Eur Spine J (2017) 26:3216–3224
https://doi.org/10.1007/s00586-017-4980-3

ORIGINAL ARTICLE

Local and systemic diffusion of antineoplastic drugs following vertebroplasty using acrylic cement mixed with cisplatin or methotrexate: experimental study in pigs

Rafael Llombart-Blanco[1] · Carlos Villas[1] · Álvaro Silva[2] · Azucena Aldaz[3] · Iñigo Navarro[4] · Jeronimo Forteza[5] · Salvador Martin Algarra[6] · Matías Alfonso[1]

Received: 14 February 2016 / Revised: 16 January 2017 / Accepted: 24 January 2017 / Published online: 6 February 2017

Abstract

Purpose To determine the efficacy of cisplatin- or methotrexate-containing acrylic cement for local and systemic antineoplastic drug diffusion. Among the uses of acrylic cement or Polymethylmethacrylate (PMMA), there is the possibility to employ it as vehicle for drug diffusion. This capability is of interest in the treatment of pathological fractures: The curative effects of the cement (cytotoxicity of the monomer and increased temperature) are added to the antineoplastic effect of the drugs.

Methods In the experimental study, two groups of ten pigs underwent vertebroplasty using cement mixed with 500 mg of powder cisplatin or 1000 mg of powder methotrexate. Vertebroplasty was performed in two non-consecutive lumbar vertebrae with bipedicular cement injection. Transpedicular bone biopsy was performed weekly to measure levels of antineoplastic agent in bone tissue and blood plasma. Cisplatin was studied by atomic absorption spectrometry and methotrexate by fluorescence polarization immunoassay. Renal and hepatic function and blood analysis were performed weekly.

Results Cisplatin and methotrexate levels were found in bone tissue at more than 5 weeks following surgery. The cisplatin peak occurred at week 3 (mean 1269 μg/g bone) and the methotrexate peak at week 1 (mean 862.76 μg/g bone). Plasma drug levels were found 72 h after surgery, with a peak at 24 h for cisplatin (mean 0.23 μmol/L) and at 30 min for methotrexate (mean 0.92 μmol/L). None of the animals died during the study. Animals with intracanal cement leaks showed no neurological involvement. Renal, hepatic and hemogram studies remained within normal limits.

Conclusions There is local diffusion of antineoplastic agents from the cement to bone and plasma. We found

✉ Rafael Llombart-Blanco
rllombartb@gmail.com

Carlos Villas
cvillas@unav.es

Álvaro Silva
alvarosilva@me.com

Azucena Aldaz
aaldaz@unav.es

Iñigo Navarro
inavarro@unav.es

Jeronimo Forteza
Jeronimo.Forteza.Vila@sergas.es

Salvador Martin Algarra
smalgarra@unav.es

Matías Alfonso
malfonsool@unav.es

[1] Department of Orthopaedic Surgery, Clínica Universidad de Navarra, Pio XII 36, 31008 Pamplona, Spain

[2] Department of Orthopaedic Surgery, German Clinic of Santiago, Universidad del Desarrollo, Av Maquehue Norte 1410, Vitacura, Santiago, Chile

[3] Department of Hospital Pharmacy, Clínica Universidad de Navarra, Pio XII 36, 31008 Pamplona, Spain

[4] Department of Chemistry and Edafology, Universidad de Navarra, Edificio de investigación, C/Irunlrrea 1, 31008 Pamplona, Spain

[5] Instituto Valenciano de Patologia, Universidad Catolica de Valencia, C/Quevedo 2, 46001 Valencia, Spain

[6] Department of Oncology, Clínica Universidad de Navarra, Pio XII 36, 31008 Pamplona, Spain

methotrexate and cisplatin levels in bone at up to 5 weeks, comparable to previous in vitro reports. At the doses administered, there were no cases of myelosuppression, hepatotoxicity, or nephrotoxicity.

Keywords Vertebroplasty · Acrilyc-cement · Acrilyc · Cisplatin · Methotrexate · Diffusion

Introduction

Polymethylmethacrylate (PMMA) or acrylic bone cement has long been used in the field of orthopaedic surgery—mainly to anchor several kinds of prosthesis to the bone, to fill spaces in bone lesions or even in the treatment of fractures. PMMA is used as a vehicle for drug diffusion. This capability is of interest in the treatment of pathological fractures.

Vertebroplasty is the injection of PMMA cement into a vertebral body to obtain improvements in strength and stability of the fractured vertebra. It was first described by Galibert [1] in 1987 for the treatment of painful, aggressive angiomas. Osteoporotic compression fractures are the most common indication for cement augmentation [2]. Pathologic or pending fractures in the context of painful primary bone tumours (e.g. aggressive haemangioma [1], giant cell tumour [3]) or lytic metastatic tumours are also an indication for cement augmentation.

Metastatic bone lesions that result in pathologic fractures occur in 8–14% of patients with cancer. The most common malignancies that metastasize to the spine are breast, prostate, lung, renal and thyroid [4]. Pain due to pathological fractures caused by metastases can be differentiated into mechanical pain caused by the fracture and pain caused by the tumour. Cement augmentation can provide relief from mechanical pain, whereas tumour-based pain is often best treated with radiation therapy. Nevertheless, some studies have pointed out the possible beneficial effects of cement in the treatment of pathological fractures [5].

