



Transcutaneous Electrical Nerve Stimulation for Local Anaesthesia

Clinical Trial Protocol

The efficacy of Transcutaneous Electrical Nerve Stimulation versus local anaesthetic cream in alleviating the pain of local anaesthetic injections in adults - A Randomised Controlled Trial

IRAS Project ID: 256620

Protocol Version 1.0

Date: 29/10/2018

Sponsor: University Hospitals of Leicester

Sponsor Number EDGE 113691

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For and on behalf of the Study Sponsor:

Signature:

.....

Date:

...../...../.....

Name (please print):

.....

Position:

.....

Chief Investigator:

Signature:

.....

Date:

...../...../.....

Name: (please print):

.....

TABLE of Contents.

	Signature Page	2
	Table of Contents	3
	Summary	4
1	INTRODUCTION	6
2	TRIAL DESIGN	
2.1	Overview	9
2.2	Settings	10
2.3	Sample Size	10
2.4	Eligibility	10
2.5	Ethical Considerations, Information Giving and Written Informed Consent	11
2.6	Randomisation	11
2.7	Trial Intervention	11
2.8	Adverse Events	13
2.9	Outcome Assessment	13
2.10	Data Collection and Management	13
2.11	Monitoring	13
2.12	Analysis	14
3	TRIAL ORGANISATION	
3.1	Sponsorship	14
3.2	Protocol Committee	14
3.3	Collaborator's Responsibilities	15
3.4	Publication and Dissemination of Results	16
4	LIST OF ABBREVIATIONS	16
5	REFERENCES	16/17
6	APPENDICES	18

SUMMARY

Full Title of Study The efficacy of Transcutaneous Electrical Nerve Stimulation versus local anaesthetic cream in alleviating the pain of local anaesthetic injections in adults - A Randomised Controlled Trial
Short title Transcutaneous Electrical Nerve Stimulation for Local Anaesthesia
Trial Acronym TENS-LA
EDGE ID:
Protocol version 1.0 dated 29/10/2018
Sponsor: University Hospitals of Leicester
Background Even a simple local anaesthetic procedure is associated with much anxiety for the patient involved. This is compounded by the process of local anaesthetic injection which involves not only the pain of the needle puncture but the stinging sensation as the local anaesthetic is infiltrated into the site. Many methods of easing this pain have been used such as using smaller gauge needles, slow infiltration, buffering the anaesthetic and prior application of local anaesthetic creams. There has been a lot of research conducted in dentistry which has shown the effectiveness of Transcutaneous Electronic Nerve Stimulation (TENS) as an anaesthetic agent ¹ . But the research has not extended to other fields of surgery such as in minor local anaesthetic cases.
Aim TENS-LA trial will be able to provide evidence regarding the possible efficacy of TENS as a local anaesthetic and its ability to alleviate the pain associated with local anaesthetic injection. The effectiveness will also be compared to that of local anaesthetic cream which is being used at present prior to local anaesthetic injections.
Outcome Primary Outcome: The primary outcome is pain of local anaesthetic injection after application of TENS or LA cream as measured by two Numeric Pain Rating Scale Secondary Outcomes: Changes in blood pressure and pulse rate in response to injection of local anaesthetic
Trial Design A prospective randomised controlled trial.

