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ORIGINAL ARTICLE

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Clinical results of an open prospective study of a bis-GMA composite in percutaneous vertebral augmentation

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Abstract In this open prospective trial, 53 patients with acute pain from osteoporotic vertebral fracture related to osteoporosis or malignancy underwent vertebral augmentation with a new bisphenol-a-glycidyl dimethacrylate (bis-GMA) resin (Cortoss, Orthovita, Malvern, Pa, USA). Treatment consisted of up to 8 ml of Cortoss injected into a given vertebra. The procedure encompassed single and multiple injections (including the contralateral hemivertebra, to a maximum of 3 vertebral levels). Follow-up was at 4 and 8 days and at 1, 3, and 6 months. The primary efficacy end point was patient-rated pain using a 100-point visual analog scale (VAS, with 100 as severest pain) on day 4 following treatment; secondary end points were analgesic use and quality-of-life and disability scores from the Oswestry Disability Index (ODI) and a short-form 12-item questionnaire (SF-12). The present report contains interim results collected up to the 1-month post-treatment time point. At baseline, the group's mean VAS score was 69, indicating moderate to severe pain; at day 4, 32 of 53 patients (60.4%) reported a 30% or greater reduction in baseline pain accompanied by a VAS pain score less than 50 (mean 38.1). Pain reduction was maintained at 1 month (mean VAS 31.3). The average ODI score at baseline was 55, suggesting significant disability among participants prior to Cortoss treatment. Following treatment, the ODI scores were significantly reduced from these baseline levels (day 8, 47.4; 1 month, 33.6). Further, SF-12 physical and mental component scores at 1 month after treatment increased from baseline by 26% and 11%, respectively; while analgesic use decreased concomitantly, primarily among patients with underlying osteoporosis. A total of 20 adverse events were deemed to be device-related. The most frequent clinically significant adverse events attributed to Cortoss were leakage of Cortoss from within the vertebral body at placement (12%), back pain (7%), and unspecified pain (7%). These results indicate that vertebral augmentation with Cortoss rapidly reduces pain, decreases disability, and improves physical functioning in patients with painful vertebral compression fractures.

Keywords Vertebral fracture repair · Percutaneous vertebral augmentation · Bis-GMA · Bone substitutes · Methacrylates

Introduction

Vertebral compression fractures, usually resulting from osteoporosis or metastasis, are a common cause of morbidity. A longitudinal population-based study in the United States conservatively estimated the annual incidence of painful vertebral compression fractures in the white population alone to be about 163,000 among persons aged 50 years and older [4]. As the population ages, the expected number of such fractures increases. In addition to chronic fracture-associated pain that can last from weeks to months, evidence suggests that these fractures are costly and also negatively affect overall health through loss of lung capacity, decreased appetite, impaired mobility, and increased risk of depression. Such effects impair the ability to carry out daily activities and reduce quality of life (QoL) [16, 20, 21]. Moreover, clinically evident osteoporotic vertebral body compression fracture has been associated with a 15% age-adjusted increase in mortality, while increased mortality has not been observed in clinically evident osteoporotic distal radius fracture [3].

For many patients, conservative treatment, involving bed rest and analgesics, is sufficient to relieve pain. However, patients with continuing, unrelieved severe pain require more aggressive treatment. Polymethyl methacrylate (PMMA) has long been used for vertebral augmentation in patients with pathologic vertebral compression fractures or epidural compression related to malignancy [6, 11, 17, 22]. Since 1987, X-ray-guided percutaneous injection of PMMA into vertebral bodies has been used for the treatment of pain related to tumor invasion [7, 10, 24] and, more recently, osteoporotic compression fractures [5, 12, 14, 25]. The relief of pain is presumed to result from reinforcement and subsequent strengthening of the partially collapsed vertebra. Recent studies of PMMA treatment demonstrate excellent and immediate analgesic performance with low complication rates. Jensen et al. found significant pain relief immediately following PMMA injection in nearly all (90%) of 29 patients treated, and follow-up revealed no neurologic complications [14].

In the largest clinical series of percutaneous vertebral augmentation (over 300 patients), Chiras et al. found radiculopathies in only 1% of patients with fractures caused by osteoporosis [2]. While no systematic analysis of the rate of infection with percutaneous vertebral PMMA instillation has been conducted, this complication appears to be rare according to case series reports, and is estimated by Chiras to be under 0.5% [1, 2, 5, 12]. As a result of immediate pain relief, patients can return to normal activity levels more quickly after percutaneous vertebral augmentation than after conservative treatment. Early mobilization may reduce the incidence of complications of conservative therapy caused by inactivity and analgesics.

