Vertebroplasty Using Calcium Triglyceride Bone Cement (Kryptonite™) for Vertebral Compression Fractures

A Single-Centre Preliminary Study of Outcomes at One-Year Follow-up

GIANLUIGI GUARNIERI¹, MARIO TECAME², ROBERTO IZZO¹, PASQUALE VASSALLO¹, ANGELA SARDARO², FRANCESCA IASIELLO², CARLO CAVALIERE¹, MARIO MUTO¹

¹Neuroradiology Service, Cardarelli Hospital; Naples, Italy

²Radiology Service, Seconda Università degli Studi di Napoli SUN; Naples, Italy

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Summary

This study assessed the one-year clinical and radiographic outcomes, in terms of pain-relief, vertebral re-fracture and complications, after vertebroplasty (VP) using a new osteoconductive cement (calcium triglyceride bone cement - Kryptonite™ bone cement, Doctors Research Group Inc., Southbury, CT, USA) to treat osteoporotic vertebral compression fractures.

Sixteen consecutive osteoporotic patients (12 women and four men, mean age 68+/-10.5) were treated with VP using Kryptonite™ bone cement for a total of 20 vertebral fractures. All the patients complained of a pain syndrome resistant to medical therapy and all procedures were performed under fluoroscopy control with neuroleptoanalgesia using a monopedicular approach in 12 patients and bipedicular approach in four patients. All patients were studied by MR and MDCT and were evaluated with the visual analogue scale (VAS) and the Oswestry disability index (ODI) before treatment and at one and 12 months after the procedure.

A successful outcome was observed in 80% of patients, with a complete resolution of pain. Differences in pre and post treatment VAS and ODI at one-year follow-up were significant ($P<0.0001$). We observed a disk and venous

leakage in 66% of patients but only in one case did an asymptomatic pulmonary embolism occur during cement injection. Two cases of vertebral re-fractures at distant metamers were observed during follow-up.

VP using Kryptonite bone cement is a helpful procedure that allows complete and long-lasting resolution of painful vertebral symptoms. The cost of the material is very high and the rate of disk and venous leakage is too high compared to standard cement.

Introduction

Vertebroplasty (VP) is a percutaneous minimally-invasive technique introduced in clinical practice by Galimbert and Deramond in 1987¹. It consists in a transpedicular approach introducing acrylic material, polymethylmethacrylate (PMMA), into the vertebral body that has become pathological^{1,2}. The main indications are osteoporotic and non-osteoporotic vertebral fractures, primary and secondary vertebral tumours and symptomatic vertebral haemangioma. The aim of the procedure is to stabilize the fractured vertebra obtaining an antalgic effect by PMMA injection into the vertebral body^{3,4}. The 2007 consensus statement developed by

the American Society of Interventional and Therapeutic Neuroradiology, Society of Interventional Radiology, American Association of Neurological Surgeons/Congress of Neurological Surgeons, and American Society of Spine Radiology recognized this technique as a safe, efficacious, and durable procedure in appropriate patients with vertebral compression fractures (VCFs) by⁵. However, the *extra-vertebral leakage* of cement into the spinal canal or into the pre/paravertebral venous plexus, with consequent compression of nerve structures or pulmonary embolism, and the *vertebral re-fracture* risk at adjacent or distant metamers remain the main limitations of this procedure.

In order to reduce or influence VP complication rates, new biodegradable bone cement substitutes with different activity and different grades of viscosity have recently been developed as alternatives to PMMA thanks to their biocompatibility or absorbability and stiffness or mechanical or bone-remodelling proprieties^{6,7}.

Calcium triglyceride bone cement (Kryptonite™ bone cement, Doctors Research Group Inc., Southbury, CT, USA) is a non-toxic biocompatible polymer derived from castor oil with adhesive, bioabsorbable and osteoconductive properties. The opacity of the material is

guaranteed by barium sulphate (67%) mixed with calcium carbonate (33%). The cost of this cement is more than double that of standard PMMA.

The aim of this preliminary study is to assess the one-year clinical and radiological outcomes, in terms of pain relief, vertebral re-fracture and cement leakage, after VP using Kryptonite™ to treat of osteoporotic VCFs.

Materials and Methods

No approval from the ethical committee was required because VP is considered a standard rather than experimental treatment. Informed consensus was obtained for all patients.

