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

Michael Glotzbecker MD, Brian Snyder MD PhD, Leslie A. Kalish, ScD

Principal Investigator:
Michael P. Glotzbecker, MD
Assistant Professor, Harvard Medical School
Department of Orthopaedic Surgery
Children's Hospital Boston
300 Longwood Avenue
Boston, MA 02115
Michael.Glotzbecker@childrens.harvard.edu
Office: (617) 355-6617
Fax: (617) 730-0465

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of Boston Children's Hospital demonstrated at 10% infection rate in neuromuscular scoliosis over a 3 year period (unpublished data) and a recent multicenter study (unpublished data) demonstrated a 9.2% rate in neuromuscular scoliosis across 3 centers.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 single-center, single-blind pilot 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 instrumentation surgery

D.1.b. Exclusion criteria: Patients having any of these criteria will be *ineligible:* (1) Documented renal failure, (2) abnormal TSH, (3) documented allergy to iodine or shellfish, (4) previous spine fusion surgery

D.2. Randomization and Blinding

Patients will be randomized to saline or povidone-iodine irrigation via an envelope system. Patients, study coordinators and post-operative healthcare providers, other than the surgeon, 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 (25mg/kg) IV within one hour prior to skin incision. Patients will also receive IV gentamycin or tobramycin (2.5mg/kg) every 8 hours if they have a neuromuscular diagnosis. Appropriate every 4 hour 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 of the surgical wound will be performed prior to irrigation (aerobic and anaerobic cultures) to establish the baseline incidence of bacterial contamination. This will be performed by swabbing the wound under the retractor at the inferior aspect of the wound. 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 further 2 liters of normal saline will then be used for both treatment groups to irrigate the wound further which will remove traces of the iodine irrigant from the surgical site. A second sample (aerobic and anaerobic 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 culture will be obtained after decortication but prior to placement of bone graft/antibiotics to obtain culture as

close to closure as possible without allowing the application of local antibiotics to influence the results. Use of pulse or low pressure lavage will be up to the discretion of the surgeon.

D.4. Definition of Endpoints

-(1)Thyroid stimulating hormone (TSH) levels preoperatively and post-operative day 3, (2)proportion of patients with an initial positive bacterial culture prior to irrigation (3) 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, during surgery and on post-operative day (POD) 3 (see Table 1.) Renal function testing is part of standard care but TSH and wound cultures will be tested specifically for research to evaluate the safety and efficacy, respectively, of *povidone-iodine*.

Table 1. Schedule of Measurements

Measurement	Baseline	Follow-up	
	Pre-op	Surgery	Post-op Day 3
Demographics	X		
Medical history	X		
Safety labs (renal function)	X		
Safety labs (TSH)	X		X
Surgical site culture		Pre & post irrigation	
Operative time		X	
Surgery/OR data		X	

Demographic and medical history data will be collected including diagnosis, height, weight, race, gender, diagnosis, and current medication usage and health status. Safety blood labs will be run to ensure that the patient has normal thyroid and renal function. Data will be collected during the fusion operation (duration of surgery, blood loss, complications, etc.) and a standard culture swab of the surgical site will be taken before and after irrigation of the wound.

D.6. Adverse Events

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. In the highly unlikely event that a thyroid or renal abnormality developed that was not screened at the pre-operative appointment, and a patient's TSH levels rose post-operatively, further bloodwork would be done including: free T4, TPO and thyroglobulin antibodies, as well as urinanalysis of iodine and creatinine. This would allow for the underlying cause of the thyroid disease to be determined and appropriately treated.

D.7. Statistical Considerations

We project an accrual of 100 patients, resulting in 50 per treatment group. TSH will be monitored to establish safety of povidone-iodine irrigation. Within each patient we will calculate the pre- to post-operative (Day 3) change in TSH levels and compare the change-scores between groups to test whether povidone-iodine has an impact on thyroid function. Data from Kovacikova et al[34] suggest that the distribution of TSH across patients is lognormal with a coefficient of variation of about 1.0. The following power calculation is based on analysis of the log-transformed data assuming a within-person correlation of .5, which is likely a conservative assumption. A sample size of 50 per group will provide power of 80%, 94% and 99%, respectively, to detect a 1.6, 1.8 or 2.0-fold difference between groups. While it may seem like there should be high power for detecting even smaller differences, the upper and lower limits of the normal range of TSH differ by approximately 10-fold so these are actually small effects. 100 patients will provide good statistical precision for estimating the probability of a positive pre-irrigation culture, (see table). The table shows exact 95% confidence intervals (CI) for the estimated percentage over a plausible range of observed outcomes.

Observed percentage:	15/100=15%	25/100=25%	35/100=35%
95% CI:	(9%, 24%)	(17%, 35%)	(26%, 45%)

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 77%, 90% and 98% power, respectively, to detect relative risks (RR) of 2.5, 3.0 and 4.0, respectively.

Finally, we expect that the percentage of the control group with positive post-irrigation cultures will be about 10%, with a further reduction to perhaps 1% to 4% in the povidone-iodine group. These results would correspond to relative risks (RR) of .10 to .40. Because positive post-operative cultures are projected to be fairly rare events, the size of this pilot study will not provide high statistical power for detecting even these large treatment effects. 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, 6 or 8 percentage points lower than in the control group, assuming the true control rate is .10 and the true RR is .10, .25 or .40. Calculations are based on exact binomial probabilities.

Observed percentage point reduction	True rates .10 vs .04	RR .40	True rates .10 vs .025	RR .25	True rates .10 vs .01	RR .10
≥4% reduction	72%		**83%**		92%	
≥6% reduction	57%		69%		82%	
≥8% reduction	41%		53%		66%	

For example (see bolded entry), if the true rates of post-irrigation positive cultures are .10 and .025 in the control and povidone-iodine groups, respectively, there is an 83% chance that the observed rates will differ by 4 percentage points or more. There is a similar probability of observing a reduction of 6 points or more if the RR is .10

E. 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 two scheduled interim analyses, 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, change in TSH level from pre-operative to post-operative day 3, using a two-sample t-test. 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 these scheduled interim analyses, if any patient requires additional testing to follow up on a thyroid or renal abnormality that develops, the safety monitor will review the case and advise on whether a wider discussion of early stopping should take place. Such cases will also be reported to the IRB.

F. Project Timeline

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

F. References

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