



Severe pain during wound care procedures: A cross-sectional study protocol

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Abstract

Aim: The aim of this study is to: (a) develop and evaluate a model to predict severe pain during wound care procedures (WCPs) so that high-risk patients can be targeted for specialized dressings and preventive pain control; and (b) identify biological factors associated with severe pain during WCPs so that novel pain control strategies can be developed.

Background: Wound care procedures such as dressing changes can cause moderate to severe pain in 74% of patients, with nearly half (36%) of all patients experiencing severe pain (rated as 8–10 on a 10-point numeric rating scale) during dressing change. Additionally, clinicians have little direction with current guidelines regarding pain control during WCPs including the selection of the appropriate advanced wound dressings and the appropriate use of analgesics.

Design: This is a cross-sectional study.

Methods: The National Institute of Nursing Research approved and funded the study June of 2015 and the appropriate Institutional Review Board approved all study protocols prior to funding. Study enrolment is underway at the University of Iowa Hospitals and Clinics with a target of 525 participants. Potential participants must be adults (21+ years) and have a nonburn, nondiabetic foot, full-thickness wound. The research team performs a one-time study dressing change on enrolled participants and collects all study data.

Discussion: This study will allow the development of a tool for clinicians to use to predict severe pain during WCPs and identify biological factors significantly associated with severe pain during WCPs.

KEYWORDS

cytokines, microbiome, nursing/nurses, wound care, wound pain

1 | INTRODUCTION

Wound care procedures (WCPs), such as dressing changes, cause moderate to severe pain in 74% of patients. Nearly half (36%) of all patients experience severe pain (rated as 8–10 on a 10-point

numeric rating scale) (Gardner et al., 2014). Severe pain causes substantial stress for both patient and nurse performing the dressing change. Unfortunately, the high prevalence of severe pain during WCPs is under-recognized and understudied. The objective of the study is to examine wound pain during dressing changes.

1.1 | Background

Despite guidelines for administering preventive analgesics (World Union of Wound Healing Societies' Initiative, 2004, 2007; Wounds UK, 2004), current practice sometimes involves performing WCPs without analgesia or chasing pain with opioids after the procedure has started when pain is severe (Stotts et al., 2004). When given, opioids are sometimes administered repeatedly or at doses resulting in prolonged, problematic, postprocedure sedation. Opioids can also delay healing (Martin et al., 2010; Rook, Hasan, & McCarron, 2009). In addition to analgesics, current practice guidelines recommend advanced wound dressings, such as foam, hydrofibres and alginate, but provide no guidance on which patients should be targeted for these advanced wound dressing materials (World Union of Wound Healing Societies' Initiative, 2004, 2007; Wounds UK, 2004). As a result, clinicians may not consider advanced wound dressings based on the dressings' ability to minimize wound pain (Vermeulen, Ubbink, de Zwart, Goossens, & de Vos, 2007).

Finally, organisations responsible for setting practice guidelines recognize the need to develop innovative pain control strategies that target specific mechanisms given the potential for adverse effects of analgesics, (World Union of Wound Healing Societies' Initiative, 2007). Therefore, the mechanisms that lead to severe pain during WCPs need to be identified and targeted for novel pain control interventions.

2 | THE STUDY

2.1 | Aims

Aim 1 of this study is to develop and evaluate a clinical risk model to predict severe pain during WCPs so that high-risk patients can be targeted for specialized dressings and preventive pain control.

Aim 2 of this study is to identify biological factors associated with severe pain during WCPs so that novel pain control strategies can be developed.

2.2 | Design/Methodology

2.2.1 | Design

This is a cross-sectional study which began in December 2015. The research team performs a one-time study dressing change (i.e., WCP) on enrolled participants and collects data to measure all study variables. Figure 1 depicts the study variables included for Aims 1 and 2. The development of the conceptual model of the study has been published (Gardner, Abbott, Fiala, & Rakel, 2017).

2.2.2 | Setting and sample

Participants are recruited from the inpatient units at large academic hospital in the Midwest using a customized report listing all hospital inpatients with wounds, generated through EPIC© (Epic Systems

Why this study is needed?

This study has the potential to make significant contributions to clinical care by:

- Aiding clinicians in targeting patients in need of preventative pain control, resulting in the reduction of pain during wound care procedures
- Improving the appropriate use of advanced wound care dressings and preventive analgesics including opioids

Corporation, Verona, WI), the electronic medical record. Table 1 lists inclusion and exclusion criteria. Only nonburn, nondiabetic foot, full-thickness wounds are included. Burn wounds are not included because the pain associated with burn wounds is substantially different than other types of wounds and people with diabetic foot ulcers often have significant neuropathy that alters the perception of pain in both the foot and the ulcer. Only open, full-thickness wounds are included because our interest is in the pain associated with packing and dressing wounds, which is not a component of care for wounds healing by primary intention. The sample includes only adults as wound care for children and adolescents are often performed in the operating room at UIHC.

