

An Evaluation of the Safety and Efficacy of an Alternative Material to Polymethylmethacrylate Bone Cement for Vertebral Augmentation

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ABSTRACT

The following human clinical study compared Cortoss™ Bone Augmentation Material (Cortoss) to polymethylmethacrylate (PMMA) for the treatment of pathological vertebral fractures of the thoracic and lumbar spine. It was performed in mostly elderly patients suffering from painful vertebral compression fractures (VCFs). The primary outcomes measured were pain, function, maintenance of vertebral alignment, and absence of subsequent interventions. Patients were evaluated at 72 hours as well as 1, 3, 6, 12, 24, and 36 months.

Follow-up rates were high, with over 80% of patients seen at 24 months. The results demonstrate that vertebroplasty with either Cortoss or PMMA provides a safe and effective treatment of painful osteoporotic vertebral fractures, sustaining their efficacy over time and with a low rate of serious complications. Based on the FDA-defined composite endpoint, the results confirm with a high degree of certainty the hypothesis that Cortoss is non-inferior to PMMA at 24 months. Regarding pain at 3 months and function at 24 months, the results for Cortoss are statistically significantly better than for PMMA. Moreover, Cortoss-treated patients exhibit a lower incidence of subsequent fractures, especially in patients with one level treated and no previous fractures.

Based on review of the medical literature, this study represents the largest randomized, controlled, prospective investigation of a vertebral augmentation device with long-term follow-up to date.

INTRODUCTION

Over the past 20 years, vertebroplasty has become the standard of care for vertebral compression fractures, providing effective and immediate pain relief for thousands of patients. Until now, PMMA has been established as the only viable material for use in vertebral augmentations. While acceptable, PMMA possesses several significant limitations such as a viscosity that changes with time, toxic monomer release, high exothermic reaction, and bolus-like distribution that may cause stress on adjacent vertebra.^{1,2,3} Jasper, et al., noted that a decrease in mechanical strength is an unintended consequence of adding radiopacifying agents to PMMA to allow visibility, and of altering the monomer-to-polymer ratio to lower viscosity as a means of extending its working time.² This study was conducted to evaluate whether an alternative material specifically designed for vertebroplasty provides comparable or better safety and efficacy than PMMA bone cement in vertebroplasty procedures.

Cortoss Bone Augmentation Material is an injectable, non-resorbable composite consisting of cross-linking resins and reinforcing glass ceramic particles. Included in the composite is a bioactive glass ceramic, also known as Combeite, which among other effects has been shown to cause natural hydroxyapatite to form on the material's surface and promote the direct apposition to bone over time.⁴ As part of the FDA clearance, Cortoss was evaluated in the largest randomized, controlled, prospective trial performed to date for augmentation of osteoporotic vertebral compression fractures using the vertebroplasty technique. Based on a review of the medical literature, it also is the only randomized study with long-term follow-up (24 months) in over 80% of study patients.

Each year 1.5 million osteoporotic fragility fractures are diagnosed in the United States alone, the most common being vertebral compression fractures (~750,000

per year), and these numbers are expected to rise with the aging of the baby boom generation. Between 50% and 80% of these fractures are asymptomatic and found incidentally on routine chest radiographs or clinically by progressive height loss.⁵ By current estimates, approximately 200,000 vertebral augmentation procedures (vertebroplasty or kyphoplasty) are performed annually, with growth expected due to increases in physician awareness and clinical experience, as well as expansion of the patient population.

A historical perspective of vertebroplasty

Percutaneous vertebroplasty with injectable bone cement was first performed in 1984 in France on a patient with severe cervical pain and impending vertebral body collapse due to a hemangioma. The injection of PMMA resulted in stabilization of the vertebra and complete pain relief.⁶ Over time the procedure has been modified, refined, and its indications expanded. It was introduced to the United States in the early 1990s, where the most common application today is the treatment of pain resulting from osteoporotic VCFs.^{7,8} More and more, this minimally invasive procedure is being chosen over conservative care (i.e., bed rest, analgesic use, physical therapy, bracing), as conservative therapy carries risks for the elderly population of functional decline, contractures, pressure sores, deep vein thrombosis, hypotension, decreased cardiac output, and further mineral loss of the already osteoporotic bone, and the pain relief results are variable.⁹

