EFORT open reviews

GENERAL ORTHOPAEDICS | 8:9 | 672–679

Outcomes of single- vs two-stage primary joint arthroplasty for septic arthritis: a systematic review and meta-analysis

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- *Purpose:* Septic arthritis (SA) is an intra-articular infection caused by purulent bacteria and the only effective method is surgical intervention. Two-stage arthroplasty is considered the gold standard treatment for SA, but recent studies have found that single-stage arthroplasty can achieve the same efficacy as two-stage arthroplasty. This study aimed to compare the efficacy of single- vs two-stage arthroplasty in the treatment of (acute or quiescent) SA.
- *Methods:* The review process was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We searched the PubMed, EMBASE, Medline, and Cochrane Library databases to identify all literature on the treatment of SA using single- and two-stage arthroplasty from the date of database inception to November 10, 2022. Data on reinfection rates were expressed as odds ratios and 95% CIs.
- *Results:* Seven retrospective studies with a total of 413 patients were included. Pooled analysis showed no difference in the reinfection rate between single- and two-stage arthroplasty. Subgroup analysis found no difference between the single- and two-stage arthroplasty groups in the incidence of purulent infection of the hip and knee. Cumulative meta-analysis showed gradual stabilization of outcomes.
- *Conclusions:* Based on our meta-analysis of available retrospective studies, we found no significant difference in reinfection rates between single- and two-stage arthroplasty for SA. Further prospective cohort studies are needed to confirm our results, although our meta-analysis provides important insights into the current literature on this topic.

Keywords

- septic arthritis
- arthroplasty
- reinfection
- single-stage
- two-stage

EFORT Open Reviews (2023) **8**, 672–679

Introduction

Septic arthritis (SA) is an intra-articular infection caused by purulent bacteria that most commonly affects the knee joint (45%), followed by the hip (15%) (1). SA presents as local redness, swelling, heat, and pain in the affected joint, along with systemic symptoms such as fever (1). The disease progresses rapidly, has a high teratogenic rate, and has a mortality rate of up to 11% for hip SA (2). For knee SA, the reported 90-day mortality was 7% (3). The most common pathogen causing SA is *Staphylococcus aureus*, followed by *Streptococcus* spp. and other gram-positive bacteria (4). The infection can occur through circulatory spread or through factors such as local trauma or medical intervention (5). SA can cause great damage to joints, erode joint cartilage, increase the fragility of soft tissues and ligaments around the joints, and deteriorate soft tissue conditions (6).

Acute SA is defined by those patients that present with altered clinical (fever, phlogosis, swelling, and pain) and laboratory parameters (leukocyte count, erythrocyte sedimentation rate, and C-reactive protein). Quiescent SA refers to a state in which patients who have a previous history of acute SA demonstrate normalization of laboratory values and the absence of clinical signs suggestive of ongoing infection after appropriate treatment. During this phase, there is a lack of joint-related symptoms such as pain, swelling, redness, and limited range of motion, and laboratory tests indicate no ongoing inflammatory response (7). In the management of acute SA, it is crucial to isolate the causative pathogen through joint aspiration and culture before initiating antibacterial treatment,