PMMA bone cement is also used to help weakened vertebral bodies withstand compressive loads [1, 11]. Long-term follow-up of patients with giant cell tumors treated with PMMA cement to augment vertebral compressive load resistance shows appreciable treatment durability without significant failures or secondary fractures [1, 15, 18].

Despite PMMA's long clinical history, its use in vertebral augmentation is not straightforward. Surgeons have empirically adjusted the formulation of PMMA over a 25-year period to improve its handling characteristics in this application. For example, to extend the working time of PMMA, the amount of monomer is increased. To increase visibility under fluoroscopic control, radiopaque materials are added. Some evidence suggests that increased monomer concentration can adversely affect the biomechanical properties of PMMA [13], and radiopaque additives like barium sulphate are associated with increased bone resorption [19]. Other known disadvantages of PMMA include awkward mixing procedures, restricted working time, noxious odor, and poor visualization on X-ray examinations.

In recent years, improved synthetic bone void fillers have been under development to circumvent the known shortcomings of PMMA, but they have been slow to receive acceptance, as their clinical use has not resulted in outcomes sufficiently superior to PMMA. Cortoss (Orthovita, Malvern, Pa), a modified bisphenol-a-glycidyl dimethacrylate, like PMMA, is a member of the methacrylate class of resins used for 20 years in vertebral augmentation. Unlike PMMA, Cortoss is readily available since it does not require premixing and can be used on demand, allowing the filler to be dispensed as needed throughout the surgery; it is supplied as a 2-part paste that mixes when released from the delivery gun (Table 1). The composite hardens within 5–8 min of mixing at an exotherm of approximately $63° \pm 5°C$ and can fully support weight-bearing loads immediately after setting. Further, it is inherently radiopaque, allowing placement under fluoroscopy without adulteration and ready visualization on postoperative X-rays. Additionally, Cortoss has higher compressive strength and better compressive and tensile fatigue than PMMA. Its modulus of elasticity is closer to that of bone, being 3 times higher than that of PMMA [8]. In a head-to-head animal study, the interface between bone and this new cortical bone void filler appeared to become more intimate during the months after placement, with increasing bone formation and integration over time, in contrast to the interface between bone and PMMA, which has been reported to develop an interposed fibrous layer [8].

Clinical investigations of this synthetic cortical bone void filler are needed to confirm its short and long-term efficacy and to explore its potential to minimize the negative effects on QoL and economic status caused by

Table 1 Composition of Cortoss synthetic cortical bone void filler

Component	Function
Resin materials	
Bisphenol-a-glycidyl dimethacrylate	Matrix polymer; high molecular weight, highly cross-linked; imparts strength and reduces leaching
Bisphenol-a-ethoxy dimethacrylate	Matrix polymer; high molecular weight, highly cross-linked; imparts strength and reduces leaching
Triethylene glycol dimethacrylic acid	Matrix polymer; improves viscosity
Dihydroxyethyl-p-toluidine	Accelerator
Benzoyl peroxide	Initiator
Reinforcement materials	
Boro-alumino silicate glass	Radiopacity and reinforcing particles
Silica particles	Reinforcing particles; improves viscosity, handling, and mechanical strength
Combeite glass-ceramic particles	Reinforcing particles; increases bioactivity; improves mechanical strength
Silane coupling agent	Helps bind reinforcing particles to polymer matrix

vertebral body fractures. The present report reflects findings from 1-month interim data derived from an ongoing prospective, open-label, multicenter trial of Cortoss. The study was undertaken in a group of patients with moderate to severe pain associated with documented acute osteoporotic vertebral fracture, metastatic osteolytic vertebral lesion, or angioma, and was designed to evaluate the performance and safety of Cortoss in percutaneous vertebral augmentation.

Materials and methods

Study design

This ongoing, prospective, open-label, multicenter study is designed to assess the performance and safety of Cortoss in percutaneous vertebral augmentation for the management of pain and for the repair of at least one vertebral body damaged as a result of severe osteoporosis, aggressive malignant tumor, or metastasis. Patients were enrolled at nine different study sites and were evaluated at seven scheduled visits, beginning at screening and extending over a 6-month period. Interim analysis was performed when all patients had at least 1 month of follow-up.

