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INTERVENTIONAL NEURORADIOLOGY

Osteoporotic vertebral compression fractures augmentation by injectable partly resorbable ceramic bone substitute (Cerament™|SPINE SUPPORT): a prospective nonrandomized study

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Abstract
Introduction The aim of this study is to evaluate the long-term stabilizing–healing effectiveness and influence on adjacent intact vertebral bodies of a new injectable partly resorbable calcium sulfate (60 wt.%)/hydroxyapatite (40 wt.%) bone substitute employed in vertebral augmentation of osteoporotic collapses.
Methods From April 2009 to April 2011, 80 patients underwent vertebral augmentation. Patients enrolling criteria were age >20 years and symptomatic osteoporotic vertebral collapse from low-energy trauma encompassed between levels T5 to L5. Preoperative and postoperative imaging studies consisted of computed tomography, plain X-ray, dual X-ray absorptiometry scanning, and magnetic resonance. Pain intensity has been evaluated by an 11-point visual analog scale (VAS) and physical and quality of life compromise assessments have been evaluated by Oswestry Disability Questionnaire (ODI). All procedures have been performed fluoroscopically guided by left unilateral approach under local anesthesia and mild sedation.
Results VAS-based pain trend over the 12-month follow-up has shown a statistically significant ($p<0.001$) decrease, starting from 7.68 (SD 1.83) preoperatively with an immediate first day decrease at 3.51 (SD 2.16) and 0.96 (SD 0.93) at 12 months. ODI score dropped significantly from 54.78% to 20.12% at 6 months. No device-related complication has been reported. In no case a new incidental adjacent fracture has been reported.
Conclusion Data show how this injectable partly resorbable ceramic cement could be a nontoxic and lower stiffness alternative to polymethylmethacrylate for immediate and long-term stabilization of osteoporotic collapsed vertebral bodies.

Keywords Osteoporosis · Vertebral fractures · Vertebroplasty · PMMA · Ceramic bone substitute

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Introduction

Vertebral compression fractures (VCFs) represent one of the most common complications of osteoporosis [1]. Their impact on quality of life (QoL) and mortality is huge because they lead to several complications sweeping from kyphotic deformities with respiratory involvement to pain regardless of mobility and to mood changes [2–4].

Percutaneous vertebral body augmentation is a proven procedure for the treatment of osteoporotic and pathologic

acute VCFs refractory to medical therapy and without neurologic deficits due to medullar/root involvement. The treatment has been shown to improve function in more than 85% of cases [5–9].

The most employed device for vertebral augmentation is polymethylmethacrylate (PMMA), first introduced in 1984, which assures optimal and potentially eternal vertebral stabilization with immediate pain reduction [10]. Some disadvantages are embedded in its mechanical and chemical characteristics, like high stiffness with possible altered vertebral bodies load transfer, monomer toxicity, and possible heat damage on surrounding soft tissues owing to exothermal setting polymerization [11–13].

The aim of this study is to verify if an alternative cement, Cerament™|SPINE SUPPORT–BONESUPPORT AB, Lund, Sweden (CSS), with osteoconductive properties consisting of calcium sulfate and hydroxyapatite may be effective for the scope of vertebral augmentation, i.e., immediate pain relief and fracture stabilization. The main advantages are fracture stabilization by bone remodeling and the lack of chemical and temperature effect on the surrounding structures in case of leakages. Moreover, its bone-like stiffness may decrease the risk of adjacent-level fractures.

Material and methods

Ethics

From April 2009 to April 2011, 80 patients with osteoporotic vertebral compression fractures underwent vertebral augmentation using a novel injectable and partly resorbable ceramic bone substitute. The study, a prospective nonrandomized trial, was approved by our institution ethical committee and informed consent was achieved before any study-related activity (vertebral augmentation, imaging studies, and follow-up test administration).