<p>Diagnosis and Inclusion/Exclusion Criteria</p> <p>Adults 18-90 years of age undergoing a split skin graft harvest from the thigh under local anaesthesia will be included</p> <ul style="list-style-type: none"> • who do not have a pacemaker or ICD • who are not pregnant - with no history of epilepsy, aneurysm - with no history of allergy to local anaesthetic or TENS electrodes
<p>Test device and Mode of usage</p> <p>A hand-held battery-powered CE-approved TENS device will be used. Eligible patients who have been randomised to the test arm of the study will have the electrodes attached to the area adjacent to the skin graft donor site 30 minutes before injection of local anaesthetic.</p>
<p>Setting</p> <p>The trial will be conducted in Leicester Royal Infirmary, UK</p>
<p>Duration of treatment</p> <p>The TENS treatment is over a minimum period of 30 minutes from attachment of electrodes to administration of local anaesthetic.</p> <p>The LA cream treatment is over a minimum period of 60 minutes from application of the cream to administration of local anaesthetic.</p>
<p>Evaluation Criteria</p> <p>The effectiveness of the treatment is assessed using two Numeric Pain Rating Scale in the study and control groups. Pulse rate and Blood Pressure monitoring will be carried out as an objective measurement of the response to pain.</p>
<p>Planned trial start date</p> <p>1st May 2019</p>
<p>Planned date of last outcome</p> <p>30th April 2020</p>

1. INTRODUCTION

Background

Even a simple local anaesthetic procedure is associated with much anxiety for the patient involved. This is compounded by the process of local anaesthetic injection which involves not only the pain of the needle puncture but the stinging sensation as the local anaesthetic is infiltrated into the site. Many methods of easing this pain have been used such as using smaller gauge needles, slow infiltration, buffering the anaesthetic and prior application of local anaesthetic creams.

Study objectives and significance

There has been a lot of research conducted in dentistry which has shown the effectiveness of Transcutaneous Electronic Nerve Stimulation (TENS) as an anaesthetic agent¹. But the research has not extended to other fields of surgery such as in minor local anaesthetic cases.

TENS has been approved by CE as a method of pain alleviation¹. The TENS-LA trial will be able to provide reliable evidence on the possible effectiveness of TENS in alleviating pain of local anaesthetic injections and also how it compares with local anaesthetic cream for this purpose. If TENS is found to be effective, it can be used as a simple and safe device in minor surgical procedures to take away the most dreaded part of the procedure- the pain of injections.

TENS is a method of electrical stimulation to provide a degree of pain relief by stimulating either the pain gate mechanism and/or the internal opioid system.

It is a non-invasive method with hardly any side effects. The most common side effect reported is allergic reaction (2-3%) to the electrodes, gel or the tapes used for fixing the electrodes.

The intensity of current used ranges from 0-80mA into 500 Ohm load. The aim is to depolarise the sensory nerves and for this purpose the small strength provided by the machine is sufficient. This is delivered in pulses. To be clinically effective, the pulse ranges from 2-200 pulses per second (pps) or Hertz (Hz). The duration of each pulse (pulse width) may vary from 50 to 300 microseconds (μ s).

There are two primary pain relief mechanisms: the pain gate mechanism and the endogenous opioid system.

The gate control theory was proposed by Melzack and Wall in 1965². By activation of the A β sensory fibres (large fibres) with non-noxious stimuli the inhibitory interneurons in the dorsal horn are activated and the transmission of the noxious stimulus from the C

fibres (small fibres) inhibited. Thus, selective enhancement of input in large fibres shuts the Pain Gate band diminishes any ongoing pain³.

The alternative mechanism of pain relief by TENS is that it stimulates the release of endogenous opioids in the spinal cord. Low frequency and high frequency TENS function through activation of mu and delta opioid receptors respectively^{4,5}.

TENS was used by Wall and Sweet⁶ on patients experiencing pain, increasing the voltage till tingling was experienced in the area and resulted in relief of pain during the stimulation and for 30 minutes after.

The intensity or amplitude of TENS is directly related to the positive effect- a strong intensity (barely comfortable) provides significant analgesic effect⁷.

A systematic review and meta-analysis on the effectiveness of TENS on post-operative analgesia by Bjordal et al⁸ concluded that there is significant reduction in analgesic consumption for post-operative pain when TENS is administered with a strong intensity at an adequate frequency in the area.

TENS was found to be a good alternative to local anaesthetic in children requiring restorative dental procedures in many studies^{9,10}.

TENS was found to be more effective than local anaesthetic gel prior to inferior alveolar block injection in children in reducing the pain of injection in a study by Choudhari et al¹¹ which confirmed the findings from a similar study earlier by Meechan et al¹².

