

Literature Review



Vertebroplasty Augmentation Procedures: Examining the Controversy

Arif Hussain, DO, and Michael Erdek, MD

From: Johns Hopkins University, Baltimore, MD

Dr. Hussain is with the Department of Physical Medicine and Rehabilitation, School of Medicine, Johns Hopkins University, Baltimore, MD. Dr. Erdek is with the Division of Pain Medicine, Department of Anesthesia and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, MD

Address correspondence:
Arif Hussain, DO
Department of Physical Medicine and Rehabilitation
School of Medicine
Johns Hopkins University, 600 N. Wolfe St.
Phipps 160
Baltimore, MD 21287
E-mail:
ahussai1@jhmi.edu

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association, (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might post a conflict of interest in connection with the submitted manuscript.

Manuscript received:
04-30-2013

Revised manuscript received:
06-10-2013

Accepted for publication:
06-19-2013

Free full manuscript:
www.painphysicianjournal.com

Background: Vertebral compression fractures are a common pathology affecting primarily the elderly, postmenopausal women, and those with metastatic vertebral disease. Vertebral augmentation procedures are popular treatment options for stability and pain relief. Preliminary studies have suggested that such procedures are adequately efficacious. However, the first randomized controlled trials (RCTs) published in the *New England Journal of Medicine* in 2009 showed that these procedures were not significantly different than placebo with regards to pain relief and quality of life. These studies were met with considerable criticism. The matter was further complicated when *The Lancet* published an RCT of its own that demonstrated the superiority of vertebroplasty over conservative management. The conflicting evidence has sparked ongoing debate in the medical community. All sides have provided arguments supported by evidence of varying strength and validity.

Objective: To provide a concise and comprehensive presentation of the controversy surrounding vertebral augmentation procedures and the evidence cited by proponents on both sides of the debate.

Methods: We began by researching the major randomized controlled trials both for and against vertebroplasty. These articles were already known to us, and were used as a starting point. We then performed a literature search in PubMed for articles dated from 2000 through 2012. The bibliographies of major articles and reviews were also cross-referenced for additional sources.

Results: A number of articles that included comprehensive and systematic reviews, meta-analyses, and commentaries about noted studies were found. These provided a broad, detailed overview of the subject. Many of the common themes of these articles included limitations in the design, methods, and patient selection with regard to the RCTs and other available studies.

Limitations: This review does not analyze the quality of evidence available nor does it provide an opinion in this regard. The conclusions of the present article are, therefore, general and descriptive in nature.

Conclusions: The arguments presented by proponents of both sides of the debate appear to have validity. All of the major studies cited as evidence for or against vertebral augmentation procedures have limitations in their quality. Consequently, the debate cannot be concluded, convincingly, until more elaborate studies are conducted involving larger numbers of patients with clear procedure methods agreed upon by the major authorities in the field.

Key words: Vertebroplasty, kyphoplasty, vertebral augmentation procedures, controversy of vertebroplasty, vertebral cancer, vertebral pain, compression fractures, back pain, vertebral fractures.

Pain Physician 2013; 16:-E483-E490

Vertebral compression fractures are common in the elderly and have serious potential consequences. Affecting up to 1.5 million persons every year (1) in the United States alone, compression fractures lead to increased debility and have been shown to increase mortality rates in women up to 15% compared to those without these fractures (2). Women are particularly vulnerable due to postmenopausal osteoporosis—of which about 25% suffer from compression fractures (3,4). This number dramatically increases to 40% at 80 years old (5).

