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Complications - Infection

A Randomized, Clinical Trial of Preadmission Chlorhexidine Skin Preparation for Lower Extremity Total Joint Arthroplasty

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ABSTRACT

Background: Periprosthetic infections are devastating postoperative complications of total joint arthroplasty (TJA), with native skin flora commonly identified as causative organisms. We compared 2% chlorhexidine gluconate–impregnated cloths to standard-of-care antiseptic bathing in patients before TJA, to evaluate periprosthetic infection risk at 1-year follow-up.

Methods: This was a prospective, randomized, controlled trial at a single institution of patients undergoing hip or knee arthroplasty. Chlorhexidine-treated patients (275 arthroplasties) applied 2% chlorhexidine gluconate–impregnated cloths the night before and morning of admission. The standard-of-care cohort (279 arthroplasties) bathed with soap and water preadmission. Patients were excluded according to the following: (1) unable to comply with study requirements, (2) pregnant, (3) <18 years, (4) medical history of immunosuppression or steroid use, (5) chronic hepatitis B/C infection, (6) had infection around joint requiring surgery, or (7) chose not to participate. A total of 539 patients (554 arthroplasties) were included in the final population. There were no significant differences in American Society of Anesthesiologists grade, cut time, risk scores, or diabetes and smoking prevalence between cohorts ($P > .05$).

Results: A lower periprosthetic infection rate was found in the chlorhexidine cohort (0.4%) when compared to standard-of-care cohorts (2.9%). The infection odds ratio was 8.15 (95% confidence interval = 1.01-65.6; $P = .049$) for the standard-of-care cohort compared to the chlorhexidine cohort. No differences in assessed risk factors were found between groups. No severe adverse events were observed.

Conclusions: Preoperative chlorhexidine cloth use decreased the risk of periprosthetic infection. This may be an appropriate antiseptic protocol to implement for patients undergoing lower extremity TJA.

Background

Lower extremity total joint arthroplasty (TJA) effectively increases function and reduces pain in patients with hip or knee osteoarthritis. However, periprosthetic infection is a common complication, with reported incidences of 0.7%-2.5% after hip arthroplasty and 1%-3% after knee arthroplasty [1-6]. These periprosthetic infections have serious consequences, including delayed recoveries, increased lifetime health care expenditures, multiple reoperations, and increased mortalities [7,8]. With the increased older aged population, the frequency of arthroplasty patients is expected to increase over the next decade [9], who will be at risk for periprosthetic infection. Therefore, there is a need to identify preventative methods to decrease this devastating complication [1].

Sources of wound contamination following arthroplasty include operating room air and native skin flora [10]. Protocols effective in decreasing airborne pathogen load include positive air pressure, laminar airflow, and reduced foot traffic [11-14]. To reduce native skin flora, bathing with antiseptic agents the evening before surgery is recommended by the Centers for Disease Control and Prevention and is the standard-of-care [1]. Chlorhexidine is a broad-spectrum biocide effective against Gram-positive and Gram-negative bacteria. It exerts its bactericidal effects through direct disruption of the organisms' membrane permeability [15]. Therefore, preoperative chlorhexidine showers may be an efficacious alternative to bathing to decrease postoperative infection risk [7,10,16]. However,

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maintaining bactericidal skin concentrations are challenging with bathing alone [17].

A 2% chlorhexidine gluconate–impregnated cloth was developed specifically to maintain bactericidal concentrations for skin preparation. This cloth allows for prolonged antisepsis, as chlorhexidine gluconate persists on skin [18-20]. The long-lasting antiseptic effect is attributed to chlorhexidine gluconate not being inactivated by blood or serum proteins [21]. Furthermore, significantly greater reductions in bacteria up to 6 hours following application have been found compared to standard chlorhexidine skin preparation [22].

