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Review Article

PERCUTANEOUS VERTEBROPLASTY AND KYPHOPLASTY FOR THE TREATMENT OF VERTEBRAL FRACTURES: A REVIEW

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ABSTRACT

Vertebroplasty and kyphoplasty are minimally invasive techniques applied for the treatment of vertebral fractures. Since not all vertebral compression fractures are the same, a tailored-based approach is necessary for optimum efficacy and safety results. Nowadays, different cements and materials are proposed as alternatives to the original poly-methylmethacrylate aiming to overcome the limitations and the risks governing its use. Both techniques are governed by high efficacy and low complication rates; multilevel treatment in a single session has been shown to be feasible with no compromise of the technique's safety and efficacy. The purpose of this article is to describe the basic concepts of spinal augmentation by means of vertebroplasty and kyphoplasty. The current status and future of cements used will be defined. Controversies upon issues concerning both techniques will be addressed. Finally, the necessity for a tailored-based approach applying different techniques for different fractures will be addressed

Keywords: Vertebroplasty, Kyphoplasty, Fracture, Pain, Spine

INTRODUCTION

Percutaneous vertebroplasty was first introduced in everyday clinical practice by Galibert and Deramond for the treatment of an aggressive hemangioma in the cervical spine, whilst a few years later, Lapras and Duquesnel provided the first indications for this new technique[1, 2]. More than a decade later, the first variation of the standard vertebroplasty technique emerged, called kyphoplasty, and it was introduced to everyday clinical practice by Garfin, Reilley and Lieberman[3, 4]. The pioneers in the era of vertebroplasty were using cement and needles for performance of the technique; later on, vertebroplasty kits and balloon kyphoplasty appeared in the market. Recently, curved needles, biologic cements and implant-based technologies further expanded the indications and applications of these techniques[5-9]. The substrate of vertebral fractures includes osteoporotic, pathologic, traumatic (burst and other complex types) as well as cancer-related cases which can be lytic, blastic or of mixed appearance. Due to the wide substrate variety, the evolution of all these techniques was a necessity since not all vertebral compression fractures are the same and a tailored-based approach is necessary for optimum efficacy and safety results. The purpose of this article is to describe the basic concepts of spinal augmentation by means of vertebroplasty and kyphoplasty. The role of biomechanics and cements used will be defined. Controversies upon issues concerning both techniques will be addressed. Finally, the necessity for a tailored-based approach applying different techniques for different cases and locations will be addressed.

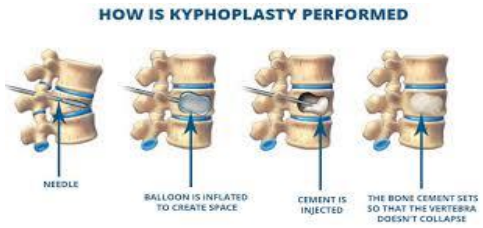
Patient Selection:

Vertebral fracture (VF) can be often secondary to high- or low-energy trauma due to osteoporosis. Pathologic VF is secondary to osseous involvement by a localized debilitating condition, mainly tumors. Spine is the most affected target by metastases[10]. Conventional radiographs are usually the first technique used to study patients suspected for VF. Radiographic evaluation should include spinal alignment, the presence of any rotation or translation, assessment of the kyphosis and loss of vertebral height[11-13]. CT scan provides further information on the extent of bony injury, and MRI scan shows edema inside the vertebral body[14]. In the past years, several classifications have been suggested for VF: The most commonly used is the Magerl's classification that categorizes trauma in compression, rotation and distraction injuries[15]. Magerl A1 type is considered a main indication for percutaneous vertebroplasty (PVP) and percutaneous balloon kyphoplasty (BKP). However, it is important to underline that these subjects can be treated also with orthosis devices, bed rest as well as medical and/or physical therapy. Common indications for PVP include osteoporotic VF of more than 3–4-week refractory by medical therapy, Kummel's disease, symptomatic hemangioma, painful vertebra with extensive osteolysis or invasion secondary to malignant tumor (metastasis, multiple myeloma, etc.), traumatic fractures and need for anterior stabilization prior to surgical operation performed in the spine's posterior elements[16, 17]. The most common indication for BKP is a recent (less than 7–10 days) traumatic vertebral fracture (A1 type according to the Magerl classification) with a kyphotic angle at the specific level >15 BKP is indicated in all the other cases where PVP can be applied as well[16, 17]. Contraindications are common for both techniques; any patient reporting improvement in symptoms with conservative treatment,

asymptomatic VF, tumor mass with spinal canal involvement, pregnancy, uncorrectable coagulopathy, severe cardiorespiratory disease, cement allergy and systemic and especially local infection cannot be eligible for standard vertebral augmentation.

