A randomized controlled trial comparing cosmetic outcomes of pediatric laceration closure using a tissue adhesive (Dermabond™) versus adhesive strips (Steri-Strips™) versus absorbable sutures

Study Protocol

NCT ID: NCT03280628

Document Date: 8/10/2017

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I. Specific Aim and Study Hypothesis

Specific Aim: The specific aim of this study is to determine the best of 3 different methods of closure of simple pediatric lacerations in terms of cosmetic outcome, pain, need for sedation, cost and length of ER stay.

Hypothesis: We hypothesize that the closure of simple pediatric lacerations with either a tissue adhesive (Dermabond™), or adhesive strips (Steri-Strips™) will provide clinically equivalent cosmetic outcomes to absorbable sutures while reducing pain, need for sedation, cost and length of ER stay without increasing the risk of complications.

II. Summary of Approach

To address the Specific Aim we will conduct a 3-arm randomized controlled trial comparing methods of closure of simple pediatric lacerations. The 3 arms will be: Dermabond™, Steri-Strips™, and absorbable sutures (our control arm).

We will examine the association between closure method and the primary outcome variable, cosmesis of the resultant scar.

As a secondary aim we will assess for statistically significant differences in the degree of pain experienced by the patient, in the need for sedation, in the cost of each closure method, and in the length of the patient's ER stay. We anticipate that the treatment arms (Dermabond™, Steri-Strips™) will demonstrate no clinically significant difference in cosmetic outcomes while reducing the pain experienced by patients during laceration closure, reducing the need for sedation, reducing costs and reducing the length of patients' ER stays.

III. Background

Lacerations are a very common presentation in pediatric Emergency Departments (ED). In fact, over the past 2 years (February 2015-2017), there were a total of 3100 lacerations repaired in the ED at Monroe Carell Jr's Children's Hospital at Vanderbilt (VCH). This can be a painful and traumatic procedure for children, especially young children. Given that most lacerations occur in young children (74.1% in those less than 6 years old), it is important to use noninvasive and painless closure methods when possible.[10, 11, 15]

Historically, sutures have been the preferred method of closure for lacerations.[18] While they have been made of different materials over the years, the general concept of needle and string has remained mostly consistent.[18] However, new methods of wound closures have been developed since. Surgical tape was first developed by surgeon Horace Day in 1845.[5] The earliest versions of surgical tape had several issues including proper adhesion, skin irritation, blocking of perspiration, etc.[5] The modern version of surgical tape that we are now familiar with (Steri-Strips™) has been around since the 1960s, and except for a few minor modifications, it has largely gone unchanged.[35]

Tissue adhesives, derived from cyanoacrylate, were invented in the 1940s and have been used for decades for wound closure outside of the United States.[3] However, it wasn't until 1998 that the Food and Drug Administration approved 2-octyl cyanoacrylate (Dermabond™) for use in the United States.[36]

Despite the availability of both adhesive strips and tissue adhesives, a large study at an urban ED showed that while tissue adhesives are more likely to be used in children compared to adults, especially in facial lacerations, they are still wildly underused.[31] In fact, out of the 3100 lacerations repaired at VCH, only 108 (3.5%) lacerations were closed using tissue adhesives, and none were closed with surgical tape exclusively. This is surprising given that tissue adhesives are very versatile (they have even been used to close tongue lacerations and nail bed injuries), and

have good tensile strength.[6, 13, 28] Whether the clear preference for traditional sutures is due to a lack of knowledge or confidence in alternative methods remains unclear.

IV. Rationale

The aim of this study is to compare different methods of pediatric laceration closure. Although Steri-Strips™ and other surgical tapes have been available for decades, there are few studies looking at their use in pediatric lacerations.[26, 34] Tissue adhesives such as Dermabond™ have also been largely understudied, though this may be due to the fact that they are a relatively newer addition on the market. In fact, a metanalysis in 2008 examining the use of tissue adhesives for simple traumatic lacerations found only 11 applicable studies, with only 6 using exclusively pediatric patients, only 5 using Dermabond™ and some studies not using validated scoring systems.[1, 7] Most studies have used older versions of tissue adhesives, had small sample sizes or were used on iatrogenic lacerations (laparoscopic trocar incisions for example).[2, 4, 9, 19, 22, 24, 27, 29, 30] Two studies compared cosmetic outcomes of scars closed with Dermabond™ versus Steri-Strips™ but neither study used sutures as controls.[26, 34] In addition, preliminary studies show that tissue adhesives and surgical tape are less costly and may lead to less sedation, which in turn can lead to decreased length of stay in the ED.[8, 14, 20, 21, 25, 33] The proposed study will provide a definitive cosmetic comparison of two alternatives to suturing for pediatric lacerations while examining the patient/parent experience in terms of pain, cost and length of ED stay in the hope that this will allow for improvement in clinical care.

