High rate of vertebral refracture after vertebroplasty in patients taking glucocorticoids: a prospective two-year study

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Abstract

Objective

To assess vertebral fracture (VFx) occurrence after percutaneous vertebroplasty (PVP) in patients with osteoporosis (OP), primary or secondary to chronic glucocorticoid (GC) therapy.

Methods

Prospective study of a 2-year follow-up. Primary outcome: proportion of patients with new VFx 24 months after PVP. Eligible patients were osteoporotic patients with VFx and pain resistant to conventional therapy, under GC therapy (n=70) or not (n=71), who underwent PVP. X-rays of dorso/lumbar spine were performed before PVP and 12 and 24 months after the procedure. All the patients were given secondary fractures prevention with oral bisphosphonates plus calcium and vitamin D.

Results

The two groups were comparable with respect to male to female ratio, age, BMI, pain score, number of prevalent VFx and their score according to Genant, time interval between VFx and PVP, number of VFx that were treated, vitamin D and PTH plasma levels, and bone mineral density at femur sites. The proportion of patients with new VFx was higher at 12 and 24 months in the group taking GC; at 24 months was 44.3% in GC group and 22.6% in non-GC group (RR 1.96; 95% CI 1.19–3.26, p=0.0087). All new VFx were clinically evident. GC-treated patients had more falls than the patients who were not on GC: 43 falls per 100 pts/y and 32 falls per 100 pts/y, respectively (p<0.05); however, only 4 and 6 falls, respectively, caused a VFx (p=NS). Finally, logistic regression model showed that the increased risk of new VFx was associated with GC use (OR 4.53; 95% CI 1.50–13.69, p=0.0073) and low femoral neck T-scores (OR 3.57; 95% CI 1.82–7.02, p=0.0002)

Conclusion

Patients under treatment with GC show a two-fold increased risk of new VFx after PVP with respect to patients with primary OP. This should be weighed in the individual risk/benefit assessment of the procedure.

Key words

glucocorticoids, osteoporosis, vertebral fracture, vertebroplasty, re-fracture

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Introduction

Vertebral fragility fractures are a common consequence of osteoporosis (OP). Patients who experience severe debilitating back pain resistant to conservative treatment (analgesics, bed rest, and orthoses) may be candidate to percutaneous vertebroplasty (PVP) or kyphoplasty (PKP), in which the fractured vertebra is stabilised by injection into the vertebral body of cement, usually polymethyl-metacrilate (PMMA). These procedures reportedly produce rapid pain relief in most patients (1-3). However strengthening the treated vertebral body with PMMA may lead to increased mechanical forces on the adjacent vertebrae, thereby predisposing them to fracture (4, 5). Glucocorticoid (GC) therapy can increase vertebral fractures (6); in this view, patients on chronic GC therapy who undergo PVP or PKP may have an even higher risk of subsequent fractures after the procedure. In fact, three retrospective studies showed that the risk of vertebral refractures after PVP or PKP is as much as 2 to 4 times higher in patients with GC-induced OP than in those with primary OP (7-9). Therefore, the aim of this prospective study was to assess vertebral refracture after PVP in two groups of osteoporotic patients, one group who were taking glucocorticoids (GCs) and the other not.

Patients and methods

Patients

The inclusion of patients into this 2-year prospective study started in January 2013 and ended in August 2015 and was carried out at the university hospital of Pisa, Rheumatology and Neurology Units; the 2-year follow-up ended in October 2017. We considered for inclusion all consecutive patients of both sexes who had at least one painful vertebral fracture for which they had been referred to our Units to perform PVP. Only osteoporotic patients were included: the diagnosis of OP was based on the fragility nature of the vertebral fractures and on the evidence of a low bone mineral density, as assessed by double-energy x-ray absorptiometry (DXA) performed at vertebral and femoral sites, according to the WHO criteria (10). Only patients with a DXA T-score < -1.0 at either site were included in the follow-up. Any secondary form of OP was excluded, with the exception of glucocorticoid-induced OP. Furthermore, a baseline biochemical evaluation was made to exclude abnormality in calcium metabolism: plasma calcium, phosphorus, total alkaline phosphatase, 24-hour urinary excretion of calcium, serum PTH, plasma levels of 25(OH) vitamin D. Patients with both insufficient and low 25(OH) vitamin D levels (<20 ng/ml) were included only if they did not show any other biochemical alteration suggesting osteomalacia. Nonetheless, these patients were supplemented before the procedure of PVP with a single starting dose of 300.000 IU of vitamin D followed by at least 1,000 IU/day throughout the study period. Patients with normal vitamin D levels only received the daily supplementation. Individual calcium intake (dietary and supplemental) was routinely assessed by a brief questionnaire and corrected to 1.2 g/day when insufficient. Previous treatment with PVP or PKP was a reason for exclusion from this study.