Of those patients that meet inclusion criteria, those that are non-English speaking or with a moderate to severe cognitive impairment are excluded because English and cognition abilities are essential to complete self-report tools in the study protocol (i.e., Generalized Anxiety Disorder-7 [GAD-7]; Patient Health Questionnaire-8 [PHQ-8]; and Pain Catastrophizing Scale). Similarly, those with sensory impairment (e.g., spinal cord injuries, nerve blocks, or other conditions resulting in lack of sensation) at the wound site are excluded because of their potential influence on pain at the wound site during the study dressing change; the primary outcome for both Aims. Wounds covered with 100% nonviable tissue (slough or eschar) are excluded because slough/eschar precludes the ability to collect wound specimens for bioburden and cytokine analyses. Wounds with a fistula are excluded because fistulous drainage may change the composition of wound specimens collected for bioburden and cytokine analyses. Malignant wounds are excluded because the pain associated with malignant wounds is substantially different than for other types of open wounds. Finally, wounds that require debridement during the study dressing change are excluded because debridement may cause higher levels of pain independent of the dressing change procedures.

2.2.3 | Target enrolment

Target enrolment (consent) is 525 participants over 3½ years. Based on our data, we expect a 15% attrition rate leaving 445 participants with complete study data. Previous data suggest 36% of inpatients at UIHC have severe pain ($\geq 8/10$) with WCPs (Gardner et al., 2014) so we expect 160-445 participants to have severe pain during the

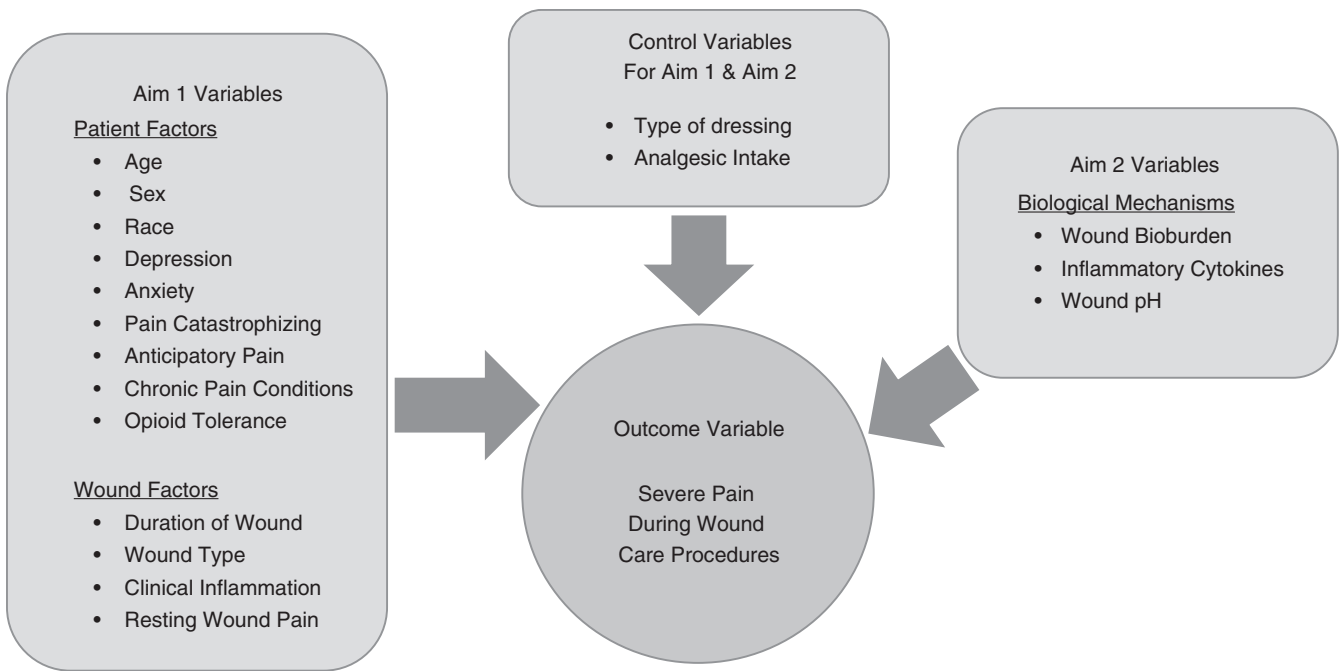


FIGURE 1 Study variable model

TABLE 1 Inclusion and exclusion criteria

Inclusion criteria
<ul style="list-style-type: none"> • Having a nonburn, nondiabetic foot, open full-thickness wound • Required dressing changes • Age ≥ 21 years • Inpatient status
Exclusion criteria
<ul style="list-style-type: none"> • Non-English speaking • Moderate or severe cognitive impairment or MMSE of <19 • Sensory impairment at the wound • 100% of the wound is covered with nonviable tissue • Fistula in the wound • Malignancy in the wound

WCP. With this sample, we will be able to estimate with 95% confidence the true accuracy of discriminating low/moderate from severe pain (i.e., the receiver operating characteristic [ROC] area under the curve, or *c*-statistic) within a margin of error ≤ 0.058 . Our variance estimate formulas are from Zhou, Obuchowski, and McClish (2002).

