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SCIENTIFIC ARTICLE

Percutaneous bone cement refixation of aseptically loose hip prostheses: the effect of interface tissue removal on injected cement volumes

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Abstract
Objective To quantify whether injected cement volumes differed between two groups of patients who underwent experimental minimally invasive percutaneous cement injection procedures to stabilize aseptically loose hip prostheses. One patient group was preoperatively treated using gene-directed enzyme prodrug therapy to remove fibrous interface tissue, while the other group received no preoperative treatment. It was hypothesized that cement penetration may have been inhibited by the presence of fibrous interface tissue in periprosthetic lesions.
Materials and Methods We analyzed 17 patients (14 female, 3 male, ages 72-91, ASA categories 2-4) who were treated at our institution. Osteolytic lesions and injected cement were manually delineated using 3D CT image segmentation, and the deposition of injected cement was quantified.
Results Patients who underwent preoperative gene-directed enzyme therapy to remove fibrous tissue exhibited larger injected cement volumes than those who did not. The observed median increase in injected cement volume was 6.8 ml. Higher cement leakage volumes were also observed for this group.
Conclusion We conclude that prior removal of periprosthetic fibrous interface tissue may enable better cement flow and penetration. This might lead to better refixation of aseptically loosened prostheses.

Keywords Gene therapy · Prosthesis loosening · Osteolysis · CT · Vertebroplasty

Introduction

Standard treatment of symptomatic aseptic loosening of a hip prosthesis comprises revision of the loose components, with concomitant removal of the fibrous interface tissue that formed in the periprosthetic osteolytic bone lesions [1, 2]. Worldwide, the rate of hip prosthesis revision at 10-year follow-up is estimated at 12 % [3]. Revision rates are predicted to increase in the coming decades[4].

Revision surgery has higher perioperative mortality and morbidity rates in elderly and high-risk groups, with some authors reporting up to 51 % postoperative complications in these patients [5]. In the subset of patients with significant comorbidity, the risks of revision surgery might outweigh the benefits. Percutaneously injecting bone cement into the periprosthetic osteolytic lesions was demonstrated as an experimental alternative treatment for these symptomatic patients [6–8]. During this procedure, one or more hollow vertebroplasty needles are inserted under spinal anesthesia, and vertebroplasty cement is injected into the periprosthetic space to stabilize and fixate the loosened prosthesis [8, 9].

The incompressible periprosthetic fibrous tissue is not removed during percutaneous cement injection and might impede sufficient cement flow. De Poorter et al. investigated preoperatively removed interface tissue by using a gene-

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directed enzyme prodrug therapy (GDEPT) approach [6, 7]. However, it remained unclear whether cement volumes following GDEPT differed from those cases where interface tissue were left intact.

The aim of this study was to quantify whether injected cement volumes differed between patients who underwent percutaneous cement injection only compared to those who also underwent preoperative gene-directed enzyme prodrug therapy to remove fibrous interface tissue.

Materials and methods

Our candidate population consisted of 22 patients at our hospital who consecutively underwent hip stem refixation by means of percutaneous bone cement injection. CT image data were collected retrospectively. Before 2006, CT imaging was not standard after cement injection at our hospital, and we consequently had to exclude patients for whom no postoperative CT images were available. The study was performed under approval of the Medical Ethics Committee (CME) of our institution.

Our study population comprised two groups that were treated consecutively, not blinded, and over the course of several years. The 12 patients in the "GDEPT group" had interface tissue treated with gene-directed enzyme therapy prior to cement injection as described by de Poorter et al [7, 10]. Each had a single hip treated between 2004 and 2006. Of these patients, five were excluded due to postprocedure CT image volumes not being available, yielding a total of seven GDEPT hips for our analysis. The "cement-only" patients received no treatment before cement injection and were treated between 2005 and 2011. One patient was excluded because no post-procedure CT was available. Of the remaining nine patients, one was treated bilaterally. For this patient, we included both hips separately in the analyses, yielding a total of ten cement-only hips.

