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ORIGINAL ARTICLE

Antibacterial hydrogel coating in joint mega-prosthesis: results of a comparative series

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Abstract

Purpose Joint mega-prosthesis after bone tumors, severe trauma or infection is associated with high rates of post-surgical septic complications. A fast-resorbable antibacterial hydrogel coating (DAC®, Defensive Antibacterial Coating) has previously been shown to be able to significantly reduce surgical site infection in various clinical settings. Aim of the present study was to evaluate the safety and efficacy of the DAC hydrogel coating to prevent early periprosthetic joint infection after joint mega-prosthesis.

Methods In this three-centers, case–control study, 43 patients, treated with an antibacterial hydrogel coated mega-prosthesis for oncological ($N=39$) or non-oncological conditions ($N=4$), were retrospectively compared with 43 matched controls, treated with mega-implants without the coating. Clinical, laboratory and radiographic examinations were performed to evaluate the occurrence of post-surgical infection, complications and adverse events.

Results At a mean follow-up of 2 years, no evidence of infection or adverse events were observed in the DAC-treated group, compared to six cases of post-surgical infection in the control group.

Conclusion This matched case–control study shows that a fast-resorbable, antibiotic-loaded coating can be safely used to protect joint mega-prosthesis, providing a reduction of early surgical site infections with no side effects. Larger prospective trials with longer follow-ups are warranted to confirm this report.

Trial registration RS1229/19 (Regina Elena National Cancer Institute Experimental Registry Number)

Keywords Infection · Prevention · Mega-prosthesis · Mega-implants · Coating · Hydrogel · DAC

Introduction

Modular mega-prosthesis is a widely accepted procedure for joint reconstruction after segmental resection for bone tumors, even if burdened by a relatively high complication rate, when compared to primary joint replacements [1].

Among various complications, post-operative infection remains the most frequent and challenging. In fact, while periprosthetic joint infection (PJI) is reported in the range of 0.25–2.0% after primary hip and knee arthroplasty [2] and 5–8% in revision surgery [3], peri-mega-implant infection (PMI) following tumor resection has a documented incidence ranging from 7.4% in metastatic tumors to more than 20% in sarcoma, also depending on tumor location and associated co-morbidities [4–6]. As a matter of fact, in spite of current prophylactic measures, PMI remains the leading reason for early failure and reoperation of mega-implants [7]. Moreover, the management of PMI is particularly challenging, often requiring complex surgeries for implant removal and reconstruction and need for prolonged antibiotic treatment and hospitalization, with an increased risk of limb amputation and mortality rate [8].

Over the years, several options have been considered to mitigate the risk of post-surgical septic complications

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following mega-implants, including prolonged peri- post-operative antibiotic prophylaxis [9] and pre-manufactured antibacterial coatings, based on silver or iodine [10–12]. Although showed to be successful in some non-randomized clinical trial, these technologies are currently not yet available in the market (iodine coating), or suffer some limitations that is preventing their large-scale use (silver coatings) [11, 12].

Recently, a point-of-care antibacterial coating that can be directly applied to the implant at the time of surgery, has been introduced for the clinical use in orthopedic and trauma. This fast-resorbable, hyaluronan-based hydrogel coating [DAC® (Defensive Antibacterial Coating), Novagenit Srl, Mezzolombardo, Italy] can be intraoperatively loaded with various antibacterial agents and has been experimentally shown to provide a protective barrier against bacterial adhesion and biofilm formation [13, 14]. Clinical trials have further demonstrated its ability to significantly reduce post-surgical PJI and other implant-related infections [15–18], but no data are currently available concerning its safety and efficacy in reducing PMIs in oncological and non-oncological patients.

Aim of the present multi-center, retrospective, comparative study was hence to evaluate clinical performance of the DAC hydrogel coating, following large bone resection and joint reconstruction with joint mega-implants.

A demonstrated effectiveness could provide an important option to decrease the risk of mega-implant failure; indeed, infection can be considered the main cause of prosthesis failure after bone tumor resections.

Material and methods

Study design and population

The present study was conducted in accordance with the Helsinki declaration and approved by the institutional review board (RS1229/19—Regina Elena National Cancer Institute Experimental Registry Number—Rome—Italy).

In this matched case–control observational study, a consecutive series of 43 patients, comprising 24 males and 19 females, undergoing DAC-coated joint mega-prosthesis from September 2014 to February 2016 in three Italian orthopedic-oncological centers, were compared with a retrospective series of matched controls, operated on a mega-prosthesis without the coating. Controls were selected by the propensity score matching, on the basis of age, sex, pre-operative diagnosis and host type (cf. Table 1) [15].

Patients with soft-tissue defects preventing direct skin closure, hosts with life-expectancy less than 1 year and patients with less than 12 months follow-up were excluded from this analysis.

Pre-operative clinical assessment, including host type according to McPherson et al. [16], laboratory tests and radiographic examinations, were performed in all cases.