2.3 | Methodology

2.3.1 | Study variables

Primary outcome variable

Pain intensity during the study dressing change is defined as the maximum pain intensity experienced during the dressing change, inclusive of removal, cleansing, specimen collection and redressing. The vertical 0–10 Numeric Rating Scale (NRS) with 0.5 increments is used to assess pain experienced in the wound during the study dressing

change. The NRS pain scale is used in clinical practice, has established validity (correlation with the Visual Analogue Scale $r = 0.847$, $p < 0.001$) (Paice & Cohen, 1997) and reliability (test–retest $r = 0.93$) (Jensen, 2003) for assessing acute pain and is associated with higher compliance and lower failure rates than the Visual Analogue Scales (Herr, Spratt, Mobily, & Richardson, 2004). For exploratory analyses, we are also assessing the quality of pain during the dressing change using the Short Form McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987). This study will use the 15 pain quality descriptors from the SF-MPQ. The 15 items on the SF-MPQ have established validity ($r = 0.77$ – 0.88) when compared with the Long Form McGill Pain Questionnaire (Dudgeon, Raubertas, & Rosenthal, 1993); and reliability (within patient correlation = 0.88 – 0.96 between sensory, affective and average pain scores) (Grafton, Foster, & Wright, 2005).

Aim 1 study variables (see Table 2 for a listing and brief explanation of the variables for Aim 1). The variables for this aim are based on the literature, described in an article by Gardner et al. (2017).

Patient factors

Patient factors associated with high pain include younger age (Stotts et al., 2004), female sex (Morin, Lund, Villarroel, Clokie, & Feine, 2000), African-American race (Stotts et al., 2004; White, Asher, Lai, & Burton, 1999), high anxiety (Woo, Sadavoy, Sidani, Maunder, & Sibbald, 2008), depressed mood, pain catastrophizing (Baker, 2003), high levels of anticipatory pain (Woo et al., 2008), chronic pain condition(s), and opioid tolerance (Gardner et al., 2017).

Age, sex, race These variables are defined using the National Institute of Health categories and definitions. Sex is categorized as male versus female. Race is categorized as white versus non-white (i.e., African American/Black, American Indian or Alaskan native,

TABLE 2 Aim 1 variables

Variable	Method of measurement	Operational definition	Level of measurement
Age	Medical Record/Patient Report	Age (in years)	Continuous
Sex	Medical Record/Patient Report	Male versus Female	Dichotomous
Race	Medical Record/Patient Report	White versus non-White	Dichotomous
Anxiety	Generalized Anxiety Disorder-7 (GAD-7) Scale	Score 0–21	Continuous
Depressed	Patient Health Questionnaire-8 (PHQ-8)	Score 0–24	Continuous
Pain Catastrophizing	Pain Catastrophizing Scale (PCS)	Score 0–52	Continuous
Anticipatory Pain	Numeric Rating Scale (NRS) 0-10	0–10 on NRS	Continuous
Chronic Pain Conditions	Medical Record/Patient Report	No versus Yes	Dichotomous
Opioid Tolerance	Medical Record/Patient Report	No versus Yes	Dichotomous
Duration of Injury	Medical Record/Patient Report	Time from injury/tissue loss ≤7, 8–30, 31–90, 91–256, >257 days	Categorical
Type of Wound	Medical Record/Patient Report	Acute versus chronic	Dichotomous
Clinical Inflammation: Erythema AND Temperature	Clinical Signs and Symptoms Checklist (CSSC) Infrared Thermometer	No versus Yes AND No versus Yes	Dichotomous
Resting Wound Pain	0–10 NRS	0–10 on NRS	Continuous

Asian, multiracial/two or more races, Native Hawaiian, or Pacific Islander).

Anxiety, depression, pain catastrophizing Standardized questionnaires with established validity and reliability are used to measure anxiety (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006), depression (PHQ-8) (Kroenke, Spitzer, & Williams, 2001; Kroenke et al., 2009), and pain catastrophizing (Pain Catastrophizing Scale [PCS] [Osman et al., 2000; Sullivan, Bishop, & Pivik, 1995]). Table 3 summarizes the measurement tools for Anxiety, Depression, Pain Catastrophizing, and Anticipatory Pain; and their validity and reliability.

