



Silver-coated (Agluna®) tumour prostheses can be a protective factor against infection in high risk failure patients



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ABSTRACT

Introduction: Endoprostheses in the treatment of extremity sarcomas are associated with late complications including periprosthetic infection. This study analysed the incidence of infection in patients undergoing endoprosthetic replacement (EPR) with a silver-coated prosthesis.

Materials and methods: The study comprised a retrospective single centre study of 394 consecutive patients treated with resection and EPR for primary extremity bone tumours.

Results: 89 patients at risk for infection were treated with a silver-coated (Agluna®) EPR (22.6%), compared to 305 patients treated with a non-silver EPR (77.4%). The incidence of periprosthetic infection, requiring revision as the primary endpoint was 34/394 (8.6%); 11 patients (12.4%) in the silver group and 23 patients (7.5%) in the non-silver group ($p = 0.154$). Overall implant survival was 90.9% and 95.3% at 1-year and 86.8% and 91.8% at 5-years in the silver-coated and non-silver coated group, respectively ($p = 0.193$). Infection was treated in the silver group by washout of the prosthesis in 2/11, debridement and implant retention (DAIR) in 1/11 and single-stage revision in 1/11, and in the non-silver group by washout in 1/23 or DAIR in 2/23. Two-stage revision was successful in 2/11 in the silver group, and in 11/23 in the non-silver group. Amputation was required in 4/11 in the silver group and 9/23 in the non-silver group. One patient in the silver group died due to disease with an infected EPR.

Conclusions: Silver-coated prostheses in high risk patients show similar infection free survival as non-silver coated prosthesis in standard sites in primary bone tumours of the extremities.

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Introduction

Endoprosthetic replacement (EPR) has gained favour amongst orthopaedic surgeons in the management of primary and secondary tumours of bone. Whilst revision rates of EPR for mechanical failure is comparatively high, limb salvage rates remain high ranging from 87% at 5 years to 84% at 20 years [1].

Despite this, EPR, particularly in the setting of tumour reconstruction is associated with a high incidence of periprosthetic infection, often requiring multiple further procedures, and in the worst-case scenario, necessitating amputation to eradicate

infection. In the case of patients treated for a bone sarcoma, this risk is increased. Figures vary but the accepted incidence of periprosthetic infection in this group is around 10% [2–4]. Any intervention, therefore, that can reduce this risk can only be a positive step.

Silver coatings have gained favour in orthopaedic oncology due to their antimicrobial activity with a low level of toxicity [5]. We have reported favourably on the use of a silver-coated prosthesis in terms of reduction in the incidence of infection, and success of more limited revision procedures should infection occur, when applied to both tumour resection and revision arthroplasty. However, in that study, the number of primary bone tumour patients included was low and the follow-up period was short [6].

In the Agluna® coating process, ionic silver is 'stitched' into the surface of the titanium alloy using a patented method (Accentus Medical Ltd, Oxfordshire, United Kingdom). This is achieved by

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anodisation of the titanium alloy followed by absorption of silver from an aqueous solution. The engineered surface modification is integrated into the substrate and loaded with silver by an ion exchange reaction. This results in the formation of circular features of 5 µm diameter in the surface of the implant, containing an amorphous titania species within which the bulk of the ionic silver has been stored. Using this technique, the maximum inventory of silver for a typical endoprosthesis is 6 mg, more than 300 times lower than the no-observed adverse-effect level.

The aim of this study was to analyse the incidence of infection in patients undergoing resection and reconstruction of a primary tumour of bone treated with a silver-coated (Agluna®) EPR. The incidence of infection, risk factors for infection and outcome of treatment, was compared to a concurrent cohort of patients reconstructed with a non-silver coated EPR.

Material and methods

All patients treated at a single centre between May 2007 and September 2014 were included in the study. Patients were identified from the institution's prospectively maintained database. The study comprised a retrospective analysis of 89 consecutive patients who underwent excision of an extremity sarcoma, or GCT of bone, and reconstruction using a custom-made EPR (Stanmore Implants Worldwide, Elstree, UK) augmented with an Agluna® silver surface treatment (Accentus Medical Ltd, Oxfordshire, United Kingdom). This group was compared to a second cohort comprising 305 consecutive patients treated with a non-silver coated, custom-made EPR.

