REVIEW

Risks and benefits of percutaneous vertebroplasty or kyphoplasty in the management of osteoporotic vertebral fractures

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Abstract Vertebral fracture (VF) is the most common osteoporotic fracture and is associated with high morbidity and mortality. Conservative treatment combining antalgic agents and rest is usually recommended for symptomatic VFs. The aim of this paper is to review the randomized controlled trials comparing the efficacy and safety of percutaneous vertebroplasty (VP) and percutaneous balloon kyphoplasty (KP) versus conservative treatment. VP and KP procedures are associated with an acceptable general safety. Although the case series investigating VP/KP have all shown an outstanding analgesic benefit, randomized controlled studies are rare and have yielded contradictory results. In several of these studies, a short-term analgesic benefit was observed, except in the prospective randomized sham-controlled studies. A long-term analgesic and functional benefit has rarely been noted. Several recent studies have shown that both VP and KP are associated with an increased risk of new VFs. These fractures are mostly VFs adjacent to the procedure, and they occur within a shorter time period than VFs in other locations. The main risk factors include the number of preexisting VFs, the number of VPs/KPs performed, age, decreased bone mineral density, and intradiscal cement leakage. It is therefore important to involve the patients to whom VP/KP is being proposed in the decision-making process. It is also essential to rapidly initiate a specific osteoporosis therapy when a VF occurs (ideally a bone anabolic treatment) so as to reduce the risk of fracture. Randomized controlled studies are necessary in order to better define the profile of patients who likely benefit the most from VP/KP.

Keywords Kyphoplasty · Osteoporosis · Vertebral fracture · Vertebroplasty

Introduction

VF is the most common complication of osteoporosis. It is associated with increased morbidity and mortality and, in a minority of patients, with considerable pain. It is estimated that 3 % of all VFs are pathological, 14 % are trauma-related, and 83 % are osteoporotic [1]. For women at the age of 50, the residual risk for VF is 32 % [2]. In both the USA and Europe, annual risk increases with age, ranging from 0.4–0.6 % in women who are between 50 and 54 to 1.2–1.3 % in those who are between 65 and 69, and to 2.9–3.8 % in those who are 85 or older [3, 4].

VF is widely underdiagnosed in all countries. The IM-PACT study showed this for North America, South America, Europe, Australia, and South Africa [5]. However, the underdiagnosis may be related to a problem of qualitative or quantitative definition of VF. Nearly 70 % of VFs are not clinically recognized as such because they are asymptomatic or only slightly symptomatic, or they are not diagnosed [6, 7].

Symptomatic VFs cause as many days of confinement to bed and functional incapacity as hip fractures, if not more [8]. Quality of life can be very much lowered following symptomatic or asymptomatic VF [9-12]: height loss and kyphosis, besides physical pain, symptoms include sleeping disorders, fear of a fall that may lead to new fractures, loss of confidence, and psychological disorders ranging from anxiety to depression. When serious, thoracolumbar static disorders may cause a reduction in respiratory function (restrictive syndrome) as well as digestive disorders (early satiety) accompanied by loss

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of weight. The simple movements of daily life become more and more difficult. All these problems may lead to isolation, a situation that is much feared in geriatric medicine. Moreover, the VF increases the risk of mortality. The consequences of VF, especially the mortality, increase with the number and the severity of VF.

The presence of a VF increases the risk of new vertebral and non-vertebral fractures. In the Rochester study, the cumulated incidence of suffering a new fracture (or several fractures) during the year following the first VF was around 20 %; at 10 years, cumulated risk was more than 70 % [13]. The presence of a VF increases the risk of new VFs from 3 to 12 and the risk of non-vertebral fractures from 1.5 to 4 [6, 13-17]. The more severe the VF is, and the more VFs there are, the more the risk of vertebral and non-vertebral fracture recurrence increases [18]. In the MORE study, over the 3 years, the risk of VF recurrence increased from 10.5 % in the presence of a prior VF of grade I to 38.1 % when the VF was grade III [19].

Many antiresorptive and anabolic therapies have shown efficacy in lowering the risk of VF recurrence in randomized trials against placebo. The percent of fracture reduction given below should not be compared. SERMs, oral bisphosphonates, and strontium ranelate have been reported to lower this risk by around 50 %; zoledronic acid, denosumab, and teriparatide by nearly 70 %. The antifracture effect is obtained after 6 to 12 months. These therapies are also particularly efficacious for reducing the risk of multiple VFs, and so may lower the ensuing pain and morbidity. Of the common osteoporosis therapies, teriparatide was the only one to have shown efficacy in reducing back pain compared with other osteoporosis therapies or placebo [20-22]. As the risk of subsequent fractures is very high during the first months that follow a VF, and as the therapies are rapidly efficacious, it is essential to initiate these therapies without delay. Patients receiving an osteoporosis therapy must have a sufficient intake of calcium (around 1,200 mg/day) and vitamin D (around 800–1,000 IU/day or 20–25 μg/day). This intake optimizes the effect of osteoporosis treatments and improves musculoskeletal health while lowering the risk of falls and fractures.

