

Research Article

Revision Arthroplasty: Novel Intraoperative Irrigation Solution to Reduce Infection

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Introduction

As a major complication of revision arthroplasty, periprosthetic joint infection (PJI) can result in both significant medical morbidity and high economic burden. As such, renewed effort is needed to reduce its occurrence. The aim of this review is to evaluate the impact of a novel intra-operative antiseptic irrigation solution on the incidence of PJI, in patients undergoing revision total knee arthroplasty (TKA) and total hip arthroplasty (THA).

Methods

In a single-arm review, Prontosan® Wound Irrigation Solution (0.1% Betaine, 0.1% Polyhexanide (PHMB), which was previously added to the intra-operative wound irrigation (IOWI) protocol in consecutive patients undergoing revision TKA and THA. Postoperative PJI rates were assessed at ninety days and one year post-surgical appointments.

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Results

A total of 86 revision arthroplasty (72 TKA, 14 THA) patients were enrolled. Thirteen (12 TKA; 1 THA) of the patients presented preoperatively with deep PJI. Within the global 90 day postoperative period, review of postoperative status of two patients were lost to follow-up. Of the remaining patients, in the ninety days after the intra-operative use of Prontosan, none (0/84, 0%) of the remaining revision patients demonstrated signs of infection nor PJI. The one year postoperative evaluation of the remaining revision patients continued to demonstrate no signs or symptoms of infection.

Conclusion

In a single surgeon, consecutive series of revision hip and knee arthroplasty, use of Prontosan was associated with 0% postoperative infections or PJI in patients undergoing revision arthroplasty. Such findings represent a promising infection-reducing and cost-avoidance solution.

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INTRODUCTION

Periprosthetic joint infections (PJI) are devastating complications of total knee arthroplasty (TKA) and total hip arthroplasty (THA). Much research has documented the human and financial tolls (Pulido et al. 2008; Zardi and Franceschi 2020; Patel 2023). PJIs are among the most common indications for revision arthroplasty (Mian et al. 2022; Alrayes and Sukeik 2023). By 2030, in the United States, PJI-related hospital costs are projected to reach \$1.85 billion (Premkumar et al. 2021). PJI is a dreaded complication, as it can lead to significant morbidity, prolonged hospital stays, increased healthcare costs, and even mortality (Sandiford, Franceschini, and Kendoff 2021). The emergence of antibiotic resistant organisms poses a substantial challenge in the management of PJI, (Chindera et al. 2016) reported that traditional antibiotic prophylaxis may not effectively prevent or treat these infections. Consequently, alternative strategies, such as antiseptic intra-operative wound irrigation (IOWI) solutions, have gained attention as potential solutions. Antiseptic solutions, such as povidone-iodine, chlorhexidine, and hydrogen peroxide, have been commonly used for wound irrigation due to their broad-spectrum antimicrobial properties. These solutions have demonstrated efficacy in reducing bacterial load and preventing infection in various surgical procedures. However, their potential cytotoxicity and adverse effects on wound healing have raised concerns. Therefore, the selection of an appropriate irrigation solution should consider the balance between its antiseptic properties and potential harm to the wound or even the patient.

Prontosan® (B. Braun Medical Inc./ Innovice LLC), containing 0.1% Betaine, and 0.1% Polyhexanide is a novel in-

tra-operative wound irrigation solution that satisfies the balance of having effective antiseptic properties and a non-cytotoxic formulation. Additionally, PHMB (polyhexamethylene biguanide) demonstrates some particular characteristics that further enhance its use for IOWI.

As antimicrobial resistance continues to be a major concern in healthcare, caution should be taken to preserve the efficacy of valuable treatment options. As with the treatment of post-operative pain, infection control and prevention should be addressed with a multimodal approach. The mode of action of PHMB is complex and selective, rather than non-discriminant as is the case for many antimicrobials. Aside from cell membrane disruption, PHMB displays differential access to bacterial and mammalian cellular DNA and selectively binds and condenses bacterial chromosomes. Because acquired resistance to PHMB has not been reported, selective chromosome condensation provides an unanticipated paradigm for antimicrobial action that may not succumb to resistance (Chindera et al. 2016).

