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Two-stage cementless hip revision for peri-prosthetic infection with an antibacterial hydrogel coating: results of a comparative series

Luigi Zagra[1] · Enrico Gallazzi[1] · Delia Romanò[2] · Sara Scarponi[2] · Carlo Romanò[3]

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Abstract

Purpose The aim of this study was to investigate the hypothesis that a two-stage exchange procedure, performed with an antibiotic-loaded, fast-resorbable hydrogel coating, may provide better infection cure rate than a two-stage procedure without the coating, in patients affected by peri-prosthetic hip infection.

Methods In this case-control study, 27 patients, treated with a two-stage procedure, using cementless implants coated with an antibiotic-loaded hydrogel (DAC®, "Defensive Antibacterial Coating"), were compared with 27 matched controls, treated with a two-stage cementless revision procedure, without the coating.

Results At a mean follow-up of 2.7 (minimum 2.1–maximum 3.5) years, no evidence of infection, implant loosening, or adverse events were observed in the DAC-treated group, compared to four cases of infection recurrence in the control group.

Conclusions Although in a relatively limited series of patients our data show that cementless two-stage hip revision, performed with an antibacterial hydrogel coating, may provide better infection control than two-stage without the coating, with reduced hospitalization time, these findings warrant further studies in the possible applications of antibacterial coating technologies to treat implant-related infections.

Keywords Antibacterial coatings · DAC · Peri-prosthetic joint infection · Revision surgery · Total hip replacement

Introduction

Peri-prosthetic joint infection (PJI) remains among the first reasons for failure of total hip replacement (THR) [1, 2], with an incidence that is on the rise, according to registry data [3, 4]. Furthermore, PJIs are associated with an increase in morbidity and even in mortality rate and represent a worrisome cost concern for public health systems [5]. The risk of post-surgical infection is even higher following prosthetic revision surgery: according to the North European Joint Registry data, the percentage of diagnosed PJIs goes from 8.1% after the first revision surgery to 23.3% after the second revision procedure [6].

✉ Luigi Zagra
luigi.zagra@fastwebnet.it

[1] Hip Department, IRCCS Istituto Ortopedico Galeazzi, Via R. Galeazzi 4, 20161 Milan, Italy

[2] Department of Reconstructive Surgery of Osteo-articular Infections, IRCCS Istituto Ortopedico Galeazzi, Milan, Italy

[3] Centro Medico, Corso Venezia 2, 20121 Milan, Italy

Current diagnostic and treatment strategies of PJI offer suboptimal results, with reinfection rates that may exceed 10% after two-stage revision surgery [7–9]. In this context, antibacterial coating of implants has been proposed to reduce post-surgical infections [10–12]. Among various technologies, recently, a fast-resorbable antibacterial hydrogel coating (DAC®, Novagenit Srl, Mezzolombardo, TN, Italy), composed of covalently linked hyaluronan and poly-D,L-lactide, has been shown to be able to decrease early post-surgical infection rate after both joint replacement and osteosynthesis [13–15]. Acting as a physical barrier to bacterial adhesion and intra-operatively loaded with antibiotic(s), the coating is thought to provide a key advantage to the host's cells in the "race to the surface" of the implant [16].

The present study was performed to investigate the hypothesis that a two-stage cementless revision of infected hip prosthesis, performed with DAC-coated implants, may provide better results with a lower reinfection rate than a two-stage revision, without the coating. As a secondary endpoint, the safety of the device was considered analyzing possible adverse events.

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Materials and methods

Study design and population

The present study was conducted in accordance with the Helsinki declaration and was approved by the local Ethical Committee (protocol IDAC-2013-THA/TKA—IRCCS San Raffaele Hospital, Milan, Italy). All patients gave their informed consent to data collection and analysis.

In this retrospective, case-control study, a consecutive series of 27 patients, affected by peri-prosthetic hip infection and undergoing a two-stage procedure using DAC-coated implants from November 2013 to July 2015, were compared with a series of 27 controls, matched for age and host type, operated on with a two-stage procedure, without the coating in the same time period. The patients were selected for the DAC treatment according to the availability of the hydrogel that was limited at that time due to production and supply limitation, thus generating a non-selective utilization.

Inclusion criteria were delayed or late peri-prosthetic hip infection as defined by the International Consensus Meeting criteria [17], treated with a two-stage procedure and a cementless revision implant. Reasons for exclusion were large soft-tissue defects, preventing skin closure not suitable for second stage and previous failed revision operations for infection.

