Cohort Study

A Longitudinal Cohort Investigation of the Development of Symptomatic Adjacent Level Compression Fractures Following Balloon-assisted Kyphoplasty in a Series of 726 Patients

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Background: Balloon-assisted kyphoplasty (BAK) is a well-accepted treatment for symptomatic vertebral compression fractures (VCF) secondary to osteoporosis. Some have raised a concern of an increased incidence of adjacent fractures due to alterations in spine biomechanics after cement augmentation. The incidence of subsequent VCFs following BAK is poorly understood. The aim of this study was to investigate the timing, location, and incidence of new VCFs following BAK and to identify risk factors associated specifically with the occurrence of new adjacent level fractures.

Objectives: The study was performed to determine the incidence of symptomatic subsequent adjacent and remote level compression fractures in a cohort of patients undergoing BAK.

Study Design: Longitudinal cohort investigation at an academic medical center and a central referral center for VCFs.

Setting: A consecutive single surgeon series of 726 patients with osteoporotic compression fractures.

Methods: A prospectively collected cohort of 726 patients who underwent BAK between 2001 and 2014 for osteoporotic VCFs was evaluated. Seventy-seven patients were identified who underwent a second BAK for a new compression fracture and were include in the present series. The indication for BAK treatment was pain unresponsive to non-surgical management for all cases. Variables were recorded for each patient, including the time between index and subsequent fracture, fracture level, and number of initial fractures as well as with tobacco use, body mass index (BMI), and chronic steroid use.

Results: Seventy-seven of 726 patients (10.6%) underwent a second BAK procedure on average 350 days following the initial procedure (range 21 to 2,691 days). Third and fourth procedures were less common, treated in 11 and 3 patients, respectively. Forty-eight of 77 patients (62%) suffered a fracture at a level immediately adjacent to the index level at mean time of 256 days. Remote level fractures were treated at a mean time of 489 days, but no statistical difference was noted. There was no statistically significant difference between tobacco use, BMI, and chronic steroid use between patients suffering from remote and adjacent level VCFs.

Limitations: This was not a population based study, and the true incidence of subsequent fractures after BAK might be underestimated by this analysis.

Conclusions: Symptomatic compression fractures after BAK are relatively uncommon and may occur long after the initial kyphoplasty procedure. Only half of subsequent fractures occur immediately adjacent to the initially treated level; the others occur remotely. Patients with a single symptomatic thoracic or lumbar fracture suffered from remote and adjacent level fractures equally. In contrast, all patients who suffered both a thoracic and lumbar fracture at the same time had a second fracture at an adjacent level. Specific risk factors for remote versus adjacent level fractures could not be determined.

Key words: Balloon kyphoplasty, cement augmentation, osteoporosis, vertebral compression fracture, adjacent level fracture, vertebroplasty

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Osteoporosis is a debilitating, progressive demineralizing disease of the skeleton leading to the loss of bone mass and an increased propensity for fractures (1). Approximately 1,400,000 new cases of osteoporotic vertebral compression fractures (VCFs) are diagnosed each year throughout the world (2). VCFs are a significant cause of pain, deformity, decreased mobility, and in many cases, secondary morbidity and mortality in the elderly population (3,4).

The management of VCFs ranges from medical management of symptoms, physical therapy, open surgical fixation, and percutaneous vertebral augmentation via vertebroplasty or balloon-assisted kyphoplasty (BAK). There is a growing body of evidence in the literature demonstrating that BAK is a safe and effective treatment for medically refractory pain secondary to VCFs (5-10). However, the incidence of subsequent VCFs following BAK is controversial. Some authors postulate that vertebral augmentation leads to a biomechanical alteration of the osteoporotic spine predisposing a patient to the development of subsequent VCFs. These fractures can occur in levels immediately adjacent to the index level or at remote levels.

This study was performed in order to examine the timing, location, and incidence of secondary VCFs following the treatment of osteoporotic VCFs in a large patient cohort. An attempt was made to determine those risk factors that may be associated with subsequent compression fractures and to better determine the nature of this complication after BAK.

