Efficacy Of Transcutaneous Electrical Nerve Stimulation (Tens) And Therapeutic Ultrasound (Tus) In The Management Of Hemiplegic Shoulder Pain: A Randomized Control Study

Sub title: TENS and Therapeutic Ultrasound in Hemiplegic Shoulder Pain

Ojoawo Adesola Ojo (PhD)*[1*]

Department of Medical Rehabilitation, Faculty of Basic Medical Sciences, College of Health Sciences, Obafemi Awolowo University, Ile Ife. Nigeria aoojoawo@yahoo.com

Adepoju* Ajibola *Faderera (PhD)[2]* *Ibraheem Saheed Areoye (BMRPT)[1]

Department of Physiotherapy, Faculty of Basic and Health Sciences, College of Health Sciences, Bowen University, Iwo

***Abstract*—Transcutaneous electrical nerve stimulation (TENS) and therapeutic ultrasound (TUS) have been effectively used for pain relief in physiotherapy; however there is dearth of literature on comparative efficacy of both modalities in the management of hemiplegic shoulder pain. Hence this study**

Forty six stroke survivors with HSP were recruited and assigned into two (TENS 23) and TUS 23) treatment groups randomly. Subjects in TENS group were treated with low frequency TENS. The intensity was regulated to the subjects' own comfort level. The treatment was for 15 minutes per session, twice per week, for 6 weeks duration. The patients in TUS group received continuous ultrasound using Sonopuls 490s, the function was regulated to 1 MHz frequency and 1.5 W/cm2 intensity twice per week, for 6 weeks duration. Shoulder pain and disability index (SPADI) was used to assess functional outcomes at baseline, third and sixth weeks respectively. The obtained data were classified and level of significance among the variables were ascertained with p value of 0.05 as level of significant

Results showed that the average length of time each subjects had lived in the TENS and TUS groups are 64.25+ 8.42 and 60.50 + 11.03 years respectively. Considering the TENS group, a noteworthy improvement was observed in pain severity and disability scores (p=0.035) when the first week was compared with the six weeks. However, there was no significant improvement in the TUS group (p> 0.05) over the same period. For both groups after six weeks, comparative analyses showed significant differences in pain intensity (at rest), pain intensity during movement and disability (p< 0.050)

It can be concluded that TENS was however more efficacious than TUS in the management of HSP.

Keywords Hemiplegic shoulder pain (HSP), Transcutaneous Electrical Nerve Stimulation (TENS), Therapeutic Ultrasound (TUS).

I. INTRODUCTION

Hemiplegic shoulder pain (HSP) begins early during the course of recovery post-stroke and its prevalence vary between 16% and 80% in stroke cases reported (1,2). HSP affects stroke outcome negatively; interfering with recovery by causing extreme anxiety and decrease in agility both of which seriously obstruct restoration of health (3,4). There are many factors that can bring about discomfort at the shoulder joint of patients with paralysis of one side of the body with the following postulations: partial dislocation of

joint of articulation of glenoid and humeral bone, abnormal contraction of muscles of the shoulder joint, deposition of foreign body in the joint injury to the soft tissue, tearing of muscles surrounding the shoulder joint, inflammation of the capsules around the shoulder joint , inflammation of tendon of the bicep muscles and a combination of some signs that affects shoulder and hand (4,5)

Prevention is the best management of discomfort of patient with paralysis of one side of the body. If stroke patients are aware of potential injury, especially at the shoulder joint, the frequency of shoulder pain will definitely reduce. More so members of health care team, patients and parent's carers should endeavour to provide information and instruction on how to avoid injuries to the affected limb. Recovery from shoulder pain may occur in 80% (6) and for effectiveness of prophylaxis it is a function of starting the treatment immediately after the stroke (7).

Transcutaneous neuromuscular electrical stimulation (TENS) is a treatment option proposed to be effective through the gate-control theory of pain; myelinated sensory fibres are activated to disrupt pain signals from unmyelinated C-fibres. High intensity TENS has been shown to effectively relieve hemiplegic shoulder pain (8,9). Therapeutic ultrasound (TUS) has been used to relieve muscle tightness, sprains, and shoulder-hand syndrome (10-12). However evidence for its relative efficacy in management of HSP is scarce. This study addressed the following research questions? The objectives of the research were to evaluate the effectiveness of TUS and TENS on pain intensity and disability scores in patients with HSP and to compare the effects of TUS and TENS pain intensity and disability scores in patients with HSP

A. ***Methods*** *Selecting a Template (Heading 2)*

Participants: Eighteen stroke survivors who presented with shoulder pain were purposively recruited. To be included, participants must be able to comprehend instructions; must have experienced pain on active or passive motion of the hemiplegic shoulder consistently for not less than two weeks.

