CAPÍTULO 15

PHYSICAL DISTRIBUTION AND RADIOLOGICAL CONTRAST OF CEMENTS IMPLANTED *IN VITRO* VERTEBRAE

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ABSTRACT: Vertebroplasty and Kyphoplasty have been studied for several years as percutaneous procedures for treatment of bone fractures, osteoporosis and other abnormalities in the skeletal system. Currently, these procedures have already been established as effective minimally invasive surgical procedures very promising in orthopedics and traumatology. Those procedures are guided by fluoroscopy using radiopaque substances such as barium sulfate ($BaSO_4$). The improvements of the radiological contrast at the image is still necessary. In present study, we addressed the benefits of Hydroxyapatite (HAp) as radiopaque element in the bone cement and the possibility of removing barium sulfate to reduce the toxicity of the material.

KEYWORDS: Bone cement, Hydroxyapatite, Radiological contrast.

DISTRIBUIÇÃO FÍSICA E CONTRASTE RADIOLÓGICO DE CIMENTOS IMPLANTADOS NAS VÉRTEBRAS *IN VITRO*

RESUMO: La Vertebroplastia e Cifoplastia foram estudadas por vários anos como procedimentos percutâneos para tratamentos de fraturas ósseas, osteoporose e outras anomalias no sistema esquelético. Atualmente, esses procedimentos já tem sido estabelecidos como procedimentos cirúrgicos minimamente invasivos muito promissórios na ortopedia e traumatologia. Aqueles procedimentos estão guiados por meio da fluoroscopia usando substâncias radiopacas tais como sulfato de Bário $BaSO_4$. As melhoras do contraste radiológico na imagem é ainda necessário. No presente estudo, encaminhamos os benefícios do Hidroxiapatita (HAp) como o elemento radiopaco no cimento ósseo e a possibilidade da remoção do sulfato de Bário para reduzir a toxicidade do material.

PALAVRAS-CHAVE: Cimento ósseo, Hidroxiapatita, Contraste radiológico.

1 I INTRODUCTION

A procedure was developed and first described in France in 1987 known as Vertebroplasty used as a percutaneous technique by means of an acrylic injected with a syringe into the fractured vertebra body. In the surgical context to this procedure, it is a minimally invasive technique for ambulatory nature. The technique was initially implemented for the treatment of vertebral hemangiomas and later was applied for decompression of fractures of osteolytic metastases and osteoporosis. Another percutaneous technique was introduced with use of PMMA (polymethylmethacrylate with chemical nomenclature $[CH_2C(CH_3)(CO_2CH_3)]_n$) as bone cement to join the fractured bone parts. In addition, it has been inserted into a balloon that it is inflated in order to restore the anatomical structure of the vertebra. Such percutaneous technique is known as Kyphoplasty. One of the major problems of the percutaneous techniques is the possible extravasations of cement outside the bone region where it aims to be located. One solution to this undesirable event is the decompression of the vertebra by re-intervention by surgery (CHEN; LUO; ZHANG; NALAJALA *et al.*, 2013; GERSZTEN, 2007; HENDRICKSON; SHEHATA; KIRCHNER, 1976). These percutaneous procedures are complementary to therapeutic treatments within tumor control (KANEKO; SEHGAL; SKINNER; AL-GHAZI *et al.*, 2010). In most cases patients have advanced metastatic disease stage and the radiation therapy is palliative. Some studies have proposed IMRT (Intensity Modulated Radiotherapy) or IGRT (Image-Guided Radiotherapy) as therapeutic treatments with less neurological impact on the marrow. Although demyelinating phenomenon of nerve tissues may occur since such structures are highly radiosensitive; it presents in lesser extension with IMRT and IGRT (EMAMI; LYMAN; BROWN; COLA *et al.*, 1991; RYU; FANG YIN; ROCK; ZHU *et al.*, 2003; RYU; JIN; JIN; ROCK *et al.*, 2007; YAMADA; BILSKY; LOVELOCK; VENKATRAMAN *et al.*, 2008). At 2006, other options have been proposed in the field of radiation therapy based on the idealization of radioactive bone cement by our research group (MONTAÑO; CAMPOS; LEMOS; YOSHIDA *et al.*, 2020). Such radioactive cement was addressed to treat bone metastases dealing with the elimination of the clonogenic properties of the cancer cells together with the reinforcement of the bone structure. At 2009, it has been followed by the use of Quadramet (^{153}Sm-EDTMP) administered percutaneously in the affected region by means of protocol Khyphoplasty (Kyphon) (ASHAMALLA; CARDOSO; MACEDON; GUIRGUIS *et al.*, 2009).