Compression fractures are also common in cancer patients. An increased risk may be associated with metastases to the vertebrae from primary tumors (commonly breast, prostate, lung, bladder, thyroid cancer) (6), osteoporosis associated with the original cancer process like with multiple myeloma (6,7), or cancer treatments like radiation, aromatase inhibitors or anti-androgens and others (6). Accordingly, the incidence of vertebral compression fractures is estimated to be 24% for patients with multiple myeloma; 14% with breast cancer; 6% with prostate cancer; and 8% with lung cancer (6,8). Those with such fractures will suffer a significant amount of pain which is described as axial, nonradiating, and mostly absent of neurological symptoms (unless resultant instability is causing neurologic compromise) (1). The pain is often exacerbated with positional changes, particularly with flexion of the back, which causes increased compressive force upon the vertebrae. Chronic pain from compression fractures presents an even greater clinical challenge for physicians. Early and aggressive intervention is of critical importance.

Vertebroplasty—a procedure which involves percutaneous injection of polymethylmethacrylate (PMMA) into the vertebra—was first described in 1987 by Galibert et al (9) as a method of stabilizing cervical vertebrae weakened by a hemangioma. (10) For over a decade, it continued to be used principally for hemangiomas and metastatic disease of vertebrae (11). Later, it became a popular operative treatment for symptomatic vertebral compression fractures as well.

A new procedure—kyphoplasty—was then developed. It first introduces a balloon into the vertebral body producing a cavity within which the PMMA is injected (10). Proponents of kyphoplasty (over traditional vertebroplasty) suggest that PMMA extravasation is minimized (1,10-13) while vertebral height can also be reconstituted, thus improving segmental kyphosis (1,14,15). Even in this regard, there is debate as to

which procedure is more effective in providing symptom relief. A meta-analysis by Han et al (16) concluded that there is no difference between them in terms of long-term pain relief and functional improvement. Consequently, they recommended vertebroplasty because of its lower burden of systemic and individual expense. Conversely, a recent systematic review by Papanastasiou et al (17) showed that kyphoplasty was superior to vertebroplasty for improved quality of life, disability, kyphosis, and frequency of PMMA extravasation.

Early studies showed promising results regarding pain relief and vertebral stability for these procedures (18,19). However, they lacked rigorous research methods and there were no randomized controlled trials (RCTs) until 2009 when Buchbinder et al (20) and Kallmes et al (21) published the results of their studies in the *New England Journal of Medicine* (NEJM). These articles initiated a heated debate that continues today.

The primary objective of this review is to consolidate some of the major studies addressing the effectiveness of vertebral augmentation procedures for managing pain resulting from vertebral compression fractures. In so doing, the authors intend on providing a concise and balanced presentation of the literature which stimulated the heated debate among practitioners who actively treat this patient population. The reader will, therefore, be introduced to the comprehensive conversation which exists about this controversial intervention and may then understand the evidence and arguments maintained by both sides of this debate. Lastly, we encourage researchers to pursue more detailed and rigorous studies that may provide more definitive guidelines for physicians.

METHODS

We began by researching the major randomized controlled trials by Buchbinder et al (20), Kallmes et al (21) and Klazen et al (22). We then performed a literature search in PubMed for articles dated from 2000 through 2012. The initial search was focused on epidemiological information regarding vertebral compression fractures with the keywords “vertebral compression fractures,” “statistics for compression fractures,” “prevalence of compression fractures,” “cancer and compression fractures,” and “metastasis to the vertebrae.” We then moved to articles providing a review of vertebroplasty and kyphoplasty using the key words “vertebroplasty,” “kyphoplasty,” “vertebroplasty versus kyphoplasty,” and “debate regarding vertebroplasty.” Lastly, we searched “commentary,” “criticism,” or

“debate” along with the name of the intended article of interest. The bibliographies of key articles and reviews were also cross-referenced for additional sources.

Discussion

In August of 2009, NEJM, one of the leading American medical journals, published the first 2 RCTs evaluating the efficacy of vertebroplasty for painful osteoporotic spinal fractures (20,21). Contrary to promising earlier reports, these studies failed to show significant improvement compared to placebo. This, expectedly, stimulated a wide array of criticism and review. The discussion would be further complicated by another RCT published by The Lancet (22) a year later, showing positive results with vertebroplasty. It is therefore appropriate to highlight current discussions in light of these pivotal studies (Table 1) in order to facilitate the most evidence-based care for patients.

