect, with the reduction in the mean VAS score at one year of 2.0 (1.13 – 2.80, \( P < 0.0001 \)). The MCID threshold proposed for 0 – 10 pain rating scales after lumbar spine surgery is 1.2 (27).

Relevant Secondary Outcomes
Secondary outcomes were cost-effectiveness at one month and one year; medical costs, time without burdensome pain, and quality-adjusted survival time were also reported. The cost difference between vertebroplasty and conservative treatment at one year was approximately the cost of vertebroplasty for the trial (£2463 or approximately $3,500 US dollars). An average of 120 (95% CI; 163 – 177) pain-free days (VAS 0 – 3) were gained in the 12 months after vertebroplasty. Significant pain relief (reduction of VAS from baseline by 3 points or more) was achieved earlier and in more patients after vertebroplasty (30 days until significant pain relief, 95% CI; 11 – 48) than with conservative treatment (116 days, 95% CI; 86 – 145) (\( \chi^2 = 55.6, P < 0.0001 \)).

Relevant Limitations
A major limitation to the VERTOS II trial was the lack of blinding, which can overestimate treatment benefit (28). Notably, later analysis of the patients in the conservatively treated arm by the VERTOS II investigators revealed that 60% of patients in the conservatively treated arm had sufficient pain relief (VAS ≤ 3) at 12 months, with the vast majority achieving this within 3 months (30).

The Cancer Patient Fracture Evaluation (CAFE) trial was an international multicenter open label randomized conservative management controlled trial of kyphoplasty for fractures in cancer patients published in 2011 (31). A total of 134 patients were randomized into balloon kyphoplasty (n = 70) and conservative therapy arms (n = 64).

Major Inclusion Criteria
This included severe disabling back pain with an intensity score of 4 or more (on 10 point scale) and RDQ score of 10 or more from a clinically diagnosed vertebral fracture in a patient with cancer. Fractures were confirmed with plain radiographs or MRI; patients were aged 21 years or older. Patients with primary or osteoblastic bone tumors were excluded.

Primary Outcome Measure
The primary outcome measure was change in RDQ score at one month.

Relevant Primary Baseline Characteristics
Median estimated symptomatic fracture age was 3.5 months; 70% of patients had edema on MRI. Mean baseline RDQ scores were 17.6 points in the kyphoplasty group and 18.2 in the control group.

Primary Outcomes
Kyphoplasty resulted in significantly reduced back pain related disability than did conservative treatment. Mean baseline RDQ scores were 17.6 points in the kyphoplasty group and 18.2 in the control group. By one month, the mean RDQ score in the kyphoplasty group was 9.1, while the mean RDQ score in the control group was 18.0. The treatment effect for kyphoplasty on RDQ at one month was 8.4 points (95% CI; -7.6 to -9.2, \( P < 0.0001 \)). The MCID in RDQ ranges between 2 and 3 points (32). By one month, 51 of 63 patients in the kyphoplasty group improved by at least 2 RDQ points compared with 14 of 50 patients randomly assigned to non-surgical management (\( P < 0.0001 \)).

Relevant Secondary Outcomes
Secondary outcomes included back pain scores, Karnofsky performance status scores, and quality of life (measured by SF-36 PCS) at one, 3, 6, and 12 months.
Patients in the kyphoplasty group had significant reductions in back pain. Both groups had baseline mean back pain score of 7.3; the mean score at 7 days was 3.5 in the kyphoplasty arm compared with 7.0 in the conservative arm \( (P < 0.0001) \). This difference remained of similar magnitude and significance at one month \( (P < 0.0001) \). Mean baseline Karnofsky performance score was approximately 56 in both the kyphoplasty and control groups. The MCID estimate for KPS in cancer patients is about 5 points \( (33) \); 70 points is a clinically meaningful threshold for self-care \( (34) \). By one month, the mean Karnofsky score in the kyphoplasty group had increased by 15.3 points \( (95\% \text{ CI}; 13.5 – 17.1; \ P < 0.0001) \) compared to no significant change in the control group. By one month 75% of the patients in the kyphoplasty group had improved to a KPS score of at least 70 compared to 39% of the conservative arm. Patients in the kyphoplasty arm also had significant increases in the SF-36 PCS scores at one month \( (8.4 \text{ points}) \) \( (95\% \text{ CI}; 7.7 – 9.1; \ P < 0.0001) \) compared to the conservative arm.

