Digital Weight Bearing Shape Capture Socket Technology to Preserve Limb Health and Improve Rehabilitation Outcomes

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1.0 Background

Combat-related amputations remain one of the most common major disabling war-related injuries from modern armed conflict. Since the beginning of combat operations in Iraq and Afghanistan in 2001, more than 1,300 major lower extremity amputations have been sustained by or performed on US service members and women[1]. Adequate rehabilitation post-amputation enable our nation's heroes to reach their maximum functional recovery and independence[2]. Socket comfort is achieved by appropriately loading and off-loading the residual limb, where optimal biomechanical performance of the prosthesis is achieved by transfer motions of the residual limb without loss or excess motion to the prosthesis. Socket design and fit are critical for successful prosthetic use especially for service members with combat related lower extremity limb amputations. Sub-optimal fit and comfort of the prosthetic system are known to cause rejection of the prosthesis and preference toward other assistive devices such as wheelchairs[3].

In an effort to maximize socket performance and comfort without adversely affecting residual limb health, a prosthetist custom fits a socket for every patient using plaster wraps or computer aided design. Currently, this process suffers from a lack of quantitative feedback to determine appropriate socket volume, and fit. Prosthetists aim to create a comfortable and intimate socket interface, but current techniques are limited as they rely on anecdotal visual cues along with subjective verbal feedback from the patient. We have optimized and reported[4] limb health outcomes that help provide objective feedback to patient and prosthetist fitting the socket. Although the use of the socket is to ambulate in full weight bearing condition, currently almost all of fittings and plaster casting takes place in a seated non-weight bearing position.

The art of socket fabrication must rely on more objective approaches in the interest of robustness. Attempts have been made to develop a socket fabrication technique that requires little or no prosthetic skill. The clinical models range from all traditional techniques with no use of Computer Aided Design and Manufacturing (CAD/CAM), to full in-house suites of CAD/CAM equipment with extensive utilization, to a simplified office with minimal in-house equipment and minimal fabrication and a near total dependency on central fabrication[5]. Once the digital representation of the residual limb is obtained, software is used to add the modifications that transform the digital shape from an exact mold of the amputated limb, to the shape of a functioning prosthetic socket. An exact mold of the residual limb is not a good socket. The socket must be accurately modified by a skilled prosthetist in areas that can better tolerate the transfer of forces, and the socket must be relieved out away from the residual limb in areas that are less tolerant of force and pressure. These special areas of the socket that require modification are called regions and the process is called rectification[5]. Most CAD/CAM software

packages have templates that will identify these regions and add these modifications in a similar fashion even for different sized and shaped limbs after the prosthetist identifies the correct anatomical landmarks for rectification. One major advantage of automated digital technology is that one could robustly fabricate multiple sockets very efficiently over the early rehabilitation time, and thus keep up with the changing shape and volume of the residual limb during the first 12 to 18 months following amputation[5].

Achieving a comfortable and functional relationship between an amputee and their prosthetic socket is critical to the success of the prosthesis. Therefore, the prosthetic socket and interface are the most significant component for the overall rehabilitative success of the prosthesis[6, 7]. Over 75% of patients with lower-limb prosthetics have skin problems[8, 9]. Ulcers or pressure sores, are the most common skin conditions in prosthetic users[6] and can vary in size and magnitude requiring prolonged recovery time out of the prosthesis, a new socket fitting and sometimes surgical interventions[8, 9]. To preserve and promote residual limb health, one key factor is to maintain the functional integrity of the skin, perfusion and oxygenation[10]. Functional integrity of the skin is a critical determinant of ulcer formation[11, 12]. Our group and others have demonstrated that trans-epidermal water loss (TEWL) measures the functional integrity of the skin, a reliable early marker of skin ulceration[13-16]. Breach in physical integrity of the skin is preceded by breach of functional integrity of skin as measured by elevated TEWL. Previous research lends credence to the hypothesis that the residual limb skin is susceptible to breakdown and ulceration in response to repeated stress from use of prosthesis.