Treating a symptomatic VF often requires immobilization and antalgic agents. The role of contention on pain is controversial, partly because of a lack of data. Acute treatment only applies to symptomatic fractures. Nonsteroidal analgesics at reasonably high doses are the treatment of choice. Morphine derivatives may be included in case of failure, and calcitonin may be used for 4 weeks [23]. Both confinement to bed and the use of certain analgesics over long periods are associated with several side effects that are particularly worrying in the elderly, such as deconditioning, respiratory superinfection, impaired balance, and increased risk of falling. To avoid these side effects, or when pain cannot be controlled, minimally invasive treatment may be suggested. VP and KP are proposed to relieve VF-related pain; KP also enables vertebral height to be partially restored and secondary kyphosis to be limited.

Method

The authors conducted a MEDLINE search using relevant search terms including osteoporosis, osteoporotic vertebral compression fracture, kyphoplasty, and vertebroplasty. This article is a review of the randomized controlled studies that have been published comparing VP or KP with conservative treatment, or VP with KP following osteoporotic VF (Table 1). Because there are not many randomized studies on this subject, case series and retrospective and prospective cohort analyses were included whenever they provided pertinent additional information. In order to limit the length of this article, we based our research on literature reviews as well as on meta-analyses of good quality [24-26].

First, we summarized the historical and technical aspects of VP and KP. Second, the articles were analyzed in terms of benefits: pain relief, quality of life, functional improvement, and increase of vertebral height. Third, we analyzed the side effects and complications of VP and KP.

Vertebroplasty and kyphoplasty: history and technical aspects

The first VPs were performed in 1984 in order to treat symptomatic vertebral angiomas [27]. Their use was next extended to the treatment of symptomatic vertebral metastases, and then to traumatic VFs. It was at the beginning of the 1990s that the procedure was used in the analgesic treatment of osteoporotic VFs.

VP involves the injection of a radiopaque cement under X-ray guidance, usually a polymethylmethacrylate resin (PMMA) [28]. The procedure is performed via the transpedicular approach (ideally bilaterally) through a trocar under local or general anesthesia. PMMA is a two-component (liquid/powder) resin. It is combined with a contrast agent so that the procedure can be followed. After between 8 and 10 min, the PMMA polymerizes and hardens, a process which is accompanied by an exothermic reaction reaching up to around 75 °C in the center of the vertebra. The analgesic effect of VP is attributed to several factors, including the thermal reaction, as well as the consolidation and stabilization of the fracture. VP requires that the resin be injected at relatively high pressure because of its low viscosity [29]. This is accompanied by a high risk of cement leakage. It is often said that VP must be performed fairly soon after a VF to obtain the analgesic effect. However, authors have shown analgesic benefits for VFs up to 1 year after their occurrence [30, 31]. Nieuwenhuijse et al. analyzed the relationship between the fracture date and VP efficacy in 115 patients who had undergone 216 VPs [31]. The mean time from fracture to VP was 6.0±2.9 months. The authors concluded that the analgesic benefits and improvement in quality of life obtained were independent of the length of time between the VF and VP.

Table 1 Randomized controlled trial comparing percutaneous vertebroplasty (VP) or kyphoplasty (KP) to conservative management, or VP to KP

Ref	Author	Year	Time to operation	No.	Study follow-up	Cement leakage	Pain Between groups difference	QOL or physical functioning Between groups difference	New VF Between groups difference
[37]	Voormolen	2007	6w-6 m	VP=18 PB=16	2 w	nm	sig. better for VP (1d), ns (14d)	sig. better for VP (2w)	nm
[41] [42]	Rousing Rousing	2009 2010	<8 w	VP=25 PB=24	3 m/12 m	nm	ns (3m)	ns (3/12m)[a]	sig. higher for VP RR 2.9 (3m)
[35]	Buchbinder	2009	<12 m	VP=38 PB=40	6 m	37 %	ns (1w, 1/3/6m)	ns (1w. 1/3/6m)	ns
[36]	Kallmes	2009	<12 m	VP=68 PB=63	3 m	nm	ns (3/14d, 1m)	ns (3/14d, 1m)	nm
[46]	Klazen	2010	<6 w	VP=101 PB=101	12 m	nm	sig. better for VP (1d. 1w, 1/3/6/12m)	nm[b]	ns
[47]	Farrokhi	2011	4 w-12 m	VP=40 PB=42	36 m		sig better for VP (1w, 2/6m)	sig better for VP (1w, 2/6/1 2/24/36m)	sig. higher for PB at 2y (13.3 vs 2.2 %)
[48]	Blasco	2012	<12 in	VP=64 PB=61	12 m	49 %	ns (2w. 2/6/12m)	ns (2/6/12m)	sig. higher for VP at 6 m (27 vs 13 %)
[52] [53]	Wardlow Boonen	2009 2011	<3 m	KP=149 PB=151	12m/24m	27 %	sig. better for KP (1/3/6/12m)	sig. better for KP (1/3/6/12/24 m)	ns
[55]	Liu	2009	<6 m	VP=50 KP=50	6 m	nm	ns (3d, 6m)	nm	ns

d day, *KP* kyphoplasty, *m* month, *n* number, *nm* not mentioned, *ns* not significant, *PB* placebo, *QOL* quality of life, *Ref* reference, *sig* significant, *VF* vertebral fracture, *VP* vertebroplasty, *w* week

[a] Except for Bartel index at 12 months

[b] Qualeffo-41 and Roland Morris Disability questionnaire: improvement greater and faster after VP

KP was developed to improve VP [32], using the same approach route as for VP. An inflatable balloon is inserted via the trocar, allowing a void to be made. The balloon is then removed, and the cement is injected at lower pressure into the void. The theoretical advantages are a lowering of the risk of cement leakage and (partial) restoration of anterior and middle vertebral wall height. KP was approved by the US Food and Drug Administration in 1998.