There are a number of biophosphonates considered bioceramics which have already been studied. Among those that can highlight is the Hydroxyapatite (HAp with chemical nomenclature $[Ca_5(PO_4)_3(OH)]$), contains 69% of its composition equivalent to naturally bone and the 20% of collagen matrices fibers as connective tissue. Therefore, since HAp is part of the nature of the bone, it has already been proposed to be mixed with the PMMA reaching optimal adhesion's response of osteoblasts in the biomaterial (DOROZHKIN,

2009; 2010; HIRSCH; ROSENSTEIN; MEDICH; MARTEL *et al.*, 2009).

Considering the cement implant, the improvement of the radiological contrast at the image is still necessary. In present study, we addressed the benefits of HAp as radiopaque element in the bone cement and the possibility of removing barium sulfate to reduce the toxicity of the material. Radiological images from X-ray and Ultrasonography are evaluated in cement implants in vertebrae.

2 | METHODS

2.1 *In vitro* anatomical sample preparation

The separation of a section of a pig vertebral column, in a special cut provided by a meat market, was performed *in vitro* embed in an equivalent muscle tissue, maintaining anatomically its structure without considering distinct anthropometric characteristics of the model. The structure was immediately cooled to -18 C to reduce the effect of decomposition.

2.2 Synthesis of the composite

The composite was prepared in cold based on PMMA, HAp, barium sulfate so that the dilution held excess water as dissolvent. The solution in deionized water was done primarily to modulate the phases of the acrylic in order to increase the polymerization time by mean of stirring of the mixture. Both PMMA as the instruments in the mixture were also cooled due to polymerizing effect that is proportional to the temperature increase. The HAp was synthesized by the sol-gel method according to (LEGEROS; LIN; ROHANIZADEH; MIJARES *et al.*, 2003; MONTAÑO; CAMPOS; LEMOS; YOSHIDA *et al.*, 2020) after to mix the components the solution was left for 24 hours in a closed beaker to force the precipitate's product, the nucleation and formation of colloids. The compounds used for the synthesis of HAp were 3.937 g of $Ca(NO_3)_2 \cdot H_2O$, 0.69 mL of H_3PO_4, 2 mL of $CH_3(OH)$ and water as solvent in excess. Subsequently the sample was heated in an oven ramped from room temperature to 100 °C for 22 hours as follows: from room temperature to 80 ° C at a rate of 0.306 $°C.min^{-1}$, then an isotherm 360 minutes, subsequently to 100 °C a ramp at the rate of 0.333 $°C \cdot min^{-1}$ and finally an isotherm 720 minutes. The next day, the sample was heated from room temperature to 720 °C at a rate of 6 $°C \cdot min^{-1}$, then 60 min isotherm. The HAp powder is macerated and mixed in different proportions with the PMMA (Metil Etil Metacrilate ($C_5H_8O_2$)) to produce 0.5 g of bone cement in a binary system (1-x)PMMA-xHAp, where [x] is the concentration of HAp in the mixture as shown in Table 1. The concentrations (1) and (2) were presented in this preparation only.

Nº	Concentration [x]	PMMA ($C_5H_8O_2$)	HAp($Ca_5(PO_4)_3(OH)$)
1	0.00000	0.50000	0.00000
2	0.50000	0.08310	0.41690

Table 1. Concentrations [x] bone cement to produce 0.5 g of the binary system (1- x)PMMA-xHAp.

2.3 Cement injection

The cement was injected into vertebral models designed in the laboratory drilling the vertebral body with a bent 45° to the midsagittal plane simulating drilling needle Vertebroplasty kit.

2.4 Radiological contrast

The X-ray machine used was the BR 100, a transportable model with performance 100 mA and 90 kV. The BR 100 is composed with an X-ray tube sealed and linked to a telescope that is connected to the apparatus column than have an arm which allows depending on the movement necessary adjustment of the distance between tube and film that is studied radiographically. It also has a command table with the control elements necessary for desired voltage and intensity. According to the radiological techniques, exposure time of 0.50 s, current of 70 mA, voltage of 60 kV and DFF of 85 cm were applied in thoracic vertebrae. After the development processing, films were digitized to study the radiological contrast in each of the vertebrae that was implanted the bone cement. Contrast was evaluated in different points.

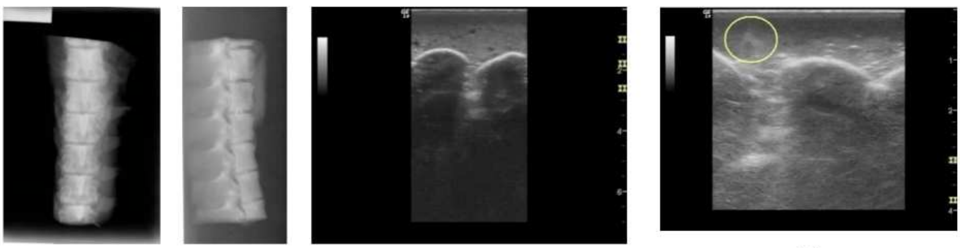
2.5 Ultrasonography images

The GE Healthcare ultrasound equipment LOGIQe REF. 5199704 made in China in 2008 was used for image guided in the Vertebroplasty simulating procedure with the pig vertebral column. One 12L-RS probe was used in B-cine mode with a signal of 12 MHz and with a maximum depth of 7 cm for the configuration abdominal type examination in addition before to the application of the contact gel for pig column model in vitro. In the second image signal was 10 MHz and the depth of field of ultrasound was defined to 4 cm.

