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Original research

Prosthetic Joint Infection and Wound Leakage After the Introduction of Intraoperative Wound Irrigation With a Chlorhexidine-Cetrimide Solution: A Large-Scale Before-After Study

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ABSTRACT

Background: Intraoperative chlorhexidine irrigation could be a valuable additive to systemic antibiotics to prevent infections after total joint arthroplasties. However, it may cause cytotoxicity and impair wound healing. This study evaluates the incidence of infection and wound leakage before and after the introduction of intraoperative chlorhexidine lavage.

Methods: All 4453 patients receiving a primary hip or knee prosthesis between 2007 and 2013 in our hospital were retrospectively included. They all underwent intraoperative lavage before wound closure. Initially, wound irrigation with 0.9% NaCl was standard care (n = 2271). In 2008, additional irrigation with a chlorhexidine-cetrimide (CC) solution was gradually introduced (n = 2182). Data on the incidence of prosthetic joint infections and wound leakage, as well as relevant baseline and surgical characteristics, were derived from medical charts. Chi-square analysis was used to compare the incidence of infection and wound leakage between patients with and without CC irrigation. Multivariable logistic regression was used to assess robustness of these effects by adjusting for potential confounders.

Results: The prosthetic infection rate was 2.2% in the group without CC irrigation vs 1.3% in the group with CC irrigation ($P = .021$). Wound leakage occurred in 15.6% of the group without CC irrigation and in 18.8% of the group with CC irrigation ($P = .004$). However, multivariable analyses showed that both findings were likely due to confounding variables, rather than by the change in intraoperative CC irrigation.

Conclusions: Intraoperative wound irrigation using a CC solution does not seem to affect the risk of prosthetic joint infection or wound leakage. Observational data easily yield misleading results, so prospective randomized studies are needed to verify causal inference.

Level of Evidence: Level III—uncontrolled before and after the study.

Introduction

A prosthetic joint infection (PJI) is one of the most serious complications after a total joint replacement. With the increase of multiresistant bacteria, [1] prevention of PJI is crucial. Several factors have helped to reduce the incidence of PJI, including modern aseptic techniques, shortening of operation time, and prophylactic antibiotics [2]. Intraoperative wound irrigation with antibacterial or diluted antiseptic solutions (chlorhexidine, hydrogen peroxide, and povidone-iodine [PVI]) before wound closure could provide a valuable additive to further reduce the infection rate after total joint arthroplasties [1,3–6]. Major advantages of antiseptics are that their application is simple, they have a rapid effect, and resistance is virtually nonexistent. However, in addition to being bactericidal, antiseptics are cytotoxic to the patient's own tissues when applied in adequate concentrations [6–9]. This cytotoxicity can have a negative effect on wound healing, [10] which may subsequently increase postoperative infection rates.

Chlorhexidine is an antiseptic agent which is effective against a wide variety of organisms responsible for total joint infections and acts by disrupting the cellular membranes, resulting in leakage of

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cell content. In vitro studies support the bactericidal effect of chlorhexidine in water at concentrations between 0.8 and 2 g/L at short exposure times of 1 to 2 minutes [8,11]. In higher concentrations, it also causes coagulation of intracellular contents [12,13]. Chlorhexidine uptake by the bacteria is extremely rapid, with a maximum uptake within 20 seconds and bactericidal effects occurring immediately [14]. Minor additional binding occurs with increased exposure times. This rapid action makes chlorhexidine an ideal antiseptic agent for intraoperative lavage.

To reduce the incidence of PJI, irrigation with a chlorhexidine-cetrimide (CC) solution in water before wound closure after total knee arthroplasties (TKAs) and total hip arthroplasties (THAs) was introduced in our large public teaching hospital. CC is a commonly used disinfection solution. Although the implementation of this practice seems supported by in vitro data, careful review of the current literature does not provide a vast clinical basis for its usage to prevent PJI [15]. Also, the cytotoxic effects on wound healing after a joint arthroplasty have not been investigated [10]. Therefore, this study evaluated the effect of CC irrigation on the incidence of PJI and wound healing, by comparing large numbers of hip and knee arthroplasties before and after its implementation in standard care.

Material and methods

In this uncontrolled before-and-after study, [16] we included data from all patients who received a primary THA or TKA between January 1, 2007, and December 31, 2013, in our large public teaching hospital OLVG (location East) in Amsterdam. There were no other inclusion or exclusion criteria, and all data were collected within standard care. Approval for this study was obtained by the local medical ethics committee (study number WO 15.099) and informed consent was waived.