Before performing VP/KP, magnetic resonance imaging (MRI) must be conducted to verify that the posterior wall is intact. Table 2 summarizes the usual contraindications to VP/KP [33]. VP takes less time than KP and costs less. These highly promising procedures were very popular between the years 2000 and 2009. They are mainly performed by radiologists, orthopedists, and neurosurgeons. In the USA, the number of VPs performed increased from around 14,000 in 2001 to nearly 30,000 in 2005, and the number of KPs from around 43,000 in 2006 to more than 50,000 in 2008 [34]. Following the publication of reports that called into question the clinical benefit of VP in 2009, the number of VPs and KPs performed decreased by 10 % [34-36].

Vertebroplasty and kyphoplasty: efficacy

Efficacy of vertebroplasty

The first publications that included case reports and case series all concluded that VP had an outstanding analgesic effect in around 90 % of patients. In 2009, a large literature review of VP and KP for osteoporotic VFs was published [25]. The results of that review suggested that there were analgesic and functional benefits observed during the first 3 months following VP compared with conventional medical treatments. Of the 74 studies analyzed, 70 were case series. There was only one randomized controlled study comparing VP with medical

Table 2 Usual contraindications to percutaneous vertebroplasty or kyphoplasty

Osteoporotic vertebral fracture related contraindications

- Fracture with posterior wall defect
- Severe vertebral body collapse (vertebra plane)
- Prophylaxis with no evidence of acute fracture
- Asymptomatic stable fracture

Other vertebral diseases related contraindications

- Osteomyelitis or spondylodiscitis
- Tumor extension into epidural space

General contraindications

- Uncorrected coagulation disorders
- Allergy to any required component
- Pregnancy

treatment [37], and there were three prospective non-randomized controlled studies comparing the two treatment strategies [38-40]. The Vertos randomized controlled study included 34 patients, 18 in the VP group and 16 in the optimal medical therapy (OMT) group [37]. Analysis at day 1 and at week 2 showed an analgesic and functional benefit in the VP group. Due to the low number of patients and high rate of switching from the OMT group to the VP group, no conclusions could be drawn regarding potential long-term benefits. The three non-randomized controlled studies confirmed these rapid benefits for the patients who had undergone VP. Diamond et al. compared 55 patients treated by VP with 24 receiving OMT [38]. The analgesic and functional benefits observed at the beginning were no longer significant after 1.5, 6, and 12 months. Alvarez et al. compared 101 patients treated by VP with 27 receiving OMT [39]. In the VP group, the analgesic benefit was significant at 3 and 6 months; the functional benefit was significant at 3 months. At 12 months, there was no longer any difference between the two groups. In a second trial, Diamond et al. prospectively followed up 88 patients treated by VP and 38 who received OMT [40]. The analgesic and functional benefits were significant in the VP group at 6 weeks, but there was no difference at 1 and 2 years. The other 70 case series all reported an immediate analgesic benefit [25]. Thus, there was a trend in the literature supporting a rapid analgesic and functional benefit with VP when performed for osteoporotic VF management. Also in 2009, but not included in the meta-analysis of McGirt et al., Rousing et al. published a randomized controlled study, which, however, exhibited methodological shortcomings regarding pain evaluation [41]. The VP group had an immediate analgesic benefit within 12 to 24 h of the procedure that was significantly greater than that of the control group. The authors reported two new VFs in the VP group, whereas there were none in the control group, after 3 months. Follow-up at 3 and 12 months showed no difference in terms of analgesic benefits between the two groups [41, 42].

There was controversy when two prospective randomized sham-controlled studies were published in the New England Journal of Medicine in 2009 [35, 36]. The patients in both the VP and control groups were managed under the same conditions: treatment in the interventional radiology room, local anesthesic infiltration of the posterior longitudinal ligament, and cement prepared beside the patients. A sham insertion of a trocar into the vertebra was performed in the control group; only the VP group was injected with cement. Buchlinder et al. enrolled 78 patients who had suffered one or two painful MRI-confirmed osteoporotic VFs within the previous 12 months with unfavorable clinical evolution [35]. The patients were stratified according to the duration of symptoms (<6 weeks or ≥6 weeks). They were evaluated at 1 week and at 1, 3, and 6 months. The primary outcome was overall pain on a scale of 0 to 10. VP showed no benefit at any time compared with the