In addition to the above-mentioned parameters, the following data were collected: age, BMI, smoke, previous diagnosis of OP, other fragility fractures, previous treatment of OP, time of painful vertebral fracture occurrence, duration of symptoms, number and level of other prevalent vertebral fractures, GC mean daily and cumulative doses. To perform the procedure of PVP the patients were hospitalised in the Rheumatology Unit of our Hospital and discharged the day after the procedure, if no adverse event had occurred. The patients were informed about the benefit/risk ratio of the procedure of PVP, the possibility of an increased fracture risk, and the follow-up programme. After that, the patients gave their written informed consent to the procedure and the study, which was approved by the local ethics committee.

Prevalent fractures

Antero-posterior and lateral x-rays of the dorso-lumbar spine (T4-L5) were obtained at baseline to identify the

number and the site of prevalent fractures. A prevalent vertebral fracture was defined as a decrease of at least 20% in any vertical dimension, according to the Genant method (11). Patient history or older radiological examinations served to differentiate chronic from acute compression fracture and to establish the time of the fracture event. Furthermore, all patients underwent a magnetic resonance (MR) imaging study of the dorso-lumbar spine due its sensitivity for bone marrow oedema. Bone oedema is defined as increased signal intensity at the T2 weighted and STIR images and decreased signal intensity at the T1 weighted images, and its detection suggests acute, subacute and non-healed fractures (12). Patients candidate to PVP had to show spontaneous pain at the site of vertebral fracture identified on x-ray films, provoked pain after digital pressure on the same level during physical examination, and either bone marrow oedema in MR imaging or increased uptake in bone scan. Finally, before performing the procedure of PVP a limited computed tomography scan through the intended level was performed in order to assess the intactness of the vertebral walls.

Technique of PVP

The same operator (MP) carried out all PVP procedures. The surgical technique for PVP is described in an earlier paper (13).

Follow-up

As a standard practice after every PVP, the patients were asked to return to control visits after 1, 3, 6 months and every 6 months thereafter. The preplanned evaluation period for the entire population was set at 24 months. According to normal clinical practice, x-rays film of the dorso-lumbar spine (T4-L5, antero-posterior and lateral views) were repeated every 12 months, or when a patient complained of vertebral pain that would suggest the occurrence of a fracture. For this purpose, we invited the patients to notify immediately by phone call any painful symptoms at the spine. An incident fracture was defined as an increased Genant's deformity grade of a vertebra, previously fractured or not. Only fragility fractures were considered. We did not include patients assigned to therapy other than oral bisphosphonates: alendronate 70 mg or risedronate 35 mg, if not previously prescribed. Both adherence and compliance to anti-fracture therapy were assessed at each follow-up visit. Patients, and their relatives when appropriate, were instructed to take note in a diary of every missed dose of the weekly bisphosphonate. Patients taking GC were also monitored by the referring physicians; those who withdrew GC were excluded from the follow-up.

Table I. Characteristics of the population studied.

	GC+ (n=70)	GC- (n=71)	*p*-value
Female, no. (%)	56 (80%)	58 (82%)	NS
Age, years	70.2 ± 9	71.9 ± 9	NS
BMI	23.6 ± 4.0	23.2 ± 4.9	NS
Current smokers, no. (%)	7 (10%)	7 (10%)	NS
Cumulative GC* dose, g	6.4 ± 2.9	---	---
Baseline GC* daily dose, mg	7.3 ± 3.1	---	---
GC* dose at 24 months, mg	5.5 ± 1.4	---	---
Pain score, mm	77 ± 12	79 ± 11	NS
Previous treatment of osteoporosis, no. (%)	29 (41%)	17 (24%)	0.03
Prevalent vertebral fracture	2.8 ± 1.5	2.8 ± 1.8	NS
Mean Genant's score	4.6 ± 2.4	4.9 ± 2.4	NS
Previous non-vertebral fracture	7 (13%)	9 (14%)	NS
Time from fracture to PVP, months	5 ± 5	7 ± 13	NS
no. of vertebral bodies treated with PVP	2.4 ± 1.5	2.2 ± 1.5	NS
Calcium intake #, g/day	0.79 ± 0.21	0.71 ± 0.23	NS
Plasma 25(OH) D levels, ng/ml	28 ± 9	26 ± 20	NS
PTH, pg/ml (n.v. 7-78)	50 ± 26	46 ± 18	NS
Total Hip T-score	-2.5 ± 1.1	-2.5 ± 1.0	NS
Femoral neck T-score	-2.3 ± 0.9	-2.1 ± 1.0	NS

*6-methylprednisolone.
#dietary plus pharmacological supplementation.

