An Overview of Research for the Application of a Novel Biofilm-Preventing Surgical Irrigation System for Total Joint Arthroplasty Procedures in Order to Reduce the Risk of Periprosthetic Infection

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ABSTRACT

Periprosthetic joint infection (PJI) is a serious postoperative complication in joint arthroplasty procedures that carries substantial morbidity and mortality associated with it. Several strategies have been developed both in the preoperative, perioperative, and postoperative periods to both combat and prevent the development of this devastating complication. Intraoperative irrigation is an important modality used during arthroplasty procedures prior to the implantation of final components that seeks to eradicate any biofilm formation. In this updated review, we discuss the XPERIENCE™ Advanced Surgical Irrigation solution (Next Science, Jacksonville, Florida) and the various completed, ongoing, and planned basic science and clinical investigations associated with it. Although there is already an impressive body of literature supporting its widespread utilization, future basic and clinical trials will continue to be performed to comprehensively characterize the effect this antimicrobial solution has on eliminating the risk of PJI following arthroplasty procedures.

INTRODUCTION

Periprosthetic joint infections (PJIs) are devastating complications following primary joint arthroplasty that are associated with substantial morbidity and mortality. The incidence of PJIs is rising, at least in part due to the rapidly increasing rate of primary hip and knee arthroplasties. Several studies estimate that the incidence of PJI following primary arthroplasty is around 1% to 2%, and the incidence of revision arthroplasty is 4% or more.[1–3] There was one study that estimated the incidence of PJI after routine primary arthroplasty would increase over threefold by 2035.[4,5] Not only is the incidence of PJI dramatically increasing, but the economic burden of revision arthroplasty for PJI has placed an enormous strain on healthcare systems across the globe. For example, the annual cost of infected revision arthroplasty in the United States increased from $320 million in 2001 to $566 million in 2009, and it is estimated to be five times this cost by 2030.[6]

This article will serve as a compilation of various ongoing and completed protocols, detailing the basic and clinical science impact of the XPERIENCE™ Advanced Surgical Irrigation solution (Next Science, Jacksonville, Florida). There are several basic scientific and clinical studies that have already been performed, demonstrating the efficacy of this irrigation solution in reducing the incidence of PJI and superficial infection among primary total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients. Ongoing and upcoming clinical studies will serve to augment the data of previous studies to further validate this irrigation solution and also demonstrate that this solution is effective in other orthopaedic procedures as well. To understand the role of this antimicrobial solution, we will briefly describe the spectrum of various PJI preventative measures and where antimicrobial solutions fit in. This will be followed by a detailed description of the XPERIENCE™ Advanced Surgical Irrigation solution and its usage, which will be a prelude to the scientific evidence section of this report.

GENERAL INFECTION PREVENTION TECHNIQUES

As a result of the rising incidence and cost burden, the prevention of PJI is of considerable interest in the arthroplasty community and has been tremendously studied.[1,3,7] Preoperatively, surgical candidates for arthroplasty are evaluated by a multidisciplinary team in order to optimize medical comorbidities, such as diabetes mellitus, that may increase the risk of PJI if not adequately controlled prior to the operation. In fact, several studies have identified many comorbidities, including hepatitis, obesity, renal failure and dialysis, anemia, and malignancy, among others, as risk factors for the development of surgical site infections and PJI.[6–11]

The skin overlying the operative site should be cleansed with an antiseptic cloth or detergent the night before surgery. In a large meta-analysis of eight randomized control trials, Mastrocola et al. determined that povidone-iodine and chlorhexidine solutions were the most commonly utilized to clean the surgical site and concluded that chlorhexidine exhibited a lower positive culture incidence than povidone-iodine (relative risk=0.53; 95% confidence interval=0.32 to 0.88).[12] A series of studies have evaluated the use of a preadmission chlorhexidine cloth to aid in the reduction of surgical site and periprosthetic joint infection.[13,14] In fact, a randomized control trial of over 500 primary arthroplasties found that the use of a chlorhexidine cloth the night before and morning of surgery was associated with an eight-fold reduction in infection rate when compared to standard-of-care prophylaxis.[13]

