Project plan & protocol

Study title:

Home use of TENS for bladder function improvement in chronic spinal cord injury: a pilot translational study

Short title:

Home Bladder Neuromodulation for Chronic SCI

- TENS-SCI Protocol V 1.3 (2021) DATE: 18/10/2021
- Australian New Zealand Clinical Trials Registry (ANZCTR: ACTRN12621000869875p)
- Ethics approved (HDEC-Ethics Ref: 21/STH/171)

Project summary / overview

Background & rationale: New Zealand has significant 3,500 people suffering from spinal cord injury (SCI) through traumatic and non-traumatic causes. Due to medical advances, most people living with SCI now have a near-normal life expectancy, and the focus has shifted to improving their quality of life. Neurogenic bladder dysfunction after SCI occurs in nearly every case and has a significant impact on their quality of life and their families. Our systematic literature review and meta-analysis have found that the use of transcutaneous electrical nerve stimulation (TENS) following SCI at home can improve bladder function.

Objectives: We propose a pilot translational study to evaluate that TENS is safe and feasible to be performed at home in people with chronic SCI.

Methods/Design: Participants are 20 chronic SCI adults (>1year post-injury) who currently utilise intermittent catheterisation for bladder management in the community will be recruited. All participants will receive transcutaneous electrostimulation using a FDA-approved TENS device via skin-surface electrodes to stimulate the S3 dermatomes by self-administration or caregiver 15 minutes daily for 4 weeks, in their homes. Primary outcomes will be the safety, feasibility and compliance of a daily home TENS protocol. Secondary outcomes will include efficacy based on a bladder diary and Neurogenic bladder symptom score (NBSS) of 4-week home use of TENS.

Discussion: During the 2-year project, we will investigate whether using TENS at home is safe and feasible to be performed in people with chronic SCI. We will study overall satisfaction with TENS as a bladder management option based on the survey questionnaire available in both paper-based and secure online platforms. A bladder diary will be used to evaluate changes in the Neurogenic bladder symptom score (NBSS), frequency of incontinence with TENS compared to baseline, as well as the frequency of catheterisation and whether volumes voided improve with TENS use. This research project is achievable and will be translated into better health outcomes and a community benefit for New Zealanders living with chronic SCI.

If successful, the study has the potential to substantially improve bladder management and quality of life of people with SCI. It will add to our knowledge regarding neuromodulation in bladder dysfunction in general for the ultimate benefit of all New Zealanders. This project is a partnership with the Auckland Spinal Rehab Unit and is allied with the NZ spinal cord impairment action plan by the Ministry of Health to support people with SCI to enhance their health outcomes and maximise their quality of life.

Background

New Zealand has a very high incidence (49.1 per million people) of spinal cord injury (SCI) with approximately 80–130 SCI participants each year [1],[2] and 217 new cases were reported between 1 January and 31 December 2018 [3]. Currently, spinal cord impairment affects approximately 3,500 people in New Zealand [4]. Neurogenic bladder dysfunction after SCI significantly impacts participant's quality of life and entails a substantial clinical burden. Survey studies report that bladder problems are the second leading reason SCI participants seek medical care [5]. Almost 80% of SCI participants report some degree of bladder dysfunction within one year of injury and 42% are hospitalized for urinary problems every year [6],[7]. Renal failure and urinary sepsis historically were the major causes of death in SCI participants after recovery from the initial injury [8]. Most SCI people have urinary retention and/or incontinence, often resulting in restricted social activities and impaired quality of life [9].

Advances in urological care, specifically the introduction of clean intermittent catheterisation (CIC) have improved the care of SCI participants [10],[11]. However, due to significant inconvenience, potentially increased dependence and frequently continued leakage, non-compliance and discontinuation of CIC are common among SCI participants [12]–[14]. Currently available treatments including pharmacologic therapy, botulinum toxin injections, surgical bladder augmentation and surgically implantable neuromodulators are often unsatisfactory with side effects and high complication rates, therefore new modalities should be explored.

To overcome these limitations, non-invasive modalities of neuromodulation such as transcutaneous electrical nerve stimulation (TENS) have been employed for the treatment of neurogenic bladder following SCI [15]. The advantages of such non-invasive modalities are better safety profiles, lower morbidity and lack of significant adverse effects with transdermal stimulation [16]. The safety of TENS is based on the occurrence of no significant adverse reactions to transcutaneous electrostimulation encountered in many studies. Electrotherapy was used previously to improve bladder control with different conditions, including acute SCI [17], multiple sclerosis [18], myelomeningocele [19] and spina bifida [20], performed in children [21] or elderly [22] participants. This strengthens the evidence that the TENS technique is safe and well-tolerable therapy.

