

Study Protocol Title: Prospective randomized trial of Dermabond Prineo Wound closure system on operating room time and wound closure time in Total Knee Arthroplasty

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Regulatory Sponsor:

This study is an Investigator Initiated research trial. Each study site will be considered its own regulatory sponsor and is responsible for internal data monitoring and any study reporting required by ClinicalTrials.gov.

Introduction

Total knee arthroplasty is an effective orthopaedic procedure to improve function, correct gait, and alleviate symptoms of late-stage arthritis in patients who have failed non-operative management. With constant introduction of various techniques for wound closure, assessment of closure times and outcomes will be a topic of marked importance.

Background and Significance

The DERMABOND PRINEO (Ethicon, Johnson and Johnson, Somerville, New Jersey) system is a unique two-part skin closure system that consists of: a 2-octyl cyanoacrylate topical skin adhesive for proven strength and microbial protection in vitro, and a flexible, self-adhesive polyester mesh for excellent approximation and healing. It is aimed to add strength and protection when closing medium to long incisions. In addition, it is designed to replace the use of subcuticular sutures or staples, with greater holding strength, with the potential to reduce skin closure time.

Various studies have evaluated the outcomes of different closure devices, however, there are no reports assessing the length of closure times using DERMABOND PRINEO (Ethicon, Johnson and Johnson, Somerville, New Jersey) Knotless Tissue Control Devices during superficial closure in orthopaedic surgery. Huemer et al.(1) performed an observational study of 180 patients who had 224 excisional body-contouring surgeries utilizing Dermabond Prineo for superficial closure. Authors concluded that this closure type enables the surgeon to perform a quick and smooth skin closure. However, 4 patients (1.8%) developed local allergic reactions, which necessitated early removal and topical corticosteroid treatment. Parvizi et al.(2) performed an open, prospective, randomized clinical study of superficial wound closure on 60 patients undergoing abdominoplasty with either Dermabond Prineo or conventional superficial closure. They found significantly lower price (\$134.79 cheaper) and significantly better Hollander Cosmesis Scale scores in Dermabond Prineo cohort. In addition, there was a significantly better cosmetic outcome at 6 and 12 months after surgery. The use of Dermabond Prineo may be able to decrease operative time and costs in other surgical fields, such as orthopedics. Careful patient allergy history is necessary to avoid adhesive allergic reactions.

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Study Design:

In this prospective pilot study examining the superficial closure during total knee arthroplasty, active subjects will receive the STRATAFIX Spiral Knotless Tissue Control Device for subcuticular closure in addition to DERMABOND PRINEO (Ethicon, Johnson and Johnson, Somerville, New Jersey) system for dermal closure. The control subjects will receive staples (standard-of-care).

The purpose of this study is to compare end points (see below):

- **The primary endpoint of the study** will be cosmesis observation using the modified Hollander scale (Table1).
- **Secondary endpoints** will examine: wound closure time, patient satisfaction with wound appearance, wound related complications, cost comparison including time and materials

As a pilot study, hypothesis testing will not be performed.

Post-operatively, patients will be assessed at clinic visits at 6 weeks and 3 months. At these time points, we will assess (**Table 2**):

- Incidence of any wound complications
- Wound appearance using the Hollander cosmesis questionnaire (**Table 1**)
- Patient satisfaction with wound appearance using visual analogue scale (VAS)

Table 1. Hollander cosmesis questionnaire	
Stepoff borders	0 for yes, 1 for no
Contour irregularity – puckering	0 for yes, 1 for no
Scar width – greater than 2mm	0 for yes, 1 for no
Edge inversion – sinking, curling	0 for yes, 1 for no
Inflammation – redness, discharge	0 for yes, 1 for no
Overall cosmesis	0 = poor, 1 = acceptable

Table 2: Research Procedures				
REQUIRED STUDIES	Pre-Op	Intra-operative	6 weeks post-op	3 months post-op
Informed Consent	x			
Length of surgery		x		
Length of closure time		x		
Amount of suture material used		x		
Surgeon experience level		x		
Incidence of wound complications			x	x
Hollander cosmesis questionnaire			x	x
Patient satisfaction with wound appearance (VAS)			x	x

Methods

- A prospective randomized pilot study

Sample

- 60 subjects for a pilot study

Inclusion Criteria:

1. Males and females, between the ages of 18 to 80 years at the time of signing the informed consent document.
2. Understand and voluntarily sign an informed consent document prior to any study-related assessments/procedures are conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Able to fluently speak and understand the local language
5. If female, is nonpregnant (negative pregnancy test results at the baseline/randomization visit) and nonlactating.
6. End-stage osteoarthritis patients planning to undergo primary total knee arthroplasty
7. BMI less than 40 kg/m²

Exclusion Criteria:

1. BMI greater than or equal to 40 kg/m²
2. History of known bleeding disorder

3. History of medical co-morbidity that may result in poor wound healing (ie. diabetes mellitus, peripheral vascular disease)
4. Patients <18 or >80 years of age
5. Patients who are prisoners
6. Mentally unable to sign informed consent
7. Has an uncontrolled illness that, in the opinion of the investigator, is likely to cause the patient to be withdrawn from the trial or would otherwise interfere with interpreting the results of the study.

