Research Protocol: Effects of Relaxation on Wound Healing

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Introduction

Recovery after an injury or surgery relies on successful wound healing. Poor wound healing can increase the risk of infection, patient discomfort, morbidity, and mortality (Eming & Tomic-Canic, 2017; Gouin & Kiecolt-Glaser, 2011). Not only are there direct patient impacts, but poor wound healing can also put extra strain on the healthcare system by increasing the length of hospital stays and therefore costs related to hospital care (Broadbent et al., 2003; Eming & Tomic-Canic, 2017; Robinson et al., 2017). As a process of healing disrupted tissue, wound healing involves the stages of clot formation, inflammation, proliferation, and remodelling (Irwin & Vedhara, 2007). The duration and success of healing at each stage depend on the immune system's functioning, which is vulnerable to the effects of psychological variables, including stress (Walburn et al., 2009).

Stress can work through several fundamental mechanisms to adversely impact wound healing processes (Gouin & Kiecolt-Glaser, 2011; Walburn et al., 2009). Psychological stress is the imbalance between a high demand on a person and a low perceived ability to cope (Cox & Mackay, 1976). Stress activates the hypothalamic-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes in the body, which release catecholamines (epinephrine and norepinephrine) and glucocorticoids (cortisol). These stress hormones have immunosuppressant effects on the cytokines and growth factors available to regulate each stage of wound healing. The cascading effects from these disturbances prolong the wound healing process and increase the risk of problems, including infections (Glaser et al., 1999; Kiecolt-Glaser et al., 2005; Li et al., 2007; Rodriquez et al., 2008). Stress also has indirect effects on wound healing by increasing poor health behaviours such as smoking, alcohol, poor diet, lack of sleep or exercise, and non-adherence to medication (Robinson et al., 2017).

As stress can impair the wound healing process, several studies have investigated whether psychological interventions can reduce stress and improve wound healing. Psychological interventions can reduce physiological arousal, stress, and anxiety and alter patients' health behaviours and expectations of recovery and pain (Robinson et al., 2017). Systematic reviews by Robinson and colleagues (2017) and Geers and colleagues (2018) support the hypothesis that wound healing can be positively affected by a range of different psychological interventions including relaxation (Broadbent et al., 2012; Gouin, 2008; Han, 2002; Holden-Lund et al., 1988; Rice et al., 2001; Robinson et al., 2015), expressive writing (Koschwanez et al., 2013; Weunman et al., 2008), social support (Ginandes, 2003; Robles 2007) and yoga (Oswak et al., 2011; Rao et al., 2008).

Of these interventions, relaxation was found the most beneficial for wound healing outcomes (Robinson et al., 2017). Relaxation interventions can include deep breathing, guided imagery, biofeedback, and progressive muscle relaxation techniques. These techniques aim to counterbalance the stress response by reducing autonomic arousal and lowering stress hormones at the wound site, resulting in improved healing (Jacobs, 2001; Robinson et al., 2015). Relaxation interventions have been found to significantly increase the amount of collagen deposition (Broadbent et al., 2012), lower erythema (Holden-Lund et al., 1988), increase peripheral perfusion in foot ulcers (Rice et al., 2001), induce faster healing of stomach ulcers, and increase skin barrier recovery rates (Robinson et al., 2015). These findings demonstrate that relaxation is associated with better wound healing in a variety of different wound types.

Traditional methods of audiotapes and human-led relaxation are the most studied delivery method. Audiotapes are instructional and can be used from home, but they only provide passive information and guidance. Unlike audiotapes, human involvement can add

social support, interaction, accountability, and feedback while guiding patients through a relaxation script and teaching relaxation techniques. Studies in other health conditions such as tension headaches have found that audiotaped instructions and treatment manual are more cost-effective and are comparable at reducing headaches compared to therapist-led or supported relaxation sessions (Teders et al., 1984). However, there is no research comparing delivery methods for reducing stress and wound healing.