Statistical analysis

Data were expressed as mean ± standard deviation. Primary end-point was the cumulative incidence of new fragility vertebral fractures after 24 months. In comparing variables between the two groups we used the *t*-test to compare the calculated means, and patient proportions were compared by the χ^2 test. The association between incident fractures and potential risk factors was modelled using multiple logistic regression analysis. The results were expressed as odds ratios and relative risk.

Results

From January 2013 to August 2015, 160 osteoporotic patients were treated with PVP and included in the follow-up programme. Nineteen patients were excluded from the analysis: 10 withdrew GCs within the first 12 months of observation, 7 were lost to follow-up, and 2 died (one 4 months and the other 11 months after PVP). We here report the results of 141 patients: 70 of them were taking GCs, 71 were not. Table I shows the characteristics of the population: the two groups were comparable in all parameters, with the exception of the proportion of patients who were taking anti-fracture therapy, which was higher for those taking GCs. Among the patients with GC-induced OP, 19 had rheumatoid arthritis, 18 polymyalgia rheumatica, 13 systemic lupus erythematosus and other connective tissue diseases, 10 Horton's arteritis and other vasculitides, 7 chronic obstructive pulmonary disease, and 3 Myasthenia Gravis.

The aim of the study was to assess the proportion of patients with new vertebral fractures, both radiological and clinical. Over a 24-month follow-up, 31 patients taking GCs and 16 not taking GCs had new vertebral fractures, signifying a cumulative incidence of 44.3% and 22.5%, respectively: the RR was 1.96 (95% CI 1.19–3.26, p=0.0087) (Fig. 1). Twenty-six patients (55.3%) had a new fracture within 6 months after VP, and 33 (70.2%) patients within

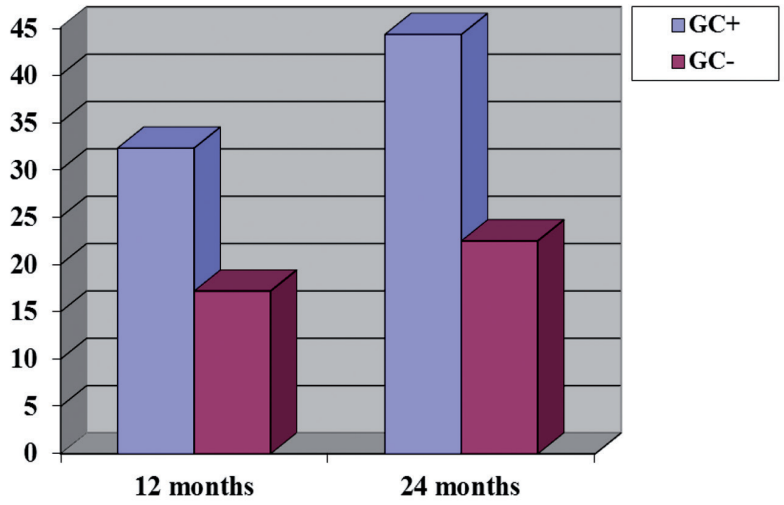

Fig. 1. Proportion of patients GC+ (n=70) and GC- (n=71) with new vertebral fracture after 12 and 24 months of follow-up. At 12 months 32.3% *vs*. 17.2%; at 24 months 44.3% *vs*. 22.5% (RR 1.96; 95% CI 1.19–3.26, p=0.0087)

12 months after VP. The mean interval between VP and time of new fracture did not differ between patients taking GCs and those not: 9.8±11.8 months *vs*. 10.7±9.1 months (p=0.79). Patients taking GCs had 65 new vertebral fractures, whereas those not taking GC had 35 new vertebral fractures. All new fractures were clinically evident, in that the patients themselves contacted the physician immediately after having experienced new back pain. Radiological investigation of the spine performed in the patients who did not develop new symptoms did not reveal any additional vertebral fractures to those identified clinically.