In the past, pulsed lavage with 0.9% NaCl was standard care. From 2007 onwards, wound irrigation with a CC solution was gradually introduced. Specifically, the standard pulsed lavage with 0.9% NaCl was preceded by irrigation with a 0.015% chlorhexidine-in-water solution (0.15 mg/ml chlorhexidine and 1.5 mg/ml cetrimide). After implantation of the prosthesis, the CC solution was poured in the wound for irrigation of the deep and superficial layers for 1 minute. After closure of the deep layers, the subcutis was irrigated again for 1 minute. Initially, one of the senior authors started using CC irrigation in all his patients. Due to positive experiences, the other orthopedic surgeons gradually started using CC irrigation as well. In 2010, CC irrigation became standard care.

According to surgeon preference, the cemented and uncemented THAs were performed using a standard posterolateral or straight lateral (Hardinge) approach. All TKAs were cemented, and a medial parapatellar approach was used for their implantation. Standard care over the study period included preoperative and perioperative wash with chlorhexidine (shampoo and nose gel), skin closure with clips, antibiotic prophylaxis consisting of cephalosporin for 24 hours (for all patients, including those with penicillin allergy), a low vacuum drain for the first 24 hours, and discharge from the orthopedic ward on the fourth postoperative day. Identification of delayed wound healing without other signs of infection did not affect postoperative management, for example no additional antibiotic treatment was provided.

All electronic patient records were scrutinized to extract relevant data on patient characteristics, surgical characteristics, PJIs, and wound leakage. Patient characteristics included age, body mass index (BMI), American Society of Anesthesiologists (ASA) classification, diabetes, smoking, immunosuppressant drugs, malignancy in the past, and antiplatelet or anticoagulation therapy. The surgical reports were thoroughly reviewed to obtain information on the type of lavage used before wound closure (with or without chlorhexidine), affected joint, indication for a surgery, type of fixation of the implant, type of venous thromboembolism (VTE) prophylaxis, and type of anesthesia. Antibiotic-loaded cement was used for all TKAs and all cemented THAs. Any data not available in the records were labeled as missing, and no imputation was applied. Age and BMI were analyzed as continuous variables. ASA score was reported as a categorical variable, as were anticoagulation therapy (none vs antiplatelet vs anticoagulation with or without additional antiplatelet) and VTE prophylaxis (fondaparinux vs dabigatran vs no or other VTE prophylaxis). Arixtra (Mylan IRE healthcare limiter, Dublin, Ireland) was the main manufacturer for fondaparinux and Pradaxa (Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany) for dabigatran. All other variables were dichotomous, as detailed in Supplementary Table 1.

The primary outcome was the incidence of PJI. Due to the retrospective nature of this study, it was not possible to classify patients according to the criteria recommended by the International Consensus Meeting or Musculoskeletal Infection Society. Therefore, PJI was defined as any type of postoperative joint infection that resulted in Debridement, Antibiotics and Implant Retention (DAIR) or a revision arthroplasty with at least 2 positive cultures with the same microorganism or negative cultures and a macroscopically infected total joint arthroplasty (eg, sinus tract to the joint). Hematogenous infections were discarded from the analysis. All non-hematogenous PJIs were divided into early infections (<3 months after the initial joint replacement) and late infections (≥3 months after the initial joint replacement). The secondary outcome measure was wound leakage. This was defined as leakage recorded in the medical records after the fourth postoperative day. The majority of the wound leakage data were extracted from wound culture reports because it was standard care to obtain a swab of a leaking wound on the fifth postoperative day. Additional wound leakage data were extracted from the complication registry and medical charts. The final date of data extraction was February 1, 2017, so the follow-up time was at least 3 years and 1 month for each patient.

Statistical analysis

A statistical analysis was performed with SPSS software (version 21; IBM Corporation, Armonk, NY), and the standard level of statistical significance was 0.05. We first compared baseline and surgical characteristics as well as outcomes (infection and wound leakage) between groups, using independent t-tests (normally distributed variables), Mann-Whitney U tests (abnormally distributed variables), and chi-square tests (categorical variables).