Screening and Recruitment: Informed Consent

Informed consent will be obtained by one of the study coordinators/co-investigators during a clinical visit prior to procedure in the privacy of an examination room or an office. Patients will be informed about the study and inquired about their interest to participate. A consent document will be given and key parts of the research study will be explained in lay-terms to the patient to ensure full understanding. Any questions regarding the research study will be answered at that time. It will be emphasized that participation is voluntary. Those patients who are willing to participate will be asked to sign the consent document along with the consenting researcher. A signed copy of the consent document will be handed to the patient while another copy is kept in their study file.

In the event that an approach prior to the day of surgery is not feasible, same day of procedure consenting will be attempted. Patients will be contacted by telephone (see phone script), and those interested in participating in the study will be informed about what is involved, the follow-up visit, and that participation in the study is strictly voluntary, and will not affect the scheduling of their upcoming surgery. If the patient is interested in participating, the patient can be either mailed or emailed a copy of the informed consent form, and then arrangements will be made to complete the informed consent process prior to the patient being taken back into the preoperative area on the day of surgery. The patient will be asked to come to the hospital on the day of surgery earlier than the time they were told to arrive by surgical scheduling in order to make sure there will be adequate time to discuss the study, including what is involved, risks, benefits, and alternatives. We do not believe that an eventual approach on the same day of procedure would represent an added stress for the patient or delay the start of the procedure. Similar to obtaining informed consent prior to the day of procedure, the process will occur in a

private setting with ample time to discuss the study's implications, risks, benefits, and alternatives. No procedures or tests will be conducted on the screening visit after consenting the patient.

Randomization procedures:

Patients will be randomized to either arm of the study as follows: sealed envelopes in a random order will be used to place study participants in either the active arm or in the control arm of the study. Patients will be randomized in a one to one ratio. At the commencement of each arthroplasty, a random envelope will be drawn which dictated the type of suture to be used, thus blinding the patients to the type of suture they received.

Research Procedure:

A medial parapatellar approach will be performed. All closures will be performed in 3 layers, with the knee in approximately 90° of flexion to minimize potential imbrication of the capsule. For the traditional closure (control group), the arthrotomy (deep layer) is repaired using number 1 Vicryl followed by closure of the intermediate layer with a 2-0 Vicryl and the skin will be closed with staples (Standard of care).

For the active arm of the study, the arthrotomy (deep layer) is repaired using number 1 Vicryl, the subcutaneous layer will be then closed with simple interrupted knots using number 2-0 braided absorbable sutures (Vicryl), followed by closure of the subcutaneous layer using a STRATAFIX Spiral Knotless Tissue Control Device in addition to DERMABOND PRINEO (Ethicon, Johnson and Johnson, Somerville, New Jersey) system for dermal closure. (See table 3).

Closure with the bidirectional barbed suture involves starting at the midpoint of the wound and proceeded simultaneously both proximally and distally to the ends. At the ends of the wounds, the suture is backstitched at this subcuticular level (2-3 throws) toward the midpoint for further reinforcement before bringing the needle out through the skin; the suture is then cut flush with the skin tissue at its free end. With each throw, the leading end of the suture is pulled with only enough tension to engage the barbs with the surrounding tissue, thereby locking the wound edges into approximation. As with the traditional closure and in concordance with our routine protocol, skin will be closed with staples.

Table 2: Suture Type for Closure Following Total Knee Arthroplasty.		
Layer	Control Group	Active Group
Capsule	Vicryl #1 (J947H#1)	Vicryl #1 (J947H#1)
Subcutaneous	Vicryl 2.0 (J945H 2-0)	Vicryl 2.0 (J945H 2-0)
Subcuticular	Staples	STRATIFIX Spiral Knotless tissue control device (undyed)
Skin		DERMABOND PRINEO

Patient Protection:

All data collection sheets will be de-identified. All patients will be assigned a study ID. All data collected will be entered into Excel sheet and stored on Cleveland Clinic secure computers. Only members of the study team (listed on the IRB application) will have access to protected health information of patients included in this study.

Safety Monitoring Plan

Procedural safety will be documented in this study through patient and surgeon reported adverse events. AEs will be documented for all cases in this study. An Unanticipated Problem involving risks to participants or others is any event that (1) is unforeseen, (2) caused harm or placed a person at increased risk of harm, and (3) is related to the research procedures.