An overview of the current standard of care

Polymethylmethacrylate cement, while generally effective, has a variety of drawbacks. Polymethylmethacrylate must be batch mixed and follows a linear progressive

viscosity profile before finally hardening. To minimize leakage outside the vertebral body, physicians often opt for material injection at a high viscosity state. However, cement injected at high viscosity does not spread well through vertebral intra-trabecular spaces but instead forms a bolus with minimal interdigitation with the remaining trabecular bone of the vertebral body.^{10,11} While most cement leaks are asymptomatic, they can cause severe adverse effects such as pulmonary emboli, neurologic complications including paraplegia, and cardiac complications.^{12,13,14} Additionally, the two-dimensional structure of the PMMA polymer chain permits free radicals and unreacted monomers to leach out during polymerization.^{15,16} Especially in joint replacement procedures, this leachate has shown the potential to cause a severe hypotensive response in patients.¹⁷ Due to the difference in material volume, caution should be exercised when extrapolating these findings to the treatment of VCFs as the response may vary.

As PMMA polymerizes, it does so through an exothermic process that generates a significant amount of heat.¹⁸ The temperature can rise up to 100 degrees Celsius and remain in excess of 60 degrees Celsius for several minutes, potentially causing thermal necrosis and eliciting a response from the body in the form of a fibrous tissue layer around the PMMA bolus.¹⁹ This layer often includes the presence of giant cells and remnants of the radiopacifying agents added to the cement to improve fluoroscopic visualization during the injection.

Originally it was thought that thermal necrosis of nerve endings in the vertebrae was the mechanism of pain relief.¹⁹ However, a study by Belkoff and Mollow calls this into question.²⁰ A second theory for pain relief involves the chemical toxicity of the unreacted methacrylate monomer; however, measurements have shown that the concentrations of the monomer that occur in the tissues are unlikely to reach toxic levels.²¹ Current thinking follows that pain relief is caused by the vertebral augmentation procedure eliminating or greatly limiting (micro)motion at the fracture site.²² To limit motion and facilitate healing, a balance needs to be achieved between mechanical stability and flexibility^{23,24} because excessive stiffness can cause refracture to occur around the injected bone cement.²⁵

Studies have shown that a small amount of strategically placed material may be all that is needed to restore stiffness to pre-fracture levels. Large fill volumes render the system more sensitive to the location of placement because asymmetric distributions of large volumes can promote single-sided load transfer and thus lead to 'toggle'.²⁵ The lack of interdigitation seen with a bolus may be a contributing factor in adjacent vertebrae

fractures.²⁶ Finite elemental analysis shows that an interdigitated fill pattern may be better able to distribute stresses over the entire vertebra and result in a more physiological load transfer.²⁷

A new alternative

Cortoss is an injectable, bioactive material that has been designed to closely mimic the important mechanical characteristics of bone. Engineered specifically for the treatment of VCFs, it obviates many of the issues inherent with the use of PMMA bone cement.

The constant flow characteristic of Cortoss allows low-pressure, manual delivery without the need to create an artificial void or to use a high-pressure delivery tool. The dispersed fill pattern requires approximately one-third less material than the bolus fill pattern, and decreases the displacement and embolization of fat and marrow. Compared to PMMA, Cortoss is more hydrophilic, which enables the material to coat and support the existing trabecular structure rather than displacing it.

Inherent radiopacity, lower polymerization temperature, minimal leachate, and optimized mechanical characteristics all reflect that Cortoss has been formulated for safety. The benefits of this composition are: radiographic visualization without the need for secondary contrast agents, elimination of the risk of thermal necrosis, elimination of toxicity caused by released volatile monomer, and reduced stress on adjacent levels.

The mix-on-demand design of the Cortoss delivery offers a level of control and procedural flexibility not previously possible. The ready-to-use dual-chamber cartridge allows the physician full control over material delivery timing. The low-pressure, low-inertia delivery provides easy intra-operative handling and stops quickly when the injection pressure is released, minimizing the risk of extravasation.

MATERIALS AND METHODS

This study, which was conducted under an Investigational Device Exemption (IDE) granted by the Food and Drug Administration (FDA), evaluated the safety and effectiveness of Cortoss as compared to PMMA bone cement in vertebral augmentation using the vertebroplasty technique. The study hypothesis formulated at the outset was that Cortoss is non-inferior to PMMA at 24 months with a confidence interval (CI) of 90% and a δ of 12.5%. Conducted at 21 sites in the United States over a three-year period beginning February 2004 and ending February 2007, 256 patients suffering from pain associated

with osteoporosis-induced vertebral compression fractures (Cortoss, n=162; PMMA, n=94) were enrolled in the randomized, controlled, prospective clinical trial.