Patients

Patients enrolled in the study were at least 18 years of age and had radiographic lesion(s) in 1–3 vertebral bodies from levels T7 to L5 that were attributed to severe osteoporosis, aggressive malignant tumor, or metastasis. At screening, participants were required to report localized pain, at the level of the treated compression fracture, whose severity the patient rated on a visual analog scale (VAS) as at least 50 mm on a scale of 0–100 mm (50%), and pain or disability requiring analgesics or lifestyle alteration. All participants were required to provide informed consent.

Exclusion criteria included neurologic deficit (other than localized pain) related to the compression fracture, radiculopathy (symptomatic herniated nucleus pulposus), and increased risk, in the opinion of the investigator, of percutaneous vertebroplasty such as advanced kyphotic deformation and/or loss of balance. Also excluded were patients with absence of integrity of the posterior vertebral wall or vertebral lesions that extended into the spinal canal, those with burst fractures, or fractures with retropulsion of the posterior wall occupying 20% or more of the surface of the spinal canal. Patients who had an active infection or bleeding disorder, who were pregnant or planned to become pregnant within 6 months of treatment, or who had participated in another investigational study within the last 30 days were also excluded. Women of child-bearing potential were admitted into the study if they used adequate contraception.

Study procedure

Patients were evaluated prospectively on the day of screening, on the day of treatment (day 1), and on subsequent follow-up visits on days 4 and 8, and after 1, 3, and 6 months. At each of these evaluations, anterior-posterior and lateral X-ray images of the thoracic and lumbar spine were taken, and patients rated their pain intensity, QoL, and level of disability using a patient-assessed VAS, which ranged from 0 to 100 (with 100 as severest pain). At baseline, on follow-up day 8, and at

months 1, 3, and 6, the Oswestry Disability Index (ODI) and the 12-item short-form questionnaire (SF-12), respectively, were administered. Patient use of concomitant medications was also recorded. At screening, a complete medical history was obtained and a physical examination was conducted. Concomitant medications, including analgesics, were administered at the discretion of the investigator; the dosages and objectives of analgesics were recorded on Case Report Forms (CRFs) at each scheduled visit.

At all follow-up evaluations, patients were questioned about the presence of any adverse events. Reports of adverse events and concomitant treatments were recorded continuously. An adverse event was defined as any untoward medical occurrence that appeared or, if preexisting, worsened from the time of enrollment to the 6-month end point in the study. Any form of leakage during the vertebral augmentation procedure was to be reported as an adverse event. Adverse events were assessed by the investigator for severity, causality, and seriousness at screening, on days 1, 4, and 8, and after months 1, 3, and 6. The original fracture or neoplasm for which a patient may have been treated was not reported as an adverse event unless the condition worsened within the 6-month follow-up period. Adverse events that were considered by the investigator to be definitely, probably, or possibly related to the device were attributed to Cortoss.

Surgical procedures

Each vertebra was localized fluoroscopically, preferably in 2 planes, and a needle was placed within the vertebral body by a transpedicular or posterolateral approach at or near the junction of the anterior and middle third of the vertebral body, approximately 1.25–1.5 cm from the anterior wall. Care was taken not to breach the anterior wall or endplates of the vertebral body. After removing the stylet, an obturator could be inserted into the needle with rotation to create a channel, if desired, to prepare for the insertion of the catheter. Ideally the catheter extended 1.25 cm from the tip of the needle (Fig. 1).

While checking for leakage into surrounding veins (including those in the epidural space and under fluoroscopic control), the surgeon injected Cortoss from a 1-ml syringe fitted with a Luer-lock connection through a catheter penetrating the anterior space of the vertebral body. If venous leakage was detected, the injection of the synthetic bone void filler was stopped and the catheter was removed to ensure patency of the needle. 2–4 min later, the injection was resumed using a new catheter. When no venous leakage was detected, Cortoss was continuously injected, refilling the 1-ml syringe as necessary to achieve the desired fill as the catheter was withdrawn from the needle. Ideally, the injection was stopped when the tip of the catheter was 2–3 mm from the tip of the needle. If this procedure did not fill the vertebra across the midline, the procedure was repeated in the contralateral hemivertebra. Up to three vertebrae were permitted to be treated per patient during a single surgery. Following surgery, patients remained recumbent for 2 h prior to loading.