To the best of our knowledge, no trials were conducted to investigate the feasibility of implementing TENS within a bladder management protocol in chronic SCI participants in NZ. The current study aims to investigate the safety and efficacy of TENS using this novel approach to establish feasibility, usability and safety as an adjunctive intervention for improving bladder management in chronic SCI care.

Our project has met clinical trial research regulation during COVID-19 using telehealth and courier services for participant recruitment, consent and a 4-week trial at participants' homes. Conducting research away from research facilities helps to minimise interpersonal contact as we continue to

respond to COVID-19 and reduce travel costs for our participants. Avoiding university research visits during lockdown is aimed to keep participants safe. The research team can also carry out participant recruitments and conduct trial by phone including video conference, to courier investigational packages to participants' dwellings.

Objectives

Neuromodulation techniques have been safely used for improving neurogenic bladder in chronic SCI for many years. However, bladder neuromodulation is only being performed in the clinic setting requiring frequent visits, limiting its use in a population known to have high healthcare costs and barriers to accessing medical care. Based on our experience, we believe we can develop a home-based translational study.

Aim 1: Determine the safety, feasibility, and compliance of a daily home TENS protocol in chronic SCI provided by self-administration or by caregiver for 4 weeks. (Primary outcomes)
Hypothesis 1.1: TENS at home is feasible and safe with high compliance.
Hypothesis 1.2: TENS protocol will demonstrate participant's satisfaction as a bladder management option based on the survey questionnaire.

Aim 2. Determine the efficacy of a 4-week home TENS protocol. (Secondary outcomes)
Hypothesis 2.1: Neurogenic bladder symptom score (NBSS) and frequency of incontinence will improve with TENS compared to baseline.
Hypothesis 2.2: Frequency of catheterisation and volumes voided will improve with TENS compared to baseline measurements based on the bladder diary.

Study Design

- Anticipated number of participants to screen: 40
- Anticipated number of participants to enroll: 20
- Anticipated dropout or loss to follow-up: 4
- Expected duration of participation: 4 weeks
- Approximate time to complete study recruitment and conduct trial: 2 years

Study population
Participants will be chronic SCI adults (> 1-year post-injury) who are interested and meet the inclusion criteria (Table 1). We will use digital recruitment campaigns including flyers, community/library notice boards, and social media to advertise our clinical research study and recruit participants. We also collaborate with the Catwalk Spinal Cord Injury Research Trust, New Zealand Spinal Trust and New Zealand Spinal Cord Injury Registry to recruit individuals through their networks and media resources.

Screening and enrolment

If participants are interested and eligible after completing the self-screening survey, they will be invited to watch a short video demonstration of the procedure (3D animation) and contacted by phone call or video conference for pre-screening questions and explaining the study. Then they

will receive the participant information sheet and consent form either paper-based or online platform for review and sign. After completing the informed consent, they will be enrolled in the study prior to complete questionnaire. Those with tetraplegia will unlikely to have the ability to sign and we will have a 3rd party or caregiver attest to the consent.

Participants will participate at their home and will receive the delivery package (protocol instructions, a bladder diary, a urine measuring cup, a TENS device and accessories) sent to their home within 5-7 working days after the investigator receives and checks the participant consent form. TENS use tutorial with a mannequin torso will be performed during a video conference with the participant and the investigator.

Participant replacement
Participants who dropout will be replaced by recruitment as described above and asking for informed consent from those who meet the I/E criteria.

Table 1. Inclusion/ Exclusion Criteria

Inclusion	**Exclusion**
• 18-75 years old, living in the North or South Island	• Normal voluntary urination control at home
• Neurologically stable SCI for ≥ 12 months	• Other diagnoses to explain incontinence (UTI, bladder stones, multiple sclerosis, TBI, Stroke, etc.)
• SCI may have varying causes: traumatic and non-traumatic SCI e.g., infection, tumours, disc herniation, etc.	• Cutaneous pathology preventing electrode placement e.g., bedsore, pressure ulcer at the perineum
• Level of injury T12 or above (upper motor neuron bladder dysfunction) with no lower motor neuron lesions	• Known lower motor neuron pathology to the sacral nerve, bladder or the lower urinary tract • History of autonomic dysreflexia
• Intermittent catheterisation to empty bladder	• Inability to participate in assessments due to dementia, cognitive impairment, language difficulties
• Stable bladder, no symptoms of UTI • Medically stable for urination ≥ 3 months	• Current pregnancy, febrile pathology, UTI, cachexia, malignant cancer, cancer at the stimulation site
• Able to understand risks and benefits of participating in the study	• Demand-type cardiac pacemaker or implanted electronic medical devices