Patients who had previously undergone surgery to the area, for example curettage for a GCT of bone, or low-grade chondrosarcoma, were included in the analysis. Patients with a pathological fracture or extra-articular resection were also included in the analysis. Patients undergoing revision of a previous EPR were excluded.

The decision to use a silver-coated prosthesis was made on a case by case basis with silver generally being added in cases at particular risk of infection [1,2,6]. This often included tibial replacements and cases where the patient had either received or was likely to receive radiotherapy or where there was an anticipated need for soft tissue resection. Patients who had undergone previous surgery, were often included in the silver-group.

Data collection comprised demographic data, histological diagnosis, previous procedures, pathological fracture, the use of neo-adjuvant or adjuvant therapies (chemotherapy or radiotherapy), the resection length and any significant risk factors for infection. The timing, indication and nature of any revision procedure was also recorded. All the patients were followed-up for a minimum of 24 months, or until death.

In all cases, the prostheses were implanted using antibiotic-laden cement (Palacos R + G, Heraeus Medical, Hanau, Germany) and all patients had routine peri-operative antibiotic prophylaxis according to the hospitals guidelines. In the case of proximal tibial reconstructions, the reconstruction was augmented by the use of a medial gastrocnemius flap with or without a split skin graft.

A periprosthetic infection was diagnosed in accordance with the Musculoskeletal Infection Society criteria and confirmed if three of the following were met [7]:

- C-reactive protein (CRP) level of >10 mg/dL or erythrocyte sedimentation rate of >30/hr
- Positive culture of synovial fluid
- Elevated white blood cell count in synovial fluid
- Positive intraoperative histologic culture

Where it occurred, the timing from the primary procedure, the infecting organism and the sensitivities to antimicrobial agents were recorded. The method of treatment of a periprosthetic joint infection was also recorded, both in terms of the first attempt and the final attempt at cure, unless the infection persisted at the time of final follow up. Cure was defined as no clinical evidence of infection and a normalisation of the serum CRP.

Statistical analysis

The primary endpoint of the study was periprosthetic infection without any previous revision surgery. The secondary endpoint was the outcome of treatment for any periprosthetic infection that occurred during the study period. Implant survival was assessed with the Kaplan-Meier method using log-rank test for univariate analysis and Cox regression analysis to identify independent factors affecting the survival. Implant survival was calculated from the date of prosthesis implantation to the date of revision for infection, latest follow-up date or death. Continuous variables between two groups were compared using the Mann-Whitney *U* test. Differences in proportions were assessed using Fisher's exact test. All analysis was completed using SPSS Statistics 21.0 (IBM, Armonk, New York) and *p*-value < 0.05 was considered significant.

Results

The patient specific details are shown in Table 1. The mean age was 32.4 years (range 4–95). 89 patients were treated with a custom-made silver-coated EPR (22.6%), compared to 305 patients (77.4%) treated with a conventional, custom made non-silver EPR.

The mean age at the time of surgery was 29.9 years (range 4–80) in the silver-group, and 33.8 years (range 4–95) in the non-silver group (*p* = 0.200). The mean follow-up was 55.2 months (range 2–136) in the silver-group and 54.9 months (range 3–136) in the non-silver group (*p* = 0.467). 22 patients (24.7%) in the silver-group were treated for a pathological fracture, compared to 6 (19.4%) in the non-silver group (*p* = 0.366). 17 patients (19.1%) in the silver-group had undergone previous surgery, most often curettage and cementation of either a giant cell tumour (GCT) or low-grade chondrosarcoma, compared to one patient (3.2%) in the non-silver group (*p* = 0.024). 67 patients (75.3%) in the silver-group had received neo-adjuvant therapy, most commonly in the form of chemotherapy, compared to 208 patients (68.2%) in the non-silver group (*p* = 0.200). Preoperative radiotherapy was given to 5 patients (5.6%) in the silver-group and 3 patients (1.0%) in the non-silver group (*p* = 0.017). All primary malignancies of bone were included and represented comparably in the final population, except chondrosarcoma which was more common in the non-silver group where it accounted for 70 patients (23%), compared to 11 patients (12.4%) in the silver-group (*p* = 0.018). Other rare tumours were more common in the silver group accounting for 12 patients (13.4%), compared to 8 patients (2.6%) in the non-silver group. High infection risk locations like proximal tibial (37 (41.6%) compared to 45 (14.8%), *p* < 0.001) and total bone compared with diaphyseal (16 (18%) compared to 13 (4.2%), *p* < 0.001) replacements accounted for a significant proportion of the implants in the silver group when compared to the non-silver group. Patient demographics are summarized in Table 1.

