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Two-Stage Treatment Protocol of Fungal Periprosthetic Hip and Knee Joint Infections: the Clinical Experience from a Single Center Experience

Dvoustupňový léčebný protokol mykotických periprotetických infekcí kyčelního a kolenního kloubu: klinická zkušenost jednoho centra

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ABSTRACT

PURPOSE OF THE STUDY
To evaluate the clinical results and safety of fungal periprosthetic joint Infections (fPJIs) using two-stage treatment protocol.

MATERIAL AND METHODS
8 patients with fPJIs (3 hips and 5 knees) using two-stage revision were reviewed retrospectively and followed up at least 2 years. The preoperative demographic data, two-stage treatment protocol, results of microbiology and histologic workup and postoperative follow-up results (reimplantation success rate and infection free time) were recorded.

RESULTS
7 patients got successful reimplantation, with a 75% reimplantation success rate. Two patients got knee arthrodesis eventually. All patients were infection free with a median follow-up of 4.0 ± 2.0 years (range, 2–7 years). Of them, *Candida* species were found in 7 patients, while non-*Candida* specimen was only isolated in 1 patient with *Aspergillus*. Only 2 patients had coexisting bacterial infection (*Methicillin-resistant coagulase-negative Staphylococci* and *Proteus mirabilis* respectively). The average interval between the initial surgery and diagnosis of fPJIs was 21.50±34.79 months (range, 4–104 months). The mean time of spacer implantation was 7.75±2.77 months (range, 6–14 months). None serious complication or above knee amputation was found.

DISCUSSION
fPJIs are very rare and considerable challenge after total hip or knee arthroplasty. The goal of therapy is to eradicate local infection and maintain function. *Candida* species were the most common pathogen. The duration between spacer placement and staged reimplantation was highly variable, and generally dependent upon the results of joint aspirates and inflammatory markers. The current study shows that the two-stage treatment protocol is recommended for fungal periprosthetic hip and knee joint infections.

CONCLUSIONS
The two-stage treatment protocol is recommended for fungal periprosthetic hip and knee joint infections. The safety and efficacy of biantibiotical impregnated (antifungal + antibiotics) cement spacer is confirmed. Further evidence-based work is needed to determine the optimal drug dose and reimplantation time.

Key words: two-stage treatment protocol, fungal periprosthetic infections, hip spacer, knee spacer.

INTRODUCTION

Fungal periprosthetic joint infections (fPJIs) are very rare and considerable challenge after total hip arthroplasty (THA) or total knee arthroplasty (TKA). It constitutes about 1% of all periprosthetic joint infections (1), but may pose an increasing problem in future. Till now, no guideline about fPJIs has been established on basis of little instructive evidence in the literatures. Schoof et al. showed a heterogeneity after reviewing 45 patients with fPJIs of hip. The patients were treated with debridement, antibiotic therapy, retention of the prosthesis or not, one-stage or two-stage procedures, and even local antimycotic agents (2). It is difficult to interpretate the presented data on the base of the small sample size and various treatment concepts in each report (1).

To the best of our knowledge, there has been few literatures concerning two-stage treatment protocol used in fPJIs. The primary aim of this study was to detective the results of fPJIs using two-stage treatment protocol. The safety of two-stage treatment protocol was also evaluated as a secondary endpoint.

MATERIAL AND METHODS

This retrospective study was designed and approved by the Ethics Review Committee of Nanjing Jinling Hospital. Informed consent was obtained from all patients.

From June 2015 to August 2020, a total of 8 patients with fungal periprosthetic joint infections (3 hips and 5 knees), aged 61–75 (average, 67.50 ± 5.53) were retrospectively analyzed in this retrospective study. Of them, 4 males and 4 females. The inclusion criteria were fungal periprosthetic joint infections treated with two-stage treatment protocol; no other diseases before affecting the lower limb function; no other infection affecting the blood test; an available complete clinical data. All data were summarized in Table 1.

Diagnosis of fungal periprosthetic joint infections

The diagnosis of fPJIs was made on the base of Past medical history, clinical criteria (local redness, tenderness, pain, or sinus tract), laboratory parameters (C-reactive protein, leukocyte blood count, or erythrocyte sedimentation rate), histopathologic findings and the microbiology of joint aspiration preoperatively. Preoperative joint aspiration was regularly performed in each case indicating a fungal infection. Fungal serologic examination was routinely performed to exclude hematogenous fungal infection (1, 3).