In vitro studies have demonstrated the release of a monomer [6], which has been proven to be cytotoxic to osteoblasts. Free-radical release from PMMA can induce bone cell alterations, as shown in osteoblast-like cell cultures [7]. Furthermore, the temperature achieved during cement polymerization may be sufficiently high to cause thermal necrosis of bone tissue and intraosseus neural tissue [8].

Since the 1970s, PMMA polymer has been used as a drug carrier for antibiotics [9] and for other types of drugs such as NSAIDs [10]. The idea of using cement to deliver an anticancer drug that could maintain a high concentration in bone tissue is not new: Hernigou in 1989 demonstrated the release of methotrexate from cement in patients with bone tumours [11]. Greco [12] in 1992 demonstrated that loaded antiblastic compounds (doxorubicin or cisplatin) did not affect PMMA polymerization and the antiblastic drugs maintained their cytotoxicity in colon and breast cancer cultures [1]. Later, in vitro studies showed that cement with cytotoxic drugs, such as methotrexate, cisplatin or doxorubicin, maintains its biomechanical properties and allows local diffusion of drugs, even at a temperature as high as 100 °C [13]. The release of anticancer drugs such as methotrexate to bone tissue has shown a cytotoxic effect on osteosarcoma cell lines [14] and could reduce the incidence of recurrence in the treatment of giant cell tumours [15]. Also, studies have proven that drugs with added PMMA display good mechanical properties [16].

The aim of this study is to assess the efficacy of local and systemic diffusion of anticancer drugs after vertebroplasty using acrylic cement. We hypothesise that local levels of antineoplastic drugs can be found for a period of time after vertebroplasty in pigs.

Materials and methods

Study design: experimental study in pigs

We obtained approval for this study from the local institutional review committee (Comité de Ética para la Experimentación Animal).

Animals

Twenty large, white landrace female pigs with an average age of 10–12 weeks and mean body weight of 39.55 kg were provided by a professional stockbreeder and housed in stalls. The animals were divided into two groups: the first group underwent vertebroplasty using cisplatin-containing cement and the second group, cement-containing methotrexate.

Surgical procedure

Preanaesthetic sedation (intramuscular ketamine 10 mg/kg) was administered in the stall. The animals were transported to the operating room where general anaesthesia was administered (intramuscular azaperone 2 mg/kg, atropine 1 mg intramuscular, intravenous etomidate 3 mg/kg and pancuronium 0.2 mg/kg) followed by orotracheal intubation. Anaesthesia was maintained with isoflurane 0.8–1% plus oxygen 40%, intravenous pancuronium 0.2 mg/kg and fentanyl 0.05 mg/kg every 30 min. Animals were placed in the prone position on a radiolucent table. The skin on their backs was shaved and cleaned with antiseptic soap,

disinfected with chlorhexidine and draped with sterile surgical fields. Prophylactic antibiotics (ampicillin 1 g) were administered before skin incision. We performed vertebroplasty in two non-consecutive lumbar vertebrae (L2 and L4). We used C-arm radioscopic guidance (Siemens Powermobil) in the anteroposterior and lateral views. Four 13-gage trocars (Osteo-Site, Cook, IN, USA) were introduced in the pedicles.

The cement was manually prepared by adding 500 mg of powdered cisplatin or 1000 mg of powdered methotrexate to 22.5 g acrylic cement powder polymer (polymethylmethacrylate, PMMA) (Vertebroplastic, De Puy Spine, Raynham, MA, USA) and mixing. Then, 9 mL of the monomer was added and manually mixed. With a luer-lock syringe, 0.5 cc of acrylic cement (1 mg of cisplatin or 2 mg of methotrexate) was injected into each pedicle level under fluoroscopic guidance. A central venous catheter was placed on the external jugular vein, and blood samples were taken 30 min and 8 h after surgery and daily during the three subsequent 72 h periods for plasma level measurements.

After surgery, the animals received postoperative analgesia (buprenorphine 0.005 mg/kg). The animals were returned to the stall and observed for general status and limb motor function using the Tarlov scale [17], sphincter function and any pain behaviour or end-point criteria.

Bone biopsies

A transpedicular bone biopsy was performed weekly to measure levels of antineoplastic agents in bone tissue. Preanaesthetic sedation was administered in the stall and animals were transported to the operating room. Blood samples were obtained from a peripheral vein. Sedation was performed with continuous intravenous propofol (40 mL/h). After skin preparation and draping, we used a 13-G trocar to perform a bone biopsy under fluoroscopic guidance, obtaining a bone cylinder (Fig. 1). We followed the scheme shown in Fig. 2 to perform weekly bone biopsies: the first in the right pedicle of the upper level, a second in the left pedicle of the upper level, a third in the right pedicle of the lower level, a fourth in the left pedicle of the lower level and a fifth biopsy again in the right pedicle on the upper level.