TENS was found to be almost equally effective as 2% local anaesthetic injection during minor paediatric dental procedures and more comfortable and preferred by 93.3% of the patients over the local anaesthetic in a study by Dhindsa et al¹³.

Objectives

The primary aim of this study is to evaluate the possible effectiveness of TENS in reducing the pain associated with local anaesthetic injection and to compare it with the use of topical anaesthetic cream. The hypothesis is that TENS is effective in alleviating/reducing the pain of local anaesthetic injection and more or equally effective compared with local anaesthetic cream for this purpose.

Methods and design

The study is planned as a randomised control trial with 2 arms:

- 1- The control group will have a local anaesthetic cream EMLA (Eutectic Mixture of Local Anaesthetics) applied for a minimum period of 60 minutes before injection of local anaesthetic
- 2- The study group will have TENS applied for a minimum period of 30 minutes before injection of local anaesthetic

Two electrodes will be placed - one proximal and the other distal to the area marked for harvest of skin graft on the thigh a distance of 10 cm.

Conventional treatment mode Programme 1 will be used with a rate of 80Hz -100Hz and pulse width of 200 micro seconds. The intensity will be gradually increased till patient experiences steady continuous stimulation but no muscle contraction. This is maintained for a period of 30 minutes after which the local anaesthetic injection is carried out.

Rationale

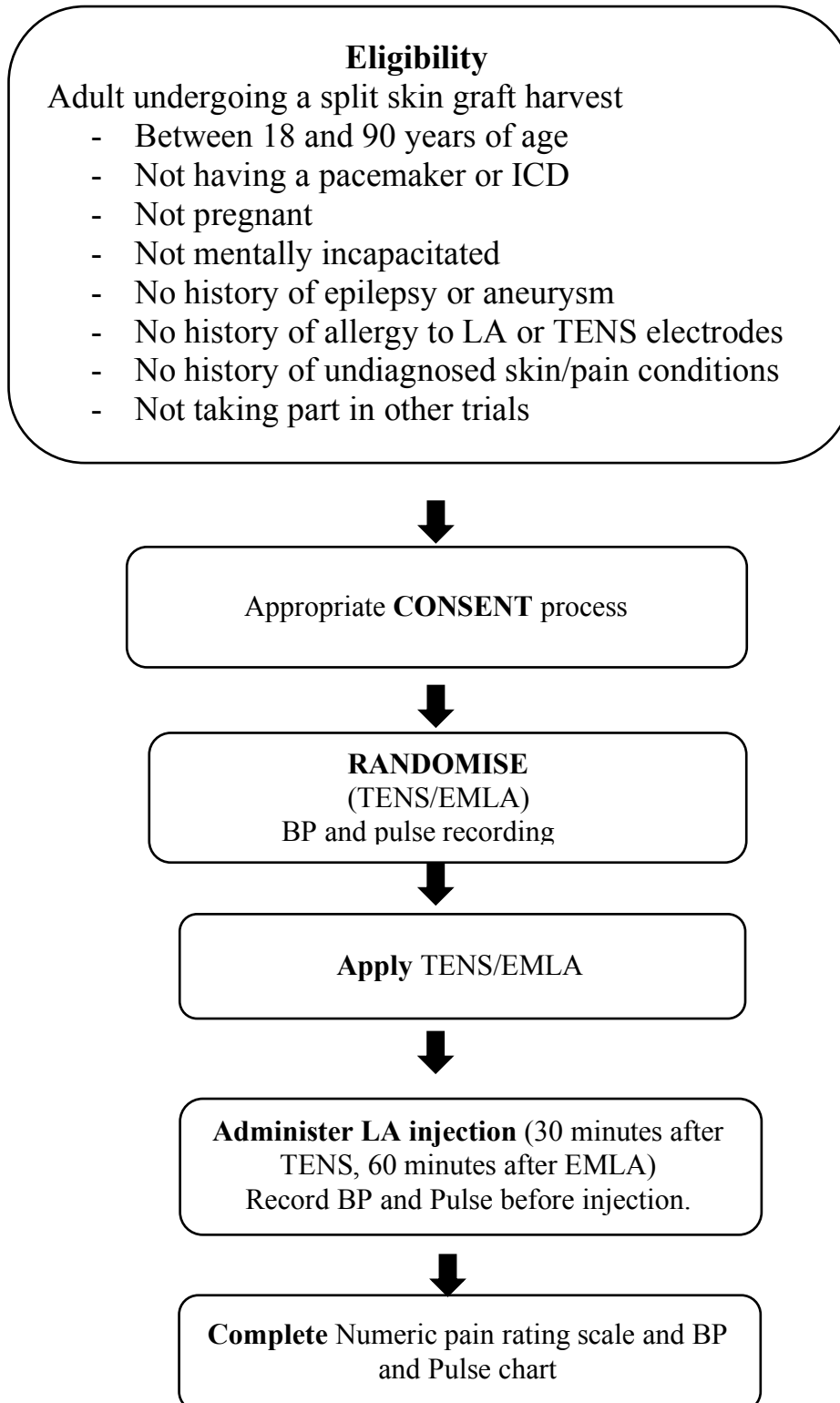
Though there have been several publications on the benefits of TENS as a local anaesthetic and also to reduce the pain of local anaesthetic injections, such a research is lacking in the surgical specialties. This trial would help to fill in this gap in evidence and help to make better evidence-based decisions.