Chronic pain conditions are defined by any diagnosis documented in the medical record or reported by the participant that the participant reports as painful, such as migraine, fibromyalgia and rheumatoid arthritis. These data are validated with the participant prior to the study dressing change. The participant is asked if they have the condition and if so, if it is painful. Those responding affirmatively are categorized as having a chronic pain condition(s).

Opioid tolerance is defined as a decrease in the response to the medication following the repeated and/or prolonged administration of the medication (Dumas & Pollack, 2008). Participants who had the equivalent of 60 mg of morphine every day for the 5 days prior to the study dressing change are categorized as opioid tolerant. The type, route, and dose of opioids in milligrams or micrograms taken or administered to the participant are recorded. If/when the participant has not been hospitalized for the 5 days prior to the study dressing change, the participant is asked if and what pain medication they have taken during the designated time. This information is used to convert each to morphine equivalents in milligrams using established conversion factors (Dowell, Haegerich, & Chou, 2016). Equianalgesic

calculation provides a point of reference when comparing two medications that differ in potency yet which are supposed to provide the same amount of pain relief (Gordon et al., 1999).

Wound factors

Wound factors believed to be associated with high levels of pain during WCPs include shorter duration of injury (Meaume, Teot, Lazareth, Martini, & Bohbot, 2004), chronic wounds (Price et al., 2008), clinical inflammation (Gardner et al., 2014), and high levels of resting wound pain (Gardner et al., 2017).

Duration of injury is defined as the time from injury/tissue loss to the time of enrolment. Time from injury/tissue loss is categorized as (a) ≤7 days; (b) 8–30 days; (c) 31–90 days; (d) 91–256 days; or (e) >257 days. Although this definition has face validity, in practice its reliability is unclear, especially for chronic wounds that have been present for weeks, months, or years. To enhance validity, we cross-check duration of injury with the medical record and the participant.

Type of wound is categorized as acute versus chronic. Wound type is defined by diagnosis in the medical record by physician or by the Certified Wound Ostomy Nurse (CWON) if the provider has not identified the type of wound in the medical record. Pressure injuries, venous ulcers and arterial ulcers are categorized as chronic while surgical, traumatic, mixed (traumatic wound with surgical fix), and other wounds are categorized as acute. The validity of medical record differentiation is enhanced by observation/assessment of CWON based on known differential criteria for wound type (i.e., participant and wound history, location, appearance) (Doughty & McNichol, 2015).

Clinical inflammation is defined as the presence of erythema extending 2 cm from the wound edge and heat, defined as a positive temperature gradient at the wound margin compared with a control

TABLE 3 Validity and reliability of survey instruments used to measure patient-level factors

Variable	Instrument	Construct and general information	Reliability	Validity	Study
Anxiety	GAD-7	Seven-item questionnaire identifies likely cases of generalized anxiety disorder. Items are rated for past 2 weeks on 4-point scale for the frequency of anxiety symptoms. Scores can range from 0–21, with cut points at 5, 10, and 15 representing mild, moderate, and severe levels of anxiety.	Cronbach's $\alpha = 0.92$	$r = 0.72$ – 0.74 correlated with the Beck Anxiety Inventory, anxiety subscale of the Symptom Checklist-90 Can be used among the general population	Spitzer et al. (2006)
Depression	PHQ-8	Eight-item questionnaire identifies likely cases of depressive disorder (s). Items are rated for the past 2 weeks on a 4-point scale for the frequency of depression symptoms. Scores can range from 0–24, with <10 = negative for depression, ≥ 10 = major depression, and $20+$ = indicates severe major depression.	Cronbach's $\alpha = 0.86$ – 0.89	AUC = 0.95 in discriminating between patients with and without major depression Can be used among the general population	Kroenke et al. (2001, 2009)
Pain Catastrophizing	PCS	Thirteen-item pain questionnaire which measures three domains (magnification, rumination, & helplessness) about pain. Items are rated on a 5-point scale with anchors being “not at all” and “all the time”. Scores can range from 0–52, with a score of 30 representing clinically relevant level of catastrophizing.	Cronbach's $\alpha = 0.95$	$r = 0.80$, $p < 0.001$ when compared with the Fear of Pain Questionnaire Can be used in the general population	Osman et al., (2000); Sullivan et al. (1995)
Anticipatory Pain Intensity	NRS	Self-report on vertical 0–10 Numeric Rating Scale with 0.5 increments. The participant is asked how much pain they expect to have during the dressing change.	The NRS was not developed to assess Anticipatory Pain, thus there is no validity or reliability data for this indication. However, Woo et al. (2008) & Woo (2015) used the 11-point NRS (0–10) to assess anticipatory pain associated with dressing change procedures, and found the NRS is the best method for accurately and reliably determining the participant's real-time pain experience and expectations. *The 0-10 NRS has been assessed for Reliability and Validity for Pain Intensity, this information can be found with the “Pain Intensity” variable.		