Pre-operative clinical, radiographic, and laboratory test examinations, including host type according to McPherson et al. [18], were recorded in all cases. All patients underwent routine pre-operative workup, including pre-operative ultrasound-guided joint fluid aspiration and culture of the collected fluid.

The total study population was 54 patients. Eleven men and 16 women were included in the DAC group and 14 men and 13 women in the control group (mean age 63.9 ± 11.7 and 64.8 ± 10.1 years in the DAC and in the control group, respectively, p = ns). The time from infection onset to revision surgery was 2.5 ± 1.8 years in the DAC series and 2.6 ± 1.8 months in the control group (p = ns). According to McPherson's classification 19 (70.4%) patients were type B and 7 (25.9%) were type C in the DAC group, while type B and C hosts were 22 (81.5%) and 4 (14.8%) in the control series, respectively; the remaining patients were one type A per each group.

All removed implants during the first stage were sent with samples of peri-prosthetic tissue for microbiological analysis. Identified bacteria for each group are reported in Table 1. Overall, bacterial population was similar among the two groups, in particular concerning the MRSA percentage was the same (18.5% of MRSA in DAC group vs 18.5% MRSA in controls).

Surgical treatment and DAC preparation

First-stage surgery consisted in the removal of infected prosthesis, debridement of soft tissues and infected bone, removing of foreign bodies following a standardized surgical procedure, and the placement of an antibiotic-loaded spacer (StageOne Zimmer Biomet, Warsaw, IN, USA, or Vancogenx-Space, Tecres, Sommacampagna, Italy). After the first surgery, each patient, independently from the groups, underwent a 4–6-week antibiotic therapy, starting with a broad spectrum coverage with vancomycin 1 g bid and meropenem 1 g tid, and then switched to targeted oral therapy based on intraoperative culture.

The second procedure, for definitive implant placing, was performed after CRP normalization and in the absence of clinical signs of infection, according to the IDSA guidelines [19], at a mean interval of 11.3 (minimum 9, maximum 14) weeks. At the time of reimplantation, the antibiotic-loaded spacer was removed and another debridement of bone and soft tissues was performed. After adequate preparation, a cementless prosthesis of different manufacturers was implanted according to bone stock and surgeon's preference (Fixa T-Pore®, Pinnacle®, Delta TT®, or Trabecular Metal™ cups and Aequa®, Reclaim®, Alloclassic Zweymuller®, or Lima Revision® stems).

The DAC hydrogel was prepared intra-operatively according to the manufacturer's indications. In brief, the syringe prefilled with 300 mg of sterile DAC powder was mixed with a solution of 5 mL of sterile water and with the tailored antibiotic, either alone or in combination. According to first-stage antibiograms, vancomycin was used in 17 cases, teicoplanin and ceftazidime in one case, respectively, a combination of vancomycin and rifampicin in one other case, and a combination of vancomycin and meropenem in seven patients. In particular, the association vancomycin and meropenem was the

Table 1 Microorganisms identified at the time of surgery. *MRSA* methicillin-resistant *Staphylococcus Aureus*

DAC treated		Controls		p
Staphylococci	15 (55.6%)	Gram-positive cocci	15 (53.1%)	ns
(of which) MRSA	5 (18.5%)	(of which) MRSA	4 (18.5%)	ns
Streptococci	6 (22.3%)	Streptococci	4 (12.6%)	ns
Gram negative cocci	1 (3.7%)	Gram-negative cocci	1 (3.1%)	ns
Anaerobes	1 (3.7%)	Anaerobes	1 (3.1%)	ns
Negative	4 (14.8%)	Negative	6 (18.6%)	ns

preferred choice in those cases in which the pathogen was not known. Five minutes after mixing, the DAC was placed on both the acetabular and the femoral components, by directly spreading it on the surfaces of the implant (Fig. 1). Care was taken to spread the hydrogel on all implant surfaces, including the extra-medullary parts of the implant and on the fixation screws when used. On the average, 10.2 mL ± 1.3 mL was used per patient. The implant was then inserted in the bone in the usual way, with the same surgical technique in the two groups.

After the surgery, systemic antibiotic therapy was continued until the results of intra-operative cultures, and for a minimum of two weeks post-operatively. Low-molecular-weight heparin was used as deep vein thrombosis prophylaxis for four to six weeks.

Endpoints and follow-up

The primary endpoint was the rate of infection recurrence defined according to the International Consensus Meeting [17, 20]. Secondary endpoints were the length of hospital stay after surgery, including the first and the second stages, that was considered a positive predictor of recovery and the clinical score at follow-up (Harris Hip Score).