Chlorhexidine gluconate–impregnated cloths have been shown to reduce infection risk; however, there is limited evidence in orthopedic-related prophylaxis. We, therefore, conducted a prospective, randomized, controlled study comparing chlorhexidine cloths to standard-of-care antiseptic bathing in patients before TJA, to evaluate any differences in periprosthetic infection risk. Secondary end points were factors that may affect infection risk and adverse event incidences. We anticipated that risk factors would be similar between groups, and this intervention would significantly decrease infection risk as an alternative to standard-of-care preoperative skin preparation. Primary and secondary end points followed Food and Drug Administration guidance as agreed on with Food and Drug Administration as part of a Special Protocol Assessment.

Methods

Study Oversight

This prospective, randomized, controlled trial was performed at a tertiary care center, after institutional review board approval. It was conducted in accordance with Declaration of Helsinki and current regulatory requirements and registered with Clinicaltrials.gov (NCT02469311). It was designed by all authors and supported by an educational grant from Sage Products, LLC (Cary, IL). Data management, trial monitoring, and statistical analysis were performed and supervised by the participating authors. Sage Products, LLC had the opportunity to review and provide comments before manuscript submission; however, they had no role in trial design, data collection or analysis, or the decision to submit. All authors assume responsibility for data, vouch for integrity and completeness of data and analyses, and assume responsibility for the fidelity of this report toward the study protocol.

Patient Enrollment

Patients were enrolled between March 1, 2012 and November 30, 2012. Consecutive patients undergoing a joint arthroplasty, specifically a total knee arthroplasty or total hip arthroplasty (total knee arthroplasty or total hip arthroplasty) were eligible. Patients were excluded according to the following: (1) unable to comply with study requirements (n = 18); (2) pregnant (n = 0); (3) under 18 years of age (n = 0); (4) medical history of immunosuppression, for example, human immunodeficiency virus, status-post organ transplantation, or received >10 milligrams prednisone equivalent for >10 days within 90 days of enrollment (n = 9); (5) chronic hepatitis B or C infection (n = 6); (6) had infection around joint requiring surgery (n = 6); or (7) chose not to participate (n = 32) (Fig. 1).

Study Design

Patients provided written informed consent before randomization. They were randomized via a computer-generated algorithm preoperatively to receive either advance preadmission chlorhexidine (treatment) or standard-of-care (soap bathing). Eight patient cohorts were formed; 4 each of the treatment and standard-of-care groups involving: (1) primary knee arthroplasty patients, (2) revision knee arthroplasty patients, (3) primary hip arthroplasty patients, and (4) revision hip arthroplasty patients.

Primary and revision arthroplasty patients randomized to standard-of-care received bathing instructions with antibacterial soap and water the night before surgical admission. Patients randomized to chlorhexidine were provided with 2 packets containing six 2% chlorhexidine gluconate–impregnated cloths (Sage Products LLC), along with instructions for use the night before and morning of surgery. Patients used one cloth at the following cutaneous sites: (1) neck, chest, and abdomen; (2) back; (3) left and right upper extremity; (4) left lower extremity; (5) right lower extremity; and (6) surgical site. The chlorhexidine protocol specified that if patients were to bathe or shower, they should wait for a minimum of 2 hours before cloth application. Following cloth use, patients were not allowed to shower, rinse, or apply any topical cream or powder.

To verify compliance, patients submitted adhesive stickers from packets at the time of application, which were collected in the preoperative waiting area. If patients used the first packet correctly, the second packet was administered in hospital. Patients were excluded from the study if one or both cloth packs were not used as indicated (n = 28).

Enrolled patients underwent standard infection control practices during admission. All patients had the same perioperative skin preparation and postoperative care protocol, as described in the following section. As per the Centers for Disease Control and Prevention, intravenous antibiotic prophylaxis (1 gram cefazolin) was commenced 1 hour before surgery. The incision site was cleaned with alcohol using a scrub and paint technique. This was followed by skin preparation, using aniodine povacrylex and isopropyl alcohol solution (DuraPrep Surgical Solution, The 3M Company, Saint Paul, MN). Nonpermeable paper drapes were used during surgery, with surgical adhesive tapes. Postoperatively, prophylactic antibiotics were stopped within 24 hours.

