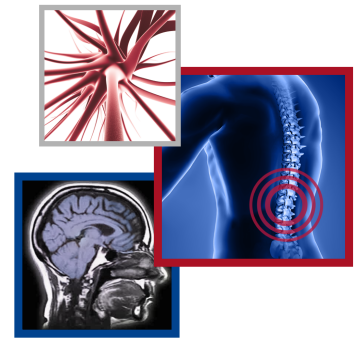
Clinical Trial Evaluation

For reprint orders, please contact: reprints@futuremedicine.com

Pain Management



Study protocol of hypoalgesic effects of low frequency and burst-modulated alternating currents on healthy individuals

Érika Patrícia Rampazo da Silva[1], Viviane Ribeiro da Silva[1], Anabelly Sato Bernardes[1], Fabio Massao Matuzawa[2] & Richard Eloin Liebano*[,1]

[1]Departamento de Fisioterapia, Universidade Federal de São Carlos (UFSCar), Rod. Washington Luis, km 235, São Carlos/SP, 13565–905, Brazil

[2]Universidade Paulista, Cidade Universitária, Av. Torres de Oliveira, 330 – Jaguaré, São Paulo/SP, 05347–020, Brazil

* Author for correspondence: Tel.: +55 16 3351 8448; liebano@gmail.com

Practice points

- Transcutaneous electrical nerve stimulation (TENS), interferential currents and Aussie current are different electrical currents used in the management of acute and chronic pain.
- Analgesic effect of electrical currents is related to action mechanism in PNS and CNS.
- High intensity and high frequency of TENS are important parameters to improve the pressure pain threshold (PPT).
- PPT has been reported to reflect mainly pressure pain sensitivity of deeper tissues.
- Hypoalgesic effect will be evaluated by using a PPT test with a digital algometer.
- Sensorial comfort between electrical currents will be evaluated by using a visual analogue scale.
- It is important to investigate the hypoalgesic effect between the different electrical currents and placebo stimulation.
- Hypoalgesic effect and sensorial comfort will be investigated between TENS, interferential current, Aussie current and placebo stimulation.

The aim of the study will be to compare different types of analgesic electrical currents in relation to the pressure pain threshold and sensory comfort in healthy individuals. A total of 100 individuals will be randomly assigned to four groups: transcutaneous electrical nerve stimulation, interferential current, Aussie current or placebo. The electrical stimulation will be administered with a strong level for 30 min and to the placebo group, the electrodes will be positioned while the equipment will remain switched off. The pressure pain threshold and sensory comfort will be measured with an algometer and the visual analogue scale, respectively. The level of significance will be $p < 0.05$. Study registration: NCT01950728 (clinical trials).

First draft submitted: 27 October 2017; Accepted for publication: 2 January 2018; Published online: 16 February 2018

Keywords: algometry • pressure pain threshold • pain • transcutaneous electrical nerve stimulation • interferential current • Aussie current

The earliest historical records of the use of electrical stimulation for pain relief date from the fifth dynasty of ancient Egypt [1]. The gate control theory of pain developed by Melzack and Wall [2] is the most accepted mechanism of action for explaining the analgesic effect obtained with electrotherapy and provides a theoretical basis for the use of electrical currents for pain relief [1,3]. This theory proposes that stimulation of large diameter afferent nerve fibers (Aβ) activates the local inhibitory neuronal circuits of the dorsal horn of the spinal cord, inhibiting nociceptive afferent stimuli transported by small diameter fibers (C and Aδ) and preventing them from reaching the higher centers of the CNS [2,3].

The publication of this theory served as a catalyst for the development of the first transcutaneous electrical nerve stimulation (TENS) units [1,4]. TENS is a noninvasive treatment modality widely accepted and used by various health professionals for the treatment of acute or chronic pain [5]. In addition to the inhibitory effect of

Future Medicine

the nociceptive afferent stimuli, TENS releases different opioids at the level of the spinal column and the rostral ventral medulla through stimulation with different frequencies [5]. Low frequencies, usually below 10 Hz, activate μ-opioid receptors and high frequencies, usually over 50 Hz, activate δ-opioid receptors [5]. The majority of TENS units deliver a low-frequency biphasic pulsed current (1–250 Hz) [1,3,6].