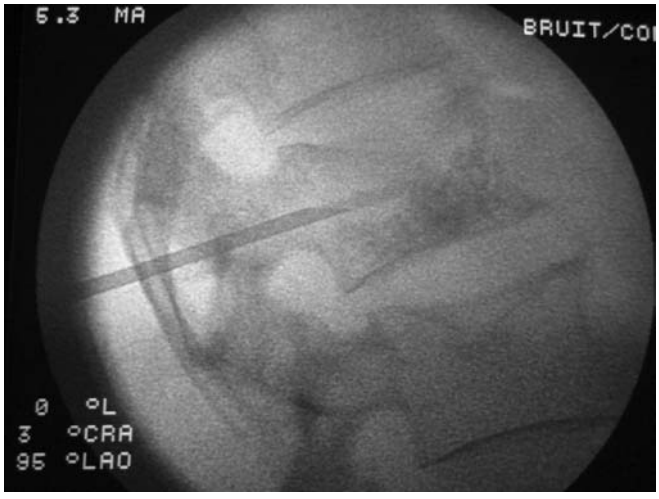


Fig. 1 Extension of catheter from tip of needle

Data analysis

Patient populations analyzed

The analysis of the safety of Cortoss injections in this study is based upon all available data from clinical assessment of enrolled patients for whom Cortoss was used. The evaluation of efficacy will be performed on an intention-to-treat (ITT) basis. The ITT population consists of the patients of the safety population for whom at least one follow-up assessment of pain is available; this population includes those patients with protocol deviations.

Primary and secondary outcome measures

The primary performance end point was change from baseline in VAS pain scores, with a decrease in score indicating improvement. The secondary performance end points were improvement in baseline QoL (which was assessed with the ODI as well as the SF-12 physical and mental component scores) [9, 23] and safety. Improvement in ODI is indicated by a decrease in score from baseline [9]. Improvement in SF-12 scores is indicated by an increase in score from baseline [23]. Safety was primarily assessed on the basis of reported and observed adverse events. Concomitant

analgesic medication use served as a secondary safety end point.

Evaluation of analgesic use was assessed by a clinician in a systematic fashion, based on lists of analgesic use reported for each individual patient. Analgesic use per patient before and after vertebral augmentation was classified according to the World Health Organization (WHO) analgesic ladder (i.e. minor analgesics, including NSAIDs and acetaminophen [WHO step 1], weak opioids including codeine, tramadol, and dextropropoxyphene [WHO step 2], and strong opioids including morphine and fentanyl [WHO step 3]). Significant change in analgesic use was defined as a change in dose of 50% or more within the same WHO class, as well as a change in WHO class. Patients for whom dosage was not specified, missing, or unclear, were considered not to have changed their pre-intervention analgesic usage.

Statistical analysis

Results from the analysis of this study's initial 1-month period are contained in this interim report. A final analysis, including the follow-up data, will be performed when all patients have completed the 5-month follow-up. For this interim report, descriptive statistics were generated for the primary pain outcome measure (decrease from baseline VAS pain scores) and secondary outcomes regarding QoL, based on scores for disability, health-related quality of life, and safety. VAS pain scores and ODI scores were further submitted to comparative statistical testing using a repeated measures analysis of variance (ANOVA). In the case of a significant time effect for either of these outcome measures, paired *t*-tests were planned to compare mean scores at successive visits. SF-12 data were not comparatively tested. All statistical tests were performed two-tailed and at the 5% significance level.

Results

Patient demographics and baseline characteristics

The demographic and baseline characteristics of ITT patients ($n = 53$) receiving treatment with Cortoss are summarized in Table 2. Patients ranged in age from 44 to 90 years (mean 67.5), and more women were included in the study than men (35 vs 18). Most patients suffered from vertebral fractures related to osteoporosis or metastasis ($n = 47$, 89%) and had experienced pain for a median of 77 days prior to study screening. For pain relief, many of these patients ($n = 24$, 41%) were receiving an opioid analgesic designated as belonging to class III (i.e., ''strong opioid'') by the WHO.

Table 2 Demographic and baseline characteristics at first augmentation (intention-to-treat population, $n = 53$)

Age (years)	
Mean (SD)	67.5 (11.12)
Range	44–90
Sex,*n* (%)	
Men	18 (34)
Women	35 (66)
Body mass index (kg/m^2)	
Mean (SD)	24.4 (4.39)
Range	15.6–39.2
Duration of pain at screening	
Median	77 days
Range	0 days–4.6 years
Origin of pain, *n* (%)	
Osteoporosis	38 (72)
Metastatic lesion	9 (17)
Osteoporosis and metastatic lesion, or other	6 (11)
Origin of compression fracture, *n* (%)	
Osteoporosis or metastasis	48 (91)
Angioma	2 (4)
Post-radiotherapy osteonecrosis	2 (4)
Myeloma	1 (2)
Pre-treated with analgesia[a], *n* (%)	
None	2 (4)
WHO class I (minor analgesic)	11 (19)
WHO class II (weak opioid)	21 (36)
WHO class III (strong opioid)	24 (41)

