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One-stage exchange with antibacterial hydrogel coated implants provides similar results to two-stage revision, without the coating, for the treatment of peri-prosthetic infection

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Abstract

Purpose Aim of this study was to verify the hypothesis that a one-stage exchange procedure, performed with an antibiotic-loaded, fast-resorbable hydrogel coating, provides similar infection recurrence rate than a two-stage procedure without the coating, in patients affected by peri-prosthetic joint infection (PJI).

Methods In this two-center case–control, study, 22 patients, treated with a one-stage procedure, using implants coated with an antibiotic-loaded hydrogel [defensive antibacterial coating (DAC)], were compared with 22 retrospective matched controls, treated with a two-stage revision procedure, without the coating.

Results At a mean follow-up of 29.3 ± 5.0 months, two patients (9.1%) in the DAC group showed an infection recurrence, compared to three patients (13.6%) in the two-stage group. Clinical scores were similar between groups, while average hospital stay and antibiotic treatment duration were significantly reduced after one-stage, compared to two-stage (18.9 ± 2.9 versus 35.8 ± 3.4 and 23.5 ± 3.3 versus 53.7 ± 5.6 days, respectively).

Conclusions Although in a relatively limited series of patients, our data shows similar infection recurrence rate after one-stage exchange with DAC-coated implants, compared to two-stage revision without coating, with reduced overall hospitalization time and antibiotic treatment duration. These findings warrant further studies in the possible applications of antibacterial coating technologies to treat implant-related infections.

Level of evidence III.

Keywords Infection · PJI · One-stage revision · Two-stage revision · Coating · DAC

Introduction

Infection remains one of the most common reasons for revision of joint prosthesis [1, 10, 24, 45, 46]. Peri-prosthetic joint infection (PJI) is associated with increased health-care costs for prolonged hospitalization and rehabilitation and increased use of antibiotics [38]. Moreover, PJIs are associated with an increase in morbidity and even mortality, since PJI patients usually undergo repeated surgeries [2]. Two-stage exchange is considered by many as the procedure of choice, with the highest number of procedures reported worldwide for both the knee [24] and the hip [14], even if its superiority in terms of lower infection has not been demonstrated [13, 14, 18, 24, 27, 35]. In addition, compared to the one-stage procedure, two-stage revision is associated with delayed functional recovery [19, 26], higher costs, and possible higher morbidity and mortality [2, 20, 21, 42, 50].

Recently, a fast-resorbable hydrogel coating composed of covalently linked hyaluronan and poly-D,L-lactide, termed defensive antibacterial coating (DAC®, Novagenit Srl, Mezzolombardo, Italy), has been shown to be safe and effective in reducing early postsurgical infections after joint replacement [41] and internal osteosynthesis [29]. However, no data are available concerning its possible use in the treatment of infected joint prosthesis. Based on in vivo data, showing

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that DAC hydrogel coating is effective in significantly reduce post-surgical infection in a model of highly contaminated orthopaedic implant [4, 15], the present study was undertaken to test the hypothesis that a one-stage revision of infected joint prosthesis, performed with DAC-coated implants may provide results similar to a two-stage revision, without the coating.

Materials and methods

In this two-center, case–control study, a prospective series of patients affected by peri-prosthetic joint infection, undergoing a one-stage procedure using DAC-coated implants, were compared with a retrospective series of matched patients, treated with a two-stage procedure without the coating. Twenty-two patients, treated between 2013 and 2015 with a one-stage procedure, were compared with a retrospective series of 22 controls matched for age, sex, site of infection and host type according to McPherson's classification [32], operated on with a two-stage procedure. In particular, sex and site of infection were matched 1:1, while age and number of co-morbidities may differ, in matched patients, in the range ± 10 years and ± 1, respectively. All patients gave their informed consent to data collection and analysis.

Surgical treatment and DAC preparation

All one-stage group patients underwent routine pre-operative work up, including pre-operative joint fluid aspiration and culture of the collected fluid. Inclusion criteria for one-stage revision were delayed or late prosthetic knee or hip infection as defined by Musculoskeletal Infection Society (MSIS) criteria [39]. Reasons for exclusion were lack of pre-operative identification of the pathogen, large soft-tissue defects preventing skin closure, patient refusal to undergo a one-stage approach.