Buchbinder et al (2009)

The first study, by Buchbinder et al (20), was a multicenter, randomized, double-blind, placebo-controlled trial. The trial enrolled 78 patients who had back pain of no more than 12 months duration and had one or 2 recent vertebral fractures with at least a grade I collapse according to the assessment system outlined by Genant et al (23) along with edema (an indication of acute injury), a fracture line, or both identified on magnetic resonance imaging (MRI). The patients were then separated into 2 groups: those that underwent actual vertebroplasty according to standard protocol (38 patients) and those that underwent a sham procedure (40 patients). The sham procedure entailed all steps similar to the vertebroplasty except actual insertion of the 13-gauge needle into the vertebral body and sub-

sequent injection of the PMMA. The PMMA was prepared in the room, however, in order to allow the smell to reach the patient. All the patients received standard postprocedure care.

The primary outcome was a score for overall pain on a 10 point scale while the secondary outcome was a measurement of quality of life using a number of scales including the Quality of Life Questionnaire of the European Foundation of Osteoporosis (QUALEFFO), a 41-item vertebral-fracture-specific and osteoporosis-specific questionnaire, Assessment of Quality of Life Questionnaire, and the European Quality of Life- 5 Dimensions scale. At 3 months there was no significant difference between the 2 groups in terms of pain—a mean reduction of 2.6 ± 2.9 for vertebroplasty and 1.9 ± 3.3 for placebo—as well as quality of life for all scales except the QUALEFFO. The QUALEFFO score at one week actually favored the placebo group. The authors, consequently, concluded that there was no beneficial effect of vertebroplasty compared to placebo for pain relief and quality of life.

The (INVEST) Trial by Kallmes et al (2009)

This study was published in NEJM at the same time as the Buchbinder et al (20) study described above. Entitled the Investigational Vertebroplasty Safety and Efficacy Trial (INVEST) (21), this multi-center, randomized, controlled trial studied 131 patients with one to 3 painful osteoporotic vertebral compression fractures—with onset of symptoms less than one year prior to evaluation— between vertebral levels of T4 and L5. For fractures of uncertain age (in which exact onset of pain was not identified), an additional requirement of marrow edema on MRI was included. Patients also must have had inadequate pain relief with standard medical

Table 1. *Vertebroplasty augmentation major randomized controlled trials.*

Study	Method	Results
Buchbinder et al (2009) (20)	38 patients who received vertebroplasty were compared to 40 patients who underwent sham procedure.	At 3 months, no significant difference between the 2 groups in terms of pain—a mean reduction of 2.6 ± 2.9 for vertebroplasty and 1.9 ± 3.3 for placebo.
Kallmes et al INVEST(2009) (21)	68 patients who received vertebroplasty were compared to 63 patients who underwent sham procedure.	At one month, no significant difference between the 2 groups with regard to modified Roland-Morris Disability Questionnaire and pain scale rating.
Wardlaw et al FREE (2009) (34)	149 patients who received balloon kyphoplasty were compared to 141 patients who received nonsurgical management.	Difference of improvement in mean SF-36 PCS score, between the kyphoplasty and control groups, was 5.2 points ($P < 0.0001$) at one month; 4.0 points ($P = 0.0008$) at 3 months; 3.2 points ($P = 0.0064$) at 6 months; and 1.5 points ($P = 0.208$) at 12 months.
Klazen et al VERTOS II (2010) (22)	88 patients who received vertebroplasty were compared to 77 patients who received traditional conservative management.	Difference between the groups in reduction of mean VAS score of 2.5 ($P < 0.0001$) at one month and 2.0 ($P < 0.0001$) at one year.

therapy, and a current pain rating of at least 3 out of 10 on the Numeric Rating Scale.

