RESEARCH ARTICLE

The Performances of Conventional Titanium and Silver-Coated Megaprostheses in Non-oncological and Post-oncological Patients: An Analysis of Infection Failures in 142 Patients

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Abstract

Background: Megaprostheses are one of the preferred choices of reconstruction after tumor resection. Periprosthetic joint infections are one of the most serious complications of joint prostheses surgeries. In this study, our aim was to analyze the efficacy of silver-coated megaprostheses in reducing the risk of prosthesis-related infection.

Methods: One hundred forty-two patients who had undergone implantation of a mega-endoprosthesis for non-neoplastic or post-neoplastic conditions were included in this retrospective study. The end-point of the survival analysis was the prosthesis failure due to infection.

Results: Thirty-eight patients had undergone implantation of a silver-coated megaprosthesis and 104 patients a megaprosthesis without silver coating. The survival analysis showed an overall infection-free survival rate of 82.3% at five years and 61.9% at 10 years. Silver-coated prostheses had an HR of 0.72 (95% CI: 0.26-2.05; *P=0.54*).

Conclusion: Implantation of a silver-coated mega-prosthesis in non-oncological patients did not significantly reduce the risk of prosthesis-related infection.

Level of evidence: III

Keywords: Endoprosthesis, Infection, Megaprosthesis, Periprosthetic infection, Silver, Silver-coated

Introduction

Megaprostheses are one of the preferred choices of reconstruction in case of a large bone defect after tumor resection (1, 2). Megaprostheses are also increasingly used in non-oncological reconstruction to allow for early weight-bearing for patients who have had severe bone loss after acute trauma or multiple operations due to various conditions (e.g. periprosthetic fractures, periprosthetic infections, non-unions, etc.) (3-15).

Periprosthetic joint infections (PJIs) are one of the most serious complications after the implantation of joint prostheses. These infections have very high rates of morbidity and mortality. The overall PJI rate is higher following a megaprosthesis implantation than standard primary or revision prostheses. Orthopedic surgeons are likely to deal with more and more infections in the near future given the spread of multi-resistant bacteria and the increased incidence and prevalence of PJIs (16-19).

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Despite the continuous improvements in the workflow of surgical interventions, the availability of newer antiseptic tools, and the up-to-date knowledge about management of patients and operating theaters, the infection rates after implantation of megaprostheses remain high (20-22).

Since the prosthesis itself constitutes a major risk for the development of chronic infections due to the bacterial colonization on the implant surfaces (biofilm creation), the industry and researchers focused on the development of antimicrobial prosthesis surfaces (23, 24).

Silver has always been considered a promising material since its particles have a high antimicrobial activity coupled with low human toxicity. Many manufacturers have developed prostheses with a silver coating, inducted by different techniques. In vitro studies showed very encouraging results that have been confirmed by different retrospective studies on mega-endoprostheses used on oncological patients (25-31). In non-oncological populations, there are pieces of evidences that suggest that silver coating could be a safe and effective technique to reduce the infection rates after implantation of tumor prostheses (32-37). We conducted a retrospective study about a series of 142 modular mega-endoprostheses (38 with silver coating, 104 without silver coating) of the lower limb in non-oncological and in post-oncological patients and analyzed the efficacy of silver-coated megaprostheses in reducing the risk of prosthesis-related infection.

Materials and Methods

An analysis of the database of the patients who had undergone mega-endoprosthesis implantation between January 2001 and December 2017 in the Department of Orthopaedic Surgery and Traumatology of Pisa, the Department of Orthopaedic Oncology and Reconstructions of Florence, and the Department of Orthopaedic and Traumatology of Lausanne CHUV was performed. Inclusion criteria of the study were: implantation of a lower limb modular mega-endoprosthesis for non-neoplastic or post-neoplastic conditions (considering the latter as those surgically treated after the failure of a previous oncological surgery or irradiation therapies). Exclusion criteria were the diagnosis of active neoplastic disease at the time of index procedure. One hundred forty-two patients who fulfilled the inclusion criteria were included in the study.