TENS Protocol

A non-invasive portable unit uses a battery-operated electrical circuit with a fixed mode setting. TENS will be applied with two surface electrode pads (6x8 cm) over S_3 dermatomes at the junction of buttock and upper thigh (Fig. 1) during a comfortable and stable position e.g., lateral recumbent position. Participants will receive an intervention with 50 mA (Level 6 of 10) intensities, stimulation frequency of 25 Hz and pulse width of 400μs. A burst mode of 4-second stimulation and 1-second pause is applied for 15 minutes (Auto-Off) daily for 4 weeks to achieve a modulating effect without causing skin injury. Participants will be called weekly to capture the information from the bladder diary log (available in both paper-based and secure online platforms) and to monitor any side effects of TENS with the progress of protocol.

Pre/post-intervention

On the first day, the bladder diary will be filled in to provide a baseline without TENS (pre-intervention). After finishing the 4-week protocol with TENS-intervention at home, the recording

will be continued for one more day without TENS (post-intervention) to monitor ongoing function after stopping stimulation and to confirm that the improved outcomes are due to the intervention.

Final assessment, post-study, follow-up and procedures
Upon completing the 4-week study, participants will complete final questionnaires and surveys (available in both paper-based and secure online platforms) and return the recorded documents with the TENS device using courier service provided. The data will be statistically analysed in the post-study records and follow up by phone. If withdrawal occurs, no evaluation will be required at the final study, regardless of the withdrawal reason.

Table 2. Timeline of the protocol per participant, weeks in study protocol

Activities	**0**	**W1**	**W2**	**W3**	**W4**
Self-screening survey	X				
TENS video demonstration (3D animation)	X				
Phone call or video conference	X				
Informed consent	X				
Participant information questionnaire	X				
Neurogenic bladder symptom score (NBSS) baseline	X				
TENS tutorial and practice on dummy (video conference)	X				
Home					
Intervention (TENS – 4 weeks)		□ - - -	- - -	- - -	- - - □
Bladder diary and adverse event recording (4 weeks)		□ - - -	- - -	- - -	- - - □
Phone call or video conference weekly		X	X	X	X
NBSS / TENS satisfaction questionnaire after TENS use					X
Completion Data					X

Assessment

During enrolment, participant's data will be retrieved via telephone call or video conference and placed into a data spreadsheet. Clinical demographics and motor level of incomplete SCI will be obtained during the interview between participants and the investigator. Video and telephone calls will not be recorded and no information from hospital or GP records will be collected. Medications that may influence the bladder will be recorded. The bladder diary will be used to collect the following data; use of TENS with a fixed setting, a log of frequency of catheterisation (count per day) and volumes per void (ml per collection) as well as a log of incontinence episodes (Table 3). Missing data in the bladder diary, questionnaire and survey will be requested directly from the participants at week 4. Skin inspection will be performed before and after the stimulation session at the electrode sites by participants or caregivers daily and recorded in the logbook.

Description of other observed changes, including but not limited to fatigue, pain, spasticity, bowel program changes, and sexual function changes will be recorded. The investigator will call participants weekly to capture the written data and monitor progress with the protocol including any adverse events. Participant information will be tabulated on a password protected Excel spreadsheet in a de-identified form. All paper-based data (e.g., bladder diary) will be de-identified and kept in a secured lockable filing cabinet. All electronic recordings will be stored on secure password-protected files in the appropriate University of Auckland managed storage. Study databases will be securely kept allowing for publication and re-analysis and deleted after 10 years.

For an alternative option, study data can be collected and managed using the Research Electronic Data Capture Tool (REDCap, Version 6.12.1, Vanderbilt University) managed by the University of Auckland. REDCap is a secure web platform for building and managing online databases and surveys designed to support data capture for clinical research studies [23,24]. It has secure web and mobile applications which are password protected and not accessible by third parties.

