ORIGINAL ARTICLE

Bioceramic vertebral augmentation with a calcium sulphate/hydroxyapatite composite (Cerament™ SpineSupport) in vertebral compression fractures due to osteoporosis

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Abstract A prospective, non-randomized multicenter study was initiated to study efficacy and safety of a partly resorbable composite of calcium sulphate and hydroxyapatite (Cerament™ SpineSupport), a novel, injectable bioceramic, in osteoporotic patients with vertebral compression fractures during 18-month follow-up. Fifteen patients with low-energy trauma and 1–2 vertebral compression fractures verified by magnetic resonance imaging were recruited to undergo percutaneous bioceramic vertebral augmentation under fluoroscopy. The patients were treated with a highly flowable bioceramic containing calcium sulphate, hydroxyapatite and the non-ionic radiocontrast agent iohexol, with final setting time within 1 h. After the procedure, the patients were allowed to mobilize after 2 h. Pain (VAS), occurrence of remote and adjacent fractures, and Quality of Life (QoL; SF-36 and EQ-5D) was recorded during 18 months. The injected volume of the composite material ranged from 2.8 to 9 mL (mean 4.2 mL). Pre-operative VAS score was mean 70.3 (CI95% ±8.7) with an immediate post-operative pain relief, which was maintained at the 4-week visit (mean 26.4 with CI95% ±16.1) and 8-week visit (mean 18.0 with CI95% ±13.5 pain relief). Eighty percent of the patients demonstrated a clinical improvement. The pain relief was maintained over 18 months and no adjacent fractures were observed. There was a statistically significant improvement of physical components in the QoL assessment. No extra-vertebral leakage or neurological deficits were reported in this series. This first prospective multicenter study on a partly resorbable bioceramic material indicate that fracture healing can be achieved with sustained pain relief over a follow-up period of 18 months in an osteoporotic patient population with vertebral compression fractures.

Keywords Bioceramic · Compression fracture · Osteoporosis · Pain · Vertebroplasty

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Introduction

Osteoporosis causes more than 8.9 million fractures annually worldwide and about 700,000 of these fractures are vertebral compression fractures [13]. Approximately 40–50% of women above 80 years of age are reported to

have suffered at least one vertebral fracture [22]. Percutaneous vertebroplasty has emerged as a treatment option for vertebral compression fractures refractory to conservative treatment. Vertebroplasty involving the injection of a bone cement, polymethylmethacrylate (PMMA), was introduced in 1984 [9].

The incidence of clinically diagnosed vertebral compression fractures (VCF) in women (123/100,000 patient years) is comparable to that for hip fractures [7], with fracture pain usually lasting from 2 weeks to 3 months, associated with intense, deep, and sometimes intractable pain [17]. Each additional new VCF is associated with a further increase in functional limitation, of a magnitude similar to that in patients with diabetes, ischemic heart disease and rheumatism [23]. Both low bone mass and previous fracture independently predict subsequent fracture [30]. Further, women with clinically diagnosed vertebral fractures have a 15% higher mortality than women who do not [6]. A novel, injectable bioceramic bone substitute (Cerament^{TM} SpineSupport) which exerts a dual action by its composition of resorbable calcium sulphate to allow bone in-growth, hydroxyapatite to provide long-term support, and the water-soluble and non-ionic radiocontrast agent iohexol [31] was used. This newly developed material has an immediate compressive strength similar to that of cancellous bone [24], with the purpose of minimizing the risk of implant-induced adjacent fractures. Over weeks and months the calcium sulphate component is replaced by in-growing bone that remodels to form trabeculae [38], while the hydroxyapatite component remains as an armouring of the osteoporotic bone.

The present study was designed to investigate safety aspects, pain relief, Quality of Life (QoL) and the rate of subsequent adjacent fractures following vertebroplasty with this new composite of calcium sulphate and hydroxyapatite that aims for healing of vertebral compression fractures.

Methods

The study was preceded by an initial phase to optimize the treatment procedure and to follow-up on material visibility during fluoroscopy. During this run-in phase one patient suffered from atypical signs (e.g. atrial fibrillation) for 24 h. The CT scan of the lungs and the treated spine region showed no evidence of any suspect material or signs of leakage. Subsequently, a flushing procedure (with saline) of the treated vertebrae was abandoned and the composition of the bioceramic material was improved to give optimum visibility during the injection.

