


STUDY PROTOCOL

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Efficacy of the preformulated irrigation solution Bactisure[®] in acute periprosthetic joint infection debridement surgery: study protocol for a randomized controlled trial

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Abstract

Background Despite significant progress in orthopaedic surgery, the prevalence of periprosthetic joint infections (PJIs) remains persistent, and future increases are expected due to the increasing number of joint arthroplasties. PJIs are intricately connected to biofilm-producing bacteria, which encase infected prostheses, impairing the effectiveness of antibiotics and the immune system. Acute PJIs with immature biofilms are traditionally managed with debridement, antibiotics, and implant retention (DAIR). However, to date, there has not been a conclusive direct clinical comparison (in vivo) demonstrating the superiority of one irrigation solution over others. Recently, there has been a growing interest in irrigation solutions with antibiofilm properties demonstrated in in vitro studies, exemplified by the preformulated Bactisure[®] irrigation solution, which contains ethanol, acetic acid, sodium acetate, benzalkonium chloride, and sterile water. The main objective of this study was to evaluate the effectiveness (infection cure rate) of preformulated Bactisure[®] irrigation solution in vivo compared with saline solution in a control group of patients with acute knee and/or hip periprosthetic infections treated with DAIR.

Methods Prospective single-centre randomized controlled trial involving patients with acute or haematogenous PJI who received standard DAIR surgery from December 2022 to December 2024. The type of irrigation solution used during surgery will include two groups allocated at a 1:1 ratio: a control group ($n=25$) with saline solution and an experimental group ($n=25$) receiving the Bactisure[®] preformulated solution. The sample size was calculated based on an expected reduction in reinfection rates from 45% in the control group to 10% in the experimental group. Data on baseline patient characteristics, clinical and radiological information, and healthcare questionnaires will be recorded. All patients will be followed for minimum of 12 months. The infection cure rate at 1 year will be the primary outcome.

Discussion This study is the first to compare the effectiveness of preformulated Bactisure[®] irrigation solution with that of saline solution in real clinical practice (in vivo) in patients with acute knee and/or hip periprosthetic infections treated with DAIR. Our main hypothesis is that, compared with saline solution, Bactisure[®] provides a better infection cure rate at 1 year post-DAIR.

Trial registration International Standard Randomized Controlled Trial Number (ISRCTN): <https://doi.org/10.1186/ISRCTN10873696>. Registered on December 19, 2023.

Keywords Periprosthetic joint infection, Knee, Hip, Debridement antibiotic and implant retention (DAIR), Irrigation solution

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Background

Periprosthetic infection (PJI) is one of the most common complications following joint replacement surgery. PJI has a significant impact on both patients and surgeons, and it places a considerable financial burden on the healthcare system, increasing the cost by up to five times that of primary joint replacement surgery [1]. Currently, PJI has an approximate incidence of 2%, and it is expected to increase in the coming years in line with the increasing trend in the number of joint replacements being performed [2, 3]. In A-PJI, where there is no mature biofilm, the infection can be treated with debridement and irrigation, implant retention, and systemic antibiotics with activity against immature biofilms, also known as DAIR. A subtype of A-PJI includes acute haematogenous infections where periprosthetic infection is acquired haematogenously, and the standard therapeutic approach is DAIR [4]. Reported efficacy rates for DAIR in periprosthetic joint infections show significant variability across studies, ranging from 45 to 60% [4–7]. The success of DAIR depends on a constellation of factors: the duration of the infection, the specific pathogen involved, host health conditions, and the thoroughness of debridement and irrigation [6].

Although normal saline solution has historically been used for irrigation, the use of multiple additives, such as surfactants or detergents, antibiotics, and antiseptics, has been increasing in recent years [8–12]. Surfactants contain detergents, whereas antibiotic irrigation usually involves bacitracin and/or polymyxin. Antiseptic solutions include povidone-iodine (PI), chlorhexidine gluconate (CHG), hydrogen peroxide, sodium hypochlorite, acetic acid, and hypochlorous acid (HOCl). There are also preformulated solutions that contain various types of additives. However, identifying the optimal irrigation agent remains a challenge, as data on its superiority are very limited [10]. Furthermore, most of the literature on irrigation solutions focuses on PJI prevention, with limited data on the definitive management of established PJI and subsequent reinfection rates. Recent meta-analyses have concluded that washing with diluted povidone-iodine compared with normal saline appears to reduce the risk of periprosthetic infection, although the results do not reach statistical significance when different antiseptics are compared [11, 13].