The incidence of periprosthetic infection, requiring revision as the primary endpoint was 34/394 (8.6%). This comprised 11 patients (12.4%) in the silver-coated EPR group and 23 patients (7.5%) in the non-silver prosthesis group (*p* = 0.154). The overall implant survival at one year without infection was 90.9% in the silver-coated group, and 95.3% in the non-silver coated group, and at 5-years 86.8% in the silver-coated group and 91.8% in the non-silver

Table 1
Patient characteristics.

Patient characteristics	Total	Silver-coated	Non-silver coated	p-value
Eligible patients	394	89 (22.6%)	305 (77.4%)	
Mean age at surgery years (range)	32.4 (4–95)	29.9 (4–80)	33.8 (4–95)	0.200
Mean follow-up months (range)	54.9 (2–136)	55.2 (3–136)	54.9 (2–133)	0.467
Pathologic fracture	28 (23.3%)	22 (24.7%)	6 (19.4%)	0.366
Previous procedure	18 (15.0%)	17 (19.1%)	1 (3.2%)	0.024
Adjuvant treatment	275 (69.8%)	67 (75.3%)	208 (68.2%)	0.200
Preoperative radiotherapy	8 (2.0%)	5 (5.6%)	3 (1.0%)	0.017
Postoperative radiotherapy	46 (11.7%)	9 (10.1%)	37 (12.1%)	0.709
Chemotherapy	223 (66.4%)	59 (68.6%)	164 (65.6%)	0.692
Histology				
Osteosarcoma	204 (51.8%)	46 (51.7%)	158 (51.8%)	0.000
Chondrosarcoma	81 (20.6%)	11 (12.4%)	70 (23.0%)	
Ewing sarcoma	42 (10.7%)	11 (12.4%)	31 (10.2%)	
Spindle cell sarcoma	22 (5.6%)	5 (5.6%)	17 (5.6%)	
Giant cell tumour	26 (6.6%)	5 (5.6%)	17 (5.6%)	
Other	20 (5.1%)	12 (13.4%)	8 (2.6%)	
Site				
Distal femur	169 (43.0%)	20 (22.5%)	149 (49.0%)	0.000
Proximal tibia	82 (20.9%)	37 (41.6%)	45 (14.8%)	
Proximal femur	54 (13.7%)	5 (5.6%)	49 (16.1%)	
Proximal humerus	49 (12.5%)	5 (5.6%)	44 (4.5%)	
Total femur	5 (1.2%)	2 (2.2%)	3 (1.0%)	
Total humerus	7 (1.8%)	6 (6.7%)	1 (0.3%)	
Midshaft tibia	3 (0.8%)	3 (3.4%)	0	
Midshaft humerus	3 (0.8%)	3 (3.4%)	0	
Midshaft femur	12 (3.0%)	2 (2.2%)	10 (3.3%)	
Other	9 (2.3%)	6 (6.7%)	3 (1.0%)	
Patients with infection as primary end point	34 (8.6%)	11 (12.4%)	23 (7.5%)	0.154
Patients with infection over whole study period	39 (9.9%)	13 (14.6%)	26 (8.5%)	0.091

coated group. The difference was not statistically significant, $p = 0.193$ (Fig. 1). The secondary end point of the study defined by periprosthetic infection over the whole study period was 9.9% (39 patients), 13 (14.6%) in the silver-coated EPR group and 26 (8.5%) in the non-silver EPR group ($p = 0.091$). This increase in the incidence of infection was due to infection of a prosthesis revised for implant failure not due to infection. Two patients in the silver-coated group and 3 patients in the non-silver group became infected after revision surgery either for exchange of the bushes of the prosthesis or following invasive lengthening of the prosthesis.