control group in terms of pain, functional status, quality of life, or even perceived improvement. For example, at 3 months, the mean reduction in the pain score was 2.6±2.9 in the VP group and 1.9±3.3 in the control group (adjusted between-group difference, 0.6; 95 % CI, −0.7 to 1.8). Kallmes et al. enrolled 131 patients who had between one and three painful CT- or MRI-confirmed osteoporotic VFs for less than 12 months with unfavorable clinical evolution [36]. The primary outcomes were scores on the modified Roland-Morris Disability Questionnaire (RDQ) and overall pain on a scale of 0 to 10 at 1 month. There was an immediate improvement with regard to pain in both groups. At 1 month, there was no significant difference between the VP and control groups in either the RDQ score (difference 0.7; 95 % CI, −1.3 to 2.8; $P=0.49$) or the pain score (difference 0.7; 95 % CI, −0.3 to 1.7; $P=0.19$). At 3 months, there was a high rate of crossover (51 %) in the control group. It was therefore not possible to evaluate VP's benefit at 3 or 6 months. Despite the negative results of these two prospective randomized sham-controlled studies, several authors voiced objections, pointing out that VP should be reserved for patients with acute VF of recent onset (<6 weeks), for those who have severe pain, or for those in whom MRI has shown edema to be present [43, 44]. In response to some of these objections, a meta-analysis of these two studies was conducted using the individual data of the 209 patients [45]. The analyses took into account the date of the VF (≤ or >6 weeks) and severity of pain on a scale of 10 (≥ or <8). For the patients with recent pain (≤6 weeks), between-group differences at 1 month for pain and disability scores were 0.1 (95 % CI, −1.4 to 1.6) and 0.2 (95 % CI, −3.0 to 3.4), respectively. For patients with severe pain (≥8), between-group differences at 1 month for pain and disability scores were 0.3 (95 % CI, −0.8 to 1.5) and 1.4 (95 % CI, −1.2 to 3.9), respectively. At the beginning of the study, 68 % of patients in the different groups were on opioids. Surprisingly, at 1 month, there were more VP patients than control patients on opioids (64 versus 46 %; $P=0.018$). The authors of this meta-analysis concluded that VP did not offer any benefit, not even in the subgroups of patients who theoretically should have benefited the most.

VERTOS II, an open-label randomized trial, was published in 2010 [46]. The authors enrolled 202 patients who had a VF and met strict criteria: pain for less than 6 weeks, a visual analogue scale (VAS) score ≥5, and edema on MRI. The patients who were randomized into the VP group had better pain control at 1 month and 1 year than the control group. The difference between the groups in the reduction of mean VAS score from baseline was 2.6 (95 % CI, 1.7–3.4; $P<0.0001$) at 1 month and 2.0 (95 % CI, 1.1–2.8, $P<0.0001$) at 1 year. One randomized controlled study involving 82 patients (refractory to analgesic therapy for >4 weeks and <1 year) showed a highly significant improvement in pain relief for 6 months and quality of life for at least 36 months [47]. All patients in the OMT group were treated with analgesic agents, calcitonin

and alendronate. After 2 years of follow-up, the incidence of new VFs in the OMT group was higher than in the VP group (13.3 versus 2.2 %; $P<0.01$). The VP was made via a unilateral parapedicular approach in 87.5 % of patients. The cement leakage was only 14 % (including intervertebral disc, epidural and paravertebral space). Ten patients in the OMT group with persistent pain and low level of quality of life 1 year after the study started crossed over to VP. They had a significant pain relief. An open-label randomized trial published in 2012 enrolled 125 patients [48]. There was a significant decrease in VAS in both groups. However, at 2 months, VAS improvement was greater in the VP group than in the control group (mean differences 1.59±0.42 versus 3.07±0.45, $P=0.017$). The quality of life questionnaire of the European Foundation for Osteoporosis (Qualeffo-41) was significantly improved in the VP group at the evaluation time points, whereas the improvement in the control group was significant only after 6 months. There were no differences between the two groups at 1 year, be it for VAS or Qualeffo-41. However, there were significantly more new VFs in the VP group (OR 2.78; 95 % CI, 1.02–7.62, $P=0.046$).

Efficacy of kyphoplasty

An initial meta-analysis published in 2006, which was mainly based on case series, included 26 studies involving 1,490 patients who had undergone 2,643 KPs [49]. The analysis results documented a mean VAS reduction of −5.1, an augmentation of anterior vertebral wall height of 13.4 %, a reduction in kyphosis as measured by Cobb's angle of −7.7 %, and an improvement in functional indices of +20 %. However, the authors emphasized the methodological shortcomings of these studies and the insufficient follow-up of patients. By 2009, 35 studies pertaining to KP had been published [25]. Thirty-three studies were case series, and all concluded that there was a rapid analgesic effect. There was no randomized controlled study, and only one prospective non-randomized controlled study, which was published in two parts [50, 51]. Forty patients treated by KP were compared with 20 patients receiving conventional medical treatment. There was an analgesic benefit and functional improvement at 3, 6, and 12 months in the KP group. The Fracture Reduction Evaluation Study (FREE) has been the only randomized controlled study to have compared KP with conventional medical treatment [52]. A total of 300 patients were randomized after a mean 6-week period following a VF (osteoporosis-related in 95 % of cases). The primary outcome was the difference in change from baseline to 1 month in the short-form SF-36 physical component summary (PCS) score (scale 0–100). Mean SF-36 PCS score improved by 7.2 points (95 % CI, 5.7–8.8), from 26.0 at baseline to 33.4 at 1 month, in the KP group, and by 2.0 points (95 % CI, 0.4–3.6), from 25.5 to 27.4, in the control group (difference between groups 5.2 points, 2.9–7.4; $P<$

0.0001). This benefit for the KP group was still present at 1 year. The same applied to five other scores concerning pain and/or functional capacity. The beneficial effect was significantly better for the KP group at each time point (1, 3, 6, and 12 months). Analgesic benefit and some functional benefits were still higher in the KP group compared with the control group after 24 months of follow-up [53]. There was no significant difference in the occurrence of new radiological VFs after 24 months of follow-up: 47.5 % in the KP group versus 44.1 % in the control group. Around 80 % of VFs occurred during the first year. A prospective study comparing KP with conservative treatment during the first 3 weeks following a symptomatic VF showed that KP had an analgesic benefit only during the first month after the procedure [54]. The authors concluded that patients should be treated conservatively before KP is considered.