Of the 17 hips investigated in this study, 14 were from female and 3 from male patients. The median patient age at operation was 82 years (range 72-91). All patients presented with invalidating hip pain, and all were deemed unfit for traditional revision surgery. The American Society of Anesthesiologists (ASA) classifications[11] of the patients ranged from ASA-2 to ASA-4. There was no difference in the age distribution between the cement-only and GDEPT groups.

Percutaneous bone cement injection was performed in all patients by the method described by De Poorter et al. (Figs. 1, 2 and 3) [7, 9, 10]. All procedures were performed under guidance by the same orthopedic surgeon and intervention radiologist. Patients underwent CT guided percutaneous injection of polymethyl-methacrylate (PMMA) cement (Osteopal, Biomet; Disc-O-Tech, Disc-O-Tech Medical Technologies, Herzeliya, Israel; Vertaplex, Stryker Orthopedics, Detroit, MI, USA) via

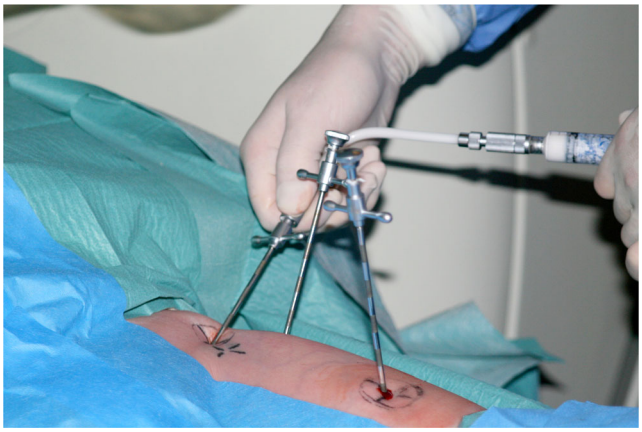

Fig. 1 Cement being percutaneously injected into the periprosthetic space via vertebroplasty needles

vertebroplasty needles of 3.2 × 100 mm (Biomet, Dordrecht, The Netherlands). Cement injection was performed under spinal anesthesia and guided fluoroscopically. Cement injection was halted either when the target lesion was filled to the extent that additional cement flow leaked beyond the intended region (i.e., extraosseously) or when cement flow ceased because of being high resistance at the injection cannula (Fig. 4). A postoperative CT scan of the hip was made on the same day as the minimally invasive procedure.

The extent of the preoperative osteolytic zones and the injected cement volumes were measured in three dimensions using the acquired CT image volumes. The image volumes were created on a helical CT scanner (Toshiba Aquilion, Toshiba Medical Systems, Japan) with slice thicknesses ranging from 0.4 mm to 1.0 mm and in-plane resolutions between 0.39 mm and 0.74 mm. Osteolytic lesions and cement volumes were manually segmented by an expert user in a slice-by-slice fashion using the Medical Imaging Interaction Toolkit