[a]Patients may have been pretreated with more than one class of analgesic

Details of primary surgeries

In the ITT patient population, vertebral bodies were approached transpedicularly in 62% (33/53), posterolaterally in 25% (13/53), and by both approaches in 13% (7/53). General anesthesia was used for 60% (32/53), local anesthesia for 4% (2/53), and local anesthesia with conscious sedation for 36% (19/53). A total of 83 vertebrae were augmented using Cortoss: 1 vertebra in 60% (32/53), 2 vertebrae in 28% (15/53), 3 vertebrae in 6% (3/53). Three patients in the ITT population (3/53, 6%) deviated from the original study protocol in that they received augmentation in 4 vertebrae. The mean volume of synthetic cortical bone void filler used in each vertebra was 4.3 ml (from 1.5 to 8 ml).

Patient disposition

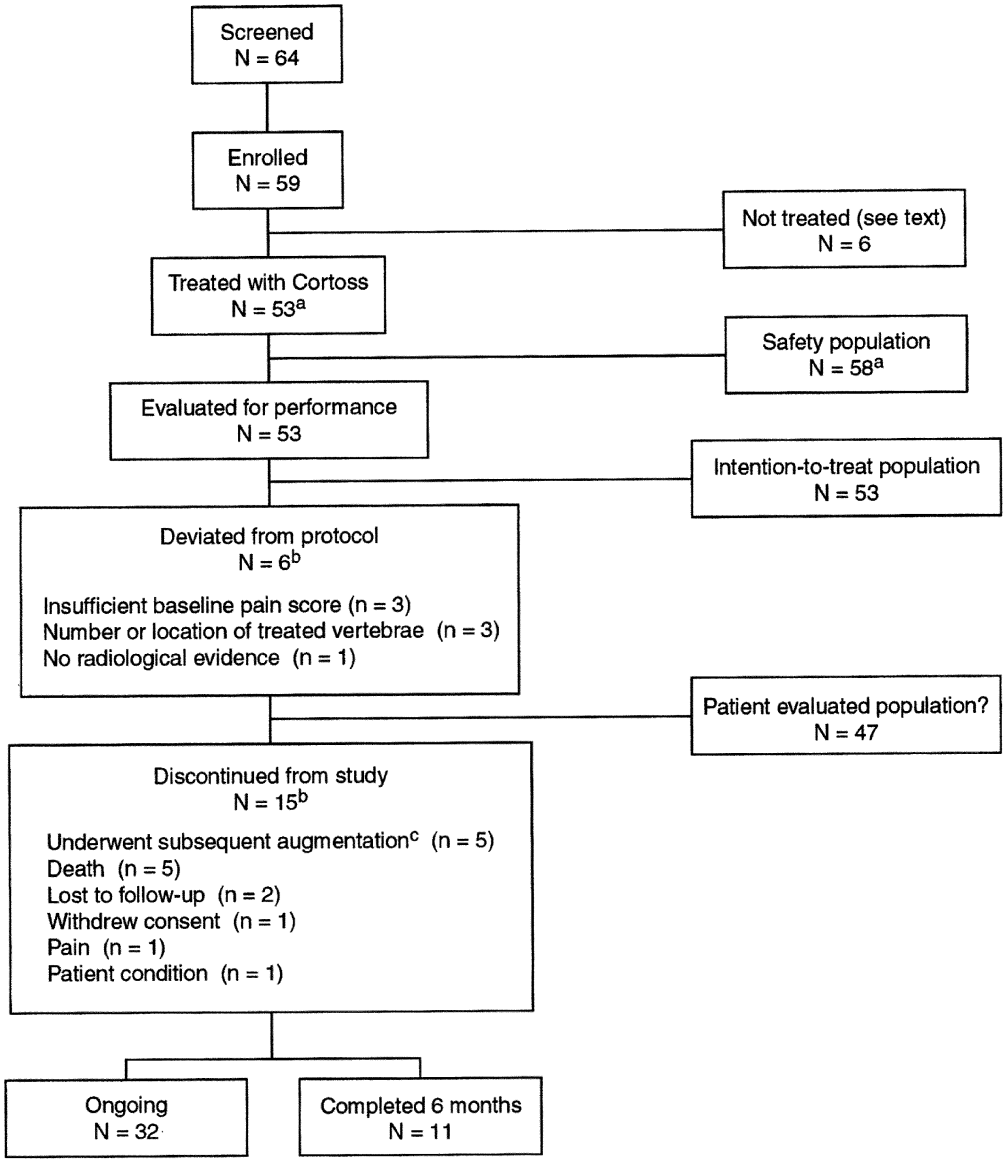
Fifty-nine of 64 screened patients from 9 centers were enrolled in this study. Of the 59 patients, 53 were in the ITT population. Six patients were not treated after enrollment - each for one of the following reasons: acute respiratory insufficiency during anesthesia, pain