Due to the increasing strain on the healthcare system from overpopulation, understaffing, lack of resources and the recent COVID-19 pandemic, it is not feasible for all patients to access and afford human-led interventions (Bradbury et al., 2014; Fagherazzi et al., 2020). It is, therefore, crucial that effective health interventions, such as relaxation can be delivered remotely. Patients are already beginning to use mobile apps and the internet to access healthcare, including relaxation and stress management. Relaxation instructions on the internet include online relaxation programs (Alfonsson et al., 2015), computer administration (Carbring et al., 2007), audio tracks available on YouTube, Soundcloud and Google Drive platforms (Cancer Society NZ, 2021), guided audio clips on a website (Pizzoli et al., 2020), and mobile applications (Weekly et al., 2018). Taking advantage of technology for healthcare can offer a delivery approach that is affordable, easily accessible and integrated alongside existing healthcare practice, and can reduce healthcare burden, provide support for the most vulnerable patients and be a safe alternative to human-led relaxation during a pandemic (Bradbury et al., 2014; Fagherazzi et al., 2020; Murray et al., 2016).

As a novel digital health intervention, digital humans are a form of embodied conversational agent (ECA) that includes a computer-based dialogue system and a virtual embodiment (Cassell et al., 2000; Sagar et al., 2014). A virtual embodiment refers to an animated face or body presented on a computer screen. Digital humans use artificial

intelligence in the form of neural networks to learn and respond to user input, such as human facial expressions, movement, and speech (Loveys et al., 2020; Sagar et al., 2016).

Digital humans may have additional benefits to audiotapes because of their multimodal emotional expression and virtual embodiment features. Through multimodal emotional expression, digital humans may provide social and emotional engagement and support (Loveys et al., 2020). Other ECAs have been found to have a greater social presence than disembodied social agents (Lee et al., 2006) and similar social presence to physically embodied agents (Thellman et al., 2016) suggesting that the virtual embodiment of digital humans may increase social presence during the delivery of relaxation.

There is also the opportunity for digital humans to become digital therapists to deliver health or mental health interventions, such as Cognitive Behavioural Stress Management (CBSM; Loveys et al., in prep), cognitive behavioural exercises for loneliness and stress in older adults (Loveys et al., in prep) or medical interviews (Micoulaud-Franchi et al., 2016). The features of digital humans are likely to increase social presence, detect emotions, be supportive and provide feedback, which could then help people to form relationships with the digital human. Together, this may provide a delivery method that could be more engaging, naturalistic, and interactive than a website, mobile app, or audiotape. Digital humans are a practical delivery method as their benefits are similar to human-led delivery but without the cost, poor accessibility and safety issues.

Because digital humans are increasingly being used to deliver healthcare interventions, it is important to test whether they can effectively reduce stress by giving relaxation instructions. This study will measure stress reduction and its effects in several ways, including self-reports, biological and physiological indices, and wound healing. Wound healing offers an outcome that reflects the functioning of the immune system and is also

clinically relevant. Including immunological measures such as skin barrier recovery (SBR) and multiple stress measures in the current study will further understand the underlying mechanisms through which relaxation works on wound healing. The knowledge gained from this study will help determine whether digital humans, as an accessible, affordable, engaging, and naturalistic delivery method, effectively reduce stress and improve wound healing. This new knowledge can then help improve health outcomes in patients with wounds to reduce the risk of infection, mortality and patient discomfort. If digital humans are similar or more effective than audiotapes in delivering relaxation in a healthy population, future research could investigate the feasibility of using digital humans in clinical or vulnerable populations and different cultures.

Aims

The primary aim of this study is to investigate the effects of different delivery methods of a brief relaxation intervention, including audiotapes, a digital human and magazines (control), on wound healing, as indexed by SBR after tape stripping.

The secondary aim is to investigate whether stress reduction (biological, physiological and self-reported) mediates the relationship between relaxation and wound healing.

The tertiary aim is to investigate the effects of different delivery methods of a brief relaxation on levels of anxiety, pain, stress and relaxation (psychological measures) and the level of engagement, satisfaction, and opinions of the digital human delivery in comparison to the audiotape delivery.

Hypotheses

1. It is hypothesised that both the digital human and audiotape conditions will have improved SBR after a tape-stripping wound, as assessed by trans-epidermal water loss (TEWL), compared to the control group, who did not receive a relaxation intervention (only magazines).
2. It is hypothesised that there will be no differences in SBR after a tape-stripping wound, as assessed by TEWL, between the digital human and audiotapes condition.
3. It is hypothesised that the relationship between relaxation and SBR will be mediated by levels of stress (biological, physiological, and self-reported) .
4. It is hypothesised that the digital human condition will have greater improvements in anxiety, stress, pain and relaxation levels and better compared to the audiotape delivery and magazines (control group).