Preformulated solutions, which have recently emerged, are promising options as adjuvant treatments in PJI debridement surgery because of their antibiofilm properties [14]. Bactisure® wound wash solution, approved by the Food and Drug Administration (FDA) in 2020 and indicated for use in the field of prosthetic infection, consists of ethanol, acetic acid, sodium acetate, and benzalkonium chloride in sterile water. The

combination of surfactants, chelating agents, and salts in Bactisure destroys the extracellular matrix, which serves as a physical barrier to bacteria and is crucial in biofilm formation [15, 16]. In vitro studies have demonstrated the superiority of Bactisure over other solutions in reducing the bacterial load with biofilms [15–18].

To date, no direct clinical comparison (in vivo) of different antiseptic irrigation solutions has identified an optimal irrigation solution, and all review articles and meta-analyses on the subject have reached the same conclusion: there are currently no clear recommendations regarding the ideal irrigation solution for the management of acute or chronic PJI [10, 19]. This randomized clinical trial aims to determine whether the preformulated irrigation solution Bactisure®, which contains ethanol, acetic acid, sodium acetate, and benzalkonium chloride in sterile water, is more effective than saline irrigation as part of the debridement, antibiotic, and implant retention (DAIR) procedure for acute or haematogenous periprosthetic joint infection (PJI). Effectiveness is defined as achieving lower reinfection rates. The specific objectives of our study are detailed in Table 1.

Methods/design

Aim

The primary aim of this study was to evaluate the effectiveness (infection cure rate) of preformulated Bactisure® irrigation solution in vivo compared with saline solution in a control group in cases of acute or haematogenous knee or hip periprosthetic infections treated with DAIR.

Design and setting

This study is a prospective single-centre randomized controlled trial involving patients with acute or haematogenous PJI who receive standard DAIR surgery from December

Table 1 Specific objectives

Type	Description
Primary objective	- Evaluate the effectiveness (infection cure rate) of the preformulated Bactisure® irrigation solution, compared to a control group using saline solution, in patients undergoing DAIR for acute or haematogenous periprosthetic joint infection (PJI)
Secondary objectives	- Identify potential complications (e.g. infections, reoperations) - Compare the length of hospital stays between the two irrigation solution groups - Perform subgroup analyses based on the identified microorganism, the type PJI (acute or haematogenous), and the location (knee or hip) - Identify potential confounding factors related to infection risk

2022 to December 2024. The type of irrigation solution used during the surgery will define the two groups allocated at a 1:1 ratio: a control group with saline solution and an experimental group receiving the Bactisure® preformulated solution. This interventional study will be single-blinded, with the participants blinded for group allocation.

This study will be under the oversight of the Vall d’Hebron Institut de Recerca (VHIR) in Barcelona, Spain. While the institution itself will not directly participate in the study design, data collection, analysis, management, interpretation, or dissemination of results, it provides a supportive environment for the study’s execution. The day-to-day operations and coordination of the trial will be managed by the faculty members of the Septic and Reconstructive Surgery Unit from the Orthopaedic Surgery Department at Vall d’Hebron University Hospital. This department is responsible for trial oversight, ensuring adherence to the study protocol, and conducting regular meetings to review progress.

The trial was set up according to CONSORT guidelines [20], and we also used the SPIRIT checklist when writing our report [21]. Ethical approval has already been acquired by Vall d’Hebron University Hospital Clinical Research Ethics Committee (approval number: PR(AT)192/2022). Additionally, the patients’ written consent will be obtained before they participate in the study. The study is listed with the International Standard Randomized Controlled Trial Number (ISRCTN): <https://doi.org/https://doi.org/10.1186/ISRCTN10873696> (registered on 19/12/2023).