https://doi.org/10.1530/EOR-22-0142

whenever possible (8). The initial surgical intervention typically involves washout, either arthroscopic or open, to remove the infected material and reduce the microbial load. Following the resolution of SA, there is an increased risk of requiring total knee arthroplasty (TKA) within 1 year, with reported rates as high as 1%, and the long-term risk of periprosthetic joint infection (PJI) is elevated, reaching 6% at 15 years (approximately six times higher than the general population) (3, 9). In cases where SA does not resolve or when joint destruction is significant, a two-stage primary joint arthroplasty with bony cut and spacer may be considered to first sterilize the joint and subsequently reconstruct it. However, some authors suggest that a single-stage approach is feasible when the infection is controlled. The decision regarding the appropriate surgical approach should be made by an experienced orthopedic surgeon in consultation with an infectious disease specialist, taking into account the patient's medical history, the severity and location of the infection, and the condition of the affected joint. Debridement and antibacterial therapy can lead to the resolution of SA in certain patients, although there is a risk of subsequent stiffness and contracture, which has an incidence of approximately 9% (10). Stiffness and contracture management may require additional interventions to improve joint mobility and functionality (11). In summary, the management of septic arthritis involves identifying the causative organism through joint aspiration, initiating appropriate antibiotic therapy, and considering surgical interventions such as joint drainage or arthroplasty when conservative measures fail or joint destruction is severe (12). The treatment approach should be individualized based on the patient's specific circumstances and requires collaboration between orthopedic surgeons and infectious disease specialists (13). It was previously believed that surgical fusion was an ideal method to remove the infection, reduce pain, and enhance the stability of the knee joint; however, the loss of joint function after joint fusion surgery inevitably led to shortening of the patient's limbs and lameness, affecting the patient's ability to perform activities of daily life, reducing the quality of life, and leading to low levels of patient satisfaction. Furthermore, the infection rates may be higher in men, people with concomitant antibiotic-resistant organisms, and patients with diabetes. Various treatment strategies for SA have been reported, but there is a lack of science-based high-level evidence (14). A systematic review performed by Balato *et al.* found that both single- and two-stage surgery are effective in treating hip SA (15). It is clear that primary arthroplasty for SA (single or two-stage) might be considered in patients with SA, but there are two different settings, which are not exactly the same. The rate of infection recurrence ranged from 0% to 16.7% in the single-stage arthroplasty group and from 0% to 33.3% in the two-stage arthroplasty group (7, 16, 17). Although multiple studies have attempted to standardize the diagnostic process and treatment of SA, there is currently no consensus due to the small number of patients included in existing studies. Therefore, the present study combined and reviewed the existing research data to investigate the efficacy of single- and two-stage arthroplasty for (acute or quiescent) SA regarding the rate of infection recurrence.

Methods

This meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (18). The protocol for this meta-analysis was registered in PROSPERO (Registration No: CRD 42022377017).

Inclusion criteria

This study included randomized controlled trials, retrospective or prospective cohort studies, and case–control studies. The study population comprised patients with SA (including shoulder, hip, and knee), including patients with quiescent and acute (responding or non-responding) SA. The intervention and control were single-stage arthroplasty in the treatment group and two-stage arthroplasty in the control group. The outcome indicator was the rate of reinfection.

Exclusion criteria

The exclusion criteria were letters, case reports, animal trials, or republished studies; patients under the age of 15 years; previous prosthesis or osteosynthesis material in the affected joint; follow-up of less than 1 year.

Outcomes

The primary outcome was to evaluate the reinfection rate of single-stage vs two-stage joint arthroplasty in patients with SA.

Search strategy

Two authors (HNH and YZ) searched PubMed, EMBASE, Medline, and the Cochrane Central Register of Controlled Trials databases from their respective inception dates to November 10, 2022. The following keywords were used: '(Two-stage or 2-stage or two stage or second-stage or double-stage) and (Single-stage or one-stage or 1-stage) and (arthroplasty or replacement) and septic arthritis and (unhealed or infection or relapse).' No language restrictions were applied.

Study selection

Two researchers (YZ and GYY) individually screened the retrieved literature against the inclusion and exclusion criteria. Based on reading the title and abstract, articles that met the inclusion criteria were read in full and the relevant articles were identified. If the two researchers disagreed about the literature screening process, the final decision on study inclusion was made by the senior researcher (HL).

Data collection process

Two authors (HL and HNH) extracted the following data from the included studies: author, country, sample size, study design, date range, and number of reinfections.

Risk of bias and quality of evidence assessments

Two researchers (YZ and GYY) independently assessed the quality of all included randomized clinical trials using the Cochrane risk-of-bias criteria (19). The Newcastle–Ottawa scale (NOS) was used to evaluate the quality of retrospective studies (20).

Statistical analysis

The meta-analysis was performed using Stata software (version 17; StataCorp, 2021). Heterogeneity was assessed using the Q test and I^2 calculation. If heterogeneity was not present ($P > 0.1$ and $I^2 < 50\%$), the data were combined using the Mantel–Haenszel method for fixed-effect model. If heterogeneity was present ($P < 0.1$ or $I^2 > 50\%$), the inverse variance method for random-effects model was used. The odds ratio (OR) and the associated 95% CI were used to assess outcomes, and a *P* value of less than 0.05 indicated that the difference was statistically significant. Harbord testing was performed with Stata 17 software to assess publication bias.