Surgical procedure, DAC preparation and post-operative follow-up

All patients received a mega-prosthetic implant according to the standard of care of each participating center. Anatomical sites of segmental reconstruction are reported in Table 1.

The surgical protocol and the type of implant device were selected at the discretion of each surgeon. The following implants were used: GMRS™ (Global Modular Replacement System, Stryker, Kalamazoo, MI, the USA) for tumors located in the inferior limb; Mutars® (ImplantCast GmbH, Buxtehude, Germany) for lesions located in the inferior and superior limbs; custom-made prostheses produced by Adler Ortho S.P.A. (Cormano, Italy) and MT-Ortho S.R.L. (Aci Sant'Antonio, Italy). The prosthesis was fixed with antibiotic-loaded bone cement in six and seven patients in the treated group and control groups, respectively. Trevira® [polyethylene terephthalate (PET)] mesh tube for re-attachment of soft tissues was used in two patients in both groups. Bone grafts were applied in three patients in the treated group and in four controls.

DAC hydrogel reconstitution was performed intraoperatively, according to the manufacture specifications, as previously described elsewhere [17]. In brief, the prefilled syringe, containing 300 mg sterile DAC powder, which is provided with the DAC kit, was mixed at the time of surgery with a solution of 5 mL sterile water for injection and the antibiotic(s) chosen by the surgeon, at a concentration ranging from 25 to 50 mg/mL. More specifically, gentamicin alone was used in 23 patients, vancomycin in 9 and a combination of vancomycin and tobramycin or gentamicin in the remaining 12 patients (Fig. 1a).

In the treated population, a particular care was taken to spread a uniform layer of the hydrogel onto each component of the mega-implant, including all modular parts, in order to provide a complete coating (Fig. 1). An average volume of 9.4 ± 6.5 mL of gel (range 5–20 mL) was applied. The coating procedure was accomplished immediately before implantation of the mega-implant into the anatomical site. In the six cases, in which the prosthetic stem was cemented, the antibacterial coating was applied to all the implant surface with the exception of the cemented aspect of the prosthesis.

Among the oncologic population, chemotherapy was administered one to 12 months before surgery in 12 treated patients and in ten controls. Three patients in the treated and in the control group, respectively, received chemotherapy and radiotherapy; 28 treated patients and 30 controls received no therapy. Systemic antibiotic prophylaxis was administered in all patients at the time of surgery

Table 1 Demographics, pre- and intra-operative data

	Treated ($N=43$)	Controls ($N=43$)
Demographics		
Total number (male/female)	43 (24/19)	43 (24/19)
Mean age ± standard deviation (min–max) (years)	45.6 ± 21.3 (13–85)	47.4 ± 19.5 (18–84)
BMI	29.5 ± 6.7 (18.1–38.3)	30.6 ± 6.8 (17.8–38.5)
Host type [McPhersons' classification]		
A	1	1
B	30	30
C	12	12
Diagnosis		
Osteosarcoma	11	11
Chondrosarcoma	6	6
Ewing's sarcoma and other sarcomas	7	7
Giant cell tumor	7	7
Other neoplasia	9	9
Infection	1	1
Aseptic prosthetic loosening	1	1
Fracture	1	1
Resection and reconstruction site		
Proximal femur (oncologic/non-oncologic)	13/2	13/2
Distal femur (oncologic/non-oncologic)	14/1	14/1
Proximal femur/pelvis	2	2
Proximal femur/distal femur	1	1
Proximal humerus	2	2
Proximal tibia	1	1
Proximal humerus/distal humerus	1	1
Proximal humerus/scapula	1	1
Pelvis (oncologic/non-oncologic)	3/1	3/1
Tarsal bone	1	1

and postoperatively for 6.5 ± 3.9 days (range 2–28) in the treated cohort and for 6.4 ± 4.0 days (range 3–28) in the control group.

Patients were followed-up at one, three and six months after surgery, and every 6 months thereafter, with a standard X-ray and other exams based on the primary diagnosis and the specific case.

Primary outcome was the evidence of periprosthetic joint infection as defined by the first International Consensus Meeting of Philadelphia [18]. Infection was considered present when one major criterium or three out of five minor criteria were met (Table 2). Sonication was applied in the cases where prosthesis was removed to increase the possibility to distinguish aseptic from infective failure and isolate the microorganism [19].

Secondary outcome was the rate of complications, including any adverse event related to the use of the coating. Complications were defined as any condition requiring additional surgery or unplanned treatment, whenever at follow-up. Adverse events included all those complications that in the opinion of the clinician, could be directly related to the use of the coating.

Statistical analysis

Descriptive statistics were used to summarize the data and calculated using the Microsoft Excel 2013 software (Microsoft, Redmond, Washington). Categorical data were analyzed using Fisher's exact test; continuous data were compared using the Student's *t* test (http://graphpad.com/). p values < 0.05 were considered statistically significant.

Results

The average length of surgery was similar in the two groups (cf. Table 3).