Table 1. *Patient demographics and time between BAK procedures for the study population.*

Male/Female	26/51
Smoking	15
Chronic Steroids	16
BMI (mean)	27
Age at first BAK (mean; years)	71
Mean days between first to second BAK (standard deviation)	350 (543)
Mean days between second and third BAK (standard deviation)	206 (215)
Mean days between third and fourth BAK (standard deviation)	50 (39)

Methods

Patients

Seven hundred twenty-six patients with osteoporotic VCFs underwent BAK at a single regional referral center between 2001 and 2014. The minimum length of follow-up was one year. A total of 922 fractures were treated during this period. All patients who underwent a second BAK for a symptomatic VCF were included for retrospective review in this series. Patients who suffered a pathological fracture implying an underlying malignancy were excluded from this study. In all cases, the indication for the initial and subsequent treatments was debilitating pain unresponsive to medical management. The study was approved by the Institutional Review Board of the University of Pittsburgh School of Medicine (PRO07060042).

Seventy-seven patients (a total of 130 fractures) who subsequently developed symptomatic second compression fractures were identified; 51 women and 26 men. All 77 patients underwent a second BAK at either an adjacent or remote level from the index level. The mean age was 71 years at the time of the initial BAK procedure. The time between index and subsequent fracture, fracture level, and number of initial fractures were recorded along with tobacco use, body mass index (BMI), and chronic steroid use (Table 1).

Surgical Technique

The Kyphon Balloon Kyphoplasty System (Medtronic, Minneapolis, MN) was used in all cases. Briefly, the patient is placed under general anesthesia and positioned prone. The affected level is localized using fluoroscopy. A small stab incision is made lateral to the pedicle, and a cannula is docked onto the lateral aspect of the pedicle. The cannula is advanced through the pedicle into the vertebral body under fluoroscopic guidance. An inflatable balloon is inserted and inflated to create a cavity and restore vertebral height when possible. The balloon is removed, and polymethylmethacrylate (PMMA) is slowly injected under fluoroscopic guidance to ensure there is no leakage of cement outside of the vertebral body (Fig. 1). The maximum amount of cement is placed in all cases until the cement approaches the posterior wall of the vertebral body. The cannula is removed, and the skin incision is closed with a single absorbable suture. All surgeries were performed by the senior author, and there was no alteration to the procedure over the study period.

