Does VeraFlo with Prontosan® decrease time to wound and fracture healing in patients with infected lower extremity fractures with indwelling hardware?

Principal Investigator: Brett D. Crist, MD

Sponsor:
University of Missouri
Orthopaedic Surgery
1 Hospital Drive, Columbia, MO 65212
cristb@health.missouri.edu
(573)882-6562

Funding Company: KCI USA, Inc.

Hypothesis: Prontosan instillations will decrease time to wound and fracture healing and decreases bacterial load.

Null Hypothesis: Prontosan instillations do not decrease time to wound and fracture healing and decrease bacterial load.

Background: Surgical site infections (SSIs) are a devastating and relatively common surgical complication, occurring in 2% to 5% of patients undergoing surgery in the United States. SSIs can significantly increase patient morbidity, hospital stay duration, healthcare costs, and patient mortality (Anderson 2011).
Negative Pressure Wound Therapy (NPWT) with Vacuum-Assisted Closure (VAC) is an established adjunctive treatment option for open wounds that offers the ability to promote healing. However, there is limited evidence for its utility with active infections. Wounds that are acutely infected or that contain an adherent biofilm present a challenging problem (Kim et al 2015).

Wound VAC therapy involves cleaning the wound, applying a custom-fit foam to cover the wound, placing a transparent drape over the wound and adjacent skin, and attaching tubing to connect the foam to a VAC suction canister. NPWT is achieved with a pulling force supplied by the VAC suction canister. Typically, suction will remain at a constant pressure until the dressing is removed. Continuous VAC therapy was recently reported to be more effective than standard moist wound care in surgical site infection after ankle surgery (Zhou et al. 2015). VAC therapy with instillations is a novel treatment option that provides the combination of negative pressure with intermittent instillation of a solution. Polihexanide (Prontosan®) is a modern antiseptic that combines a broad antimicrobial spectrum with low toxicity, high tissue compatibility, no reported adsorption and good applicability as solution, gel, ointment, foam and in wound

dressing. Unlike other antiseptics, the antimicrobial efficacy of Prontosan® is not impaired in human wound fluid, human tissue or by high loads of blood or albumin. Furthermore, Prontosan® blocks the microbial attachment to surfaces and has been shown to effectively remove biofilms in vitro and in vivo (Hubner *et al* 2010).

Study Recruitment: 20 subjects, not including screen failures. The small sample size will serve as a pilot study to determine an adequately powered study after completion.

Study Design: The objective of this study is to determine if Prontosan instillations (in conjunction with NPWT treatment) decrease time to wound and fracture healing and decrease bacterial load compared to NPWT treatment without Prontosan.

With IRB approval, up to 30 patients will consent and enroll, with a goal of 20 completed subjects. Patients with infected lower extremity wounds, status-post ORIF, undergoing standard of care operative debridement will be enrolled and randomized to either the VeraFlo with Prontosan group or standard negative pressure group. There will be 10 patients in each group. The standard negative pressure group will receive the V.A.C Ulta Negative Pressure Wound Therapy System. NPWT device settings for both arms will be 125mmHg. The following setting will be used for the VeraFlo group: Prontosan, 20min dwell time 2 hour cycle. The amount of Prontosan to be infused is based on the size of the wound and will vary between subjects.

Subject weight, BMI, comorbidities, and smoking status will be collected from the medical record and/or the subject, and will be used for research purposes.

All NPWT dressings will be applied sterilely in the OR after debridement and irrigation per standard of care practice. Only the standard negative pressure device or Veraflo dressing may be used on enrolled participants (based on randomization designation), without any silver dressing, Adaptec or Xeroflo. Dressings will be changed every 72 to 96 hours (based on patient progress and clinical presentation) in the OR for a minimum of 1 more debridement (indicating at least one debridement and NPWT application).

Bacterial load (organism quantities are listed as scant, moderate, or heavy), identification of organism, and susceptibility will be analyzed and reported by the University of Missouri Hospital Laboratory, via semiquantitative wound culture(s) done at each debridement procedure. A maximum of 3 would cultures will be used for the purposes of research, and the sponsor will cover the cost of up to 3 wound cultures. The culture will be done in the OR, after negative pressure dressing removal, prior to surgical prepping.

The subject will sign consent, be enrolled, and then be randomized at the pre-operative/screening visit. During the initial surgical debridement procedure, information about the wound characteristics, the wound culture results, and information about the dressing that is placed in the OR will be collected for research purposes.

Wound healing will be evaluated at weekly intervals until the sutures are removed and the wound is deemed healed. To assess wound healing, weekly photos of the wound/incision will be done either in clinic, or will be obtained from the subject after they take the photo at home. When applicable, weekly phone visits will be completed to obtain a photo of the incision, (starting after discharge from the hospital), until the subject returns for their SOC clinic visit for suture removal (around 3 weeks post-op). The wound/incision will be assessed with a VAS Incision Healing Assessment Form.