The end-point of the survival analysis was the prosthesis failure due to infection as defined in the Henderson Classification System of mega-endoprosthesis failures (infection: complication Type IV).

We reviewed data from the departments' follow-up medical records. Infections were usually diagnosed using the 2013 MusculoSkeletal Infection Society (MSIS) criteria. Two positive periprosthetic cultures from the same pathogen or a sinus tract communicating with the joint were used as the major criteria, while elevated serum C-reactive protein level and erythrocyte sedimentation rate, elevated synovial fluid white blood cell (WBC) count, and elevated synovial fluid polymorphonuclear neutrophil percentage were considered as the minor criteria.

Patients who did not have a satisfactory follow-up report were interviewed by telephone.

Statistical analysis

The categorical data were expressed as frequency and percentage.

Survival analysis

Failure-Free Survival (FFS) was defined as the end-point and the survival time as the time from the prosthesis implantation to failure.

Survival curves were calculated using the Kaplan-Meier method. Seven risk factors were assessed in the survival analysis (gender, age, previous infection, implanted bone segment, previous radiation therapy, prosthesis type, and the number of previous interventions) including each factor in a univariate Cox regression model. The results of the Cox regression were expressed using hazard ratios (HRs) with their related 95% confidence interval (95% CI) and p value. Differences were considered significant at the $P<0.05$ level. All analyses, descriptive and inferential, were performed using the SPSS v.25 software.

Results

One hundred forty-two (88 females [62%], 54 males [38%]) patients were included in the study with a mean age of 61 years (SD: 21.9) at the time of index operation. The mean follow-up period was 55 months (range: 24 to 216 months). In all 142 cases, a MEGASYSTEM-C® prosthesis (Waldemar Link GmbH & Co. KG, Hamburg, Germany) was used. Thirty-eight patients (27%) underwent implantation of a silver-coated megaprosthesis (Por-Ag®; LINK, Germany) and 104 patients (73%) underwent implantation of a megaprosthesis without silver coating.

Within the group that received a silver-coated megaprosthesis, 12 patients were treated with a proximal femur prosthesis, 18 with distal femur replacement, four with a total femur prosthesis, three with knee arthrodesis, and one with a proximal tibia prosthesis. In the group that received a titanium prosthesis, 41 patients underwent a proximal femur reconstruction, 42 had a replacement of the distal femur, 12 of the proximal tibia, and four of the entire femur; while five patients underwent an arthrodesis.

Forty-one patients (29%) were implanted megaprostheses after acute trauma or trauma sequelae coupled with severe bone loss, 34 patients (24%) after failures of total hip replacements, 27 (19%) after total knee replacement failures, and 40 patients (28%) after complications of oncologic surgeries (e.g. failures of massive allografts or fractures on previously irradiated bones).

Overall, 39 patients (27%) were previously operated in an oncological setting (but had been considered tumor-free at the time of index procedure), while in 39 patients (27%) a previous surgical site infection had been detected. In patients who already experienced an infection 27 received a silver-coated prosthesis (i.e.

Table 1. Population Characteristics, percentages (intragroup) in brackets

	Titanium	Silver Coated
Number	103 (73)	37 (27)
Previously Infected	12 (11,6)	27 (73)
Previous Radiotherapy	14 (13,6)	7 (18,9)
Previous Chemotherapy	6 (5,8)	1 (2,7)
Previous Surgery (more than 2)	6 (5,8)	2 (5,4)
Location (proximal femur)	44 (42,7)	12 (33,4)

71% of all the silver-coated prosthesis implanted), while 12 did not. Twenty-one patients had received external beam radiation therapy and seven chemotherapy. Eight patients had undergone implantation of megaprostheses after two previous surgical failures [Table 1]. The overall rate of infection failure was 20.4% (29 out of 142 cases); the rate of infection failure in the titanium prosthesis group was 19.2% (20 out of 104 cases), while the same rate in the silver-coated prosthesis group was 23.7% (9 out of 38 cases). Survival analysis showed an overall infection-free survival rate of 82.3% at five years and 61.9% at 10 years.