Vertebroplasty versus kyphoplasty

There has been only one randomized controlled study comparing VP with KP for osteoporotic VFs. Liu et al. enrolled 100 patients presenting with a VF that had occurred less than 6 months before [55]. The time period between the VF and the procedure was 17.0 days for KP and 15.8 days for VP. There was an excellent analgesic effect in both groups, with no significant difference. A reduction in the kyphosis angle was observed in both groups, but it was significantly greater in the KP group ($P < 0.001$). More PMMA was used in the KP group than in the VP group (5.56 ± 0.62 versus 4.91 ± 0.65 mL, $P < 0.001$). Follow-up lasted 6 months, and there were two new VFs, both of which occurred in the KP group. There have been nine case series comparing VP with KP, with between 45 and 154 patients enrolled in each [56-64]. The groups were highly heterogeneous, making it very difficult to compare the results. Mean age ranged from 62 to 78, and the duration of follow-up varied between 6 and 42 months. When it was mentioned, the volume of PMMA injected ranged from 2.5 to 5.8 mL in the VP groups and from 1.8 to 5.6 mL in the KP group. An excellent meta-analysis comparing VP with KP has recently been published [26]. In the 10 studies analyzed, which encompassed 783 patients, there was no difference between the VP and KP groups in terms of short- and long-term analgesic effects or short- and long-term functional benefits. Operation time was the same for both procedures. But KP was superior to VP with regard to the following points: long-term improvement of kyphosis angle (mean difference= −2.64, 95 % CI, −4.66 to −0.61; $P = 0.01$), improvement in anterior height of vertebral body (mean difference=3.67 mm, 95 % CI, 1.40 to 5.94; $P = 0.002$), and reduction in cement leakage (RR=0.70, 95 % CI, 0.52 to 0.95; $P = 0.02$). The risk of a VF adjacent to the treated vertebra was 7.1 and 3.7 % for the KP and VP groups, respectively, with no significant difference noted. It is not certain that a difference of 2° to 3° on the kyphosis angle or an increase of 3 to 4 mm of the anterior height of vertebral body will have a clinical relevance. To answer this question, it is necessary to have a randomized study with the kyphosis angle as primary endpoint.

Side effects and complications of vertebroplasty and kyphoplasty

Main side effects

Complications are more common when VP/KP is performed for metastatic VFs than when it is performed for osteoporotic VFs. It is necessary to distinguish between asymptomatic side effects, symptomatic side effects, and long-term complications. Asymptomatic side effects are associated with cement leakage along the trocar route, in the epidural and intradiscal regions, or with intravenous cement leakage. Cement leakage is much less frequent with KP than VP [33, 65-68]. It may concern up to 70 % of patients depending on the series and study methods, but is most often neglected [69]. However, some asymptomatic side effects are a cause of worry. In VERTOS II, pulmonary embolisms were screened by chest CT and found in 26 % (95 % CI, 16–39 %) of patients [70]. All the patients were asymptomatic. Cement leakage into the azygos vein was the only risk factor identified for pulmonary embolism (OR 43; 95 % CI, 5–396). The short-term symptomatic side effects of VP/KP for osteoporotic VFs usually concern between 1 and 3 % of patients, and seem to be even less in more recent series. In Hulme's review, the risk of complications was 3.9 % after VP and 2.2 % after KP [65]. Leakage into the epidural space, spinal canal, or foramen may cause medullary or spinal damage. Venous leakage may, in rare cases, result in symptomatic pulmonary embolism. Infections and hematomas are very rare. Table 3 provides the main side effects of these procedures, as well as their rate of occurrence. In an Italian series involving 4,547 patients who had undergone at least one VP (of whom 73 % for osteoporosis), the side effects observed were as follows: venous cement leakage 930 (20.5 %), intradiscal cement leakage 490 (10.8 %), symptomatic pulmonary embolism 45 (1.0 %), cement leakage into spinal canal 5 (0.1 %), hematoma 2 (0.04 %), and infection 2 (0.04 %) [71]. For all these, side effects should be taken into account the date of publication. Indeed, the quality of biomaterials improves and operators experience increases. This is particularly true for cement leakage, less frequently described in recent studies

Risk of new vertebral fracture

This risk was not analyzed in the first studies of VP/KP, since osteoporotic vertebral fragility was in itself a strong risk factor for refracture (Tables 3 and 4). What is more, in the studies,

Table 3 Side effects and complications of percutaneous vertebroplasty or kyphoplasty

		Technique	References
Asymptomatic side effects			
Intervertebral disc cement leakage	10–27 %	KP	[51, 52, 68]
Intervertebral disc cement leakage	10–75 %	VP	[51, 68, 76]
Paravertebral veins cement leakage	20 %	VP	[71]
Asymptomatic pulmonary embolism	26 %	VP	[70]
Symptomatic side effects	1–3 %	VP/KP	[68, 71]
Neurological complications	>1 %		[36, 68, 71]
Infection	>1 %		[35, 67, 71]
Symptomatic pulmonary embolism	≤1 %		[71]
Hematoma	<1 %		[52, 71]
Risk of secondary VF			
Clinical VF at 12 months	13–27 %	VP/KP	[48, 68, 74, 75, 77]
Clinical VF at 24 months	21–27 %	VP	[69, 78]
Radiological VF at 12 months	30–38 %	VP/KP	[53, 79]
Radiological VF at 24 months	44–48 %	KP	[40, 53]