site. Erythema is measured using an item from the Clinical Signs and Symptoms Checklist (CSSC) that was developed and tested ($\kappa = 0.70$) by Gardner, Frantz, and Doebbeling (2001). The wound and a control site temperature is measured using a self-calibrating, portable, infrared thermometric probe (Exergen Model DT 1001; Exergen Products, Watertown, MA), that measures temperature in increments of 0.1°F and is accurate to within $\pm 0.2^{\circ}\text{F}$ (Exergen Corporation, 2016). The wound perimeter is “outlined” using the thermometric probe and the highest detected temperature displayed is recorded. This is repeated at a control site that is either at a contralateral location or on another site distant from the wound where the tissue appears normal (e.g., no erythema, wound, scarring). Two measures of inflammation, which is a cluster of physiological responses (i.e., heat, erythema, pain, and oedema), to increase the validity of the presence of clinical inflammation, because these signs and symptoms are subtle and have low reliability when assessed individually, are used (Doughty & McNichol, 2015).

Resting wound pain intensity is measured using a vertical 0–10 NRS with 0.5 increments as described under “pain during study dressing changes” above. The validity and reliability of the NRS was described in that section. The participant is asked how much pain they are having in their wound when resting quietly.

Aim 2 study variables (see Table 4 for a listing and brief explanation of the variables for Aim 2).

Biological mechanisms

Several biological variables represent mechanisms linked to nociceptive sensitivity during WCPs (Brennan, 2002; Sluka, Deacon, Stibal, Strissel, & Terpstra, 1999; Sluka, Vance, & Lisi, 2005). These include wound bioburden (Tengvall, Björnhagen, Lindholm, Jonsson, & Wengström, 2006), inflammatory cytokines (Czeschik et al., 2008; Fukuoka, Kawatani, Hisamitsu, & Takeshige, 1994; Junger & Sorkin, 2000; Kawasaki, Zhang, Cheng, & Ji, 2008; Sorkin, Xiao, Wagner, & Myers, 1997), and wound pH (Kim, Freml, Park, & Brennan, 2007).

TABLE 4 Aim 2 variables

Variable	Method of measurement	Operational definition	Level of measurement
High Wound Bioburden	Swab specimen processed using 16S rRNA sequencing	Microbial load (number of bacterial cells) Microbial diversity: <i>Shannon index</i> <i>Faith's index</i> Relative abundance of: <i>Staph Genre</i> <i>Anaerobic Genre</i>	Continuous Continuous Continuous Continuous Continuous
High Inflammatory Mediators	Swab specimens processed to extract cDNA using qPCR	Cycle threshold (Ct) values	Continuous
Low Wound pH	pH paper (6.5–13.0 pH with 0.5 incremental readings)	pH value	Continuous

Wound bioburden is measured by assessing three dimensions of bioburden: microbial load, microbial diversity, and relative abundance of potential pathogens. These dimensions are measured using swab specimens for high-throughput sequence analysis of the 16S rRNA gene yielding total microbial load, a variety of diversity metrics and the relative abundance of all microbes.

Wound specimens for the 16S rRNA analysis are obtained using Levine's technique, which has established validity compared with wound tissue specimens (Gardner et al., 2006). A pipeline for recovering, amplifying, and sequencing bacterial 16S rRNA genes from wound swab specimens has been optimized (Figure 2). DNA is isolated from samples to maximize both Gram-positive and Gram-negative bacterial and fungal recovery, as described in Grice et al. (2010). Broad-range PCR primers, with barcodes unique for each sample, will amplify hypervariable regions 1–3 (V1–V3) of the bacterial 16S rRNA gene and sequenced on the Illumina MiSeq instrument (Caporaso et al., 2012). Sequences are processed in QIIME (Caporaso et al., 2010; Kuczynski et al., 2011), prior to downstream analyses. Briefly, sequences are first clustered into OTUs (operational taxonomic units, a proxy for "species") using UCLUST (Edgar, 2010) at 97% sequence similarity.

Microbial load is measured using quantitative real-time PCR. Microbial load is extrapolated from real-time PCR data normalized to a well-characterized standard (i.e., *E. coli*); this allows estimation of 16S gene copy number and the number of bacterial cells.