The patients were then assigned to a vertebroplasty group (68 patients) or a control group (63 patients). All patients first had an injection of 1% lidocaine in the subcutaneous tissue surrounding the pedicle of the target vertebra followed by 0.25% bupivacaine in the periosteum of the pedicle. They were then randomly assigned to undergo the vertebroplasty or control procedure. The control intervention involved verbal and physical cues, including pressure on the patient's back, without actual needle insertion. A methacrylate monomer was also opened to simulate the odor of mixed PMMA. The measured primary outcomes included disability utilizing the modified Roland-Morris Disability Questionnaire and pain using a 10-point pain rating scale. Though both groups had improvement with these primary outcomes, there was no significant difference between them with follow-up at one month. At 3 months, however, there was a higher cross-over rate in the control group than in the vertebroplasty group (51% vs 13%) (21).

Commentary Regarding the New England Journal of Medicine Studies

Although well-publicized, these studies were not well received by many pain practitioners. These were the first RCTs comparing vertebroplasty to placebo, and the influence of the findings could potentially affect standard physician procedure globally. Expectedly, criticism and debate was generated upon their publication. Those that criticized these studies (24-27) outlined a number of faults with the design including (but not limited to) the limited number of patients, high refusal rate, insufficient amount of PMMA injection, inappropriate sham procedure, and others. Many have argued that the results of these studies are far from definitive given these proposed deficiencies.

An editorial by Aebi (24), published in the *European Spine Journal*, laid out some of the foundational criticisms of the Buchbinder (20) study. He highlighted that the type of back pain was not illustrated or defined by the authors, as there is a difference between pain associated with mechanical instability (facetogenic [28]) and that which is associated with compressive forces (vertebral). Furthermore, it was argued that the authors neglected the other benefits of vertebroplasty such as stabilizing segmental kyphosis which can contribute to worsened arthritis and facetogenic pain as revealed by Wilson et al (28).

Also highlighted was that the injected PMMA volume (2.8 ± 1.2 mL) was not sufficient for optimal effectiveness, a point reiterated by Bosczyk (25) and Smith (27). Bosczyk elaborated that basic science indicates a fill volume of 13-16% of the vertebral body volume is necessary for relevant biomechanical effect on the restoration of vertebral strength. Thus, for the most commonly treated vertebrae at the thoracolumbar junction, a fill volume of at least 4 milliliters would be most appropriate. (25)

A few authors (27-29) drew attention to the curious, rapid improvement in pain that both the active treatment and placebo groups demonstrated in these studies. Douglas Orr (29) highlighted that symptom relief usually takes several weeks after vertebroplasty. So, what can account for the quick relief found with both treatment groups in these studies? The likely cause, as postulated by these authors, was the injection of local anesthetic around the facets which, as cited before, are known to contribute to pain resulting from mechanical forces caused by segmental instability. The anesthetic itself breaks the pain cycle, effectively providing therapeutic relief. Knowing this, critics have argued that the sham treatment was not a placebo after all (27,29). Wilson et al (28), in particular, took this hypothesis a step further. They studied whether treatment of the facet joints, with local anesthetic and steroid, can be an effective option for this population. They found that out of the 75 patients who were referred to them for treatment, 21 responded well to facet joint intervention alone—though not all patients were offered this option. This study essentially confirmed that treatment of facetogenic pain may provide sufficient relief, so as to preclude patients from more invasive vertebral augmentation procedures. Conversely, it also filters patients who would not respond well to vertebroplasty in the first place; this presents some indication that vertebroplasty would be more appropriate for patients with true vertebral pain from compression fractures.

In response to both NEJM studies, Smith (27) and Munk (26) emphasized the small number of patients: 78 for the Buchbinder (20) study and 131 for the Kallmes (21) study. Smith argued that an adequate number would be at least 300 patients. He further underlined the fact that many patients refused to be randomized. These patients, he speculates, were most likely those suffering from the greatest pain as they would want the fastest, most effective treatment possible. In support of this assumption, he cites the fact that Kallmes et al (21) had to decrease their inclusion pain score to

3 out of 10 in order to recruit more patients. Along the same lines, others have maintained that severity of pain directly correlates with response to vertebroplasty (30,31). Nevertheless, the basis of this argument cannot be confirmed since there is no data regarding those that refused to participate in the study.