Method

Study design.

This randomised controlled trial will use a 3 (time-point) x 3 (condition) mixed factorial experiment to investigate the effects of different delivery methods (digital human v audiotape v control) of relaxation on SBR after tape-stripping.

Participants

Inclusion criteria. Participants will be eligible for inclusion if they are over the age of 18 and can speak, read, and write in fluent English.

Exclusion criteria. Participants will be excluded from the study if they are allergic to adhesive tape, have any inflammatory skin diseases/immunological-related health problems,

are taking medication that affects immune functioning (e.g., prednisone), are pregnant, over the age of 60 or have hearing difficulties or vision loss.

Sample size. The sample size was calculated using G*Power (Faul et al., 2007) with a *mixed factorial ANOVA*. A power level of .80 and a two-tailed significance level of $\alpha = .05$ was chosen, with an expected effect size of $f = 0.30$, based on previous research investigating a relaxation intervention on SBR (Robinson et al., 2017). Using these parameters gives a required sample size of 75. Like previous tape-stripping studies, this will be increased by 20% to account for possible errors in the TEWL measurements (Law et al., 2020), giving a final sample size of 90 participants (30 participants per group).

Procedure

Ninety participants will be recruited from the local community using flyers, email lists and online advertisements between March and September (or until the sample size has been fulfilled). To ensure appropriate recruitment of Māori, researchers will use their connections with a Māori health organisation and the local community to talk, distribute flyers/information, network and build relationships (whakawhanaungatanga) with potential participants and their whānau. Participants interested in the study will be asked to email the researcher to fill in an eligibility screen and read the participant information sheet (PIS). Participants are offered the option of talking with whānau or support people if they would like to, before choosing to participate in the study. Eligible and interested participants will be then contacted to organise an appointment time when they are available.

Following salivary procedures and to reduce interference in the TEWL measures, participants will be asked not to drink caffeine, juice or alcohol 18 hours before the study and not eat, shower, exercise or apply moisturiser in the hour before the study (Law et al., 2020a). Appointments will be conducted in the afternoon as cortisol is typically higher in the morning (Fries et al., 2009), and in a ventilated room also in accordance with Tewameter probe recommendations (Robinson et al., 2015). When participants come into the clinic, they will be asked whether they would like to open with a karakia if appropriate to them. They will get the chance to re-read the PIS and ask any questions before deciding whether to give their free and full informed consent. After consent, the baseline questionnaires (demographics, health-related behaviours, and psychological variables) will be completed. Following this, baseline measures of cortisol and alpha-amylase (through a saliva sample) will be taken. Participants will be instructed to start wearing the wrist sensor for the rest of the experimental session (as a measure of heart rate and skin conductance).

After collecting baseline measures, the researcher will conduct the tape stripping procedure. Tape-stripping is a non-invasive experimental wound technique and standardised wound healing model that removes the outer layer of skin (the stratum corneum) through repeated application of the adhesive tape (Altemus et al., 2001; Irwin & Vedhara, 2007). By doing this, the skin cannot regulate water movement in and out of the skin, creating skin barrier disruption (Walburn et al., 2009). To get a baseline measure of this skin barrier function, a TEWL measurement will be obtained using a Tewameter 300 probe which measures the evaporation rate (g/m2h) in the air layer next to the skin (Law et al., 2020b). TEWL, the skin's ability to prevent water loss, increases when the stratum corneum is disrupted and decreases when it heals. The probe must first be calibrated and preheated to 34°C (skin temperature), with constant ambient room conditions (Koschwanez & Broadbent, 2011). On each participant's non-dominant forearm, four 1cm2 sites will be marked, with one

being the (undamaged) control. The probe will take one measurement every second for 60 seconds to measure the baseline values for each of the four sites one at a time. New pieces of tape will then be applied with pressure to the three test sites and gently peeled until the TEWL reaches 15 g/m2h above baseline or 40 pieces of tape have been used. A TEWL measurement for each site will then be measured to examine the level of skin barrier impairment because of the tape-stripping. Immediately after the tape-stripping, participants will complete the post-tape-stripping questionnaire, the second saliva and TEWL measurements.