The Cox regression model about infection-free survival analysis showed an HR of 0.7 (95% CI: 0.2-1.3; *P=0.183*) regarding the presence of a previous infection. The male gender had an HR of 1.1 (95% CI: 0.4-2.9; *P=0.763*); age less than 50 years had an HR of 0.8 (95% CI: 0.3-2.8; *P=0.725*); the implantation of the modular prosthesis on the proximal femur versus total and distal femur or proximal tibia had an HR of 1.5 (95% CI: 0.6-3.9; *P=0.409*);

Table 2. Univariate Failure Free Survival analysis of the risk factors

Factor	HR (95% CI)	*P value*
Gender		
(0) Male; (1) Female	1.1 (0.4-2.9)	0.763
Age		
(0) <50 y; (1) >50 y	0.8 (0.3-2.8)	0.725
Previous Infection		
(0) no; (1) yes	0.7 (0.2-1.3)	0.183
Segment		
(0) PR; (1) Others	1.5 (0.6-3.9)	0.409
Previous RT		
(0) yes; (1) no	1.6 (0.4-7.1)	0.513
Prostheses		
(0) Ag; (1) Ti	0.5 (0.2-1.2)	0.130
Previous Failures		
(0) 1; (1) 2	19,8 (7,8-50)	0.001

Legend. HR: Hazard Ratio; 95%CI: 95% Confidence Interval; PR: proximal femur; Others: proximal tibia+distal femur and total femur; RT: radiation therapy.

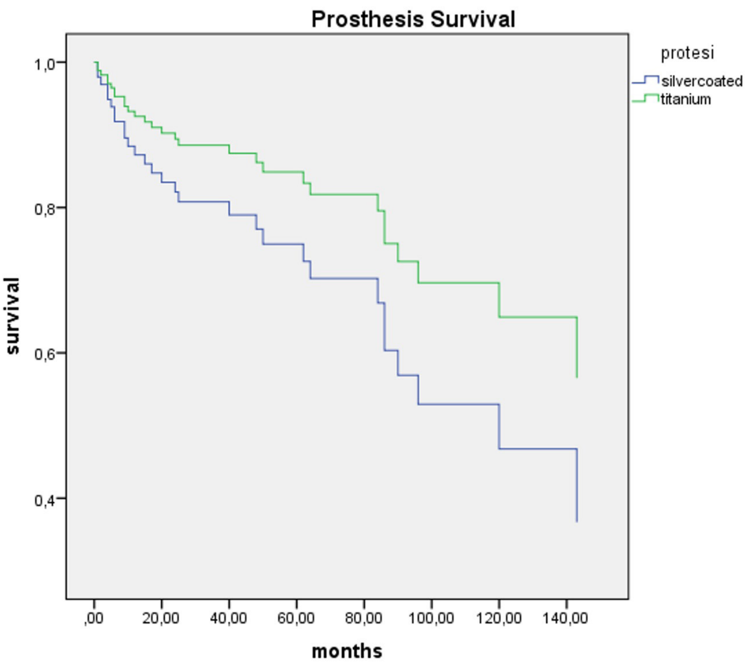

Figure 1. Survival curve for infection (silver-coated prosthesis vs non-coated prosthesis).