A final argument focuses on the population of patients who would most benefit from vertebroplasty. Both NEJM studies included patients with vertebral fractures as old as one year. Citing Ryu and Park (32), Smith argues that age does in fact impact the effectiveness of vertebroplasty, wherein older fractures would be significantly less likely to improve after vertebroplasty (27). It was argued that the studies should have been limited to acute fractures. This opinion contrasts with an earlier article by Kaufmann et al (33) which found no difference of response associated with the age of the fracture.

Fracture Reduction Evaluation (FREE) Study (2009)

The proposed safety associated with balloon kyphoplasty has made it an increasingly popular procedure compared to traditional vertebroplasty, despite considerable cost. One multicenter randomized controlled trial by Wardlaw et al (34) compared kyphoplasty to nonsurgical management of acute vertebral compression fractures. They evaluated patients with one to 3 vertebral fractures between the T5 and L5 levels, with at least one demonstrating edema on MRI and one with $\geq 15\%$ height loss. Single vertebral fractures required both criteria. The patients also had to have back pain scores of 4 points or more on a 0-10 scale. Out of the available patients, 300 met inclusion criteria while 266 completed follow-up at one month and 235 at 12 months. The primary outcome measure was the difference in change from baseline in the short-form (SF)-36 physical component summary (PCS) scale between the kyphoplasty and control groups. The SF-36 PCS scale is a global quality of life measure weighted for physical abilities, which demonstrates a better quality of life with higher scores. Patients in the kyphoplasty group improved their score from 26 to 33.4 at one-month follow-up. The control group improved from 25.5 to 27.4. Additionally, the difference of improvement in the mean SF-36 PCS score between the kyphoplasty and control groups was 5.2 points ($P < 0.0001$) at one month; 4.0 points ($P = 0.0008$) at 3 months; 3.2 points ($P = 0.0064$) at 6 months; and 1.5 points ($P = 0.208$) at 12 months. Therefore, the quality of life improvement in

the kyphoplasty group was greater than the nonsurgical group—most notably within the first month.

Vertos II Trial (2010)

To further investigate matters, a major European journal, *The Lancet*, published another randomized controlled trial by Klazen et al (22) commonly known as the Vertos II trial. The authors identified 431 patients who fulfilled the inclusion criteria: 50 years or older; the presence of vertebral compression fractures on spine radiograph (minimum 15% height loss, level of fracture T5 or lower, and bone edema on MRI); back pain of 6 weeks or less; and a visual analog score (VAS) of 5 or greater. Out of these 431 eligible patients, 229 had spontaneous resolution of symptoms prior to treatment. The remaining 202 patients were randomly allocated to either vertebroplasty or conservative treatment. The treatment was not blinded. All patients received bisphosphonates, Vitamin D, and calcium supplements as well as an individually tailored analgesia regimen according to the World Health Organization classification (22,35).

The primary outcome was pain relief at one month and one year, measured with a VAS score assessment. Clinically significant pain relief was defined as a decrease in VAS score of 3 or more points from baseline. Pain-free days were defined as days with a VAS score of 3 or less. A total of 86 patients completed the study at one year follow-up in the vertebroplasty group and 77 in the conservative group. The vertebroplasty group had an average reduction in VAS scores of 5.2 points at one month and 5.7 points at one year. The conservative treatment group also noted some improvement in pain with an average reduction in VAS scores of 2.7 at one month and 3.7 at one year. This made for a difference between the groups in reduction of mean VAS score of 2.5 ($P < 0.0001$) at one month and 2.0 ($P < 0.0001$) at one year. The authors concluded that pain relief with vertebroplasty was significantly greater than conservative treatment.