Clinical follow-up visits will be standard after wound healing with clinical radiographs to document fracture healing--6 weeks after initial surgery (+/- 1 week), 3 months (+/-1 week), 6 months (+/-2 weeks), and 12 months (+/-2 weeks) or until fracture healing with minimum of 6 months f/u. Any further debridement or procedures done for fracture healing, including bone stimulator use, will be documented. A clinical photo(s) will be taken at all visits following the initial surgical debridement to document wound healing.

Primary Endpoints:

1. Time to wound and fracture healing (indicating successful resolution of infection)
2. Bacterial load (organism quantities are listed as scant, moderate, or heavy)

Secondary Endpoints:

Number of surgeries:

1. # of operative debridements until wound healed
2. # of surgeries for fracture healing (nonunion and bone grafting)
3. VAS (Incision Healing Assessment Form) scores, based on standardized digital image

Inclusion/Exclusion Criteria

Inclusion:

- Patients 18 years and older

- Patients who will be undergoing surgical management (including the use of NPWT therapy) of an infected lower extremity status-post open reduction and internal fixation (ORIF)

Exclusion:

- Pregnant females
- Incarcerated patients and those not able to give informed consent

Withdrawal of Subjects: Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator(s) may elect at any time to withdraw a subject from the study for any reason unrelated to the study if such a decision is in the subject's best medical interest. If a subject discontinues the study prematurely, or is withdrawn by the Investigator(s), as much follow-up data as possible will be obtained. The primary reason for termination or discontinuation will be documented in the report of the final results.

Safety:

Adverse Events:

If an AE/SAE occurs, the details will be collected on an AE/SAE form.

An adverse effect (AE) is any undesirable experience (e.g., sign, symptom, illness, clinically significant abnormal laboratory value, or other medical event) occurring in a subject during the course of the study, whether or not it is related to the investigational device or procedure.

An AE <u>does</u> include a/an:

- Exacerbation of a pre-existing illness
- Increase in frequency or intensity of a pre-existing episodic event or condition
- Condition detected or diagnosed after study device use even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study

An AE <u>does not</u> include a/an:

- Medical or surgical procedure (e.g., surgery, endoscopy, transfusion); the condition that leads to the procedure is considered an AE

- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions)
- The disease or disorder being studied, or sign or symptom associated with the disease or disorder, unless the disease, sign or symptom is more severe than expected based on the subject's condition and/or requires intervention.

Serious Adverse Events:
A Serious adverse event is an adverse event that:

- Led to death,
- Led to serious deterioration in the health of a subject that
  - resulted in a life-threatening illness or injury,
  - resulted in permanent impairment of a body structure or body function,
  - required inpatient hospitalization or prolongation of existing hospitalization, or
  - resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
- Led to fetal distress, fetal death or a congenital anomaly or birth defect.

The following clarifications are provided for the serious adverse events:

- Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. The definition does not include an event that, had it occurred in a more severe form, might have caused death.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered a serious adverse event.
- "Inpatient" hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a causality or emergency room.
- Important medical events that may not result in death, or be life-threatening, however based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Is significant for any other reason.

Anticipated Adverse Events:
Anticipated adverse events are those events that are reasonably expected to occur as a result of the subject's disease state or treatment. For this study, anticipated

adverse events associated with the procedure or post-procedure include, but are not limited to, the following;

- Infections, both deep and superficial
- Allergies or other reaction to device materials
- Temporary or permanent nerve damage as a result of pressure or hematoma.
- Cardiovascular complications including venous thrombosis, pulmonary embolism, and cardiac arrest.
- Wound hematoma and delayed wound healing.

Device-related adverse events are those events that can be directly attributed to the study device and are adjudicated as such by the Investigator. These events may include, but are not limited to:

- Infections, both deep and superficial
- Allergies or other reaction to device materials
- Loosening of the implant as a result of changed condition in load transfer, respectively fatigue wear or tissue reaction to implant or as result of inadequate anchoring technique.
- Dislocation, subluxation or inadequate scope of movement as a result of failure to achieve optimum positioning of the implant.
- Bone fractures as a result of one-sided overload or weakened bone structure.
- Temporary or permanent nerve damage as a result of pressure or hematoma.
- Wound hematoma and delayed wound healing.

Unanticipated Adverse Events:
An Unexpected Adverse Experience (UAE) is defined as any adverse reaction, the nature and severity of which is not consistent with the applicable product information. These events will be documented as described below.

An Unexpected Adverse Device Effect (UADE) is defined as any adverse effect on the study subject's health or safety, or any life-threatening problem or death caused by or associated with the device. Also, the effect must not have been previously identified in the Investigational Plan or Instructions for Use in its nature, frequency or severity. UADEs may also include other serious problems associated with the device that affect the rights or welfare of study subjects.

Adverse Event Documentation:
The Principal Investigator or designee will report adverse events for the study analysis. Adverse events will be evaluated and differentiated by:

- Severity of the event, defined below.