**Relevant Limitations**

A limitation of the CAFE trial is the lack of historical confirmation of vertebral fracture etiology. Thus individual fractures may have been caused by metastasis, osteoporosis, radionecrosis, or a combination of all of these etiologies. Nonetheless, 78% of patients in the kyphoplasty arm had stable or progressive cancer (mainly multiple myeloma or breast cancer), and 34% had received previous radiation for spinal or bony metastasis. Thus a high rate of metastatic fractures can be expected. Further limitations include the lack of blinding that can overestimate treatment benefit and the significant crossover from the control group — 34 of 64 patients randomized to the conservative arm crossed over to kyphoplasty; 21 patients crossed over within one week of the one-month assessment. Nonetheless, these cross-over patient outcomes were separately reported and no patients were allowed to cross over before the one-month assessment, thus the one-month outcome measures remain robust.

**Meta-analyses or Systematic Reviews of Efficacy Including Recent Prospective Studies of Vertebral Augmentation**

A pooled analysis using data from the prospective multicenter sham-controlled studies was published in 2011 \( (35) \). The primary aim was to assess whether vertebroplasty was more effective than a sham procedure for a subgroup of patients with recent onset (6 weeks or less) or severe (score of 8 or more) pain. Outcome data for the total 209 patients at one month was analyzed, as the INVEST trial allowed patient cross over after one month. For participants with pain of recent onset or severe pain, there was no significant difference in pain (VAS) and disability (RDQ) at one month. The authors also report extension of their analysis to match the inclusion criteria of the VERTOS II trial and were unable to show treatment benefit for vertebroplasty (data not published). Although some of the statistical power limitations in the original 2 studies may have been overcome, the remainder of the limitations to interpretation of the original data in the 2 studies as previously detailed remains.

A systematic review and meta-analysis limited to prospective randomized and non-randomized controlled studies comparing kyphoplasty, vertebroplasty, and non-surgical management for osteoporotic vertebral fractures was published in 2012 \( (36) \). Twenty-seven trials were included. Both vertebroplasty and kyphoplasty resulted in greater pain relief (10 point scale) and reduced disability (RMD and Oswestry Disability Index) compared to conservative management.

Another meta-analysis limited to prospective randomized controlled trials comparing vertebroplasty or kyphoplasty to conservative or sham treatment for osteoporotic fractures was published in 2012 \( (37) \). Six trials compared vertebroplasty or kyphoplasty to conservative management or a sham procedure — the INVEST, Australian, VERTOS, VERTOS II, and FREE trials were included. Outcomes were analyzed as early \( (\leq 12 \text{ weeks}) \) and late \( (\geq 26 \text{ weeks}) \) effects on pain relief (VAS score), disability (RDQ or Oswestry), and quality of life measures \( \text{QUALEFFO and the EuroQol-5 dimensions [EQ5-D]} \). Overall, the meta-analysis showed greater pain relief, reduced disability, and improved quality of life in favor of vertebral augmentation for treatment of symptomatic osteoporotic compression fractures.

A further meta-analysis that included prospective randomized and non-randomized controlled trials comparing vertebroplasty to conservative or sham treatment for osteoporotic fractures was also published in 2012 \( (38) \). Nine trials \( (\text{total } n = 886) \) were analyzed, including the INVEST, Australian, and VERTOS II trials. There was no difference in pain scores (VAS) between the vertebroplasty group and the sham treatment group at 1 – 29 days and 90 days \( (P = 0.68 \text{ and } 0.29, \text{ respectively}) \). Vertebroplasty resulted in significantly greater pain relief than did conservative medical treatment at all time points, including in patients with frac-
tures less than 6 weeks old. There were also significant reductions in disability and improvement in quality of life as measured by RDQ and QUALEFFO at 30 days in favor of vertebroplasty.

There is only a single randomized controlled trial of vertebral augmentation in cancer patients; thus no meta-analysis in this cohort is possible.

**Procedural Safety**

Randomized trials offer the best approach for providing safety data but are limited in the detection of rare harms. Overall, major complications occur in less than one percent of patients treated for osteoporotic compression fractures and in less than 5% of treated patients with neoplastic involvement (39).