Antineoplastic level measurement

Bone samples were stored at −20 °C in clean polypropylene bags labelled with pig identification numbers until analysis. In blood samples, the measurement was made directly after centrifugation to obtain plasma. Cisplatin was studied by atomic absorption spectrometry. Bone cylinder samples were treated with sub-boiling nitric acid and hydrogen peroxide in a high-pressure Teflon digestion vessel using a microwave digestion system (Ethos Plus, Millestone, Sorisole, Italy). A Perkin Elmer AAnalyst 800 atomic absorption spectrometer (Norwalk, CT, USA) equipped with a transverse heated graphite atomiser, a Zeeman background corrector and an AS-800 autosampler was used for the measurement of platinum.

Methotrexate was studied by fluorescence polarization immunoassay (FPIA). Methotrexate was obtained from bone tissue through an extraction process based on a combined system of the QuEChERS extraction method and dispersion after homogenization of the sample in buffer, pH 7 with ultra-turrax. FPIA was performed in an automated TDxFLx® Scientific Abbott autoanalyzer. The concentration values obtained were adjusted for the sample weight and expressed as micrograms per gram of bone (μg/g) or micrograms per litre of blood plasma (μg/L).

Euthanasia

Animals were killed with an intravenous injection of sodium pentobarbital 18% 200 mg/kg, 6 weeks after

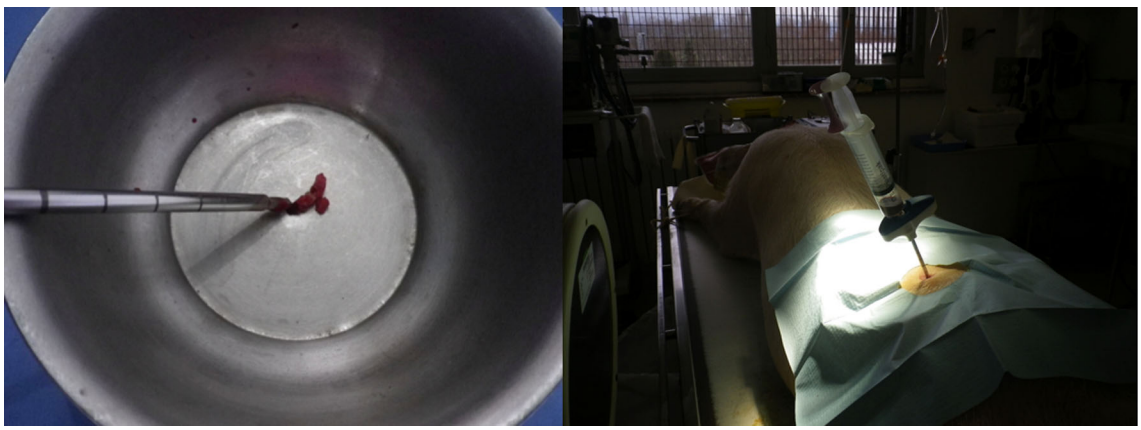

Fig. 1 Bone cylinder obtained in a biopsy

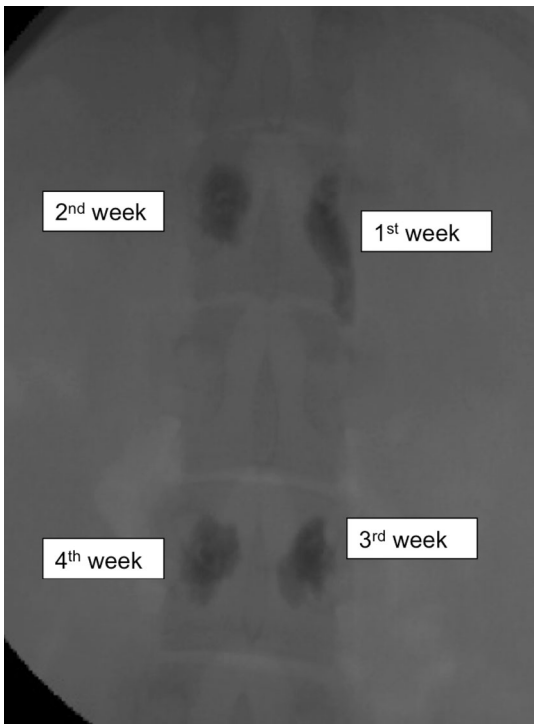

Fig. 2 Timing of bone biopsies schema. A cement anterior leakage is visible on the right L2 pedicle

surgery. We utilized a posterior approach to perform a dissection of the lumbar spine of each animal, maintaining the anterior muscles. We looked for cement leaks in contact with anterior muscles or the dural sac in cases of intracanal escape. Samples of muscle or dural sac in contact with cement were taken and marked with Chinese ink. All samples were placed in formaldehyde. Every tissue was dehydrated with ethanol, fixed in wax and then cut with a microtome and stained with haematoxylin–eosin. A senior pathologist inspected all tissue samples under light microscopy.

Statistic analysis

Differences between groups were compared using a non-parametric Mann–Whitney U test. A p value of <0.05 was considered statistically significant. Statistical analyses were conducted with the IBM SPPS statistical software package (v21.0 SPSS Inc., Chicago, IL, USA).