There was no statistical difference in infection rates identified between the silver-coated and the non-silver coated prostheses when stratified by location (Table 2). This confirmed that proximal tibial replacements were at most risk of infection (22%) compared to all other sites (6.4%).

The success rate of the first attempt to treat the periprosthetic infection was also compared between the two groups. In the silver-coated group, washout was successful in treating the infection in 1/9 patients. In the non-silver coated group, washout was successful in 2/7 and debridement, antibiotics and implant retention (DAIR) was successful in 1/11. Two-stage revision was successful in 2/3 in the silver-coated group, compared to 7/10 in the non-silver group ($p = 0.706$). The overall success rate to treat the periprosthetic infection in the silver-coated group, was washout in 2/11, DAIR in 1/11 and one-stage revision in 1/11. In the non-silver group washout was successful in 1/23 and DAIR in 2/23. Overall, two-stage revision was successful in 2/11 in the silver-coated group, and in 11/23 in the non-silver group. Amputation (including hindquarter amputation) was the final treatment solution in 4/11 patients in silver-coated group and 9/23 in the non-silver group. One patients with a silver-coated EPR died due to disease with a known periprosthetic infection.

Overall, the rate of amputation due to infection was 36.4% (4/11) in the silver-coated group, compared to 39.1% (9/23) in the non-silver group ($p = 0.591$). The results are summarized in Table 3.

Details of the infected cases are given in Table 4. The overall revision rate was 24.9% in the non-silver coated EPR group (7.4% infection, 6.9% local recurrence, 3.9% aseptic loosening, 3.0% pain, 1.3% mechanical problems, 1.0% soft tissue problems and 0.3% for periprosthetic fracture) and 29.2% in the silver-coated EPR group (12.4% infection, 7.9% local recurrence, 3.4% soft tissue problem, 2.2% aseptic loosening and 1.1% for pain and dislocation). No local or systemic features of argyria were observed in patients treated with silver-coated EPRs.

The median time to diagnosis of infection in the silver-group was 7 months (range 0–22) but in the non-silver EPR patients it was 10 months (0–58 months) ($p = 0.456$). The time between implantation and revision for infection was a mean of 7 months (range 0–27) in the silver-coated group, and 15 months (range 0–63) in the non-silver group ($p = 0.071$).

In the silver-group, 4/11 infections developed within the first month due to soft tissue wound breakdowns and two of these patients required amputation. All of the other infections arose due to coagulase negative staphylococcus, with two arising more than a year following insertion of the prosthesis. In the non-silver group, only 3 of 23 arose in the first month, and the later infections were due to a variety of organisms with eight arising after more than a year.

Univariate analysis of the whole study group identified any adjuvant treatment ($p = 0.009$), site (proximal tibia) ($p = 0.003$) and previous procedure ($p = 0.028$) as significant factors for infection. In multivariate analysis, significant factors were adjuvant treatment (hazard ratio [HR], 4.536; 95% confidence interval [CI] 1.196–17.206, $p = 0.026$), and proximal tibial location (HR, 4.368; 95% CI, 2.227–8.566, $p < 0.001$).