If found to have a statistically significant benefit over the use of EMLA to alleviate the pain of local anaesthetic injection, TENS will be the way forward for minor operations for the purpose. The most dreaded part of the procedure for the patient is made more tolerable.

2. TRIAL DESIGN

2.1 OVERVIEW

Flow Chart: Study Overview



TENS-LA trial is a randomised control trial to assess the possible efficacy of Transcutaneous Electrical Nerve Stimulation (TENS) on eliminating or reducing the pain of local anaesthetic injection for minor surgical procedures. Comparison is done with a mixture of local anaesthetic cream (EMLA) which is used at times for the same purpose. Though local procedures are carried out in various parts of the body, this trial will be conducted specifically on patients undergoing a split skin graft harvest from the thigh. Patients who meet the eligibility criteria and are willing to participate will be randomised to receive either TENS or EMLA.

Eligible patients: Adult patients listed to have a split skin graft harvest under local anaesthesia will be assessed for eligibility for taking part in the trial.

2.2 SETTINGS

The study will be conducted at Leicester Royal Infirmary by the Department of Plastic Surgery.

2.3 SAMPLE SIZE

The study is designed to detect a difference of 3 units in pain scale between the 2 groups at 0.05 significance level and 90% power. We assume the standard deviation as 3 and the number of participants in each group has been calculated as 22. The total number of the patients including both arms of the trial will be 44.

2.4 ELIGIBILITY CRITERIA

Both interventions will be carried out in adult patients. For the purpose of standardisation and avoiding the variations from different sites in the body, and different surgical procedures, the site will be the thigh in both groups which is the donor site for a split skin graft.

Inclusion criteria:

Adult patients aged 18 to 90 years undergoing a split skin graft harvest under local anaesthesia

Exclusion criteria:

Patients below 18 and above 90 years of age

Patients with dementia or any other mental abnormalities who do not have the capacity to consent.

Pregnant ladies

Patients with pace maker or ICD

Patients with history of epilepsy or aneurysm
Patients with history of allergy to local anaesthetic or TENS electrodes
Patients with undiagnosed skin or pain conditions
Patient taking part in other studies

2.5 ETHICAL CONSIDERATIONS, INFORMATION GIVING AND WRITTEN INFORMED CONSENT

As outcome assessment involves a pain scale rating which has to be carried out by patient and requires that the patient be capable of providing this rating, the trial will not involve patients who are mentally incapacitated.