Results

Surgical procedure, bone biopsies and complications

Most of the surgical interventions were performed without incident. In one case, a pedicle fracture occurred during bone biopsy without any further complication. Animals recovered well from surgery with normal locomotion, including the one who suffered the pedicle fracture. None of the animals died during the study. Animals with intracanal cement leak showed no neurological involvement. In five cases, an anterior cement leak was registered during surgery, two in the cisplatin group and three in the methotrexate group. Only three animals had intracanal cement leaks, which were observed after dissection of the lumbar spine. The leaks were minimal and all were found in the cisplatin group.

Blood tests

Tables 1 and 2 summarize the results of blood cell counts and renal and hepatic function tests. Haemoglobin levels and platelet and leukocyte counts were unaffected in all groups. Some statistical differences were found, but the mean levels were always within the normal range. Creatinine blood levels did not show any sign of renal dysfunction, as they were within the normal range in both groups during the entire experiment. Transaminase (alanine transaminase and aspartate transaminase) levels were not elevated in any of the groups.

Diffusion of antineoplastic drugs to bone tissue

Cisplatin and methotrexate levels were found in bone tissue at more than 5 weeks following surgery as seen in Table 3 and Fig. 3. The highest drug concentration in bone tissue in the cisplatin group occurred at week 3 (mean 1269 μg/g bone). In the methotrexate group, the highest level was found at week 1 (mean 862.76 μg/g bone). In the 5th week of the experiment, the mean drug concentration in the cisplatin group was 600 μg/g, but in the methotrexate group, the concentration had decreased to minimal levels (mean 7.53 μg/g bone).

Diffusion to blood plasma

Plasma levels of cisplatin and methotrexate were found at 72 h after the surgical procedure. The highest level was found 24 h after surgery in the cisplatin group (mean 0.23 μmol/L) and 30 min in the methotrexate group (mean 0.92 μmol/L). Results are shown in Table 4 and Fig. 4.

Anatomopathological study

Dissection of the lumbar spine showed three minimal intracanal leaks in the cisplatin group. Histological changes were found in only two cases. In one sample, the study of the spinal medullar tissue showed spongiosis (Fig. 5a) and, in another, nuclear pyknosis was found (Fig. 5b).

Table 1 Blood tests results

	Haemoglobin			Leukocytes count			Platelet count		
	CPT	MTX	*p*	CPT	MTX	*p*	CPT	MTX	*p*
Basal	11.05	11.14	0.85	16.36	17.26	0.48	456.9	408.2	0.31
72 h	10.64	10.34	0.43	18.14	19.74	0.52	390.8	400.4	0.79
Week 1	10.09	9.69	0.14	19	15.94	0.052	499.6	370	0.16
Week 2	10.56	10.2	0.43	17.23	14.33	0.023	439	279.6	0.03
Week 3	10.77	10.28	0.14	18.81	14.43	0.023	392	257.5	0.05
Week 4	10.95	10.51	0.28	15.89	14.45	0.39	361.7	302.2	0.12
Week 5	11.73	10.98	0.02	14.91	12.92	0.02	312.9	325.5	0.97
Normal range	10–16 g/dL			7–20 $\times$ 10^3/μL			200–500 $\times$ 10^3/μL		

Haemoglobin, leukocytes and platelet counts

Table 2 Renal and hepatic function tests

	Creatinine			AST			ALT		
	CPT	MTX	p	CPT	MTX	p	CPT	MTX	p
Basal	0.99	1.09	0.123	38.2	39	0.48	31.4	32.1	1
72 h	0.88	1.06	0.01	43.5	24.5	0.75	35.9	33.1	0.39
Week 1	0.82	0.05	0.07	30.7	35.4	0.97	26.2	29.2	0.39
Week 2	1.04	1.04	0.79	41.2	33.2	0.91	30.7	32.1	0.79
Week 3	1.08	1.13	0.39	27.2	40.1	0.28	28.1	37.3	0.97
Week 4	1.13	1.17	0.73	31.6	25.5	0.89	26.9	27.6	0.57
Week 5	1.16	1.17	1	31.8	31.4	0.63	29.1	29.9	0.31
Normal range	0.8–2.3 mg/dL			17–45 U/L			25–50 U/L		

Table 3 Antineoplastic drug concentration in bone tissue

Bone tissue	Cisplatin (mcg/g)	Methotrexate (mcg/g)
Week 1	1160.3 (0–4903)	862.76 (2.23–4496.96)
Week 2	920.2 (0–2285)	605.98 (2.27–3516.29)
Week 3	1394.6 (1–8166)	169.93 (0.52–662.31)
Week 4	482.1 (6–3751)	214.85 (0.82–762.7)
Week 5	600.5 (0–3012)	7.53 (0.1132–19.2)

Discussion

This study confirms that anticancer drugs diffuse from acrylic cement after vertebroplasty. Moreover, we found a different pattern of drug release between cisplatin and methotrexate. To our knowledge, this is the first reported experiment of a model of vertebroplasty using acrylic cement mixed with antineoplastic drugs. Due to the morphology and size of the animal's vertebrae, the vertebroplasty model in pigs is very similar to the procedure that we normally perform in our patients. In our experiment, we used drugs commonly utilized in the treatment of tumours that tend to metastasize, which had also been previously demonstrated to elute from acrylic cement [13–15].