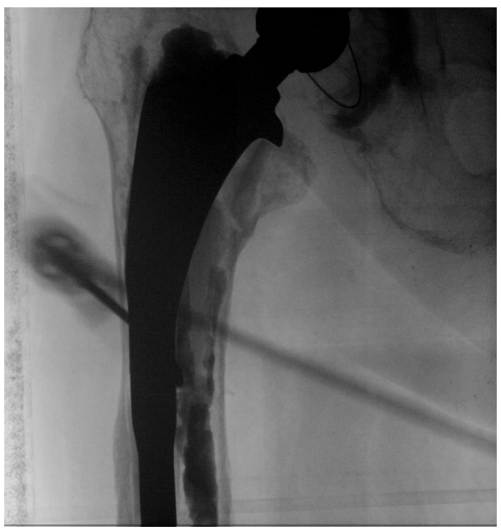

Fig. 2 Cement flow was monitored using intraoperative fluoroscopy

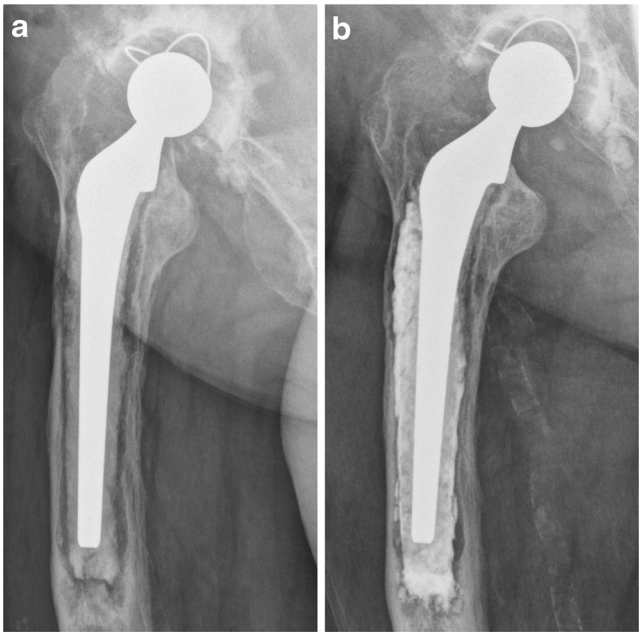

Fig. 3 Lateral view X-rays taken before (**a**) and after (**b**) percutaneous cement injection to refix a loosened hip stem. This patient was part of the cement-only group

(MITK 0.12.2), an interactive medical image segmentation software tool [12] (Fig. 5). In a previously published cadaveric study examining periprosthetic femoral lesions, the interobserver variability of this volumetric segmentation method was

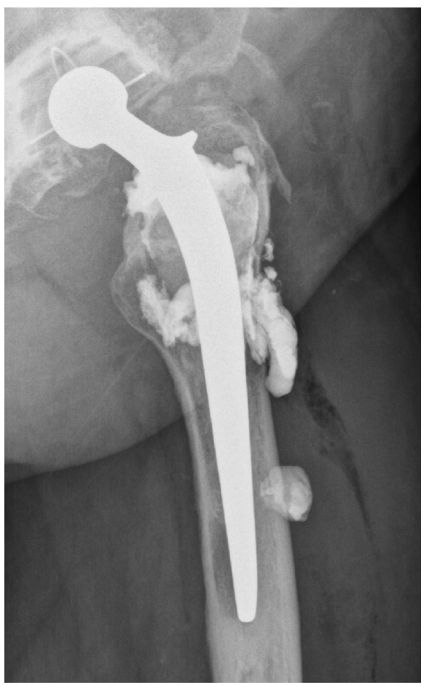

Fig. 4 Lateral view X-ray of a patient's hip after cement injection. Of all examined cases, this patient had the highest cement leakage percentage at 73 % leakage of the injected 11.95 ml. This patient was part of the GDEPT group

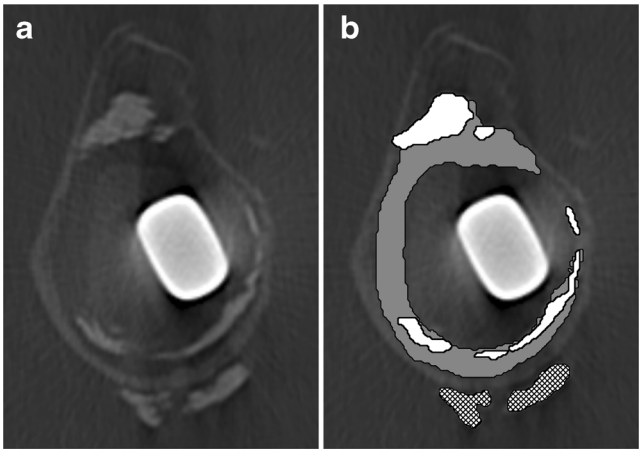

Fig. 5 A single axial slice through the CT volume of the same patient as in Fig. 4. In (**a**) the original image is shown. In (**b**) the regions of interest are labeled: remainder of interface tissue zone (gray), injected cement at desired location (white), and leaked cement (hatched)

found to span an interquartile range (IQR) of 0.4 ml, with an SD of 0.5 ml and a bias of 0.1 ml [13]. Another study that applied this segmentation method to various periprosthetic tissues in clinical CT volumes reported a spatial volumetric interobserver agreement of between 90 % and 95 % (median Dice coefficient between 0.9 and 0.95) for segmentations performed by two subsequent human operators [14].