In 1950, Hans Nemec developed interferential currents (IFCs), aiming to promote a stimulation that reached deeper tissues and was more comfortable than the low-frequency currents [7]. Since then, many clinicians have replaced the use of TENS machines with interferential stimulators, which are widely used in Canada [8], the UK [9] and Australia [10]. The IFC is composed of two independent medium frequency currents, one current being used at a frequency of 4000 Hz and the other between 4001 and 4250 Hz, producing a modulated sinusoidal wave of low frequency at the value of the difference between the frequencies used [1,6,11,12].

Some controversies regarding IFC are found in the literature. One suggestion is that IFC cannot equally stimulate the entire area of the electrode pairs, as only the intersection region of the two medium frequency currents would receive the fully modulated sinusoidal wave [13]. Recent studies suggest that the ideal burst duration for sensory and motor stimulation should be 1–4 ms [13–16]. When using the IFC with amplitude-modulated frequency (AMF) of 100 Hz, the duration of the bursts is 10 ms, causing the nerve to trigger the action potential several times in each burst. This high number of triggers could cause neural blockage and/or synaptic fatigue, impairing the therapeutic action of the current [12].

Thus, with the aim of producing a current more adequate for sensory and motor stimulation, Ward *et al.,* developed a type of alternating current modulated in rectangular bursts of short duration (2–4 ms) [15,16]. This type of current became known commercially as Aussie current [14,15]. Aussie current has an adjustable carrier frequency of 1 or 4 kHz, with the first frequency being indicated for neuromuscular stimulation and the second for analgesia due to being more comfortable. For analgesia, a 20% duty cycle (4 ms burst) and modulation frequency of 50 Hz [14–15,17] have been suggested. Some studies have shown that shorter duty cycles make Aussie current more comfortable than the low-frequency pulsed current, with a lower chance of stimulating multiple motor neuron action potentials leading to less muscle fatigue [14,15,17].

A systematic review performed by Claydon and Chesterton verified that the level of hypoalgesic efficacy of TENS is clearly dependent on TENS parameter combination selection (intensity, frequency and stimulation) and experimental pain model. Then, they concluded that high frequency has strong evidence of efficacy in pressure pain models and high-intensity stimulation has been shown to have higher rankings of supporting evidence and more favorable hypoalgesic profiles in terms of both magnitude and longevity of response [18].

Beatti *et al.*, in their systematic review, evaluated the effectiveness of IFC in reducing pain. They concluded that there is inadequate evidence to support the effectiveness of IFC in pain management and clearly, there is a need for randomized clinical trials with high methodological quality to establish IFC efficacy [19].

However, few studies have been performed to compare the analgesic effect between TENS and IFC. Alves-Guerreiro *et al.* reported that both TENS and IFC did not present significant results in increasing the pressure pain threshold (PPT) [1]. Johnson and Tabasam reported that TENS and IFC significantly reduced experimentally induced ischemic pain; however, there was no statistically significant difference between them [6]. Cheing and Hui-Chan reported that TENS and IFC significantly increased the heat pain threshold with no statistical difference between them; however, the duration of the analgesic effect was greater with IFC [20]. Shanahan *et al.* found that TENS was statistically more effective than IFC in increasing the cold pain threshold [11].