GC-treated patients had more falls than the patients who were not on GCs: 43 falls per 100 patients/year and 32 falls per 100 patients/year, respectively (p<0.05); however, only 4 and 6 falls, respectively, caused a new vertebral fracture (p=NS). Finally, logistic regression model which included total hip and femoral neck T-score, age, BMI, GC use, and previous vertebral fractures showed that the increased risk of new vertebral fractures was associated with GC use (OR 4.53; 95% CI 1.50–13.69, p=0.0073) and low femoral neck T-scores (OR 3.57; 95% CI 1.82–7.02, p=0.0002)

Compliance to medical anti osteoporotic therapy was high and similar in the two groups, with more than 90% of doses taken, as assessed by means of interview at each control visit (calcium and vitamin D) and by the calcualtion of doses missed (alendronate and risedronate).

Discussion

The present study suggests that after PVP patients with GC-induced OP have a two-fold risk of having new vertebral fracture with respect to those not taking GC. The proportion of GC-treated patients who after 24 months had at least one new vertebral fracture was 44.3%, which is a percentage that should induce caution when considering PVP to resolve pain from vertebral fractures in patients taking GC. Of note, this percentage of refractures was observed despite a soundly effective anti-fracture therapy, such as bisphosphonates (14), and a high rate of compliance by the patients, including calcium and vitamin D supplementation. Moreover, the patients were followed in a tertiary care centre (Fracture Liaison Service of the Azienda Ospedaliero Universitaria di Pisa, which is a multi-disciplinary outpatient facility served by rheumatologist, orthopaedics and physiatrists), which is supposed to improve the outcome of fractured patients.

GC increase fracture risk (15), especially at vertebral site. It is well known that GC lead to decreased bone formation and increased bone resorption (16-19); in addition, GCs promote osteocyte apoptosis, which causes defective bone repair and a decrease in bone quality (16). Therefore, it is not surprising that GC patients have more vertebral fractures than those not taking GCs, after PVP. Our results are in line with those of three previous retrospective studies (7-9). In 2004 Harrop *et al*. published a study (7) reporting that after PKP and a mean follow-up of 11 months, patients taking GCs (n=35) had an incidence of new vertebral fractures of 48.6%, which was significantly (p<0.0001) higher than that observed among patients not on chronic GC therapy (n=80), 11.35%. In 2006 Syed *et al*. (8) reported after PVP and a follow-up of 1 year an incidence of new vertebral fractures of 37.8% in those taking GCs (n=37) and of 20.6% in those not taking GCs (n=350), with a relative risk of 1.84 (95% CI 1.16–2.92). Finally, Hiwatashi *et al*. in 2007 (9) published that after PVP and a mean of 535 days of follow-up incidence of new vertebral fractures was 69% in patients on long-term GC therapy (n=16) and 23% in those with primary OP (n=39), which was statistically significant (p<0.01). The prospective, observational design of the present study allows adding strong evidence to these retrospective reports, as we strictly controlled three main factors that may interfere with the results in terms of new vertebral fractures: anti-fracture therapy with bisphosphonates, adherence to treatment, and number of falls. It is known that low adherence to treatment greatly reduces anti-fracture efficacy (20). In the present study, adherence to therapy was high, with more than 90% of doses of bisphosphonates taken and with full compliance with the instructions, including calcium and vitamin D supplementation. Moreover, it is also known that GCs can increase the risk of fall by inducing muscle wasting and myopathy (21); and this risk may be particularly high in rheumatic patients with, for example, arthritis in the lower limbs and gait impairment. Assessment of both risk of fall and the number of falls that occurred since the last visit is a fundamental clinical point in osteoporotic patients, and this is performed as routine in all osteoporotic patients

referred to our Fracture Liaison Unit, including those included in this study. Actually, we were able to show that GC-treated patients had a higher number of falls compared to non-treated; however, this did not influence the number of new vertebral fractures.

Taken together, our results and those of the above-mentioned studies cannot prove that PVP increases the number of new vertebral fractures in GC-treated patients, since they are intrinsically predisposed to an increased fracture risk. To prove that, we should have included in the study a control group of matching patients with vertebral fractures eligible for PVP but not treated because they had refused the procedure or because they had contraindications to the procedure. However, we considered this methodological solution not to be feasible: most patients would be eligible for PVP or not, and those eligible would accept the procedure, leaving the third group with very few patients. Furthermore, a control group of patients not treated with PVP because they were not eligible would have made it unsuitable for comparison.

Although we did not prove the causal relationship between PVP and the high rate of fracture in patients on chronic GC therapy, our view is that the proportion of 44.3% re-fractured patients after 2 years despite an effective anti-fracture therapy should point to a more cautious use of PVP or PKP in such a condition. This is particularly true as we continue to be uncertain about the effectiveness of the procedures (22).

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