Primary outcome Post-surgical infection was observed in 6/43 (13.9%) control patients, compared to no infections in the treated group ($p=0.028$), at an average follow-up of

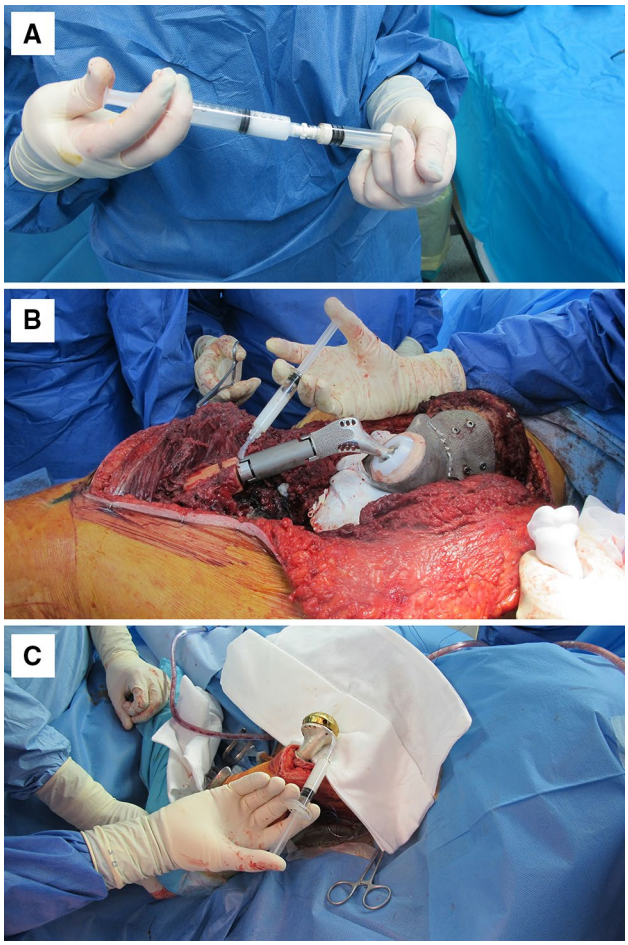

Fig. 1 Intraoperative images of ALHBG preparation (**a**) and application over the surface of the megaprosthetic implants (**b** and **c**)

24.3 ± 11.7 and 24.2 ± 11.5 months, respectively. More specifically, 3/37 (8.1%) patients in the control group showed a surgical site infection after extremity bone resection and reconstruction and 3/6 (50%) after pelvic resection and implant positioning. Mega-implant infections were managed with surgical debridement and suppressive antibiotic treatment in two cases, implant revision in three patients and limb amputation in one. In the treated cohort, a wound dehiscence was observed in one patient 15 days after surgery; it healed uneventfully with local medications. No deep or organ space infections or implant revision due to septic complications were observed.

Secondary outcome Secondary outcomes are resumed in Table 4.

Treated group One patient suffered an intra-operative fracture of the pelvis and another patient suffered a femoral diaphysis fissure. Post-operative bleeding with a vast hematoma requiring surgical wound revision was noted in one case. Two additional patients underwent aseptic revision of the implant for mechanical failure at, respectively, 14 and 28 months. In both cases, intra-operative cultures were negative for infection. One more patient required arthroplasty revision for tumor reoccurrence 12 months after the primary surgery; after revision, he developed a wound infection (positive to *Proteus* and *E. coli*) with dehiscence of the surgical incision, treated with early debridement and antibiotic treatment. Three more patients required limb amputation for disease progression at 13, 17 and 26 months, respectively. One patient died at 18 months follow-up, due to his underlying malignancy (Ewing's sarcoma).

No adverse events related to the use of the antibacterial hydrogel were reported.

Control group One patient showed a hip implant dislocation, managed conservatively, and two more had an

Table 2 First International Consensus Meeting of Philadelphia Criteria. Infection was considered present when one major criterium or three out of five minor criteria were met

Major criteria	Two positive periprosthetic cultures with phenotypically identical organisms
	A sinus tract communicating with the joint
Minor criteria[a]	Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
	Elevated synovial fluid white blood cell (WBC) count OR ++ change on leukocyte esterase test strip
	Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
	Positive histological analysis of periprosthetic tissue;
	A single positive culture

[a]The threshold for the minor diagnostic criteria was distinguished for acute (< 90 days) and chronic (> 90 days) infection

Erythrocyte sedimentation rate (mm/h): not helpful in acute, > 30 in chronic

C-reactive protein (mg/L): > 100 in acute, > 10 in chronic

Synovia white blood cell Count (cells/µl): > 10.000 in acute, > 3.000 in chronic

Synovial polymorphonuclear neutrophils (%): > 90 in acute, > 80 in chronic

Leukocyte esterase: + or ++ both in acute and chronic

Histological analysis of tissue: > N5 neutrophils per high power field in 5 high power fields (×400) both in acute and chronic

