Bacterial Wound Contamination Prior to Closure: Povidone-iodine versus Saline Irrigation in Pediatric Spine Fusion Surgery

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A. Scientific Aims

The overall goal is to evaluate the safety and efficacy of surgical site irrigation with povidone-iodine in children and young adults undergoing spinal deformity surgery. More specifically, we will: (1) Establish safety of use of dilute povidone-iodine irrigation, (2) Establish baseline tissue colonization prior to closure, (3) Establish bacteriology of tissue contamination prior to closure, (4) Establish population (ie idiopathic vs neuromuscular) specific differences in tissue colonization prior to closure, and (5) Establish estimates for the effect that povidone-iodine/saline have on reducing bacterial contamination.

B. Significance

Due to their profound financial, personal, and societal costs, interventions focusing on preventing post-operative spine infection are of considerable interest.[1-5] The proposed study will hopefully demonstrate that using povidone-iodine irrigation in pediatric spinal patients is safe and reduces bacterial contamination of the spinal surgical wound prior to closure. Following this pilot and assuming there is a reduction in bacterial contamination, we would conduct a multicenter randomized controlled trial (RCT) to assess whether the reduction leads to a lower postoperative spinal infection rate.

C. Background

The rate of wound infection in pediatric and adolescent spine fusion populations has been reported at 0.5-4.3%[4, 6-9] and 8-24% in populations with neuromuscular disease.[4, 10-21] A recent retrospective review of Boston Children's Hospital demonstrated at 10% infection rate in neuromuscular scoliosis over a 3 year period (unpublished data) and a recent multicenter study (unpublished data) demonstrated a 9.2% rate in neuromuscular scoliosis across 3 centers. Based on recent research, we know that there is bacterial contamination of the spinal surgical wound prior to closure. Dietz et al. obtained positive wound cultures in greater than half of patients undergoing clean, elective orthopaedic procedures with no antibiotic prophylaxis.[22] Nandyala and Schwend reported a 23% rate of positive tissue cultures from pediatric patients undergoing posterior spinal fusion, which included a rate of 37% in neuromuscular patients.[23]

Povidone-iodine has long been used topically as a solution to disinfect the skin, and has been used as an intra-operative irrigant for general, cardiothoracic and genitourinary procedures.[24] The standard protocol for irrigation prior to wound closure in spine surgery entails the use of sterile normal saline as an irrigant. Based on its theoretical ability to disinfect the surgical wound prior to closure, two RCTs comparing povidone-iodine to normal saline irrigation prior to wound closure in an adult spine population have demonstrated benefit without complications related to treatment.[25, 26] A recent systematic review on the use of povidone-iodine as a surgical irrigant in adult and pediatric patients concluded that the published studies showed compelling evidence of decreased infection with the use of povidone-iodine, although the level of evidence of these studies was sub-optimal.[27] Based on a number of in vitro and clinical studies, the best available evidence suggests that a concentration of 0.35% is both safe and effective.[27-34]

D. Methods

This will be multi-center, single-blind pilot randomized clinical trial (RCT) comparing povidone-iodine irrigant to normal saline alone.

D.1. Recruitment, Screening and Eligibility

Participating orthopaedic surgeons and the study coordinator will be responsible for case finding and subject recruitment. Patients will be screened and those found eligible will be offered participation. Informed consent will be obtained from the patient or from a parent or legal guardian for patients less than 18 years of age.

D.1.a. Inclusion criteria: Patients must meet all of the following criteria to be *eligible:* (1) Age 3 to 18 years on day of surgery, (2) diagnosis of spinal deformity, (3) undergoing elective posterior spine multi-level instrumentation surgery

D.1.b. Exclusion criteria: Patients having any of these criteria will be *ineligible:* (1) Documented renal failure, (2) documented allergy to iodine or shellfish, (3) previous spine fusion surgery, (4) undergoing elective posterior spine instrumentation surgery fusing fewer than six levels, (5) undergoing anterior or anterior-posterior spine multi-level instrumentation surgery; (6) current antibiotic use.

D.2. Randomization and Blinding

Patients will be randomized to saline or povidone-iodine & saline irrigation via an envelope system. Patients will be blinded to the type of irrigant used. Ideally, surgeons would also be blinded to treatment group; however, it is not possible because they will be irrigating the surgical wound in the operating room and the two solutions will be identifiable because they are a different color.

D.3. Description of Study Treatments

D.3.a. Standardization of Periprocedure interventions

All patients will receive cefazolin (25 to 50 mg/kg, dependent on standard of care) IV within one hour prior to skin incision. Patients will also receive IV gentamycin or tobramycin (2.5 mg/kg) every 8 hours if they have a neuromuscular diagnosis. Appropriate every 3 or 4 hour (according to standard of care) dosing will be continued intraoperatively and for 24 hours post-operatively. If a patient allergy to cefazolin exists, clindamycin dosed every 6 hours or vancomycin dosed every 12 hours may be substituted. Skin will be prepped with chlorhexidine.[24] Surgical approaches, fusion levels, deformity correction techniques, and hardware selection will be at the discretion of the surgeon.