From January 2011 to December 2011, 16 consecutive osteoporotic patients (12 women and four men, mean age 68+/-10.5) were treated with VP using bio-absorbable calcified triglyceride Kryptonite™ bone cement (Doctors Research Group Inc, Southbury, CT, USA) for a total of 20 metamers. All the patients complained of a pain syndrome resistant to medical therapy, whereas patients with diffuse not circumscribed pain, systemic or local infectious disease, or uncorrectable coagulation disorders

Table 1 Patients' VAS and ODI data before vertebroplasty and at the end-point with p value.

PATIENTS	PRE-VAS	POST-VAS	PRE-ODI	POST-ODI
1	10	6	47	22
2	10	8	50	31
3	9	6	44	17
4	10	6	41	17
5	10	2	46	11
6	10	6	50	32
7	10	4	50	17
8	10	6	46	17
9	10	5	47	32
10	9	4	47	32
11	10	6	50	32
12	10	5	45	17
13	9	6	47	22
14	10	6	47	22
15	9	6	50	17
16	8	5	50	17
P VALUE	P <0.0001		P <0.0001

Figure 1 A-G) (Left to right) A 75-year-old woman complained of a pain syndrome resistant to medical therapy. A) Sagittal STIR MRI showed a VCF at L4 with a hypersignal due to bone marrow oedema. B-D) PA fluoroscopy control before, during and after VP using bioabsorbable calcified triglyceride Kryptonite™ bone cement (Doctors Research Group Inc., Southbury, CT, USA). E-G) Thoracic-lumbar axial and sagittal MPR MDCT reconstruction showed a stable result with no evidence of new VCFs at adjacent or distant metamers at 1-year follow-up.

Figure 2 Joined distribution of VAS score before and after VP. The mean preoperative VAS of 9.63 ± 0.15 dropped to 5.44 ± 0.33 . The two-tailed P value was < 0.0001 . By conventional criteria, this difference is considered to be extremely statistically significant ($p < 0.0001$, $t = 11.76$).

Figure 3 Joined distribution of ODI score before and after VP. The mean preoperative ODI scale of $47.31\% \pm 0.66$ dropped to $22.19\% \pm 1.8$ at 1-year follow up. The two-tailed P value was < 0.0001 . By conventional criteria, this difference is considered to be extremely statistically significant ($p < 0.0001$, $t = 15.2$).

were excluded. Patients were studied by MRI (protocol: Sagittal T1W, T2W and STIR) and MDCT with MPR and were evaluated with the visual analogue scale (VAS) and the Oswestry disability index (ODI) before the treatment

and at one day and 12 months after the procedure, when they underwent thoracic-lumbar MDCT at one-year follow-up.

All the procedures were performed by interventional neuroradiologists under fluoroscopy

control and under neuroleptoanalgesia, by a monopedicular approach in 12 patients and by a bipedicular approach in four patients, using a 13 G bevelled needle. Once the mixture of the material was obtained, the bioabsorbable calcified triglyceride Kryptonite™ bone cement was injected with a 1 ml syringe. The amount of cement injected varied depending on the grade of vertebral collapse while the injection was always performed under fluoroscopic guidance with a slow and careful injection of cement.

Our endpoints were to evaluate: 1) pain relief according to VAS and ODI at one-month and one-year follow-up; 2) the incidence of disk or venous leakage; 3) the incidence of vertebral compression re-fractures at distant or adjacent metamers.

Statistical Analysis

Data were exported and analysed using the Sigma-Plot 10.0 program with Sigma Stat 3.0 integration (SPSS Erkrath, Germany). Data were analysed by two-tailed matched-pair t-test (* $p \leq 0.01$; ** $p \leq 0.001$). All data shown are the mean $\pm$ SEM (Table 1).

Results

The results were analysed by two generalists neuroradiologist, according to VAS and ODI methods before treatment and at one day and 12 months after the procedure performing thoracic-lumbar MDCT at one-year follow-up. A successful outcome was observed in 80% of patients within one month, with a complete resolution of pain symptoms and a reduction of four points on the VAS and 20% on ODI at one-day follow-up (Figure 1).