After removal of the infected implant and throughout surgical debridement, one-stage revision was performed according to current practice [22] with the use of cementless or hybrid (partially cemented) implants. All hip revision prostheses ($N=5$) were cementless, whereas knee revision implants ($N=17$) were cemented only in the epiphyseal part of the prosthesis. At the time of surgery all implants were coated with a uniform layer of DAC® (Novagenit Srl, Mezzolombardo, Italy), a fast-resorbable, hydrogel coating. The hydrogel was reconstituted intra-operatively according to the manufacturer's indications. In brief, the content of a syringe prefilled with 300 mg of sterile DAC powder was mixed with a solution of 5 mL of sterile water for injection and with the desired antibiotic(s) selected on the basis of pre-operative culture, at a concentration ranging from 25 to 50 mg/mL. On the basis of pre-operative culture, the DAC hydrogel was loaded with vancomycin 5% in 14 patients (63.3%) and with a combination of vancomycin 5% and meropenem 5%. in 8 patients (27.4%). Approximately 3–5 min after mixing, the DAC hydrogel was placed directly onto the implant, which was then inserted in the joint in the usual way. 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 ± 1.3 mL were used per patients.

Controls were identified in a database of patients operated on with a two-stage procedure at the same centers between 2012 and 2014. Inclusion criteria were a peri-prosthetic knee or hip infection as defined by MSIS criteria [39] treated with a two-stage procedure, using a preformed antibiotic-loaded spacer (Spacer G or Spacer K, Tecres SpA, Sommacampagna, Italy) and a cementless or hybrid revision implant, without DAC coating.

The total study population was 44 patients. Nine men and 13 women were included in each group (mean age 71.3 ± 13.6 and 71.9 ± 8.3 years in the one-stage and the two-stage group, respectively). In each group, 5 underwent joint revision for septic hip arthroplasty and 17 for septic knee prosthesis. The time from infection onset to revision surgery was 21.6 ± 9.2 months in the DAC series and 23.7 ± 10.7 months in the two-stage group. Gram-positive pathogens were isolated in most cases (21/23 or 91.3% and 20/23 or 86.9% in the one- and the two-stage group, respectively). Methicillin-resistant *Staphylococci* accounted for 52.1% (12/23) of all the isolates in the one-stage cohort and for 30.4% (7/23) in the two-stage group (Tables 1, 2).

Follow-up and endpoints

The primary endpoint was the rate of infection recurrence defined according to MSIS criteria [39]. Secondary endpoints were the length of hospital stay after surgery, including the first and the second stage for two-stage procedures, the duration of antibiotic therapy, and the clinical scores at

Table 1 Pre- and peri-operative data

Data	One stage ($N=22$)	Two stage ($N=22$)	P value
Sex (male/female)	9–13	9–13	(n.s.)
Age (years)	71.3 ± 13.6	71.9 ± 8.3	(n.s.)
Site (hip/knee)	5–17	5–17	(n.s.)
Duration of infection (months)	21.6 ± 9.2	23.7 ± 10.7	(n.s.)
Host type (McPherson)			
A	3	4	(n.s.)
B + C	19	18	(n.s.)

One-versus two-stage cohorts. P values > 0.05 are considered not significant (n.s.)

Table 2 Isolated pathogens

Microorganism	One stage ($N=22$)	Two stage ($N=22$)
MSSA	5	4
MSSE		3
MRSE	6	3
MRSA	6	4
Staphylococcus lugdunensis	1	
Staphylococcus capitis		1
Staphylococcus hominis		1
Streptococcus salivarius		1
Streptococcus gallolyticus		1
Streptococcus agalactiae		1
Streptococcus mutans	1	
Streptococcus mitis	1	
Propionibacterium acnes		1
Enterococcus faecalis	1	
Escherichia coli	1	
Pseudomonas aeruginosa	1	1
Klebsiella pneumonia		1
Acinetobacter baumannii		1
Negative culture		3
Mixed flora	1	3

MSSA methicillin-sensitive *S. aureus, MRSA* methicillin-resistant *S. aureus, MSSE* methicillin-sensitive *S. epidermidis, MRSE* methicillin-resistant *S. epidermidis*

follow-up (SF-12 score, Harris Hip or Knee Society Scores, as appropriate).

Radiographic examination, including the evaluation of osteolysis or progressive (>2 mm) radiolucent lines around the implant or signs of implant loosening or subsidence [7], was also performed.

The study was approved by the local Ethical Committee (protocol IDAC-2013-THA/TKA, IRCCS San Raffaele Hospital, Milan, Italy).