Meta-analysis of the New England Journal of Medicine Studies (2011)

In light of the above-mentioned criticism, Staples and colleagues (36)—including Kallmes and Buchbinder—conducted a meta-analysis drawing data from the NEJM studies. The intent was to determine the effect of vertebroplasty for patients with an acute onset of pain (less than 6 weeks) or severe pain (greater than 8 on a 0-10 scale). This would address some of the main criticisms of the initial NEJM studies—namely, that the

authors failed to focus on patients with acute fractures and/or those with severe pain. With these parameters, 25 patients from the control group and 32 from the vertebroplasty group had acute onset of pain while 50 from the control group and 49 from the vertebroplasty group had severe pain at baseline.

The outcome was measured using a 0 to 10 pain scale and a modified Roland-Morris disability questionnaire to assess resultant pain and function at one month follow-up. They found that these special populations were not dissimilar to the rest of the group; there was no significant difference between vertebroplasty and placebo in terms of pain relief and functional improvement. In view of the Vertos II (22) study, the authors also extended their analysis to include patients with a pain score of 5 or greater; again, they were unable to demonstrate a treatment benefit with vertebroplasty. Thus, they attributed the positive results of the Vertos II study to a lack of blinding and inadequacy of control (36). Though this analysis would help answer some of the questions regarding the initial studies, it did not subdue much of the other criticism regarding patient selection, treatment methodology, and high patient refusal, among others.

European Spine Journal Systematic Review (2012)

There were now 2 major medical journals with conflicting studies. Naturally, there continued to be an exchange of commentary from advocates of both opinions. Most recently, in 2012, the European Spine Journal published a systematic review by Papanastassiou et al (17). The authors analyzed 27 studies regarding the treatment of vertebral compression fractures due to osteoporosis. These were prospective comparative studies — limited to level I and II evidence — that involved vertebral augmentation procedures and enrolled at least 20 patients. Nine of these articles compared vertebroplasty to nonsurgical management, 6 studies compared kyphoplasty to nonsurgical management, and 12 articles compared vertebroplasty to kyphoplasty.

The authors found that pain reduction for those treated with vertebroplasty or kyphoplasty was superior to those treated with nonsurgical measures, while

there was no significant difference between the 2 augmentation procedures for pain relief. Kyphoplasty, however, was superior to vertebroplasty with regards to quality of life, disability improvement, kyphosis reduction, and frequency of PMMA extravasation. Based on these results, it would appear that kyphoplasty is the safest and most effective treatment option for vertebral compression fractures. There is, however, conflicting evidence in this regard, some of which has been mentioned above. Furthermore, Papanastassiou and his colleagues (17) drew attention to the disparity of the available literature and its delivery of inconsistent messages. They suggested, like many others, that further trials were needed to clarify conflicting data.

CONCLUSION

In an attempt to provide the most safe, evidence-based care for patients with vertebral compression fractures, physicians have a dilemma. Four major randomized controlled trials (20-22, 34) have been published by prominent medical journals. These RCTs have had conflicting conclusions. Buchbinder et al (20) and Kallmes et al (21), both found vertebroplasty to be equivalent to placebo. How might one reconcile these results with the positive efficacy of vertebroplasty noted in the Vertos II trial (22), and kyphoplasty in the FREE trial (34)? It is important to note that the 2 models of study were not identical in design, as the former (Buchbinder et al and Kallmes et al) compared vertebroplasty to sham procedure while the latter (Vertos II and FREE study) compared vertebroplasty or kyphoplasty to traditional conservative management. All studies have received considerable criticism, with authors arguing for both sides. This is not to mention the variance of the non-RCT literature highlighted partially by the Papanastassiou et al (17) systematic review. Undoubtedly, each study has its own deficiencies. Consequently, the debate cannot be concluded, convincingly, until more elaborate studies are conducted involving larger numbers of patients with clear procedure methods agreed upon by the major authorities in the field.

