
DOI: [http://dx.doi.org/10.1016/j.spinee.2016.06.011](http://dx.doi.org/10.1016/j.spinee.2016.06.011)

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Date deposited: 10/08/2016

Embargo release date: 30 June 2017
Abstract: Background Context Percutaneous vertebroplasty is a surgical minimally invasive procedure and is frequently needed in humans for surgical treatment of vertebral fractures. It depends on cement injection into the vertebral body and achieves rapid and significant pain relief.

Purpose The testing of novel biomaterials depends on suitable animal models. The aim of this study was to develop a reproducible and safe model of percutaneous vertebroplasty in sheep.

Study Design Ex vivo and in vivo large animal model study (Merino sheep).

Methods Ex vivo vertebroplasty was performed through a bilateral modified parapedicular access in twenty four ovine lumbar hemivertebrae, divided into four groups (n=6). Cerament™ (Bone Support, Sweden) was the control material. In the experimental group a novel composite was tested - Spine-Ghost® –, which consists of an alpha-calcium sulphate matrix enriched with micrometric particles of mesoporous bioactive glass. All vertebrae were assessed by microCT and underwent mechanical testing. For the in vivo study sixteen sheep were randomly allocated into control and experimental groups (n=8), and underwent percutaneous vertebroplasty using the same bone cements. All vertebrae were assessed post-mortem by microCT, histology and rt-PCR.

This work has been supported by the European Commission under the 7th Framework Programme for collaborative projects (600,000-650,000 USD).

Results In the ex vivo model the average defect volume was 1275.46 ± 219.29 mm3. Adequate defect filling with cement was observed. No mechanical failure was observed under loads which were higher than physiological. In the in vivo study cardiorespiratory distress was observed in two animals, and
one sheep presented mild neurological deficits in the hind limbs, before recovering.

Conclusions
The model is considered suitable for pre-clinical in vivo studies, mimicking clinical application. All sheep recovered and completed a 6 month implantation period. There was no evidence of cement leakage into the vertebral foramen in the post-mortem examination.
PERCUTANEOUS VERTEBROPLASTY: A NEW ANIMAL MODEL


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Abstract

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Introduction

Percutaneous vertebroplasty (PVP) is a minimally invasive technique of vertebral augmentation for compression fractures. Its aim is to augment and stabilize the defective vertebral body by percutaneously injecting a material that will fill the bone defect, thus achieving immediate pain relief and functional recovery [1-5].

Sheep are considered a suitable model for biomedical research due to availability, low cost, easy handling and housing, and good homogeneity (when selected for age, breed, and sex) [6]. Moreover, due to the anatomical similarities to human bones (regarding weight, size, structure, remodelling process and biomechanical behaviour) [7-9], sheep are considered a good model for orthopaedic research [6,8].

To date only a small number of PVP studies have been performed in animals. Most were executed using “open surgery” techniques, wherein an incision through the skin and muscles is made to expose the vertebrae [10-12]. Studies using minimal invasive techniques, including the ones with a modified parapedicular approach, encountered varied issues, including cement leakage into the vertebral foramen [6], incomplete defect filling or lack of information on postoperative evolution [13, 14].

Our study aimed to develop ex vivo a reproducible and feasible model of percutaneous vertebroplasty, and its use in vivo. A large animal model was used based on Merino sheep due to its potential to support pre-clinical translation [7-9]. Consideration of the differences between sheep and human vertebrae [6] resulted in the development of a modified approach, enabling the creation of large enough defects as to ensure testing of novel biomaterials without neurological or biomechanical compromise [15].

Material and methods

Ex vivo model development

Animal model

Twenty four vertebral segments (L4-L6) were excised from 8 skeletally mature Merino sheep, collected from cadavers from different sources, with no access to further information on their background. The segments were randomly distributed (n=6) into four groups: A – intact vertebrae; B – vertebrae with
defects; C – vertebrae with defects injected with a well-known biphasic commercial cement, Cerament™; and D – vertebrae with defects injected with a novel composite – Spine-Ghost® –, which consists of an alpha-calcium sulphate matrix enriched with micrometric particles of mesoporous bioactive glass [16]. Soft tissue was extracted, and the spinous and transverse processes were removed, using a bone saw, in order to fit the vertebrae into the microCT chamber while preserving the vertebral arch. Vertebrae were stored at -18°C.