Many surgeons utilize a multimodal approach for managing intra-operative wounds which stresses the importance of compatibility between IOWI solutions and adjunct therapies. Intra-wound antibiotics are commonly used prior to wound closure with the hopes of reducing post-operative infection rates. One study found that no antagonism was observed between PHMB and the most commonly used antibiotics while synergism was found with some bacteriostatic antibiotics (Fabry, Kock, and Vahlensieck 2014). In another study, the researchers assessed the antimicrobial efficacy of the combined use of antiseptics and antibiotics in vitro (Hubner and Kramer 2010). This is of particular interest, because the combined use of local antiseptics and systemic antibiotic therapy is common in clinical prac-

tice. While PHMB is not absorbed and therefore does not interact systemically, antibiotics do reach the wound and can interact locally. Using microtiter assays, they were able to show that PHMB acted synergistically with commonly used antibiotics, while chlorhexidine did not.

Additionally, allergenic potential for antiseptic solutions should be considered as well. PHMB seems to carry only a slight allergic risk and remains an uncommon contact allergen. Prontosan has a well-established history of safe clinical use. Information from the manufacturer documents that well over 50 million patients have received treatment with Prontosan in the last ten years. This data reports an incidence of allergy or adverse event occurring in only 0.8 patients per one million treated, B.Braun Medical Data sheet on file.

Management of PJIs continues to evolve with particular attention on intra-operative factors. There is discussion that while debating the role of intra-articular irrigation in treating PJI, most experts agree the goal is eradication of the biofilm (Mian et al. 2022). In a case series of 308 primary TKA and THA, intraoperative utilization of Prontosan was associated with a 0% postoperative infection rate (Jacob et al. 2023). PJI rates in revision arthroplasty cases are approximately double that of primary arthroplasty (Mortazavi et al. 2010). The aim of this review is to evaluate the impact of intra-operative utilization of Prontosan in patients undergoing revision TKA and THA.

METHODS

DESIGN AND SAMPLE

This was a single-arm retrospective review of prospectively collected data, designed to evaluate the efficacy of Prontosan which was added to revision of total knee and hip procedures performed at a single center with one experienced, fellowship-trained, orthopedic surgeon. The CDC's Surgical Care Improvement Project, (SCIP) guidelines are standard of care and followed with each surgical procedure. Consecutive patients undergoing cemented and cementless revision TKA or THA between January 4, 2021 and December 12, 2022 were evaluated. All data that had been prospectively submitted to the American Joint Replacement Registry (AJRR) were retrospectively analyzed to measure the incidence of postoperative infection. The study was determined to be exempt by the WCG institutional review board.

INTRA-OPERATIVE IRRIGATION

Prontosan was utilized in the protocol (Table 1) for revision arthroplasty, similar to the primary cemented and cementless TJA protocol published in JOEI 2023 (Jacob et al. 2023).

RESULTS

SUBJECTS

A total of 86 patients (72 revision TKA, 14 revision THA) with variable comorbidities were enrolled. Pre-operatively, 13 (12 TKA; 1 THA) of the patients presented with deep PJI (Table 2) with various pathogenic microorganisms (Table 3). It is also noted that seven of the thirteen patients presented with polymicrobial pathogenic infections.

OUTCOMES MEASURES

This review is composed of 86 revision arthroplasty (72 TKA, 14 THA) patients. All medical records and American Joint Replacement Registry (AJRR) reports were monitored for postoperative outcomes. PJI rates were analyzed ninety days after surgery through the one-year anniversary date. Two patient records were unavailable for review, of the remaining patients, ninety days after the intraoperative use of Prontosan, none (0/84, 0%) of the revision patients' demonstrated signs of infection nor PJI. The one-year post-operative evaluation of the remaining revision patients continued to demonstrate no signs or symptoms of infection.