Technique:

Detailed description of both techniques is beyond the scope of this review and can be found at CIRSE guidelines on percutaneous vertebral augmentation[17]. High-quality fluoroscopy equipment is essential, but a hybrid technique using both fluoroscopy and CT has been described by some authors[18, 19]. PVP and BKP can be carried out under local or epidural anesthesia, sedation or general anesthesia depending on the spine level and number of vertebrae treated[17, 20, 21]. Vertebroplasty uses high-power cement injection; the force of PMMA injection has to surpass the local pressure of the trabecular bone of the treated vertebra (i.e., the bone cement is transferred under pressure)[22]. During injection of the cement, continuous observation is necessary in order to prevent excessive bone cement leakage.technique was introduced in 1990s with the aim of stabilizing the vertebral fracture and restoring the vertebral height and the associated kyphotic deformity with reduced cement leakages[23]. BKP is performed with the introduction of an inflatable balloon into the compressed vertebral body aiming to elevate the endplates. This is carried out by creating a cavity inside the vertebral body that is filled with cement; during BKP, the cement injection is held at low pressure[22].



Figures: Showing Balloon kyphoplasty (BKP)

Cements and Alternatives:

The cement most commonly used is poly-methylmethacrylate (PMMA) mixed to an opacifying agent. In the market, there is a wide variety of PMMA products differing upon the opacifying agent used (barium sulfate, zirconium, tantalum or hydroxyapatite), the viscosity (low, medium, high), the working time (up to 20 min) and the exothermic reaction (present or not) [24-26]. During polymerization, there is an exothermic reaction of variable degree with resultant temperature increase; postmortem histologic findings suggest that in cases where PMMA is injected into tumor there is a macroscopic and microscopic rim of tumor necrosis [27]. In vitro temperature measurements at three key locations of vertebral bodies undergoing vertebroplasty (anterior cortex, center and spinal canal) report a rise in the temperature over 50 C in the vertebrae's center without, however, significant rise in the epidural canal (temperature there remained below 41C[28]. Latest techniques aiming to improve application, delivery and characteristics of PMMA such as viscosity and working time include radiofrequency-targeted augmentation as well as implants such as stents and peek cages[29, 30]. During radiofrequency-targeted augmentation, an articulating osteotome creates channels inside the vertebral

body and bone cement that is heated by means of a radiofrequency source is then injected[29]. Recently, there is an increasing interest for the use of a synthetic bone substitute (calcium phosphate cement) capable of remodeling or integrating into the surrounding bone. This is expected to work as a carrier for osteo-inductive proteins. Recent studies showed that few new-generation bioactive bone cements have been found to induce new bone formation, have good mechanical stability and showed satisfactory radio-opacity[31, 32]. A radio-opaque silicon polymer might be proposed as an alternative to bone cement[33, 34]. This silicon polymer is characterized by enhanced bone interdigitation and acts as compliant polymer that conforms to the implant site; its viscosity increases gradually, resulting in a longer working time and a stiffness which is close to that of the intact vertebrae[33, 34]. There are various goals for next-generation cements which are going to be used in PVP and BKP. Handling properties such as adequate injectability, setting property, cohesion, and radiopacity are necessary for augmenting safety of the technique; other goals include provision of immediate reinforcement by means of sufficient mechanical strength and at the same time osteoconductivity and osteoinductivity for new bone formation, moderate biodegradability so that the resorption of cement material matches new bone formation, adequate porosity in order to allow body fluid circulation, cell migration and new bone in-growth[35]. Furthermore, the addition of anticancer drugs (e.g., methotrexate, doxorubicin or cisplatin) to PMMA could result into both local and systemic diffusion of the drug whilst incorporation of bioactive additives (such as strontium, magnesium, zinc, copper, fluoride and growth factor) has been shown to promote bone metabolism[35, 36].

Clinical Outcome and Complications:

According to the CIRSE guidelines on percutaneous vertebral augmentation, any osteoporotic vertebral fracture [4 months old is considered chronic; vertebral augmentation should be proposed only when chronic fractures are accompanied by cavitation or bone edema (imaging findings of osteonecrosis or incomplete healing). Both PVP and BKP prevent morbidity, save and prolong patients' lives[37-42]. Response rates to PVP depend upon different parameters and pathologies. Pain reduction rate is 90% for acute and 80–100% for chronic osteoporotic fractures, 60–85% for malignant cases and 80–100% for aggressive hemangiomas[43-49]. Mobility improvement is 84–93% for acute and 50–88% for chronic osteoporotic fractures. Pain reduction effect is similar between PVP and BKP[49, 50]. In case of malignant substrate, both augmentation techniques should be combined to systemic and local therapies for disease and tumor control. For both PVP and BKP, complications include cement leakage, infection, pedicular or rib fracture, bleeding, allergic reaction and adjacent vertebral body collapse. In this latter case, it is not clear whether these new fractures located at adjacent levels are the result of mechanical variations attributed mainly to cement's stiffness or are the result of osteoporosis' evolution. As far as complications are concerned, a recommended threshold of 2% should apply for all osteoporotic indications and one of 10% for malignant substrate.