On the morning of surgery, perioperative antibiotics are given by the anesthesia team, and the patient is transported in the most efficient manner to the operating room, being careful to avoid unnecessary traffic and contamination of the patient's skin. The American Academy of Orthopaedic Surgery (AAOS) consensus guidelines recommend the use of a first- or second-generation cephalosporin or glycopeptide antibiotic (vancomycin) for antibiotic prophylaxis.[15] Another study recommends that antibiotics be completely infused 30 minutes prior to the time of incision.[16] Once the patient is appropriately positioned, the operative limb skin is thoroughly prepped with either chlorhexidine or povidone-iodine, and sterile adhesive draping is implemented to demarcate the sterile field.[17]

The main intraoperative modality, other than the maintenance of a sterile surgical field and instrumentation, to prevent PJI is the use of intraoperative irrigation into the surgical wound. Intraoperative irrigation is used to eradicate any biofilm formation prior to the implantation of the final components. Multiple studies have added antibiotics or antimicrobials to the irrigant. One study evaluating orthopaedic pediatric procedures found that, in 162 patients (182 procedures), povidone-iodine was associated with no cases of infection compared to 2.74% in the normal saline control cohort. Another study by Brown et al., specifically evaluating 2,550 total joint arthroplasty patients, found that povidone-iodine is associated with a lower (0.15%) incidence of infection compared to a normal saline control cohort (0.97%) (p=0.04).[18] A study by Frisch et al. of consecutive total joint arthroplasty patients found that there was no difference in infection rate between chlorhexidine and povidone-iodine intraoperative irrigation.[19] The XPERIENCE™ Advanced Surgical Irrigation solution is an alternative to chlorhexidine and povidone-iodine and is composed of four key ingredients aimed at eliminating planktonic bacteria implicated in the formation of biofilm around prosthetic devices, which will be the subject of this article. A large study comparing various solutions found that a combination product with ethanol, acetic acid, sodium acetate, and benzalkonium had the greatest reduction of mature *Pseudomonas aeruginosa* biofilms, while povidone-iodine had the greatest reduction in nascent methicillin-resistant *Staphylococcus aureus* compared to the other solutions.[20] Some of these solutions have been associated with cytotoxicity, especially to human osteoblasts.[21] This article will detail if there are cytotoxic effects the XPERIENCE™ Advanced Surgical Irrigation solution has against planktonic bacteria while preserving osteoblast development.

In a typical primary arthroplasty procedure, the XPERIENCE™ Advanced Surgical Irrigation solution is disseminated into the operative site via a pulsed lavage system. Previous studies have shown that a pulsed lavage system is effective in reducing bacteria intraoperatively.[22,23] One study of a series of spine surgeries found that more bacteria were cultured in the posterior muscle layer when bulb syringe irrigation was used during posterior interbody lumbar fusion than when pulsed lavage was implemented.[24] Another study determined that pulsed lavage was a cost-effective protocol for PJI prophylaxis during primary joint arthroplasty.[25]

In the immediate postoperative period, the patient receives additional antibiotics to prevent the formation of any early postoperative infection. The sterile surgical dressing is typically kept on the surgical incision until the first postoperative visit in order to avoid any contamination of the surgical incision with the outside world. Some studies have advocated for the use of extended oral antibiotics for high-risk patients. In an important study of 3,855 consecutive primary arthroplasty patients, the use of a seven-day course of antibiotics was associated with a lower rate of PJI in high-risk patients, but there was no difference in low-risk patients, suggesting that high-risk patients may benefit from extended oral antibiotic prophylaxis.[26]

There are also ways to perform additional infection prophylaxis once the surgical wound has been appropriately sewn closed. There are a few surgical wound gels on the market that allow for additional infection prevention[27-9] and will be the subject of a future article.

INTRODUCTION TO XPERIENCE™ ADVANCED SURGICAL IRRIGATION SOLUTION

Since we will be summarizing the clinical benefits of the XPERIENCE™ Advanced Surgical Irrigation solution later, the following section will be a brief description of its contents, mechanism of action, application, and real-time clinical implementation. This solution is a surgical lavage system composed of four key ingredients, including 32.5 grams/liter (g/L) citric acid, 31.3g/l sodium citrate, and 1.00g/l sodium lauryl sulfate in water, to preferentially target the development of a bacterial biofilm near the prosthetic devices (Table I). Each of the aforementioned ingredients serves an important role in inducing an environment that targets planktonic bacteria and prevents the formation of a bacterial biofilm near arthroplasty components. The citric acid serves to sequester metal ions from the extracellular matrix, the sodium citrate acts as a buffer to maintain pH, and the sodium lauryl sulfate is the surfactant (Fig. 1).