spontaneously resolved, withdrawal of consent, pain not intense enough to lead to disability or analgesic treatment (inclusion criterion No. 3 was not met), kyphoplasty, and paraplegia. The disposition of all 64 patients who were screened for this study is presented in Fig. 2.

Of 15 patients who terminated the study prematurely, 5 patients were discontinued because they received second augmentations with Cortoss following secondary fractures of the treated or adjacent vertebrae (3 patients after 1 month, 1 after 2 months, and 1 after 3 months). For these patients, second vertebral augmentations were regarded as separate from their initial treatments; data from these additional augmentation procedures were included in the analysis of safety, bringing the number of augmentation procedures in the safety dataset up to 58. However, only data from the primary fracture treatment were retained in the current ITT analysis of efficacy. Five patients died (no death was attributed to Cortoss), 2 patients were lost to follow-up, 1 patient was discontinued for pain, 1 for overall condition, and 1 for withdrawn consent.

All 53 patients who were treated with Cortoss have received all evaluations up to and including the day-8 visit; 47 patients have been evaluated at 1 month; 28 patients have been evaluated at 3 months; and 11 patients have been evaluated at the 6-month study end point. Thirty-two patients continue to receive scheduled

Fig. 2 Patient disposition



evaluations. The 5 patients with secondary fractures and additional Cortoss vertebral augmentation continue to be followed up and have been evaluated at 1 month after their second augmentation procedures. These data, however, are not included in the outcomes analysis presented here.

Six patients deviated from the study protocol: 3 had baseline VAS pain scores less than 50 mm (30–47 mm - the patient with VAS of 47 mm also had no radiologic evidence of vertebral compression or fracture), and 3 were treated outside the levels of T7–L5 (1 patient had only a lesion at T5) and/or surpassed the limit of 3 augmentations stated in the study protocol. These 6 patients were included in the ITT population, and data obtained from them were evaluated to assess the performance of the device.

Clinical outcomes

Pain

At baseline, the mean VAS pain score was 69.0 (range 39–95). Following treatment, significant decreases in baseline pain severity emerged on day 4 (mean VAS 38.8; a 44% decrease) and have remained stable up to the 1-month time point ($P < 0.001$) (Table 3).

Level of disability and QoL

Planned repeated measures of ANOVA and pairwise comparisons in the ITT population indicate significantly decreased ODI scores from a baseline high of 55.0 to 47.4 on day 8, with a further significant decrease to 33.6 at 1-month post-treatment (Table 3) ($P < 0.001$). Similar improvements in QoL were also evident from improved SF-12 scores in this group of patients following treatment with Cortoss. At the 1-month evaluation, physical and mental component SF-12 scores increased from baseline (26.7 and 41.1, respectively), to 33.7 (26% improvement) and 45.6 (11% improvement), respectively.

Overall success

Nine of 11 patients who have completed the 6-month evaluation met criteria for overall success - pain reduction, improvement in QoL, and no serious adverse events.

Analgesic use and concomitant medications

After vertebral augmentation, analgesic medications within the same WHO classifications as those used prior to surgery were administered to 60% (35/58) of the 58 cases included in the safety patient population. Weaker analgesics were administered to 28% (16/58) of the patients after surgery, and stronger analgesics were administered to 12% (7/58) of the patients after surgery. The majority of patients who required stronger analgesics after surgery relative to baseline had malignant tumors at the operative site. A reduced WHO class of opioid was used in 22% (10/45) of patients who received opioids before surgery; 9 of these patients were osteoporotic.