After the tape-stripping procedure, participants will be randomised to either the digital, audiotape, or control condition using a random online number generator by a researcher not involved in the study, completed in advance. Group allocation will be revealed after the researcher opens the sealed, opaque envelope containing each participant's assigned condition, after which the researcher will no longer be blinded to the conditions. As previous research has found that a relaxation session before and after tape-stripping can improve wound healing, this study will deliver the relaxation after the tape-stripping procedure for clinical practicality as there is often little time for relaxation to be done before an acute wound or pre-surgery (Robinson et al., 2015).

Participants allocated to the digital intervention will complete the digital human delivered relaxation intervention for 25 mins. During this time, the digital human will guide participants through progressive muscle relaxation and guided deep breathing. Those in the audiotape condition will be instructed to follow instructions on the computer (using the same script as the digital human condition). Those allocated to the control condition will be told to wait 25 minutes for their skin to recover while given magazines to read. The researcher will leave the room but will be next door in case there are any issues.

The researcher will return to the room once the intervention period is over, and participants will be asked to complete the post tape stripping questionnaires and the final TEWL measurements and saliva sample. The TEWL measured after the intervention period will be used to calculate SBR, an index of how fast the skin barrier recovered from the skin barrier disruption caused by the tape-stripping procedure. At the end of the session, participants will be given a $30 voucher as compensation for their time.

Intervention

Relaxation intervention delivered by the digital human. Participants will interact with the digital human for 25 minutes. During this time, the digital human will guide participants through progressive muscle relaxation and guided deep breathing.

Relaxation intervention delivered by the audiotapes. Participants will be asked to listen to the audio recording on the computer to guide them through a relaxation intervention (the same progressive muscle relaxation and guided breathing script as the digital human) for 25 minutes.

Control. The control condition will not be provided with a relaxation intervention, only magazines while participants are told to wait and see how their skin recovers. Magazines have been used as a control condition in previous studies as a neutral activity to prevent participants from becoming too bored (Robinson et al., 2017).

In all conditions, the lights in the room will be dimmed to make the room more relaxing.

Baseline Measures

These are measured to describe the sample and control for any differences between groups, because these variables have been previously shown to affect healing and immune parameters (Law et al., 2020a, 2020b; Robinson et al., 2015).

Demographics. Participants will be given a demographics questionnaire which includes questions regarding age, weight, height, ethnicity, and education level. Collecting data on these variables will allow for subgroup analysis and comparisons of the groups at baseline.

Health behaviours. Participants will be given a questionnaire that includes questions about alcohol consumption, physical exercise, diet, smoking status, and sleep. Alcohol consumption will be assessed from 1 (never) to 6 (every day) in the past three months. Participants will be asked how often they did physical exercise for more than 30 minutes in an average week from 1 (never) to 8 (every day). Diet will be assessed from 1 (very poor) to 5 (very good) in the past week. Participants will be asked to give their smoking status and the number of hours slept in the past 24 hours.

Perceived stress. The Perceived Stress Scale (PSS) measures the appraisal of how stressful situations in one's life are perceived (Cohen, 1983), and will be assessed at baseline only. It uses a 10-item Likert scale to rate how often respondents felt or thought a certain way in the last month from 0 (never) to 4 (very often). Scores are totalled across items and range between 0 and 40. High scores on the PSS indicate participants are experiencing a greater level of perceived stress. The scale has shown good reliability ($\alpha > .70$) and validity in different ethnicities and clinical samples (Lee, 2012).

Primary outcome measures

Tape stripping and SBR. The final SBR value for each site is determined by the TEWL readings from the three time-points. An overall TEWL reading comes from averaging 20 consecutive measurements with a standard deviation below 0.5 for each site and time point. To get the SBR percentage from the TEWL readings the following formula is used: (TEWLelevated – TEWLrecovery) / (TEWLelevated – TEWLbaseline) x 100 (Robles, 2007; Robles et al., 2009). A higher percentage means a higher SBR during the intervention period (faster wound healing). SBR values will be excluded if there is incomplete data, are more than two standard deviations above the mean, or sites are not within 30g/m^2h of each other (Law et al., 2020a). This outcome has concurrent validity with gravimetrically assessed absolute water loss rates (Fluhr et al., 2006).