**MicroCT assessment**

All vertebrae underwent initial microCT scanning (Skyscan 1174, Kontich, Belgium) while still intact. The vertebrae were posed in a rotation stage fixed by commercial play-dough, with their longitudinal axis matching the system’s rotational axis. Scans were performed with 50 kVp, 800 µA, and a 1 mm aluminium filter. The pixel size was 62.08, exposure time 2200 ms, rotation step 0.8°, full rotation over 360°, with 2 average frames per image. Each vertebra went through two consecutive automated scans (oversize scan), over approximately 110 min, to assure the imaging of the whole vertebral body, comprising 906 cross-sections. The cross-section images were reconstructed using N-Recon software (Skyscan, Kontich, Belgium). The following parameters were evaluated in the analyzing software (CTAn, Skyscan, Kontich, Belgium): vertebral body height (VBH), endplates area, and trabecular bone mineral density (BMD). A uniform threshold method was applied.

**Bone defect creation**

In all vertebrae from groups B, C, and D vertebral body defects were created, in order B-C-D, under visual and tactile control and fluoroscopic guidance (Digital C-Arm ZEN 2090 Pro, Genoray, Co., Ltd., Korea). With the vertebrae fixed in a radiolucent table, in their ventral position, an osteo introducer system (Medtronic Spine LLC, Portugal) was used to create two interconnected defects (one in each side of the cranial hemivertebra). A 3.5 mm-blunt stylet was positioned through a 4 mm-cannula to manually access the dorsolateral cortex of the vertebral bodies – between the pedicles and transverse processes of each vertebra in a parapedicular approach. The stylet was then removed and a 3.35 mm-manual drill was advanced towards the centre of the cranial hemivertebra – orientation: 30-50° regarding a transverse plane
(figure 1); 0º-30º regarding a frontal plane (figure 2), creating a V-shaped defect of two intersecting cylinders. Bone debris were removed from the defects.

**Cement injection**

Group B vertebrae defects remained empty. Vertebrae defects from groups C and D were injected with their corresponding cement. During the vertebroplasty procedure all vertebrae were fixed in a radiolucent table and injected under fluoroscopic guidance. Biomaterial injection was performed using a bone filler system device (Medtronic Spine LLC, Portugal). Cerament™ and Spine Ghost® were prepared at room temperature, according to the manufacturers’ instructions. Regard was taken towards handleability, injectability and radiopacity.

All these vertebrae underwent rescanning using the same procedure as outlined above for initial scanning. In CTAn a volume of interest (VOI) was defined for each bone defect and its area was calculated. Cement distribution and integrity of the anatomic structures were assessed. Vertebrae were stored at -18ºC, with vertebrae from every group undergoing the same number of freezing and thawing cycles.

**Mechanical testing**

After vertebroplasty all vertebrae were mechanically tested under axial compression to assess stiffness and fracture strength. End caps for the vertebrae were made using polymethylmethacrylate resin (PMMA, Vertex Cold Cure), with care taken to try to keep the two outer flat surfaces parallel. The tests were conducted using a Shimadzu Autograph AG-50 kNG, Shimadzu Corporation, Japan. The load was applied over a ventral point of the vertebral bodies relative to 25% of their heights with a crosshead speed of 2 mm/s.

**Statistical analysis**

Results from the microCT analysis (vertebral body height, bone mineral density and volume of interest of each bone defect), and stiffness assessment, were analysed using SPSS 22. One way ANOVA analysis
was performed. Normality was verified using the Kolmogorov-Smirnov test, homogeneity of variance was verified with resource to Brown-Forsythe test and means compared using Tukey.

**In vivo model application**

**Animal model**

Animal handling and surgical procedures were conducted according to European Community guidelines for the care and use of laboratory animals (Directive 2010/63/UE) and after obtaining approval from the national competent authorities [17-19]. Sixteen skeletally mature female Merino sheep with an average body weight of 56.8±5.3 kg underwent PVP, divided in to two groups: Group E (n=8), a control group injected with Cerament™; and group F (n=8), an experimental group injected with a novel biphasic cement, Spine-Ghost®. Prior to surgery the animals fasted for 24 hours.

**Anaesthetic protocol**

The animals were pre-medicated with atropine (0.05 mg/kg subcutaneous), xilazine (0.1 mg/kg intramuscular), butorphanol (0.01 mg/kg intravenous) and carprofen (2 mg/kg subcutaneous); induction was achieved with thiopental sodium 5% (5-10 mg/kg intravenous) and maintenance with isoflurane 1-2% under spontaneous ventilation. After pre-medication the sheep were inducted and positioned in ventral decubitus with the hind limbs retracted caudally and fixed to the surgery radiolucent table (figure 3). The surgical field was prepared with povidone-iodine solution and alcohol at 70º and the anaesthetic monitoring equipment was connected to the animal (figure 4). Anaesthetic monitoring included: cardiac electric activity; respiratory rate; partial CO₂ concentration in expired air; partial blood O₂ concentration and non-invasive arterial blood pressure. Orogastric intubation was performed.