Two-stage treatment protocol

All operations were performed by the same surgery team major in arthroplasty. First, the preexisting approach was used again in all patients. All the foreign materials (including prostheses, cement remnants, and infected tissue) and potential infected tissues were debrided radically. The removed tissues were taken for microbiology and histologic workup. The punctate was processed into BLOOD AGAR MEDIA (Thermo Fisher Biochemical Products (Beijing) Co., Ltd) and analyzed by Biomerieux Vitek 2 Compact ID/AST Microbial Analyzer.

Following the recommendations of the PRO-IMPLANT Foundation (15), a biantibiotical impregnated (antifungal+ antibiotics) cement spacer was conducted. 800mg voriconazole + 4 g vancomycin were added to the 80 g cement spacer. All spacers were manually molded individually to achieve a good ligament tension. Of them, knee spacer was block spacers without metallic endoskeleton, while hip spacer acted as a hemarthroplasty with a K-wire endoskeleton. The systemic antifungal therapy was administered after operation, including 1 month of intravenous antifungal agents and followed by a no less than 3 months of oral antifungal agents as needed.

The prosthesis reimplantation was performed with a minimum interval of 4 months after three times of normal ESR, CRP, and fungal culture results of joint aspiration in the monthly rechecks. The choice of implant was considered individually based on the bone loss and quality. Intraoperative deep tissue specimens were taken again for microbiology and histologic workup. At positive findings, the spacers should be only exchanged with radical debridement. After prothesis reimplantation or arthrodesis, all patients were administrated with 1 month of intravenous antifungal agents, followed by no less than 6 months of oral antifungal agents as needed.

Table 1. The baselines of patients with fPJIs

Patient	Age/gender	Initial surgery	Comorbidities	Pathogen organism	Bacteria	No. of previous surgeries	Time between stages (m)	Follow-up duration (y)
1	71/F	TKA	DM	*Candida guilliermondii*		1	4	2
2	62/M	TKA	HP	*Candida pelliculosa*	*Proteus mirabilis*	2	6	3
3	61/M	THA	DM	*Candida guilliermondii*		2	14	7
4	62/M	TKA	None	*Candida parapsilosis*		1	8	2
5	74/F	TKA	HP/DM	*Candida guilliermondii*		1	6	4
6	75/F	TKA	None	*Aspergillus*	*Methicillin-resistant coagulase-negative Staphylococci*	4	9	7
7	68/M	THA	HP/DM	*Candida parapsilosis*		2	6	4
8	67/F	THA	DM	*Candida parapsilosis*		1	6	3

F: female; M: male; TKA: total knee arthroplasty; THA: total hip arthroplasty; DM: diabetes mellitus; HP: hypertension; COPD

Rehabilitation regime

Isometric muscle strength training was performed at the day after operation. All patients were permitted to mobilize with partial weight bearing using crutches. The range of motion was allowed if tolerated.

The infections occurred in the first year after new prosthesis implantation were defined as "reinfection". The Delphi-based consensus definition of successful infection eradication was used to assess the prognosis (8).

Statistical analysis

All statistical analyses were carried out by SPSS 24.0 (SPSS Inc, Chicago, IL, USA). Kolmogorov–Smirnov test was employed to evaluate the normality distribution of continuous variables. Mean (standard ± deviation) or median (interquartile range) were used as appreciate. A $P<0.05$ was considered statistically significant.

RESULTS

In total, 8 patients (3 hips and 5 knees) with fPJIs were enrolled and followed up (Table 1). In serum marker levels at diagnosis, the average C-reactive protein (CRP) levels and erythrocyte sedimentation rate and (ESR) were 126.41 ± 62.68 mg/L and 40.88 ± 21.07 mm/h, respectively. 6 patients got successful reimplantation, with a 75% reimplantation success rate. Two patients got knee arthrodesis eventually. One of the arthrodesis patients required arthrodesis herself and the other didn't have adequate bone stock for reimplantation. All patients were infection free with a median follow-up of 4.0 ± 2.0 years (range, 2–7 years). No radiological signs of loosening, as well as reinfection was found. All patients achieved daily-life activity and 2 of them returned to previous work.