In the event that protocol modifications are necessary after the trial has commenced, a request for

review will be submitted to the Ethics Committee. Any modification that could significantly impact participant welfare will require obtaining new informed consent and updating the revised protocol in the trial registry.

Participants

The inclusion and exclusion criteria are shown in Table 2.

Patients meeting the inclusion criteria will be presented by investigators with the option to participate in the clinical trial. They will be adequately informed via the patient information sheet (Annex 1), and patients who wish to participate in the clinical trial must sign the informed consent form (Annex 2).

Interventions

All patients with acute or haematogenous PJI will undergo standard surgical treatment, debridement, antibiotic, and implant retention (DAIR), with the type of irrigation solution used during surgery depending on the assigned group: saline solution (group 1) or preformulated Bactisure solution (group 2). During the DAIR surgery, irrigation will use a low-pressure pulsatile lavage system with the assigned irrigation solution at preintervention randomization:

- Group 1: 3 L (L) of saline solution, followed by 3 L of saline solution and then another 3 L of saline solution (9 L in total).
- Group 2: 3 L of saline solution, followed by 1 L of Bactisure®, and then another 3 L of saline solution (7 L in total).

Table 2 The inclusion and exclusion criteria of the subjects

Type	Description
Inclusion criteria	<ul style="list-style-type: none"> - Age > 18 years - Patients with hip or knee prostheses - Diagnosis of periprosthetic joint infection according to the criteria established in the Second International Consensus on Musculoskeletal Infections [22, 23] - Acute PJI: < 6 weeks since the initial arthroplasty surgery - Acute haematogenous PJI: < 3 weeks from symptom onset, documented bacteraemia (positive blood culture) with the same microorganism in joint fluid - No previous debridement surgeries - Surgery performed: DAIR
Exclusion criteria	<ul style="list-style-type: none"> - Patients who do not voluntarily and without coercion agree to participate - Patients under 18 years of age - Prosthetic reinfections or a history of multiple debridement - Known sensitivity or allergic reaction to ethanol, acetic acid, sodium acetate, or benzalkonium chloride - Diagnosis of chronic PJI: presence of fistula or > 6 weeks - Multiple infected implants (> 1) - Medically unfit for DAIR surgery - Pregnancy - Legal incapacity

The necessary variables for the clinical trial will subsequently be collected throughout the clinical follow-up, which will last up to 12 months post-surgery. The detailed schedule of these collections is presented in Fig. 1, while

the flowchart illustrating the trial's participant progression is depicted in Fig. 2.

Data collection will be conducted via the SAP software program (SAP SE, Germany) in an anonymized Microsoft Excel online database. To safeguard the data,

TIMEPOINT (months)	STUDY PERIOD						
	Enrolment	Allocation	Post-allocation				
	<i>Pre-op</i>	<i>Operation</i>	<i>Post-op</i>	<i>0.5</i>	<i>2</i>	<i>6</i>	<i>12</i>
Interval windows	<i>Prior to surgery</i>	<i>Surgery</i>	<i>Before discharge</i>	<i>+/- 1 week</i>	<i>+/- 1 month</i>	<i>+/- 1 month</i>	<i>+/- 1 month</i>
ENROLMENT:							
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
<i>Saline irrigation</i>		X					
<i>Bactisure irrigation</i>		X					
ASSESSMENTS:							
Demographics and clinical data		X					
Microbiologic cultures		X	X				
Surgical wound assessment			X	X	X	X	X
Radiological control			X		X	X	X
Analytical control			X		X		
Pain (VAS)					X	X	X
OKSS/ HHS						X	X
Adverse effects	AR		AR	AR	AR	AR	AR
Infection healed?							X

Fig. 1 Content for the schedule of enrolment, interventions, and assessments (SPIRIT 2013). AR as required