The mean baseline VAS was 9.63 ± 0.15 . The mean VAS score after VP at one-year follow-up had decreased to 5.44 ± 0.33 . The two-tailed P value was less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant ($p < 0.0001$, $t = 11.76$) (Figure 2). The mean baseline ODI scale was $47.31\% \pm 0.66$. The mean ODI score after VP at one-year follow-up had decreased to $22.19\% \pm 1.8$. The two-tailed P value was less than 0.0001. By conventional criteria, this difference is considered to be extremely statistically significant ($p < 0.0001$, $t = 15.2$) (Figure 3).

We observed disk and venous leakage in ten

out of 16 patients (66%), but only in one case did an asymptomatic pulmonary embolism occur during cement injection that did not require medical therapy. At 12-month follow-up thoracic-lumbar MDCT control, only two of the 16 patients had developed symptomatic vertebral re-fractures at distant metamers which had been augmented by traditional PMMA cement VP.

Discussion

Despite the success of VP in reducing pain, the procedure has several potential drawbacks including extravertebral leakage of cement into the spinal canal or pre/paravertebral venous plexus - with consequent compression of nervous structures or pulmonary embolism - and an increased vertebral re-fracture risk at distant or adjacent levels after treatment. However, these two "limits" are recognized to be similar to the natural history of porotic patients or they depend on the type of procedure and cement used.

Polymethylmethacrylate (PMMA) bone cement is the material most commonly used during vertebral augmentation procedures. It is reportedly bioinert, easy to handle with a good biocompatibility over long-term follow-up, and cost-effective. On the other hand, PMMA's mechanical and biologic properties may not be ideal: it has no biologic potential to remodel or integrate into the surrounding bone, no direct bone apposition, high polymerization temperature, potential monomer toxicity and especially excessive inherent stiffness which contributes to increase the rate of vertebral re-fracture or leakage.

The prevalence of extravertebral leakage is directly related to the pressure regulation capability of the injection, the low viscosity of the cement and the type of VCF. It occurs more frequently in metastatic vertebral fractures (30-60% of cases) and less often in osteoporotic fractures (10% of cases)⁸.

Different risk factors contribute to VP-related complications such as patient age, sex, spinal deformity, fracture age, level, type, the presence of an intravertebral cleft and/or cortical disruption on preoperative MR, and the viscosity of the bone cement used. It is well-demonstrated that high fracture severity grade and low viscosity of PMMA are general, strong, and independent risk factors for cement leakage. For cortical leakage (in 95% intradiscal leakage),

the presence of cortical disruption on MRI and an intravertebral cleft on MRI are identified as additional strong risk factors⁹.

Clinical studies have shown that the risk of leakage is greater as the volume of injected PMMA increases¹⁰ and biomechanical studies suggest that factors such as the placement and viscosity of the injected cement may also be important¹¹⁻¹³. However, the rate of leakage complications can be reduced considerably by increased operator experience and especially using a denser cement.

Thanks to the development of new more viscous materials, the rate of venous leakage, especially in osteoporotic fractures, has now dropped to 0.5-1%⁸.

The cause of vertebral re-fractures at distant or adjacent metamers remains controversial and complex. Even if re-fractures are the natural evolution of osteoporosis disease with a 19.2% risk of developing new fractures in the year after the first VCF¹⁴⁻¹⁶, they could be recognized by the post-VP spinal biomechanical modification increased by different property and stiffness grade of the cement used¹⁷⁻¹⁸. PMMA is the most widely employed commercially available cement 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 surrounding nerve structures may be ambiguous. However, data on its mechanical and bone integration properties are clear. Young's modulus of PMMA (1.8-3.1 GPa) is significantly higher than that of normal bone, thus interfering mechanically with the load stresses and preventing surrounding bone remodelling; in case of osteoporotic bone, PMMA strength is eight to 40 times higher. Such high stiffness may account for the risk of re-collapse of the spared, not impregnated, cancellous bone of the same vertebral body and the risk of incidental adjacent fractures⁷.

Recently, new filler materials such as bioactive or osteoconductive biodegradable bone substitutes, (synthetic bone substitutes, composite resin materials, calcium phosphate or calcium sulphate cements) have been developed to reduce the VP-related complication rate (leakage and post-VP re-fracture) and to

improve biocompatibility and absorbability¹⁹⁻²⁰ thanks their different grade of viscosity, absorbability and stiffness or bone-remodelling proprieties which might make them alternatives to PMMA⁶⁻⁷.