Micro-vasculopathy is known to complicates limb health [17, 18]. We reported the first post-processing of binary raw data from a high-resolution LSCI camera. This tool is valuable in determining micro-vasculopathies compromising limb health following use of a specific type of socket. These studies described above clearly demonstrate value of in-socket and out-of-socket non-invasive unique measurement tools developed by our group for monitoring limb health of residual limb in sockets. These studies also demonstrate experience of our group in performing such clinical studies in this area[4, 10, 13-16, 19-23].

2.0 Objective(s)

2.1 Primary Objective

Evaluate the efficacy of the Symphonie Aqua Digital System (SADS) and the health of the residual limb outcomes compared to non- weight bearing standard of care sockets.

2.2 Secondary Objective

The secondary objective includes

i) pressure inside the socket
ii) assessment of functional outcomes
iii) patient reported (PR) outcomes

We hypothesize that digital shape capture of a residual limb using EMTS under full weight bearing environment will provide accurate anatomical shape of the residual limb, improved fit of the prosthetic socket; thus, preserving limb health and volume during activities of daily living (ADL). Such accuracy will improve limb health and rehabilitation outcomes following amputation.

3.0 Aims

3.1 Aim 1

Evaluate the efficacy of the SADS on long-term limb health of the residual limb outcomes (TEWL and LSCI measurements) compared to traditional non-weight bearing shape capture techniques.

3.2 Aim 2

Long-term assessment of functional outcomes, and patient reported (PR) outcomes in response to use of SADS.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Ages 18 and above
- Unilateral trans-tibial amputees
- Ambulate at a K3 level or higher
- At least 3 months post-amputation per physician discretion
- Trans-tibial limb length greater than 4.5 inches in length
- Able to follow directions and independently give informed consent
- Must be able to ambulate without assistance

4.2 Exclusion Criteria

- Age < 18 years
- Conditions that prevent wearing a prosthetic socket
- Soc Socket made with weight bearing system
- Cognitive deficits or mental health problems that would limit ability to consent and participate fully in the study protocol
- Women who are pregnant or who plan to become pregnant in the near future
- Weight > 280 lbs

5.0 Study Design

This is a 16-week pilot, prospective, cross over study to meet the objective of the study where the novel EMTS based digital weight bearing system will be compared to SoC non-weight bearing socket design for improving limb health and functional outcomes post 6 weeks use. The subject (n=12) lower extremity unilateral trans-tibial subjects will participate in both study arms sequentially: Arm 1 (SoC- non-weight bearing): and Arm 2: EMTS based shape capture in full weight bearing using (SADS, Symphonie Aqua Digital System, Romedis GmbH).

5.1 Enrollment

The subject (n=12) lower extremity unilateral trans-tibial subjects will begin the study on Arm 1 (SoC- non-weight bearing (Socket A) : and then move to Arm 2: EMTS based shape capture in full weight bearing using (SADS, Symphonie Aqua Digital System, Romedis GmbH, Socket B).

5.2 Study Procedures

Study Visit 1a-c (Initial Evaluation/Fitting; Weeks 0-6): Immediately post-enrollment, socket shape capture will be completed with Digital and non-digital weight bearing Aqua systems. Baseline measurement for SoC will be performed. The following baseline measurements will be performed for SoC Socket (Socket A) at this first visit:

- **TEWL measurement**
- **Laser Speckle Flowmetry (LSI)**
- **In-Socket Sensors**
- **Motion Capture Analyses**
- **6 Minute Walk Test (6MWT)**
- **Timed Up-and-Go (TUG)**
- **Houghton Scale**

- **Socket Comfort Score**
- **Veterans RAND 36-Item Health Survey**

The fitting of the digital and non-digital weight bearing sockets will continue for up to 4-6 weeks to ensure proper fitting of the weight bearing socket and comfortability during this time the subjects will continue to use their SoC socket A.