A survey of the literature, found no comparative studies on the analgesic effect between IFC and Aussie current, with only one study comparing the analgesic effect between TENS and 4 kHz Aussie current. Authors concluded that the two types of currents increased the cold pain threshold with no statistically significant difference between them; however, Aussie current was reported to be more comfortable [14]. Despite several studies comparing TENS and IFC in terms of hypoalgesia and a single study comparing TENS and 4 kHz Aussie current, there is still no consensus on which modality is more efficient for increasing the pain threshold. Furthermore, there are no reports in the literature of any studies comparing the effects of IFC and Aussie current and of TENS, IFC and Aussie current with regard to the hypoalgesic response in healthy subjects.

Therefore, the aim of this study will be to compare the effect of TENS, IFC, Aussie current and placebo stimulation regarding the PPT and sensory comfort in healthy individuals.

Methods

Study design

This protocol study was written following the recommendations of Standard Protocol Items: Recommendations for Interventions Trials (SPIRIT) and the randomized placebo-controlled trial will follow the guidelines recommended by Consolidated Standards of Reporting Trials (CONSORT). The individuals and the evaluator will be blinded. The study has been approved Human Research Ethics Committee of the Federal University of São Carlos (UFSCar; CAAE: 67222317.0.0000). The study was registered under number NCT01950728 on clinical trials [21]. This study will be carried out at Universidade Federal de São Carlos and the individuals will be recruited through oral communication and posters in the grounds of the university.

Eligibility criteria

Inclusion criteria

The study will include healthy individuals of both genders, aged between 18 and 45 years and being unfamiliar to therapeutic electrical currents.

Exclusion criteria

Individuals with damage to upper and/or lower limb nerves (changes in sensitivity, muscle strength or reflex), pain, pregnant women, chronic diseases, cardiac pacemaker, epilepsy, allergy to the used electrode, individuals who made use of painkillers during previous 24 h and skin lesions or lack of sensitivity in the electrode positioning areas will be excluded. Individuals with any of these items may present an altered PPT and it may compromise the results of the study.

Calculation of sample size

The sample size was calculated based on the PPT values evaluated with an algometer. A difference of 100 kPa with standard deviation of 98 [22], statistical power of 80%, alpha of 5% and possible sample loss of up to 15% were considered. Accordingly, 25 individuals per group will be required (100 in total). The sample calculation was performed using the Minitab, v.17, software, Minitab, Inc, PA, USA.

Randomization & blinded allocation

Individuals will be stratified by gender to ensure equal numbers of women and men in each group and randomly allocated to one of four groups (n = 25 per group): TENS, IFC, Aussie current and placebo. The order of measurement of the PPT between the upper and lower limbs will also be randomized. A researcher not involved in data collection will perform the online randomization [23] and the allocation blinding will be performed with the use of opaque and sealed envelopes.

Study period

Data collection will be carried out from September 2017 to January 2018. Data analysis and the writing of the article are planned for January and February 2018.

Study procedures

Individuals will first receive information about the study and will be screened to check for inclusion criteria. If they meet the eligibility criteria mentioned earlier, they will be asked about their interest in participating in the study, and if they respond positively, they will receive guidance about the consent form. After signing the consent form, demographic data – such as age, gender, race, weight and height – will be collected and the individuals will be asked to lie down on the stretcher so that the dominant upper limb and ipsilateral leg can be cleaned with soap and water in the areas of electrode positioning and the algometry points marked with a pen. The first area of measurement of the PPT will be marked on the dominant upper limb; for this, a straight line will be drawn between the lateral epicondyle of the elbow and the midpoint between the medial and lateral border of the wrist. The first electrode will be positioned on the forearm at the elbow fold next to the lateral epicondyle and the second electrode will be positioned 3 cm from the end of the first electrode on the previously drawn straight line (Figure 1). The measuring point of the algometer will be exactly midway between the two electrodes [24,25]. The second area of PPT measurement will be marked on the leg ipsilateral to the dominant arm. A tape measure will be used to define the midpoint of the tibialis anterior muscle belly [26]. After the positioning of the individual and the electrodes, the