Local diffusion occurred at least 5 weeks after surgery with a higher and longer-lasting concentration of cisplatin in bone tissue compared with that of methotrexate, even when the dose of cisplatin administered in cement was lower. The highest concentration of cisplatin in bone was found 3 weeks after surgery and the tendency was for cisplatin release to be continued after 5 weeks, as shown in Fig. 3.

On the other hand, systemic drug levels were found 72 h after surgery. The highest methotrexate release into the blood plasma occurred 30 min after surgery and was four times higher than the highest concentration of cisplatin. The greatest blood plasma concentration of methotrexate was higher than the minimum inhibitory concentration (MIC, 1×10^{-8} M) required to inhibit DNA synthesis [18], which means that systemic therapeutic levels of methotrexate can be diffused from the cement after vertebroplasty. As the potential local effect of cytostatics on the tumour tissue of vertebral metastases has never been studied before, the dose of the drug diffusing out of the cement should also be estimated in further studies. Previous studies have pointed out that high systemic levels of chemotherapy drugs do not reach effective concentrations in tumours [19]. Therefore, high systemic levels of a cytotoxic drug often cause systemic toxicity without reaching good local concentrations in the tumour area.

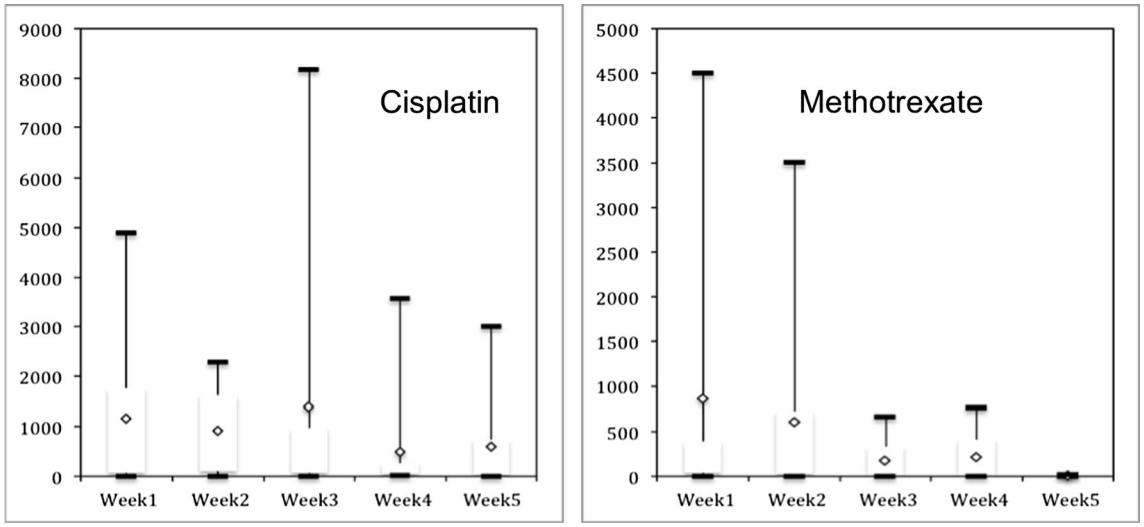

Fig. 3 Box plot showing drug levels (mean, minimum and maximum) in bone tissue in both groups

Table 4 Antineoplastic drug concentration in blood plasma

Plasma tissue	Cisplatin (μmol/L)	Methotrexate (μmol/L)
30 min	0.198 (0.06–0.49)	0.922 (0.12–3.12)
8 h	0.2 (0.08–0.46)	0.492 (0.11–1.29)
24 h	0.222 (0.08–0.62)	0.044 (0.02–0.07)
48 h	0.202 (0.12–0.49)	0.024 (0–0.04)
72 h	0.151 (0.09–0.39)	0.023 (0.01–0.04)

Cisplatin is widely used for the treatment of testicular, bladder, head and neck and small-cell and non-small-cell lung cancers. Methotrexate is used as a chemotherapeutic agent in the treatment of breast, head and neck, lung and bladder cancers; leukaemia; lymphoma and osteosarcoma. Systemic therapeutic levels of cisplatin and methotrexate are difficult to assess. They depend on the primary tumour to be treated, the general status of the patient and whether chemotherapy is used in mono- or combined therapy.

Rosa compared the diffusion of various antineoplastic drugs, including methotrexate, from acrylic cement. A larger quantity of eluted drug and longer duration of release were obtained in cement mixed with methotrexate [13]. Their results contrast with ours, as we found a higher concentration of cisplatin in bone tissue. On the contrary, the release of methotrexate in our study followed the same pattern as published by Kim [14], in which the eluted quantity of methotrexate was greatest during the first day,