Study Visit 2 – SoC final visit (week 6 +/- 2 Weeks): Participants will return to the hospital. Participants will be asked to wear clothing that is comfortable for them while they may be participating in physical activity prior to attending the visit. Study members will offer specific guidance on study if necessary. If they do not have any comfortable clothing, they will be asked to speak with research personnel. Research personnel will provide them with the appropriate clothing if they are unable to bring any during this visit. The following procedures will be performed during this visit with their Socket B.

- **TEWL measurement**
- **Laser Speckle Flowmetry (LSI)**
- **In-Socket Sensors**
- **Motion Capture Analyses**
- **6 Minute Walk Test (6MWT)**
- **Timed Up-and-Go (TUG)**
- **Houghton Scale**
- **Socket Comfort Score**
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At this visit, the definitive **socket B** will be ready & fitted; the measurements in this visit will serve **as the baseline visit values for Socket B**; End of this visit the participants will start using the Socket B for next 6 weeks Study members will offer specific guidance on study as necessary.

Study Visit 3 (week 12 +/- 2 Weeks):

- Participants will return to the hospital. They should wear clothing that is comfortable for them while you may be participating in physical activity. Study members will offer specific guidance on study if necessary. The following procedures will be performed during this visit with their test Socket B following 6 weeks of use.

- **TEWL measurement**

- **Laser Speckle Flowmetry (LSI)**
- **In-Socket Sensors**
- **Motion Capture Analyses**
- **6 Minute Walk Test (6MWT)**
- **Timed Up-and-Go (TUG)**
- **Houghton Scale**
- **Socket Comfort Score**
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Study procedure details.

- **Baseline TEWL measurement**: Small non-invasive probe that compares relative humidity of skin surface to indicate epidermal barrier functioning. The TEWL probe will be placed on the skin and each measurement takes approximately 7-20 seconds to obtain. An additional reference (control) TEWL measurement will be taken from intact skin at the anatomically matched site on the patient's contralateral side. TEWL measurements will be captured 3 times on the anterior, lateral, medial, and posterior surfaces on both limbs.
- **Laser Speckle Flowmetry (LSI)**: LSI is a non-invasive blood flow imaging technique. LSI is very routinely used for blood perfusion measurement in clinical applications. We do not anticipate any radiation exposure.
- **Pressure Socket Sensors**: In-socket sensors will be positioned into the socket which will function to detect the amount of residual load (pressure) that is placed on the limb through the use of an iPad under a dynamic environment. This research functions to better understand the participant's in-socket pressure in a non-weight bearing socket compared to the Symphonie Aqua Digital System (SADS) system.
- **Motion Capture Analyses** Initiation of the in-socket sensors will ensue and walking tasks will be completed by subjects.
- **6 Minute Walk Test (6MWT)**: Subject will walk for 6 consecutive minutes and, once the 6 minutes has elapsed, the distance covered will be measured. The reliability and/or concurrent validity of this assessment have been verified and reported in subjects with lower-limb amputations.
- **Timed Up-and-Go (TUG):** In the timed up-and-go outcome, the patient rises from a seated position, walks three meters at a self-selected speed, turns around, and returns to the chair where they reseat themselves. This measure is simply a timed event with the clinician timing from the moment the patient leaves the chair until they are reseated. Again**,** the reliability and/or concurrent validity of this assessment have been verified and reported in subjects with lower-limb amputations.

- **Houghton Scale:** A score of nine or more defined as successful prosthetic rehabilitation.
- **Socket Comfort Score:** This score is a subjective measure of how comfortable the amputee feels in the socket at the time the score is taken.
- **Veterans RAND 36-Item Health Survey:** Is a brief, generic, multi-use, self-administered health survey comprised of 36 items. The instrument is primarily used to measure health-related quality of life, to estimate disease burden and to evaluate disease-specific impact on general and selected populations.
- The fitting procedures and/or techniques of the research socket will mirror the techniques of the subject's primary prosthetist used to fabricate their SOC socket. The only difference is the method of capturing the shape of the residual limb: weight-bearing vs non-weight-bearing.
- There may be risks that we don't know about at this time. While the goal of this project is to create a more comfortable prosthesis, it is possible that subjects will experience discomfort such as perspiration, dry skin, rash, itching, irritation, blisters, high pressure in the socket, looseness in the socket, and mechanical rubbing which may cause ulcerations.