In the meta-analyses limited to prospective randomized controlled trials comparing vertebroplasty or kyphoplasty to conservative or sham treatment for osteoporotic fractures there were no statistically significant differences in medical adverse events between the conservative and vertebral augmentation arms (37). Minor procedural complications in the vertebral augmentation arm included asymptomatic cement leaks, soft tissue hematoma, exacerbation of asthma, and vagovagal reactions. Major procedural complications included one postoperative osteomyelitis following vertebroplasty in a patient who did not receive prophylactic antibiotics, and severe radiculopathy secondary to cement leakage that required laminectomy. No death was directly related to either conservative or vertebral augmentation therapy. In the only prospective randomized conservative management-controlled clinical trial for patients with painful vertebral compression fractures in cancer patients, the only procedural complications were one superficial wound infection and one patient with a cement leakage to the adjacent disc who had an adjacent fracture the day after the procedure (31).

Although uncommon, the potential complications that have been reported in the literature include symptomatic cement leakage, nerve or spinal cord injury resulting in paralysis or bowel/bladder dysfunction or need for emergent decompression; cement or fat pulmonary emboli; osteomyelitis; vascular injury; rib, pedicle, or vertebral fracture; hypotension or depressed myocardial function; pneumothorax (for thoracic levels); and death from cardiovascular collapse or anaphylaxis to the cement.

Cement leakage is common after vertebral augmentation. In VERTOS II, 72% of treated vertebral bodies had leaks on post procedural computed tomography (CT) (29). No leaks were into the spinal canal; all patients were asymptomatic. For kyphoplasty, there is theoretically a lower rate of cement leakage, as balloon tamp inflation creates a large low resistance cavity with cancellous bone compacted around the periphery prior to infusing PMMA. In FREE, cement extravasation occurred in 27% of treated vertebrae; however, this was assessed with intra-operative fluoroscopy and postoperative radiographs (26). No leaks were into the spinal canal; all patients were asymptomatic. In the CAFE trial, cement leaks were reported in 2 of 70 patients, one of which was discal and associated with adjacent level vertebral body fracture the following day (31). No patients experienced procedure related neurological deterioration or pulmonary embolism.

There are conflicting results when individual trials are examined with regard to the incidence of secondary fractures after vertebral augmentation compared to conservative management. However in the 3 recent meta-analyses presented, the risk of secondary fractures after vertebral augmentation is not higher than in patients managed conservatively (36-38).

**Cost Effectiveness And... Increased Survival?**

In order to justify resource allocation for vertebral augmentation, it is important to consider cost-effectiveness data. Studies that model cost effectiveness must take into account the potential health related quality of life benefits, length of hospital stay, and potential mortality benefits. Health related quality of life data is available from the randomized controlled trials published to date and those powered to detect improvements in health related quality of life measures as primary outcomes have been summarized above.

Large cohort length of stay data has recently become available. Patients hospitalized for vertebral fractures and treated with vertebral augmentation are discharged from hospital earlier and less likely to be re-admitted in the short term. Examination of North American national databases reveals a mean length of stay of 10 days for patients hospitalized for a vertebral fracture that receive conservative management (40,41); those treated with vertebral augmentation have an average length of stay of between 3–6 days (42). An analysis of the French Hospital National Database for admissions for osteoporotic vertebral fractures during 2009 (n= 13,624), revealed that patients undergoing vertebroplasty were significantly more likely to be discharged within 1 week compared to conservatively
managed patients (68% vs 47%; \( P < 0.0001 \)) (43). However these patients were also younger and had less co-morbidities. A nationwide cohort study from Taiwan (\( n = 9,238 \)) revealed a 2 day reduction in length of stay in patients treated with augmentation compared to conservative management, in spite of those treated with augmentation being older and less healthy (44). Furthermore, re-admission for fracture or musculoskeletal concerns within 7 and 30 days were significantly lower in patients treated with vertebral augmentation. By 6 months there were no longer significant differences in re-admission rates.

Large cohort long and short-term baseline mortality data has been recently published. Population studies reveal excess mortality in vertebral fracture patients compared to age-matched controls that persists for at least 5 years (45). A retrospective review of the US Medicare dataset between 1997 and 2004 identified a total of 97,142 patients vertebral fracture patients that were compared with 428,956 controls. The mortality rate after a vertebral fracture was twice that of controls. Mortality rates at 3, 5 and 7 years for vertebral fracture patients were 46%, 69% and 90% compared to 22%, 36% and 48% for matching controls (46). The cause of this excess mortality is not known; a cause and effect should not be assumed. Notably most deaths after osteoporotic fractures occur within the first 3—6 months (47). The 6-month mortality rate after a vertebral fracture from the Korean National Claim Registry sample was approximately 5 and 10% for women and men aged 50 and older (48).