Table 3. Assessment parameters

Primary outcome		**Secondary outcome**
Safety	*Feasibility & Compliance*	*Efficacy*
Local skin reactions (erythema and erosion)	Dropout rate	Neurogenic bladder symptom score (NBSS) [25]
General effects, such as discomfort of any nature	Percent of adherence to the prescribed regimen	Bladder diary: frequency and volume of catheterisation, incontinence episodes
Other potential adverse effects e.g. UTI, autonomic dysreflexia	Program satisfaction (e.g., easy to use, embarrassing to use, not painful, enjoyed using)	Other related observations: bowel/sexual changes, pain relief, muscle spasticity

Adverse event assessments

Based on our systemic review [15], we believe this protocol can be performed safely at home by participants and/or their caregivers if given detailed instructions. Adverse reactions to electric stimulation will be explained during the recruitment and on the information sheet. There are few known adverse reactions to electric stimulation. The common ones include:

- Pain with electric stimulation: TENS application should not be painful due to the low-intensity setting, even though some SCI participants have sensory deficit. However, the participant who feels discomfort or pain can choose to reduce 20% of the intensity by pressing the “SOFT” button for gentle stimulation with a recoding of the setting changed. If the pain persists the intensity dial can be reduced e.g., from level 6 to 5. .
- Skin irritation: it is common for redness to occur on the skin at the surface-electrode site. This typically dissipates within an hour of removing the electrode. In some cases, the redness remains the next day. In these cases, they are likely sensitive to the adhesive used and a hypoallergenic skin-electrode will be provided.

- Skin inflammation and electrode burn beneath the electrodes are potential adverse events directly related to electric stimulation which is unlike to occur within the 15-minute auto-off mode

(Omron HVF128). TENS will not be applied to sleeping participants to avoid the risk of skin irritation while a participant cannot sense it. If skin inflammation remains longer than 24 hours, change the site of electrode pads nearby the previous areas in an alternating day would be a helpful solution. In the unlikely event that electrode burn occurs at the skin beneath electrode areas, the participant can contact the research team for advice and see a healthcare provider.

- Involving a caregiver is recommended if the participant lack skin sensation in stimulating areas. Therefore, the participant with assistant of a family member or caregiver will check the skin symptoms and record any side effects that occur during and after using TENS (e.g. skin redness or burn at the electrode sites, nausea, headache, etc.).

- Autonomic dysreflexia may occur in people with spinal cord injuries with lesions at or above thoracic level 6 (T6). It can be caused by stimulation of the skin, distension of the urinary bladder (urine retention) or colon (fecal compaction) and/or muscle spasms. It is over-activity of the autonomic nervous system resulting in a spike in blood pressure and a drop in heart rate with symptoms (e.g., nausea, headache, blurred vision, sweating, nasal stuffiness) to severe hypertension with potentially life-threatening complications. However, the chance is very small. Based on our extensive review (between 1947-2020), there is no report of autonomic dysreflexia associated with the use of TENS to improve bladder dysfunction in people with SCI. Additionally, a study shows that using TENS can prevent and treat autonomic dysrefexia in chronic SCI [24]. If participants are unsure, or have limited symptoms of autonomic dysreflexia, they can contact the research team (24/7 available on a mobile phone: 0221843224), contact a normal healthcare provider or call an ambulance (111).

- Urinary tract infection (UTI): there is no direct association between using TENS and UTI. In most cases, the infection occurs due to the sterile technique of CIC or long-term use of CIC.

- Symptoms of UTI & autonomic dysreflexia will be monitored and enquired about with every phone call.

Participants may withdraw from the study or stop using the device at any time if they find it bothersome or ineffective and any such events will be recorded as a study outcome. If they have any questions, they will be able to contact the study investigators by phone (24/7 available on mobile phone: 0221843224), video conference or email at any time during the study. The investigator will be responsible for collecting and reporting adverse events during the study. The research assistant and the principle investigator will collect adverse events related to the clinical trial.

Statistical and analytical plans

This pilot study will serve as an earlier-phase developmental function that will enhance the probability of success in a larger subsequent randomization intervention trial.

In Aim 1, for safety, we hypothesize that there will be no unusual adverse events. However, because skin reaction is directly related to the TENS applied, we will focus on the occurrence of skin irritation or damage. For feasibility and compliance, we will calculate descriptive statistics to determine the dropout rate and percent of adherence to the prescribed regimen as well as program satisfaction. If the dropout rate is less than 25%, and if participants complete greater than 70% of daily TENS use in the 4 weeks, we will consider the study has high feasibility/adherence. If more than 80% of participants report that they are satisfied with the

program, then we will consider the study has high satisfaction. TENS satisfaction will be based on the scores of a TENS survey and descriptive analysis will be provided as well. We will also assess the associations between these changes from baseline as well as bladder medication associations.