Controversies:

Vertebral Augmentation or Conservative Therapy? When compared to age-matched controls, patients with vertebral fractures have a 40% lower survival after 8 years; this increased risk of mortality can be

associated with weight loss and physical frailty with associated markers of decreased function. Edidin et al.[51] performed a population-based comparison of mortality risk between surgical and non-surgical patient groups suffering from vertebral fractures concluding that at up to 4 years of follow-up patients undergoing PVP or BKP had a higher adjusted survival rate of 60.8% compared with 50.0% for patients in the non-operated cohort (p\.001) and were 37% less likely to die [adjusted hazard ratio (HR) = 0.63, p\.001]. Gerling et al. performed in a group of patients with vertebral fractures a survivorship analysis comparing mortality post-cement augmentation to that of inpatient pain management and bracing; authors concluded that as far as refractory osteoporotic vertebral fractures are concerned, cement augmentation improves survival for up to 2 years when compared with conservative pain management regardless of age, sex and number of fractures or comorbidities[40]. Chen et al.[42]evaluated the impact of non-operative treatment, PVP and BKP upon survival and morbidity after vertebral compression fracture in the medicare population concluding that vertebral augmentation procedures appear to be associated with longer patient survival than non-operative treatment does. Zampini et al.[51]in a level III therapeutic study used the Nationwide Inpatient Sample database to evaluate complications, mortality, post-hospital disposition and treatment costs of kyphoplasty compared with non-operative treatment in patients with vertebral compression fractures concluding that BKP accelerates the return of independent patient function whilst the initially higher cost of treatment is offset by the reduced use of post-hospital medical resources. Lange et al.[52] used the German claims data to evaluate survival and cost post-cement augmentation or non-operative management reporting a higher overall survival rate for operated than non-operated patients with vertebral fractures. Comparison of percutaneous vertebroplasty versus conservative treatment for one-level thoracolumbar osteoporotic compression fracture favors the former for early pain control and restoration of the compressed vertebral body[53]. VERTOS II study which was an open-label randomized trial comparing vertebroplasty to conservative therapy concluded that the technique is effective and safe with pain relief post-PVP being immediate, sustained for at least a year and significantly greater than that achieved with conservative treatment at an acceptable cost[54]. The results of VERTOS II study additionally reported that the incidence of new vertebral fractures was not different between the two therapies and that PVP contributed to stature preservation by decreasing both the incidence and severity of further height loss in the treated vertebrae. Repercussions of conservative management for vertebral fractures include immobility, loss of bone density and muscle strength, muscle contracture and pressure sores, decreased cardiac performance and pulmonary compromise, deep vein thrombosis, gastrointestinal difficulties, urinary tract and central nervous system symptoms; therefore, in properly selected patients complications from performing vertebral augmentation may be less than from not performing the procedure. As far as cancer-related fractures are concerned, economic analyses report that the use of kyphoplasty or vertebroplasty may be a cost-effective strategy at commonly accepted willingness-to-pay thresholds [55].

Percutaneous Vertebroplasty or Balloon Kyphoplasty?

An analysis of the Medicare population concludes that BKP has a statistically significant higher survival rate (of 62.8% as compared to 57.3% for PVP) and a 23% lower mortality rate than that for vertebroplasty

patients (p\0.001). Another analysis of the Medicare Provider and Review File database concludes that BKP tends to have a more striking association with survival than vertebroplasty does, but it is costly and may have a higher rate of subsequent vertebral compression fracture. A UK cost-effectiveness analysis concludes that BKP may be a cost-effective strategy for the treatment of patients hospitalized with vertebral compression fractures compared to PVP or non-surgical management[56]. A recent meta-analysis of the literature comparing PVP and BKP for single-level vertebral compression fracture concludes that both techniques are safe and effective with a similar long-term pain relief, function outcome and new adjacent fracture rate[57]. BKP was found superior as far as injected cement volume, short-term pain relief, improvement in short- and long-term kyphotic angle and lower cement leakage rate were concerned; however, the technique has a longer operation time and higher material cost[57]. Prospective randomized trials published by Liu et al. and Evans et al.[58, 59] conclude that in terms of clinical outcome (i.e., pain and disability reduction) percutaneous vertebroplasty and balloon kyphoplasty are equally effective techniques with the latter coming at a higher cost. The KAVIAR study was another randomized trial comparing the two augmentation techniques; the study recorded similar long-term improvement rates and safety profiles for PVP and BKP although there was a trend for a longer fracture-free survival in the kyphoplasty arm[60]. In a retrospective comparison, both techniques were found equally effective for functional recovery and pain relief in osteoporotic vertebral fractures although BKP seems to have better radiological outcomes without, however, any clinical relevance[61]. Finally, a systematic review and meta-analysis including ten randomized controlled trials for vertebroplasty and kyphoplasty concludes that both techniques improve function and have a less clear effect upon quality of life; however, vertebroplasty may provide better pain relief than balloon kyphoplasty in patients with osteoporotic vertebral fractures[62]. It is evident that throughout the literature there is no clearly proven superiority of one technique over the other; all the aforementioned provocative results and conclusions could easily be related to selection biases. Ideally, a prospective randomized direct comparison of the two methods for the treatment of vertebral compression fractures in similar patient groups would provide the answers. However, the question still remains: How easy is it to design and perform such a study?