V. Inclusion and Exclusion Criteria

a. Inclusion criteria

i. Age 0 to <18 years
ii. Parents speak English
iii. Chief complaint of laceration
iv. Single, linear laceration
v. Laceration less than 5 cm in length and 0.5 cm in width
vi. Laceration less than 12 hours old
vii. Laceration minimally contaminated (no visible dirt in wound)

b. Exclusion criteria

i. Significant medical history that may impact wound healing (hematologic or oncologic diagnosis requiring chemotherapy, ichthyosis, epidermolysis bullosa, etc.)
ii. Use of oral steroids (more than 5 days in the past month)
iii. History of keloid formation
iv. Allergy to tissue adhesives, adhesive strips, or topical anesthetics
v. Lacerations requiring deep sutures
vi. Lacerations caused by animal bites or scratches
vii. Lacerations located on the scalp, eyebrow, eyelid, lip, mucosa, joint or nail bed
viii. No access to photographic capabilities (camera or smartphone) and/or e-mail, or unable to return to the VCH ED to have a picture taken

VI. Subject Recruitment and Enrollment

We will enroll a sample of 90 children and adolescents 0 to <18 years of age. All eligible patients will be recorded in the Screening Log (see Appendix I).

Subject identification and enrollment will be performed by trained study staff stationed in the VCH ED. The study staff enrolling the patient will obtain written informed consent and/or assent, as applicable (see Consent Form and Assent Forms). Study staff will also complete a Subject Enrollment Form (see Appendix II) and Subject Data Form (see Appendix III) which will be maintained in a locked file in the ED.

VII. Study Procedures

Study Design

The study design will be a single-blind, randomized controlled trial. After enrollment, all participants will have LET placed and their wound washed out with sterile normal saline.

Depending on which arm they are randomized to, participants will have their laceration closed by either Dermabond™, Steri-Strips™, or absorbable sutures per the treatment arm protocols (Protocols, see Appendix IV). Unfortunately, given the nature of the study, neither the patient, parent nor health care provider will be blinded to the method of closure. Additional topical or injected anesthetics or the use of sedation will be left up to the patient/parent and provider's discretion. After the procedure, both patient (if older than 3 years old) and parent/guardian will be asked to fill out a short questionnaire (Questionnaires, see Appendix VI). The parent/guardian will be asked to rate the appearance of 3 images of random scars. All parents/guardians in the study will rate the same 3 scars to establish a baseline for each parent. The health care provider will also be asked to fill out a short questionnaire (Questionnaires, see Appendix VI). Upon discharge, the participant and their parent/guardian will be provided with verbal and written return precautions by the study staff (Care Instructions, see Appendix V).

Parents/guardians will be called 3 months after their initial visit for a brief over-the-phone interview (Questionnaires, see Appendix VI). At this time, they will be prompted to take a picture of the scar and send it to the Investigator by e-mail. A Vanderbilt email address has been set-up and is secure per Vanderbilt criteria. As an alternative, they can come back to the VCH ED where study staff will ask them a couple of questions in person and take a picture of the scar.

Every effort will be made to de-identify the images of the scar (using image editing software to crop everything on the image but the scar with some surrounding skin). The images will then be collected and presented to two Plastic Surgeons who will be blinded to the method of closure. They will subsequently score the scar as seen in the images (Questionnaires, see Appendix VI). All data will be collected on paper and then transferred to REDCap®. Each piece of data will be transferred to REDCap® by two study staff independently and then examined for any differences which can be reconciled by examining the paper forms. This will prevent errors in transferring data from paper to electronic format.

Participants will be compensated with a $15 check after completion of the 3 month questionnaire and sending of photo.

Randomization

Randomization will be accomplished using randomizer.org software to generate a set of 90 numbers from 1 to 3 for 90 enrolled participants. Each digit from 1 to 3 will correspond to a study arm.

Data Acquisition

Study data will be acquired through the means of the aforementioned questionnaires (Questionnaires, see Appendix VI), phone interviews, and by simple chart review. The secondary outcome of "cost of visit" will be acquired through Medical Records.