**Surgery**

L4 was identified under tactile and fluoroscopic guidance (Digital C-Arm ZEN 2090 Pro, Genoray, Co., Ltd., Korea) and 2.5 mm surgical osteo introducer stylet (Kyphon, Express®, Osteo Introducer® System, size 2, Medtronic Spine LLC, Portugal) was positioned inside a 3 mm cannula approximately 2-3 cm
apart from the spine midline in a 45º angle regarding a transverse plane. At this point, the surgical
instrumentation was introduced, crossing the skin and muscles, until the vertebra was reached. As
advocated in the *ex vivo* study, the access point into the vertebral body was the space between the pedicle
and the cranial side of the transverse process.

After penetrating the cortical bone of the vertebral body, the osteo introducer stylet was replaced by a 2.5
mm precision manual drill which advanced 1 to 2 cm until reaching the cranial hemivertebra’s midline
(orientation: 30-50º regarding a transverse plane; 0º-30º regarding the frontal plane). The same procedure
was performed contralaterally, and care was taken to interconnect both defects and extend them as much
as possible, again creating a V-shaped defect (figure 5).

**Biomaterial injection**

Cerament™ and Spine-Ghost® were prepared at room temperature, according to the manufacturers’
instructions. The osteo introducer system was replaced by a nozzle (Kyphon® Express™ Bone Biopsy
Device size 2, Medtronic, Portugal) and sterile cement was injected into the defect, under fluoroscopic
guidance, using a bone-filler system device (Medtronic Spine LLC, Portugal). The mean time of injection
was one minute (as shown in the animation Online Resource 1) and the injected volume was
approximately 1.2 mL (figure 6).

**Post-surgery**

After injection all sheep remained anaesthetized for two hours, assuring immobilization to allow the
curing process of the cement. Upon recovery, sheep were moved into a pen, inside the Veterinary
Hospital of the University of Évora, and treated with amoxicillin and clavulanate acid (15 mg/kg, once a
day, subcutaneous), carprofen (2 mg/kg, once a day, subcutaneous) and butorphanol (0.15 mg/kg, twice a
day, intramuscular), for 7 days. Fifteen days postsurgery a fluorochrome (calcein green, 15 mg/kg) was
subcutaneously injected, and sheep were released into the pasture. Another fluorochrome (alizarin
complexone 25 mg/kg) was subcutaneously injected two weeks before sacrifice. After six months of
implantation time, the animals were sacrificed by pentobarbiturate intravenous injection. Biological
response and material integration were assessed by micro-CT, histological studies and rt-PCR.
Results and Discussion

Ex vivo model

A known limitation of the ovine vertebral model is the anatomical differences from human vertebrae. Due to the orientation angle of the lumbar facet joints and pedicles, and the relatively short and sagitally oriented pedicles, a conventional transpedicular approach is associated with the risk of pedicle fracture and vertebral foramina disruption. Additionally, the access angle is limited, resulting in smaller and isolated defects.

Previous studies have detected cement leakage into the vertebral foramen in more than half the injected vertebrae [6]. To overcome these limitations, a parapedicular approach limited to the cranial hemivertebrae was developed [15], since the nutritional foramina are very prominent and act as low resistance accesses to the vertebral foramen. Precaution had to be taken to preserve vertebral and nutritional foramina in order to prevent neurologic and vascular complications.

The surgical limitations were: the high trabecular bone density; the hardness of the cortical bone of ovine lumbar vertebrae when compared with human; and the wide lumbar vertebrae nutritional foramina (figure 7). The L6 vertebrae, due to its shortness may be more prone to vertebral foramina disruption with the described technique. The resulting interconnected bone defect is illustrated in figure 8, but minor cement leakage into the vertebral foramen was observed in two out of six vertebrae in the ex vivo study.

This model could potentially be used with alternative percutaneous vertebral augmentation techniques, most obviously kyphoplasty, as long as adequate-size instrumentation and suitable means for creating a bone defect in the highly dense trabecular network of the vertebral body was ensured. Application for SKyphoplasty would depend on the ability of the plastic device to break through the trabecular structure; however, since this technique demands a larger cannula and only a fixed degree of expansion of the devices is possible, its use would also be highly dependent on proper sizing of the instrumentation [4, 20].