In Aim 2, descriptive statistics will be provided for incontinence episodes, catheterisation frequency (count per day) and volumes voided (ml per collection). The results along the time will be compared to baseline by paired t test. Mixed-effects linear regression modelling will be used with the bladder diary variables to evaluate the changes over time adjusting for participant variability. Since this is a feasibility study with the small number of participants enrolled, the efficacy of TENS investigated in this study will be assessed as an exploratory outcome only and further explored in future larger studies.

Ethical considerations

Informed consent
The principal investigator will send informed consent forms to participants meeting I/E criteria after screening via the telephone call or VDO conference. Ideally, they can receive a package within 4-5 working days and they can decide that day or up to 4 weeks. Ethics-approved study participation material will be provided to the participants. Non-English speakers will be excluded.

HDECs review
This protocol and the associated informed consent documents will be submitted to the Health and Disability Ethics Committees (HDECs) for review and approval or pending.

Clinical trial registration: The trial will be registered on the ANZ Clinical Trial Registry prior to starting.

Confidentiality of data and participant records
All participant records will remain confidential. Data with protected health information will be de-identified and given a number assignment found on a linking log, a separate file in a separate folder found on the appropriate University of Auckland managed file storage. During the study and post-study, study-specific source documents will be maintained and stored in locked file cabinets in locked rooms and password protected databases via password protected computers including the appropriate University of Auckland managed file storage. For health information and data monitoring safety, we will register the trial with the Health and Disability Ethics Committees.

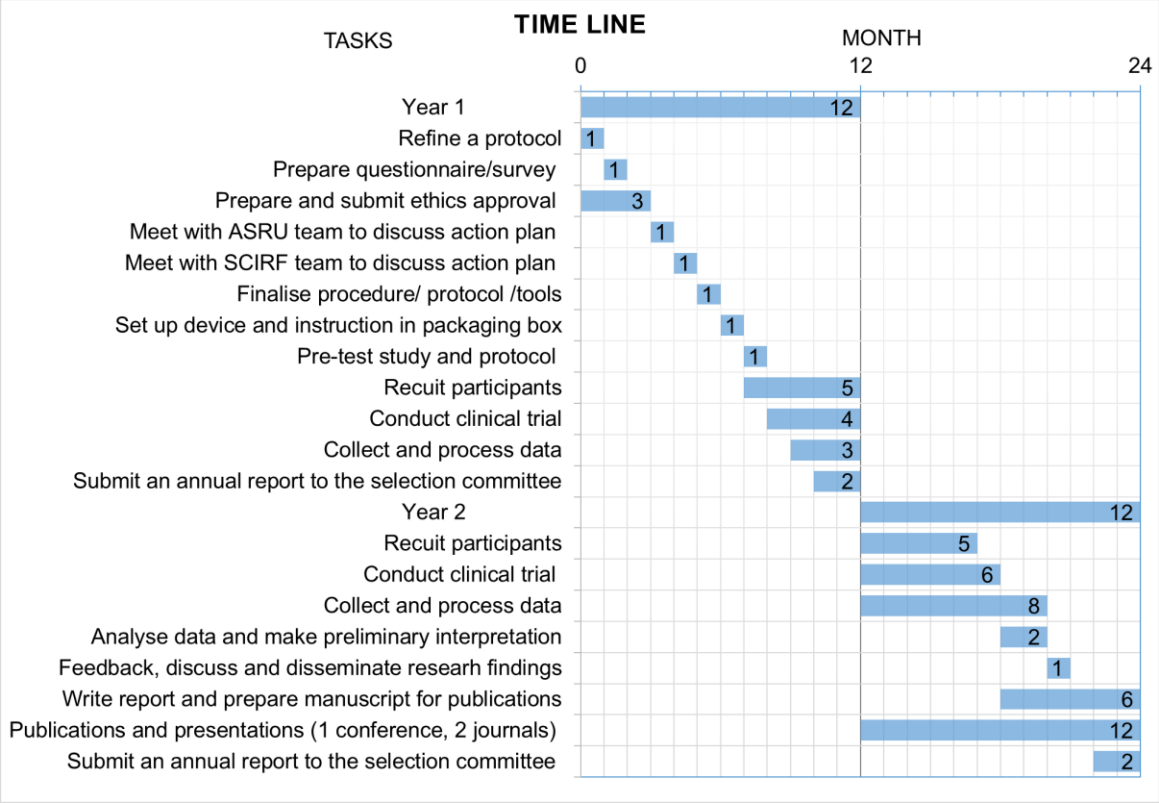
COVID-19 and research ethics

All research conducted during COVID-19 alert levels must be consistent with the national ethical standards, as at any other time (https://neac.health.govt.nz/publications-and-resources/neac-publications/national-ethical-standards-health-and-disability). For all research approved by the Health and Disability Ethics Committee (HDEC) or due to be reviewed by the HDEC, researchers should ensure they are aware of HDEC's most up to date COVID-19 guidance and operating procedures.