Table 3 Post-operative results

	Treated ($N=43$)	Controls ($N=43$)	p
Mean surgery duration ± standard deviation (min–max) (h	5.4 ± 3.1 (2–15)	5.3 ± 3.0 (2–14)	0.87
Mean follow-up ± standard deviation (min–max) (months)	24.3 ± 11.7 (12–42)	24.2 ± 11.5 (12–41)	0.96
Surgical site infections	0 (0%)	6 (13.9%)	**0.02**

The bold was used to emphasized the statistically significant value

Table 4 Post-operative complications

Treated group	Control group
Intra-operative fracture: 1	Hip implant dislocation: 1
Intra-operative femoral fissure: 1	Intra-operative femoral fissure: 2
Hematoma and surgical revision: 1	Transient femoral nerve palsy: 1
Aseptic implant revision: 2	Aseptic implant revision: 2
Oncological disease progression: 5	Oncological disease progression: 6

intra-operative femoral fissure. One patient showed a transient femoral nerve palsy after hip joint reconstruction. Aseptic implant revision was performed in two patients, 20 and 22 months after index surgery, respectively. Oncological disease progression was observed in six cases at 13, 14, 15, 20, 24 and 28 months, respectively, requiring implant revision in two patients, limb amputation in two patients, while the remaining two died for tumor recurrence.

Discussion

Infection is the main cause of mega-prosthesis failure. This can be related to several factors, such as the fragility of the patient who has often undergone chemotherapy, the invasiveness of the surgery, the surgical access and its duration. Furthermore, it is considered a dramatic event which can compromise the prosecution of treatment, preventing adjuvant chemotherapy and indirectly influencing survival as well [20].

The develop of new methods to decrease infection rate is one of the main goals in reconstructive surgery and this study wants to propose a possible solution in muscular-skeletal oncologic surgery.

This study is, to our knowledge, the first showing the ability of a fast-resorbable, antibacterial hydrogel coating to reduce the occurrence of post-surgical peri-mega-implant infections (PMIs) for oncological and non-oncological patients. Furthermore, our analysis points out the absence of side effects of the coating in the studied population at an average follow-up of 2 years.

In spite of current prophylaxis and sterility procedures, mega-implants are still characterized by an unacceptable high incidence of post-surgical infections, ranging from 7 to 50%, depending on the diagnosis and the implant location [4, 7–9, 21]. In fact, infection is currently reported as the leading reason for early failure and revision of mega-prosthesis [7]. On the other hands, the management of peri-mega-implant infection is extremely costly and challenging, requiring repeated surgeries, prolonged antibiotic treatment and hospital stay and associated with a higher risk of limb amputation and increased mortality rate [8, 21].

Over the years, several options have been proposed in the attempt to decrease the risk of PMI (Table 5), including prolonged peri- post-operative antibiotic prophylaxis [9, 22] and silver or iodine implant coatings [10, 23, 24].

Concerning antibacterial coating technologies, povidone–iodine, used as an electrolyte, forms an adhesive, porous anodic oxide with the antiseptic properties of iodine. Although not yet available in the market, promising results of this coating, applied to various titanium implants, have been reported in not comparative clinical trials, in which mega-implants and oncological patients were included [24, 25].

Also, the use of active organic antibiotic coating should be an option; recently, a meta-analysis of Tsikopoulos et al. evidenced its effectiveness versus both methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible *S. aureus*, moreover when active coating was administered in conjunction with degradable carriers [26].

On the other hands, various silver coating technologies for orthopedic mega-implants are available since decades in the clinical setting, with reported favorable outcomes [24]. Among others, Hardes et al. showed a significant reduction of the infection rate (8.9% vs. 16.7%) in 56 silver-coated implants of the proximal tibia, compared to 42 uncoated titanium implants, at a median follow-up of 8.2 years [25]. Similar results have been recently published by Streitbuerger et al. [27] and by Sambri et al. [28]. In spite of these encouraging reports, the large-scale clinical use of silver coatings appears still limited by several factors. First, silver coating is only available for a few types of (mega-)implants; secondly, silver cytotoxicity limits the application of the coating only to the extra-medullary part of a prosthesis, thus leaving large parts of the prosthesis and in particular those in direct contact with the bone, exposed to possible bacterial colonization [29]. In addition, interlocking mechanisms of modular

Table 5 A resumptive table showing the main studies on possible strategies to prevent infections in muscular-skeletal oncologic surgery