Patients selection

All patients were identified at our institution outpatient department. Patients were enrolled if they met the following criteria: age more than 20 years, symptomatic osteoporotic vertebral compression fracture from low-energy trauma encompassing levels T5 to L5 and classified as A1.1 to A1.2 according to the AO classification system [14], vertebral height compression within 0–75% compared to the posterior (dorsal) wall, bone edema of collapsed vertebral body evident on magnetic resonance imaging (MRI), client history confirming compression fracture dating at least 4 weeks and resistant to medical therapy, >and patients able to understand the procedure and participate in the study. Patients with known illness such as cancer, irreversible coagulopathy or bleeding disorder, preexisting calcium disorder (e.g., hypercalcemia), diabetes, and renal failure (dialysis) were excluded. Patients presenting a compression fracture with retropulsed fragment or patients who had previously undergone vertebroplasty/kyphoplasty at the fracture site were also excluded. Moreover, patients were considered not eligible if they presented infections or other skin damage at the puncture site, history of anaphylactic reaction to iodine-based contrast media, and a body mass index more than 30.

Clinical assessment and follow-up

A careful physical examination, including neurological examination, was conducted prior to the procedure to assess patients' clinical condition. During the screening investigation, the use of painkillers was recorded. In most cases, patients attending the screening session provided an MRI exam performed elsewhere of their own; in these cases, they undertook the scheduled first day MRI examination anyway. In all cases where patients attended the screening examination without an MRI exam, this was performed the day after at our institution as part of the screening. MRI exams performed at our institution the day after the screening examination were not repeated during the first admittance day.

Patients who met the above criteria were scheduled to be treated as soon as possible according to our institution daily bed availability; treatment in most cases took place 1 week later, while in four cases, 2 weeks later. Post-procedural physical examination checks were scheduled at day 7 and at months 1, 6, and 12.

All patients were treated the day after hospitalization. During the admittance day, they undertook plain roentgenograms (X-ray), MRI if not performed at our institution the week before, and computed tomography (CT) of the spinal segment involved. Dual X-ray absorptiometry (DXA) scanning was performed on the same day to assess osteoporosis [15]. Follow-up imaging investigations were scheduled as follows: plain X-ray, CT, and MRI at months 1 and 6, plain X-ray and CT at 12 months. To minimize patient radiation exposure during the four-step CT follow-up, post-procedural CT scans were confined to one segment above and one below the treated vertebral body.

Pain intensity was evaluated by an 11-point visual analog scale (VAS) administered before and after the procedure at days 1 and 7 and at 1, 6, and 12 months. Physical and QoL compromise assessment was evaluated by Oswestry Disability Questionnaire (ODI) administered the day before the procedure and at months 6 and 12 [16, 17].

Operational technique and device

All procedures were performed with patients in prone position under local anesthesia (lidocaine/bupivacaine 1%/0.25% for skin incision; ropivacaine 10 mg/mL for periosteal anesthesia) with fluoroscopic guidance and, in some cases, supported by mild sedation. In all cases, the approach was transpedicular. The favorite approach was represented by the left unilateral approach, according to the habit of the first operators and good visibility of the bilateral pedicles cortical boundary. Our technique did not differ substantially from the standard well-established procedure described elsewhere [18]. To set the intravertebral cement spread as homogeneously as possible, the 13-G straight injection cannula was at first advanced up to the anterior third of the vertebral body (Fig. 1). Cement was gently injected, paying careful attention to any leakage (intradiscal or intravenous); if it happened, injection was stopped for 3–4 min to allow partial cement hardening and then restarted. Once maximum cement spread was achieved at this site, the tip of the cannula was retracted to the posterior third, retrying cement injection. This two-step injection, in our experience, allowed us to achieve cement filling as completely as possible.

At the end of the procedure, patients were kept for 20 min in prone position before rolling over into a bed where they were kept for 3 h in supine position before letting them go to the outpatient clinic. CSS setting time (in blood at 37°C) is 41±3.6 min, but we preferred to keep the patients in bed longer. Because most patients used analgesic medications before hospital admittance, they were encouraged to terminate these on the following few days after the procedure, and they were instructed to contact us in case of any discomfort. Patients, in the absence of complications, were planned to be discharged the day after the procedure. CT scans targeted on the treated level were performed 5 to 8 h after the procedure to visualize the cement spread and rule out fluoroscopy occult leakage.