The XPERIENCE™ Advanced Surgical Irrigation solution is used throughout the surgical procedure prior to the implantation of final components and is used to thoroughly cleanse bony surfaces of all contaminants and biofilm prior to final implantation. In two previous reports for THA and TKA, the use of this surgical irrigation solution was described in detail.[30,31] These two articles also explained the classic implementation of the surgical irrigation solution, notably after trial components are removed and prior to the final implantation of components. Other articles on this topic further describe this agent as well as include initial study protocols, which will be updated in this report.[32-34]

Table I
Mechanisms of action of XPERIENCE™ irrigation surgical ingredients

Ingredient	Description	Mechanism of Action
Citric Acid	Chelator/Buffer	Chelates (bonds) with metal ions of the EPS and buffers solution to maintain an optimal pH
Sodium Citrate	Buffer	Buffers solution to maintain pH
Sodium Lauryl Sulfate	Surfactant	Reduces the surface tension of biofilm
Combined Ingredients	Osmolarity and Surfactant	Kills pathogens within the solution

Basic science studies

In an important basic science study that evaluated the efficacy of the XPERIENCE™ Advanced Surgical Irrigation solution, Bashyal et al. evaluated bacterial strains of microorganisms cultured in a growth-inducing medium and how they responded to exposure to the XPERIENCE™ Advanced Surgical Irrigation solution.[35] These bacterial strains were grown in 1% tryptic soy broth, and a single colony of the microorganism was transferred into a test tube containing sterile growth medium. After the growth phase of the bacteria was complete, 0.01mL of the target organism was transferred to a new test tube containing the XPERIENCE™ Advanced Surgical Irrigation solution. Drip-flow reactors were used to incubate bacteria with the assigned solution, and biofilm quantification was performed. Their results indicated that in vitro testing of the bacterial medium with treatment with the XPERIENCE™ Advanced Surgical Irrigation solution resulted in a six-log reduction in planktonic bacteria within five minutes. Furthermore, testing of soft tissues demonstrated minimal cytotoxic effects, suggesting that this irrigation system would likely not deleteriously impact the healthy soft tissue of the arthroplasty procedure. This finding is an advantage over traditional solutions for intraoperative irrigation, including povidone-iodone, which has been implicated in soft-tissue toxicity and cartilage damage.[36]

Another basic science study investigated the effects of the XPERIENCE™ Advanced Surgical Irrigation solution on osteoblast viability compared to povidone-iodine solutions.[37] In an in vitro analysis, osteoblasts were exposed to the

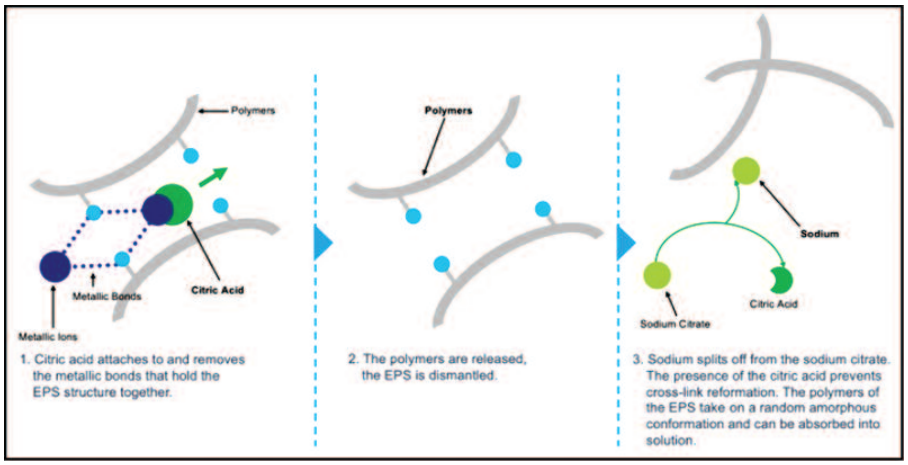

Figure 1. Mechanism of action of the XPERIENCE™ Advanced Surgical Irrigation solution against planktonic bacteria.