Discussion

Periprosthetic infection remains a common and devastating complication in orthopaedic oncology. The rate of infection has

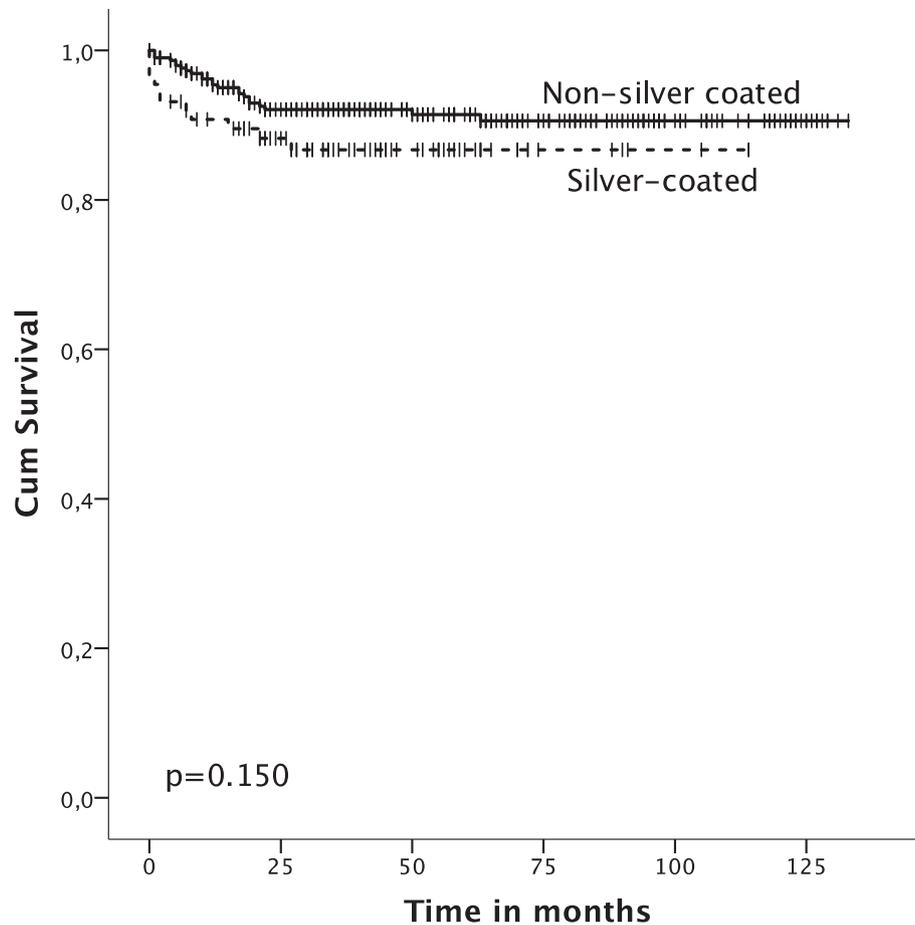


Fig. 1. Implant survival for patients with infection as primary end point. Stratified by silver coating.

Table 2

Rate of infection in different anatomic locations in silver-coated or non-silver coated EPR.

Site	Total	Infection as primary endpoint to revision surgery		p-value
		Silver-coated	Non-silver coated	
Proximal femur	3/54 (5.5%)	1/5 (20.0%)	2/49 (4.1%)	0.257
Distal femur	10/169 (5.9%)	1/20 (5.0%)	9/149 (6.0%)	0.664
Proximal tibia	18/82 (22%)	8/37 (21.8%)	10/45 (22.2%)	0.582
Proximal humerus	1/50 (2.0%)	0/5 (0%)	1/45 (2.3%)	0.900
Midshaft femur	0/12	0/2 (0%)	0/10 (0%)	–
Other locations	2/27 (7.4%)	1/20 (5%)	1/7 (14.3%)	0.459
Total	34/394 (8.6%)	11/89 (12.4%)	23/305 (7.5%)	0.141

Table 3

Successful treatment of revision for infection as the primary endpoint.

Final result to infection	Washout	DAIR	One-stage revision	Two-stage revision	Amputation/hindquarter	Dead with infected prosthesis
Silver-coated	2/11	1/11	1/11	2/11	4/11	1/11
Non-silver coated	1/23	2/23	0	11/23	9/23	0

remained surprisingly static, despite a number of adaptations to prosthesis design and surface treatments [2,3,8–10]. Ionized silver has known antimicrobial properties [11] and several new dressings and silver-coated devices have been developed capitalising on this property [12]. Silver-coating of EPRs was first reported by the Münster group in 2007 [5] and has since shown promising results in the short-term in a number of centres [6,9].