KP kyphoplasty, *VF* vertebral fracture, *VP* vertebroplasty

the radiological and clinical VFs have to be distinguished. There does indeed seem to be an increased risk of subsequent VF, in particular to the vertebrae adjacent to the percutaneous procedure. Already in 2003, a series involving 177 patients who had undergone VP reported the occurrence of 36 VFs in 22 (12.4 %) of them [72]. Of these 36 VFs, 24 (67 %) occurred in vertebral levels adjacent to the VP, and two thirds of the VFs occurred in the first 30 days after the VP. A small series published in 2004 showed an increased risk of adjacent VFs in the first 2 months following KP [73]. In 2006, two new studies described an increased risk of VF adjacent to the VP. In the first series, the risk was 24 % (16/66) at 1 year [74]. These 16 patients suffered 26 new VFs, of which 50 % were in vertebrae adjacent to the VP. Trout et al. retrospectively analyzed the data of 432 patients who had undergone VP and been

Table 4 Risk factors for new VF after percutaneous vertebroplasty or kyphoplasty [47, 68, 76, 78, 79]

	Strong risk factors
Patient-level risk factors	
Age (>80 years)	
Low bone mineral density (T-score<−3 DS)	+
Low 25OH vitamin D (<20 ng/mL or<50 nmol/L)	
Glucocorticoid therapy	
Number of preexisting VF	
Vertebra-level risk factors	
Intervertebral disc cement leakage	+
Short time from fracture to procedure	+
Thoraco-lumbar localization	+
Number of treated vertebrae	

VF vertebral fracture

followed up for 1 year [75]. A total of 186 new VFs occurred in 86 patients (19.9 %), and in 41 % of these cases, the new fractures were in vertebrae adjacent to the VP. Interestingly, the adjacent VFs occurred earlier than the other fractures (58 versus 127 days, $P<0.001$). According to the author, this time aspect appeared to indicate that mechanical forces acting between the osteoporotic and cemented vertebrae were to blame, and not the fact that osteoporotic VFs mostly occur in particular spinal locations. However, Diamond et al. compared a VP group with a control group and reported a similar radiological refracture risk of 43 and 44 %, respectively [40]. Half of these new VFs were adjacent to the initial VF. In the FREE trial, which compared KP with conventional treatment, between 22 and 27 % of patients suffered a new radiological VF at 3 months, 38 % at 12 months, and between 44 and 48 % at 24 months, with no difference noted between the two groups [53]. This was also the case in VERTOS II, in which there was no difference in the risk of refracture at 1 year between the two groups [76]. The only risk factor for a new VF was the number of preexisting VFs. In the Italian EVEREST cohort, the risk of new clinical VFs in osteoporosis (maximum follow-up 12 months) was 13 %, of which 70 % were immediately above or below the vertebra treated by VP [71]. In the randomized study of Blasco et al., 29 new radiological VFs were observed in 17/64 patients treated by VP, whereas there were eight in 8/61 control patients [48]. Of these VFs, 71 and 9 % were clinical in the VP and control groups, respectively. The risk of new radiological VF was 2.78 higher (OR 2.78; 95 % CI, 1.02–7.62, $P=0.046$), and the risk of new clinical VF was 25.67 higher (OR 25.67; 95 % CI, 3.04–216.8, $P=0.029$), in the VP group compared with the control group. Intradiscal cement leakage was more frequently observed in patients with new VF (OR 7.17; 95 % CI, 1.69–30.42, $P=0.008$).

In an Alabama cohort involving 212 patients who had suffered a VF, 48 underwent VP/KP and 164 received conservative treatment [77]. The adjusted relative risk of suffering a new radiological VF was 6.8 (1.7–26.9) at 3 months and 2.9 (1.1–7.9) at 12 months for the group treated by VP/KP. In a series of 144 patients who had undergone VP and were followed up for 2 years, the risk of new clinical VF was 27 %, of which 56 % adjacent to the vertebra treated [78]. The adjacent VFs occurred within 149 days, and the other VFs within 367 days. Multivariate analysis showed that the risk factors for a new VF were the number of VPs, inhomogeneous cement distribution, and a low Hounsfield unit value on CT. In the randomized controlled study published by Blasco et al., multivariate analysis showed that the risk factors for a new VF following VP were: 25 OH vitamin D level <20 ng/mL (RR 15,47, 95 % CI, 2.99–79.86), glucocorticoid therapy (RR 3.64, 95 % CI, 1.61–8.26), and age >80 years (RR 3.20, 95 % CI, 1.70–6.03) [48, 79]. The risk of suffering a new radiological VF was modeled in a series of 115 patients having undergone 216 VPs [80]. The probability of being fracture-free at 1 year ranged from 98.3 % (97.5–100) to 17.5 % (1.17–33.8) depending on the risk factors. Poor prognostic factors were lowered bone mineral density (especially <−3 SD), the severity of vertebral deformation, recent fracture, fracture in the thoracolumbar junction, and intradiscal cement leakage. There was a clear link between the volume of intradiscal cement and refracture risk. In fractures adjacent to the vertebra that was treated, mean intradiscal cement volume was 0.45 mL, compared with 0.21 mL in the group with no new fractures ($P < 0.004$). A systematic review included 24 observational studies published between 2004 and 2012 covering 3, 789 patients who had undergone 5,464 vertebroplasties [69]. Mean follow-up was 22.8 months. The risk of a new clinical VF was 25.5 %. The authors identified three strong risk factors for fracture recurrence (decreased bone mineral density, intradiscal cement leakage, and vertebral height restoration) and six moderate risk factors (old age, decreased BMI, number of existing VFs, number of VPs, cement leakage, and VP of the thoracolumbar junction). There did not appear to be a difference in the risk of refracture following either VP or KP [26]. Table 4 summarizes the main risk factors for a new vertebral fracture. Even though everyone recognizes that VF is a strong risk factor for VF recurrence, it can clearly be seen from the latest studies and analyses that VP/KP is an additional risk factor for new VFs. What is more, it would seem that it may be possible to identify patients who are at high- or low risk of recurrence.