The majority of patients in both the Cortoss (124 patients) and control (75 patients) groups underwent single-level procedures. Of the remaining 57 patients, all but two underwent two-level procedures – one Cortoss and one control patient were treated at three levels.

On average, 51.7% more material was used for each level treated with PMMA (3.49 cc) when compared to Cortoss (2.30 cc). Cortoss was delivered using a co-axial catheter method that is part of the Aliquot™ Delivery System. No specific delivery system requirements were in place for PMMA cases; investigators used their system of choice. The majority of patients in both groups (64.2% Cortoss, 67.0% control) were treated under local anesthesia with conscious sedation.

Surgical characteristics were similar between the two groups, with a mean procedure duration of 30.8 minutes for the Cortoss group and 30.7 minutes for the control group for single-level treatment; the average duration for two or more levels was 43.7 minutes in both groups.

Outcome measures

A primary composite endpoint was used to assess clinical outcomes. The primary measures and their definitions of success were as follows: (1) Pain: an improvement of at least 20 points on the Visual Analogue Pain Scale (VAS) and an overall VAS score of no more than 50 on a 100-point scale, (2) Function: maintenance or improvement in Oswestry Disability Index (ODI), (3) Stability: maintenance of vertebral height and alignment (an independent radiologist blinded to treatment assignment developed and applied a consistent method for analyzing vertebral height and alignment), and (4) Safety: no device-related subsequent surgical interventions at the study treated level.

Secondary endpoints included the following four measures: (1) pain medicine usage, (2) ODI walking score, (3) quality of life score through the Short Form 12 (SF-12), and (4) patient satisfaction surveys. In addition, overall safety was assessed through the regular assessment of neurological status and the recording and analysis of all adverse events.

Patient evaluations were made at the following intervals: baseline, on the day of treatment before and after the procedure, and post-surgically at 72 hours, 1 week, 1 month, 3 months, 6 months, 12 months, and 24 months. In addition, data were collected for a number of patients at the 36 month time point. The protocol and follow-up regimen were consistent with the requirements

as described in the FDA guidance for studies on vertebral augmentation devices (www.fda.gov/cdrh/ode/guidance/1543/pdf).

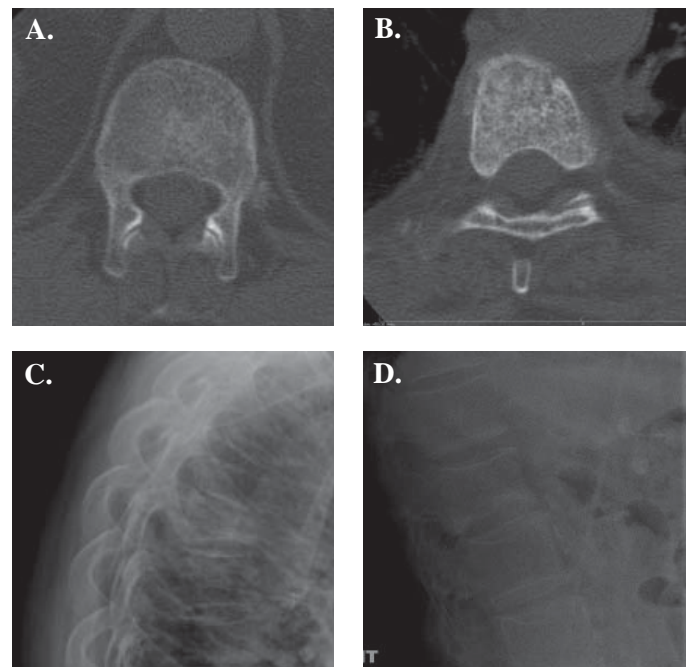


Figure 1. Pre-operative evaluations included imaging studies to assess the baseline condition. Axial CT and lateral x-rays identify the fractured levels in patients randomized with Cortoss (A & C) and PMMA (B & D).

Patient demographics

Patient demographics of the two study groups were similar, except that at study entry a larger proportion of the Cortoss group had respiratory comorbidities (39.5% Cortoss vs. 24.5% control), and more PMMA patients had nervous system comorbidities than Cortoss patients (16.0% Cortoss vs. 36.2% control). The median age of the patients in both groups was 78. The mean height and weight were also similar (approximately 65 inches and 152 lbs.). Also well matched was gender, with 71.6% females in the Cortoss group and 77.7% females in the control group.