Randomized Trials:

Up until 2009, there was a great enthusiasm for vertebroplasty mainly driven by the outcomes reported in the everyday clinical practice and by meta-analyses of large observational and retrospective series showing pain reduction, mobility and life quality improvement[63]. In this year, two placebo-controlled vertebroplasty randomized trials were published in the New England Journal of Medicine (NEJM) supporting that pain and pain-related disability improvement in patients with osteoporotic fractures treated with vertebroplasty were similar to the improvements in a control group treated with a simulated procedure without PMMA (a sham procedure)[64]. Both trials have been criticized concerning limitations and weaknesses including patient selection (and exclusion of the interventional radiology from this procedure), enrollment, the sham procedure itself and selection bias[65]. VAPOUR trial was a multicentered study recruiting patients with one or two osteoporotic vertebral fractures of less than 6-week duration and numeric rating scale (NRS) back

pain greater than or equal to 7 out of 10; during this study, patients were randomly assigned and compared to either a vertebroplasty or a placebo arm[66, 67]. VAPOUR trial concluded that PVP is superior to the placebo intervention for pain reduction in patients with acute osteoporotic spinal fractures of less than 6 weeks in duration; additionally, this trial has shown that conservative management is not free of adverse events and complications since fracture collapse and retropulsion led to spinal cord compression in two patients of the placebo group[67]. The authors of the two NEJM studies commented upon VAPOUR trial that it may overestimate the benefit of PVP due to a number of reasons including problems with blinding, reporting and selection bias[68]. The advantages of VAPOUR trial over previous masked RCTs are clear and include earlier treatment of vertebral compression fractures in patients with severe pain (NRS C 7) more than half of whom (57%) were hospitalized with a 5.5-day reduction in hospital stay reported in the vertebroplasty group[69]. Furthermore, the placebo intervention applied in the VAPOUR trial was much closer to a true sham procedure since the periosteal local anesthetic infiltration applied in the previous masked RCTs could have provided pain relied especially in cases of chronic fractures; finally, the X-rays at 6 months post-PVP illustrated a 30% greater vertebral height preservation without an increase in additional vertebral fractures [69].

Adjacent Vertebral Body Fractures:

It is not yet clear whether new fractures at adjacent levels are the result of mechanical variations attributed mainly to cement's stiffness or are the result of osteoporosis' evolution. There are studies reporting a slight but significantly increased risk of vertebral fracture in the vicinity of an augmented vertebra, whilst others conclude that vertebroplasty does not increase the risk of adjacent vertebral fracture[70]. A recent biomechanical study on cadaveric spines has shown that vertebral fracture itself adversely affects both fractured and adjacent levels in terms of compressive load sharing and vertebral deformation increase with vertebroplasty partially reversing all these effects[71]. Osteoporosis and poor mineral bone content have been proven as predictive factors for secondary new vertebral compression fractures; on the other hand, intra-discal cement leakage during vertebral augmentation seems to be also associated with a higher incidence of fracture at adjacent levels[72, 73].

CONCLUSION

The wide variety on fracture morphology and substrate in combination with each patient's different characteristics and comorbidities demand a tailored lesion and a patient centered approach. Next-generation cements to be used in PVP and BKP aim to improve handling properties, reinforcement, osteoconductivity, osteoinductivity and biodegradability and to act as drug carriers. Vertebral augmentation techniques prolong survival and prevent morbidity in patients with vertebral compression fractures. Both PVP and BKP are more efficient than conservative therapy for the management of painful fractures. As far as osteoporotic fractures are concerned, there is no clearly proven superiority of one technique over the other; however, BKP comes with a longer operation time and at a higher cost. VAPOUR trial is a well-constructed, masked, randomized placebo-controlled trial clearly illustrating that PVP is a safe and effective procedure for symptomatic patients with acute osteoporotic fractures suffering from severe pain refractory to conservative management. These

results are in accordance with the everyday clinical practice and the hundreds of articles published upon vertebroplasty during the last 5 years post-NEJM RCTs reporting high efficacy and safety rates.

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