For the purpose of the study, evaluation at follow-up for the DAC group was performed by a physician blinded to the type of treatment (DAC or no-DAC coating). Clinical assessment included the Harris Hip Score and the evaluation of any sign of infection at the site of surgery (pain, redness, warmth, swelling, draining wound, fistulas, etc.). Radiographic examination, including the evaluation of osteolysis or progressive (> 2 mm) radiolucent lines around the implant or signs of implant loosening or subsidence, was also performed.

Patients in the DAC group were also screened for any adverse event during the hospital stay and at the outpatient consultation.

Statistical analysis

Descriptive statistics were used to summarize the data. Categorical data were analyzed using Fisher's exact test; continuous data were compared using Student's *t* test (http://graphpad.com/). *P* values of less than 0.05 were considered statistically significant.

Results

At an average follow-up of 2.7 ± 0.6 years (minimum 2, maximum 3.5 years), the Harris Hip Score was 81.6 ± 15.2 and 84.6 ± 15.8 in the control and in the DAC-treated group, respectively ($p = 0.4$).

No infections were observed in the DAC group, compared to four (14.8%) (two *Staphylococcus epidermidis*, one *S. Capitis*, and one MRSA) in the control group ($p = 0.11$). The recurrences were caused by the same pathogen isolated in the first episode.

The average total hospital stay including rehabilitation differed significantly between groups: 28.2 ± 3.9 and 33.8 ± 5.4 days in the DAC and in the control group, respectively ($P < 0.0001$; 95% CI from − 8.172 to − 3.028).

Concerning safety of the device, no local or systemic adverse events directly attributable to the DAC hydrogel were observed. One patient in the control group had a delayed wound healing. The patient was treated conservatively and second-intention healing of the wound was eventually obtained. One dislocation was recorded in each group. The patient in the control group was treated with closed reduction, while the dislocation in the DAC group required an open reduction, with exchange of the modular parts of the implant.

Radiographic examination revealed no signs of focal osteolysis around the implant in either group; no signs of implant loosening or subsidence were reported in either group and no Brooker 3 or 4 heterotopic ossifications were observed.

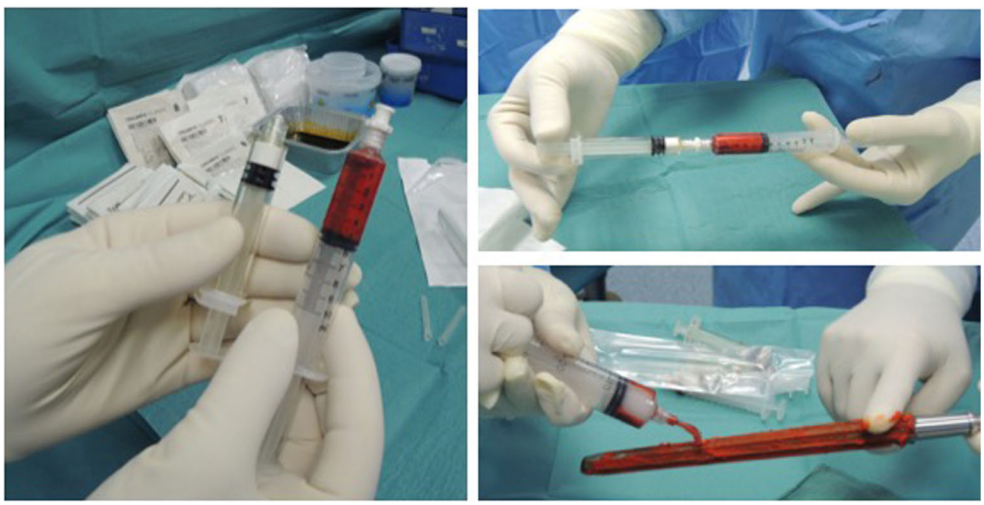

Fig. 1 Intra-operative DAC preparation. In the left panel, the surgeon holds in his left hand the syringe prefilled with 300 mg of sterile DAC powder, and in his right hand 5 mL of a solution of 5% rifampicin. In the top right panel, the surgeon mixes the content of the two syringes. In the bottom right panel, the hydrogel is applied to the prosthesis stem

Discussion

This study shows that two-stage hip revision surgery using cementless implants and an antibacterial hydrogel coating can be safely performed, with a reduction of average hospital stay and a trend towards a better infection control, when compared to matched patients receiving uncoated implants.