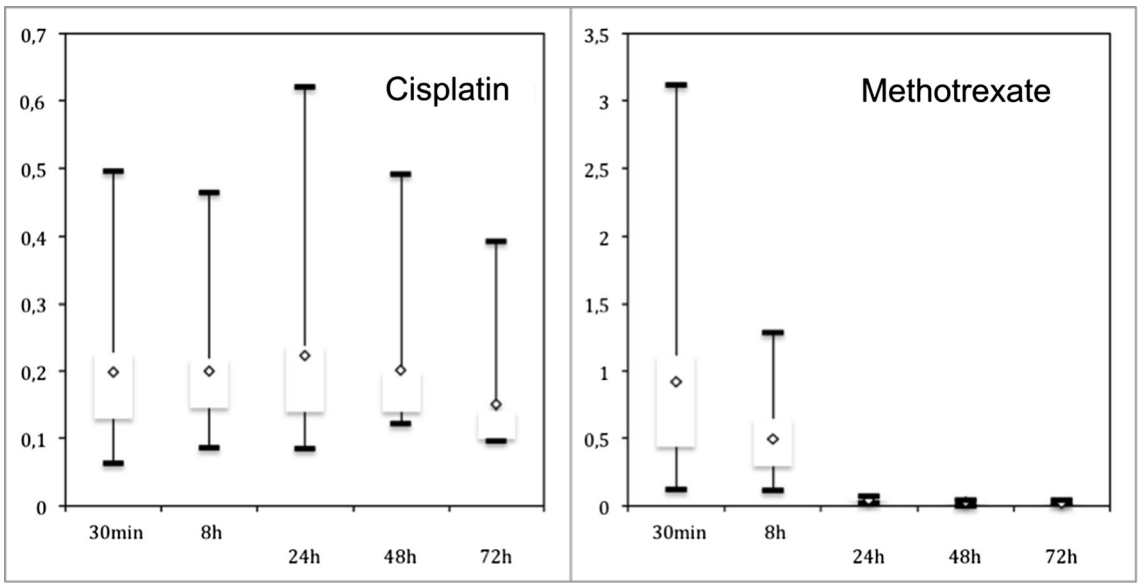

Fig. 4 Box plot showing drug levels (mean, minimum and maximum) in blood plasma in both groups

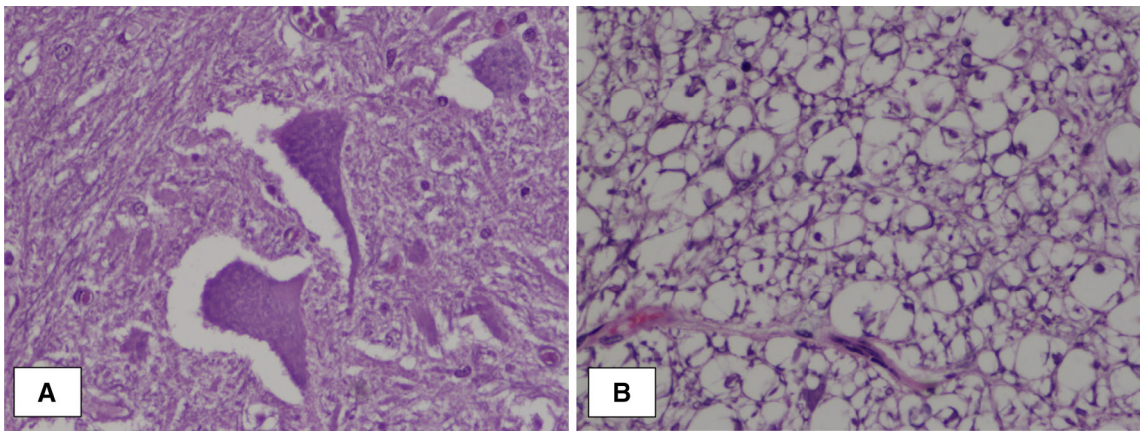

Fig. 5 Images show the findings of the anatomopathological study in two of the subjects with intracanal cement scapes with cisplatin. **a** Nuclear pyknosis. **b** Spongiosis

followed by a rapid decrease until the end of the first week. In an in vitro study, Wasserlauf et al. [20] also found that methotrexate was more capable of leaching than cisplatin or 5-fluorouracil. They also performed drug level measurements in an in vivo model, implanting cement in rabbit femurs. Levels of 5-fluorouracil and methotrexate were measured from the wound exudate and circulating blood and urine, whereas cisplatin was only measured in the urine. Levels in the exudate were the highest after 3 days; however, in the blood circulation, levels were undetectable after 14 days. In the urine, levels were detected 28 days after surgery. The amount of methotrexate was also higher than those of 5-fluorouracil and cisplatin. Özben et al. [21] did not perform a kinetic study of drug release from cisplatin-loaded cement, but changes in the viable cell ratios of Saos-2 cultures allowed them to conclude that the cytotoxicity of cisplatin was directly proportional to the amount of drug released and that the release might depend on the amount of drug added in the initial period, a dependency that decreased over time.

The main reason we used the pig model is that the technique and instrumentation are the same as those used in our clinical practice. Pigs' vertebrae are smaller and narrower in the anteroposterior plane, especially in the middle third of the vertebral body. In our model, we injected 0.5 cc of acrylic cement into each pedicle, which makes a total of 1 cc of cement in each vertebra. Other studies have performed vertebroplasties with higher volumes of cement in pigs [22]. We used a lower volume in an attempt to avoid anterior cement leaks, which also happened in our series.