Microbial diversity is calculated using the following alpha diversity indices: (a) Shannon diversity index, an ecological measure of diversity that incorporates the total number of different OTUs and the relative proportion of those OTUs; (b) faith's phylogenetic distance (PD), a measure of biodiversity that incorporates phylogenetic differences between species; and (c) number of observed OTUs. Beta-diversity, or "shared" diversity, is calculated using the UniFrac metric in forms both weighted and unweighted for relative abundance to identify association of microbial community structure with variables (e.g., level of pain). Taxonomic classification of sequences is made using BLAST, as implemented in QIIME (Caporaso et al., 2010).

Relative abundance of putative pathogens in the wounds (e.g., *S. aureus* and anaerobes) is calculated along with other bacterial taxa present, which allow us to identify additional, unrecognized putative pathogens among the wound microbiota.

Using these measures of bioburden, we found that wound duration was positively associated with the number of species-level OTUs ($r = 0.41$; $p = 0.022$) and with a higher Shannon diversity index ($r = 0.32$; $p = 0.020$). Wound depth was negatively associated with *Staphylococcus* ($r = -0.47$; $p = 0.0005$) and positively associated with anaerobic bacteria relative abundance ($r = 0.33$; $p = 0.0182$) (Gardner, Hillis, Heilmann, Segre, & Grice, 2013). These findings demonstrate concurrent validity. Strict quality control measures ensure the results are consistent and reproducible.

Inflammatory mediators (cytokines) Pro and anti-inflammatory cytokines (IL-1b, IL-6, IL-8, and TNF-a) are measured using gene expression. RNA is extracted from the swab specimen (Qiagen RNeasy Mini Kit, Valencia, CA) and reverse transcribed into cDNA (Invitrogen SuperScript IV VILO Kit, Carlsbad, CA). cDNA is amplified using quantitative PCR on the Vii7 real-time PCR platform (Applied Biosystems; Foster City, CA) and custom TaqMan Array Microfluidic cards (Thermo Fisher Scientific; Waltham, MA) to perform 384 reactions simultaneously. Cycle threshold (Ct) values will be measured and relative expression values will be calculated in the Vii7 software by normalizing to an internal control/housekeeping gene to provide consistent results across samples and batches.

Wound pH is defined as the numeric value of acidity or alkalinity on a scale of 6.5–13.0, measured in increments of 0.5 using Micro Essentials, Hydriion pH paper, which was quality tested by the manufacturer using NIST traceable standards. Validity and reliability of using litmus paper for measuring pH of wound fluid has not been reported in the literature. Shukla, Shukla, Tiwary, Agrawal, and Rastogi (2007) used litmus paper to assess pH of standard solutions of known pH and confirmed accuracy of the litmus strips.

Control variables

Dressing and analgesic-intake variables (see Table 5 for a listing and brief explanation of these variables). As previously noted, these variables will be used as additional covariates for estimating the Aim 1 risk model and as covariates when assessing associations in Aim 2).

Type of dressings Dressings are categorized as standard (i.e., gauze- with or without solutions such as Normal Saline or Dakins,