6.0 Study Calendar

	Study Visit 1 (0-6 weeks)	**Study Visit 2** (6+/- 2 Weeks)	**Study Visit 3** (12+/- 2 Weeks)
Informed consent[1]	X		
Enrollment	X		
Socket Shape capture	X		
Initial Evaluation/fitting	X		
TEWL measurement	X	X	X
Laser Speckle Imaging (LSI)	X	X	X
Pressure Socket Sensors	X	X	X
Motion Capture Analysis	X	X	X
6-minute Walk Test	X	X	X
Timed UP and GO	X	X	X
Houghton Scale	X	X	X
Socket Comfort Score	X	X	X
Veterans RAND36-item health survey	X	X	X

7.0 Reportable Events

Protocol deviations and Unanticipated Problems involving risks to subjects or others, Adverse Events, and Other Problems will be reported to Indiana University per IU IRB reporting requirements.

Unanticipated problems can occur in any type of research (medical or non-medial) and may include occurrences such as adverse events, subject complaints, protocol deviations, and other untoward events involving risk. Events requiring prompt reporting by investigators and research staff may involve physical, psychological, social, legal, or economic harms.

Event reports and accompanying information will be screened for completeness by research staff members, additional clarifications will be requested from the investigator, as necessary. Research staff members and the principal investigator will make an initial determination about whether the event represents a possible unanticipated problem involving risks to subjects or others and/or potential noncompliance. Reports of events determined during screening to represent possible unanticipated problems involving risks to subjects or others and/or serious/continuing noncompliance will be forwarded to the IRB for convened review. Reports of events that do not meet the requirements for prompt reporting may be reported at time of study renewal.

8.0 Data Safety Monitoring

A clinician/certified prosthetist who is a member of the study team and the study coordinator will meet at the following timepoints to review the study data and any adverse events to ensure continued subject safety: prior to initiation of the study, after the 5th subject is enrolled, after the 10th subject is enrolled, and 60 days following the conclusion of study procedures for all subjects. Data will be reviewed at least annually.

9.0 Study Withdrawal/Discontinuation

Patients will be informed during the informed consent process (in writing and verbally) that they are free to withdraw from the trial at any time. The investigator may exercise his medical judgement to terminate a patient's participation in the trial due to clinically relevant changes in any clinical or laboratory parameter. The Sponsor-Investigator also reserves the right to discontinue/terminate the trial at any time.

Discontinuation criteria for individual subjects include: (1) Non-compliance with the inclusion/exclusion criteria, (2) treatment non-compliance, such as use of another socket prosthesis, (3) withdrawal from the study due to reasons not related to the treatment, (4) prosthetic socket becomes uncomfortable.

10.0 Statistical Considerations

This is a pilot study that is expected to generate preliminary data that will inform sample size for an adequately powered phase 2 study (in future). In this study, a total of n=12 subjects will be enrolled.