The criteria for inclusion were symptomatic vertebral fractures with a medical history confirming the age of the vertebral compression to be within 8 weeks, low energy trauma causing 1–2 symptomatic vertebral compression(s) at level Th5 to L5 verified by MRI, impaction grade A1.1, A1.2 and A1.3 according to the AO classification, and height compression of the affected vertebra/vertebrae within 0–60% compared to the dorsal vertebral wall.

Exclusion criteria were age below 50, retropulsion of fracture fragment, and concomitant diseases which might be worsened by invasive treatment of the fracture such as local tumor. Patients were also excluded if they had a history of anaphylactic reaction towards iodine-based radio contrast agents, known hyperthyreosis and/or thyroid adenoma, known bleeding disorders, or were treated with anticoagulant medication. Moreover, patients were considered non-eligible for the study if they had an extreme body weight (>100 kg) or had a local infection or otherwise compromised skin of the puncture site.

The screening procedure took place at six investigational sites. Patients with osteoporotic vertebral compression fractures refractory to standard pain medication were consecutively screened for eligibility between 14 days prior to and up to the day of surgery. No study-related procedures were performed before the subjects had signed the informed consent form, which had been approved by the local ethics committee responsible for the research conducted at the respective hospital. If the subjects were found eligible for participation, the fractures were verified by magnetic resonance imaging (MRI) and the patients' symptoms were recorded. The protocol stipulated a bilateral transpedicular vertebral injection under fluoroscopy. After the procedure, the patient had to stay in prone position for at least 15 min before rolling over in a bed to remain in horizontal position for 2 h while the hardening process was completed.

A total of 16 vertebral levels were treated in 15 patients with primary osteoporotic vertebral compression fractures.

The composite material (Cerament^{TM} SpineSupport, Bonesupport AB, Sweden) is composed of 60 wt% calcium sulphate alpha-hemihydrate and 40% sintered hydroxyapatite. When mixed with the liquid component, iohexol 300 mg/mL in water, it becomes a viscous paste possible to be injected transpedicularly (Fig. 1).

Follow up

Patient visits were scheduled at the first post-operative day, at 4 and 8 weeks and at 6 and 18 months. X-ray was taken pre-operatively and at 8 weeks to confirm fracture healing and at 18 months to exclude refracture of the treated vertebra or fractures at adjacent vertebral levels. A CT scan was taken within the first 24 h post-operatively to examine possible extravertebral leakage. Pain was assessed using a 100 mm visual analogue ruler (score 0–100) where a score

Fig. 1 Mixed paste of calcium sulphate/hydroxyapatite composite (Cerament^TM SpineSupport) in a 1 mL syringe (23G needle)

of 0 represents "no pain" and a score of 100 represents "maximum pain". QoL was followed through SF-36 Health Surveys [39] and EQ-5D questionnaires [5]. Safety was assessed by the registration of adverse events and adverse device effects, and by physical examination and laboratory measurements. The possible occurrence of adjacent or remote vertebral fractures was recorded by two independent examiners using standard radiological images.

Statistical methodology

Data are presented using count of mean and confidence interval as appropriate. Two-sided Student's paired t test, was used to assess differences between baseline and subsequent VAS measurements, SF-36 and EQ-5D scores. SAS^TM statistical software (version 9.1) was used for all analyses. Statistical significance was considered at a probability level <0.05.

Results

Fifteen patients (10 female) with a mean age of 76 (range 68–94) were treated for vertebral compression fractures at spine levels with positive MRI signals that corresponded clinically to the back pain. Sixteen fractures, including seven thoracic and nine lumbar vertebrae, were treated. The injected volume of the composite in each vertebral body ranged from 2.8 to 9 mL (mean 4.2 mL). The radiopacity and intratrabecular material spread are shown in Fig. 2.