The investigational device (CSS) is a CE-approved medical device intended for augmentation of vertebral compression fractures. It is an injectable and partially resorbable ceramic bone substitute. The device consists of synthetic calcium sulfate (60 wt.%) and hydroxyapatite (40 wt.%) mixed with the radiocontrast agent CERAMENT™|C-TRU (iohexol, 300 mg iodine/mL). The device allows bone ingrowth after curing.

Statistical methodology

Data are presented as average, standard deviation, and significance level. Given the sample size (80 patients), raw data were recorded and analyzed on SAS™ statistical software by two-tailed, matched-pair, two-sample t test. Differences in averages were accepted as significant at $p<0.001$.

Theory

The investigational device (CSS) is an injectable and partially resorbable ceramic bone substitute consisting of 60% synthetic calcium sulfate and 40% hydroxyapatite, mixed with the radiocontrast agent CERAMENT™|C-TRU (iohexol, 300 mg iodine/mL). Once mixed, powder and liquid compose a viscous paste able to be easily injected (Fig. 2). During the complete hardening period (about 2 h), CSS becomes solid, providing fracture mechanical stabilization. The calcium sulfate dehydrate component will be gradually resorbed, allowing the implant to be remodeled through bone ingrowth [19]. The hydroxyapatite component remains intact for years, providing an osteoconductive matrix for new bone ingrowth and long-term armoring of

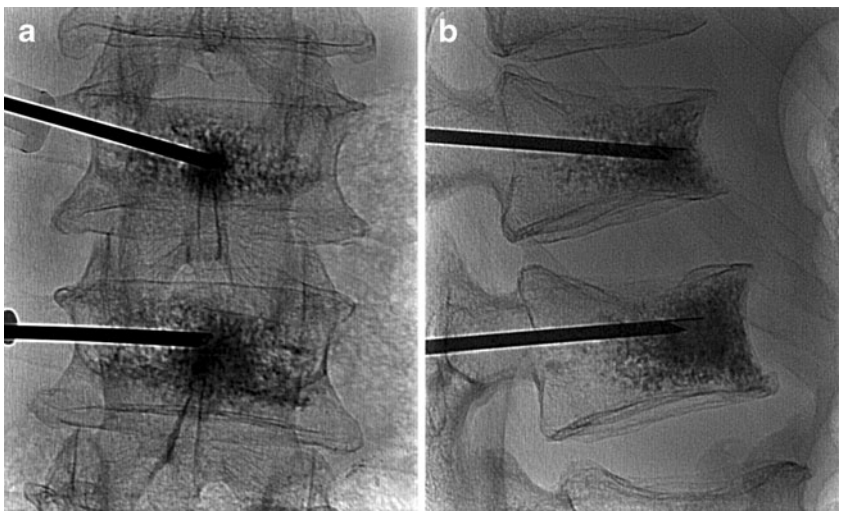

Fig. 1 Anteroposterior (**a**) and lateral (**b**) intraprocedural fluoroscopic view. Good cement impregnation showed by its good radiopacity

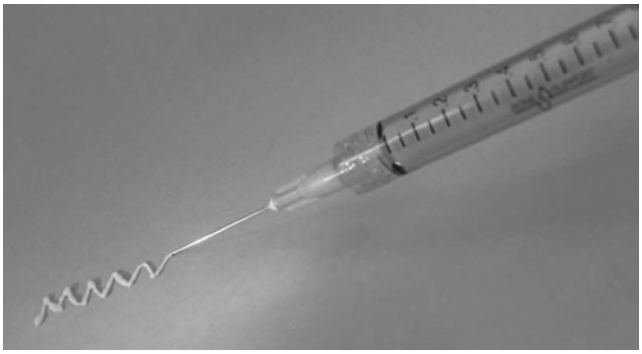

Fig. 2 CERAMENT™ is highly injectable and can be extruded through cannulae with minimum inner diameter of 0.191 cm

the osteoporotic vertebra. The components of CSS have been used in humans for decades and are proven to be highly biocompatible. The compressive strength of CSS is similar to cancellous bone, with the potential of minimizing the risk of implant-induced adjacent fractures [20–22].