Subgroup analyses

We performed subgroup analyses for similar subsets of patients across studies.

Sensitivity analyses

We performed a sensitivity analysis by case-by-case exclusion using a random-effects model.

Results

The search strategy retrieved a total of 172 relevant studies (79 from PubMed, 66 from EMBASE, and 27 from MEDLINE). After removing duplicate articles, 122 articles were left. After reading the titles and abstracts, 111 extraneous studies were excluded. The full text of the remaining 11 studies was read, and 4 more studies were excluded. Two of the excluded studies discussed the treatment of infection after shoulder replacement and the advanced active tuberculosis of the hip (21, 22), respectively. Papanna *et al.* (23, 24) and Tan *et al.* (9, 25) reported the results from the same institute twice, and we included only the most recent studies from each author group (9, 24). Finally, a total of seven studies with 413 participants met our eligibility criteria and were included in the meta-analysis (Fig. 1). All included studies were retrospective studies. The information on the included studies is detailed in Table 1. The quality of the included studies was assessed using the NOS scale, and all studies had a NOS rating of 5 or more stars (Table 1).

Reinfection

A total of seven studies reported reinfection (7, 9, 16, 17, 24, 26, 27). The rate of infection recurrence ranged from 0% to 16.7% in the single-stage arthroplasty group and from 0% to 33.3% in the two-stage arthroplasty group. We pooled OR values for the seven included studies using Stata 17 and found no difference in outcomes between the two groups (OR: 0.70, 95% CI: 0.35–1.36, $P = 0.286$, $I^2 = 20.7\%$, Fig. 2).

Sensitivity analysis

When any one study was excluded, the remaining studies were combined using the OR values. No individual study had a significant impact on the results (Fig. 3).

Risk of bias

Considering the small sample size (<10) in our meta-analysis, publication bias was not applicable for the determination of publication bias.

Discussion

Our study included seven retrospective studies with a total of 413 patients. The results showed that the rate of infection recurrence in the single- and two-stage arthroplasty groups was 0–16.7% and 0–33.3% respectively. The rate of infection recurrence did not significantly differ between groups (OR: 0.70, 95% CI: 0.35–1.36, $P = 0.286$), which supports the findings of previous studies (9, 27). The 95% CI of the pooled OR (0.35–1.36) suggests that the true OR may be anywhere within this range with 95% CI, and we acknowledge that it includes both values of 0.35 and 1.36. Therefore, while our meta-analysis provides a pooled estimate of the OR, it is important to note that there is some uncertainty around this estimate. We plan to discuss the possible implications of the range of values within the CI, including the limitations and uncertainties