According to the pathophysiological model for PJIs of the "race for the surface," the first hours after the implant placement are crucial for the development of an infection [16, 21, 22]. In line with this, several technologies have been proposed to prevent bacterial colonization [10–12, 23].

In previous reports, DAC hydrogel coating was proven to be safe and effective in reducing early post-surgical infection both in arthroplasties and in internal osteosynthesis [15]. Our results confirm the previous observations, in two-stage hip revision surgery, at a longer term follow-up. In particular, even in this study, no detrimental effects on implant osseointegration were noted, which is a key requirement for any antibacterial coating of orthopaedic implants.

Currently, antibacterial coatings have no definite role in proposed treatment algorithms for PJIs [22], even if several preclinical studies have shown the efficacy of different coating technologies in preventing implant-related infection [10]. On the other hand, however, clinical studies on antibacterial coatings remain particularly few. In this regard, silver coating is probably the most studied [24]. In a retrospective analysis, Wafa et al. showed that the use of silver-coated tumour prosthesis was effective in reducing early post-operative septic complications both in oncological patients and in two-stage revision for infection [25]. On the other hand, Zajonz et al., in a prospective study on 34 patients, found only a limited efficacy of silver-coated prosthesis in revision surgery for PJIs [26]. Silver-coated implants also suffer several limitations that prevented, until now, their larger clinical use, including silver cytotoxicity, impossibility to coat all the implant, and high costs [27].

While there are several reports on the use of other antimicrobial agents, such as intra-operative use of vancomycin powder or antibiotic-impregnated bone pellets [28–30], they work in a different way from DAC coating. As a matter of fact, DAC acts at the bone-prosthesis interface, thus preventing biofilm formation on the implant; moreover, as previously shown, it can be used on any implant surface (excluding bone/cement and cement/prosthesis interface) and in most situations. On the other hand, local vancomycin powder is placed in the soft tissues, which makes it difficult to protect the implant at its bone interface; antibiotic-impregnated bone pellets are used when there is a need for a bone graft, and usually only in the acetabular side, and have no evidence in comparative studies in the hip.

To the best of our knowledge, the present study is the first one showing that a fast-resorbable antibacterial hydrogel coating may reduce the reinfection rate of two-stage cementless revision surgery, without any detectable side effect. A secondary finding was a shorter hospitalization time in the cohort of patients treated with DAC. Even if this is a doubtful effect, a better and shorter recovery could be hypothesized with a positive effect both on patient recovery and on costs.

This study has several limitations. First, the study population was relatively small, so only a trend towards a superiority of the DAC-treated cohort concerning our first endpoint (recurrence of infection) could be shown. This was due to the fact that the CE mark (the European Conformity certification that is necessary for the introduction of a device in the market for routine use) for the DAC hydrogel was put on hold in July 2015 and until January 2017. This, together with the limited supply of the hydrogel in the study period, restricted our possibility to continue the study in a larger population. For this reason, we consider the present report as a pilot study that may form the basis for further investigations. Second, patient cohorts were matched for age, and host type. However, it should be noted that it was not possible to include specific co-morbidities in the cohorting process (e.g., diabetes and smoking vs no diabetes and smoking) or all types of pathogen(s). Differences in these and other variables may have introduced a bias in the comparison between series and should therefore be taken into consideration.

Another limitation is the relatively short follow-up period anyway long enough to exclude side effects of the hydrogel, lack of implant stability, and reinfection. A further limitation is the lack of standardized systemic antibiotic therapy. This may have had an impact on infection control and on the measurement of overall treatment duration. Similarly, the duration of hospital stay may have been influenced by variables not analyzed adequately in this retrospective study, but anyway the discharge criteria were standardized.

These limitations notwithstanding our findings disclose for the first time the efficacy of a possible approach to managing peri-prosthetic joint infections with a two-stage procedure, using cementless prostheses, coated with a fast-resorbable, antibiotic-loaded hydrogel at least as adjuvant of systemic antibiotic therapy and with no detrimental effects. If confirmed in larger studies and at longer term follow-up, this solution, applied on a large scale, may contribute to significantly improve the overall outcomes, length, and costs of peri-prosthetic joint infection management.

Compliance with ethical standards

The present study was conducted in accordance with the Helsinki declaration and was approved by the local Ethical Committee (protocol IDAC-2013-THA/TKA—IRCCS San Raffaele Hospital, Milan, Italy).

Conflict of interests LZ, EG, DR, SS have nothing to disclose related to this paper. CLR received consultant fees from Novagenit Srl.

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