The rationale of the ideal bone substitute lies in specific biomechanical and biological properties to support the spinal column. In fact, once deposited into a load-bearing environment, they are able to withstand cyclic and static complex loading patterns. They have the ability to be resorbed at a rate equal to new bone ingrowth, achieving complete bone remodelling and healing, while being able to tolerate the motion-load stresses the spine usually undergoes without modifying spinal biomechanics. Different types of osteoconductive cement have been developed such as Cerament™ (Spine Support AB, Lund, Sweden), calcium phosphate cement (Bonesource; Stryker Orthopaedics, Mahwah, NJ, USA) and calcium triglyceride bone cement (Kryptonite™ bone cement, Doctors Research Group, Southbury, CT, USA)^{6,7,21-25}.

Cerament™ consists of resorbable calcium sulphate (60%) and hydroxyapatite (40%) with osteoconductive properties; the hydroxyapatite acts as a slow or non-absorbable framework that slows down the absorption rate of calcium sulphate and at the same time acts as an osteoconductive template for new bone ingrowths. The mechanical properties, low stiffness of the device, and the bone remodelling processes decrease the shear stresses at the bone/Cerament border. Masala et al. reported on 80 patients who underwent VP with no intraprocedural or periprocedural complications, except small cement leaks, and no cases of new adjacent vertebral at one-year follow-up^{7,21}.

Calcium phosphate cement offers the potential for reabsorption of the cement over time and replacement with new bone as a biological method to restore vertebral body mass and avoid any potential thermal effects of PMMA²¹. Nakano et al. reported that among 86 consecutive osteoporotic patients who underwent VP with calcium phosphate cement, 21 had newly developed vertebral fractures including eight vertebral fractures at an adjacent level (9.3%). In their series, they reported no pulmonary cement embolism but there was a small amount of cement leakage into the spinal canal in seven cases (6.6%), into the intervertebral disc in seven cases (6.6%), and into the paravertebral muscle in one (0.9%)²²⁻²⁴.

Calcium triglyceride bone cement is a non-

toxic biocompatible polymer derived from castor oil with adhesive, bioabsorbable and osteoconductive properties. It has been approved by the FDA and received a CE mark. It is made of a bioabsorbable calcified triglyceride, which is extremely adhesive with bone-like mechanical properties. The adhesive bonds specifically and directly to bone and within 24 hours results in rigid bone fixation and stability. The porous network within the product allows osteo-integration with host bone over time. The unique property of this material resides in its osteoconductivity secondary to its porous structure that develops once hardened; moreover it is reabsorbed over time and is replaced with bone²⁵.

In our very small preliminary series we recorded only two cases of vertebral re-fractures but only at distant metamer level during the one-year follow-up that seems to be recognized as the natural evolution of osteoporosis disease rather than a post-VP related complication. No symptomatic intraprocedural or periprocedural leakages were reported, but ten out of 16 cases (66%) of disk and venous leakage were observed with one case of pulmonary leakage that remained completely asymptomatic. This rate of disk and venous leakage was higher than that of other new or conventional cements^{7,8,21-24} and could be due to the fact that the cement is difficult to handle even if it is injected very slowly

and under continuous fluoroscopy control. In our institution, we perform about 250 VP/year using different devices and bone cements. Kryptonite bone cement could be a good cement thanks to its osteoconductive proprieties but its high rate of leakage and high cost compared to other bioactive bone cements do not justify its utilization.

This preliminary study has several limitations: it is a single-centre recruitment, non-randomized series with a small cohort of patients but with a follow-up up to one year. Our endpoints were pain relief, evaluation of leakage and vertebral re-fractures, without data on vertebral augmentation or any study of Kryptonite stiffness or mechanical or bone remodelling proprieties. Future improvements are recommended.

Conclusions

Kryptonite bone cement, a new osteoconductive cement for vertebral augmentation, showed immediate and long-term effectiveness leading to immediate and long-lasting pain relief, improved quality of life, and absence of any device-related complication but with a higher cost and higher rate of disk and venous leakage compared to other materials, including new incidental adjacent fractures.

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Gianluigi Guarnieri, MD
Neuroradiology Service
Cardarelli Hospital
Via A. Cardarelli 8
80122 Naples, Italy
Tel.: 00393473549657
Fax: 00390817473125
E-mail: gianluigi@guarnieri@hotmail.it