REFERENCES

- Alexandru D, So W. Evaluation and management of vertebral compression fractures. *Perm J* 2012; 16:46-51.
- Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ, 3rd. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol* 1993; 137:1001-1005.
- Old JL, Calvert M. Vertebral compression fractures in the elderly. *Am Fam Physician* 2004; 69:111-116.
- Melton LJ, 3rd. Epidemiology of spinal osteoporosis. *Spine (Phila Pa 1976)* 1997; 22:2S-11S.
- Melton LJ, 3rd, Kan SH, Frye MA, Wahner HW, O'Fallon WM, Riggs BL. Epidemiology of vertebral fractures in women. *Am J Epidemiol* 1989; 129:1000-1011.
- Berenson J, Pflugmacher R, Jarzem P, Zonder J, Schechtman K, Tillman JB, Bastian L, Ashraf T, Vriouis F; Cancer Patient Fracture Evaluation (CAFE) Investigators. Balloon kyphoplasty versus non-surgical fracture management for treatment of painful vertebral body compression fractures in patients with cancer: A multicentre, randomised controlled trial. *Lancet Oncol* 2011; 12:225-235.
- Coleman RE. Skeletal complications of malignancy. *Cancer* 1997; 80(8 Suppl):1588-1594.
- Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. *Cancer* 2007; 110:1860-1867.
- Galibert P, Deramond H, Rosat P, Le Gars D. Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty. *Neurochirurgie*. 1987;33(2):166-8.
- Asenjo JF, Rossel F. Vertebroplasty and kyphoplasty: New evidence adds heat to the debate. *Curr Opin Anaesthesiol* 2012; 25:577-583.
- Hargunani R, Le Corroller T, Khashoggi K, Murphy KJ, Munk PL. Percutaneous vertebral augmentation: The status of vertebroplasty and current controversies. *Semin Musculoskelet Radiol* 2011; 15:117-124.
- Theodorou DJ, Theodorou SJ, Duncan TD, Garfin SR, Wong WH. Percutaneous balloon kyphoplasty for the correction of spinal deformity in painful vertebral body compression fractures. *Clin Imaging* 2002; 26:1-5.
- Garfin SR, Buckley RA, Ledlie J, Balloon Kyphoplasty Outcomes Group. Balloon kyphoplasty for symptomatic vertebral body compression fractures results in rapid, significant, and sustained improvements in back pain, function, and quality of life for elderly patients. *Spine (Phila Pa 1976)* 2006; 31:2213-2220.
- Lieberman IH, Dudeney S, Reinhardt MK, Bell G. Initial outcome and efficacy of "kyphoplasty" in the treatment of painful osteoporotic vertebral compression fractures. *Spine (Phila Pa 1976)* 2001; 26:1631-1638.
- Gaitanis IN, Hadjipavlou AG, Katonis PG, Tzermiadianos MN, Pasku DS, Patwardhan AG. Balloon kyphoplasty for the treatment of pathological vertebral compressive fractures. *Eur Spine J* 2005; 14:250-260.
- Han S, Wan S, Ning L, Tong Y, Zhang J, Fan S. Percutaneous vertebroplasty versus balloon kyphoplasty for treatment of osteoporotic vertebral compression fracture: A meta-analysis of randomised and non-randomised controlled trials. *Int Orthop* 2011; 35:1349-1358.
- Papanastassiou ID, Phillips FM, Van Meirhaeghe J, Berenson JR, Andersson GB, Chung G, Small BJ, Aghayev K, Vriouis FD. Comparing effects of kyphoplasty, vertebroplasty, and non-surgical management in a systematic review of randomized and non-randomized controlled studies. *Eur Spine J* 2012; 21:1826-1843.
- Barr JD, Barr MS, Lemley TJ, McCann RM. Percutaneous vertebroplasty for pain relief and spinal stabilization. *Spine (Phila Pa 1976)* 2000; 25:923-928.
- Fourney DR, Schomer DF, Nader R, Chlan-Fourney J, Suki D, Ahrar K, Rhines LD, Gokaslan ZL. Percutaneous vertebroplasty and kyphoplasty for painful vertebral body fractures in cancer patients. *J Neurosurg* 2003; 98(1 Suppl):21-30.
- Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, Graves S, Staples MP, Murphy B. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. *N Engl J Med* 2009; 361:557-568.
- Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, Edwards R, Gray LA, Stout L, Owen S, Hollingworth W, Ghdoke B, Annesley-Williams DJ, Ralston SH, Jarvik JG. A randomized trial of vertebroplasty for osteoporotic spinal fractures. *N Engl J Med* 2009; 361:569-579.
- Klazen CA, Lohle PN, de Vries J, Jansen FH, Tielbeek AV, Blonk MC, Venmans A, van Rooij WJ, Schoemaker MC, Juttman JR, Lo TH, Verhaar HJ, van der Graaf Y, van Everdingen KJ, Muller AF, Elgersma OE, Halkema DR, Fransen H, Janssens X, Buskens E, Mali WP. Vertebroplasty versus conservative treatment in acute osteoporotic vertebral compression fractures (vertos II): An open-label randomised trial. *Lancet* 2010; 376:1085-1092.
- Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res* 1993; 8:1137-1148.
- Aebi M. Vertebroplasty: About sense and nonsense of uncontrolled "controlled randomized prospective trials". *Eur Spine J* 2009; 18:1247-1248.
- Boszczyk B. Volume matters: A review of procedural details of two randomised controlled vertebroplasty trials of 2009. *Eur Spine J* 2010; 19:1837-840.
- Munk PL, Liu DM, Murphy KP, Baerlocher MO. Effectiveness of vertebroplasty: A recent controversy. *Can Assoc Radiol J* 2009; 60:170-171.
- Smith SJ, Vlahos A, Sewall LE. An objection to the new england journal of medicine vertebroplasty articles. *Can Assoc Radiol J* 2010; 61:121-122.
- Wilson DJ, Owen S, Corkill RA. Facet joint injections as a means of reducing the need for vertebroplasty in insufficiency fractures of the spine. *Eur Radiol* 2011; 21:1772-1778.
- Orr RD. Vertebroplasty, cognitive dissonance, and evidence-based medicine: What do we do when the 'evidence' says we are wrong? *Cleve Clin J Med* 2010; 77:8-11.
- Johnson J, Rogers W, Jeffrey RL. The controversy over vertebroplasty: An analysis of the debate and proposals for a way forward. *J Med Imaging Radiat Oncol* 2012; 56:449-451.
- Clark WA, Diamond TH, McNeil HP, Gonski PN, Schlaphoff GP, Rouse JC. Vertebroplasty for painful acute osteoporotic vertebral fractures: Recent medical journal of australia editorial is not relevant to the patient group that we treat with vertebroplasty. *Med J Aust* 2010; 192:334-337.

32. Ryu KS, Park CK. The prognostic factors influencing on the therapeutic effect of percutaneous vertebroplasty in treating osteoporotic vertebral compression fractures. *J Korean Neurosurg Soc* 2009; 45:16-23.
33. Kaufmann TJ, Jensen ME, Schweickert PA, Marx WF, Kallmes DF. Age of fracture and clinical outcomes of percutaneous vertebroplasty. *AJNR Am J Neuro-radiol* 2001; 22:1860-1863.
34. Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, Eastell R, Shabe P, Talmadge K, Boonen S. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): A randomised controlled trial. *Lancet* 2009; 373:1016-1024.
35. McHugh GA, Luker KA, Campbell M, Kay PR, Silman AJ. A longitudinal study exploring pain control, treatment and service provision for individuals with end-stage lower limb osteoarthritis. *Rheumatology (Oxford)* 2007; 46:631-637.
36. Staples MP, Kallmes DF, Comstock BA, Jarvik JG, Osborne RH, Heagerty PJ, Buchbinder R. Effectiveness of vertebroplasty using individual patient data from two randomised placebo controlled trials: Meta-analysis. *BMJ* 2011; 343:d3952.