XPERIENCE™ Advanced Surgical Irrigation solution and povidone-iodine and evaluated for the expression of alkaline phosphatase, cell viability, and extracellular matrix collagenous deposition between the two groups. There were 10 cultures of osteoblasts for each treatment group incubated in standard culture medium and then exposed to both the surgical lavage solution and povidone-iodine. Fluorescent cell viability, alkaline phosphatase expression, and collagen assays were performed to determine the expression of these markers between the two cohorts. Results demonstrated that the cells treated with the XPERIENCE™ Advanced Surgical Irrigation solution were associated with significantly higher collagen deposition when using a 10% diluted solution, no difference in alkaline phosphatase activity, and a statistically significant higher survival of live osteoblasts following a five-minute antimicrobial wash when compared to povidine-iodine. Taken together, these findings suggest that the XPERIENCE™ Advanced Surgical Irrigation solution is minimally cytotoxic to osteoblasts and does not inhibit bone health as opposed to povidone-iodine.

Yet another basic science study has sought to analyze how the XPERIENCE™ Advanced Surgical Irrigation solution can clear bony debris and other soft-tissue debris prior to the final implantation of arthroplasty components to enhance the interdigitation of polymethylmethacrylate (PMMA) cement.[38] In this study, 18 total bovine cancellous slabs of bone were utilized. A 6mm cylindrical defect was drilled into 10mm slabs of bovine cancellous bone and treated with either a solution of 3% hydrogen peroxide, saline, or the XPERIENCE™ Advanced Surgical Irrigation solution. Cement interdigitation was assessed using micro-computed tomography and radiographs, which revealed that the saline group had a consistently thin gap between the cement and bony interface. This gap likely implies that there was persistent soft tissue and hydrophobic material that prevented the formation of the grout and physical intercalation between the PMMA cement and bone.

In summary, several basic science studies have explored the efficacy of the surgical lavage solution in eradicating harmful planktonic bacteria implicated in the development of biofilm and PJI. One of the previously mentioned studies incubated planktonic bacteria and administered doses of this surgical lavage solution and compared bacterial survival, concluding that this irrigation solution was able to demonstrate a six-log reduction in bacteria compared to controls.[35] Another basic science study evaluated the safety of the irrigation solution by evaluating key markers necessary for osteoblast growth and survival, demonstrating that this irrigation solution is associated with high levels of collagen, alkaline phosphatase, and cell viability.[37] Another study demonstrated that this lavage solution can actually help reduce soft-tissue debris that may interfere with cement interdigitation.[38] It is clear from these studies that this solution has a multimodal benefit, not just in the potential reduction of PJIs but in the retention and survival of implants.

CLINICAL STUDIES

Several clinical studies have been performed to evaluate the efficacy of the XPERIENCE™ Advanced Surgical Irrigation solution.[39-42] For example, a retrospective analysis of 1,295 consecutive patients who underwent primary hip and knee arthroplasty determined that no patients in the XPERIENCE™ Advanced Surgical Irrigation solution group developed a PJI up to one year following index arthroplasty compared to 0.5% (4 of 824) of patients in the betadine group, though this did not reach statistical significance ($p=0.3$).[39] Return to the operating room was also lower in the XPERIENCE™ Advanced Surgical Irrigation solution cohort (0.21%, 1 of 471) compared to 0.85% (7 of 824) in the control group, though this comparison also did not reach statistical significance ($p=0.4$). Regardless, this study demonstrated that the use of XPERIENCE™ as the surgical lavage system in primary hip and knee arthroplasty cases was associated with a low incidence of PJI.