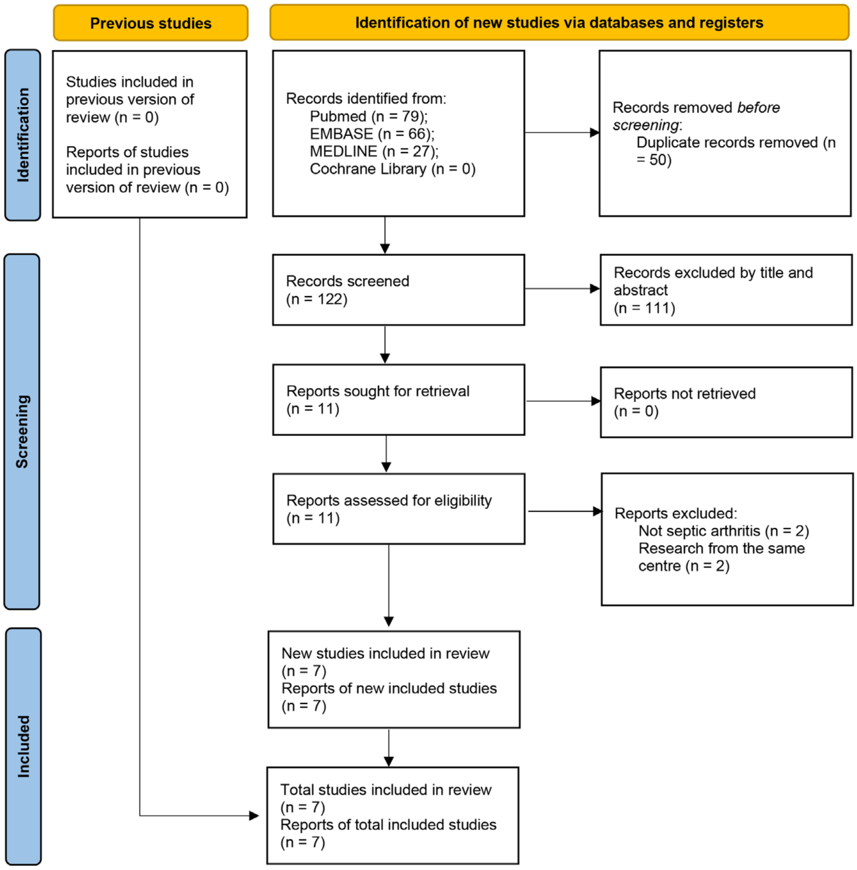

Figure 1
Flow diagram for search and selection of included studies.

of our analysis, in order to provide a thoughtful and nuanced interpretation of our findings. We considered different surgical sites as the main source of the mild heterogeneity and conducted analyses with the hip and knee as subgroups. With only three studies included in the subgroup analysis, the results may not have been generalizable to the broader population. Additionally, the small number of studies made it difficult to control for confounding variables and to detect any true differences between subgroups. Therefore, we dropped the subgroup analysis.

The treatment of SA is complex, and standard treatment remains controversial. Early acute SA is treated with arthrotomy or arthroscopic debridement in combination with antibiotics to preserve joint function as much as possible (28). However, in some patients, the disease lasts for a long time during the initial treatment, resulting in the destruction of articular cartilage and bone, or osteomyelitis. These patients often require partial joint removal to control infection, but this leads to joint dysfunction (15). Elisissy *et al.* reported that two-stage arthroplasty obtains satisfactory eradication rates in patients with SA (29). Anagnostakos *et al.* found that although the rate of infection eradication with two-stage arthroplasty was 87%, the mortality rate was as high as 8.8% (30). In fact, due to poor health, recurrent infections, and related complications, many patients do not have the opportunity to complete the second stage of surgery. Furthermore, the first-stage procedure requires the placement of an antibiotic spacer. Although the local antimicrobial effect of spacer placement appears to be negligible (31), there has been a high incidence of spacer-related complications over the past few years, including spacer dislocation, displacement, rupture, and femoral fracture (32, 33). In addition, infection in patients with SA involves only articular cartilage, subchondral bone, and intracapsular soft tissue. The spacer insertion may introduce the infection to the distal femoral bone marrow cavity, leading to the spread of infection and complicating surgical management (34). The use of a spacer can also lead to muscle contractures that prevent reimplantation, resulting in unequal lower extremity length and poorer functional outcomes (35). Six patients in the two-stage arthroplasty group had a spacer implanted (7, 9, 16, 17, 26, 27), but the occurrence of related complications was not reported due to the small sample sizes.

With improvements in surgical strategies and techniques, both single- and two-stage revision procedures can effectively cure PJI to the same extent (36, 37, 38). These successful PJI treatment experiences

Table 1 Characteristics of included studies.