We have previously demonstrated a reduction in periprosthetic

joint infections with the addition of silver from 22% to 12% at one year [6]. In this study, the overall infection rate following EPR was 8.6%, comparable to the literature [13]. The infection rate of silver-coated prosthesis in this study was 12.4%, higher than that for non-silver coated EPR where the rate was 7.5% (though not statistically significant), and higher than reported in the literature [6,9,14].

The use of adjunctive silver on prostheses has changed at our institution. At the beginning of the study period, the use of silver on

Table 4
Characteristics of the patients with periprosthetic infection leading to revision.

Site	Age at diagnosis	Silver	Histology	Adjuvant treatment	Micro-organism	Resection length	Comments	Time to revision	End result
Prox tibia	64	Yes	CS	–	CNS	7.0 cm	Extra-articular resection, fell down in stairs	7 months	Amputation
Prox tibia	13	Yes	OS	CT	CNS	8.4 cm	Postop hematoma evacuation	3 months	Two-stage revision
Prox tibia	12	Yes	OS	CT	Staphylococcus aureus	7.5 cm	High risk VTE patient with postop antithrombotic medicine -> postop hematoma evacuation	2 weeks	Amputation
Prox tibia	47	Yes	OS	CT	CNS	8.6 cm	diabetes	27 months	Two-stage revision
Prox tibia	13	Yes	OS	CT	CNS	6.0 cm	Prolonged wound discharge	2 months	Amputation
Prox tibia	13	Yes	OS	CT	MSSA	10.0 cm	No gastroc flap, line infection	20 months	DAIR
Prox tibia	14	Yes	OS	CT	CNS	16.0 cm	Prolonged wound discharge	9 months	DAIR
Prox tibia	46	Yes	Spindle cell sarcoma	CT	CNS	10.0 cm	Proximal tibia and distal femur extra-articular resection	1 months	DAIR
Midshaft tibia	80	Yes	Spindle cell sarcoma	RT	Enterobacter cloacae	3.5 cm	Postoperative RT, age	2 weeks	Amputation
Proximal femur	65	Yes	Spindle cell sarcoma	RT	Not recorded	22.0 cm	Died due to cancer with infected prosthesis	2 weeks	Washout
Dist femur	24	Yes	OS	CT	CNS	14.0 cm	Pathologic fracture, massive soft tissue resection	10 months	One-stage revision
Prox tibia	41	No	OS	–	Staphylococcus aureus	12.0 cm		5 years	Two-stage revision
Proximal femur	62	No	CS	–	MRSA	20.0 cm	Pathologic fracture	5 months	Amputation
Dist femur	26	No	CS	–	CNS	7.0 cm	Previous surgery	8 months	Two-stage revision
Prox tibia	14	No	OS	CT	CNS, vancomycin-resistant enterococci, pseudomonas	12 cm		1 month	DAIR
Prox tibia	16	No	OS	CT	CNS	13 cm		10 months	Amputation
Dist femur	22	No	OS	CT	CNS	23.5 cm		1 month	Washout
Dist femur	23	No	OS	CT	Staphylococcus aureus	15 cm		12 months	Amputation
Prox tibia	12	No	OS	CT	E. coli	7.0 cm		7 months	Two-stage revision
Dist femur	14	No	OS	CT	CNS	8.0 cm	Pathologic fracture	4 years	Two-stage revision
Dist femur	19	No	OS	CT	Multi drug resistant CNS	12.0 cm	No gastroc flap	10 months	Two-stage revision
Prox tibia	15	No	OS	CT	CNS	12.0 cm		6 months	Two-stage revision
Prox tibia	12	No	OS	CT	Not recorded	5.5 cm		18 months	Amputation
Prox tibia	26	No	OS	CT	Staphylococcus aureus	16.0 cm		5 months	Amputation
Prox tibia	22	No	OS	CT + RT	CNS	12 cm		1 months	Amputation
Dist femur	13	No	OS	CT + RT	CNS + streptococcus viridans	15.0 cm		21 months	Amputation
Prox tibia	14	No	OS	CT	Staphylococcus aureus Flucloxacillin-resistant	10.0 cm		22 months	Two-stage revision
Dist femur	21	No	OS	CT	CNS	9.0 cm		19 months	Amputation
Prox tibia	8	No	OS	CT	Staphylococcus aureus + Corynebacterium sp.	11.0 cm		12 months	Amputation
Dist femur	11	No	OS	CT		11.0 cm		4 months	Two-stage revision
Prox humerus	12	No	ES	CT + RT	Staphylococcus aureus	7.5 cm	Pathologic fracture	17 months	Two-stage revision
Dist humerus	15	No	ES	CT + RT	CNS + enterococcus	14.7 cm		19 months	Two-stage revision
Prox femur	18	No	ES	CT + RT	Not recorded	8.5 cm	Pathologic fracture	13 months	DAIR
Dist femur	38	No	Spindle cell sarcoma	CT + RT	CNS	7.0 cm		17 months	Two-stage revision