None of the animals died during the experiment. We did not find any signs of myelosuppression, hepatotoxicity or nephrotoxicity in any of the animals. One severe side effect of the use of cisplatin is neurotoxicity [18], which may raise questions about its safe use in spinal surgery. In our study, three intracanal leaks were found after dissection of the lumbar spine in animals of the cisplatin group. None of the animals showed any anomalies in their lower-limb motor function. Histopathological analysis of the medulla in contact with the leak showed spongiosis and nuclear pyknosis in one animal. Cement leakage happens in up to 70% of vertebroplasty [23], most of the time with no clinical correlation. Some authors in our study group previously studied the effect of provoked anterior and intracanal cement leakage in a vertebroplasty model in pigs [24]. They found that the dura mater and cerebrospinal fluid are sufficiently able to isolate the possible effects of PMMA, and in an anterior study, which has not yet been published, we observed that intracanal massive escapes of cement with cisplatin were associated with late paraparesia of the animals. Histologic changes found in our study might be the effect of cisplatin, but were only observed in one case.

Our study has some limitations. We performed bone biopsies on a different vertebra each week (scheme shown in Fig. 2). The explanation for this is the limited bone stock of the vertebra. We avoided the risk of causing a vertebral fracture by repeatedly biopsying each vertebra. We injected 0.5 cc of cement including 1 mg of cisplatin or 2 mg of methotrexate in each pedicle, totalling 4 or 8 mg per 40 kg per animal. The reason why we used half the concentration of cisplatin was that in a previous work, we found gastrointestinal problems and neurotoxicity in the animals in the cisplatin group at a higher concentration. On the other hand, the cisplatin group presented more cases of cement leaks than the methotrexate group. Most of the animals in the methotrexate group were operated on by a senior surgeon, whereas the pigs in the cisplatin group were operated on by a younger surgeon with less experience in vertebroplasties. This was the only reason we could think of to explain the intracanal leaks in the cisplatin group.

In the armamentarium for treating metastatic cancer, radiotherapy is the standard of treatment, especially in painful vertebral bony metastases. The use of cement has been reserved for treating pathologies in metastatic vertebrae. Cement can be used to fill defects after tumour resection, to give support to the fractured vertebral body through vertebroplasty or kyphoplasty or even as a reconstruction method of the anterior column after corpectomy. Salem published a case of anterior column reconstruction with PMMA in a female patient with breast cancer with bony metastases in the thoracic spine [25]. Long-term follow-up showed that after 13 years anterior bony fusion was achieved. Although one case is not evidence enough to make conclusions, PMMA might be considered a cheaper and easier alternative to metal vertebral cages to give stability to the anterior column, with the advantages of PMMA in the treatment of vertebral metastases: exothermic reaction, monomer cytotoxicity and the capability of adding antineoplastic drugs to treat residual tumour cells in the vicinity of the vertebrectomy.

The results of our study highlight the idea that antineoplastic drugs might strengthen antitumour activity locally for vertebrae with osseous metastasis without damaging adjacent tissues and reducing systemic effects occurring with classic chemotherapy. So far, there is only one study reporting the beneficial effects of adding anticancer drugs to cement in patients with vertebral metastases. Cai et al. [26] reported a better pain relief in a group of patients treated with vertebroplasty combined with chemotherapy than in the one treated with normal cement. However, the effect of this adjuvant therapy on metastasis and the surrounding bone in vertebrae requires larger studies in vivo before it can be recommended for clinical use. There are also other ways to enhance the cement used in vertebroplasty. Ashamalla et al. [27] published the results of a novel technique in which they combined cement with the radioactivity of 153-Samarium with a significant reduction of pain in patients 1 day after the procedure without untoward adverse effects.

Conclusions

There is local diffusion of antineoplastic agents from the cement to bone and plasma. We found methotrexate and cisplatin levels in bone up to 5 weeks. At the doses administered, there were no cases of myelosuppression, hepatotoxicity or nephrotoxicity. The addition of antineoplastic drugs to acrylic cement used in vertebroplasty seems to be a feasible way to improve the treatment of bone metastases.

Acknowledgements For this study, we obtained two Grands: Sociedad Española de Cirugía Ortopédica y Traumatología (SECOT) Beca proyecto de inicio a la investigación 2013. Spanish Spine Society (GEER) Beca Investigación GEER 2012.

Compliance with ethical standards

Conflict of interest No potential conflict of interest relevant to this article was reported.