DISCUSSION

This was a single-center, single-arm review designed to evaluate the impact of a novel IOWI, Prontosan, in patients undergoing revision total knee and hip arthroplasty. Ninety days after the intra-operative use of Prontosan, none (0/86, 0%) of the revision arthroplasty patients demonstrated signs of infection nor PJI.

PHMB is a wound antimicrobial that is available in the form of solutions, gels, non-adherence bacterial barriers and bio-cellulose dressings. It possesses a high therapeutic index and broad-spectrum antimicrobial activity that kills Gram-positive and Gram-negative bacteria (including *Staphylococcus epidermidis* and *Escherichia coli*), fungi, parasites and certain viruses, as reported (Worsley et al. 2019). PHMB has not been shown to cause development of resistance, is safe (non-cytotoxic) and does not cause damage to newly growing tissue (Rippon, Rogers, and Ousey 2023).

Several articles were analyzed in the generation of this review which were considered relevant for inclusion. These articles include consensus statements and position papers, representing a high level of evidence as they synthesize findings from multiple studies to provide recommendations. One consensus statement emphasizes empiric antimicrobial regimens for PJI should include Gram-positive coverage as Gram-positive bacteria are the most commonly isolated organisms regardless of timing from surgery, type of arthroplasty, or geography (Tai et al. 2022). Other articles shed light on some of the unique attributes PHMB exhibits, further emphasizing its potential as an ideal IOWI solution.

Table 1. Prontosan IOWI for Revision Total Joint Arthroplasty

Cementless	Cemented
1. Prepare three (3) Prontosan 1 L bottles 2. Irrigate all bony and soft tissue surfaces with 1 L of Prontosan, soak 3 minutes with a mechanical scrub 3. Irrigate with 3 L of sterile saline to remove wound debris (i.e. bone fragments) 4. Irrigate with 1 L of Prontosan with a 3-minute soak and mechanical scrub (Do not Rinse) 5. Place final implants 6. Irrigate with 3 L of sterile saline 7. Final irrigation is with 1 L Prontosan with a 90 second soak – leave remaining Prontosan in the wound (Do not rinse) 8. Close surgical wound	1. Prepare three (3) Prontosan 1 L bottles 2. Irrigate all bony and soft tissue surfaces with one (1) Prontosan 1 L bottle, with a 3-minute soak and mechanical scrub 3. Irrigate with 3 L of sterile saline to remove wound debris (i.e. bone fragments) 4. Irrigate with 1 L Prontosan with a 3-minute soak and mechanical scrub (Do not rinse) 5. Dry all bony and soft tissue surfaces with a dry surgical sponge 6. Cement the final components in the usual fashion and allow cement to set up 7. Irrigate with 3 L of sterile saline and a mechanical scrub to remove excess cement and bone debris 8. Final irrigation is with 1 L Prontosan with a 90-second soak – leave remaining Prontosan in the wound (Do not rinse) 9. Close surgical wound

Table 2. Pre-Operative Patient Characteristics

	Female		Male	
	TKA	THA	TKA	THA
	<i>n</i> = 40 (55.6%)	<i>n</i> = 7 (50%)	<i>n</i> = 32 (44.4%)	<i>n</i> = 7 (50%)
PJI	5	0	7	1
BMI>35	14 (35%)	0	9 (28.1%)	1 (14.3%)
Diabetes Mellitus	8 (20%)	4 (57.1%)	15 (46.9%)	1 (14.3%)
Nicotine – current or previous nicotine use (smoking, chewing, or vaping)	3 (7.5%)	1 (14.3%)	2 (6.3%)	3 (42.3%)
Current alcohol use	0	0	0	0
Autoimmune Disease (e.g. MS, RA, lupus)	8 (20%)	1 (14.3%)	1 (3.1%)	1 (14.3%)
MRSA	1 (2.5%)	0	0	0
Hepatitis	0	0	0	0
Anemia	4 (10%)	0	0	0
HIV	0	0	0	0
CKD	2 (5%)	0	1 (3.1%)	0
CV Disease	18 (45%)	6 (85.7%)	21 (65.6%)	2 (28.6%)
Obesity (BMI > 30)	7 (17.5%)	0	5 (15.6%)	1 (14.3%)