Patients entered the study reporting a duration of pain that ranged from less than six weeks to greater than one year. The majority of patients in both groups (48.8% Cortoss, 53.8% control) entered the study with between 6 and 12 weeks of back pain, and most experienced an increase of daytime bed rest of between 2 and 4 hours. As would be expected in an elderly population with osteoporosis, 99.2% of patients entered the study with multiple comorbidities, including respiratory, nervous system, cardiovascular, urinary, gastrointestinal, reproductive, skin, endocrine, immunological, psychological, EENT, head and neck, and other conditions. Nearly 80% had cardiovascular

comorbidities, and 76.6% had spinal comorbidities, which could have a significant impact on clinical evaluations using VAS and ODI measures.

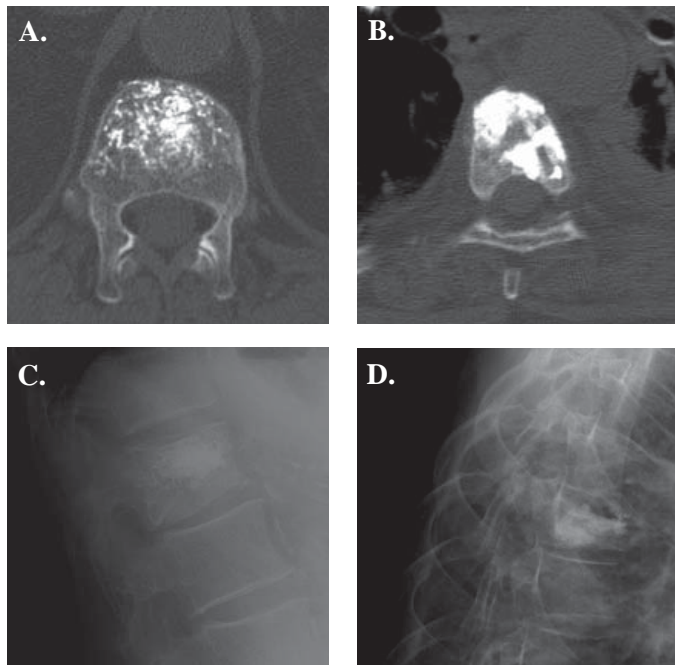


Figure 2. The post-operative axial CT and lateral X-ray images clearly show the more interdigitated fill pattern in the vertebral body treated with Cortoss (A & C) versus the more bolus fill with PMMA (B & D).

Analgesic usage at baseline was slightly higher in the Cortoss group (90.7%) than in the control group (86.2%), while back brace usage was slightly higher in the control group (19.1%) than in the Cortoss group (12.3%). The number of patients with previous fractures was similar (34% Cortoss and 33% control).

Initial VAS and ODI function scores were comparable in the two groups. The VAS baseline score averaged 80 in the Cortoss group and 78 in the control group. The average ODI score was 60 in both groups.

RESULTS

In accordance with the pre-defined statistical analysis plan for this study, non-inferiority was determined at the 24 month time point using the primary composite endpoint. To be considered a success for the composite endpoint, patients were required to be a success for every primary safety and efficacy measurement (pain, function, maintenance of height and alignment, and no subsequent intervention). The results confirm the hypothesis that Cortoss is non-inferior to PMMA in the vertebral augmentation procedures for VCFs. This conclusion can be drawn with a higher degree of certainty than originally anticipated, with a confidence interval of 95%, and a δ of 10%. Regarding the individual outcome measures and the results at other follow-up

time points, there were no significant differences between Cortoss and PMMA, except as noted in the following table.