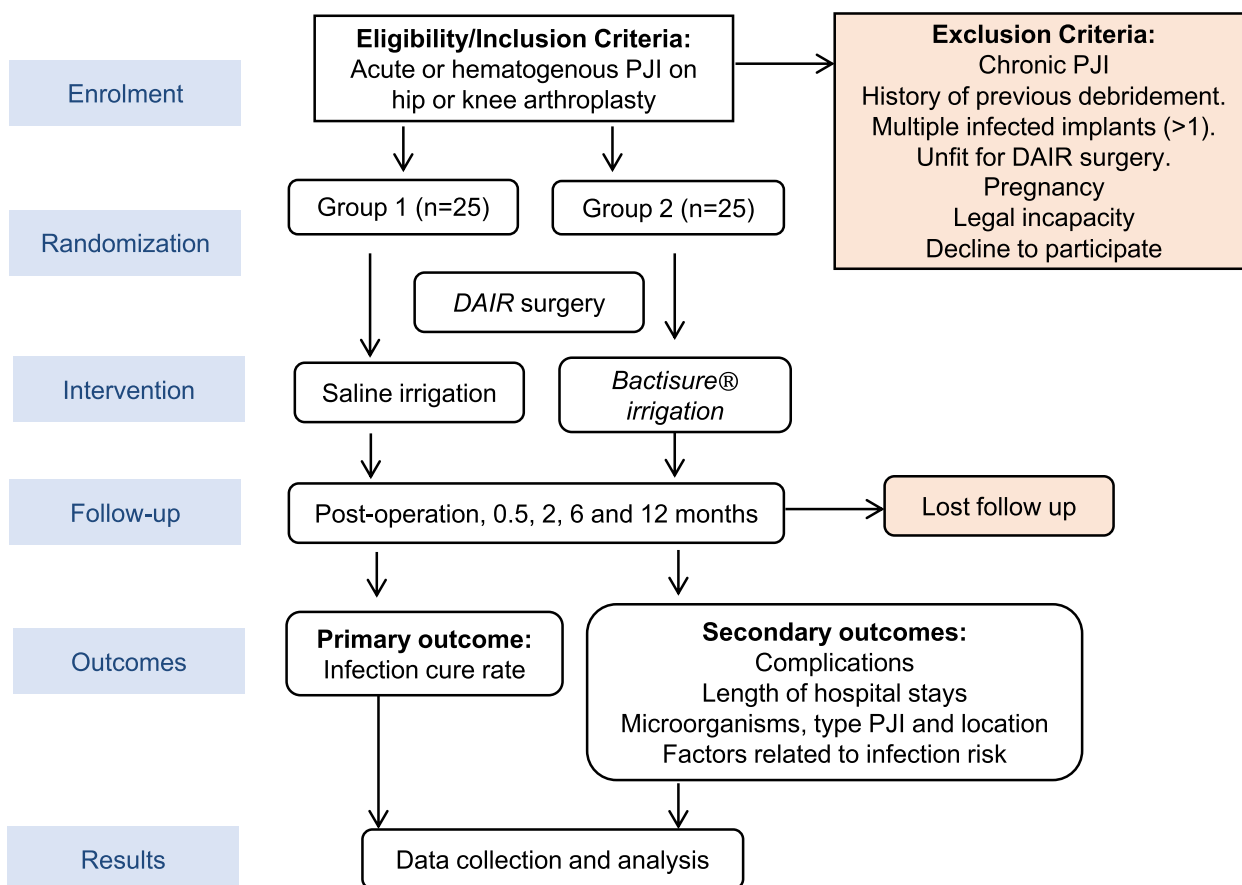


Fig. 2 Flowchart depicting patient selection

regular backups will be scheduled every quarter and stored securely in the cloud to ensure data integrity and availability.

Participant identification will be managed using unique numerical codes to ensure privacy, with all identifying information and consent forms securely stored in separate, restricted-access locations. All trial investigators are required to sign confidentiality agreements to ensure the protection of participant information throughout the study. Patient data will remain strictly confidential and will not be disclosed in any published research outputs.

One year after surgery, data collection for this clinical trial will cease, although routine follow-ups will continue within the respective healthcare units.