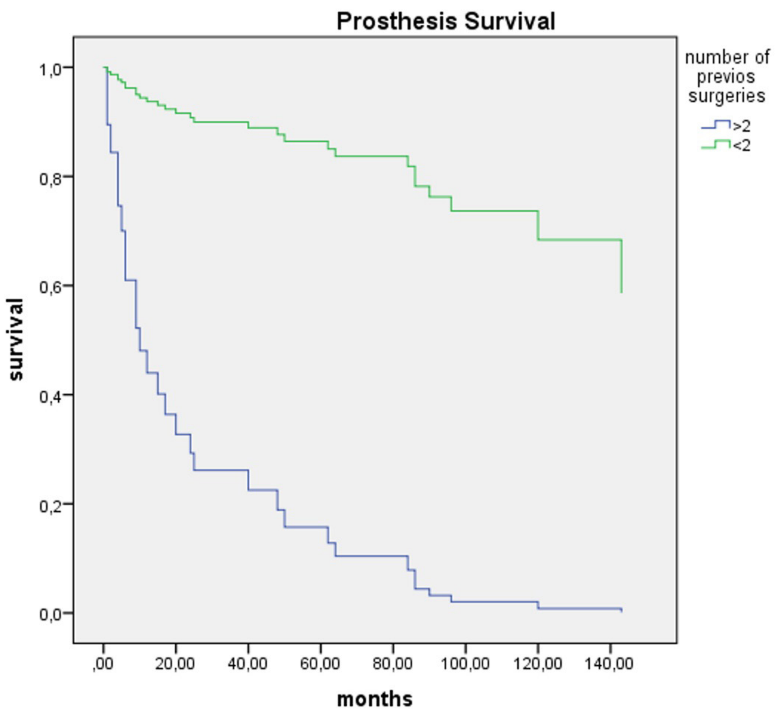

Figure 2. Survival curve for infection (more than two previous surgeries vs. less than two previous surgeries).

previous irradiation therapy had an HR of 1.6 (95% CI: 0.4-7.1; *P=0.513*); previous chemotherapy regimen had an HR of 1.1 (95% CI: 0.12-9.03; *P=0.94*); silver-coated implants had an HR of 0.72 (95% CI: 0.26-2.05; *P=0.54*); and the presence of more than two previous interventions had an HR of 19.8 (95% CI: 7.9-50; *P<0.001*) [Table 2] [Figures 1; 2]. A post-hoc power analysis was conducted on the Cox regression model about the prosthesis groups (silver-coated vs titanium) and a statistical power of 0.55 was obtained.

Discussion

Periprosthetic joint infections represent a major challenge for an orthopedic surgeon. In facts, PJIs show up as one of the worst postoperative complications after joint replacement in terms of morbidity and mortality. Infections after the implantation of megaprostheses are much more common than after the implantation of a primary standard total knee or hip prosthesis. Our study aimed to assess the infection-free survival of patients after implantation of a megaprosthesis for non-oncological and post-oncological conditions, and in particular to assess the efficacy of Por-Ag® technology in reducing the infection risk. Our results show a relatively low rate of type IV failures with an overall implant survival of 82.3% at five years and 61.9% at 10 years and an overall infection rate of 20.4%. The overall infection rate after implantation of a proximal tibia megaprosthesis was 18.2%, after distal femur replacement 23.9%, after proximal femur replacement 18.2%, and after implantation of a total femur prosthesis 14.3%.