Discussion

VF can be a painful event that has a significant impact on quality of life and that does not always respond to the available antalgic drug therapies. VP and KP are therefore logical solutions in these refractory settings. What is more, the fact that vertebral height can be partially or fully restored with KP provides great hope that the loss of quality of life associated with vertebral height loss can be limited. Although the case series that were initially published were all very encouraging, it must be recognized that the results of the randomized studies have been very mixed. Moreover, randomized studies are rare. When comparing VP with a sham-controlled group, no benefit of VP was observed [35, 36, 45]. A potential effect of local anesthesia on the level of pain may account for this. For others, the volume of cement injected (mean cemented vertebral body fraction) appeared to play a decisive role in obtaining pain relief [81]. In the study by Buchbinder et al., the quantity of cement injected per vertebra was 2.0±1.2 mL [35]. In the study by Kallmes et al., it was not mentioned [36]. In a series including 106 patients who had undergone 196 VPs, mean cemented vertebral body fraction was significantly smaller in non-responders than in patients who experienced an analgesic benefit (15 versus 21 %, $P = 0.002$) [81]. The mean volume injected was 3.94±1.89 mL (0.13–10.8 mL), but may vary with vertebral level, severity of the fracture, and gender. And indeed, injecting a bigger volume of PMMA increases the risk of cement leakage, and so it may increase the risk of symptomatic side effects and fracture recurrence [80]. Less pressure is required for injecting the PMMA in KP, and the risks of cement leakage are reduced [65, 66]. However, comparing VP with KP has not shown any difference in terms of analgesic or functional benefits or risks of refracture [26]. KP's benefit is that it limits vertebral height loss and kyphotic angle, but without any impact on the various functional scores used in the studies, usually with a follow-up period of 12 months. It is true that a potential longer term benefit remains unknown. The only randomized controlled study comparing KP with conservative management showed a considerable analgesic and functional benefit that lasted at least 2 years [52, 53]. There is unfortunately only this one study, and the control group was not sham-controlled.

It is difficult to compare the studies given the highly diverse enrollment criteria and differing measurement tools used. Moreover, the patient populations included in each of the studies were limited in size. Patient age, number of VFs, degree of the VF, time period between VF and VP/KP, volume of PMMA injected, and injection pressure were all enrollment and procedure parameters that varied from study to study. Although pain evaluation is relatively well-standardized and comparable, the tools for measuring functional status and quality of life are extremely varied, and include everything from instruments specifically for osteoporosis to very general instruments. The EuroQol Group 5-Dimension Self-report Questionnaire, SF-36 mental component standardized, SF-36 physical component standardized, Bartel Index, Oswestry Disability Index, RDQ, modified RDQ, Qualeffo-41, and

Table 5 Proposal for clinical management of symptomatic osteoporotic vertebral fracture

Day 1 to day 28

1. Confirm the fracture by a lateral radiograph of the thoracolumbar spine (or a CT scan if needed)

2. Give analgesics including nonsteroidal analgesics +/− morphine derivatives

3. If the pain is not controlled, add calcitonine

4. Make an osteoporosis and fracture risk assessment

5. Initiate an anti-osteoporotic treatment (antiresorptive or anabolic) with calcium and vitamin D

6. Reassess regularly the clinical course

Day 21 to day 42

1. In case of disabling pain, perform a MRI

2. Evaluate the indication for VP or KP

European Vertebral Osteoporosis Study questionnaire were used to assess the functional improvement and quality of life of patients. In spite of the limited clinical comparisons and scepticism raised by this literature review, a recent meta-analysis has shown greater pain relief, functional recovery, and health-related quality of life with VP or KP compared with controls [82]. VP or KP better results were significant at both the early (<3 months) and late time points (6 to 12 months), and the risk of new VF was not statistically different between the groups. One study has a large effect on these results [47]. Of the eight existing randomized controlled studies, that of Blasco et al. showing a significant increase in the risk of new VF after VP was not included, and the study of Rousing et al. was only included for certain analyses [41, 48].

What can we do with a patient with a painful VF in routine clinical practice (Table 5)? The immediate analgesic benefit of VP/KP may be an advantage provided that the related risks are low. But what is an acceptable time limit between the onset of pain and performance of the procedure? In VERTOS II for example, the time limit between the onset of pain and the procedure had to be <6 weeks. Of the 431 patients who were eligible for randomization, there was a complete disappearance of pain before the performance of VP in 229 (53 %) of them, who were therefore not included [46]. So should we wait at least 6 weeks before suggesting VP/KP? And how long can we wait before performing VP/KP? Does waiting a year lead to a chance of success, as some authors affirm? A delay of a year was seen as a cause of the absence of VP benefit in the studies of Buchlinder and Kallmes [35, 36].