Second, we used univariable and multivariable logistic regression to identify whether the association between CC irrigation and both outcomes (infection and wound leakage) was affected by potentially relevant patient and surgical characteristics. The multivariable models used a Wald backward selection process with a cutoff *P* value of .157 [17]. Initial multivariable models included all variables reported in Table 1. In order to limit the loss of statistical power due to missing data on one of the variables, we repeated the multivariable analyses using only CC irrigation and the variables that survived the backward selection process in the initial models. To provide full transparency, we report the odds ratios for CC irrigation both before and after the initial and repeated backward selection process.

Results

Population

Between January 1, 2007, and December 31, 2013, 4453 patients underwent a primary hip or knee replacement in the OLVG

Table 1
Patient and surgery characteristics.

Characteristics	Without CC irrigation		With CC irrigation		*P* value
Patient characteristics	n		n		
Age, median (IQR)	2271	66 (16)	2182	67 (13)	.001
BMI, median (IQR)	1710	26.9 (6.2)	2116	27.4 (6.1)	.192
Affected joint hip (vs knee)	2271	55.3%	2182	53.3%	.179
Indication OA (vs other)	2271	93.8%	2182	94.6%	.227
ASA	1844		2165		.026
I		27.7%		25.2%	
II		58.6%		61.6%	
III		12.9%		12.9%	
IV		0.8%		0.3%	
Diabetes mellitus	1701	10.0%	2159	12.7%	.009
Current smoker	1614	20.0%	2099	16.0%	.002
Immunosuppressant drugs	1746	2.5%	2162	2.6%	.732
Malignancy in past	1738	4.7%	2145	5.8%	.142
Antiplatelet/coagulation	1482		1587		.775
No/none		77.6%		77.6%	
Antiplatelet		17.1%		16.6%	
Anticoagulation		5.3%		5.8%	
VTE prophylaxis	2102		2039		<.001
Fondaparinux (Arixtra)		82.1%		13.9%	
Dabigatran (Pradaxa)		11.5%		80.7%	
Other		6.5%		5.4%	
Surgery characteristics					
Use of antibiotic-loaded cement (including hybrid)	2236	78.8%	2172	79.6%	.512
Anesthesia, full (vs spinal)	2120	54.9%	2163	45.7%	<.001

IQR, interquartile range; OA, osteoarthritis.

hospital. Pulsed lavage with the NaCl solution only was performed in 2271 patients, and additional irrigation with the CC solution was done in 2182 patients. All patients were included, and all data that could be collected from their charts were included in the analyses.

The extracted patient and surgery characteristics of both groups are reported in Table 1. Overall, 68% were female and 32% were male with an average age just over 65 years. The majority of the patients were classified as ASA class II. Small but significant differences in patient characteristics between the groups with and without CC irrigation were observed for age, ASA classification, diabetes mellitus, smoking status, and the type of anesthesia. There were no significant differences in BMI, affected joint, indication for a surgery, the use of immunosuppressant drugs, patients' history of malignancies, anticoagulation therapy, and the use of cement for fixation of the implant. VTE prophylaxis was substantially different between groups, due to a change in policy during the study period from fondaparinux (Arixtra) to dabigatran (Pradaxa).

Prosthetic joint infection

The overall infection rate in the 4453 patients over a follow-up period of at least 3 years was 1.8%. Table 2 shows that significantly less infections occurred in the patients that had received CC irrigation (1.3%) than in those who had not (2.2%, $P = .021$). The difference was more pronounced in the late infections (0.2% vs 0.7%, $P = .009$) than in the early infections (1.1% vs 1.5%, $P = .253$). However, Table 3 (upper part) shows that the association between CC irrigation and infection disappeared when adjusting for potentially relevant patient and surgical characteristics in a multivariable model. The only variables that survived the initial and repeated backward selection process were indication for a surgery and VTE prophylaxis.

Wound leakage

In 765 patients (17.2%), wound leakage was reported on the fifth postoperative day. A significantly increased rate of wound leakage was observed in the group of patients that received CC irrigation (18.8%) in comparison with the NaCl-lavage-only group (15.6%, $P = .004$, Table 2).

However, Table 3 (lower part) shows that the association between CC irrigation and wound leakage disappeared when adjusting for potentially relevant patient and surgical characteristics in a multivariable model. Variables that survived the initial backward selection process were indication for surgery, BMI, ASA score, age, affected joint, and VTE prophylaxis. In the repeated model, including all patients with complete data for these variables (n = 3557), CC irrigation and indication for a surgery were removed during the backward selection process.