Sub-volumes of injected cement that had leaked outside the desired target region, i.e., extraosseously adjacent to the introduced cement injection needle in the femur, were separately labeled. Preoperative fibrous tissue regions were determined as the union between residual periprosthetic radiolucent zones and the regions occupied by newly injected cement excluding regions of leaked cement. Using these segmented regions we computed the following values for each patient:

- Lesion volume: volume of preoperative radiolucent fibrous tissue lesions (ml)
- Filling fraction: the percentage of preoperative lesions filled by injected cement (%)
- Leakage fraction: the percentage of the total volume of injected cement that leaked into undesired areas (%)

Segmented volumes were measured in milliliters, and each volume distribution was characterized by its median, range and IQR. Outliers were defined as being more than 1.5 IQRs outside the interval spanned by the first and third quartiles. Results were analyzed using IBM SPSS Statistics 20 for Microsoft Windows (IBM Corp., Armonk, NY, USA).

In comparing the observed differences between two sampled case series, we used the nonparametric Mann-Whitney U-test for independent groups, as our patient groups were small and we did not assume normal distribution of our measured parameters. A p value of 0.05 was taken to be statistically significant.

Results

The cement-only group's radiolucent lesion volumes ranged from 13.8 ml to 36.2 ml (median 27.8 ml, IQR 18.8 ml). The GDEPT group had lesion volumes ranging from 8.5 ml to 52.0 ml (median 20.9 ml, IQR 25 ml). These two distributions (Fig. 6) were statistically indistinguishable as measured by the Mann-Whitney U-test (p=0.96).

The injected cement volumes for the cement-only group ranged from 3.4 ml to 13.0 ml (median 5.2 ml, IQR 4.1 ml). For the GDEPT group, the injected cement volumes ranged from 6.9 ml to 27.8 ml (median 12.0 ml, IQR 14.3 ml). The observed difference in median injected cement volume was 6.8 ml, which is more than one order of magnitude larger than the interobserver variability in the volume measurement technique as reported by Malan et al.[13]. This difference in distributions was statistically significant (p=0.007) and is shown in Fig. 7.

The cement filling percentages achieved for the cement-only group ranged from 10.2 % to 58.3 % (median 20.7 %, IQR 16.5 %). The GDEPT group's larger injected cement volumes also translated to higher cement filling fractions compared to the cement-only group. For the GDEPT group, the cement filling percentages ranged from 16.5 % to 52.1 % (median 33.6 %, IQR 31.8 %).

There was a single outlier in the cement-only group representing an exceptionally high filling percentage (58.3 %), which occurred for the femur with the smallest osteolytic lesion (13.8 ml) in this group (Fig. 8). Omitting this outlier resulted in a statistically significant difference in filling percentages between the cement-only and GDEPT-only groups (p=0.05).

Without omission of the outlier in the cement-only group, the differences in cement filling fractions between the two groups did not reach statistical significance (p=0.16).

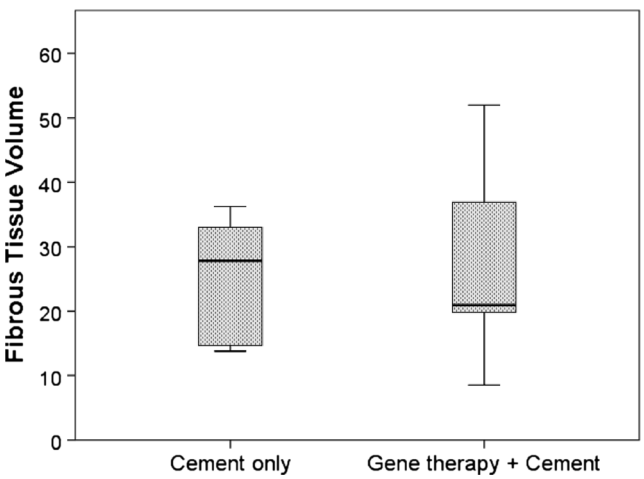

Fig. 6 Volumes of osteolytic fibrous tissue for patients in the cement-only and GDEPT groups