OS; osteosarcoma, CS; chondrosarcoma, ES; Ewing sarcoma, CT; Chemotherapy, RT; Radiotherapy, CNS; coagulase-negative staphylococcus, DAIR; debridement antibiotics and implant retention, MSSA; methicillin sensitive staphylococcus aureus, MRSA; methicillin resistant staphylococcus aureus.

prostheses was limited to patients deemed at high-risk of infection and selected on a case-by-case basis by only two nominated surgeons. Later, when evidence began to appear on the benefits of adjunctive silver, the use of silver-coated prostheses became a standard treatment for patients deemed at higher risk of periprosthetic infection. The inclusion criteria for the addition of silver,

whilst not absolute, included previous surgery, previous inadvertent tumour excision, pathological fracture and tumour types necessitating neo-adjuvant therapy. This is reflected by the differences in the two study groups where these criteria are seen more frequently in the silver-coated group. Cognisant of the high-risk of soft tissue failure, silver tended to be used more often for proximal

tibial and intercalary replacements, representative of the high risk of infection in these sites [2,6]. The absence of absolute inclusion and exclusion criteria for the use of silver in the patients included in this study is a limitation in our study design. However, despite these differences, we have demonstrated that the addition of a silver surface treatment effectively normalises this patient group resulting in a risk of infection comparable to those deemed at lower risk. Previous work has demonstrated an infection rate following proximal tibial reconstruction of 23% [2]. Patients included in this study were not stratified for risk of infection. It is therefore reassuring that the addition of silver to the prosthesis resulted in a comparable rate of infection for those without silver, the infection rate in whom was comparable to our previously published results. Whilst we have demonstrated an effect of silver in normalising the higher risk group, it could be expected that this effect would become more apparent at the proximal tibia, which could be regarded as the highest risk site, outside the pelvis. However, infection rates at this site were the same regardless of the addition of silver. This could be explained in part, by the inference that this single intervention, on its own, would not be sufficient to produce a demonstrable reduction in infection rates. Essentially, at this high-risk site, if an infection is going to happen, additional silver may not, on its own, be enough to prevent this happening.

Hardes et al. have reported results supporting the use of silver-coated prostheses for reconstruction of the proximal tibia. The authors report a reduction in revision for infection as the primary endpoint from 16.7% to 8.9%, though not statistically significant ($p = 0.247$). It should be noted however, that in their study, they included two series of patients collected sequentially over a long-time period. The duration of follow-up will therefore have been much longer in the non-silver group. Patients deemed high risk by our own criteria, were excluded from the analysis, including those who had undergone previous surgery, or extra-articular resections. 50% of patients in the non-silver group also required a revision procedure prior to the development of infection but were still included in the study. Revision procedures, not requiring removal of the implant (for example, rebushing procedures) are known to increase the risk of subsequent peri-prosthetic infection and so in part may explain the higher rate of infection seen in the non-silver group reported by Hardes [14].