- Mild: Awareness of signs and symptoms, but easily tolerated; are of minor irritant type, causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.
- Moderate: Discomfort severe enough to cause interference with usual activities; requiring treatment, but not extended hospitalization or intensive care for the subject.
- Severe: Incapacitating with inability to do work or usual activities; signs and symptoms may be systemic in nature or require medical evaluation and/or treatment; requiring additional hospitalization or intensive care (prolonged hospitalization).

    - Serious Code, as defined in Section "Serious Adverse Events"

    - Relatedness to the device or procedure, defined as:

- Unrelated: AE is due to the underlying disease state or concomitant medication or therapy not related to the study-specific devices or procedures.
- Probably not Related: AE had minimum or no temporal relationship to the study-specific devices or procedures and/or more likely alternative etiology exists.
- Possibly Related: AE had a strong temporal relationship to the study-specific devices or procedures and alternative etiology is equally or less likely compared to the potential relationship to the study-specific devices or procedures.
- Probably Related: AE had a strong temporal relationship to the study-specific devices or procedures and another etiology is unlikely.
- Unknown: Relationship of the AE to the study-specific devices or procedures and alternative etiology is unknown.

Any severe adverse event or device related unanticipated advent must be reported to the study Sponsor by telephone or fax within 24 hours of the event. Additionally, the full details of the event will be documented in the study data base and with a follow up fax if the details of the event cannot be enter into the database promptly. Arthrex Inc. will submit the applicable reports required by each reviewing regulatory authority when appropriate**.**

Unanticipated Adverse Device Effect (UADEs):

A UADE is any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3).

Expectedness
All Serious Adverse Events will be assessed for expectedness based on the following definitions:

- Expected, Anticipated: the effect, problem, or death had been previously identified in nature, severity, or degree of incidence in the study or product documentation.
- Unexpected, Unanticipated: if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the study or product documentation

UADE Reporting to KCI, USA Inc.
UADEs and SAEs must be reported by the Investigator to KCI and the reviewing Institutional Review Board (IRB) per their reporting requirements.

Risks Associated With NPWT Therapy/Dressing

Risks	Disorders/Conditions
Skin and Subcutaneous Tissue Reaction/Allergy	• Desiccation/injury • Skin rash, irritation, blistering • Pruritus/itching • Skin excoriation/breakdown • Skin stripping • Skin scarring if significant skin irritation were to occur • Maceration • Skin hyper/hypo-pigmentation at and/or around dressing application area • Erythema/redness, edema, inflammation, or swelling at and/or around dressing application area
Mild Pain or Discomfort	• Tenderness/minor ache at and/or around dressing application area • Perspiration associated with wearing dressing • Auditory irritation (due to mild buzzing sound of negative pressure unit) • Decreased sleep or sleep quality • Paresthesia (numbness, tingling, prickling, creeping sensation)

Other	• Bleeding • Cardiac compromise (vagal response, bradycardia) • Pulmonary compromise • Accidental instillation in a body cavity • Localized infection • Autonomic dysreflexia (in subjects with spinal cord injury) • Retained foreign debris (e.g.foam) in the wound • Impairment of mobility/activity (limitation secondary to weight and attachment of therapy unit) • Possible tubing entanglement/trip or slip hazard leading to fracture, tissue damage • Incorrect therapy unit settings resulting in incorrect frequency/dosing • Tunneling • Stalled healing/non-progression of healing • Deterioration of the wound • Systemic reaction (due to allergic reaction to dressing materials) • Burn secondary to therapy unit or power cord malfunction

Prontosan:
In very rare cases there may be a mild burning sensation after Prontosan is applied. This should subside after a few minutes. In Rare cases (less than 1 out of 10,000), anaphylactic shock has been reported after the use of Prontosan. Protosan can also cause allergic reactions such as itching and rashes.

Quality Assurance of Data Collection:
Patient confidentiality is maintained by adherence to the rules of HIPAA and the University of Missouri IRB. Close assessment of perioperative events and complications will be performed to ensure no significant deleterious effects are resulting from research activity.

Statistical analysis plan:
Treatment groups will be compared for statistically significant ($p<0.05$) differences in bacterial load (category of amount of growth) using a rank sum test and proportion of wounds healed at each time point and proportion of fractures healed at each time point using Fisher's Exact Tests.

References:

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2. Kim PJ, Attinger CE, Steinberg JS, Evans KK. Negative Pressure Wound Therapy with Instillation: Past, Present and Future. Surg Technol Int. 2015 Jun; 26:51-56. PMID: 26054991
3. Zhou ZY, Liua YK, Chenb HL, Liua F. Wound management with vacuum assisted closure in surgical site infection after ankle surgery, Int J Surg. 2015 May; 17:15-18. PMID: 25791994
4. Hubner NO, Kramer A. Review on the Efficacy, Safety and Clinical Applications of Polihexanide, a Modern Wound Antiseptic. Skin Pharmacol Physiol. 2010; 23(suppl)17-27. PMID: 20829658