Outcomes

The primary outcome will be the infection cure rate measured via the following criteria at the 12-month follow-up. A case is considered cured if it meets all of the following requirements:

- The absence of local recurrence, indicated by the absence of dehiscence, exudation, or fistula.
- Radiographic evidence of no osteolysis.
- There is no ongoing suppressive antibiotic treatment.
- Absence of any reinterventions.
- No deaths related to periprosthetic infection occurred.

The secondary outcome measurements will be as follows:

1. Length of hospital stay, in days, measured via medical records at one timepoint.
2. Potential postoperative complications (e.g. infections, reoperations, osteolysis) at hospitalization or in ambulatory controls measured via medical records at one timepoint.
3. Microorganisms identified on perioperative cultures at hospitalization were measured via standard laboratory methods at one timepoint.

Sample size

To calculate the required sample size (n), we used the online software GRANMO (version 7.12, April 2012) from the Hospital del Mar Medical Research Institute (IMIM). Assuming a type α error of 0.05 and a type β error of 0.20, providing a statistical power of 80% in a bilateral test, 50 subjects (25 in each group) are required to detect a statistically significant difference between two proportions (reinfection rate). An expected reinfection rate of 0.45 for the control group (group 1) and 0.1 for the experimental group (group 2) was estimated. A follow-up loss rate of 5% was assumed. The sample size calculation is based on reinfection rates drawn from published literature, which have been adapted to meet the specific requirements of our clinical trial, assuming a reduction from 45% in the control group to 10% in the experimental group.

Randomization

This single-centre randomized controlled trial comprises two groups allocated at a 1:1 ratio. To ensure balanced patient distribution, a restrictive randomization method using a computer-generated sequence will be employed, whereby cases are paired for randomization. The first case is assigned to either group 1 or group 2, and the second case is then placed in the opposite group. This process is repeated for each new pair of cases until the required sample size is reached.

Blinding

A single-blind protocol will be employed throughout the trial, ensuring that patients remain uninformed regarding the specific irrigation solution utilized during their debridement procedures until the study's completion. In contrast, surgeons will possess full knowledge of the irrigation solution being used; this is due to the distinct visual cues present in the packaging of the different solutions. Furthermore, the Bactisure[®] irrigation solution releases a distinctive, robust scent as a result of its acetic acid composition, which may be noticeable during its application. To minimize bias as much as possible, we have determined that an external investigator, blinded to group allocation, will conduct the analysis of the results.

Data analysis and statistical tests

Upon completion of the clinical study, data will be analysed using R software, version 4.10 (R Foundation for Statistical Computing, Vienna, Austria). Quantitative variables will be compared via the Kruskal–Wallis exact test, whereas qualitative variables will be analysed via the chi-square test. A significance level of $p < 0.05$ will be applied to identify statistically significant differences. Univariate analyses will also be performed to identify

potential risk factors for treatment failure. For variables showing statistical significance, a multivariate analysis will be conducted, employing logistic regression for qualitative variables. The primary analysis will be conducted using the intention-to-treat population. To compare treatment success and failure, both a time-to-event (survival) analysis and a final follow-up analysis will be performed. This approach allows us to capture both the timing of events and the overall outcome at the study's conclusion.

An interim safety analysis will be performed upon completing interventions for the first 12 patients in each group. This analysis will assess adverse effects and the provisional effectiveness of both treatments.

Dissemination plans

A variety of dissemination channels will be utilized to share information about the project and the study's results with clinicians, patients, and the general public, including the following:

- The study protocol will be published in a peer-reviewed, open-access journal before the recruitment phase concludes.
- Upon completion of the study, the trial's findings will be presented at both national and international meetings organized by orthopaedic surgeon-focused organizations. This will include events hosted by organizations such as the Spanish Society for Orthopaedics and Traumatology (SECOT) and the European Bone and Joint Infection Society (EBJIS).
- The study report will be published in high-impact, peer-reviewed medical and orthopaedic journals with broad readership.