D.3.b. Standardization of Culture/Irrigation Procedure

Prior to closure, a swab or tissue of the surgical wound will be performed (aerobic cultures) to establish the baseline incidence of bacterial contamination. This will be performed by excising the tissue or swabbing the wound under the retractor at the inferior aspect of the wound, using the routine surgical pathology protocol of the institution. Following, any nonviable tissues will be debrided and the irrigant solution (0.35% povidone-iodine or sterile saline) of sufficient volume to fill the wound will be in contact with all areas of the wound for three minutes. A second sample (aerobic cultures) will be collected immediately after lavage with saline or povidone-iodine from the same location to determine reduction in the incidence of bacterial contamination achieved by

each irrigant. This sample will be obtained prior to placement of bone graft/antibiotics to obtain samples as close to closure as possible without allowing the application of local antibiotics to influence the results. A further 2 liters of normal saline will then be used for the povidone-iodine treatment group to irrigate the wound further which will remove traces of the iodine irrigant from the surgical site. If deemed appropriate by surgeon, a patient in the saline treatment group will then be irrigated with povidone-iodine and saline as per standard of care. Use of pulse or low pressure lavage will be up to the discretion of the surgeon.

D.4. Definition of Endpoints

(1)Proportion of patients with an initial positive bacterial culture prior to irrigation (2) Bacteriology of tissue in cases of positive cultures, and (4) Proportion of patients with a positive bacterial culture after irrigation

D.5. Data Collection Methods, Assessments and Schedule

Data will be collected on standardized paper case report forms (CRF) by the study coordinator and entered into a study-specific REDCap database. Study data will be collected at the pre-operative consultation, and during surgery (see Table 1.) Wound cultures will be tested specifically for research to evaluate the efficacy, respectively, of *povidone-iodine*.

Table 1. Schedule of Measurements

Measurement	Baseline (Pre-Operative)	Surgery
Demographics	X	
Medications	X	
Medical history	X	
Laboratory results	X	X
Surgical site cultures (2)		X
Surgery/OR data		X

Demographics, medications, medical history, and laboratory results will be collected from medical records. Surgical data will be collected during the fusion operation and two standard cultures of the surgical site will be taken during the surgery using the routine surgical pathology protocol at each institution. Results from the cultures taken at the fusion operation, in addition to any other associated post-operative cultures, will also be collected post-operatively from medical records.

D.6. Adverse Events and Reporting Procedures

The only foreseeable, but highly unlikely adverse event associated with participation in this trial is an increased level of iodine in the blood as a result of washing the wound site with povidone-iodine. Extra iodine in the body is excreted through urine. A healthy body without thyroid or renal abnormalities is able to excrete excess iodine without any problems.

The monitoring of adverse events will be conducted on an ongoing basis for the duration of the study. If an adverse event occurs, it will be reported immediately to the IRB and the investigators will re-assess the risk/benefit ratio of the study and submit any modifications deemed necessary to the IRB for approval.

D.7. Statistical Considerations

We project an accrual of 150 patients, resulting in 75 per treatment group. Patients will be recruited from “low risk” and “high risk” patient populations in a 3:1 fashion, respectively. “Low risk” patients are defined as those with an idiopathic condition and the “high risk” group will encompass all others. Within each patient “risk” group, randomization will be split evenly between saline and betadine in a 1:1 fashion. Positive cultures before and after irrigation will be monitored to establish the efficacy of povidone-iodine irrigation. 150 patients will provide good statistical precision for estimating the probability of a positive pre-irrigation culture, as shown in the following table. The table shows exact 95% confidence intervals (CI) for the estimated percentage over a plausible range of observed outcomes.

Observed percentage:	30/150=20%	37/150=24.7%	45/150=30%
95% CI:	(14%, 27%)	(18%, 32%)	(23%, 38%)

It will be of interest to examine how the tissue colonization rate varies across subgroups such as neuromuscular and idiopathic patients, which we anticipate to accrue in approximately a 3:7 ratio. Under this assumption, and assuming an overall pre-irrigation colonization rate of 25% and a two-sided α=.05 test there will be 69%, 90% and 98% power, respectively, to detect relative risks (RR) of 2.0, 2.5, and 3.0, respectively.

Finally, we expect that the probability of a positive post-irrigation culture in the control group with will be about .12, with a further reduction to perhaps .05 in the povidone-iodine group. These results would correspond to a relative risk (RR) of .417. Because positive post-irrigation cultures are projected to be fairly rare events, the size of this pilot study will not provide high statistical power unless the true treatment effect is quite large. However, the study should provide useful preliminary information about the size of the treatment effect. For example, the following table shows the probability that the estimated positive culture rate in the povidone-iodine group that will be at least 4, 5.33, 6.67 or 8 percentage points lower than in the control group, assuming the true control rate is .12 and the true rate in the povidone-iodine group is .05, .04 or .03 (corresponding to RR’s of .417, .33 and

.25, respectively. Calculations are based on exact binomial probabilities. Also shown is the power of the study under each set of assumptions, assuming a two-sided α=.05 chi-square test.