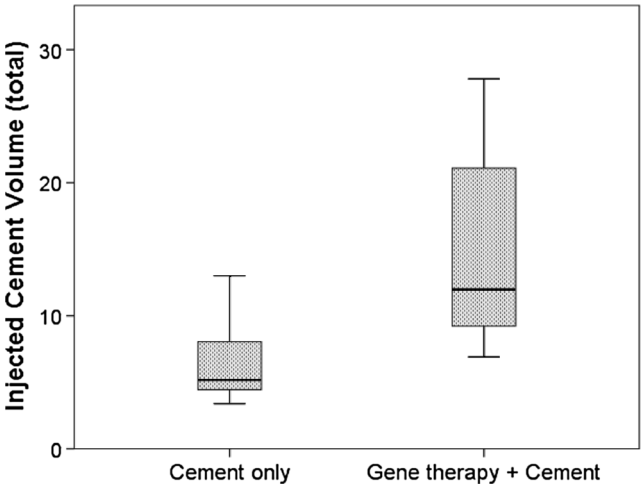

Fig. 7 Volumes of injected cement for patients in the cement-only and GDEPT groups

For the cement-only group, the percentage of the injected cement that leaked out of the intended target (i.e., extraosseously) ranged between 0 % and 40.1 % (median 5.3 %, IQR 35.6 %). In comparison, the extrafemoral cement leakage in the GDEPT group ranged from 0.2 % to 73.1 % (median 39.6 %, IQR 64.8 %) and is shown in Fig. 9. Omitting the measurement corresponding to the outlier of Fig. 8, this difference was statistically significant (p=0.05). With the outlier included, the difference between these distributions did not reach statistical significance (p=0.06).

Discussion

Refixation of aseptic loosened hip stems by percutaneous cement injection can improve clinical outcomes for patients with loosened hip prostheses [10]. Cement injection can be performed either with or without prior interface tissue

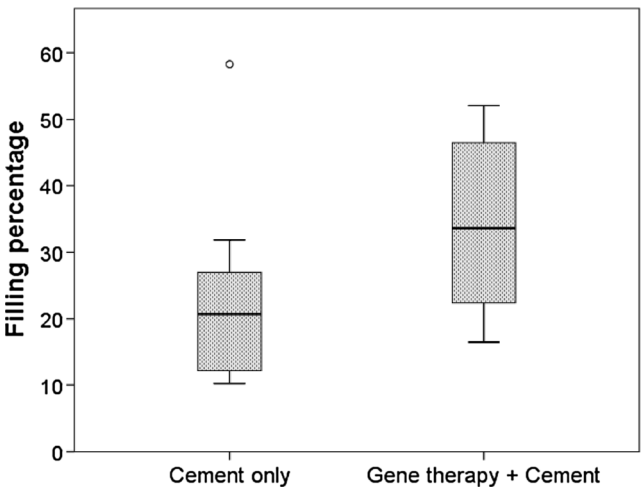

Fig. 8 Cement filling percentages of the osteolytic lesions for patients in the cement-only and GDEPT groups