Pain

Eighty percent of the patients demonstrated an immediate and statistically significant improvement in pain compared to baseline and assessed by the VAS pain score (Fig. 3). The mean pain relief compared to the assessment immediately before the intervention was 39% on the day after the
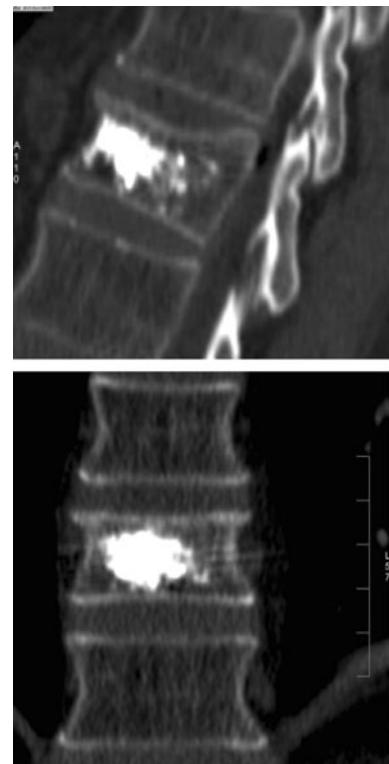
Fig. 2 CT control showing good distribution of a composite of calcium sulphate and hydroxyapatite (Cerament^TM SpineSupport)
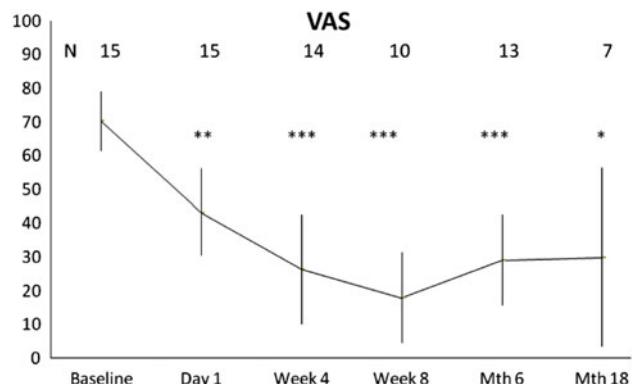
Fig. 3 Mean VAS pain score (mm). *Error bars* represent 95% confidence interval. *Numbers* in the graph represent number of patients available at follow-up. $*p < 0.05$; $**p < 0.01$; $***p < 0.001$

procedure, and 62% and 74% after 4 and 8 weeks, respectively. A pain relief of approximately 60% was maintained at 6 and 18 months after the treatment.

Quality of Life

The QoL assessed by the use of SF-36 showed a statistically significant improvement in the mean physical component summary (PCS) of approximately 40% ($p < 0.01$)

and 70% ($p < 0.01$) at 8 weeks and 18 months, respectively, from a baseline score of 26.3. The mean mental component summary (MCS) remained unchanged.

QoL as evaluated by the EQ-5D Health Index significantly improved from a value of 0.254 at baseline to 0.563 at 8 weeks ($p < 0.05$) and 0.638 at 18 months.

New vertebral fractures

No adjacent fractures occurred during the 18-month follow-up period. A new remote fracture was diagnosed in one patient.

Safety

No serious events were considered to be related to the calcium sulphate/hydroxyapatite-composite or to the percutaneous procedure. No deaths or neurological complications were reported and there was no evidence for local extravasation or pulmonary embolism. The day after the percutaneous procedure one patient was shown to have an unstable end-plate fracture in the treated vertebra. The patient was (as stipulated in the study protocol) successfully re-treated with PMMA after approximately 1 week.

Discussion

The general purpose of fracture treatment is to stabilize the fracture to allow healing in a correct position and to relieve pain. Vertebroplasty with PMMA only addresses the pain aspect. Further, implantation of a non-resorbable material may entail a risk of future device-related complications. Cerament[TM] SpineSupport has been designed to stabilize the vertebral fracture and to give both pain relief and allow fracture healing through a gradual bone ingrowth. Although both animal studies [24, 38] and studies on osteoporotic patients undergoing wrist osteotomy [1] have demonstrated a bone remodeling after treatment with Cerament[TM], the concept still has to be proven in vertebral compression fractures. The present study was designed to test the hypothesis that Cerament[TM] SpineSupport will give short-term pain relief through fracture stabilization and long-term pain relief through fracture healing in vertebral compression fractures caused by underlying osteoporosis. Further, the fracture healing concept was controlled at 18 months, a time point where the stabilizing calcium sulphate component will be resorbed [26, 28, 32]. As a secondary objective, the possible risk of causing adjacent level fractures was investigated.