Publications
We anticipate 2 publications describing the effects of home use of TENS in chronic SCI in peer-reviewed journals within 2 years since the start of the study.

Timetable

Outline from planning to completion and write up.



ASRU; Auckland Spinal Rehabilitation Unit (Counties Manukau Health), SCIRF; Spinal Cord Injury Research Facility (the Centre for Brain Research, University of Auckland)

Trial materials

TENS device is a class IIa (Australian Regulatory Guidelines for Medical Devices) that is an electrical therapy device currently used at many physiotherapy centres. The FDA-approved indications for the TENS are used for the symptomatic relief and management of chronic intractable pain and/or as an adjunctive treatment in the management of post-surgical and post-traumatic acute pain. The device has wide-ranging capability and programmability, with stimulation and wave parameters adjusted for the proposed study purpose. A low-frequency, symmetrical biphasic pulse is delivered via electrodes placed on the skin over the targeted area producing a low-frequency current. TENS units typically are battery-powered devices based on

stimulating nerves through intact skin via pulsed electrical currents. Adhesive electrodes are placed on the site of S3 dermatomes to deliver the stimulus (Fig 1).

The Omron HV-F128 Premium TENS is a portable unit, offering multiple treatment modes with the frequency between 1-1200 Hz, which can provide up to 3 months with 15-minute Auto-Off (when using 15 minutes a day continuously) including 2 x AAA batteries and long life pads (up to 150 uses or 5 months with proper maintenance)**.** The special mode (KNEAD-REPEAT) of the Omron TENS unit (HV-F128) is selected with 25 Hz burst mode for 4-second stimulation and 1-second pause during 15 minutes, Auto-Off stimulation. The biphasic waveform is generated with a pulse width of 400 µs. The intensity amplitude of 50 mA is set to avoid muscular contractions with level 6 displayed at the intensity dial/power button. These parameters are chosen regarding the recent systemic review of TENS parameters (45-80 mA, 10-50 Hz, 200 µs-200 ms, 10-30 minutes) for neurogenic bladder improvement in SCI.

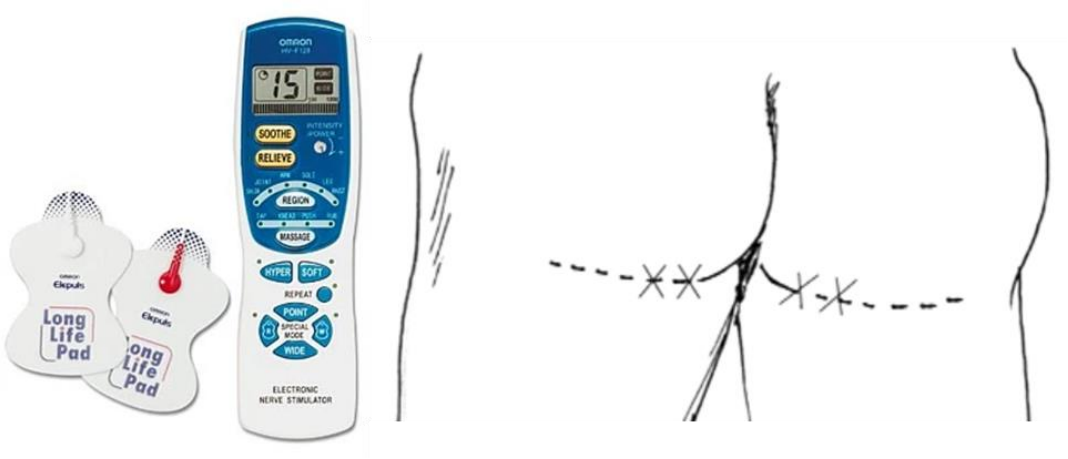


Figure 1. The Omron HV-F128 Premium TENS Device (Left), image courtesy of Life Pharmacy NZ, Adhesive electrodes are placed on the site of S3 dermatomes (situated at the junction of buttock and upper thigh) to deliver the stimulus (Right) [26].

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