An Adverse Event (AE) is any untoward or unfavorable medical occurrence, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptoms, or disease. Adverse events can encompass both physical and psychological harms. An Internal Adverse Event (AE) is an untoward medical occurrence, which occurs to participants in research conducted by Cleveland Clinic and/or Cleveland Clinic is the IRB of record. External Adverse Event (AE) is an untoward medical occurrence experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study drug/device. A Serious Adverse Event (SAE) is any adverse experience that results in any of the following outcomes:

- Death
- A life-threatening experience
- Inpatient hospitalization or prolongation of existing hospitalization

- A persistent or significant disability/incapacity.
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An Unexpected Adverse Event means any AE not previously known or included in the current Investigator's Brochure, consent form or other risk information.

Related/Possibly Related means there must be reasonable evidence to suggest the event was caused by the drug, device or investigational intervention.

1. Internal Serious Adverse Events (events that occur to participants enrolled in research being conducted by Cleveland Clinic or when Cleveland Clinic is the IRB of record) must be promptly reported to the IRB using the IRB AE Report Form within 10 working days from discovery/awareness which meet any of the following criteria as assessed by the PI/Co-I:

- a) Serious, Unexpected and Related/Possibly Related.
- b) AE's determined to be occurring at a significantly higher frequency or severity than expected.
- c) Other Unexpected AE's, regardless of severity, that changes the risk benefit ratio of the study and results in changes to the Research Protocol or Informed Consent process/document.

All Internal SAEs are also reported at continuing review using the AE Summary Log.

2. External Serious Adverse Events (events experienced by subjects enrolled at other institutions for the same study approved at Cleveland Clinic or a different study using the same study device/drug) are reportable to the IRB using the IRB AE Report Form within 10 working days from discovery/awareness when:

- a. The External SAE report includes reasonable evidence as assessed by a central monitoring entity [Coordinating or Statistical Center, or a Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC)] that the event is Serious, Unexpected, and Related/Possibly Related AND places the subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. This will require a change in the protocol and/or consent document.

- b. External SAE reports provided by the Sponsor to the investigator indicating the event is Serious, Unexpected and Related/Possibly related but without reasonable evidence or DSMB/DMC determination of greater risk are not reportable to the IRB within the 10 day window. Without Sponsor evidence or assessment the implications of the event cannot be determined by the research team and therefore need not be reviewed. These SAE' shall be placed on the AE Summary log to be submitted at the annual continuing renewal.

3. DEATHS are to be reported to the IRB using the IRB AE Report Form according to the following guidelines:

a) Internal Death:

- Related/possibly related whether expected or unexpected– within 5 working days from discovery/awareness
- Not related and expected – at time of continuing review
- Not related and unexpected – at time of continuing review except cancer studies.
- Cancer: Not related and unexpected within 10 working days from discovery/awareness

b) External Death:

Related/possibly related and unexpected – within 5 working days from discovery/awareness not related whether expected or unexpected – at time of continuing review related/possibly related and expected – at time of continuing review

c) ALL Deaths are also reported at time of continuing review using the AE summary log.

4. Non-serious Adverse events (Internal and External) that are both Related/Possibly related and unexpected are reported on the AE Summary Log at time of continuing review to assess trends.

5. An IRB staff (a qualified, licensed practitioner assigned to this function by the IRB chair and IRB Executive Director) reviews Adverse Event Reports to determine whether they represent Unanticipated Problem Involving Risks to Participants or Others. Events that are assessed, by either the IRB Staff or Investigator, to place subjects or others at a greater risk of harm than was previously known or recognized, or changes the risk/benefit ratio of the study, or requires a change in the protocol and/or consent document are referred to Full Board for review under Policy #70. Events that do not involve risk to Participants or Others or changes to the

informed consent or protocol do not require further review. Investigators are informed of the determination and the IRB file is updated.

6. The AE Summary Log is reviewed by the IRB at the time of continuing review to identify trends in frequency and severity which may impact subject safety.

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Data Analysis:

Unless otherwise indicated, all testing of statistical significance will be two-sided, and a difference resulting in a p-value of less than or equal to 0.05 will be considered statistically significant. Also, after each analysis, General Linear Models (GLM) will be used to control for possible confounders, including BMI, gender, age and ethnicity.

References

1. Huemer GM, Schmidt M, Helml GH, Shafiqhi M, Dunst-Huemer KM. Effective wound closure with a new two-component wound closure device (Prineo™) in excisional body-contouring surgery: Experience in over 200 procedures. *Aesthetic Plast Surg.* 2012;36(2):382–6.
2. Parvizi D, Friedl H, Schintler M V., Rapp T, Laback C, Wiedner M, et al. Use of 2-octyl cyanoacrylate together with a self-adhering mesh (Dermabond??? Prineo???) for skin closure following abdominoplasty: An open, prospective, controlled, randomized, clinical study. *Aesthetic Plast Surg.* 2013;37(3):529–37.