Discussion

Intraoperative lavage with antiseptics during primary joint replacements is a commonly accepted practice, although hardly any clinical evidence exists to support this. This uncontrolled before-and-after study shows the risk of observational data analyses due

Table 2
Incidence of infections and wound leakage in groups with and without CC irrigation.

Incidence	Without CC irrigation (n = 2271)	With CC irrigation (n = 2182)	*P* value
Overall infections (excluding hematogenous infections)	2.2%	1.3%	.021
Early infections (<3 mo)	1.5%	1.1%	.253
Late infections (≥3 mo)	0.7%	0.2%	.009
Wound leakage	15.6%	18.8%	.004

Table 3
Associations between CC irrigation and prosthetic joint infection (upper part) and wound leakage (lower part), without (univariable) and with (multivariable) adjustments for potentially relevant patient and surgical characteristics.

Outcome	N	Initial/repeated	Backward selection	Odds ratio for CC irrigation	95% Confidence interval	*P* value
Prosthetic joint infection (excl. hematogenous infections)						
Univariable	4453	NA	NA	0.586	0.370-0.928	.023
Multivariable	2507	Initial	Before	1.031	0.469-2.263	.940
		Initial	After[a]	NA	NA	NA
	4141	Repeated	Before	0.932	0.466-1.865	.842
		Repeated	After[b]	NA	NA	NA
Wound leakage						
Univariable	4453	NA	NA	1.257	1.075-1.469	.004
Multivariable	2507	Initial	Before	1.049	0.812-1.355	.716
		Initial	After[c]	NA	NA	NA
	3557	Repeated	Before	0.982	0.770-1.252	.883
		Repeated	After[d]	NA	NA	NA

[a] Variables that remained in the initial model for infection after backward selection: indication, VTE prophylaxis.
[b] Variables that remained in the repeated model for infection after backward selection: indication, VTE prophylaxis.
[c] Variables that remained in the initial model for wound leakage after backward selection: indication, BMI, age, joint, ASA score, VTE prophylaxis.
[d] Variables that remained in the repeated model for wound leakage after backward selection: BMI, age, joint, ASA score, VTE prophylaxis.

to known and unknown confounders. Despite significant between-group differences in PJIs (2.2% vs 1.3%) and wound leakage (18.8% vs 15.6%), multivariable logistic regression models showed that CC irrigation was not significantly associated with both outcomes. The sample size was large enough to detect significant associations with other variables, such as indication for a surgery and VTE prophylaxis.

Although the use of chlorhexidine for preoperative skin cleaning and surgical site preparation has been studied extensively, this study does not demonstrate any benefit. So far, most studies investigating the effect of intraoperative lavage with antiseptics focused on diluted PVI solutions. A meta-analysis of 24 randomized controlled trials comparing no or saline lavage with a PVI solution showed that the antiseptic solution significantly reduced the rates of surgical site infections [18]. This meta-analysis indicated that the surgical site infection rate was 13.4% in the control group (2539 patients) vs 8.0% in the PVI group (2465 patients), indicating a risk reduction of 0.58 (95% confidence interval 0.40-0.83, $P = .003$). Although the majority of included studies consisted of abdominal procedures, favorable results of PVI lavage solutions were also seen in total joint arthroplasties. Despite the favorable results in the meta-analysis, the effect of PVI lavage for the prevention of total joint arthroplasty infections is still debatable. While 2 studies showed a drop in the acute infection rate with PVI compared to saline lavage, [3,4] the reduction of the infection rate was not significant in 2 other studies [19,20]. Whether the potential inactivation of iodophors plays a role in these studies is not known and should be further investigated. In contrast to iodophors, the potential advantage of chlorhexidine is that it is not inactivated by blood [21,22]. However, a recent comparison of lavage with saline, PVI, and chlorhexidine solutions in a total of 1050 patients undergoing a hip or knee arthroplasty did not discern a difference in infection rates between the 3 lavage solutions [23]. Because there is currently no evidence in favor of one or the other irrigation solution, future clinical studies should also compare different lavage protocols with antiseptics.

Apart from its bactericidal effect, chlorhexidine can be cytotoxic at higher concentrations. In vitro cell viability was not affected by concentrations lower than 0.2 g/L [8]. However, cytotoxicity was shown at concentrations higher than 0.4 g/L [8]. In contrast to these in vitro studies, it was also demonstrated that human tissue has a higher tolerance to antiseptic agents than the cell culture models [24]. The idea that cytotoxic effects result in an actual increase of wound healing problems is not supported by the findings of our study.