Patients with VF exhibit increased mortality rates. Could performing VP/KP change this? Mc Donald et al. compared 524 patients who had undergone VP with 582 patients (371 asymptomatic, 201 symptomatic) with VF that was treated conservatively [83]. The cohorts were followed up for between 3.7 and 5.4 years. Mortality was the same in the VP group and control group with symptomatic VF. However, mortality was higher in the VP group than in the control group with asymptomatic VF. Estimated survival at 5 years was 56 % for the VP group, 61 % for the symptomatic group that had not undergone VP, and 79 % for the asymptomatic group that had not undergone VP. Another retrospective analysis with a 2-year follow-up did not show any effect on mortality [84]. Edidin et al. analyzed the mortality risk for operated and non-operated VF patients in the Medicare population [85]. The authors identified 858,978 patients with osteoporotic VF between 2005 and 2008, of whom 119,253 underwent KP and 63,693 VP. After 4 years of follow-up, 60.8 % of patients who had undergone VP or KP were alive compared with 50.0 % of patients who had not undergone any intervention (adjusted Hazard Ratio [aHR]=0.63, $P<0.001$). The risk of death was lower in the KP group than it was in the VP group (aHR= 0.77, $P<0.001$). We are faced with retrospective analyses whose results are contradictory. Despite the various adjustments that were made, the fact remains that the patients to whom we propose a procedure are undoubtedly very different from those to whom we do not propose this procedure.

Cost-effectiveness analyses allow both the advantages and disadvantages of a procedure to be assimilated best, and may be a solution with regard to the benefit of VP/KP. A few studies have been conducted, and all are in favor of VP or KP compared with conventional treatment [86-88]. The results of this study type depend on which parameters are entered into the model. As the benefits of VP/KP are debatable, it is too early for conducting such studies. The results of a recent cost-effectiveness analysis comparing VP with KP were contradictory [89].

Another decisive element is the necessity of rapidly initiating a specific treatment for osteoporosis. Patients suffering from an atraumatic VF have by definition osteoporosis and are at great risk of refracture. Treatment is clearly indicated. In a cohort study involving 9,238 patients who were hospitalized for an osteoporotic VF, undergoing VP/KP increased the probability of receiving an anti-osteoporosis therapy [90]. At 1 month following the VF, 46 % of patients who had undergone VP/ KP were on anti-osteoporosis therapy, compared with 32 % of patients who had not undergone VP/KP. At 6 months, the respective results were 59 and 47 %. These results are already better compared to clinical practice and could be further improved in a randomized controlled trial or by clinical pathway. In the FREE study, over the course of 12 months, the number of patients receiving calcium and vitamin D increased from around 50 to 85 %, and the number of those receiving a bisphosphonate increased from around 45 to 75 %, with no difference noted between the VP and control groups [52].

Limitations and prospects for the future

Further randomized controlled studies of good quality are warranted in order to better define the profile of patients

who may benefit from VP or KP. VERTOS IV will attempt to answer this question and is designed to include patients who are 50 or older, have had a painful VF for less than 6 weeks, and display edema on MRI scans. Patients will be randomized for either VP or a sham intervention [91].

Many questions remain regarding the ideal biomaterials (offering the best biomechanical properties) and best technique (material, injection pressure, or uni- or bilateral approach) to be used. Mixing the cement with a biocompatible liquid may improve the biomechanical properties, thus reducing adjacent VFs. A reduction of 51 % in cement stiffness, which was obtained by adding serum, may reduce the risk of refracture [92]. In a recent randomized controlled trial, no beneficial effect of vertebral body stenting over KP was found among patients with painful osteoporotic VF [93]. In another randomized study, KIVA, a new vertebral augmentation treatment system, yielded better results than KP did for restoring vertebral body wedge deformity, with less cement leakage [94]. In another recent study, a unipedicular approach was recommended for KP rather than a bipedicular one, the benefits obtained being the same [95]. These new techniques require further investigation.

Osteoporotic drug treatments are rarely mentioned in the studies of VP/KP. All patients suffering from a VF must be given calcium, vitamin D, and an anti-osteoporotic treatment, ideally a bone anabolic agent, on account of the severity of the underlying osteoporosis. This treatment should be initiated before VP/KP is even considered. What is more, VP/KP has never been compared with optimal osteoporotic drug therapy. Such a clinical study should comprise a randomized design with three arms: (1) VP or KP only, (2) VP or KP with a bone anabolic agent, (3) bone anabolic agent only.

Conclusion

The efficacy of VP/KP for controlling pain after VF is still a matter of controversy. VP/KP should therefore be reserved for VF patients when a properly managed analgesic treatment has failed, without omitting to initiate osteoporotic therapy. KP differs from VP in that it enables better vertebral height restoration and thus kyphotic angle reduction, but its costs are higher, while its long-term benefit is not known. Recent studies clearly show that both VP and KP increase the risk of new VFs, in particular in the vertebrae adjacent to those treated. These refractures occur within a relatively short time period. Certain risk factors have been identified. It seems therefore appropriate to involve the patients to whom VP/KP is being proposed in the decision-making process. Further randomized controlled studies of good

quality are necessary to better identify those patients likely to benefit the most from these procedures.

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