Proposed strategies for decreasing infection rate	Authors
Prolonged peri-post-operative antibiotic prophylaxis	Hettwer et al. [9]: Extended post-operative antibiotic prophylaxis may reduce the risk of PJI in patients undergoing tumor resection and endoprosthetic replacement for metastatic bone disease of the proximal femur
Silver implant coatings	Azab et al. [10]: The silver coating exhibited excellent activity against the multidrug resistant biofilm-forming methicillin-resistant *S. pseudintermedius* isolate
	Kuehl et al. [24]: The silver-coated titanium–aluminum–niobium alloy elicited a strong, inoculum-dependent activity against *S. epidermidis* and *S. aureus* in an agar inhibition assay. Surrounding tissue did not reveal histological signs of silver toxicity. In vitro, no emergence of silver resistance was observed
	Hardes et al. [25]: The use of silver-coated prosthesis reduced the infection rate in a relatively large and homogeneous group of patients undergone proximal tibia prosthesis for sarcoma. When infection occurs, it is less severe
	Streitbuerger et al. [27]: Using a silver-coated proximal femoral replacement nearly halved the overall infection rate. When infection occurs a one stage revision procedure is possible
	Sambri et al. [28]: The PorAg® coating can be more effective in two-stage revision procedures then standard coating of knee EPR. Reinfection rate in the silver group was slightly lower than in uncoated EPR (10.3% vs. 17.5%, $p=0.104$)
	Mijnendonckx et al. [29]: Comprehensive review of the use and toxicity of silver compounds in many biological applications
	Silver resistance is common in several bacteria. These resistance determinants are often located on mobile genetic elements, facilitating their spread
	Fiore et al. [30]: A review of the literature showing as Silver-coated mega-prosthetic implants are safe and effective in reduction in PJI and reinfection rate, in particular in higher risk patients and after two-stage revisions
	Wafa et al. [31]: A case–control study evidencing as silver-treated implants were particularly useful in two-stage revisions for infection and in those patients with incidental positive cultures at the time of implantation of the prosthesis
	Zajonz et al. [32]: The reinfection rate after revision for infection is lower in case of reconstruction with silver-coated prosthesis
	Romanò et al. [33]: The cost of silver coating is widely covered by the saving for decreased infection rate
Iodine implant coatings	Tsuchiya et al. [23]: Iodine-supported titanium implants are helpful in prevent infection in high-risk patient who have to undergo orthopedic surgery or to prevent reinfection in case of revision. Cytotoxicity and adverse effects were not detected
Direct local administration of vancomycin	Fleischman and Austin [34]: The evidence of the effectiveness of powered local administration of vancomycin is very low
	Tubaki et al. [35]: The local application of vancomycin powder in surgical wounds did not significantly reduce the incidence of infection in patients with surgically treated spinal pathologies. The use of vancomycin powder may not be effective when incidence of infection is low

implants, screws and all plastic components, including polyethylene shells and layers, may not be silver-coated with current technologies. Moreover, the efficacy of silver coating has never been proved in prospective randomized trials and outside oncological applications even non-randomized studies are particularly scarce and conflicting [30]. While in a retrospective, matched, comparative, analysis, Wafa et al. showed that the use of silver-coated tumor prosthesis was effective in reducing early post-operative septic complications both in oncological patients and in two-stage revision for infection [31], more recently Zajonz et al. [32], in a prospective study on 34 patients, failed to show a statistically significant efficacy of silver-mega-implants in revision surgery for previous infection. A last, but substantial factor that may be limiting a larger penetration of silver coating in the orthopedics market is represented by its relatively high costs [33].

Other strategies to reduce post-surgical septic complications, like direct local administration of vancomycin powder, show controversial results and may not currently be recommended to protect mega-implants [34]; in fact, the only randomized, comparative study, focused on topical administration of vancomycin powder at surgery during spine procedures, failed to demonstrate a significant reduction

of post-surgical infection [35]; moreover, to the best of our knowledge, no report has investigated the efficacy of this technique in preventing PMIs.

Preclinical studies have documented the antibiofilm and antibacterial effect the DAC hydrogel coating, applied to different materials, commonly used in orthopedic surgery. The ability to prevent bacterial colonization has been attributed to the antibiofouling effect of the hyaluronic acid, which composes the hydrogel [36], coupled with its capability of uploading and delivering locally large amounts of antibacterial agents for up to 72 h [15, 37].

The quick release and degradation of the hydrogel, composed of highly biocompatible polymers, probably explains the lack of adverse events and side effects reported to date and the absence of any interference with implant osteointegration. Boot et al. in an experimental study on rabbits in 2016 evidenced that hydrogel does not cause inflammatory reaction alone or when associated with vancomycin, showing the absence of possible toxic action of the antibiotic on osteoblasts [38].

At variance with the above-mentioned coating technologies, the DAC hydrogel is prepared and applied as a point-of-care directly by the surgeon on the implant, during the surgical procedure. This allows to protect any surface or implantable biomaterial and to choose the antibiotic on the basis of the local epidemiology and the preference of the surgeon [7].

On the other hands, this unique feature allows to investigate the coating in different clinical settings. In fact, until now, the hydrogel has been proven safe and effective safe and effective in several clinical trials targeting various applications, including internal osteosynthesis [17], primary and in revision hip and knee joint replacement [4, 39], one- and two-stage joint revision for periprosthetic joint infection [18, 39].

Our results confirm and expand previous observations, providing data on patients undergoing joint reconstruction with hydrogel coated mega-implants for oncological and non-oncological conditions. In particular, we found a statistically significant reduction of surgical site infection, without any evidence of adverse event, compared to a matched series of patients, without the coating.