References

1. Galibert P, Deramond H, Rosat P, Le Gars D (1987) Preliminary note on the treatment of vertebral angioma by percutaneous acrylic vertebroplasty. Neurochirurgie 33(2):166–168
2. Álvarez Galovich L, Pérez-Higueras A (2002) Vertebroplastia: indicaciones y técnica. Rev Esp Cir Ortop Traumatol 46(02):175–182
3. Paúl L, Santonja C, Izquierdo E (2006) Complete necrosis of a spinal giant cell tumor after vertebroplasty. J Vasc Interv Radiol 17(4):727–731
4. Savage JW, Schroeder GD, Anderson PA (2014) Vertebroplasty and kyphoplasty for the treatment of osteoporotic vertebral compression fractures. J Am Acad Orthop Surg 22(10):653–664
5. Chew C, Craig L, Edwards R, Moss J, O'Dwyer PJ (2011) Safety and efficacy of percutaneous vertebroplasty in malignancy: a systematic review. Clin Radiol 66(1):63–72
6. Bettencourt A, Calado A, Amaral J, Vale FM, Rico JMT, Monteiro J et al (2000) In vitro release studies of methylmethacrylate liberation from acrylic cement powder. Int J Pharm 197(1–2):161–168
7. Moreau MF, Chappard D, Lesourd M, Monthéard JP, Baslé MF (1998) Free radicals and side products released during methylmethacrylate polymerization are cytotoxic for osteoblastic cells. J Biomed Mater Res 40(1):124–131
8. Deramond H, Wright NT, Belkoff SM (1999) Temperature elevation caused by bone cement polymerization during vertebroplasty. Bone 25(Suppl. 1):17S–21S
9. Bettencourt A, Almeida AJ (2012) Poly(methyl methacrylate) particulate carriers in drug delivery. J Microencapsul 29(4):353–367
10. Corry D, Moran J (1998) Assessment of acrylic bone cement as a local delivery vehicle for the application of non-steroidal anti-inflammatory drugs. Biomaterials 19(14):1295–1301
11. Hernigou P, Thiéry JP, Benoit J, Voisin MC, Leroux P, Hagege G et al (1989) Methotrexate diffusion from acrylic cement. Local chemotherapy for bone tumours. J Bone Joint Surg Br 71(5):804–811
12. Greco F, de Palma L, Specchia N, Jacobelli S, Gaggini C (1992) Polymethylmethacrylate-antiblastic drug compounds: an in vitro study assessing the cytotoxic effect in cancer cell lines—a new method for local chemotherapy of bone metastasis. Orthopedics 15(2):189–194
13. Rosa MA, Maccauro G, Sgambato A, Ardito R, Falcone G, De Santis V et al (2003) Acrylic cement added with antiblastics in the treatment of bone metastases. Ultrastructural and in vitro analysis. J Bone Joint Surg Br 85(5):712–716
14. Kim HS, Park YB, Oh JH, Yoo KH, Lee SH (2001) The cytotoxic effect of methotrexate loaded bone cement on osteosarcoma cell lines. Int Orthop 25(6):343–348
15. Savadkoohi DG, Sadeghipour P, Attarian H, Sardari S, Eslamifar A, Shokrgozar MA (2008) Cytotoxic effect of drugs eluted from polymethylmethacrylate on stromal giant-cell tumour cells: an in vitro study. J Bone Joint Surg Br 90(7):973–979

16. Maccauro G, Cittadini A, Casarci M, Muratori F, De Angelis D, Piconi C et al (2007) Methotrexate-added acrylic cement: biological and physical properties. J Mater Sci Mater Med 18(5):839–844
17. Tarlov IM (1954) Spinal cord compression studies. III. Time limits for recovery after gradual compression in dogs. AMA. Arch Neurol Psychiatry 71(5):588–597
18. Avan A, Postma TJ, Ceresa C, Avan A, Cavaletti G, Giovannetti E et al (2015) Platinum-induced neurotoxicity and preventive strategies: past, present, and future. Oncologist 20(4):411–432
19. Shikanov A, Shikanov S, Vaisman B, Golenser J, Domb AJ (2011) Cisplatin tumor biodistribution and efficacy after intratumoral injection of a biodegradable extended release implant. Chemother Res Pract 2011:1–9
20. Wasserlauf S, Warshawsky A, Arad-Yelin R, Mazur Y, Salama R, Dekel S (1993) The release of cytotoxic drugs from acrylic bone cement. Bull Hosp Jt Dis 53(1):68–74
21. Özben H, Eralp L, Baysal G, Cort A, Fiarkalkan N, Özben T (2013) Cisplatin loaded PMMA: mechanical properties, surface analysis and effects on Saos-2 cell culture. Acta Orthop Traumatol Turc 47(3):184–192
22. Yang Z, Zhang Y, Xu D, Maccauro G, Rossi B, Jiang H et al (2013) Percutaneous vertebroplasty combined with interstitial implantation of 125I seeds in banna mini-pigs. World J Surg Oncol 11:46
23. Cotten A, Dewatre F, Cortet B, Assaker R, Leblond D, Duquesnoy B et al (1996) Percutaneous vertebroplasty for osteolytic metastases and myeloma: effects of the percentage of lesion filling and the leakage of methyl methacrylate at clinical follow-up. Radiology 200(2):525–530
24. Silva González A, Alfonso Olmos M, Villas Tomé C, Angulo MG (2013) Model of induced leakage of polymethylmethacrilate inside epidural space and prevertebral muscles during vertebroplasty in pigs: clinical, macroscopical, and histological study. Asian Spine J 7(3):159–166
25. Salem KMI, Fisher CG (2015) Anterior column reconstruction with PMMA: an effective long-term alternative in spinal oncologic surgery. Berlin Heidelberg, Eur Spine J Springer, pp 1–7
26. Cai H-Y, Liu X-D, Cao H-P, Wang X-Q, Zhang Z-Y, Dong X-C (2005) Treatment effect of percutaneous vertebroplasty combined with interventional chemotherapy on vertebral metastases. Ai Zheng 24(4):488–493
27. Ashamalla H, Cardoso E, Macedon M, Guirguis A, Weng L, Ali S et al (2009) Phase I trial of vertebral intracavitary cement and samarium (VICS): novel technique for treatment of painful vertebral metastasis. Int J Radiat Oncol Biol Phys 75(3):836–842