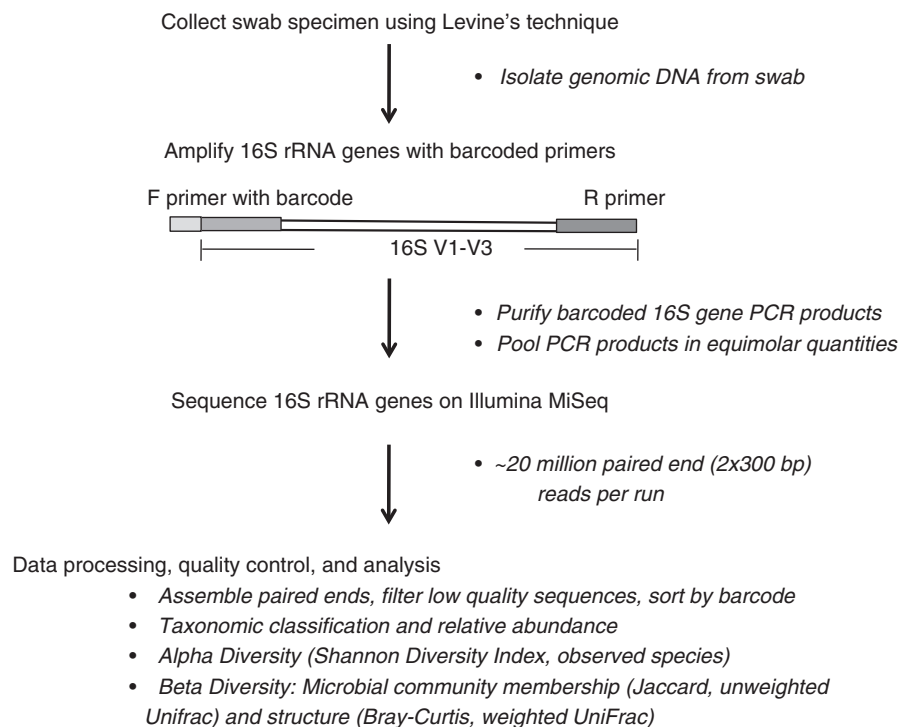


FIGURE 2 16S workflow for analysing wound bioburden

TABLE 5 Aim 1 & 2 control variables

Variable	Method of measurement	Operational definition	Level of measurement
Type of Dressing	Direct observation	Standard versus advanced dressing	Dichotomous
Analgesic intake Preprocedural	Medical record	Number of morphine equivalent opioids AND Number of nonopioid analgesic pills taken up to 1 hr prior to dressing change	Continuous Continuous
Analgesic intake Procedure	Medical record	Number of morphine equivalent opioids given during the dressing change	Continuous

etc.) versus advanced (i.e., hydrogel, negative pressure wound therapy, non-adherent (Mepitel[®], KerraContact[™]), alginate, or hydrocolloid. Type of dressing is observed during the dressing change. Reliability of this method is strong because the same CWON completes the majority of the study dressing changes, identifying the type of dressings used.

Analgesic intake Preventive analgesic intake includes oral, intravenous, or topical analgesics (opioids and non-opioids) given within 1 hr of study dressing change. Procedural analgesic intake includes those opioids and nonopioids given after the start of the study dressing change until it is completed. The type, route, and dose (mg or μ g) of opioid and nonopioid analgesics taken or administered to the participant are recorded. This information is then used to convert opioids to morphine equivalents in milligrams using established conversion factors (Dowell et al., 2016) and nonopioids to number taken/dose. Equianalgesic calculation provides a point of reference when comparing two medications that differ in potency yet which are supposed to provide the same amount of pain relief (Gordon et al., 1999).

2.4 | Data collection protocol

For consented participants, a team of at least two research members, one who is a CWON and one Registered Nurse (RN) research assistant (RA), complete the study dressing and collect study data/specimens. Using the same CWON to change the dressing, controls variability in dressing change technique that could have an impact on pain intensity.

Prior to the study dressing change the participant's medical record is reviewed by the RA for demographic information, medical history, opioid medication history for the previous 5 days and up until 1 hr prior to the dressing change, and adjuvant analgesic medication history. This information is verified with the participant before the dressing change. If the participant has any pain medications available, the team works with the participant's nurse to have them administered as ordered before the study dressing change.

The RA then administers or assists the participants with the GAD-7, PHQ-8, and PCS surveys. After survey completion, the RA asks the participant to rate their resting and anticipatory pain. If pain medications have been administered and have had appropriate time

to work, the study dressing change begins. The CWON removes the old dressing, the time is recorded, and the wound is assessed for presence of sensation while cleansing the site for specimen collection. The wound is measured, photographed, inspected for erythema, peri-wound skin temperature (and a control site, as described above), and depth of tissue involvement. Then, two swab specimens are obtained. Swab specimens are collected using Levine's technique. The wound is cleansed with nonbacteriostatic saline; and a swab (Puritan® Sterile Foam Tipped Applicators, Puritan Medical Products Co LLC; Guilford Maine) is rotated over a 1-cm² area of viable, non-necrotic wound tissue for 5 s using sufficient pressure to mechanically disrupt the extra-polysaccharide matrix of a biofilm and extract wound tissue fluid. The time is recorded when the first swab is obtained, the swab is immediately placed in a 2-ml specimen tube (Eppendorf Biopur Safe-Lock, 2 ml; Hauppauge, NY) with 500 µl of RNA-Later and the other swab in an empty 2-ml specimen tube. Swabs are transported to the lab and stored at -80°C within 30 min of collection. Cytokine and wound bioburden swab specimens are batched for cytokine expression and 16S gene sequencing, respectively. Lastly, a small strip of Micro Essentials Hydrion® pH paper is placed into the wound to absorb wound fluid, or fluid is aspirated into a sterile tuberculin syringe and placed on the pH paper to assess the pH.

After specimens are collected, the wound is then cleansed and/or redressed as ordered by the physician. After completion of the dressing change procedure the participant is then asked what their worst pain was during the dressing change procedure (using the NRS) and which part of the procedure was the most painful (dressing removal, specimen collection, cleansing, or redressing). If the participant identifies that they had pain, they are asked about the quality of the pain using the SF-MPQ pain descriptors. After answering the questions about pain quality, the participant has completed study participation.

2.5 | Data analysis

Study data are collected and managed in REDCap™ (Research Electronic Data Capture) hosted at the University of Iowa Institute for Clinical and Translational Science (NIH CTSA Grant U54TR001356) (Harris et al., 2009). REDCap™ is a secure, web-based application designed to support data capture for research studies, providing (a) an interface for validated data entry; (b) audit trails for tracking data manipulation and export procedures; (c) automated export procedures data downloads to statistical packages; and (d) procedures for importing data from external sources.