The investigator will explain to the patient that the trial is conducted to assess the effectiveness of TENS in alleviating the pain associated with local anaesthetic injection in comparison to EMLA and such trials have been conducted as research elsewhere and are safe. An information sheet will be provided and the patient is given the option to participate in the study. If they wish to be included, a written informed consent will then be taken. If the patient does not wish to enter the study, their choice will in no way affect their planned surgical treatment and post-operative care which will be carried out as per departmental standards.

2.6. REGULATORY REVIEW

Before any patients are enrolled, the Chief Investigator/Principal Investigator will ensure that appropriate approvals are in place. For any amendment to the study, the Chief Investigator in agreement with the Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment.

2.7 RANDOMISATION

After obtaining informed consent patients will be randomised to two groups using codes generated by web-based randomisation system- Research Randomizer. This is a free resource for researchers. The website is <http://www.randomizer.org>
The numbers generated will be placed in separate sealed envelopes by the department secretary and made available to the investigators.

2.8 TRIAL INTERVENTION

On the day of procedure, either the Chief Investigator or Investigator will see the patient in the Theatre Arrivals area and have a full discussion on the details of the trial and will answer all their questions. Patients willing to take part and are within the inclusion

criteria and does not have any of the exclusion criteria will be randomised to either the study group or the control group after obtaining informed consent.

The trial group will have the TENS to the area planned for injection for at least 30 minutes before injection of the local anaesthetic.

The control group will have EMLA 5% applied on the site planned for local anaesthetic injection and after a minimum period of 1 hour, will be removed and immediately injected with the same anaesthetic solution (this is already a procedure practiced by some of the surgeons).

Pain perception will be evaluated using two Numeric Pain Rating Scales in the study and control groups- one to assess the pain of needle penetration and the second to assess the pain of local infiltration. The Numeric pain scale is filled in by the doctor as indicated by the patient. Pulse rate and Blood Pressure monitoring will be carried out as an objective measurement of response to pain (these are routinely recorded when patient is in the theatre for a procedure). Patient involvement in the study ends at this point.

Analysis of the outcome will be done at the end of the trial period.

Description of device

The TENS unit comprises of an

- (1) Electric pulse generator which is battery-operated and programmable for pulse rate, width and intensity.
- (2) Lead wires connecting the unit to electrodes
- (3) Electrodes which consists of silicone rubber and adhesive to attach to skin surface.

Specifications of the unit to be used.

The device to be used in the trial is Neurotrac TENS Unit

Power supply	: PP3 Alkaline battery, 9 volts
Pulse rate	: 80Hz -100Hz
Pulse width	: 50 – 300 microseconds
Amplitude	: 0-80mA (500 Ohm load)
Type	: Continuous

Contraindications

1. In patients with pacemakers or implantable cardioverter-defibrillators (ICDs)¹⁴. This is of utmost significance for use in thoracic area as there will be interference with the electrical impulses generated except in fixed rate pacemakers.

2. Epileptic patients - as there is a risk of triggering a seizure.
3. Patients with history of aneurysm. TENS stimulates peripheral blood flow and hence can be problematic in such cases.
4. Pregnant patients. There are no definitive side effects and some studies¹⁵ have demonstrated the effectiveness and safety of TENS use during pregnancy. But as such it has not been approved for use in pregnancy.
5. By patients with undiagnosed skin or pain conditions

2.9 ADVERSE EVENTS

EMLA Cream and TENS have a well-documented safety profile. The commonest side effect for TENS reported is allergic reaction (2-3%) to the electrodes, gel or the tapes used for fixing electrodes. Any adverse events/ reactions to either EMLA or TENS machine will be collected and reported in the Case Report Form. Due to the minimal risk presented, Serious Adverse Events will not be collected for this study.

2.10 OUTCOME ASSESSMENT

Pain perception will be evaluated using two Numeric Pain Rating Scales in the study and control groups. One scale will assess the pain caused by needle piercing the skin and the second will do so for the pain caused by infiltration of local anaesthetic agent.