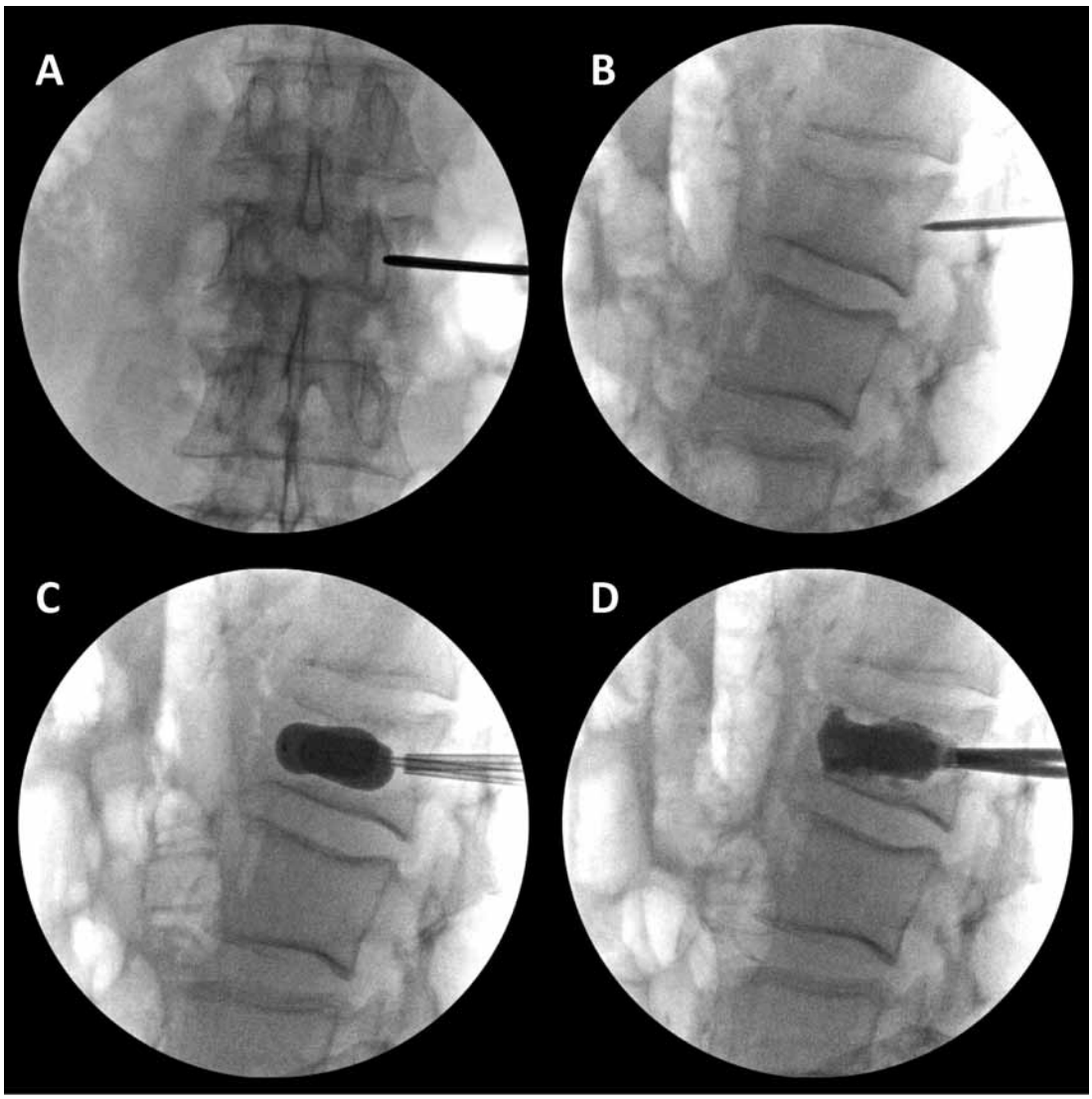

Fig. 1. *Intraoperative PA and lateral fluoroscopic images of BAK procedure. A.) The lateral aspect of the pedicle is localized with a PA projection. B.) A trochar is passed into the vertebral body through the pedicle. C.) A balloon is inflated to restore vertebral height and create a cavity for PMMA. D.) PMMA is injected slowly to avoid extravasation of cement.*

Stastical Analysis

Statistical analysis was carried out using SPSS Statistical Software version 23 (IBM Software, Armonk, NY) for PC. Descriptive statistics including mean, medians, ranges, and standard deviation were calculated in a standard fashion. Independent-sample t-test was utilized for tests of significance. In all tests, a *P*-value less than 0.05 was deemed statistically significant.

Results

Seventy-seven of 726 patients (10.6%) underwent a second BAK procedure due to the development of a new symptomatic VCF on average 350 days following the initial procedure. Eleven of these 77 patients (14%) required a third procedure and 3 of these 77 patients (4%) underwent a fourth procedure for new symptom-

atic fractures. These fractures were treated at a mean of 206 and 50 days for the third and fourth procedure, respectively. Forty-eight of 77 patients (62%) suffered a fracture at a level immediately adjacent to the index level.

A separate analysis was performed on the fractures alone. In 130 of 961 overall treated fractures (13.5%), a second subsequent symptomatic fracture developed. Eighty-one of the 130 fractures occurred at an adjacent level (62%), identical to the percentage for the patient cohort. Table 2 summarizes the number of levels initially treated by BAK. The majority of patients were treated for a single symptomatic level, and no difference between the number of levels treated and the development of adjacent level fractures was noted (Table 2). Furthermore, there was no statistically significant difference in the initial number of levels treated between those with adjacent and remote level fractures. Adjacent level fractures occurred at a mean time of 256 days following the initial treatment while remote level fractures occurred at a mean time of 489 days following the initial treatment.

Subgroup analysis demonstrated no difference in age, gender, smoking status, steroid use, or location of the index fracture between patients suffering a remote or adjacent level fracture (Table 3). Patients with a single symptomatic thoracic or lumbar fracture suffered from remote and adjacent level fractures equally. In contrast, all patients from the initial cohort who suffered both a thoracic and lumbar fracture at the same time and who developed a subsequent fracture had a second fracture at an adjacent level (Table 3).

Discussion

BAK is a well-accepted and widely used technique for the management of symptomatic VCFs. Infection, hematoma, continued pain, cement embolism, cement extrusion, and subsequent neurological deficit are well-recognized albeit unusual complications. In contrast, there is a greater degree of concern regarding the potential for adjacent level fractures that may require subsequent treatment. Some practitioners have labeled such fractures as a potential complication of the BAK procedure. However, the incidence and clinical

Table 2. *Comparison of patients who developed a second VCF by the number of levels initially treated.*

Initial Number of Levels Treated	All Patients	Number of patients with a second fracture	Number of patients with an adjacent fracture	Number of patients with a remote fracture
1	373	40	23	17
2	159	21	15	6
≥3	73	16	10	6

There is no statistically significant difference in the initial number of levels treated between those with adjacent and remote level fractures.