Candida species were the most common pathogen. Of them, *Candida guilliermondii* were found in 3 patients, *Candida parapsilosis* in 3 patients and *Candida pelliculosa* in 1 patient. Only 2 patients had coexisting bacterial infection (*Methicillin-resistant coagulase-negative Staphylococci* and *Proteus mirabilis* respectively, Table 1). *Non-Candida* specimen was only isolated in 1 patient with *Aspergillus*.

The average interval between the initial surgery and diagnosis of fPJIs was 21.50 ± 34.79 months (range, 4−104 months) without reinfection. After cement spacer used, all patients were managed with 1 month of intravenous antifungal agents, followed by a mean 6.38 ± 3.07 months (range, 3−13 months) of oral antifungal agents. The mean time of spacer implantation was 7.75 ± 2.77 months (range, 6−14 months). After prothesis reimplantation or arthrodesis, all patients were managed with 1 month of intravenous antifungal agents, followed by a mean 6.88 ± 1.73 months (range, 6−11 months) of oral antifungal agents.

None serious complication or above knee amputation was found. One patient had wound delayed healing and healed by itself after dressing change. Two patients had local pain complaints and subsided with no additional medicine.

DISCUSSION

fPJIs are considered as a difficult-to-treat PJI with higher failure rate (4). The goal of therapy is to eradicate local infection and maintain function. In present study, we confirm that the two-stage treatment protocol, mirroring that of bacterial PJI, offers a favorable encouraging outcome. Also, no serious complication is found.

The fungal infection should be considered when the standard antimicrobial treatment fails. As such, joint aspiration, specialized media for fungus and delayed incubation time are needed with rigorous control. Some emerging techniques, such as implant sonication and multiplex polymerase chain reaction, could be considered to detect accurate pathogen identification. The specific treatment for fPJIs usually refers to the successful experience of bacterial PJI, due to little instructive evidence in the literatures. The main risks for fPJIs are type II diabetes mellitus, prior PJI, revision surgery, immunosuppression and long-term antibiotic use (12). Kuo FC et al. retrospectively identified the prognosis of patients with fPJIs and found that two-stage exchange arthroplasty was a preferred treatment. The single-stage revision usually demonstrated a poor prognosis (18). To achieve better function, the prerequisite for a new reimplanted prosthesis is the eradication of local infection. All original hardware are removed to prevent biofilm formation overlying prostheses (6). The PRO-IMPLANT Foundation also advocates the core concepts of current management in PJI. First, all implant and foreign material should be debrided, although this process is difficult but critical. Sometimes, it needs two stage exchange procedure or even more. Second, antimicrobial treatment should be initialed earlier by empirical antimicrobial therapy, and adjusted based on the susceptibility of the microorganism (13).

Pathogen of infection

Candida species are the most common pathogen, about 80% of cases, which can adhere to the host tissue and implanted prosthesis in various environments (19). And the biofilm formation supplies a protect niche for microorganisms to avoid antibiotic treatment, and also creates a source of persistent infection (5 24). The polysaccharides secreted by *Candida* physically play as a barrier to prevent interaction between bacterial cell and antibiotic (17). In present study, we had the same conclusion. *Candida* species were the most common pathogen, accounting for 87.5%. Sometimes, the susceptibility of previous pathogen changes during the course of treatment. Ji et al. confirmed the susceptibility of fluconazole changed in a TKA infected with *Candida parapsilosis* (16).

Another concern is concomitant pathogens with bacteria, which is negatively related with deterioration.

Our study found 2 patients had coexisting bacterial infection (*Methicillin-resistant coagulase-negative Staphylococci* and *Proteus mirabilis* respectively). Any potential and secondary nidus of infection need to be completely removed to prevent hematogenous spread. Azzam K et al. pointed out that fungal prosthetic joint infections had a high risk of subsequent bacterial infections based on a multi-institutional experience (1). Hence, we impregnated the bone cement to bone cement with antibiotics to prevent any potential bacterial superinfection.

The choice of antifungal drugs mixed with cements

The duration between spacer placement and staged reimplantation is highly variable, and generally dependent upon the results of joint aspirates and inflammatory markers. Previous papers have confirmed the safety and efficacy of antifungal bone cement used in fPJIs. It plays an important adjunct role in improving the results (10).