Pulse rate and Blood Pressure monitoring will be carried out as an objective measurement of response to pain.

2.11 DATA COLLECTION AND MANAGEMENT

The trial will be conducted at Leicester Royal Infirmary and data collection done by investigators on site. Data on eligibility will be available in the case report form. Other data will include consent form, outcome assessment forms and data on adverse events/ reactions. Paper data will remain at the trial site itself in locked cabinet and will only be accessed by the investigators. For the purpose of analysis data will be transcribed to excel spreadsheet. Data will be used only in accordance with the data protection act and ethical considerations. Any data analysed or seen by other parties will be pseudo-anonymised by allocating a number to everyone.

2.12 MONITORING

University Hospitals of Leicester NHS Trust, as Sponsor, operates a risk based monitoring and audit program to which the study will be subject. The trial will collect data on any adverse event/ reaction. All trial related documents will be kept for at least five years after completion of the trial.

2.13 ANALYSIS

The analysis will assess the effectiveness of TENS in alleviating the pain of local anaesthetic injection with the differentiation of needle and infiltration pain and also compare the TENS with EMLA. It is expected that TENS will alleviate or bring about a significant reduction in the pain associated with injection of local anaesthetic and will be better or as effective as EMLA in this aspect. This is the hypothesis being examined in this trial.

Pain perception will be evaluated using two Numeric Pain Rating Scales in the study and control groups. Pulse rate and Blood Pressure monitoring will be carried out as an objective measurement of response to pain.

The tabulation of the results will be done by the research team after transcribing to an excel spreadsheet and the fully anonymised data will be analysed statistically by the biostatistician at The University of Leicester.

Summary statistics of 2 groups will be presented. Median score, lower and upper quartile and minimum and maximum scores will be given for each group. Two groups will be compared using Mann Whitney test.

3 TRIAL ORGANISATION

3.1 SPONSORSHIP

The TENS-LA trial will be sponsored by University Hospitals of Leicester NHS Trust.

3.2 PROTOCOL COMMITTEE

The protocol committee consists of the following investigators.

CHIEF INVESTIGATOR	CLINICAL EXPERTS
Ms Rajshree Jayarajan Specialty Doctor Department of Plastic Surgery	Mr Graham Offer Clinical Lead and Consultant Department of Plastic Surgery

University Hospitals of Leicester UK	University Hospitals of Leicester UK
	Mr Nakul Patel Research Lead and Consultant Department of Plastic Surgery University Hospitals of Leicester UK
INVESTIGATORS	STATITICIAN
Mr Reza Arya ST7 Specialist Registrar in Plastic Surgery Department of Plastic Surgery University Hospitals of Leicester UK	Dr Maria Viskaduraki BBASH Facility Manager-Biostatistics Bioinformatics and Biostatistics Hub College of Medicine, Biology and Psychology University of Leicester UK
Mr Avinash Deodhar Locum Specialty Doctor Department of Plastic Surgery University Hospitals of Leicester UK	

3.3 COLLABORATOR'S RESPONSIBILITIES

The responsibilities of the chief investigator will be detailed in advance of starting the trial and will include:

- Ensure all necessary approvals are in place prior to starting the trial
- Delegate responsibilities related to the trial only to suitably qualified and trained personnel
- Ensure that patients fulfilling eligibility criteria and considered for the trial
- Ensure patients are given adequate information regarding the trial and informed consent obtained
- Ensure that the documentation is up to date
- Ensure that all adverse effects related to the trial are promptly reported
- Ensure that the trial is conducted in accordance with the ICH GCP and fulfils local and national guidelines.
- Hold the responsibility for archiving the original trial documents for 5 years after end of trial

3.4 PUBLICATION AND DISSEMINATION OF RESULTS

The trial protocol and the final results of the trial will be published in established peer-reviewed journal. Links to the publication will be provided in all applicable trial registers. In addition, participants of the trial will be informed of the trial results if requested.