The mean total VBH (n=24) was 37.10 ± 1.80 mm; the mean total BMD (n=24) was 0.3512 ± 0.0493 gcm⁻³; and the mean total defect VOI (n=18) was 1275.46 ± 219.29 mm³. Individual group results are shown in table 1 and the distribution of defect VOI values is shown in figure 9. Despite being randomly distributed into the groups, vertebrae from group D showed lower VBH and lower BMD values. This may be explained because of individual anatomic differences between the vertebrae, which came from different sources with no background information available. Besides that, defect VOI values from group
D showed less variance than those values from the other groups, perhaps due to the surgeon gaining more experience of the technique (as the B-C groups were completed before the D group), since this is a novel approach that requires high precision to manually drill the interconnected bilateral bone defects without disrupting the vertebral and/or nutritional foramina. No statistically significant differences were found between these three groups for defect VOI values. On the basis of the defect VOI and consistent defect morphology the procedure is considered reproducible.

MicroCT information of the distinctive characteristics of ovine vertebrae facilitated decisions regarding the surgical entry points and orientation angles for accessing each vertebral body. This enabled the creation of defects without disrupting cortical bone or the vertebral and nutritional foramina. On the other hand, MicroCT analysis revealed small disruptions of the vertebral foramen in 25% of the vertebrae (figure 10), which was expected to decrease with further training and with the use of slightly smaller instruments (which were chosen for the in vivo procedures).

Cerament™ was easy to handle, with 8-10 minutes setting time, good injectability and a high radiopacity compared to bone (due to the presence of iohexol). Its higher radiopacity enabled visualization of the cement whilst injecting (figure 11) [21]. However, iohexol generates artefacts in the microCT images that prevent a correct evaluation of the cement inside the bone defect, impairing the evaluation of injected cement volume and the determination of possible leakage (figure 12).

Spine Ghost® was also easy to handle, with a smaller setting time than that of Cerament™’s, and good injectability, but only moderate radiopacity (conferred by its bioactive glass-ceramic phase [22]). MicroCT images suffered from fewer artefacts, but the material was harder to visualize during injection. A typical mechanical compression test trace is shown in figure 13a. All vertebrae withstood compressive loads much higher than the peak loads expected under physiological conditions (~1.3 kN). A vertebral stiffness was calculated from the slope of the linear section of the curve (typically this involved calculating the gradient at loads of between 2 and 5 kN). The net stiffnesses are shown in figure 13b. As BMD values were significantly lower in group D, and bone mass parameters (i.e., BMD and BV/TV) are strongly correlated with failure load, compressive stiffness, and work to failure [23], a normalised vertebral stiffness was calculated by dividing the vertebral stiffness by the BMD value of each vertebra, as shown in figure 13c. No statistically significant differences were found in stiffness or normalized stiffness between the different groups.

The developed model is reproducible and safe under much higher loads than would arise physiologically.
In vivo model

As noted previously, the in vivo procedure was performed informed by the ex vivo results. The chosen vertebra to create the bone defect was L4. The endplate height is higher, potentially permitting bigger defects than L6 would. In the second sheep intervened, from control group E, rupture of the ventral cortical bone of the vertebral body occurred, with cement leakage to the vertebral body ventral surface. During the cement injection, an abrupt drop in the arterial blood pressure was observed (probably due to pulmonary fat embolism [24, 25]), the animal went into cardiovascular arrest, and cardiopulmonary resuscitation manoeuvres were performed. No secondary neurological reactions were subsequently observed in this sheep. The fourth sheep (group E) also suffered abrupt arterial blood pressure decrease during cement injection. In order to prevent any other cardiovascular changes in the other sheep the injection speed was reduced, thus reducing the cement injection force. No further cardiovascular changes were observed in the other animals. In two sheep from the control group, contact between the two bilateral connected defects wasn’t wide enough and the cement could only be injected from only one side without risking leakage. In these two cases the defect was filled bilaterally. All sheep remained anaesthetized for two hours after injection, then recovered well and rapidly stood up and began to eat.

One sheep of the first group that underwent surgery developed proprioceptive deficits of the hind limbs, due to cement leakage around the defect entry point affecting the spinal nerve roots, but the sheep remained ambulatory. After approximately two months the animal had fully recovered.

In vivo procedures were successful with all animals completing the 6 months implantation period.

Ancillary imaging was crucial in offering visualization of vertebral landmarks and complementing the surgeon’s visual and tactile control. It is also important to emphasize that constant anaesthetic monitoring by a qualified veterinary enabled prompt intervention when necessary.