Given the baseline elevated mortality risk in vertebral fracture patients, it has been postulated that vertebral augmentation could reduce excess mortality. A retrospective review of the US Medicare dataset between 2005 and 2008 identified a total of 858,978 vertebral fracture patients, of which 182,946 underwent vertebroplasty or kyphoplasty (49,50). Patient in the vertebral augmentation cohort had a higher adjusted survival rate of 61% compared with 50% for conservatively managed patients (\( P < .001 \)) at 4 years of follow up (49). Furthermore, life expectancy gains of between 1 – 9.5 years were estimated, which were higher after kyphoplasty compared to vertebroplasty (50). Notably, the conservatively managed patient group had higher rates of stroke and pneumonia. A much smaller analysis of 524 vertebroplasty patients at a single institution did not confirm this benefit (51). None of the currently published prospective multicenter randomized controlled trials were powered to demonstrate a reduction in mortality, and they have not shown mortality benefit. Further large cohort data to clarify these findings has yet to be published.

If there is increased quality of life combined with reduced length of stay and potential reduction in mortality, vertebral augmentation may be cost effective. The same authors that analyzed the US Medicare dataset subsequently modeled cost effectiveness of performing vertebral augmentation compared to conservative management. The cost per life-year gained in the vertebral augmentation cohort was reasonably cost efficient, ranging from $US1,863 to $US13,543 (52,53). Analysis of a hospitalized vertebral fracture cohort in the United Kingdom concluded that kyphoplasty may be more cost effective than both conservative management and vertebroplasty (54). However these analyses are particularly sensitive to potential increased quality of life and reduced mortality benefit from vertebral augmentation; if these benefits do not exist, conservative management is the most cost effective treatment strategy. Importantly, the mortality data used in the base analysis was not from a randomized controlled trial, but from the retrospective review of the US Medicare dataset that was funded by a manufacturer grant (49). Moreover, a small Swedish prospective multicenter cost-effectiveness trial of 63 patients randomized between kyphoplasty (n=32) and conservative management (n=31) failed to demonstrate cost effectiveness of kyphoplasty with a cost per quality-adjusted life year gained of approximately $US134,000 (55).

**Conclusion**

For treatment of individual patients, we must integrate the best available evidence with clinical expertise and patient values. For cancer patients with disabling pain from vertebral fractures, there is a good quality randomized controlled trial that demonstrates that kyphoplasty is a safe and effective treatment that rapidly reduces disability and pain and increases quality of life. However a prospective randomized controlled trial of kyphoplasty compared to a sham procedure has not been performed and there are no data to assess the cost effectiveness of kyphoplasty in patients with cancer.

For patients with osteoporotic fractures, the data is conflicting. Two small double-blind randomized controlled trials published in 2009 did not show efficacy for vertebroplasty over a sham procedure. Two larger open label randomized controlled trials, the VERTOS II and FREE trials show efficacy for vertebroplasty and kyphoplasty respectively over conservative medical manage-
ment. All published randomized controlled trials in vertebral augmentation have limitations. Meta-analyses of prospective randomized controlled studies provide evidence in favor of the use of vertebral augmentation for osteoporotic fractures with a good safety profile. There are health related quality of life benefits and possible reductions in long term mortality; it remains unknown whether vertebral augmentation for patients with osteoporotic fractures is cost effective.

Ultimately, further randomized controlled trials of vertebral augmentation in both osteoporotic and cancer patients are required to improve the strength of evidence available to assess these procedures. Until then, the balance of evidence favors the use of vertebral augmentation in a small select cohort of patients with severe and disabling back pain refractory to conservative medical therapy. Experienced clinicians should select these patients for treatment by localizing pain to specific fractured vertebral levels using both clinical examination and modern imaging techniques such as MRI with STIR imaging. Experienced practitioners should perform vertebral augmentation to maximize the safety profile; these procedures should be performed in the setting of clinical trials or quality improvement programs where the clinical effectiveness, safety and cost effectiveness of vertebral augmentation can be best examined.

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