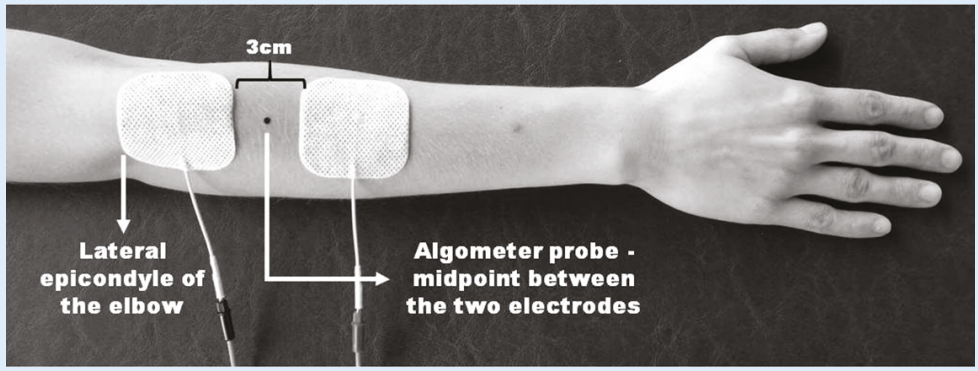


Figure 1. Electrode position and location of the pressure pain threshold recording point on the forearm.

evaluator will open the envelope to find out the order of evaluation of the PPT with the algometer. Immediately after the measurement, the therapist will open the envelope to know which group that individual belongs to and initiate the treatment procedure with TENS, IFC, Aussie current or placebo.

Treatment groups

To deliver the TENS, IFC and Aussie current, the NEURODYN unit (IBRAMED®, Amparo, São Paulo, Brazil) will be used. Two standard square self-adhesive electrodes (5 × 5 cm^2) (ValuTrode®, Axelgaard, CA, USA) will be used.

TENS group: a frequency of 100 Hz and phase duration of 125 µs (pulse duration = 250 µs) will be used.

IFC group: a carrier frequency of 4 kHz, phase duration of 125 µs (pulse duration = 250 µs) and an AMF of 100 Hz will be used.

Aussie current group: a carrier frequency of 4 kHz, phase duration of 125 µs (pulse duration = 250 µs), 20% duty cycle (4 ms burst duration) and 100 Hz frequency will be used.

For all groups, the electrodes will be positioned as described earlier, and the amplitude will be increased until the individual reports a strong but comfortable paresthesia (including motor level stimulation but no painful TENS) [6,27,28]. The application of the current will last for 30 min and at 4 min intervals, the individual will be asked whether the current sensation has decreased and the pulse amplitude will be increased until the individual again feels strong but comfortable paresthesia.

Placebo group: the electrodes will be positioned as previously described for 30 min and, every 4 min, the therapist will question the individual regarding any possible discomfort.

Outcomes & measurement instruments

PPT measurements

The evaluator will measure the PPT using a Somedic Type II pressure algometer (Somedic®, Hörby, Sweden), consisting of a circular rubber probe (1 cm^2). The algometer will be calibrated prior to the start of the study by the manufacturer. The intrarater reliability for the measurement of PPT has already been estimated by calculating the intraclass correlation coefficients for forearm extensor muscles (0.885; 95% CI: 0.601–0.967) and for the tibialis anterior muscle (0.924; 95% CI: 0.736–0.978). For this, a total of 13 healthy volunteers, uninvolved in the study, were recruited and evaluated on two occasions with a 48-h interval between them.

During the study, the evaluator will be blind to the division of the groups and the currents used. In the four groups, the device will be covered during the PPT measurement, so that the evaluator will not know whether TENS, IFC, Aussie current or placebo is being applied. In the TENS, IFC and Aussie current groups, the amplitude of the current pulse will be reduced to the sensory threshold prior to the measurement of the PPT by the therapist so that the evaluator will also be blind to whether that individual belongs to any current group, as the increase in the amplitude of the pulse can lead to muscle contraction. During the PPT measurement, the circular algometer probe (1 cm^2 area) will be placed perpendicular to the skin at a uniform and constant rate of 30 kPa/s. The participants will be instructed to close their eyes and to press the algometer sensor when the pressure sensation becomes painful.