4 LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BP	Blood Pressure
EMLA	Eutectic Mixture of Local Anaesthetics
GCP	Good Clinical practice
ICD	Implantable Cardioverter Defibrillators
LA	Local Anaesthetic
PR	Pulse Rate
TAA	Theatre Arrivals Area
TENS	Transcutaneous Electronic Nerve Stimulation
UK	United Kingdom

5. REFERENCES

1. Kasat V, Gupta A, Ladda R, Kathariya M, Saluja H, Farooqui A-A. Transcutaneous electric nerve stimulation (TENS) in dentistry- A review. *Journal of Clinical and Experimental Dentistry*. 2014;6(5):e562-e568. doi:10.4317/jced.51586.
2. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science*. 1965;150:971–979
3. Mendell LM. Constructing and Deconstructing the Gate Theory of Pain. *Pain*. 2014;155(2):210-216. doi:10.1016/j.pain.2013.12.010

4. Sluka KA, Deacon M, Stibal A, Strissel S, Terpstra A. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *J Pharmacol Exp Ther.* 1999;289:840-6.
5. Kalra A, Urban MO, Sluka KA. Blockade of opioid receptors in rostral ventral medulla prevents antihyperalgesia produced by transcutaneous electrical nerve stimulation (TENS) *J Pharmacol Exp Ther.* 2001;298:257–63.
6. Wall PD, Sweet WH. Temporary abolition of pain in man. *Science.* 1967;155:108–109.
7. Sluka KA, Bjordal JM, Marchand S, Rakel BA. What Makes Transcutaneous Electrical Nerve Stimulation Work? Making Sense of the Mixed Results in the Clinical Literature. *Physical Therapy.* 2013;93(10):1397-1402. doi:10.2522/ptj.20120281.
8. Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption: a meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain.* 2003;7:181–188
9. Varadharaja M, Udhy J, Srinivasan I et al. Comparative clinical evaluation of transcutaneous electrical nerve stimulator over conventional local anesthesia in children seeking dental procedures: A clinical study. *J Pharm Bioallied Sci.* 2014 Jul; 6(Suppl 1): S113–S117. doi: [10.4103/0975-7406.137407](https://doi.org/10.4103/0975-7406.137407)
10. teDuits E, Goepferd S, Donly K, Pinkham J, Jakobsen J. The effectiveness of electronic dental anesthesia in children. *Pediatr Dent.* 1993 May-Jun;15(3):191-6.
11. Choudhari SR, Parikrama SJ, Gaurav VK et al. Efficacy of transcutaneous electronic nerve stimulation in alleviating pain during inferior alveolar nerve block injections in pediatric dentistry. *International Journal of Pedodontic Rehabilitation.* 2017;2(2): 69-72
12. Meechan JG, Gowans AJ, Welbury RR. The use of patient-controlled transcutaneous electronic nerve stimulation (TENS) to decrease the discomfort of regional anaesthesia in dentistry: A randomised controlled clinical trial. *J Dent* 1998;26:417-20.
13. Dhindsa A , Pandit IK, Srivastava N, Gugnani N. Comparative evaluation of the effectiveness of electronic dental anesthesia with 2% lignocaine in various minor

pediatric dental procedures: A clinical study . Contemporary Clinical Dentistry. 2011; 2.1: 27-30.

14. Burri H, Piguet V. UninTENSional pacemaker interactions with transcutaneous electrical nerve stimulation. Europace. 2009;11:283–284. doi:10.1093/europace/eup008.
15. Keskin EA, Onur O, Keskin HL, Gumus II, Kafali H, Turhan N. Transcutaneous electrical nerve stimulation improves low back pain during pregnancy. Gynecol Obstet Invest_2012;74(1):76-83. doi: 10.1159/000337720.

6.APPENDICES

Appendix 1: Patient Information Sheet

Appendix 2: Informed Consent

Appendix 3: Case Report Form