The analysis was focused on the reduction or increase of the prosthesis-related failure risk, considering the prosthesis type (silver-coated vs not silver-coated), presence of a previous infection on the surgical site, previous irradiation therapy on the surgical site (proximal femur, other sites), number of previous interventions, age, and gender. In the literature, various studies have assessed the incidence of infections after implantation of a megaprosthesis. These studies show extreme variability in terms of infection rate and infection-free survival. Usually these studies consisted of retrospective series or reviews of retrospective series and two different populations were usually included separately, i.e. patients who received a megaprosthesis due to oncological conditions vs those who received them due to non-oncological conditions. Non-oncological patients do not receive chemotherapy or radiation therapy with their toxic effects. On the other hand, they usually are elderly, have serious bone stock or local vascularization impairments, or had undergone several prior operations on the involved site. As for the oncological patients, two reviews have reported opposite results. In the review by Haijie et al. (21), the infection failure rate (Type IV failures) reached a mean of 5% to 15% in the 6,000 patients included in the analyzed studies (8.5% distal femur, 16.8% proximal femur); whereas in the review of 2,174 patients by Henderson et al. (22)although failure rates are high. Because the number of these procedures is limited, failure of these devices has not been studied or classified adequately. This investigation is a multicenter review of the use of segmental endoprostheses with a focus on the modes, frequency, and timing of failure. Methods: Retrospective reviews of the operative databases of five institutions identified 2174 skeletally mature patients who received a large endoprosthesis for tumor resection. Patients who had failure of the endoprosthesis were identified, and the etiology and timing of failure were noted. Similar failures were tabulated and classified on the basis of the risk of amputation and urgency of treatment. Statistical analysis was performed to identify dependent relationships among mode of failure, anatomic location, and failure timing. A literature review was performed, and similar analyses were done for these data. Results: Five hundred and thirty-four failures were identified. Five modes of failure were identified and classified: soft-tissue failures (Type 1, Type IV failures were detected in 7.8% to 26.8% of the analyzed populations (5.4%-20.4% proximal femur, 19.7%-47.8% distal femur). In non-oncological populations, a similar variability can be found. In the review by Windhager et al. (15)especially in patients with multiple revisions, remain challenging mainly due to bone quality and loss of bone stock. Megaprostheses, although providing immediate stability and weight bearing, are rarely used in this indication. The aim of the study was to provide a description of the surgical technique and evaluate the outcome of this technique with respectable published data. Materials and methods: Systematic literature review revealed seven studies dealing with treating PPF after TKA using megaprostheses. Including the results of 11 cases treated in our institution between January 2008 and December 2014, 144 megaprostheses have been evaluated in the current literature with indication of PPF after TKA. Mean age at operation ranged from 68.4 to 81 years and mean follow-up from 6 to 58.6 months. Results: Revision rates after implantation of megaprostheses in PPFs ranged from 0 % (two studies with a mean follow-up of 6 and 33 months, respectively, studies on the distal femur and proximal tibia megaprosthesis were analyzed and Type IV failures were detected in 20% to 28% of the patients on average, while the review by Korim et al. (10) which included patients who underwent implantation of a proximal tibia or distal femur megaprosthesis showed a mean of 15% of infection failures. A recent review on total femur replacement in non-oncological patients showed a 44% failure rate due to infections (13). The current study on non-oncological patients (or post-oncological) is aiming at understanding the infection failures in an understudied subgroup of patients, with a relatively high number of patients. Silver-coated megaprostheses have been tested in several clinical studies, both in oncological and in non-oncological conditions. Hardes et al. (28) analyzed the outcomes of 51 patients in oncological conditions after implantation of silver-coated or non-coated megaprostheses. In the silver-coated group, the infection rate was very low compared to the control group (6.9% vs 17%), however, this difference was not statistically significant. Donati et al. (27) studied retrospectively 68 patients who had undergone proximal femur replacement for oncological conditions, and found that in the subgroup of silver-coated prostheses (38 patients) the infection rate was 7.9%, while it was 16.7% in the control group. Again, the difference was not statistically significant. In a retrospective series of 100 oncological patients, Schmolders et al. (30)so-called skeletal-related events, it is highly important to achieve pain relief and a stable joint situation to re-mobilize the patients immediately following surgery. To bridge the often large osseous defect zones after tumor resection, both cemented and uncemented modular endoprosthetic systems are widely used. Patients undergoing tumor-related endoprosthetic orthopedic surgery are facing high risk for developing a periprosthetic joint infection (PJI demonstrated an overall infection rate of 10% after implantation of silver-coated prostheses (all anatomical locations confounded). In a retrospective case series of 34 non-oncological patients, Zajonz et al. (37) showed an infection rate of 40% for silver-coated prostheses compared to 57% reinfection rate after implantation of a non-silver coated megaprosthesis. In a retrospective series on 170 patients affected by severe bone loss not related to oncological conditions, Wafa et al. (36) showed an 11% rate of reinfection in the silver-coated group and 22.4% in the control group. The latter was the only study in which the reduction of infection rate after implantation of a silver-coated megaprosthesis resulted to be statistically significant: in this study 85 silver-coated prostheses were included. Sambri et al. (32)68 patients were retrospectively evaluated. Median age was 30 years (range 14–83 reported similar results about the efficacy of silver-coated megaprostheses, but without reaching statistical significance. A systematic review by Fiore et al. (33) highlighted a significant efficacy of silver-coated implants in preventing infections compared to non-coated prostheses.