In general, for continuous data, means, median, standard deviations, and range will be provided. For categorical data, the count and frequency will be provided. In general, inferential tests will be tested with two-sided p-values or 95% confidence intervals, unless otherwise stated. Missing data distributions and patterns will be checked, and in the scenario of missing at random (MAR), we will consider multiple imputation procedures in data analysis. For Aim 1, TEWL values will be used as a function of overall limb health and as our primary endpoint. In addition to the primary endpoint, the secondary endpoint Laser Speckle Imaging will also be examined in aim 1. All of these endpoints are measured or quantified into continuous scale that would be used as outcomes. For Aim 2, functional outcomes will be evaluated using 2MWT and TUG, at baseline and at 6 weeks period post-socket use. To test the hypothesis, all these functional measurements will be transformed into standardized Z-scores with mean of 0 and a standard deviation of 1. These standardized scores will then be pooled into one composite score to quantify standardized functional score. The patient reported outcomes (PRO) will be assessed using validated instruments: Summary measures will be derived by summation of item specific scores for each instrument. These summary measures from functional measures and PRO will then be transformed into standardized Z-scores to create a pooled (composite) score for the overall PRO. For functional and PRO measure, generalized linear mixed methods with carryover effect, if any, will be used to examine the effect of types of socket on composite measure of the measures. A profile plot of the mean (or median) of each continuous endpoint variable will be created over follow-up time for each arm of the test-socket. All analyses will be done using SAS 9.4 or Stata 16.0 or higher.

11.0 Data Management

Clinical Data: Will be recorded in RedCap (research electronic data capture (HIPAA compliant)) as clinical research database. Prior to being given access to the data, HIPAA and human subjects certified “study staff” will be trained in the collection of patient-reported outcomes. Study data will be collected using standardized case report forms (CRFs), with clear, uniform instructions for study staff. Researcher’s access to files will be governed by institutional secure data access policies. The redcap platform is developed and operated by IU clinical research IT team.

Data Quality and Security: The study team will review all CRFs. All incoming data will be monitored, with particular attention to: 1) enrollment and follow-up reports as entered into the database; 2) potential adverse events, and 3) missing data or extreme values. The clinical database administrator will generate reports of enrollment progress and data quality control results, to be distributed to the study team bi-monthly and ad hoc as needed, as well as to the safety committee.

12.0 Privacy/Confidentiality Issues

Records of the participation in this study will be held confidential so far as permitted by law. Any information about participants will be obtained from this study will be kept confidential. The sponsor's delegates, IRB, and the United States Food and Drug Administration (FDA) have access to and may copy the medical records applicable for this study therefore absolute confidentiality cannot be guaranteed.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by U.S. law. This web site will not include information that can identify the participants. At most, the web site will include a summary of the results. The research study coordinator will have access to subject identity. All samples that will undergo analysis will only be identified by a subject code which can only be linked with protected health information (PHI) database by persons who have access to the study database (i.e., research nurses, investigators) via a password. This procedure satisfies HIPAA and is standard for clinical studies run at IU, and as overseen by the IU-CTSA.

13.0 Follow-Up/Record Retention

Study results, data, and documentation will be stored for a minimum of 6 years.

14.0 Study Device FDA Status

The proposed SADS under investigation is a device that will be used for socket fabrication for lower limb amputee. The device may eventually be included as part of the socket component and as such may fall under FDA class 1 . They fall under the FDA device description of "Component, External, Limb, Ankle/Foot" with FDA product code of "ISH". These products must be registered with the FDA prior to marketing, but they do not require 510(k) premarket clearance or Premarket approval (PMA). These devices incorporate significant improvements but they have substantial equivalence to existing products.

SADS combines individual socket production per the residual limb's anatomy while bearing the actual weight. By means of Magnetic Field Trackings, the actual form of the residual limb is hydrostatically captured in 3D while bearing full weight. The patients will place their residual limbs in the Symphonie aqua cylinder and can feel the water pressure. Once the patient is comfortable with the hydrostatic pressure, the magnetic tracking sensors will be activated by the prosthetist, the sensor data will be sent to the Central Control Unit. Based on the tracking data, the algorithm builds a 3D model of the prosthetic socket. The data may be directly sent to a 3D printer or to a Central Fabrication facility. The algorithm pre-calculates at which location and to what extent a patient's residual limb will change in the foreseeable future. Weight fluctuations, increased training frequency, water retention in body tissues as well as illness play a major role. Based on these values, a socket alteration is constructed and produced which is able to equalize the pre-calculated deviations. If required, this feature allows for the prosthetic socket to be again optimally fitted, based on the digital impression of the residual limb.