Another study examined the effects of the XPERIENCE™ Advanced Surgical Irrigation solution on the reduction of postoperative lower extremity swelling, joint function, and pain following knee arthroplasty.[40] This study was performed at multiple centers, including Genesee Orthopedics and Plastic Surgery Associates in New Hartford, New York; St. Elizabeth Medical Center in Utica, New York; and Apex Surgical in Westmoreland, New York, in which 30 adult patients who were scheduled to undergo a primary, unilateral TKA were randomized to irrigation with the surgical lavage solution prior to arthrotomy closure, and 31 were randomized to irrigation with normal saline in an identical manner. Exclusion criteria included previous major lower extremity surgery within six months, previous vein surgery or harvesting on the ipsilateral leg, pregnancy, and use of loop diuretics. This pilot study demonstrated that irrigation with the XPERIENCE™ Advanced Surgical Irrigation solution was able to reduce postoperative swelling seven days after surgery ($p<0.05$) and 14 days after surgery ($p<0.05$) compared to irrigation with the povidone-iodine solution. This study also demonstrated that the cohort with XPERIENCE™ Advanced Surgical Irrigation solution was associated with improved range of motion seven days postoperatively and less dependence on ambulatory assistive devices when compared to the control cohort.

As more arthroplasty procedures become eligible for same-day discharge, there is an ongoing paradigm shift in arthroplasty procedures being performed in ambulatory surgery centers (ASC) and on an outpatient basis. A recent clinical study evaluated how the XPERIENCE™ Advanced Surgical Irrigation solution may impact the risk of PJI following primary TKA procedures performed at a free-standing ASC.[41] Primary TKAs performed in adults aged 18 years or older from May 2021 to May 2023 at Edgewater Surgery Center in Fort Mill, South Carolina, who were treated with the XPERIENCE™ Advanced Surgical Irrigation solution were included in this retrospective cohort study. Patients who had no evidence of infection at the time of surgery and did not require additional surgical intervention unrelated to the primary TKA surgery within 90 days were included in this study. There was only one case of PJI out of 524 primary TKAs (0.2%) diagnosed within 90 days and one case of surgical site infection within 30 days. In addition, the PJI notably occurred following an exogenously acquired upper respiratory infection, which cultured the same organism, implying seeding. The XPERIENCE™ Advanced Surgical Irrigation solution can demonstrate excellent efficacy in the reduction and/or prevention of infectious complications in an ASC setting.

In another study, 423 primary hip, knee, and shoulder arthroplasties performed by nine orthopaedic surgeons at the Jack Hughston Memorial Hospital in

Phenix City, Alabama, used the XPERIENCE™ Advanced Surgical Irrigation solution.[42] The authors found no infections at 90 days postoperatively and at least 15 months for the earliest performed surgeries.

In summary, there are four clinical studies that have evaluated the utility of this surgical irrigation solution to achieve clinical benefit, namely in the reduction of surgical site and periprosthetic infections.[39-42] One study was a retrospective review of 471 consecutive hip and knee arthroplasty patients and compared this surgical irrigation solution with betadine, concluding that the irrigation solution was associated with lower rates of infection, though not to the point of statistical significance.[39] Another study was a randomized trial in which TKA patients were assigned surgical irrigation and normal saline, concluding that the irrigation cohort had a lower duration of postoperative swelling and quicker recovery than the saline cohort.[40] Also, a study evaluating the irrigation solution in an ASC context concluded that there were no cases of infection related to the surgery when retrospectively reviewing cases of TKA that used the lavage solution.[41] Another retrospective review of 423 primary hip, knee, and shoulder arthroplasties found no infections at up to 15 months with the use of this irrigation solution. These clinical studies serve to further validate the use of this irrigation solution in joint arthroplasty procedures.

ONGOING CLINICAL TRIALS

There are several ongoing clinical trials that help to better characterize the clinical benefits of the XPERIENCE™ Advanced Surgical Irrigation solution to prevent PJI. There is one based out of the Ottawa Research Institute. The primary outcome of this double-armed randomized control trial is the rate of PJI within 90 days when lavage irrigation is applied to the surgical wound prior to fascial closure versus when dilute povidone-iodine is administered. Secondary outcomes include rates of superficial surgical site infections, rates of PJI within one year, and subgroup analyses of rates of PJI in high-risk groups (patients who have diabetes mellitus, chronic kidney disease, and inflammatory arthritis, among others).

A large ongoing prospective randomized trial has been initiated at Northwell Orthopedics in New York. A total of 936 high-risk-for-PJI patients are being randomized to either the XPERIENCE™ Advanced Surgical Irrigation solution or a normal saline control. The primary outcome is a deep infection at three months postoperatively.