Discussion

The effectiveness of debridement, antibiotics, and implant retention (DAIR) in treating periprosthetic joint infections (PJIs) is influenced by multiple factors: the duration of infection, the specific pathogen, the health status of the host, and the thoroughness of both debridement and irrigation [6].

In terms of the type of bacteria, periprosthetic joint infections (PJIs) are predominantly associated with biofilm-forming bacteria, with approximately 80% caused by *Staphylococcus aureus*, *S. epidermidis*, and *Pseudomonas aeruginosa* [24]. Although there has been a recent increase in gram-negative bacterial infections, Rodriguez-Pardo et al. [25] reported that in cases of gram-negative bacterial PJIs sensitive to quinolones, the success rate of debridement, antibiotics, and implant retention (DAIR) was 79%, whereas it was only 41% for quinolone-resistant infections. Therefore, to maximize

the success of DAIR, it is crucial to adopt a multidisciplinary approach involving specialists in microbiology, infectious diseases, pharmacy, and other relevant fields. This collaborative effort is key in effectively managing and treating periprosthetic joint infection.

In the surgical management of periprosthetic joint infection (PJI), irrigation and debridement of infected tissue are recognized as the most critical components of the treatment strategy [10].

The aggressiveness of debridement is a key factor in the success of DAIR. This requires expertise; thus, it is advisable for the procedure to be performed by an experienced surgical team. It is a 'one-shot' surgery; failure of a DAIR should contraindicate a second attempt at implant retention, and prosthetic exchange should be planned [26].

With respect to the irrigation solutions used in DAIR, most studies focus on preventing periprosthetic infections, with only a few addressing established infections, primarily through in vitro research. Consequently, in standard DAIR surgery practice, there is insufficient evidence to recommend a specific antiseptic or antiseptic combination [10, 19, 27]. However, considering experimental study outcomes and the implications of DAIR failure [4–6], the use of additives in irrigation solutions to maximize bacterial load reduction seems both reasonable and cost-effective.

Various studies in the field of periprosthetic infection have reported positive outcomes with the use of the Bactisure®. Kia et al. [17] were the pioneers in demonstrating the efficacy of Bactisure® in reducing the bacterial load in patients with periprosthetic knee infections. Their study included patients who underwent DAIR or the first stage of prosthesis exchange. All the subjects underwent arthrocentesis before and after debridement, followed by irrigation with Bactisure® and saline. They reported a bacterial load reduction of 99%. However, the absence of a comparative group in their study limits the attribution of bacterial load reduction specifically to Bactisure® or saline.

O'Donnell et al. [18] conducted an in vitro analysis to assess the efficacy of various antiseptic solutions against biofilms formed by clinically relevant microorganisms. These findings revealed that povidone-iodine was particularly effective in reducing nascent MRSA biofilms. Moreover, Bactisure showed the most substantial reduction in mature *Pseudomonas aeruginosa* biofilms and a significant reduction in mature *Staphylococcus epidermidis* biofilms. Across all biofilms tested, Bactisure and povidone-iodine demonstrated significantly greater reductions than the other antiseptic solutions did.

Whitely et al. [16] conducted a comprehensive in vitro and in vivo study to assess the antibiofilm capability of Bactisure® compared with that of saline in conjunction with antibiotics. The in vitro segment revealed a

43% greater biofilm reduction with Bactisure® than with saline. Additionally, biofilms enriched with Bactisure® and vancomycin further decreased, a trend that was not observed with saline. In vivo, open infected fractures in rats were studied, revealing a minor, albeit nonsignificant, decrease in bioburden when Bactisure® was used alongside antibiotics compared with saline with antibiotics.

Our study is the first to compare the effectiveness of the Bactisure® with that of saline solution in real clinical practice (in vivo) in patients with acute or haematogenous knee or hip periprosthetic infections treated with DAIR.