Statistical analysis

Sample size was calculated assuming non-inferiority of the one-stage procedure, as compared to the two-stage exchange, using infection recurrence/persistence whenever at follow-up as the primary endpoint (https://www.sealedenvelope.com/power/binary-noninferior/). Considering an average 8% failure rate for either procedure, an alpha significance level of 5% and a power of 90%, a total of 42 patients were required to exclude a difference in favour of the two-stage procedure of more than 25%. The non-inferiority margin of 25% was chosen based on the lower and upper limits of the confidence intervals reported in the most recent systematic reviews comparing one- and two-stage revision in the hip [14] and the knee [25] and on a recent retrospective comparative study [49] that investigated cementless one-stage hip exchange versus two-stage revision.

Categorical data were analyzed using Fisher`s exact test. Continuous data were compared using Student's *t* test (http://graphpad.com/). *P* values less than 0.05 were considered statistically significant. Normal distribution of continuous data was tested using the Shapiro–Wilk Normality Test (http://sdittami.altervista.org/shapirotest/ShapiroTest.html).

Results

At an average follow-up of 29.3 ± 5.0 months, recurrence of infection developed in 2 (9.1%) patients in the one-stage group and in 3 (13.6%) patients in the two-stage group at 29.2 ± 4.9 months. One patient, with a history of recurrent erysipelas, suffered another episode of erysipelas in the operated limb 8 months after an otherwise successful one-stage procedure with vancomycin-loaded DAC, which evolved to severe soft-tissue infection and periprosthetic re-infection. The other failed one-stage procedure occurred in a patient with pre-operative cultures positive for multi-resistant *S. aureus*, while microbiological analysis of the retrieved implant yielded multiresistant *E. coli*, obviously not sensitive to vancomycin, which was the antibiotic added to the hydrogel-coating during the one-stage procedure.

In the two stage group, infection recurrence was noted in two patients after the first surgery, both of which with positive intra-operative samples, who received a re-spacer. Infection recurrence developed in another patient 12 months after revision surgery. All the other patients had negative intra-operative microbiological findings at the time of reimplantation.

There were no differences in the SF-12, Harris Hip and Knee Society Scores between the two groups at follow-up (Table 3). The average total hospital stay differed significantly: 18.9 ± 2.9 and 35.8 ± 3.4 days in the one- and the two-stage group, respectively ($P<0.0001$). Similarly, the duration of systemic antibiotic therapy was significantly longer in the two-stage group: 53.7 ± 5.6 versus 23.5 ± 3.3 days, respectively ($P<0.0001$). Antibiotic treatment was administered, on average, 28.5 ± 2.8 days after spacer implant and for 25.2 ± 5.6 days after reimplantation in patients undergoing two-stage revision. The mean time interval between stages was 78.7 ± 22.6 days.

No adverse events associated with the use of DAC were observed. Radiographic examination showed no signs of focal osteolysis around the implant in either group. Progressive (>2 mm) radiolucent lines around the implant were observed in one patient in the DAC group and in three patients in the control group. No signs of implant loosening or sinking were reported in either group and no Brooker 3 or 4 heterotopic ossifications were observed.

Table 3 Outcomes comparison

Data	One stage ($N=22$)	Two stage ($N=22$)	P value
Follow-up (months)	29.3 ± 5.0	29.2 ± 4.9	(n.s.)
HHS ($N=5$)	85.4 ± 3.6	83,6 ± 7.4	(n.s.)
KSS ($N=17$)	78.0 ± 6.1	77.3 ± 6.4	(n.s.)
SF 12 (P+M)	84.4 ± 7.4	84.3 ± 7.4	(n.s.)
Systemic antibiotic therapy (days)	23.5 ± 3.3	53.7 ± 5.6	0.0001
Hospital length of stay (days)	18.9 ± 2.9	35.8 ± 3.4	0.0001
Infection recurrence	2	3	(n.s.)

One-versus two-stage cohorts. P values > 0.05 are considered not significant (n.s.)

SF12 physical and mental component summary scales of the Health Survey Questionnaire

KSS Knee Society Score, *HHS* Harris Hip Score

Discussion

The most important finding of the present study was the observation that the rate of infection early recurrence was similar in the patients treated with a two-stage procedure and in those who received a one-stage cementless or hybrid implant, coated with an antibiotic-loaded, fast-resorbable hydrogel, without any detectable side effect. Moreover, the total length of hospital stay and the duration of systemic antibiotic therapy were significantly shorter in the one-stage cohort. Our findings share observations from the literature [37, 40] reporting average satisfaction with functional results in both patient cohorts.