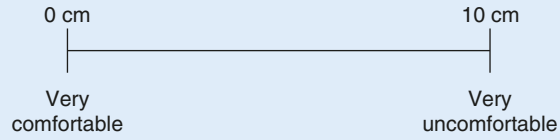


Figure 2. Visual analogue scale used to rate comfort of electrical stimulation.

Three measurements will be collected each time (t_0, 0 min; t_{15}, 15 min; t_{30}, 30 min; and t_f, 20 min after power is off), with a 30 s interval between them, and the mean will be used for data analysis. Individuals will be not permitted to see the algometer readings during measuring. The treatment will not be interrupted for the PPT measurements. All participants will have three demonstrations of the PPT measurement on their nondominant limb to ensure that they understand the PPT concept prior to the study.

Sensory comfort

Sensory comfort will be measured after current application with a visual analogue scale (VAS) [12] of 10 cm, when the individual will be asked to draw a perpendicular line on the VAS line, with lines closer to 0 cm representing more comfortable current and lines closer to 10 cm representing less comfortable current (Figure 2).

Statistical analysis

Data analysis will be performed using the SPSS software (v.17, SPSS, Inc., IL, USA) by a blinded researcher to the division of the groups. The differences between the averages of the PPT scores between the baseline and the other moments (15, 30 and 20 min after the current is switched off) of each group will be used for the analysis. The Shapiro–Wilk test will be used to verify the normality of the data. If the data present normal distribution, a parametric test will be used, otherwise a nonparametric test will be used. The level of significance adopted will be $p < 0.05$.

Discussion

The aim of this study will be to compare the effect of TENS, IFC and Aussie current, regarding the PPT and sensory comfort in healthy individuals. Evidence shows that TENS has a hypoalgesic effect with low frequency and high intensity during the stimulation and after 30 min [29]; with high frequency and high intensity [30]; with high intensity and different frequencies during and after stimulation [31]; with constant or modulated frequency and strong but painless intensity [25]; with high frequency compared with low frequency [24,32]; with high intensity compared with low intensity [27]; with fixed frequency TENS and high intensity when compared with alternating frequency [33]; with high frequency and strong but comfortable intensity [28]; and with TENS burst associated with cryotherapy [22].

Considering IFC, it has been observed that the AMF did not produce a hypoalgesic effect in healthy individuals [34]. Active IFC prior to Pilates exercise was not more effective than placebo IFC in the outcomes assessed in patients with chronic nonspecific low back pain [35]. However, the frequency of 1 kHz produced a greater hypoalgesic response when compared with frequencies of 8 and 10 kHz. Regarding sensory comfort, the frequencies of 1 and 2 kHz have been found to be more uncomfortable compared with the frequencies of 4, 8 and 10 kHz in healthy individuals [12]. A greater increase in the cold pain threshold was produced by TENS when compared with IFC [11].

Alternating current modulated in rectangular bursts (commercially known as Aussie current) proved to be as effective as TENS in increasing the cold pain threshold and it showed to be more comfortable in healthy subjects [14].

Conclusion

To conclude, an investigation about whether there are differences in PPT and sensory comfort – between TENS, IFC, Aussie currents and placebo stimulation – will be carried out. Thus, healthy individuals will be randomized in four groups. The PPT will be evaluated with a digital algometer; there will be four measurements of PPT: before, during and after the treatment, and also 20 min after the end of the treatment. Sensory comfort during

electrical stimulation will be measured using the VAS after treatment. Therefore, this study will verify whether the application of these currents produces any differences in the PPT and in the sensory comfort in healthy humans.