Adverse events

The number of adverse events reported during or after 52 of 58 vertebral augmentations was 148, involving a total of 91 vertebrae (Table 4). The most reported adverse event was leakage of Cortoss outside the vertebral body, observed 64 times in 44 patients (64/91, 70% of the augmented vertebrae). Among the other adverse events considered probably or possibly related to Cortoss (20 of 148, 14%), 5 were considered to be serious (2 vertebral body fractures, 1 case of back pain related to Cortoss leakage into soft tissue, 1 case of urine retention, and 1 case of pneumonia). Adverse events not considered to be related to Cortoss (64 of 148, 43%), such as pain, anemia, and constipation, were judged to be typical among patients who are elderly or suffering from

Table 3 Percent improvements in baseline pain and disability (intention-to-treat population). *VAS* visual analog scale, *ODI* Oswestry Disability Index, *SF-12* 12-item short-form questionnaire, *na* not applicable.*P* values shown indicate significant reductions from baseline values in VAS and ODI scores, based on repeated measures of ANOVA. Comparative statistical testing was not conducted using SF-12 scores

Outcome measure	Baseline	Mean score (% improvement) [95% CI]			*P* value
		Day 4	Day 8	Month 1	
VAS pain score	69.0	38.8 (44)	39.0 (43)	31.3 (55)	0.001
ODI	55.0	-	47.4 (14)	33.6 (39)	0.001
SF-12 (physical component)	26.7	-	30.4 (14)	33.7 (26)	na
SF-12 (mental component)	41.1	-	40.7 (−1)	45.6 (11)	na

Table 4 Clinically significant adverse events attributed to Cortoss ($n = 58$). Fifty-three patients were treated with Cortoss, 5 of whom were discontinued from the study because of secondary vertebral body fractures. These 5 patients were re-enrolled into the study and received Cortoss during second surgeries. Therefore, proportions are calculated using a denominator of 58 (53 + 5)

Adverse event	Clinically significant adverse events, *n* (%)
Leakage of Cortoss	7 (12)
Pain (unspecified)	4 (7)
Back pain	4 (7)
Transient neuralgia (leg pain)	1 (2)
Fracture of adjacent vertebra	3 (5)
Refracture of repaired vertebra	2 (3)
Transient, mild paresthesia	1 (2)
Urinary retention	1 (2)
Needle stuck into polymerized Cortoss	2 (3)
Pneumonia	1 (2)
Chills and fever	1 (2)

malignancy. Six patients died during the study. None of the deaths was attributed to Cortoss. Four patients died from malignant tumors, 1 from preexisting ischemic heart disease, and 1 during anesthesia before vertebral augmentation.

Vertebral body leakage

Leakage of Cortoss outside the vertebral body (64 events) most frequently occurred into the intervertebral disk (25 times), the venous system (19 times), and the paravertebral soft tissue (10 times). The majority of the leaks (57 cases, 89%) were judged to not be clinically significant. Seven others were judged to be clinically significant (Table 4); in 6 of these cases, leakage was reported in association with either a mild complication or no apparent clinical sequelae. In 1 patient, Cortoss leaked into surrounding tissues through the needle track, where it polymerized. This severe adverse event was treated with a local injection of corticosteroid to alleviate pain.

Adjacent vertebral fractures

Fractures of adjacent vertebral bodies occurred in 21% (12/58) of the augmentation procedures contained in the safety data set from 1 to 3 months after primary Cortoss augmentation - 2 of these were attributed to Cortoss. Five patients with such fractures had a second vertebral augmentation with Cortoss - 2 augmented vertebrae refractured in 2 patients and 3 adjacent vertebrae fractured in 3 patients. All 5 of these patients were discontinued from the study because of adverse events and were subsequently re-enrolled at the time of the second interventions.

Discussion

The most common etiologies of vertebral compression fractures are metastatic cancer and osteoporosis associated with aging or chronic steroid use. Following a vertebral compression fracture, almost all patients experience a prolonged period of pain, which can last from weeks to months [20]. This study demonstrates that percutaneous vertebral augmentation with Cortoss effectively relieved the pain associated with vertebral compression fractures caused by osteoporosis or tumor, while reducing disability and improving physical function. At screening, patients reported having experienced moderate to severe pain associated with their compression fracture(s) for a median period of 77 days; 1 patient reported experiencing pain for as long as 4.6 years. Over 40% of these patients were receiving an opioid analgesic to manage their pain. Pain relief following vertebral augmentation with Cortoss was rapid and clinically significant. By day 4, 60% of these patients reported a reduction of at least 30% in baseline pain and VAS pain scores of 50 mm or less. At 1-month follow-up, pain reduction has remained stable. Reductions in pain have been accompanied by significant improvements in patient QoL marked by significant improvements in ODI scores and improved physical and mental functioning scores from the SF-12. Some patients, particularly those with osteoporosis, also exhibited reduced analgesic use.