Results

Eighty sequential patients (47 (58.8%) women; 33 (41.2%) men) fulfilling the above inclusion criteria underwent vertebral augmentation. Patients mean age and DXA *T* score values are shown in Table 1. All female patients were osteoporotic. Forty-two women were already receiving therapy for osteoporosis; 5 women were not and were, therefore, scheduled at our institution orthopedic department for appropriate treatment. DXA scans performed on males ruled out osteoporosis in 25 patients, according to the WHO cutoff [15, 23–26]. DXA scans performed at 1 year did not show statistically significant differences in *T* score values for both men and women. The mean symptoms duration was 8.3 weeks (range, 4.5–24 weeks, from the onset to the treatment).

Table 1 Patients/levels treated summary

	Women	Men
Patients *N* (80)	47 (58.8%)	33 (41.2%)
Mean age (SD)	66.81 (14.28)	65.18 (14.21)
DXA *T* score		
Prox femur	−2.98 (0.19)	−2.73 (0.20)
Lumbar spine	−2.79 (0.21)	−2.68 (0.19)
Level treated (total 128)	Patients/levels	Patients/levels
Single	24/24	20/20
Double	15/30	9/18
Triple	8/24	4/12
Level contiguity (*N* patients)		
Double contiguous	10	6
Double sandwich	3	1
Double distant	2	2
Triple contiguous	5	3
Triple sandwich (B_n–B_{n+1}–B_{n+3})	2	1
Triple distant	1	0
Collapse type (AO classification)		
A1.1	17 (13.3%)	18 (14.0%)
A1.2	61 (47.7%)	32 (25.0%)

An overall amount of 128 levels were augmented, 50 levels for men and 78 levels for women. Collapsed vertebral bodies showed a bimodal spinal segmental distribution with peak prevalence at the midthoracic and thoracic–lumbar junction, congruous with epidemiological data [27]. Data on levels involvement and on involved level contiguity are summarized in Table 1. Data on fracture type (AO classification system) [14] were gathered as follows: 35 (27.34%) levels classified A1.1, 93 (72.66%) levels classified A1.2. Type A1.2 fractures frequency was found significantly higher in women population and with multiple level involvement (Table 1).

Bilateral transpedicular approach was in no case necessary for optimal cement spreading, also in upper thoracic levels where it is more difficult to target near-midline injection, and all procedures were performed through the left-sided pedicle. The mean volume of cement injected was 3.35 mL (SD, 0.38), with 1.5–5 mL range. At targeted CT scans performed some hours after the procedure, cement leakages were reported in 15 levels (11.7%); 9 (60%) of these were intradiscal and 6 (40%) were represented by small cement wedging inside the anterior venous plexuses. Thanks to the excellent cement radiopacity, all intradiscal leaks had been immediately identified under fluoroscopy. Given the good opacity of the cement, all intradiscal leaks were minimal because injection was immediately stopped once the leak is identified, to be restarted after 3–4 min, as described upon. Of six intravenous leaks, only three were detected during fluoroscopy, the remaining three being identified by CT scans.

At 1.5 months after the procedure, in two single-level cases, painful symptomatology suddenly arose again with the same intensity and location as the preoperative condition. Patients undertook extra-protocol MRI and CT scans. In both cases, CT scans were negative for unstable fracture, but in one case, MRI scans showed, at the treated level (L4), the typical signs of vertebral body edema just underneath the superior endplate, owing to a new collapse at the same level. This patient was retreated the day after MRI and refollowed up according to protocol. At 1 week, a six-point VAS drop was recorded; before the first treatment, VAS was 9, dropped to 2 at 1 month follow-up, raised at 8 with the recollapse, and eventually dropped to 2 to remain stable at the end of the 1-year follow-up. In the patient with both negative CT and MRI exams, a persistent spasm of

paravertebral muscles around the treated level were identified and promptly resolved in some days with analgesic drugs and thiocolchicoside.