The consensus on wound antisepsis has evolved significantly with the introduction of new antimicrobial agents and the increasing prevalence of multidrug-resistant organisms (MDROs). The updated recommendations, (Kramer et al. 2018) emphasize a targeted approach to the use of antiseptics, advocating for their application in infected or critically colonized wounds while also acknowledging the necessity for systemic antibiotic therapy when infections spread. A key aspect highlighted is the importance of selecting appropriate antiseptic agents based on the type and condition of wounds. For instance, PHMB was recommended as the preferred agent for prevention of surgical

site infection. Additionally, PHMB was selected as the first choice recommendation for critically colonized wounds, wounds at risk of infection, burns and decontamination of acute and chronic wounds.

Periprosthetic joint infections remain a major complication with associated increased mortality rates, reoperation rates, and hospital lengths of stay. PJIs remain a leading indication for revision TKA and THA. In addition, direct hospital costs are high, with an average of \$28,161 for infected TKA, and \$32,100 for infected THA (Premkumar et al. 2021).

Table 3. Pathogenic microorganisms of patients presenting with PJI

Cultured microbes	Counts (n)
MRSA	5
<i>Staphylococcus epidermidis</i>	4
<i>Candida albicans</i>	2
MSSA	1
<i>Escherichia coli</i> & scant <i>Enterobacter</i>	1
<i>Enterobacter cloacae</i> complex	1
<i>Enterococcus faecalis</i>	1
<i>Streptococcus oralis</i> and <i>mitis</i>	1

There are projected to be 115,147 revision TKAs and 43,514 revision THAs by 2040 (Shichman et al. 2023). Risk of PJI for revision arthroplasty patients is 3-7.5%, approximately double that of primary arthroplasty (Kurtz et al. 2018). In a temporal analysis of PJI rates, investigators demonstrated that PJI rates have not substantially decreased in recent years and will most likely only become a more pressing problem as joint replacement demands continue to increase. Moreover according to a recent study (Tai et al. 2022), infection rates are likely under reported, underestimating the magnitude of the problem. In prior studies, the most common pathogenic microorganism groups have been shown to be *Staphylococcus epidermidis*, *Staphylococcus aureus*, as well as species of *Streptococcus* and *Enterococcus*—in-line with the present review. Based on the 2023 AJRR Annual Report, infection remains the primary reason for revision TKA and THA, highlighting the persistent critical need for infection reducing strategies. The American Academy of Orthopaedic Surgeons Clinical Practice Guidelines around Diagnosis and Prevention of Periprosthetic Joint Infections (Tubbs et al. 2020), clearly note that given the lack of existing reliable evidence practitioners should consider emerging data around intra-operative wound irrigation.

Numerous studies have investigated the use of antiseptic solutions for wound irrigation during total joint arthroplasty. One commonly used antiseptic is povidone-iodine, which has broad-spectrum antimicrobial activity. A systematic review and meta-analysis conducted by (Wood et al. 2020), evaluated the effectiveness of various irrigation solutions and pressures in reducing the rates of PJI. The review looked at ten studies including one randomized controlled trials (RCT) and found that solutions containing Betadine® and chlorhexidine reduced the risk of PJI. However, the authors noted that the quality of evidence was low, rendering conclusions untrustworthy, highlighting the need for further high-quality studies. Further caution is emphasized, as reported in The AAOS Clinical Practice Guideline, the absence of reliable evidence, practitioners should remain alert to new and emerging studies (Tubb, Polkowsksi, and Krause 2020).