The degree, timing, and maintenance of pain relief seen following Cortoss augmentation in the present investigation is similar to that reported with PMMA treatment of vertebral fractures in comparable patient populations [5, 12]. For instance, we observed significant (44%) reductions in VAS pain scores on day 4 after Cortoss vertebral augmentation. Moreover, as with PMMA treatment, reductions in pain among the current group of patients appear to be well maintained; continued improvements in both pain scores and QoL measures were seen at the 1 month post-augmentation evaluation [5]. Continuing improvements in pain and activity level over the first month following augmentation may be explained by possibly ongoing consolidation of the vertebrae augmented with Cortoss. Incomplete fracture immobilization at the time of the procedure may account for pain that gradually abated following surgery. By contrast, the degree to which pain persists may be at least partially attributable to adjacent fractures that may arise in these patients; such fractures may interfere with pain reduction.

While the mean level of pain reduction seen in this group of patients may not seem dramatic (mean decrease from baseline pain at 1 month 55%), this level of relief is associated with a significant resumption of daily activities and improved physical and mental functioning. Clinically significant reductions in disability and

improvements in physical function were observed in the present study. The mean ODI scores decreased 14% from baseline after 8 days and 39% after 1 month. Furthermore, the physical component of the SF-12 improved 14% from baseline after 8 days and 26% after 1 month. These results are comparable to those of Cortet et al. using PMMA (20% improvement in physical functioning after 3 days and 1 month) [5] and Zoarski et al. (18% improvement in the physical component of the SF-36 after 2 weeks) [25]. In the present study, mental function also improved, although not as dramatically as physical function. Such QoL and disability improvements may be attributed to the increased mobility and reduced pain that patients experience as a result of successful vertebral augmentation.

The small number of patients involved in the present investigation and the uncontrolled nature of the study design make it necessary to exercise caution in interpreting the current findings. For instance, in the absence of a control group, it is unclear how a similar group of patients would have fared if they had been treated with PMMA. In some PMMA case reports, underlying disease was limited to osteoporosis or malignancy, making it difficult to draw appropriate comparisons with the present group of patients, which presented mixed compression fracture etiology. Moreover, the presence of serious underlying illnesses in the patients enrolled in the present study may have contributed to the incidence of certain adverse events, including adjacent vertebral fractures. While the secondary fracture of 2 treated vertebrae in the present study was attributed by the investigator to device failure, such fractures may alternatively be attributed to bone fragility resulting from severe osteoporosis, aggressive malignant tumor, or metastasis, to increased activity following successful intervention or to device placement. The incidence of such secondary fractures, while low, appears to be consistent with that reported in a study of PMMA vertebral augmentation in osteoporotic patients. Heini et al. reported new compression fractures in 1 (6%) patient after 3 months and in 2 (12%) patients after 1 year [12] versus new compression fractures in 3 (5%) patients after 1 month in the present study.

It is also difficult to ascertain whether the reported incidence of leakage of Cortoss into surrounding tissue and vasculature in the present study (76% of 58 enrolled patients, 70% of 91 augmented vertebrae) is comparable to that in studies of PMMA. The incidence of PMMA leakage is highly variable, ranging from 20% to 73% [5, 12], because PMMA is commonly adulterated for vertebral augmentations. The comparatively high detection rate of Cortoss leakage in the current study may be partly attributable to the greater radiopacity of Cortoss relative to that of PMMA - which increased the chance of detecting even small leaks that would have otherwise gone unnoticed. The high rate of reported leakages is also very likely due to the fact that investigators were required to carefully search for and report the appearance of any leaks on postoperative images. Leakage of PMMA, in contrast, may often go undetected, contributing to the low incidence of reported leaks. In a recent report of PMMA use with X-ray-guided techniques, in which the radioopacity of PMMA was enhanced with tantalum powder, a rate of PMMA leakage (65%) was reported that is more consistent with that seen in the present investigation with Cortoss [5]. Differences in viscosities and setting times of filling agents are other likely reasons for differences in the incidence of leakage between various studies.

Conclusion

The current interim data suggest that the use of Cortoss in percutaneous vertebral augmentation, performed by adequately trained physicians, is associated with good success rates in terms of patient pain reduction, lessened disability, and improved QoL (with such improvements persisting at 1-month follow up). Reductions in analgesic use, primarily observed among patients with osteoporosis, were also observed. The ease of use relative to PMMA, the good rate of treatment success, and the low rate of device-related serious adverse events observed in the present study indicate that Cortoss is a useful option in the treatment of patients with vertebral compression fractures.

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