VAS-based pain trend over the 1-year follow-up showed a statistically significant decrease at both baseline and each interval comparison, starting from 7.688 (SD, 1.825) points baseline score with an immediate first day decrease at 3.513 (SD, 2.158) points, to get through 2.363 (SD, 1.577) points at day 7, 1.875 (SD, 1.247) points at day 30, 1.325 (SD, 0.883) points at 6 months, to end at 0.963 (SD, 0.934) points at 1 year. Quality of life assessment sampled by ODI scoring also showed a statistically significant improvement with a baseline mean score of 54.78% (SD, 15.82%) that dropped to 22.61% (SD, 8.35%) at 6 months to end with 20.12% (SD, 11.53%) at 1 year. All significance levels for both VAS and ODI evaluation showed $p<0.0005$ (Figs. 3 and 4).

No intraprocedural or periprocedural complications were reported, except the above-mentioned small cement leaks. At the end of the 1-year follow-up, no cases of new adjacent vertebral fractures were reported. In four cases (all women) with monolevel involvement, a new incidental fracture per person occurred at a distant level. The first early vertebral collapse occurred 7 months after the procedure, the last at 9 months; all four cases were augmented by traditional PMMA cement vertebroplasty.

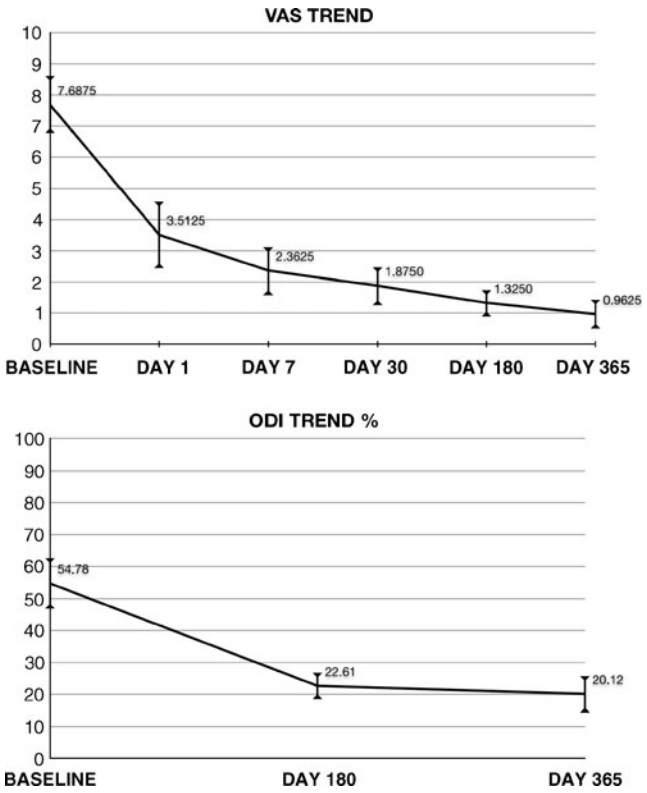

Fig. 3 Both VAS values and ODI values show a significant constant improvement over the 12-month follow-up

Discussion

Pain and kyphotic deformities account for the majority of life-threatening complications that follow the loss of mobility consequent to VCFs [28–30]. Vertebral augmentation is a technique of proven efficacy, almost immediately reducing pain related to osteoporotic and pathologic acute VCFs with great improvement in patients clinical condition and improvement in QoL [5–7, 9, 31], as also confirmed by the recently published VERTOS II study in which, with the right inclusion criteria, vertebral augmentation is effective and safe, leading to a significantly better improvement than that achieved with conservative treatment [32].