End Points

The primary end point assessed the incidence of deep periprosthetic infection. Patients were followed for 1 year postoperatively, consistent with the susceptibility period defined by Centers for Disease Control and Prevention [23]. Recently, this was redefined as within 30-90 days after operation [24]. Periprosthetic infections were identified using criteria as specified by the Musculoskeletal Infection Society [8]. Superficial infections, which involved the skin or subcutaneous site, were documented, but not considered deep infections, and were excluded from the study.

Secondary end points were the correlations between infections and American Society of Anesthesiologists (ASA) grade [25], diabetes and smoking prevalence, mean surgery time, and wound type (clean vs contaminated) in the cohorts. A National Healthcare Safety Network (NHSN) risk score was calculated to determine infection risk [23,26]. Patients were assigned points based on operation duration, wound class, and ASA score [23]. Zero points were low risk, 1 point was medium risk, and 2 or 3 points were high risk.

Overall, 1 (0.2%) arthroplasty had a contaminated wound type. Mean ASA grade was 2 (95% confidence interval [CI], 2.3-2.4), and 213 (38%) arthroplasties had patients with an ASA score of 3 or greater. Mean surgical time was 102 (95% CI, 97.7-105.7) minutes (149 [27%] >120 minutes). Overall mean NHSN risk score was 0.6 (95% CI, 0.6-0.7), with 271 (49%) low risk, 206 (37%) medium risk, and 77 (14%) high risk. Overall, these factors were found to be