VIII. Predictor Variables

Predictor variables are the 3 treatment allocation arms: Dermabond™, Steri-Strips™, and absorbable sutures. Other independent variables to be collected include demographics of the patient (age, sex, race/ethnicity), specifics of the laceration (location, length and width, time between trauma and wound closure) and level of training of the provider who will be closing the wound. Demographics will be extracted from the patient Electronic Medical Record and from the parent Questionnaire (Questionnaires, see Appendix VI). Both the specifics of the laceration and the level of training of the provider will be extracted from the provider questionnaire at the time of the procedure (Questionnaires, see Appendix VI).

IX. Outcome Variables

a. Primary outcome variable

The primary outcome will be cosmesis of the resultant scar as measured on a 100 mm Visual Analogue Scale where a score of 0 corresponds to "worst scar" and a score of 100 corresponds to "best scar." This scale has been validated as a scoring method to evaluate cosmesis of a scar.[12, 16, 17, 23, 32] Due to its sensitivity and the fact that it provides parametric data, the scale allows for smaller, more practical sample sizes to show clinically-significant differences in populations.[12, 16, 17, 23, 32] The Visual Analogue Scale will be used by two Plastic Surgeons blinded to closure method to rate a patient's scar at 3 months. In addition, parents will be asked to rate the scar on a scale of 0 to 100 during their over-the-phone interview at 3 months. We will compare their rating of their child's scar to the average of their ratings of the 3 images of random scars at the initial visit.

b. Secondary outcome variables

i. Pain experienced by patient
This secondary outcome will be evaluated by the patient (if age-appropriate), parent and provider at the time of the ER visit (Questionnaires, see Appendix VI). Patients aged 3 to 12 will be asked to rate their pain on a Wong-Baker FACES® Pain Rating Scale (licensing for use in progress). Patients aged 12 to 18 will be asked to rate their pain using a 100 mm Visual Analogue Scale with a score of 0 corresponding to "No pain" and a score of 100 corresponding to "Terrible pain." Parents and providers will each be asked to score how much pain they felt the patient experienced on the same Visual Analogue Scale.

ii. Need for anesthetics/anxiolytics/sedation
This secondary outcome examines the need for adjuncts to control pain/anxiety including LET, injected lidocaine, anxiolytics or systemic pain medications, ketamine sedation or others. Data will be collected by study staff observing the procedure. Data will also be extracted from the patient's Electronic Medical Record.

iii. Length of procedure
This secondary outcome, measured in minutes, will be collected by study staff observing the procedure.

iv. Cost of visit
This data will be extracted from the patient's Electronic Medical Records and from the Billing Department.

v. Length of ER stay
This data will be extracted from the patient's Electronic Medical Records.

vi. Resource utilization

This secondary outcome examines the need for personnel in the room to keep the child calm or still. This data will be collected by study staff observing the procedure.

vii. **Likelihood that parent would recommend wound closure type**
This secondary outcome will be measured using a 100 mm Visual Analogue Scale with a score of 0 corresponding to "Extremely unlikely" and a score of 100 corresponding to "Extremely likely." This data will be extracted from the parent questionnaire at the time of the ED visit (Questionnaires, see Appendix VI).

viii. **Complications**
Prevalence of complications (infection, dehiscence, etc.) will be evaluated. This secondary outcome will be obtained during the brief phone questionnaire with parents at 3 months after the ED visit (Questionnaires, see Appendix VI).

ix. **Poor cosmetic outcome**
This secondary outcome will be extracted from the Visual Analogue Scales used to rate a patient's scar, as evaluated by both the parent and Plastic Surgeons blinded to method of closure (Questionnaires, see Appendix VI). A score less than 35 mm on the 100 mm scale will be considered "poor cosmetic outcome" as used in previous studies.

x. **Presence of train tracks**
This secondary outcome will be extracted from the Plastic Surgeon questionnaire at 3 months (Questionnaires, see Appendix VI).

X. Ethical Considerations

Dermabond™ and Steri-Strips™ are both FDA-approved methods of laceration closure and there have been no studies demonstrating the inferiority of these closure methods compared to sutures, the traditional method of laceration closure. Thus, randomizing patients to either Dermabond™ or Steri-Strips™ treatment arms does not violate the principle of equipoise.

XI. Risks of Study Participation

Surveillance for medical risks, including but not limited to infection and dehiscence, will be performed during the study of each subject by Dr. Maureen Saint Georges Chaumet.