Study	Country	Date range	Design	Type of SA	Age, years			Subjects, *n*		FU, years	Outcomes	NOSS
					Combined	Single-stage	Two-stage	Single-stage	Two-stage			
Bauer *et al.* (26)	France	NA	Cohort	AQ (hip and knee)	58.2 (29–92)			23	30	2	Reinfection, functional outcome	9
Bochatey *et al.* (7)	Argentina	1997–2016	Cohort	AQ (hip)		49.2 (16–81)	49.25 (21–74)	12	8	1 (1–6)	Reinfection, Hip Score	7
Hooper *et al.* (16)	USA	1998–2019	Cohort	AQ (knee)		NA	NA	6	6	7*	Reinfection, knee score	9
Papanna *et al.* (24)	UK	2000–2013	CC	AQ (hip)	58 ± 11			7	11	13 (13–120)†	Reinfection, functional outcome	6
Portier *et al.* (17)	France	2005–2019	Cohort	AQ (hip and knee)	64 (29–82)			43	6	2	Reinfection, PJI	5
Tan *et al.* (9)	Multicenter	2000–2017	Cohort	NT (knee and hip)		57.7 ± 12.8	54.1 ± 15.2	105	128	1	PJI	8
Zhang *et al.* (27)	China	2008–2021	Cohort	CH (hip)		57.6 ± 17.0	54.5 ± 15.7	11	17	1	Reinfection, complications, hospital stay, hospitalization cost, HHS	9

*mean; †months.
AQ, acute and quiescent; NT, native; CH, chronic; CC, case-controlled; FU, follow-up; NOSS, Newcastle–Ottawa Scale scores; HHS, Harris Hip Score; PJI, periprosthetic joint infection; SA, septic arthritis.

inspired us to treat SA with joint arthroplasty and obtain good joint function while controlling infection. Two-stage arthroplasty for SA was performed in accordance with the treatment model for PJI. In recent years, scholars have also begun to explore the use of single-stage arthroplasty to treat SA. The reported rates of SA eradication range from 94% to 100% after single-stage arthroplasty and from 85% to 100% after two-stage arthroplasty (15). Most orthopedic surgeons (85%) opt for two-stage arthroplasty in patients with active SA and perform single-stage arthroplasty in those with inhibited phase SA (39, 40). However, the distinction between active and inhibited infections is unclear and difficult to distinguish in clinical practice. Although there was no difference in the incidence of reinfection between the single- and two-stage arthroplasty groups in the included studies, large allocation biases in the selection of surgical options led to bias in the study results. In three included studies, active SA was included in the two-stage arthroplasty group, while patients with quiescent SA were included in the single-stage arthroplasty group (7, 24, 26). This may have resulted in a higher rate of PJI in the two-stage arthroplasty group than the single-stage arthroplasty group, potentially biasing the results.

The optimal time for joint arthroplasty for SA is unclear. Most scholars recommend it 2 years after confirmation of SA cure, no clinical or biological inflammatory syndrome, and a negative joint sample taken by the system before joint arthroplasty (7, 14, 26). The lack of reliable data on this topic was highlighted by the international consensus in 2019, but 87% of orthopedic surgeons approved post-SA implantation with a minimum interval of 3 months (40). Tan *et al.* found that the optimal time threshold for arthroplasty from initial treatment was 5.9 months, but no difference in PJI rates was observed when cohorts were grouped by this threshold (25). They concluded that delayed joint replacement did not appear to reduce the risk of PJI. We found a recent study by Wei *et al.* that recommended delaying surgery by 6 months in patients with quiescent suppurative arthritis to potentially reduce the risk of PJI (41). Regardless of whether it is a single- or two-stage arthroplasty, for patients with SA, thorough debridement should be performed before joint replacement surgery. The surgical treatment of SA is currently poorly reported and the sample size is small. However, the two-stage arthroplasty method used to treat SA is also used to treat PJI. In patients with PJI, the efficacy of single-stage arthroplasty is reportedly the same as that of two-stage revision. Therefore, we conducted a comparison of single- and two-stage arthroplasty for SA. We also compared the joint function after single- and two-stage arthroplasty for SA. Three of the included studies reported the postoperative joint function (7, 16, 27). Two of these studies evaluated the hip, while one

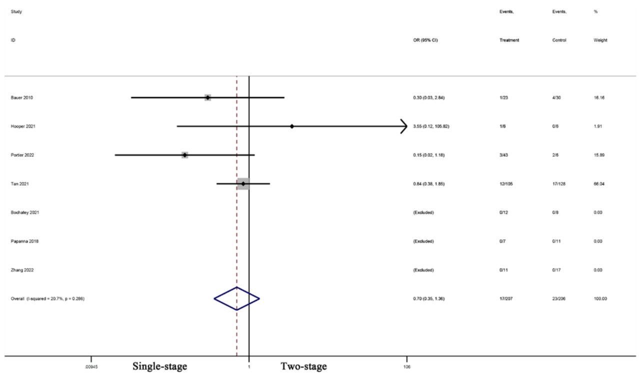

Figure 2
Forest plot of comparison: single- vs two-stage; outcome: reinfection rate. MH, Mantel–Haenszel.