3 I RESULTS

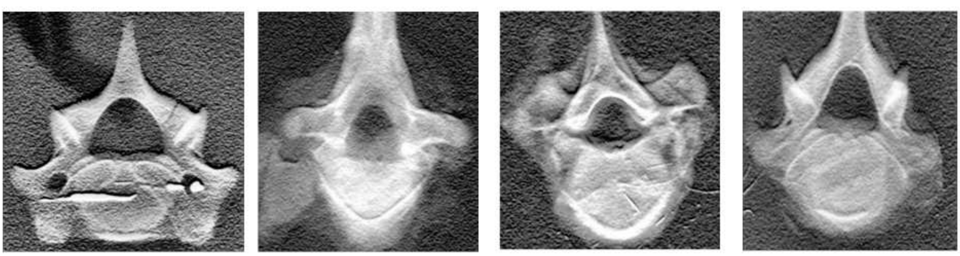
The images of the phantom taken with radiology team have good contrast even though the parts are embedded in a tissue simulating equivalent soft tissue. According to Fig. 1(a), an anterior-posterior frontal shot was made, in which the X-ray beam had to overcome apart phantom also the styrofoam lid container 2 cm that contains. The polystyrene and the surrounding soft equivalent tissue have a lower attenuation coefficient than to bone tissues.

In Fig. 1 (b), a side-sagittal image was shooting. The x- rays had to overcome two lids that are part of styrofoam container with 2 cm every one, maintaining good contrast. In Fig1(c) and Fig. 1(d), images provided by ultrasound equipment, simulating the lumbar puncture protocol, are presented. A good contrast of the spinous processes, transverse and upper and lower joints, is observed. Just as the needle is guided by the spinous processes in the lumbar puncture for patients in gestation, it is possible to do the same in Vertebroplasty, with the difficulty of invading the field temporarily while the needle is inserted into the body of the vertebra. However, to control the flow of cement during insertion fluoroscopy is necessary.



(a) (b) (c) (d)

Figure 1. X-ray and ultrasound images in vitro from vertebrae model is presented. In (a) and (b), frontal and sagittal radiological images are observed, respectively. In (c) and (d), there are ultrasound images; and, (d), a dynamic anomaly shows the insertion of the needle.



(a) (b) (c) (d)

Figure 2. Radiological images of four vertebral models. In (a) the vertebrae has molten lead. (b) PMMA injected. (c) PMMA + 10% $BaSO_4$ were injected. (d) x = 0.5 of the bone cement.

The following images as shown in Fig. 2 were taken from four vertebral bodies. In Fig. 2(a), one of them is observed with an inlay of a small mass of lead in the linear shape that will be used as reference point to evaluate the radiological contrast of the other three images. In Fig. 2(b), a vertebral body with an abnormality is observed corresponding to the perforation made to the vertebral body in which PMMA was injected. In Fig. 2(c), it was injected PMMA with 10% $BaSO_4$ and no abnormalities indicating that the cement was largely diffused in bone piece. In Fig. 2(d), polymerizing bone cement (1-x) PMMA-xHAp with a concentration [x], x = 0.5 HAp in the mix was injected. As in Fig. 2(c) the cement is well spread in the bone piece and with better contrasts which identifiable in the area of the perforation of the vertebral body. An interesting aspect was that, despite $BaSO_4$ suppress in the bone cement, this still shows a good radiological contrast.

The physical distribution of this biomaterial was observed through X-ray images after application of the cements in liquid phase. It has been spread 5 up to 20 mm into the vertebrae from the inject point. It demonstrated that such biomaterial can be incorporated adequately and a large amount of the cold cement can be well distributed in the vertebral structure. The spatial distribution of cement in regions III and IV of each vertebra is optimal intervened in the spongy tissue. Radiological response of the cement was demonstrated on the radiological films.

4 I CONCLUSIONS

The spatial distribution of this material was observed through radiological images obtained after cement application showing the possibility of incorporating adequate amount of cement mass in the bone structure. It guaranteed the radiopaque nature of the bone cement. After cross cutting in some of the vertebrae, it was observed that the compound was solidified after being injected. Also, the spreading of the material in bone tissue was larger in the spongy bone tissue. A pair of puncture on the lumbar vertebrae can reduce the unwanted effect of extravasation due to the *in situ* decompression.