The instant and sustained pain relief demonstrated in the present study indicates that Cerament[TM] SpineSupport has sufficient mechanical strength to stabilize stable

compression fractures. It has been speculated that the toxic effects of the monomer methylmetacrylate or the high temperature of PMMA during the setting process [3], may not only cause damage to nerve roots in case of leakage [25] but also contribute to the immediate pain relief seen after vertebroplasty [19]. The present data support the hypothesis that fracture stabilization is the most important factor to relieve pain in vertebral compression fractures. The calcium sulphate/hydroxyapatite composite material investigated in the present study sets at a moderate temperature increase of 4°C.

The sustained pain relief during the first 2–6 months points towards a healing of the vertebral fracture lines, which is supported by bone ingrowth demonstrated in animal studies on the material [24, 38] showing bone remodeling within this time frame. An alternative explanation could be that Cerament[TM] SpineSupport turnover is slower in osteoporotic patients than in animals and that the implant still has a stabilizing effect after 18 months. This seems, however, less probable considering that Cerament[TM] was completely remodeled into bone after 12 months, in osteoporotic patients undergoing wrist osteotomy [1]. The final answer can only be obtained by a repeat study including advanced imaging techniques or by bone biopsies in patients treated with the product.

The immediate pain relief obtained was statistically significant compared to baseline and it was maintained over time. These results appear to be in line with the results reported from vertebroplasty studies using PMMA [2, 8, 15, 16, 20, 21, 27, 29, 33, 36, 37, 41].

There was also a statistically significant improvement in QoL as evaluated by the SF-36 PCS. The positive outcome in SF-36 PCS was corroborated by the improvement noted also for the EQ-5D Health Index. Although interpretation of outcomes between studies should be performed with caution, the improvement in QoL after vertebroplasty with Cerament[TM] SpineSupport appears to be similar to that reported for vertebroplasty with PMMA [2, 8, 21, 29].

It has been reported that the risk of getting a new fracture in adjacent vertebrae following vertebroplasty with PMMA may increase as a result of the high stiffness created in the treated vertebra, with a reported incidence of adjacent fractures in the range between 10 and 25% within the first couple of months [4, 10–12, 14, 18, 34, 35, 40]. An alternative explanation to the occurrence of adjacent fractures is that certain segments of the spine is at higher risk of multiple fractures due to the underlying osteoporosis. Although speculative due to the limited number of patients in the present study and the number of patients lost to follow up at the18-month visit, it is reasonable to assume that a ceramic material, that mimics the stiffness of cancellous bone, is less prone than PMMA to cause adjacent fractures. No adjacent fractures occurred over a follow-up

period of 18 months, while one remote fracture was recorded.

Although a partly resorbable ceramic material seems to have an advantage compared to PMMA in that less long-term material-related side effects are to be expected and that the ability to bone remodeling will promote fracture healing, a remodeling implant may still entail certain limitations. Unstable fractures and fractures caused by tumours engaging the cortical walls require a material with certain properties. In the present study, one patient treated with Cerament^{TM} SpineSupport was considered to require re-treatment with PMMA due to an unstable end-plate fracture diagnosed 1 day after the percutaneous administration of the material. From this first prospective study it seems, however, as Cerament^{TM} SpineSupport might become an interesting alternative to PMMA in stable compression fractures classified as A1.1–A1.3 according to the AO classification. Radiological imaging showed no evidence of extra-vertebral leakage and there were no reports of neurological deficits. It is reasonable to believe that leakage occurs not only with PMMA, but also with a bioceramic material. A possible explanation for the lack of extravasation observed might be a propensity for pre-setting dissolution if deposited intravascularly.

Given the limitations of a non-controlled study it may be concluded that the calcium sulphate/hydroxyapatite-composite (Cerament^{TM} SpineSupport) has been shown to be a promising product for bioceramic augmentation in osteoporotic patients with vertebral compression fractures.

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