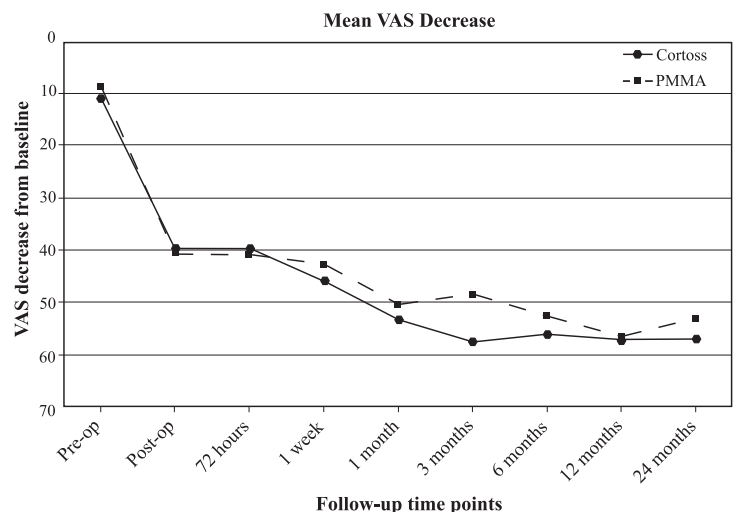
Individual Component and Combined Endpoints at 3 and 24 Months

	Cortoss		PMMA	
	3-Month	24-Month	3-Month	24-Month
Improvement in VAS Score (≥ 20 mm improvement + VAS score ≤ 50 mm)	116/134 (86.6%) ^[1]	101/123 (82.1%)	57/76 (75.0%) ^[1]	54/69 (78.3%)
Maintenance or Improvement in ODI Score	127/134 (94.8%)	119/123 (96.7%) ^[1]	75/76 (98.7%)	61/69 (88.4%) ^[1]
Maintenance of Vertebral Height and Alignment	132/133 (99.2%)	113/115 (98.3%)	76/76 (100.0%)	63/63 (100.0%)
No Subsequent Device-Related Surgical Intervention at Index Treatment Level(s)	135/137 (98.5%)	122/124 (98.4%)	77/77 (100.0%)	70/70 (100.0%)
Combined Treatment Success 24 Months ^[1]	111/134 (82.8%)	90/117 (76.9%)	56/76 (73.7%)	47/64 (73.4%)

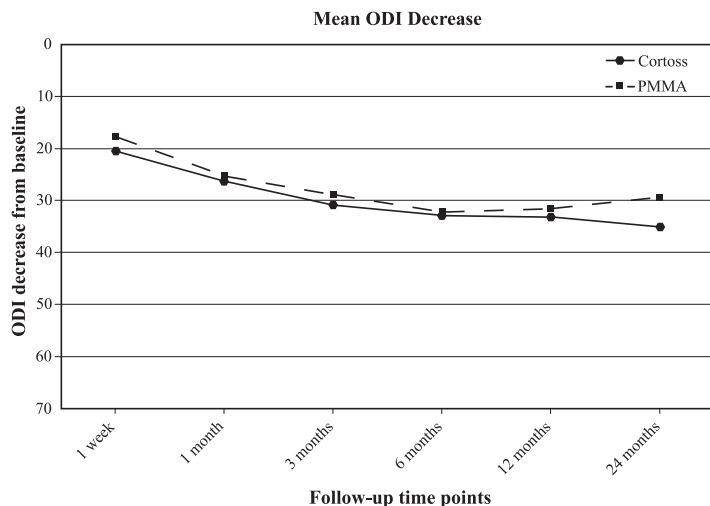
^[1] Significant difference Cortoss over PMMA at $p < 0.05$, Fischer Exact Test

With regard to individual endpoints, a statistically significant greater percentage of Cortoss patients (86.6%) than PMMA patients (75.0%) were a success for pain at 3 months, a difference of 11.6% ($p < 0.05$). The same is true for function at 24 months, when 96.7% of Cortoss patients met the definition of success as opposed to 88.4% of PMMA patients, a difference of 8.3% ($p < 0.05$). At these time points the average improvements in VAS and ODI also were significantly greater. The difference in function results at 24 months was further confirmed by a significant difference ($p < 0.05$) in the physical functioning ability as measured by the SF-12.

The following graph shows the average decrease in pain from baseline for both groups, demonstrating that Cortoss consistently provides equal or better (3 months) pain relief compared to PMMA.



The graph below depicts both materials' effect on patients' functioning. The values are the average decrease in disability, or improvement in functioning, at each time point.



Maintenance of vertebral height and alignment in each group was closely matched at all assessment intervals. On the basis of subsequent surgical interventions, two of the 162 Cortoss patients were considered a failure by requiring surgery at the treated site. One of these was for intercostal neuritis and one for further fracture. Both were treated successfully, the latter with Cortoss.

Pain medication usage dropped steadily and significantly for both groups over time, with 90.7% of Cortoss patients and 86.2% of the PMMA patients using an analgesic at baseline and declining to 44.1% of Cortoss patients and 40.0% of PMMA patients at the 24-month evaluation.