When interpreting the results of this study, important limitations should be considered. The results of this study were not based on an experimental study design but on observational data before and after a change in clinical practice in our large public teaching hospital. Therefore, this uncontrolled before-and-after study design represents level III evidence, and some bias likely exists. For instance, the change in the VTE prophylaxis policy during the study period, which we initially did not include in the multivariable analyses, substantially affects the outcomes. Similarly, there may be other factors that could not be adjusted for. Also, given the low incidence of PJI and, thus, the large sample size needed to detect clinically meaningful differences, we chose to combine total joint replacements of the hip and knee. While these are obviously different surgeries with different percentages of reported PJIs, the effect of CC irrigation was not expected to differ between hip and knee surgeries. Despite the large sample size, the number of infections was too small to draw valid conclusions on subgroups of hip and knee replacements. Nevertheless, multivariable analyses indicated that the independent variable “affected joint” (hip or knee) was significantly associated with wound leakage, but not with PJI in our study population. Another limitation is that the standard for discharge after a joint replacement surgery has shifted towards postoperative day 1-2 since our final inclusion. It is important to note that delayed wound healing may be more problematic in the setting of accelerated discharge. Moreover, we were not able to compare different types of antibiotic prophylaxis because all patients, including those with a penicillin allergy, received cephalosporin. Finally, other standard care processes may have changed during the 7-year period that we evaluated, and not all details were recorded in the study database. This is inherent to before-after study designs based on data collected within standard care and strengthens the need for randomized trials to support or contradict our findings.

The most important strength of this observational study is the comparison of 2 large patient cohorts of 2182 and 2271 patients. Since there were no exclusion criteria, this cohort represents a complete patient population in a large hospital and represents “common practice,” including patients from different ethnical backgrounds, socioeconomic status, and all ages. Therefore, the external validity is higher than it can ever be expected of a prospective study that requires a priori written informed consent. Because this is the first study detailing the effects of CC irrigation in such a large cohort, it provides a solid basis for future work evaluating the effectiveness of lavage with antiseptic agents.

Conclusions

This is the first large-scale before-after study suggesting that intraoperative wound irrigation with a CC solution does not affect the risk of PJIs and wound leakage. Further research is needed to understand the relation among wound leakage, lavage protocols with antiseptic agents, and PJI. Future work may aim to define an ideal concentration of an antiseptic agent that limits cytotoxic effects and to compare interventions for reducing PJI in prospective randomized studies with methodology rigor.

Conflicts of interest

The authors declare there are no conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2022.10.003.

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Supplementary Table 1
Variable definition.

Variable	Type	Specification/notes
CC irrigation	Dichotomous	1 = yes (if mentioned in surgical report), 0 = no (if not used and/or not mentioned)
Wound leakage	Dichotomous	1 = yes (if reported in patient chart), 0 = no (if not reported)
Infection	Dichotomous	1 = yes (if reported in patient chart), 0 = no (if not reported)
Age	Continuous	In years at the time of surgery
BMI	Continuous	Values below 18 and above 40 could not be verified and were recorded as missing
Affected joint	Dichotomous	1 = knee, 0 = hip
Indication for surgery	Dichotomous	1 = primary osteoarthritis (OA), 0 = all other indications, including but not limited to avascular necrosis, (pathologic) fractures, inflammatory arthritis, and secondary OA after dysplasia
ASA	Categorical	Physical status classification according to the American Society of Anesthesiologists
Diabetes mellitus	Dichotomous	1 = yes, 0 = no
Smoking status	Dichotomous	1 = current smoker (at time of surgery), 0 = not smoking (or quit prior to surgery)
Immunosuppressant drugs	Dichotomous	1 = yes (including but not limited to tumor necrosis factor binding proteins), 0 = none
Malignancy in past	Dichotomous	1 = yes, 0 = no
Antiplatelet/coagulation	Categorical	0 = none, 1 = antiplatelet therapy (eg, aspirin), 2 = anticoagulation therapy (eg, coumarins)
Use of antibiotic-loaded cement	Dichotomous	1 = yes (including hybrid), 0 = no
Full anesthesia	Dichotomous	1 = yes, 0 = no (spinal)
VTE prophylaxis	Categorical	0 = fondaparinux (Arixtra), 1 = dabigatran (Pradaxa), 2 = no or other VTE prophylaxis