In our study, nine out of 38 patients (24%) in the silver-coated subgroup and 20 out of 104 (19%) in the control group had a type IV failure. In the silver-coated subgroup of patients, 27 out of 38 (71%) had a previous infection on the involved site, while in the control group 12 out of 104 (12%) had already been infected. The Kaplan-Meier survival analysis showed an HR of type IV failure with a silver-coated modular prosthesis of 0.5 (95% CI: 0.2-1.2). Our results do not confirm the power of silver-coated prostheses to reduce the infection risk in a non-oncological population. Nevertheless, as the statistical power in post-hoc analysis is only 0.55, it is feasible that a difference between the two groups is not being detected even though it may exist. The excellent results of silver coating in the pre-clinical studies prove the antibacterial efficacy of the silver ions. The *in vivo* and peculiar chemical environment around the prosthesis may alter the silver ion activity and also reduce or reset the silver ion release. The Por-Ag® technology was designed to reach a constant silver ion release in a concentration that could lead to killing bacteria without having side effects. In our series, no cases of clinical argyria or silver-related side effects were detected. The end of silver ion release in effective concentration over time could explain our results since, in the first 10 months, silver-coated prostheses seem to perform better than titanium ones. In our series, the number of previous surgical failures had a significant impact on future failures. Patients who had two previous failures compared to patients who had one had a 19-fold higher probability to have a subsequent infection failure (HR: 19; *P<0.001*).

Surprisingly, the surgical site (the proximal femur compared to the distal femur, proximal tibia, and the total femur), age over 50 years old, gender, and previous irradiation therapy on the involved site did not have a significant impact on HRs. These findings which are not in line with the literature, do not depend on the follow-up time (55 months) or the population size (142 patients) of the study.

This study had several limitations. Our study is a retrospective series without a randomization process; therefore, some important risk and confounding variables have not been considered such as diabetes, smoking, eventual drug abuse, or HIV infection. The low number of patients in the silver-coated subgroup (n=38) may have reduced the power to detect the differences between prosthesis types regarding infection rate. Furthermore, the majority of patients who received a silver-coated prosthesis have already had an infection failure (71% of them) while just 11% of patients who received a titanium prosthesis had already experienced an infection. This could represent a bias regarding the performance of silver-coated vs titanium prostheses.

Our survival analyses did not show a significant reduction in failures due to infection after implantation of a silver-coated megaprosthesis in non-oncological and post-oncological patients. Nevertheless, as the power in post-hoc analysis is only 0.55, we may had not been able to detect an existing difference. Investigations with larger samples are needed to confirm the authors findings. The site of implantation, age, sex, and previous irradiation therapy did not have a significant impact on the infection risk. The presence of more than two previous surgeries raised the relative risk to have an infection failure up to fifty times. Our results question the real efficacy of silver-coated 'megaprostheses' in non-oncological or post-oncological patients. A prospective study with a randomization process and a long-term follow-up is needed to understand the real efficacy of Por-Ag® prostheses. More systematic reviews of the literature and meta-analyses are needed to reach a higher level of evidence on the role of silver coating in reducing the infection risk of mega-endoprostheses.

Compliance with Ethical Standards: This research was undertaken at CTO (Centro Traumatologico Ortopedico) in Florence, Orthopedic Oncology and Complex Reconstruction Unit.

Conflict of Interest: All authors declare that they have no conflict of interest related to the publication of this paper.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all participants included in the study.

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