While our results look promising, several study limitations should be considered. First, the study sample is relatively small and heterogenous both as to concern the primary diagnosis and the site of the disease. Although this limit is shared by many studies, dealing with antibacterial coatings and mega-prosthesis, it remains a possible source of bias. A second limitation concerns the control population. Although matched for some key factors, the type of co-morbidities, the underlying disease progression, the associated medical treatments and the post-surgical management could not be controlled and matched, in spite of our efforts to do so. A further limitation is the lack of standardized systemic antibiotic therapy administered to all the patients, even if the average duration was similar in the two groups. This sums up with the design of the present study, in which the surgeons were let free to upload the hydrogel with the antibiotic(s) of their choice. Another limit of the present study is represented by the relatively short follow-up period. Although the minimum of 12 months monitoring appears adequate to detect the majority of surgical site infections, according both to the Center of Disease Control (CDC) [40] and the Infectious Diseases Society of America (IDSA) guidelines [41], delayed or late periprosthetic infections may develop even years after index surgery and these events may not have been picked-up by the present analysis; nevertheless, late infections often do not depend on intra-operative factors but are more related to bacteremia due to secondary foci [42]. On the other hands, the 1-year minimum follow-up appears long enough to exclude adverse events related to the hydrogel, given its quick reabsorption, and confirm the absence of problems associated with lack in osteointegration [15].

These many limitations notwithstanding, our analysis provides, for the first time, statistically significant data supporting the efficacy of a fast-resorbable hydrogel coating to mitigate periprosthetic joint infections in patients undergoing mega-implants, with no detrimental side effects.

If confirmed in larger studies and at longer follow-ups, this solution may become a useful tool to reduce the burden of septic complications currently associated with mega-implants.

This consideration becomes more important considering that this strategy could also be applied in combination to other already validated ones.

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Authors' contribution C.Z., G.S. and F.L.G. contributed to conceptualization; C.Z., G.S., R.B., P.A.D., F.L.G. and D.A.C. were involved in surgeries and methodology ; C.Z. contributed to writing—original draft preparation; R.B., P.A.D. and D.A.C. were involved in supervision and writing—review and editing.

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Availability of data and materials All data are available hospital archives on request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval RS1229/19 (Regina Elena National Cancer Institute Experimental Registry Number).

Consent to participate All patients gave their consent for publication.