Although antiseptic solutions have shown promise in reducing PJI rates, it is important to consider the potential risks associated with their use. One concern is the potential

for cytotoxicity and tissue damage. A study in 2021 investigated the cytotoxic effects of various antiseptic solutions commonly used for wound irrigation, including chlorhexidine (Markel et al. 2021). The results showed that all tested antiseptic solutions exhibited varying degrees of cytotoxicity, with cells demonstrating a curling phenomenon in which the cells visibly curled and shriveled. This highlights the importance of carefully selecting the appropriate antiseptic solution and considering its potential cytotoxic effects. Researchers detailed the mechanism of action by PHMB (Chindera et al. 2016), and in a recent international consensus on wound antiseptics in practice authors (Nair et al. 2023), paid particular attention in describing the ideal wound antiseptic agent, [Table 4](#) summarizes.

Table 4. Characteristics of the Ideal Wound Antiseptic Agent

- Possess antimicrobial activity at the site of action against a broad spectrum of microorganisms, including Gram-positive and Gram-negative bacteria, fungi and viruses
- Ability to penetrate biofilm
- Does not cause resistance or cross-resistance
- Easy and safe to use
- Does not cause allergic reactions or pain
- Is not toxic, carcinogenic or mutagenic
- Tolerability should be equal to Ringer solution, or physiological saline

Further consideration must be focused on the emergence of antibiotic-resistant organisms, and the development of resistance to antiseptic solutions, one study investigated the potential for resistance development to chlorhexidine (George, Klika, and Higuera 2017). The results showed that the resistance to chlorhexidine is increasing. Since sub-therapeutic concentrations may be linked to emergence of resistance, the residual activity of chlorhexidine could promote resistance in resident skin flora. This suggests that while antiseptic solutions may be effective in the prevention of PJI, the potential for resistance development should be carefully monitored.

Polyhexanide is promoted for its high purity, which makes it an ideal choice for surgical irrigation. The chemical structure and composition contribute to the agent's antimicrobial properties. PHMB has a rapid mode of action, allowing for quick and effective elimination of pathogens, in an average of 90 seconds to two minutes (Christopher et al. 2022). It has proven to be highly effective against both gram-positive and gram-negative bacteria, including those that are resistant to traditional antibiotics. Additionally, PHMB demonstrates activity against certain fungi, yeasts, and viruses, making it a versatile antimicrobial agent. Further prospective studies should be conducted to validate these findings and assess the long-term outcomes, includ-

ing the impact on patient satisfaction, functional outcomes, and healthcare costs.

LIMITATIONS

This review has several potential limitations to consider. The results are from a single surgeon at a single hospital. Ideally, additional sites, surgeons, and patients would be valuable to include in further evaluating the generalizability of the results. Although designed as a single-arm review, further comparisons with non-Prontosan control irrigation solution (e.g. saline alone) with longer term postoperative outcomes would enable evaluation of superiority. The review design may limit the ability to establish causality between the use of the novel antiseptic solution and the incidence of PJI.

Retrospective reviews are prone to biases and confounding factors that may influence the outcomes. Therefore, caution should be exercised in drawing definitive conclusions from the findings. The inclusion of patients who received the novel antiseptic solution might be influenced by factors such as surgeon preference or patient characteristics. Therefore, it is important to ensure that the study population is well-defined and adequately matched with control groups to minimize potential bias. Changes in surgical techniques, perioperative care, and infection control practices over time may confound the results. Therefore, it is

also important to consider the potential impact of these factors when interpreting the findings.

CONCLUSION

The use of intra-operative wound irrigation with antiseptic solutions has gained popularity as a preventative strategy for reducing rates of PJI after TKA and THA. The intra-operative utilization of Prontosan offers a promising approach to PJI reduction for high-risk patients during revision TKA and THA while relatively minimizing cytotoxicity and promoting wound healing. Further prospective studies are necessary to validate the effectiveness of this novel solution in reducing the incidence of PJI.

With the persistence of PJIs, continued improvement efforts towards infection reduction are warranted. Building on the prior review of intra-operative use of Prontosan in primary TKA and THA patients, the present review demonstrates a similar 0% postoperative infection rate in revision arthroplasty patients—which may represent an important infection reducing and cost avoidance solution at scale. The observed low infection rates observed in the review are likely attributable, at least in part, to the solution's combination of an antiseptic (PHMB) and surfactant (Betaine).

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