When comparing our current findings to our previous work [6], it appears on first inspection that the promising results reported with silver prostheses have been disproved. However, the design and inclusion criteria for that study differ considerably to the current analysis. The initial study adopted a case matching model to compare silver-coated to non-silver coated prostheses. In that study, primary tumours of bone and primary reconstructions in extremities accounted for only 26 out of 170 patients. The remaining patients were revision prostheses and primary procedures for non-oncological diagnoses or pelvic location [6]. In this study, we included only patients treated for a primary tumour of bone in the extremity. However, there has been a selection bias for silver in high risk cases. Therefore, the similar infection rates reported in this series compared to the previously reported reduction in the silver group, may be explained, at least in part, by patient selection and the longer period of follow up in this current series.

The bioavailability of ionic silver in the effective joint space may help to explain our results. The infection rate in the silver-group was higher than anticipated when compared to the non-silver group. However, risk factors in the silver-group were also higher, including more extensive surgery and early wound complications, resulting in a reduction in the effective concentration of silver in the joint space. Silver elutes from the surface of the prosthesis following implantation and though the exact duration of elution remains unclear, it is becoming apparent that the duration of

elution may be measured in months rather than years. This may in part explain the absence of local or systemic argyria seen in patients with an Agluna® coated prosthesis when compared to the MUTARS (Implantcast, Buxtehüd, Germany) silver-coated prosthesis, where the incidence of local argyria was reported to be as high as 23% [15]. Therefore, once the effective concentration of silver has diminished, a silver-coated prosthesis may function as a non-silver coated prosthesis. As many of the patients undergoing EPR continue to receive adjuvant therapy often administered through indwelling venous catheters for many months following surgery, it is likely that bacteraemia, prosthetic colonisation and subsequent infection are likely to occur during this time of immunosuppression. This is shown by the time at which an infection is seen, where the majority of infections were seen within the first 20 months. Silver released from the prosthesis surface will be bound by serum proteins and removed from the effective joint space thus reducing the effective dose at the implant and increasing the potential for biofilm development [16]. Any soft tissue complication that increases the risk of colonisation will increase the risk of infection. Whilst the addition of silver may confer an advantage in terms of reduction of infection, it cannot substitute for postoperative wound complications. This was the cause of infection in 4 of the 11 infected silver coated EPRs. We observed no difference in the efficacy of prosthesis preserving interventions to treat infection between the two patient groups, which, again, contrasts with our previous findings [6]. A two-stage revision is a significant undertaking for any patient, but especially for patients with a primary bone tumour, who are often undergoing chemotherapy at the time of infection. Therefore, DAIR has been the mainstay of treatment for infection in patients who develop an infection after a short period following implantation [17]. Our results demonstrate that patients treated expediently following the development of symptoms of infection (less than one month) could, in 50% of cases, be successfully treated with a prosthesis preserving procedure such as DAIR. There is ongoing discussion about whether the success of DAIR is influenced by the infecting organism [18,19]. We had insufficient numbers to demonstrate an effect of organism type, though no difference was seen between the silver and non-silver groups. It should be noted that we were unable to demonstrate an advantage for the use of silver in terms of avoiding amputation to eradicate infection.

Conclusions

Our results suggest a promising effect of the addition of silver to prostheses when applied to a perceived high-risk population undergoing limb salvage surgery for the treatment of primary bone tumours. Whilst not as dramatic as previously expected, the reduction in the incidence of infection to a level comparable to a perceived lower risk population undergoing limb salvage surgery confers a limb survival advantage to this high-risk group. We therefore believe that silver may be a valuable adjunct when applied to endoprostheses, particularly in patients at a higher risk of periprosthetic infection. High risk patients include tumour locations with limited soft tissue coverage, including the proximal tibia and tibial intercalary locations, patients who have received preoperative radiotherapy and patients undergoing extra-articular tumour resection. The evidence for the use of silver-coated prostheses is evolving and its exact application and efficacy remain an area for debate, only answerable by a multicentre randomised study.

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