The study design includes a minimum follow-up of 1 year. This decision was made based on several factors. First, extending the follow-up to 2 years would significantly increase the overall costs of the project, which operates under a limited budget. Second, this study is part of a doctoral thesis project, and the timeline must align with the completion deadlines of the thesis programme. Lastly, there is precedent in the literature for using a 1-year follow-up period in prospective studies on osteoarticular infections, for example, the SOLARIO study [28]. Therefore, we believe a 1-year follow-up is adequate to capture relevant clinical outcomes, particularly as most complications related to acute periprosthetic joint infections tend to occur within the first 12 months post-surgery. However, routine follow-up will continue beyond this period as part of standard clinical care.

We expect a low loss to follow-up rate of 5%, based on historical data from similar studies conducted in our hospital. To maintain this rate, we will implement strict follow-up protocols, including regular communication and reminders for participants.

Study limitations

One limitation of this clinical trial is that it follows a single-blind design, meaning that surgeons will be aware of the intraoperative irrigation type due to the visually distinguishable packaging of both irrigation solutions. To minimize bias as much as possible, we have determined that an external investigator, blinded to group allocation, will conduct the analysis of the results.

Another limitation is the variation in surgical experience among different surgeons conducting the interventions. To minimize potential bias and standardize DAIR surgery as much as possible, a specific surgical protocol has been designed (refer to Annex 3). Last, it should be noted that the sample size was small, which may affect the reliability of the clinical trial.

Trial status

The protocol for this study was registered on ISRTN.com (ID: ISRCTN 10873696) in December 2023 after recruitment had commenced, due to unforeseen delays

in the administrative process. Nonetheless, all study procedures, including patient consent and ethics approval, were in place prior to recruitment. The study commenced in September 2022, with an anticipated completion date of December 2025. The recruitment process is ongoing, having started in December 2022 and expected to conclude in December 2024.

Conclusions

This research project aims to provide scientific evidence regarding the potential effectiveness of using preformulated Bactisure[®] solution, which contains ethanol, acetic acid, sodium acetate, benzalkonium chloride, and water, in reducing reinfection rates (along with associated complications) in cases of acute or haematogenous periprosthetic infection. The primary practical utility lies in the potential implementation of this irrigation solution in various periprosthetic infection (PJI) treatment protocols to assist in eradicating the infection promptly. This could help avoid the high costs associated with prosthetic replacements and reduce morbidity and mortality rates.

Supplementary information.

Abbreviations

PJI	Periprosthetic joint infection
DAIR	Debridement antibiotic and implant retention
ISRCTN	International Standard Randomized Controlled Trial Number
A-PJI	Acute PJI
C-PJI	Chronic PJI
PI	Povidone-iodine
CHG	Chlorhexidine gluconate
HOCl	Hypochlorous acid
FDA	Food and Drug Administration
UCSO	Septic and Reconstructive Surgery Unit
VAS	Visual analogue scale
OKSS	Oxford Knee Society score
HHS	Harris hip score
AR	As required
L	Litres

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-024-08637-1>.

Additional file 1. SPIRIT checklist.
 Additional file 2. Annex 1 Participant information sheet.
 Additional file 3. Annex 2 Informed consent form.
 Additional file 4. Annex 3 Surgeon information sheet.

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Trial sponsor

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Authors' contributions

All the authors contributed to the study's conception and design. Data collection and analysis were conducted by ROT and MVGC. The first draft of the manuscript was written by ROT, and all the authors commented on previous versions of the manuscript. All the authors read and approved the final manuscript.

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Data availability

Only the investigators directly involved in this trial will have access to the final dataset, strictly for scientific research purposes. They are required to comply with confidentiality protocols and are prohibited from disclosing any participant information or related materials without prior authorization.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained on 25/11/2022 from the Clinical Research Ethics Committee (CEIm) of Vall d'Hebron University Hospital (Pg. Vall d'Hebron, 119–129, Barcelona, 08035, Spain; (+34) 934893891; ceic@vhir.org) under reference number PR(AT)192/2022. Written consent from patients will be obtained before their participation in the study. The study is registered with the International Standard Randomized Controlled Trial Number (ISRCTN): <https://doi.org/10.1186/ISRCTN10873696> (registered on 19/12/2023).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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