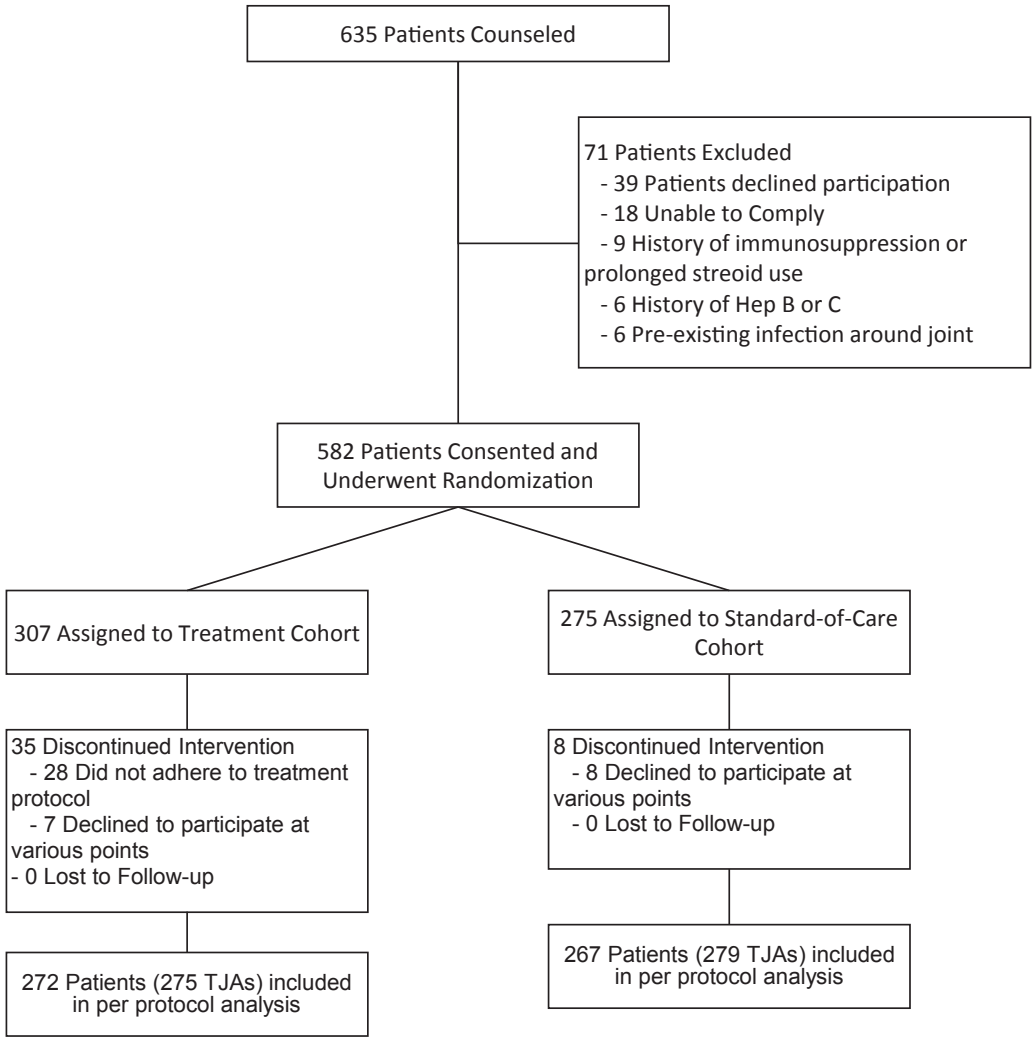

Fig. 1. Study cohort flow diagram. TJA, total joint arthroplasty.

similar between the 2 cohorts ($P > .05$) (Table 1). No significant differences in diabetes prevalence (15 vs 22%; $P = .06$) or smoking (20 vs 19%; $P = .83$) were found between the cohorts.

Safety

Adverse events recorded included wound problems, any skin reaction, or anaphylaxis symptoms possibly related to the chlorhexidine-impregnated cloths.

Statistical Analysis

The efficacy analysis was conducted using data from patients who completed the entire clinical trial. We chose this, vs an intention-to-treat analysis, to evaluate treatment effects of those who adhere, rather than to estimate effects of intervention allocation. Patient age, gender, body mass index, and diabetes were demographic variables. Surgical exposure variables, including wound class, ASA score, and surgical time, were used to calculate NHSN risk scores (0-3 points). Data were stored using an Excel spreadsheet (Microsoft Corporation, Redmond, WA).

For sample size determinations, we assumed 10% follow-up loss or noncompliance rate. The power analysis assumed 95% CIs of proportions, a power of 0.8, and an alpha of 0.05 using a tetrachoric correlation model of 2 dichotomous random variables (infection vs no infection), assuming a bivariate normal distribution in each population (treatment vs standard-of-care). For the primary

Table 1
Surgical Risk Factors.

Risk Factor	Standard-of-Care	Chlorhexidine Protocol	*P* Value
Wound class, N			
Clean	278	275	.999
Dirty	1	0	
ASA score, mean	2	2	.387
ASA score, N			
0-2	166	175	.431
3-5	113	100	
Cut time in minutes, mean (range)	105 (33-297)	99 (30-216)	.124
Cut time (min), N			
0-120	202	203	.701
121+	77	72	
NHSN risk score, mean	0.7	0.6	.374
NHSN risk group, N			
0: Low risk	132	139	.649
1: Medium risk	104	102	
2: High risk	43	34	

N, number of patients; NHSN, National Healthcare Safety Network; ASA, American Society of Anesthesiologists.

Table 2
Revision Arthroplasty Cohorts Demographic Data.

Demographic Characteristic	Revision TKA		Revision THA	
	Treatment (n = 23)	Standard-of-Care (n = 43)	Treatment (n = 17)	Standard-of-Care (n = 29)
Age in years, mean (range)	67 (55-95)	63 (45-85)	68 (41-104)	67 (41-91)
BMI in kg/m^2, mean (range)	34.2 (21.6-57)	33.7 (19.7-56)	28.8 (18.9-41.4)	31.3 (20.8-55.5)

arthroplasty cohorts, the required sample size was 1570 patients (785 patients in each cohort). In revision arthroplasty cohorts, the sample size was 388 patients (194 patients in each cohort).