Physician ease-of-use ratings of both materials was high, with a higher proportion of physicians – 63% – rating Cortoss as “very easy” compared to 54% who gave PMMA that same designation.

Both Cortoss and PMMA patients exhibited leaks in exactly 63.8% of levels treated. Most of these were asymptomatic and mentioned only for completeness of the study results, as they are not comparable to leaks that cause symptoms. Two Cortoss patients (1.2%) and 1 PMMA patient (1.1%) had clinical symptoms caused by a leak. One Cortoss patient had a ‘pipe’ of Cortoss in the soft tissue overlying the vertebra, which after steroid injections failed to provide relief and, therefore, was removed by a minor surgical procedure. All symptoms then resolved. The second Cortoss patient, who had an epidural leak, experienced a thoracic radiculopathy which was successfully treated with a Medrol Dose Pack. The PMMA patient had an epidural leak and experienced increasing pain at the level treated. This did

not respond well to various therapies and resulted in prolonged pain and discomfort. These symptomatic leaks occurred relatively early in the series. Based on preliminary quantitative analysis of 101 patients (BioImaging Technologies, Newtown, PA), the volume of Cortoss leaks tended to be less than the volume of PMMA leaks, paralleling the lower volume of Cortoss injected. More detailed analyses are being done.

The incidence of serious adverse events that were reported as related to the procedure or the device was low in both groups – 4.3% in each. These events included new fractures, muscle spasm, hypertension, and redness at the incision site.

New fractures at any level occurred more in the PMMA group than in the Cortoss group – 31.9% vs. 27.8% of patients, respectively. Studies have shown that the presence of multiple existing VCFs at baseline substantially increases the risk of developing a new VCF.^{28, 29} Patients with no previous fracture at study outset and with only one level treated comprise a “virgin back” subset of patients, which provide a more homogeneous basis for comparison of the two treatments. In this study there were 112 “virgin back” patients. In this group, 27.3% of the PMMA patients developed a new fracture while for Cortoss patients the rate was 17.6%. This represents a decreased incidence of 35% for the Cortoss group versus the PMMA group. In these patients the incidence of fractures at an adjacent level was also higher in the PMMA group – 18.2% – than in the Cortoss group – 10.3% – representing a decreased incidence of 43% in Cortoss patients. Because of the relatively small numbers, this trend did not reach significance.

DISCUSSION

The study reported here is the largest randomized, controlled, prospective investigation of vertebroplasty with long-term follow-up in patients treated for osteoporotic VCFs completed to date. Cortoss and PMMA patients were well-matched elderly cohorts with a median age of 78. The only exceptions were respiratory ailments, more prevalent in the Cortoss group, and neurological disorders, more common in the PMMA group.

This study demonstrates vertebroplasty to be a safe and effective treatment for osteoporotic VCFs, irrespective of the material used. Using stringent criteria, the clinical benefits of vertebroplasty can be measured and are maintained for at least two years after the procedure.

The results also prove with a high level of certainty (i.e., a CI of 95% and a δ of 10%) that Cortoss is non-inferior to PMMA at 24 months, and significantly better

than PMMA for some parameters at certain time points. Cortoss provides statistically and clinically better results over PMMA in the areas of pain reduction at 3 months as measured by VAS and in function at 24 months as measured by the ODI. These observations suggest that more effective pain relief in the early stages may lead to better functional outcomes in the long term. It is also notable that these results were obtained by a group of clinicians who were specifically chosen for their experience and acumen using PMMA in this setting but who had no experience with the use of Cortoss with its different flow characteristics and delivery tools.

The data also show a lower incidence of subsequent fractures in the Cortoss group, especially in first-time patients with one level treated. While these differences do not rise to the level of statistical significance, the reason for this observation may be found in the specific biomechanical conditions created by Cortoss because of its trabecular distribution, mechanical characteristics, and lower volume. Future studies will explore these observations in more detail.

CONCLUSIONS

Both Cortoss and PMMA bone cement provide effective and safe treatment of painful osteoporotic vertebral fractures, sustaining their efficacy over time with a low rate of serious complications. Cortoss consistently appears to yield slightly better results with regard to pain and function at all time points beyond one week. In addition, the use of Cortoss appears to reduce the incidence of subsequent fractures, possibly due to its trabecular distribution, mechanical characteristics, and reduced volume as compared to PMMA

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