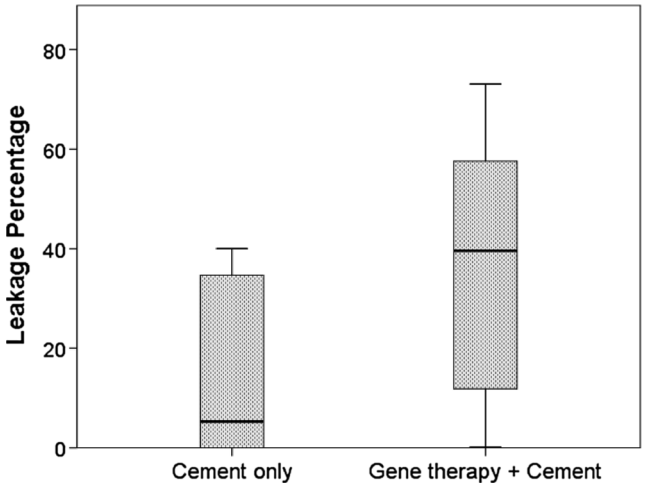

Fig. 9 Cement leakage percentages for patients in the cement-only and GDEPT groups

treatment [8, 9]. The literature on this topic is limited. Earlier phase I-II preclinical and clinical trials found that the adenoviral vector CTL102 and the prodrug CB1954 were viable for removing interface tissue despite possible transient adverse side effects including fever, nausea and leukopenia [10]. This study examines whether differences in cement-injection outcomes between these two approaches were observed.

Our results indicate that preoperative treatment of interface tissue enabled more cement to be injected into the periprosthetic osteolytic lesions. This difference was statistically significant, even in our small sample population. The larger injected cement volumes for the patients who underwent preoperative interface tissue removal was not correlated with the patients' preoperative lesion volume as the distribution of the latter was the same for the cement-only and GDEPT groups. With the exception of a single outlier, the larger injected cement volumes in the GDEPT group also manifested in higher fractions of cement filling of the target lesions. This greater degree of cement filling might translate to better refixation of loosened prostheses [15].

The disadvantage to the hypothesized improved refixation in the GDEPT group may be side effects caused by the treatment GDEPT itself as well as adverse effects caused by bone cement leaking, e.g., into surrounding muscle tissue. Given that elderly patients with aseptically loose hip prostheses present with invalidating pain and severely limited mobility, the benefits of better refixation are seen to outweigh the increased risk of transient side effects or cement leakage, which may cause temporary discomfort.

With the exception of a single outlier in the GDEPT group, the observed cement leakage percentages support the view that prior apoptosis-driven removal of fibrous interface tissue permits injected cement to flow more freely in the periprosthetic space during the cement injection procedure—both into and out of osteolytic target regions. An interesting question is whether use of more viscous cement is advisable where interface tissue has been sufficiently eliminated. We speculate that the association between lower cement viscosity and cement leakage in percutaneous vertebroplasty [16] may also apply to the scenario of periprosthetic refixation by cement injection.

Osteolysis is a progressive process and is propagated by the presence of interface tissue [17]. Failure to completely remove preexisting interface tissue may lead to progression or recurrence of osteolysis [18]. A positive aspect of fibrous interface tissue removal that was not examined in this study is that fibrous tissue apoptosis and/or removal may reduce the self-propagating progression of osteolysis. Biomechanical finite element simulation has furthermore shown that interface tissue removal increases mechanical stability of the prosthesis [15].

Limitations of this study include the small, consecutive, patient groups that arose from the experimental nature of the interventions described. A phase III study using the adenoviral vector CTL102 and prodrug CB1954 is currently awaiting funding at our institution. All bone cement used in this study was of comparable viscosity. The scope of our study excluded the research question of a possible relationship between cement leakage outside the femur and cement viscosity.

Conclusion

We conclude that the preoperative GDEPT treatment of fibrous interface tissue had a measurable effect on the efficacy of percutaneous cement injection into the periprosthetic space. Only cement injection without fibrous tissue removal is currently possible in routine clinical practice because of a lack of available tissue removal agents and methodologies. We encourage continued research into minimally invasive methods for removing fibrous interface tissue prior to refixation by cement injection.

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Conflict of interest Each author certifies that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

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We declare that this manuscript is the original work of the listed authors, has not been published before and is not currently being considered for publication elsewhere.

We confirm that the manuscript has been read and approved by all named authors and that there are no persons who were excluded from this list of authors despite satisfying the criteria for authorship.

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