Secondary outcome measures

Biological Measures. Salivary cortisol and alpha-amylase are reliable and valid measures of stress-related biological markers of stress if standardised procedures (as above) to reduce confounders are used (Strahler et al.,2017). The collection of these samples is necessary to investigate whether the intervention had any effect on physiological stress and test the secondary hypothesis regarding stress mediating the relationship between relaxation and wound healing. Having these measures is important for further understanding of the underlying mechanisms through which relaxation works on stress and wound healing.

Saliva samples will be obtained at three-time points; baseline, after tape-stripping and after the intervention period, using standardised SaliCaps collection devices (IBL, Hamburg, Germany). Participants will be asked to rinse their mouth with water beforehand and not

swallow for two minutes to collect saliva in their mouth naturally, using the passive drool technique, before transferring their saliva into the SaliCap. After collection, the saliva samples will be stored at -20°C at the University of Auckland and then shipped for analysis on dry ice to the University of Vienna. Cortisol concentrations will be determined using commercial enzyme-linked immunosorbent assay (ELISA, IBL, Hamburg, Germany), while alpha-amylase will be determined by a kinetic colormetric test with reagents from Roche (Roche Diagnostics, Mannheim, Germany; Law et al., 2020a; Robinson et al., 2017).

Physiological measures. Participants will wear a wrist sensor (Empatica E4) which will continuously measure blood volume pulse and electrodermal activity for the duration of the session. Blood volume pulse will be converted into a measure of heart rate. Electrodermal activity will be used to measure changes in electrical resistance in the skin (skin conductance). Heart rate and skin conductance will be used as physiological measures of stress and relaxation.

Psychological measures. Participants will be given a visual analogue scale at the three time points to measure participants level of relaxation, stress, anxiety, and pain where they are required to mark a cross on a 100mm line how they are currently feeling. Scores are derived by using a ruler and measuring the distance (in mm) from the "not at all" anchor to the cross the participant placed on the line. A high score indicates that at the current time the participant has greater intensities of felt stress, anxiety, and pain and lower levels of relaxation.

The relaxation scale ranges from "not relaxed at all" to "extremely relaxed", the stress scale from "not at all stressed" to "extremely stressed", the anxiety scale from "not at all anxious" to very anxious" and the pain scale from "no sensation of pain" to "most sensation

of pain imaginable". These measures have been used in previous tape stripping and psychological intervention studies to assess participant psychological state (Law et al., 2020a; 2020b; Robinson et al., 2015).

Relaxation Delivery Feedback. There will be two visual analogue scales (on a 100mm line) asking about participant's satisfaction and engagement during the relaxation session from "not engaging at all" to extremely engaging" and "not at all satisfied" to very satisfied". The second part of this section is qualitative and will ask participants to write what they liked about the session's delivery and how it can be improved. These questions have been adapted from Loveys and colleague's feasibility study investigating digital humans and CBSM (in prep). Including this questionnaire is necessary to understand how people respond to the digital human.

Analysis

A mixed factorial ANOVA will be conducted to assess differences in SBR between conditions, in addition to an ANCOVA (to control for covariates related to SBR rates such as age, number of strips of tape, and levels of skin barrier impairment; Law et al., 2020; Robinson et al., 2017). For the secondary outcomes (biological, physiological, and psychological measures), mixed factorial ANOVAs will be conducted to analyse the main and interaction effects of time-point and condition. The data will be checked for violations of the normality assumption before analysis. To investigate whether psychological and physiological stress levels mediate the relationship between the delivery condition and SBR, separate exploratory mediational analyses will be conducted.

Ethics

Participants will be required to complete written informed consent before participating, and all researchers and involved staff will sign confidentiality agreements. Questionnaire and laboratory data will be stored under an anonymous number code for each participant. Participant names and contact details will only be linked to the data via a master sheet stored in a locked file, separately from the data. Data will be securely stored in password-protected files on secure, encrypted servers at the University of Auckland. No information that could identify a participant will be published. All data and results will be reported as averages and not individual results. Human tissue in the form of saliva samples and its data collected from the study will be stored ethically and securely (Reid et al., 2017) at the University of Auckland before being transported overseas for analysis and appropriately disposed of after use. Ethics approval will be sought from The University of Auckland Health Research Ethics Committee (AHREC).

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