References

1. Heisel C, Kinkel S, Bernd L, Ewerbeck V (2006) Megaprostheses for the treatment of malignant bone tumours of the lower limbs. Int Orthop 30:452–457. https://doi.org/10.1007/s00264-006-0207-7
2. Arduino JM, Kaye KS, Reed SD, Peter SA, Sexton DJ, Chen LF, Hardy NC, Tong SY, Smugar SS, Fowler VG Jr, Anderson DJ (2015) Staphylococcus aureus infections following knee and hip prosthesis insertion procedures. Antimicrob Resist Infect Control 4:13. https://doi.org/10.1186/s13756-015-0057-4
3. Di Benedetto P, Di Benedetto ED, Buttironi MM, De Franceschi D, Beltrame A, Gissoni R, Cainero V, Causero A (2017) Two-stage revision after total knee arthroplasty. Acta Biomed 88(2-S):92–97. https://doi.org/10.23750/abm.v88i2-S.6519
4. Allison DC, Huang E, Ahlmann ER, Carney S, Wang L, Menendez LR (2014) Periprosthetic infection in the orthopedic tumor patient. JISRF Reconstr Rev 4:13–17
5. Kapoor SK, Thiyam R (2015) Management of infection following reconstruction in bone tumors. J Clin Orthop Trauma 6:244–251. https://doi.org/10.1016/j.jcot.2015.04.005
6. Mavrogenis AF, Pala E, Angelini A, Calabro T, Romagnoli C, Romantini M, Drago G, Ruggieri P (2015) Infected prostheses after lower-extremity bone tumor resection: clinical outcomes of 100 patients. Surg Infect 16(3):267–275. https://doi.org/10.1089/sur.2014.085
7. Capanna R, Scoccianti G, Frenos F, Vilardi A, Beltrami G, Campanacci DA (2015) What was the survival of megaprostheses in lower limb reconstructions after tumor resections? Clin Orthop Relat Res 473:820–830. https://doi.org/10.1007/s11999-014-3736-1
8. Ercolano LB, Christensen T, McGough R, Weiss K (2013) Treatment solutions are unclear for perimegaprosthetic infections. Clin Orthop Relat Res 471:3204–3213. https://doi.org/10.1007/s11999-013-2852-7
9. Hettwer WH, Horstmann PF, Hovgaard TB, Grum-Scwensen TA, Petersen MM (2015) Low infection rate after tumor hip arthroplasty for metastatic bone disease in a cohort treated with extended antibiotic prophylaxis. Adv Orthop. https://doi.org/10.1155/2015/428986
10. Azab MA, Allen MJ, Daniels JB (2016) Evaluation of a silver-impregnated coating to inhibit colonization of orthopaedic implants by biofilm forming methicillin-resistant *Staphylococcus pseudintermedius*. Vet Comp Orthop Traumatol 29(4):347–350. https://doi.org/10.3415/VCOT-15-08-0134
11. Wyatt MC, Foxall-Smith M, Roberton A, Beswick A, Kieser DC, Whitehouse MR (2019) The use of silver coating in hip megaprostheses: a systematic review. Hip Int 29(1):7–20. https://doi.org/10.1177/1120700018811070
12. Romanò CL, Scarponi S, Gallazzi E, Romanò D, Drago L (2015) Antibacterial coating of implants in orthopaedics and trauma: a classification proposal in an evolving panorama. J Orthop Surg Res 10:157. https://doi.org/10.1186/s13018-015-0294-5
13. Drago L, Boot W, Dimas K, Malizos K, Hänsch GM, Stuyck J, Gawlitta D, Romanò CL (2014) Does implant coating with antibacterial-loaded hydrogel reduce bacterial colonization and biofilm formation in vitro? Clin Orthop Relat Res 472:3311–3323. https://doi.org/10.1007/s11999-014-3558-1
14. Giammona G, Pitarresi G, Palumbo FS, Maraldi S, Scarponi S, Romanò CL (2018) Hyaluronic-based antibacterial hydrogel coating for implantable biomaterials in orthopedics and trauma: from basic research to clinical applications. In: Hydrogels, Sajjad Haider and Adnan Haider, IntechOpen. https://doi.org/10.5772/intechopen.73203
15. Malizos K, Blauth M, Danita A, Capuano N, Mezzoprete R, Logoluso N, Drago L, Romanò CL (2017) Fast-resorbable antibiotic-loaded hydrogel coating to reduce post-surgical infection after internal osteosynthesis: a multicenter randomized controlled trial. J Orthop Traumatol 18:159–169. https://doi.org/10.1007/s10195-017-0442-2
16. McPherson EJ, Woodson C, Holtom P, Roidis N, Shufelt C, Patzakis M (2002) Periprosthetic total hip infection: outcomes using a staging system. Clin Orthop Relat Res 403:8–15
17. Romanò CL, Battaglia A, Suardi V, Romanò D, Baldi A, Zoccali C (2019) Antibacterial hydrogel coating of implants in orthopedics and trauma: surgical technique and clinical applications. Maitrise Orthop 1:4–13
18. Parvizi J, Gehrke T (2014) Definition of periprosthetic joint infection. J Arthroplast 29(7):1331. https://doi.org/10.1016/j.arth.2014.03.009
19. Sambri A, Maso A, Storni E, Megaloikonomos PD, Igoumenou VG, Errani C, Mavrogenis AF, Bianchi G (2019) Sonication improves the diagnosis of megaprosthetic infections. Orthopedics 42(1):28–32. https://doi.org/10.3928/01477447-20181010-06
20. Mavrogenis AF, Papagelopoulos PJ, Coll-Mesa L, Pala E, Guerra G, Ruggieri P (2011) Infected tumor prostheses. Orthopedics 34(12):991–1000. https://doi.org/10.3928/01477447-20111021-24
21. Benatto MT, Hussein AM, Gava NF, Maranho DA, Engel EE (2019) Complications and cost analysis of hemipelvectomy for the treatment of pelvic tumors. Acta Ortop Bras 27(2):104–107. https://doi.org/10.1590/1413-785220192702206721
22. Müller D, Kaiser D, Sairanen K, Studhalter T, Uçkay İ (2019) Antimicrobial prophylaxis for the prevention of surgical site infections in orthopaedic oncology—a narrative review of current concepts. J Bone Jt Infect 4(6):254–263. https://doi.org/10.7150/jbji.39050
23. Tsuchiya H, Shirai T, Nishida H, Murakami H, Kabata T, Yamamoto N, Watanabe K, Nakase J (2012) Innovative antimicrobial coating of titanium implants with iodine. J Orthop Sci 17(5):595–604. https://doi.org/10.1007/s00776-012-0247-3
24. Kuehl R, Brunetto PS, Woischnig AK, Varisco M, Rajacic Z, Vosbeck J, Terracciano L, Fromm KM, Khanna N (2016) Preventing implant-associated infections by silver coating. Antimicrob Agents Chemother 60(4):2467–2475. https://doi.org/10.1128/aac.02934-15
25. Hardes J, Henrichs MP, Hauschild G, Nottrott M, Guder W, Streitbuerger A (2017) Silver-coated megaprosthesis of the proximal tibia in patients with sarcoma. J Arthroplasty 32(7):2208–2213. https://doi.org/10.1016/j.arth.2017.02.054
26. Tsikopoulos K, Sidiropoulos K, Kitridis D, Hassan A, Drago L, Mavrogenis A, McBride D (2020) Is coating of titanium implants effective at preventing *Staphylococcus aureus* infections? A meta-analysis of animal model studies. Int Orthop. https://doi.org/10.1007/s00264-020-04660-4
27. Streitbuerger A, Henrichs MP, Hauschild G, Nottrott M, Guder W, Hardes J (2019) Silver-coated megaprostheses in the proximal femur in patients with sarcoma. Eur J Orthop Surg Traumatol 29(1):79–85. https://doi.org/10.1007/s00590-018-2270-3
28. Sambri A, Zucchini R, Giannini C, Zamparini E, Viale P, Donati DM, De Paolis M (2020) Silver-coated (PorAg®) endoprosthesis can be protective against reinfection in the treatment of tumor prostheses infection. Eur J Orthop Surg Traumatol 30(8):1345–1353. https://doi.org/10.1007/s00590-020-02705-3