evaluated the knee. The pooled Harris Hip Score results suggested that there was no difference between groups in the joint function. However, the pooled results were highly heterogeneous ($I^2 = 94.5\%$) owing to the inclusion of a small number of studies and a small sample size. Therefore, our confidence in the results was low and we did not report them. The joint function after single- vs two-stage arthroplasty for SA should be investigated in future studies. As living conditions improve, people are demanding a better quality of life. Thus, it is becoming increasingly important to consider the functional activity of joints in addition to the eradication of infection.

Strengths and limitations

To our knowledge, this is the first study to compare the outcome of single- vs two-stage arthroplasty in patients with acute and quiescent SA. This meta-analysis pooled seven published studies involving 413 patients with SA; this large overall sample size may improve the statistical power of the data analysis and thus provide more reliable estimates than the single studies alone. The Harbord test and funnel chart results showed that there was no significant publication bias in the included studies. Furthermore, the overall quality of the included literature was high. However, our study also had certain limitations. First, given the difficulty in diagnosing SA, the different definitions of outcome measures in the included studies may have led to the masking of some patients' conditions and biased outcomes. Second, the included studies were retrospective and included a limited number of participants. With the improvements in living standards and medical technology, the incidence of SA has decreased. Third, the included study involved both acute and quiescent septic arthritis, and in Tan's study, only native SA was mentioned, without specifying whether it was acute or quiescent, which increased the bias of the result to some extent. Fourth, due to the number of studies included in our meta-analysis being less than 10, publication bias testing could not be performed. Furthermore, the development of arthroscopic technology and the diversity of diagnostic measures have enabled clinicians to identify pathogenic bacteria while removing lesions in the early stage and to use sensitive antibiotics for anti-infection treatment, which improves the prognosis. Therefore, the number of patients with SA requiring arthroplasty is small and it is difficult to conduct randomized controlled studies. However, we still hope that a multicenter prospective cohort study will be performed to confirm the efficacy of single- and two-stage arthroplasty in treating SA.

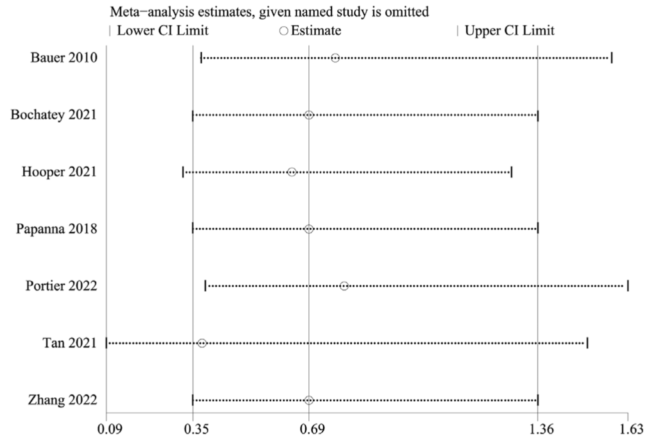

Figure 3
The result of sensitivity analysis.

Conclusions

The meta-analysis did not detect a difference but, due to the low statistical power, a lack of difference is not proved. Whether it is a single- or two-stage arthroplasty, the key is to make sure that the infection in the joint is under control before the surgery. However, this study had a small sample size, highlighting the need for a prospective cohort study before a treatment method can be recommended.

ICMJE conflict of interest statement
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding Statement
This study did not receive any specific grant from any funding agency in the public, commercial, or not-for-profit sector.

Author contribution statement
HL conceived the study. HL developed the research protocol. HNH and YZ performed the literature search. YZ and GYY screened titles and abstracts,

reviewed full texts. HNH and HL performed data abstraction. CCH submitted the review to PROSPERO. HL prepared the first manuscript draft. All authors contributed to final edits and revisions prior to submission.

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