The specific aim of this study involves the collection of Personal Health Information (PHI). HIPAA regulations pertaining to subjects' PHI will be reviewed with the Vanderbilt IRB and assurance of conformity to these regulations and protection of PHI provided. As noted, we are taking steps to protect this information. Study staff are required to honor and preserve patient confidentiality and privacy at all times and in all management of data and data files. All completed subject information forms will be initially placed in a locked box in the VCH ED after enrollment and data collection. Forms will then be promptly transferred to individual patient files and maintained in a locked data collection box in a locked office in order to maintain confidentiality and security of data. Photos will be e-mailed to a secure Vanderbilt e-mail. Access to computer files will be further restricted by file passwords. The database will be maintained on REDCap®.

XII. Reporting of Adverse Events or Unanticipated Problems involving Risk to Subjects or Others

Any unexpected problems involving risks to subjects or others will be immediately reported to the Institutional Review Board of Vanderbilt University within ten days using the IRB form #1105.

XIII. Study Withdrawal or Discontinuation

Patients and their parent/guardian(s) will be told very explicitly by the investigators that their participation in this research investigation is entirely voluntary and that they may withdraw at any time. We will further emphasize verbally and in the informed consent document that a decision on the part of the patient or parent/guardian(s) to not participate will in no way change, compromise or jeopardize the patient's care. Indeed, we anticipate that a number of eligible patients will not be enrolled on this basis.

XIV. Data Management

Participants' information (Subject Enrollment Form, see Appendix II, Questionnaires, see Appendix VI, pictures) will be kept in a separate file for each subject. Data will be transferred to the REDCap® server. This data will then be sent for statistical analysis.

XV. Statistical Considerations

We are planning a study of a continuous response variable from independent control and experimental subjects with 1 control per experimental subject. In previous studies, the response within each subject group was normally distributed with a standard deviation of 15 mm on a 100 mm Visual Analogue Scale and the minimal clinically important difference between two scars was 15 mm on a 100 mm Visual Analogue Scale.[16, 17, 32] We performed multiple sample size power calculations using STATA® 14.1 (College Station, Texas). Using one-way ANOVA, with a power of 90% and an alpha of 0.05, we would need between 5 and 21 subjects per group to detect a clinically significant difference of 5 to 15 mm between groups depending on the standard deviation in each group (in anticipation of the fact that we may have a larger standard deviation). In order to assure an effective sample size after accounting for dropouts and missing data, we propose to recruit 30 experimental subject per treatment arm and 30 control subjects, for a total of 90 subjects.

XVI. Privacy and Confidentiality Issues

After the parents have signed the consent form, and the patient has signed the assent form as applicable, one copy will be given to the parents and one copy will be kept by Dr. Maureen Saint Georges Chaumet in a locked data collection box in a locked office. All efforts, within reason, will be made to keep protected health information (PHI) private. PHI is health information that is or has been gathered or kept by Vanderbilt as a result of a subject's healthcare. This includes data gathered for research studies, and can be traced back to the subject. Using or sharing ("disclosure") such data must follow federal privacy rules. By signing the consent for this study, subjects are agreeing ("authorization") to the uses and possible sharing of PHI. If a patient or their parent/guardian decides to be in this research study, he/she is also agreeing to let the study team use and share PHI as described below.

As part of the study, Dr. Maureen Saint Georges Chaumet and her study team may share the results of a subjects' study-linked questionnaires and photos, as well as parts of the medical

record, to the groups named below. These groups may include people from the Federal Government Office for Human Research Protections, the Vanderbilt University Institutional Review Board, and insurance companies for billing purposes. Federal privacy rules may not apply to these groups; they have their own rules and codes to assure that all efforts, within reason, will be made to keep PHI private.

Dr. Maureen Saint Georges Chaumet may give health data, without a subject's name, to others or use it for other research projects. Vanderbilt and Dr. Maureen Saint Georges Chaumet and her staff will keep each subject's PHI in strict confidence, and will comply with any and all laws regarding the privacy of such information.

XVII. Follow-up and Record Retention

Research data will not be kept in a subject's medical record. Deidentified study results will be kept for up to 5 years after the study is finished but all identifying data will be destroyed once the study is finished.

XVIII. Data Safety and Monitoring Plan

Surveillance for medical risks, including but not limited to infection and dehiscence, will be performed during the study of each subject by the study investigators. Any adverse events will be reported as per IRB guidelines.

Electronic data have several levels of protection. Any file that may contain patient identifiers will be password protected. All computers upon which data are stored are likewise password protected and are running anti-virus programs that automatically update definitions. All data are automatically backed-up to a secondary hard drive on a nightly basis. Access to the Vanderbilt computer network is protected at the level of firewalls, TCP wrappers and university-assigned user IDs. Data are secured with encryption algorithms and the network is maintained by the Medical Center's Network Computer Services.

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