PMMA is the most employed commercially available device for vertebral augmentation. Its proven effectiveness in reducing pain from vertebral collapse almost immediately is considered to reside not only in its fracture-stabilizing action, but also in the secondary local nerve damage as a consequence to its high setting temperature and chemical toxicity. The available scientific literature data on PMMA setting induced heat–chemical toxicity damage on the surrounding nerve structures may be ambiguous [11–13, 33]. However, data on its mechanical and bone integration properties are clear. PMMA Young's modulus (1.8–3.1 GPa) is significantly higher than the normal bone thus interfering mechanically with the load stresses and preventing surrounding bone remodeling; in case of osteoporotic bone, PMMA strength is 8 to 40 times higher [34–38]. Such high stiffness may account for the risk of recollapse of the spared, not impregnated, cancellous bone of the same vertebral body and for the risk of incidental adjacent fractures.

Complete cancellous bone impregnation, bridging both the endplates and the axial level, appears to strengthen the whole vertebral body, reducing the risk of intrasomatic recollapse. Additionally, such complete cement distribution may also affect adjacent vertebral bodies load transfer, potentially decreasing the risk of new incidental collapses, especially in “sandwich” vertebral bodies [39–42]. It was on the basis of these hypotheses, and based on CSS lower stiffness (0.3–0.4 GPa), which is comparable to normal trabecular bone, that we strived for a complete vertebral body cement filling.

The rationale of the ideal bone substitute lies in its ability to be resorbed at a rate equal to new bone ingrowth, achieving complete bone remodeling and healing, while being able to tolerate the motion–load stresses the spine usually undergoes. Strength of calcium sulfate alone is too weak compared to that of cancellous bone, and its rate of resorption is too high to allow new bone ingrowth. CSS consists of calcium sulfate and hydroxyapatite; the hydroxyapatite acts as slow or never absorbable framework that slows down the absorption rate of calcium