In summary, there are ongoing clinical trials that are expected to definitively analyze how this surgical irrigation solution can be preventative against PJI and surgical site infection in hip and knee arthroplasty. The Ottawa Research Institute is currently underway with a multicenter randomized, double-blinded study evaluating rates of PJI and surgical site infection between cohorts who were assigned to the XPERIENCE™ Advanced Surgical Irrigation solution and those assigned dilute povidone-iodine. Northwell New York will prospectively assess PJIs with this solution versus a normal saline control group in a large, 936 patient-prospective randomized study.

UPCOMING CLINICAL TRIALS

There are also several planned clinical trials that are investigating the clinical benefits of the XPERIENCE™ Advanced Surgical Irrigation solution in the eradication and prevention of PJI following arthroplasty, extending beyond hip and knee arthroplasty procedures. For example, protocols are in development to evaluate how XPERIENCE™ Advanced Surgical Irrigation solution can prevent biofilm formation of *P. acnes* during shoulder arthroplasty. This study will randomly assign eligible patients to either this surgical irrigation solution or normal saline lavage after final implantation of components and prior to repair of the subscapularis or lesser tuberosity osteotomy. Primary outcomes of interest will include rates of PJI within one year following the arthroplasty procedure, and secondary outcomes of interest will include superficial surgical site infections.

A tibial fracture study, which includes types II and III with customized enrollments and endpoints to address the different infection rates, is currently being discussed. In addition to infection as an endpoint, evaluation of non-union, delayed union, wound dehiscence, antibiotic treatment, and operative debridement will also be evaluated. The control group would be low-flow saline. Typical infection rates at the facility are currently 15 to 20% for type III open tibial fractures.

Another potential protocol under discussion is an expansion of the postoperative knee swelling study. This pilot study will examine the swelling management and functional outcomes of anterior approach total hip arthroplasty procedures. Secondary endpoints under consideration include opioid use and infection rates.

Future protocols will even include an evaluation of the XPERIENCE™ Advanced Surgical Irrigation solution for infection prophylaxis in emergency rooms.

CONCLUSION

Periprosthetic joint infection following total joint arthroplasty is a devastating surgical complication that is associated with substantial morbidity and mortality as well as increased costs to the healthcare system. Great efforts and research have been put into the prevention of PJI following primary joint arthroplasty, with specific attention to intraoperative irrigation to eradicate the biofilm formation of planktonic bacteria, which has been implicated in the development of PJI. The XPERIENCE™ Advanced Surgical Irrigation solution is a proprietary surgical irrigation system composed of four key ingredients that help develop a safe, yet cytotoxic environment for planktonic bacteria in order to prevent the formation of biofilm. In this updated review, we examined a series of published, ongoing, and planned protocols that have evaluated this surgical irrigation solution as an intraoperative modality to reduce the formation of PJI postoperatively. Although there is already a large body of evidence pointing to the efficacy of this surgical lavage solution, the completion of the aforementioned ongoing clinical protocols and the initiation of planned protocols will help better characterize the full effects of this solution and facilitate further widespread usage in joint arthroplasty operating rooms.

AUTHORS' DISCLOSURES

Dr. Myntti and Ms. Lee are Next Science employees, and they receive stock options.

Dr. Mont is a board or committee member for the American Association of Hip and Knee Surgeons, Hip Society, and Knee Society. He holds stock in United States Medical Innovations, CERAS Health, MirrorAR, and PeerWell. Dr. Mont receives research support from

Patient-Centered Outcomes Research Institute (PCORI), Organogenesis, CyMedica Orthopedics, and the National Institutes of Health (NIAMS & NICHD), and he is on the editorial board for Surgical Technology International, the Journal of Arthroplasty, the Journal of Knee Surgery, and Orthopedics. He is a paid consultant for Kolon TissueGene, Ethicon, Exactech, Next Science, Pacira, Smith & Nephew, and Stryker. Dr. Mont receives royalties and research support from Stryker, UpToDate, and Wolters Kluwer Health - Lippincott Williams & Wilkins.

Dr. Sequeira has no conflicts of interest to disclose. STI

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