Fisher's exact tests and independent samples' *t* tests were used to compare baseline and outcome variables between patients in the cohorts. We used a logistic regression model to calculate the odds ratio (OR) and 95% CI of periprosthetic infection for patients in the cohorts. Statistical data analysis was performed in SAS version 9.4 (SAS Institute Inc, Cary, NC). A *P*-value of less than .05 was interpreted as statistically significant.

Results

Patients

Overall, 653 patients were screened for enrollment. Following those excluded (n = 71), 582 patients were consented and randomized, of which, 43 did not adhere to treatment or declined participation at various points, leaving 539 patients (554 lower joint arthroplasties) included in the final population (see Fig. 1).

In the primary arthroplasty treatment cohorts, there were 118 TKAs in patients with mean age 66 years and mean BMI 33.7 kg/m^2 and 117 THAs in patients with mean age of 62 years (range, 20-86) and a mean BMI of 29 kg/m^2 (range 18.8-45). In the primary standard-of-care cohorts, there were 116 TKAs in patients with mean age 64 years (range, 35-96) and mean BMI 34.7 kg/m^2 (range, 14.7-58) and 91 THAs in patients with mean age 64 years (range, 24-96) and mean BMI 28.9 kg/m^2 (range, 15-52.5). The data of revision arthroplasty cohorts can be found in Table 2.

All patients randomized into separate treatment cohorts (primary and revision TKA, primary and revision THA) were combined into one group, which was also done for the standard-of-care cohort. This was because before the intended completion date, the infection control officer determined that enrolling patients into standard-of-care was no longer ethical because of higher infection rates found in that cohort. When grouped together, both cohorts were adequately powered. Overall, 275 arthroplasties were randomized to the chlorhexidine cohort and 279 arthroplasties were randomized to standard-of-care (Fig. 1). There were no significant differences in age, BMI, or gender between the 2 overall randomized cohorts (Table 3).

Efficacy End Points and Safety

At a minimum of 1-year postoperative follow-up, there were 9 (1.6%) periprosthetic infections in the entire population of 554 arthroplasties. One deep periprosthetic infection was in the chlorhexidine cohort (0.4%), compared to 8 (2.9%) in the standard-of-care cohort ($P = .038$) (OR 8.15 for standard-of-care [95% CI = 1.01-65.6; $P = .049$]), with one superficial in the chlorhexidine cohort (0.4%) and 5 (2.5%) in the standard-of-care cohort. See Table 4 for infections in individual groupings.

There were no significant differences in ASA grade, surgical time, mean NHSN score, or incidence of diabetes or smoking between the 2 cohorts ($P > .05$).

Safety

Red wheals occurred in one treated patient, which resolved within 2 days with local wound care. No other adverse events or allergic reactions were found.

Discussion

Periprosthetic infections are devastating complications following arthroplasty that burden both patients and providers. Recent developments in skin preparation, such as chlorhexidine showers, have shown efficacy in decreasing infection risk. In this study, chlorhexidine gluconate–impregnated cloths the night before and morning of admission significantly decreased periprosthetic infections in TJA patients when compared to standard antiseptic bathing overall (OR 8.15).

Chlorhexidine has replaced povidone-iodine as the standard-of-care antiseptic skin preparation following multiple studies demonstrating superior efficacy at decreasing bacterial pathogen load, as well as leading to reductions in surgical site infections [24,27,28]. This superiority is attributed to rapid bactericidal action and long-lasting residual effects on the skin [20]. It inactivates microorganisms on the skin surface and prevents microbial recolonization in the presence of body fluids [10,29]. In Springer and Parvizi's book, Potter et al [24] evaluated the use of chlorhexidine and intranasal mupirocin decolonization protocol for *Staphylococcus aureus* and reported up to an 81% reduction in surgical site infections in those using this protocol [30-34].