Relatively few studies to date have compared the outcomes after one- and two-stage revision for PJI treatment, with a majority of retrospective studies [9, 27, 48]. Systematic reviews have not demonstrated the superiority of the two-stage over the one-stage approach to knee and hip revision, perhaps owing to the high heterogeneity of the data between studies [14, 18, 25].

Various techniques for one-stage exchange have been reported, including the use of cemented or cementless implants [14, 48], with or without local antibacterial protection [28, 46, 48]. According to a recent literature review [14], cementless or cemented one-stage hip revision provides, on average, similar infection control rates. With regard to local antibacterial protection, except for isolated reports [23, 46], one-stage revision is nearly always reported with the use of antibiotic-loaded bone cements, according to the original description by Buchholz [5, 51], or with antibiotic-loaded bone grafts [48]. This is based on a large body of evidence showing the efficacy of local antibacterial delivery [6]. On the other hand, research into optimizing local antibacterial protection of implanted biomaterials is still ongoing [17], with various possible new solutions, including specifically designed antibacterial and antibiofilm coatings [12, 43]. Among these, silver coating is probably the most extensively studied [8, 16, 44]. However, despite the demonstrated clinical efficacy of silver-coated implants, a recent retrospective, comparative study [47], the routine use of this technology remains limited for various reasons, including the possible toxicity of silver ions [33], inability to protect all the implant surfaces, complex manufacturing and cost issues [36].

The efficacy and safety of DAC hydrogel has been documented in preclinical studies [4, 11, 15], with no detrimental effects observed on bone healing and osteointegration [3]. Two large, multi-institutional trials demonstrated its efficacy in reducing early surgical site infection after total hip and knee replacement [31, 41] and after internal osteosynthesis [29, 30]. The present study provides further evidence for the clinical safety of this medical device, at long-term follow-up, and its potential application in one-stage exchange of infected prosthesis.

This study has several limitations. First, both hip and knee revisions were included in the analysis. This is in line with the design of a previously published study on silver coating [47] and reflects the vision according to which periprosthetic infections share comparable diagnostic and treatment protocols, regardless of the joint involved [14, 25, 34, 43]. Second, patient cohorts were matched for age, sex, site of infection and host type. However, for practical reasons, it was not possible to include specific co-morbidities in the cohorting process (e.g. diabetes and smoking versus no diabetes and smoking, etc.) or type 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-term follow-up period. 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.

Finally, it is also worth noting that this study did not address the possibility that a one-stage exchange performed without the DAC coating could have provided similar results

as with the coating, To the best of our knowledge, there is only one retrospective study, performed on a very limited cohort of 12 very selected patients, that investigated cementless one-stage revision without local antibacterial protection and reported a success rate of only 83.3%. On this basis, designing a comparative study to investigate one-stage revision with and without the DAC coating would have been extremely difficult both from an ethical and practical point of view, especially concerning patients' recruitment.

These limitations notwithstanding, our findings disclose for the first time the efficacy of a new possible approach to managing peri-prosthetic joint infections with a one-stage procedure, using cementless or hybrid prostheses, coated with a fast-resorbable, antibiotic-loaded hydrogel. If confirmed in larger studies and at long-term follow-up, this solution, applied on a large scale, may contribute to significantly reduce the overall length and costs of peri-prosthetic joint infection management.

Conclusion

The present study shows that one-stage exchange for infected total hip or knee prostheses can be safely performed with cementless or hybrid implants coated with a fast-resorbable, antibiotic-loaded hydrogel. As compared to a retrospective series of matched controls treated with a two-stage procedure, one-stage exchange provided similar infection control, with shorter duration of overall systemic antibiotic therapy and total hospital stay.

Author contribution NC and CLR were involved in study design, data collection, results interpretation and writing the manuscript. NL, EG and LD were involved in data collection, results interpretation and reviewing of the manuscript.

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Compliance with ethical standards

Conflict of interest CLR has received consulting fees from Novagenit Srl. The other authors declare that they have no conflict of interest.

Ethical approval All investigations were conducted in conformity with ethical principles of research and institutional approval of the human protocol for this investigation was obtained.

Informed consent Informed consent for participation in the study was obtained.

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