Since these compounds are used for the purpose of be absorbed and reabsorbed bone tissues, it is very important to reduce toxicity suppressing as much as possible the substances which are not completely biocompatible with organic tissues, as radiopaque compounds used in medical imaging, without affecting significantly their action. All biological effects that may be induced by the excess of HAp must be considered in order to calculate the proportions of HAp in the cement. In addition, the desirable porosity for migration of bone cells is required. Also, porosity is essential to spread the cement and facilitate the join of fractured pieces, as the case is required.

Percutaneous column procedures guided by fluoroscopy have been already proposed. One of the major problems in radioactive cements is directly related to vertebrae dose because dose must be planned with high precision to avoid negative responses subsequent to radiotherapeutic treatments. In the Ultrasound image the commercial teams gradually have improved their services and today are already possible to reconstruct live images in 3D which is known as the 4D mode. Thus, fluoroscopic image remains needed to avoid extravasation of the cement outside the vertebral body.

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CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest in this work.

REFERENCES

ASHAMALLA, H.; CARDOSO, E.; MACEDON, M.; GUIRGUIS, A. *et al.* Phase I trial of vertebral intracavitary cement and samarium (VICS): novel technique for treatment of painful vertebral metastasis. **International Journal of Radiation Oncology* Biology* Physics**, 75, n. 3, p. 836-842, 2009.

CHEN, G.; LUO, Z.-P.; ZHANG, H.; NALAJALA, B. *et al.* Percutaneous kyphoplasty in the treatment of painful osteoblastic metastatic spinal lesions. **Journal of Clinical Neuroscience**, 20, n. 7, p. 948-950, 2013.

DOROZHKIN, S. V. Calcium orthophosphates in nature, biology and medicine. **Materials**, 2, n. 2, p. 399-498, 2009.

DOROZHKIN, S. V. Bioceramics of calcium orthophosphates. **Biomaterials**, 31, n. 7, p. 1465-1485, 2010.

EMAMI, B.; LYMAN, J.; BROWN, A.; COLA, L. *et al.* Tolerance of normal tissue to therapeutic irradiation. **International Journal of Radiation Oncology* Biology* Physics**, 21, n. 1, p. 109-122, 1991.

GERSZTEN, P. C. The role of minimally invasive techniques in the management of spine tumors: percutaneous bone cement augmentation, radiosurgery, and microendoscopic approaches. **Orthopedic Clinics of North America**, 38, n. 3, p. 441-450, 2007.

HENDRICKSON, F. R.; SHEHATA, W. M.; KIRCHNER, A. B. Radiation therapy for osseous metastasis. **International Journal of Radiation Oncology* Biology* Physics**, 1, n. 3-4, p. 275-278, 1976.

HIRSCH, A. E.; ROSENSTEIN, B. S.; MEDICH, D. C.; MARTEL, C. B. *et al.* Polymethylmethacrylate and radioisotopes in vertebral augmentation: an explanation of underlying principles. **Pain Physician**, 12, n. 5, p. 887-891, 2009.

KANEKO, T.; SEHGAL, V.; SKINNER, H.; AL-GHAZI, M. *et al.* Evaluation of a radiation transport modeling method for radioactive bone cement. **Physics in Medicine & Biology**, 55, n. 9, p. 2451, 2010.

LEGEROS, R.; LIN, S.; ROHANIZADEH, R.; MIJARES, D. *et al.* Biphasic calcium phosphate bioceramics: preparation, properties and applications. **Journal of materials science: Materials in Medicine**, 14, n. 3, p. 201-209, 2003.

MONTAÑO, C.; CAMPOS, T.; LEMOS, B.; YOSHIDA, M. *et al.* Effects of hydroxyapatite on PMMA-HAp cement for biomedical applications. **Bio-medical materials and engineering**, n. Preprint, p. 1-11, 2020.

RYU, S.; FANG YIN, F.; ROCK, J.; ZHU, J. *et al.* Image-guided and intensity-modulated radiosurgery for patients with spinal metastasis. **Cancer: Interdisciplinary International Journal of the American Cancer Society**, 97, n. 8, p. 2013-2018, 2003.

RYU, S.; JIN, J. Y.; JIN, R.; ROCK, J. *et al.* Partial volume tolerance of the spinal cord and complications of single-dose radiosurgery. **Cancer: Interdisciplinary International Journal of the American Cancer Society**, 109, n. 3, p. 628-636, 2007.

YAMADA, Y.; BILSKY, M. H.; LOVELOCK, D. M.; VENKATRAMAN, E. S. *et al.* High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. **International Journal of Radiation Oncology* Biology* Physics**, 71, n. 2, p. 484-490, 2008.