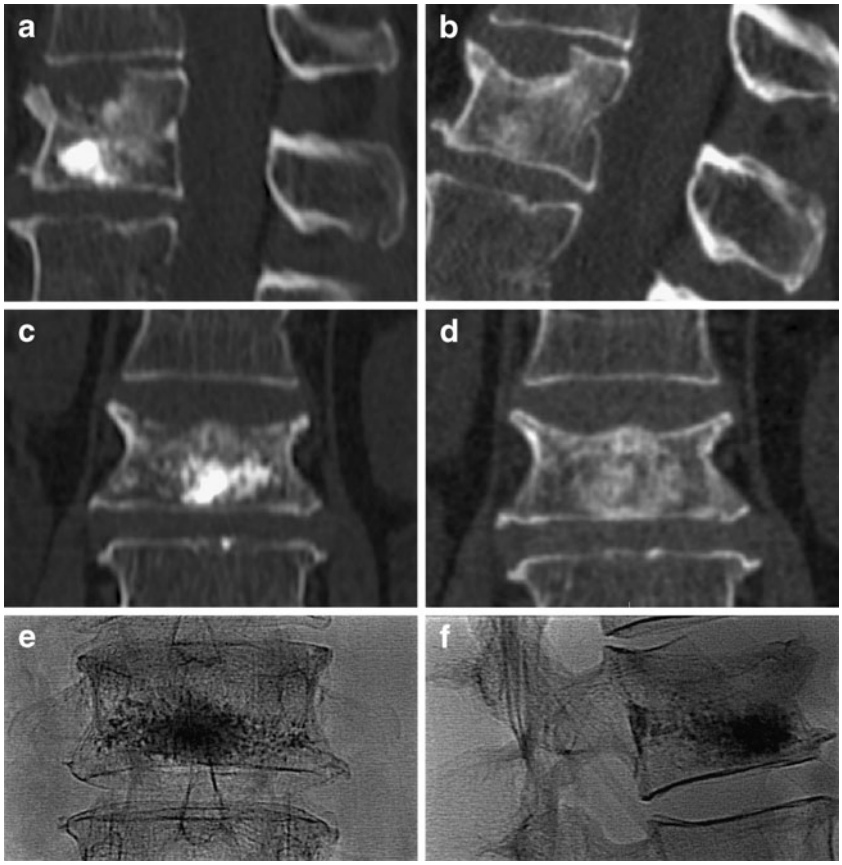

Fig. 4 Sagittal (**a**) and coronal (**c**) CT scans show the appearance of CSS spread inside the collapsed vertebral body on the first day after the procedure; appearance at 6 months (**b**, **d**), when iodine is completely resorbed and calcium sulfate should also be resorbed. Anteroposterior (**e**) and lateral (**f**) fluoroscopic view of the same vertebral body

sulfate and at the same time acts as an osteoconductive template for new bone ingrowths. The hydroxyapatite particles are completely embedded inside the new bone tissue during the new bone ingrowth. The mechanical properties, the low stiffness of the device, and the bone-remodeling processes decrease the shear stresses at the border bone/CSS [20, 22, 43–46].

In the study, one patient presented with a recollapse of the already augmented vertebral body (L4) about 1.5 months after the treatment. In this patient, there was no new trauma or any intradiscal leak from the first augmentation. The etiology of this occurrence could be explained by a combination of irregular cement filling and the lower mechanical strength of the device in the early stages of integration when calcium sulfate resorption was still in progress and new bone ingrowth was limited [43]. Anyhow, once reaugmented with CSS, the painful symptomatology in this patient decreased, becoming equal to the mean of the other patients.

The involved vertebral bodies in our patients showed the typical "load stress"-related cluster distribution, with higher frequencies of collapses at midthoracic and thoracic–lumbar junction [47–50]. We were worried by the risk of adjacent fractures in sandwich vertebral body fractures. However, based on the above considerations and on the evidence presented by some authors [47, 51] showing the incidence of a vertebral collapse to be unaffected by the augmentation of the adjacent levels, we withheld any preventive treatment.

Some authors argued that the frequency of adjacent vertebral fractures increase in case of intradiscal leakages [49]. In our study, we reported nine cases of such leakages, all minimal because early identification, but none of these patients presented with new incidental adjacent or distant collapse in the 1-year follow-up. Four women with monolevel involvement presented a new collapse at distant levels.

According to our data, immediate fracture stabilization and pain relief, assessed by imaging and VAS score, were completely accomplished by augmentation with this device. Also, the QoL, as assessed by ODI score, showed significant improvement.

Follow-up showed immediate and lasting pain relief in the absence of new incidental fractures and no device-related adverse reactions. Our results strongly suggest that CSS can be an effective alternative to PMMA. We propose that the sustained pain relief during the 12-month follow-up period is due to a new bone ingrowth, and this is supported by another study on osteoporotic patients undergoing wrist osteotomy augmentation with the same device, showing its

complete substitution by a new bone [22]. However, in this study, it was not possible, for ethical reasons, to investigate on long-term bone device integration by biopsy samples.

Grounding on our results, CSS appear to be a valid alternative to PMMA for vertebral augmentation of osteoporotic collapses, with some potential advantages embedded. Further evaluation of its validity is necessary in the way of wider inclusion criteria and longer and bigger prospective observational studies. CSS resorbable properties could limit its employment in collapses secondary to malignancies because, if a malignancy is able to erode a normal bone, it may be able to do the same with CSS too, considering its composition, leading to recollapse. However, there are some circumstances in which CSS is employed with the double purpose of being both bone void filler and antibiotic carrier [52, 53]. It should be, therefore, plausible to venture that CSS could also be an antineoplastic drug carrier, hence widening its employment to nonosteoporotic VCFs.

Conclusions

CERAMENT™|C-TRU, a new bioactive calcium sulfate/hydroxyapatite cement for vertebral augmentation, has shown immediate and long-term effectiveness, leading to immediate and lasting pain relief, improved QoL, and absence of any device-related complication, including new incidental adjacent fractures.

Conflict of interest We declare that we have no conflict of interest.

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