Pathogen directed therapy is a particularly challenge due to the lack of reliable systemic or topical antifungal drugs. There has been no conclusive evidence about the best antifungal drug mixed with cement. However, local antifungal effects and mechanical properties are two important standards we focus on. Previous studies revealed that amphotericin-B was preferable, which supplied highly antifungal activity with less dose. And it could withstand high temperature during mixing with cements (2). Sealy et al. compared the varying release of antifungals from different carriers and found that amphotericin B provided high supernatant concentrations up to 110 days (26). As a new antifungal agent, voriconazole has better activity against *Candida* species with less nephrotoxicity (27). Grimsrud et al. examined the vitro elution characteristics of voriconazole from nonabsorbable polymethylmethacrylate (PMMA) beads and absorbable calcium phosphate beads. And they found that biologically antifungal effective concentrations could be retained at least 2 weeks, which was a reasonable strategy for infected wound bed (21). In our institute, we chosen voriconazole added to cement spacer and achieved a favorable encouraging outcome.

More current clinical cases and experimental research confirm the encouraging results of antifungal loaded cement with none adverse events. However, further research is needed to establish consistent evidences about the optimal drug dose and reimplantation time.

The choice of dosage added to the spacer

Antifungal impregnated spacers play a key role in control infection, which should be strongly considered to eradicate local infections and reduce the medication time. However, there is no conclusive evidence about the choice of dosage added to the spacer (8). As of now, few literatures have been found about the formulation of antifungal and cement. Amphotericin has a relative heat stability and was wildly used in clinic. It was confirmed that the addition of amphotericin could change the mechanical properties of cement in vitro and decreased the compressive strength over time. However, none cement related fracture was reported in the literature (11). Recently, voriconazole is becoming increasingly used in impregnated cement spacer with predictable elution and less reduction in compressive strength (20). It remains unclear that the local dose of antifungal drugs is enough to destroy fungal biofilms or not. In present study, we also added vancomycin in cement spacers to control possible concurrent bacterial infection. It will be of great importance about the synergistic effect, change of properties of cement in further research.

The duration of antifungal administration

The choice of postoperative antifungal treatment is also extremely important. Fluconazole and amphotericin B have a large antifungal spectrum with good joint space penetration. However, significant side effects need to be paid enough attention, especially in patients with renal or hepatic impairment.

The duration of antifungal administration varies in different institutions. None consensus has been found. Previous study suggested that longer duration treatment with anti-fungals usually brought greater treatment success (28). In 2013, International Consensus Meeting on Surgical Site and Periprosthetic Joint Infection recommended a minimum of 6 weeks of antifungals after prothesis resection, but none conclusive conclusion was achieved about the duration after reimplantation (23). In patients with *Candida* infections, the Infectious Diseases Society of America recommended that the duration of antifungals should be 12 weeks after prothesis resection, and 6 weeks after prothesis reimplantation (22). However, the European Society for Clinical Microbiology and Infectious Disease (ESCMID) recommended a strategy with at least 14 days of parenteral antifungals after prothesis resection, followed by a minimum of 4 to 6 weeks of oral antifungals therapy (9). Hwang BH et al. proposed that the antifungal agents should be used at least 6 weeks till reimplantation of new prosthesis. And oral antibiotics should be administered also for 6 months after reimplantation (14). In our institute, the systemic antifungal therapy was administered after reimplantation, including 1 month of intravenous antifungal agents and followed by a no less than 6 months of oral antifungal agents as needed.

Limitations

There are several limitations in this present study. It's just a small sample size with only 8 patients. And none control group is set. Nevertheless, our results are encouraging and long-term follow-ups are needed. Furthermore, we paid more emphasis on infection control, and the functional results are not recorded in present study. Further prospective researches are needed.

CONCLUSIONS

Overall, the current study shows that the two-stage treatment protocol is recommended for fungal periprosthetic hip and knee joint infections. The safety and efficacy of biantibiotical impregnated (antifungal + antibiotics) cement spacer is confirmed. Further evidence-based work is needed to determine the optimal drug dose and reimplantation time.

This retrospective clinical trial was designed and approved by the Ethics Review Committee of Jinling Hospital, affiliated to Nanjing University. All methods were performed in accordance with the relevant guidelines and regulations. Written informed consent was obtained.

All data generated or analysed during this study are included in this published article and are available from the corresponding author on reasonable request.

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