Financial & competing interests disclosure

The study received funding from the National Council of Technological and Scientific Development (CNPq). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1. Alves-Guerreiro J, Noble JG, Lowe AS, Walsh DM. The effect of three electrotherapeutic modalities upon peripheral nerve conduction and mechanical pain threshold. *Clin. Physiol.* 21(6), 704–711 (2001).
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science* 150(3699), 971–979 (1965).
3. Pantaleão MA, Laurino MF, Gallego NLG *et al.* Adjusting pulse amplitude during transcutaneous electrical nerve stimulation (TENS) application produces greater hypoalgesia. *J. Pain* 12(5), 581–590 (2011).
4. Walsh DM, Lowe AS, McCormack K, Willer JC, Baxter GD, Allen JM. Transcutaneous electrical nerve stimulation: effect on peripheral nerve conduction, mechanical pain threshold, and tactile threshold in humans. *Arch. Phys. Med. Rehabil.* 79(9), 1051–1058 (1998).
5. Liebano R, Rakel B, Vance CGT, Walsh DM, Sluka KA. An investigation of the development of analgesic tolerance to transcutaneous electrical nerve stimulation (TENS) in humans. *Pain* 152(2), 335–342 (2011).
6. Johnson MI, Tabasam G. An investigation into the analgesic effects of interferential currents and transcutaneous electrical nerve stimulation on experimentally induced ischemic pain in otherwise pain-free volunteers. *Phys. Ther.* 83(3), 208–223 (2003).
7. Ozcan J, Ward AR, Robertson VJ. A comparison of true and premodulated interferential currents. *Arch. Phys. Med. Rehabil.* 85(3), 409–415 (2004).
8. Nussbaum EL, Sarah B, Johnstone L, Geraldine L, Robitaille E, Yoshida K. Use of electrophysical agents: findings and implications of a survey of practice in metro Toronto. *Physiother. Canada* 52(2), 118–129 (2007).
9. Shah SGS, Farrow A, Esnouf A, Service NH. Availability and use of electrotherapy devices: a survey. *Int. J. Rehabil.* 14(6), 260–264 (2007).
10. Robertson VJ, Spurritt D. Electrophysical agents: implications of their availability and use in undergraduate clinical placements. *Physiotherapy* 84(7), 335–344 (1998).
11. Shanahan C, Ward AR, Robertson VJ. Comparison of the analgesic efficacy of interferential therapy and transcutaneous electrical nerve stimulation. *Physiotherapy* 92(4), 247–253 (2006).
12. Venancio RC, Pelegrini S, Gomes DQ, Nakano EY, Liebano RE. Effects of carrier frequency of interferential current on pressure pain threshold and sensory comfort in humans. *Arch. Phys. Med. Rehabil.* 94(1), 95–102 (2013).
13. Ward AR. Electrical stimulation using kilohertz-frequency alternating current. *Phys. Ther.* 89(2), 181–190 (2009).
14. Ward AR, Lucas-Toumbourou S, McCarthy B. A comparison of the analgesic efficacy of medium-frequency alternating current and TENS. *Physiotherapy* 95(4), 280–288 (2009).
15. Ward AR, Chuen WLH. Lowering of sensory, motor, and pain-tolerance thresholds with burst duration using kilohertz-frequency alternating current electric stimulation: part II. *Arch. Phys. Med. Rehabil.* 90(9), 1619–1627 (2009).
16. Ward AR, Lucas-Toumbourou S. Lowering of sensory, motor, and pain-tolerance thresholds with burst duration using kilohertz-frequency alternating current electric stimulation. *Arch. Phys. Med. Rehabil.* 88(8), 1036–1041 (2007).
17. Ward AR, Oliver WG. Comparison of the hypoalgesic efficacy of low-frequency and burst-modulated kilohertz frequency currents. *Phys. Ther.* 87(8), 1056–1063 (2007).
18. Claydon L, Chesterton L. Dose-specific effects of transcutaneous electrical nerve stimulation (TENS) on experimental pain: a systematic review. *Clin. J. Pain* 27(7), 635–647 (2011).
19. Beatti A, Rayner A, Souvlis T, Chipchase L. The analgesic effect of interferential therapy on clinical and experimentally induced pain. *Phys. Ther. Rev.* 15(4), 243–252 (2010).
20. Cheing GLY, Hui-Chan CWY. Analgesic effects of transcutaneous electrical nerve stimulation and interferential currents on heat pain in healthy subjects. *J. Rehabil. Med.* 35(1), 15–19 (2003).
21. ClinicalTrials.gov. https://clinicaltrials.gov/
22. Macedo LB, Josué AM, Maia PHB, Câmara AE, Brasileiro JS. Effect of burst TENS and conventional TENS combined with cryotherapy on pressure pain threshold: randomised, controlled, clinical trial. *Physiotherapy* 101(2), 155–160 (2015).
23. Randomization website. http://www.randomization.com/