29. Mijnendonckx K, Leys N, Mahillon J, Silver S, Van Houdt R (2013) Antimicrobial silver: uses, toxicity and potential for resistance. Biometals 26(4):609–621. https://doi.org/10.1007/s10534-013-9645-z
30. Fiore M, Sambri A, Zucchini R, Giannini C, Donati DM, De Paolis M (2020) Silver-coated megaprosthesis in prevention and treatment of peri-prosthetic infections: a systematic review and meta-analysis about efficacy and toxicity in primary and revision surgery. Eur J Orthop Surg Traumatol. https://doi.org/10.1007/s00590-020-02779-z
31. Wafa H, Grimer RJ, Reddy K, Jeys L, Abudu A, Carter SR, Tillman RM (2015) Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high risk patients: case-control study. Bone Joint J 97-b(2):252–257. https://doi.org/10.1302/0301-620x.97b2.34554
32. Zajonz D, Birke U, Ghanem M, Prietzel T, Josten C, Roth A, Fakler JKM (2017) Silver-coated modular megaendoprostheses in salvage revision arthroplasty after periimplant infection with extensive bone loss—a pilot study of 34 patients. BMC Musculoskelet Disord 18(1):383. https://doi.org/10.1186/s12891-017-1742-7
33. Romanò CL, Tsuchiya H, Morelli I, Battaglia AG, Drago L (2019) Antibacterial coating of implants: are we missing something? Bone Joint Res 8(5):199–206. https://doi.org/10.1302/2046-3758.85.BJR-2018-0316
34. Fleischman AN, Austin MS (2017) Local intra-wound administration of powdered antibiotics in orthopaedic surgery. J Bone Jt Infect 2(1):23–28. https://doi.org/10.7150/jbji.16649
35. Tubaki VR, Rajasekaran S, Shetty AP (2013) Effects of using intravenous antibiotic only versus local intrawound vancomycin antibiotic powder application in addition to intravenous antibiotics on postoperative infection in spine surgery in 907 patients. Spine 38(25):2149–2155. https://doi.org/10.1097/BRS.0000000000000015
36. Romanò CL, De Vecchi E, Bortolin M, Morelli I, Drago L (2017) Hyaluronic acid and its composites as a local antimicrobial/antiadhesive barrier. J Bone Jt Infect 2(1):63–72. https://doi.org/10.7150/jbji.17705
37. Giavaresi G, Meani E, Sartori M, Ferrari A, Bellini D, Sacchetta AC, Meraner J, Sambri A, Vocale C, Sambri V, Fini M, Romanò CL (2014) Efficacy of antibacterial-loaded coating in an in vivo model of acutely highly contaminated implant. Int Orthop 38(7):1505–1512. https://doi.org/10.1007/s00264-013-2237-2
38. Boot W, Gawlitta D, Nikkels PGJ, Pouran B, van Rijen MHP, Dhert WJA, Vogely HC (2017) Hyaluronic acid-based hydrogel coating does not affect bone apposition at the implant surface in a rabbit model. Clin Orthop Relat Res 475:1911–1919. https://doi.org/10.1007/s11999-017-5310-0
39. Capuano N, Logoluso N, Gallazzi E, Drago L, Romanò CL (2018) 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. Knee Surg Sports Traumatol Arthrosc 26:3362–3367. https://doi.org/10.1007/s00167-018-4896-4
40. Borchardt RA, Tzizik D (2018) Update on surgical site infections: the new CDC guidelines. JAAPA 31(4):52–54. https://doi.org/10.1097/01.JAA.0000531052.82007.42
41. Osmon DR, Berbari EF, Berendt AR, Lew D, Zimmerli W, Steckelberg JM, Rao N, Hanssen A, Wilson WR, Infectious Diseases Society of America (2013) Executive summary: diagnosis and management of prosthetic joint infection: clinical practice guidelines by the Infectious Diseases Society of America. Clin Infect Dis 56(1):1–10. https://doi.org/10.1093/cid/cis966
42. Zimmerli W, Ochsner PE (2003) Management of infection associated with prosthetic joints. Infection 31(2):99–108. https://doi.org/10.1007/s15010-002-3079-9