Number of fewer pos. cultures (of 75) in treatment group.	Observed percentage point reduction	True rates .12 vs .05 RR .417	True rates .12 vs .04 RR .33	True rates .12 vs .03 RR .25
≥3	≥4% reduction	**79%**	86%	91%
≥4	≥5.33% reduction	70%	78%	85%
≥5	≥6.67% reduction	58%	67%	76%
≥6	≥8% reduction	47%	54%	65%
	Power:	33%	43%	55%

For example (see bolded entry), if the true rates of post-irrigation positive cultures are .12 and .05 in the control and povidone-iodine groups, respectively, corresponding to RR=.417, there is a 79% chance that the observed rates will differ by 4 percentage points or more (i.e., 3 or fewer positive cultures out of 75 in the treatment group compared with the number of positive cultures out of 75 in the control group). However, there is only a 33% chance of finding a statistically significant difference (power=33%).

E. Data Management Methods

Every center participating in the trial has a research coordinator on staff that will be responsible for screening and consenting patients, collecting and entering data, and sharing data with the data coordinating center (see paragraph below). Each institution will be given an identifying number, which will be the beginning of each patient's study identification number. Therefore, the patient study identification numbers will be linked to the patients' institution and MRN. Only members of the study group at each institution will have access to the links, which will be destroyed once all of the data is collected.

Access to the REDCap™ database will be set during the creation of the project assigning a password to only members specified in the IRB protocol. As this is a multi-center study, sites will only have access to their own site level data. Boston Children's Hospital, as the coordinating center, will have access to all data. As other investigators or centers join the study, access will be granted only with appropriate IRB approval and they will only have access to their own data.

At the local level, all hard copies of forms that the surgeons or research staff fill out with identifying information on it will be stored in a locked research cabinet in the department and entered into databases only accessible by members of the research staff. A subject's identity on these records will be indicated by a study ID number (a unique identification number created using an algorithm the study administrators will define) rather than by name, and the information linking these study ID numbers with the subjects identity will be separate from the research records and research databases. Only the researchers listed in this protocol will have access to a subject's research records, with the exception of the informed consent form, a copy of which will be kept in the medical record of each subject as this study involves a treatment based protocol. Any information about subjects from this research will be kept confidential as possible.

F. Quality Control Method

The principal investigator will conduct an evaluation of the progress of the research study on a quarterly basis including assessments of data quality and timeliness; participant recruitment, accrual, and retention; and a review of outcome and complication data to determine whether there is any change to the anticipated benefit-to-risk ratio of study participation and whether the study should continue as originally designed, should be changed, or should be terminated. A summary of these reports will be submitted to sites IRBs and to BCH as part of the annual renewal.

G. Data Safety Monitoring Plan

To ensure safety, an independent safety monitor will be appointed to assist with interim data review. The monitor and the study statistician will be completely unblinded to treatment-group-specific results. There will be one scheduled interim analysis, conducted when data from approximately 1/3 and 2/3 of the accrual goal become available. Interim analysis will focus on the comparison of the treatment groups with respect to the primary endpoint, positive culture rate before and after irrigation, using two-sample t-tests. A "stopping rule" using a truncated O'Brien-Fleming procedure will be used to guide the need for further discussion of the possibility of early stopping among a wider group, including the study investigators. (This rule will not be interpreted strictly but rather will be used as a guideline to trigger the need for a wider discussion.) Specifically, the rule is that the stopping boundary is met if the nominal p-value is $p<.001$ at the first look or $p<.0141$ at the 2nd look. The actual O'Brien-Fleming rule would use a nominal p-value boundary of $p<.00052$ at the first look but this is extremely conservative (i.e., it would take an extreme treatment effect to meet this criterion) so the boundary had been truncated to $p<.001$. Along with a criterion of $p<.0451$ at the final analysis, this algorithm ensures an overall type I error of $\alpha=.05$. The stopping rule has a minimal effect on statistical power, less than one percentage point.

In addition to the scheduled interim analysis, the safety monitor will review cases of positive culture results and adverse events. The safety monitor will also review any cases where a patient may require additional testing to follow up on a thyroid or

renal abnormality that develops and advise on whether a wider discussion of early stopping should take place. Such cases will also be reported to the IRB.

H. Project Timeline
We estimate the total time required to complete this study, including recruitment, follow-up and analysis, will be approximately two years.

H. Study Organization
Data collection will be managed by the study coordinator at each site, and overseen by the lead site at Boston Children's Hospital. The Clinical Effectiveness Research Center in the Orthopaedic Surgery department at Boston Children's Hospital will be used as a central location for data management, using REDCap (Research Electronic Data Capture) as the primary receptacle of our data management. REDCap is a software toolset and workflow methodology for electronic collection and management of research and clinical trial data. The REDCap system provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus).

REDCap servers are housed in a local data center at Boston Children's Hospital and all web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org).

In addition, data collected will be recorded in such a manner (coded) that subjects will not be identified. The key code and all study documents with coded data (such as case report forms) will be stored in a locked cabinet file and/or password-protected computer file in an access controlled office only accessible to research personnel. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

H. References

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