Table 3. *Comparison of patient characteristics of those suffering from adjacent and remote level secondary VCFs. No statistically significant differences were noted.*

	Adjacent Level Fracture (n = 48)	Remote Level Fracture (n = 29)
Male/Female	16/32	10/19
Smoking	11	27
BMI	26.3	26.9
Mean age at first BAK (years)	73.7	66.2
Mean time to second BAK (days)	262+/-495	489+/-580
Index Level		
Thoracic	19	13
Lumbar	19	16
Both	10	0

significance of adjacent level compression fractures has previously not been specifically investigated.

This study represents the largest study to date which addresses the incidence of new VCFs following BAK and estimates incidence of new fractures to be 11%, with only 62% of fractures occurring at adjacent levels. While there is a large variation in time to second fracture, the present study suggests that adjacent level fractures occurred sooner than remote level fractures. This may possibly reflect an acceleration for the development of a symptomatic compression fracture at the adjacent level following BAK or a local alteration in the biomechanics following a VCF. New remote level fractures are more likely to represent the natural progression of the underlying disease process of osteoporosis. It is also not possible to estimate the rate of asymptomatic fractures from this study as routine surveillance x-rays are not performed for asymptomatic patients. However, the clinical significance of a VCF without pain or debilitation is minimal.

The incidence and clinical significance of adjacent level compression fractures has been investigated in a number of previous studies (11-13). The estimated prevalence of adjacent level fractures after percutaneous cement augmentation currently reported is between 11% and 21% (14-17). A similar frequency of fractures was noted in a recent prospective study by Yi et al (18). This study prospectively randomized 290 patients to vertebroplasty, kyphoplasty, and conservative treatment. The study found that 31 patients (10.7%) developed 42 new compression fractures with only 14 (34.2%) occurring at adjacent levels. Of these patients, 14 were initially treated by surgical intervention and 17 were treated conservatively. There was no significant difference between the development of adjacent level and remote level fractures. It is interesting to note that patients in the treated group suffered from new fractures sooner than those managed conservatively, suggesting that operative intervention may accelerate disease progression in adjacent segments.

Few studies have attempted to identify specific risk factors for the development of new compression fractures following either vertebroplasty or kyphoplasty. In the current study, patients suffering from adjacent level fractures tended to be older; however, this was not statistically significant. It is reasonable to postulate these older patients may suffer from more advanced osteoporosis. Due to the large referral pattern bone mineral density (BMD) was not available for the majority of the patients. Therefore, this study was unable to evaluate a relationship between BMD and new fractures for this cohort. Several studies have suggested that BMD is associated with an increased rate (8,19-21) of adjacent level fractures; however, controversy (22) regarding this persists.

The volume of cement used at the index level does not appear to be related to the development of new VCFs (20,22,23). Age, gender, number of initial fractures, medical comorbidities, and the location of fractures also are not thought to be predicative of subsequent fractures (22-24). Increasing local kyphosis seems to be related to the development of new fractures in some but not all studies, while the degree of loss of vertebral body height does not seem to be related (19,20,22). This lack of consensus is reflective of the heterogeneity of the current literature on this topic and would benefit from further investigation and clarification. Future biomechanical studies and larger prospective studies may help to identify modifiable risk factors and lead to an improvement in long-term patient outcomes.

VCFs are a rising cause of debilitating pain and loss of function. A clinically important finding of our study is that new symptomatic fractures occur on average one full year following the initial treatment, with adjacent level fractures occurring earlier than remote fractures. No risk factors for the development of subsequent VCFs that might allow for prevention could be identified from this analysis. It is possible that the true incidence of subsequent fractures may be slightly higher as we were unable to account for patients who may have developed a new fracture and were referred outside of our health system or moved from the area. However, given the nature of our clinical practice, patient demographics, and unique regional expertise, it is rather unlikely that patients might have developed subsequent symptomatic fractures and gone elsewhere for treatment, thus being lost to follow-up for this study. Future work needs to identify modifiable risk factors for the development of new fractures and effective treatments to avoid the potential complication of repeated second surgical intervention.

Conclusions

Symptomatic compression fractures after BAK are relatively uncommon and may occur long after the initial kyphoplasty procedure. Only half of subsequent fractures occur immediately adjacent to the initially treated level; the others occur remotely. Patients with a single symptomatic thoracic or lumbar fracture suffered from remote and adjacent level fractures equally. In

contrast, all patients who suffered both a thoracic and lumbar fracture at the same time had a second fracture at an adjacent level. Specific risk factors for remote versus adjacent level fractures could not be determined.

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