More recently, the use of chlorhexidine cloth wipes has been demonstrated to be superior to chlorhexidine washes. Edmiston et al [21] evaluated these differences in 70 patients and following evening and morning use of antiseptic, the mean chlorhexidine skin surface concentrations were 51.6-119.6 ppm in the wash group, compared to 907-1049.6 in the cloth group [21]. The authors concluded that following cloth use, mean skin surface concentrations of chlorhexidine ranged from 12.7 to 27.4 times higher than with the wash ($P < .001$). Therefore, we believe that cloth wipes are an extremely important preadmission skin preparation currently available for joint arthroplasty candidates.

Rates of postsurgical complications, particularly infection, remain a primary concern following joint arthroplasty. Our findings are consistent with prior studies. A study by Dixon et al [35]

Table 3
Demographics of Patient Population.

Demographic Characteristic	Standard-of-Care	Chlorhexidine Protocol	*P* Value
Age (y), mean	62	61	.908
Gender, N			
Male	103	96	.596
Female	169	171	
Body mass index (kg/m^2), mean	32.2	31.4	.223
Diabetes, N			
No	215	204	.062
Yes	60	40	

N, number of patients.

Table 4
Deep Periprosthetic Infections in Individual Cohorts.

Cohort (n)	Treatment N (%)	Standard-of-Care N (%)	*P* Value
Overall (554)	1 (0.4%)	8 (2.9%)	.049
Primary THA (208)	0 (0%)	1 (1%)	
Primary TKA (234)	0 (0%)	2 (1.7%)	
Revision THA (46)	0 (0%)	2 (6.9%)	
Revision TKA (66)	1 (4.3%)	3 (7%)	

N, number of patients; THA, total hip arthroplasty; TKA, total knee arthroplasty.

demonstrated a 74% reduction in infection rates for surgical intensive care unit patients (n = 144) receiving chlorhexidine cloth application before undergoing central line placement. In addition, further studies have shown a 50% reduction in surgical patients (n = 727) using chlorhexidine cloths before admission [19] and a 60% reduction in blood stream infections in 391 intensive care patients [36,37]. Zywiel et al [38] studied 912 knee arthroplasties and found that preadmission chlorhexidine cloth use was associated with a decreased risk of periprosthetic infection when compared to patients who had standard perioperative preparation (0%-3%) [19]. A study by Kapadia et al [39] on 2458 THAs demonstrated that cutaneous chlorhexidine cloths in THAs led to a significantly lower infection incidence than no use (0.5 vs 1.7%; $P < .05$).

In addition, the introduction of a preoperative chlorhexidine cloth preparation protocol may result in overall health care cost savings. Kapadia et al [40] noted that cost benefit of using chlorhexidine in their institution was a net savings of 2.1 million dollars per 1000 knee arthroplasty patients. The authors noted an annual estimated national health care savings ranging between 0.78 and 3.18 billion dollars, based on infection rates reported by the author and the National Health Safety Network. Such savings are imperative for both surgeons and hospitals, who aim to reduce costs associated with arthroplasty.

We acknowledge that there are several limitations of our study. Due to early termination because of ethical considerations, our sample size was smaller than originally intended. Although we achieved statistical power when combining groups, we were unable to achieve the anticipated statistical power for the individual 8 cohorts due to small sample sizes. Nevertheless, we demonstrated an overall important statistical difference. Despite our best efforts to monitor and enforce compliance with the chlorhexidine protocol, we acknowledge that some patients may have deviated from the specified and proper use of the cloths. The strengths of our study included the randomized, double-blinded, controlled design and multiple levels of patient compliance monitoring. To our knowledge, this is the largest and most comprehensive study of the use of chlorhexidine cloths for any orthopedic procedure to date.

In conclusion, the use of chlorhexidine cloths decreased periprosthetic infections following TJA compared to antiseptic bathing. We believe that these cloths warrant further consideration as the standard-of-care skin preparation for joint arthroplasty. Continued study is needed to further define the efficacy of these associations according to surgical site and surgery type.

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