For Aim 1, clinically accessible wound and patient factors will be combined in a logistic regression model to produce a risk scale that predicts probability of severe pain during WCPs based on a patient's levels of wound and patient factors. The ability of this model to distinguish between severe and not-severe pain will be assessed by the area under the ROC curve (AUC), which estimates the probability of correctly discriminating between a patient with severe pain and one without severe pain. For Aim 2, we will assess the ability of each

biological mechanism to individually predict severe versus not-severe pain during WCPs, as measured by the AUC. Additionally, a "best" model for predicting severe versus not-severe pain will be determined using forward stepwise logistic regression, where all the biological mechanisms will be candidate predictors. The usefulness of this model will also be described by the AUC. Dressing factors and analgesic intake that may alter pain during WCPs are being measured and will be included as covariates in the Aim 1 logistic regression model and as control variables in the Aim 2 analysis. AUC estimated for the Aim 1 and Aim 2 multiple logistic regression models will be adjusted downward, using bootstrap validation methods as described by Harrell (2015), to account for overly optimistic AUC estimates due to estimating the regression model coefficients and AUC from the same data set (both aims), as well to account for performing variable selection (Aim 2) using the same data set.

2.6 | Ethical considerations

The appropriate Institutional Review Board (IRB) has approved all study protocols. The IRB approves all protocol modifications in addition to an annual continuing review to ensure compliance with human participant protections.

Briefly, the research team verbally describes all study procedures to eligible patients and their right to withdraw from the study at any time, the right to refuse to answer survey questions, and that their decision to participate or not will not have an impact on their care. Participants are then provided a written consent form to sign. All participants who complete the study are reimbursed for their time.

2.7 | Validity and reliability/rigour

The validity and reliability of all study measures are reported under Design/Methodology. We will also analyse and report the validity of the established survey tools (e.g., GAD-7, PHQ-8) in our population. The reliability of study data will be analysed through the use of consistency checks to identify inaccurate data and or recording. Although this is not a randomized clinical trial, we are using a CONSORT framework to describe recruitment and enrolment data according to inclusion/exclusion criteria and withdrawal from the study. Therefore, we will be able to fully describe the participants and nonparticipants in the study that may influence or bias study findings.

3 | DISCUSSION

Based on experience, adjustments were made in this application that facilitate obtaining an adequate sample, including a 3-year plan for enrolment. If we encounter difficulty obtaining the needed numbers of participants, or if enrolment of chronic wounds falls below 30% of the sample, we will seek to case-find, recruit, enrol, and collect data from outpatient UIHC clinics, including the vascular clinic.

Type of wound may have an interaction effect on pain during WCPs. Alternative strategies will be used to examine separately wound and patient factors for acute versus chronic wounds.

The proposed study addresses “severe” pain (8–10 on a 10-point NRS) because, in our view, predicting and controlling this level of pain would be a significant advance in wound care. We do recognize that moderate levels of pain (4–7) are also problematic so predictions of moderate pain will be examined in exploratory analyses and biological mechanisms associated with moderate pain will be explored by alternative analyses that treat pain during WCP as an interval level variable.

The use of 16S rRNA gene sequencing to characterize wound bioburden may fail to identify significant relationships between bioburden and pain during WCPs. An alternative strategy will be to employ much more expensive and difficult metagenomic techniques that provide a much higher resolution of microbial characteristics, such as strain and pathogenicity factors.

3.1 | Limitations

The cross-sectional study design precludes examining the role of pain during WCPs on wound outcomes, such as healing. A second limitation is recruitment of inpatients only, which may limit generalization of study findings to outpatients.

4 | CONCLUSION

Although previous studies have examined various aspects of pain during WCPs, the major innovation of this proposal over previous studies is that it is the first to systematically examine a comprehensive set of wound, patient, and biological factors for their individual and collective associations with pain during WCPs using precisely defined and rigorously measured study variables. This study has the potential to make significant contributions because the predictive risk model developed in Aim 1 will enable clinicians to target those patients requiring preventive pain control, thereby (a) eliminating the spiralling impact of painful procedures on nociceptor sensitisation and development of anticipatory pain, (b) increasing appropriate use of advanced wound dressings to minimize painful dressing changes, and (c) reducing the use of opioids and their undesirable side effects. This study will provide valuable information to begin development of a clinical tool to guide health-care provider’s management of wound pain during painful dressing changes. In addition, this study will provide information on mechanisms associated with severe pain during WCPs so novel pain control strategies can be developed.

AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE [<http://www.icmje.org/recommendations/>]):

- substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
- drafting the article or revising it critically for important intellectual content.

CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

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