24. Chen CC, Johnson MI. An investigation into the hypoalgesic effects of high- and low-frequency transcutaneous electrical nerve stimulation (TENS) on experimentally-induced blunt pressure pain in healthy human participants. *J. Pain* 11(1), 53–61 (2010).
25. Chen C-C, Johnson MI. An investigation into the effects of frequency-modulated transcutaneous electrical nerve stimulation (TENS) on experimentally-induced pressure pain in healthy human participants. *J. Pain* 10(10), 1029–1037 (2009).
26. Pelegrini S, Venancio RC, Liebano RE. Local and systemic effects of low-power laser on pressure pain threshold in healthy subjects. *Fisioter. Pesqui.* 19(4), 345–350 (2012).
27. Moran F, Leonard T, Hawthorne S *et al.* Hypoalgesia in response to transcutaneous electrical nerve stimulation (TENS) depends on stimulation intensity. *J. Pain* 12(8), 929–935 (2011).
28. Liebano RE, Vance CG, Rakel BA *et al.* Transcutaneous electrical nerve stimulation and conditioned pain modulation influence the perception of pain in humans. *Eur. J. Pain* 17(10), 1539–1546 (2013).
29. Chesterton LS, Barlas P, Foster NE, Lundeberg T, Wright CC, Baxter GD. Sensory stimulation (TENS): effects of parameter manipulation on mechanical pain thresholds in healthy human subjects. *Pain* 99(1–2), 253–262 (2002).
30. Chesterton LS, Foster NE, Wright CC, Baxter GD, Barlas P. Effects of TENS frequency, intensity and stimulation site parameter manipulation on pressure pain thresholds in healthy human subjects. *Pain* 106(1–2), 73–80 (2003).
31. Claydon LS, Chesterton LS, Barlas P, Sim J. Effects of simultaneous dual-site TENS stimulation on experimental pain. *Eur. J. Pain* 12(6), 696–704 (2008).
32. Çıtak Karakaya I, Karakaya MG, Erğun E, Elmalı S, Fırat T. Effects of different frequencies of conventional transcutaneous electrical nerve stimulation on pressure pain threshold and tolerance. *J. Back Musculoskelet. Rehabil.* 27(2), 197–201 (2014).
33. Claydon LS, Chesterton LS, Barlas P, Sim J. Alternating-frequency TENS effects on experimental pain in healthy human participants: a randomized placebo-controlled trial. *Clin. J. Pain* 29(6), 533–539 (2013).
34. Fuentes CJ, Armijo-Olivo S, Magee DJ, Gross D. Does amplitude-modulated frequency have a role in the hypoalgesic response of interferential current on pressure pain sensitivity in healthy subjects? A randomised crossover study. *Physiotherapy* 96(1), 22–29 (2010).
35. Franco KM, Franco YDS, Oliveira NB *et al.* Is interferential current before pilates exercises more effective than placebo in patients with chronic nonspecific low back pain? A randomized controlled trial. *Arch. Phys. Med. Rehabil.* 98(2), 320–328 (2017).