At the end of the in vivo study, microCT scanning was performed. The artefacts caused by iohexol in Cerament™ were less prominent due to cement resorption and new bone formation (figure 14). Iohexol may also cause hypersensitivity responses and we suspect that one of the animals developed a transient mild angioedema after PVP due to it. MicroCT analysis revealed small disruptions of: (i) the vertebral foramina in 26.7% of the vertebrae (figure 15), (ii) the vertebral cortex in 13.3% of the vertebrae, and (iii) the nutritional foramina in 20% of the vertebrae (n=15). Nevertheless no cement leakage was observed.
into the vertebral foramina, which is in accordance with the low number of animals presenting post-
surgical neurological deficits, even if mild (1 out of 16), and with the high survival rate (100%) obtained.

Biological response and material integration were also assessed by histological studies and rt-PCR.

**Conclusions**

A new ovine model for percutaneous vertebroplasty has been developed. The surgical technique
described, first developed *ex vivo*, is reproducible and safe under physiological loads. The model is
innovative both in approach and design – interconnected defects created bilaterally in each cranial
hemivertebra, allowing a controlled volume of cement to be injected with a low risk of leakage. This
model enabled a much safer approach to the *in vivo* procedure with a survival rate of 100 percent. Though
requiring surgical expertise, the procedure is suitable for pre-clinical *in vivo* studies, mimicking clinical
applications.

**Conflict of interest** The authors have no potential conflict of interest.

**References**


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21
22 **Figure Captions**
23
24 **Fig. 1** 3D partial reconstructed L4 showing the instruments’ orientation regarding a transverse plane
25 **Fig. 2** 3D partial reconstructed L4 showing the instruments’ orientation regarding a frontal plane
26 **Fig. 3** Anaesthetized sheep, with the surgical location (over the lumbar vertebrae) already clipped and
27 sheep’s position supported with foam wedges
28 **Fig. 4** Anaesthetic monitor providing data from the sheep
29 **Fig. 5** C-Arm image showing a L4 with an interconnected defect, in a dorsoventral projection
1. Fig. 6 C-Arm image showing Cerament™ filling the interconnected defects (*in vivo* study), in a dorsoventral projection.

2. Fig. 7 Scan image of an ovine lumbar vertebra showing the wide nutritional foramen (white arrow).

3. Fig. 8 3D partial reconstructed L4 showing the interconnected defect (white arrow).

4. Fig. 9 Defect VOI’s values distribution showed in a histogram with normal curve (SPSS 22 graph).

5. Fig. 10 MicroCT scan image of a L4 showing the disrupted vertebral foramen (white arrow).

6. Fig. 11 C-Arm image showing a L4 with defect injected with Cerament™, in a dorsoventral projection.

7. Fig. 12 MicroCT scan image of a L4 showing the artefact caused by Cerament™.

8. Fig. 13a Compression testing of vertebra with Cerament™ filled defect.

9. Fig. 13b Vertebrae stiffness (groups A-D) (SPSS 22 graph).

10. Fig. 13c Vertebrae normalized stiffness (groups A-D) (SPSS 22 graph).

11. Fig. 14 MicroCT scan image of a L4 injected with Cerament™, from the *in vivo* study, showing cement resorption, new bone formation and no artefact.

12. Fig. 15 MicroCT scan image of a L4 injected with Cerament™, from the *in vivo* study, showing a potential cortical disruption of the vertebral foramen (white arrow).

13. Video_1 C-Arm film showing Cerament™ filling the interconnected defects (*in vivo* study), in a dorsoventral projection.

14. Table 1 Descriptive statistics analysis for vertebrae groups (n=24).
<table>
<thead>
<tr>
<th>Vertebrae Groups</th>
<th>N</th>
<th>VBH [mm]</th>
<th>BMD [gcm$^{-3}$]</th>
<th>Defect VOI [mm$^3$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A – intact vertebrae</td>
<td>6</td>
<td>38.13 ± 2.01</td>
<td>0.397 ± 0.010</td>
<td>-</td>
</tr>
<tr>
<td>B – vertebrae with empty defect</td>
<td>6</td>
<td>37.19 ± 2.03</td>
<td>0.359 ± 0.056</td>
<td>1160.99 ± 168.26</td>
</tr>
<tr>
<td>C – vertebrae with Cerament®</td>
<td>6</td>
<td>37.23 ± 1.61</td>
<td>0.358 ± 0.029</td>
<td>1308.03 ± 312.36</td>
</tr>
<tr>
<td>D – vertebrae with Spine- Ghost</td>
<td>6</td>
<td>35.86 ± 0.96</td>
<td>0.292 ± 0.019</td>
<td>1357.35 ± 112.17</td>
</tr>
</tbody>
</table>

VBH – vertebral body height; BMD – bone mineral density; Defect VOI – defect volume of interest.
Figure 9

Defect VOI Distribution

Mean = 1275.46
Std. Dev. = 219.295
N = 18
*Disclosure - Joana Reis

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