Participants with shoulder pain prior to the ictus, impaired sensation, non-localised pain in upper limb, acute inflammation, skin infections, bony disorders, broken skin and vascular abnormalities were excluded from the study.

B. *Equations*

C. ***Determination of number of subjects for the study***

Rosner (13) proposed an equation which can be used for a research that compared the means of variables of two groups. The equation is:

$$N = \frac{4U^2 (Zcrit + Zpwr)^2}{D^2}$$

N = total number of subjects in the two groups

U= SD estimated to be equal in each of the group; 6 can be assumed in this regard

Z crit = Standard Normal Deviate equivalent to the chosen important criterium (i.e 0.05 (95%=1.960).

Zpwr=A chosen statistical normal power comparable to the standard normal deviate (i.e 0.80=0.842).

D=5 which is the least difference between the means of the two groups

Therefore;

$$N=\frac{4\times6^2(1.96+0.842)^2}{5^2}$$

N=45.22~45: therefore 46 patients were recruited which were randomly allocated into two groups of 23 each.

II Instruments

(a)Trans Electrical Nerve Stimulation A machine which stimulate nerves electrically (MH6000 Combo, MH6100 EMS, MH6200 TENS) that was Medihightec Medical Co., Ltd 30175 at Honnover Germany manufactured was used in the study. The electrode of the machine was of a squared shaped 40 by 40 mm

(b)Ultrasound Machine

The Ultrasound machine used in the study was a continuous mode type; It was of Sonopuls 490 made by Enraf-Nonius B.V. from Rotterdam in the Netherlands).

1) ***Shoulder pain and disability Questionnaire:*** *Instrument used to measure pain at the shoulder joint was called shoulder pain and disability index (SPADI). SPADI is a questionnaire with 13 items which assessed two major domains; a pain domain with 5- questions of likert subscale, and a disability domain containing 8 questions for the measurement of disability. Values obtained from each domain are added up, and converted to 100 score. An average is obtained from the two subscales of the domain from which a total score is obtained out of 100. Great impairment or disability is indicated by a high score while a low score indicated less impairment. SPADI takes 5-10 minutes to fill and is the only known region-specific measure* instrument for assessment of shoulder dysfunctions (14).

a) **Randomization of subjects**.

The process of randomization used was fish bow method. Forty-six wraps with a label of either TENS or TUS equally were enveloped. Each participant was asked to pick a wrap from that envelope on arrival in to the site of the study until the last wrap was picked. Participants were allocated to the group they picked, that is either a TENS or TUS group without bias. This was shown in Figure 1

The study was approved by an Ethical committee for Health Research at the Public Health Institution, a unit of College of Health Sciences at the University called, Obafemi Awolowo in Ile-Ife, Nigeria. Informed consent was obtained from each participant before recruitment; subjects were subsequently assigned into either of the two groups; TENS and Therapeutic Ultrasound (TUS) randomly.

b) ***Procedure***.

a. Trans Electrical Nerve stimulation Group

Subjects in TENS group were treated with TENS and mobilisation exercises

The active electrode was placed at the superolateral aspect of the shoulder while the inactive electrode was attached to the posterior

part of the neck. The intensity was regulated to the subjects' own comfort level, the subject was instructed to indicate when the level of stimulation was at a comfortable and tolerable level. The principle of operation of TENS was also explained to the individual on how the unit works and the associated sensations the individual will experience. The treatment was for 15 minutes per session, twice per week, for 6 weeks duration. According to Kitchen and Bazin (15)

D. ***Therapeutic Ultrasound (TUS) Group :*** In this group, the ultrasound machine was tested according to Kitchen and Bazin (15). The treatment head was immersed in water, after which the machine was turned on and adjusted to a continuous mode. The output of the machine was observed from the bubbling of the water molecules. The patients in this group received continuous ultrasound using Sonopuls 490s operated at a frequency of 1 MHz and intensity of 1.5 W/cm2 (spatial average temporal average) according to Ansari et al., Durmuz et al., and Ebadi et al, (16-18).

At each treatment session, the TUS beam was directed at the impaired soft tissue structure; in order to reduce the risk of hot spots, pulsed US with a duty cycle of 20% with slow circular transducer movements was applied. Participants were treated twice weekly for six weeks.

Outcome measure:

The pain intensity and disability of the patients were measure with Shoulder pain and disability index (SPADI) questionnaire . was used to assess pain intensity and disability at baseline, 3rd and 6th weeks. A physiotherapist carried out the assessments on each participant while another physiotherapist treated the subjects.

V Data Analyses: Data was analysed using SPSS package version 21 for Windows (SPSS Inc. Chicago, USA). A statistical method that describe and draw an inference were been used to sum up the collected variable. Analysis of variance using repeated measure was used to examine the similarity among the mean value before the treatment, 3rd week within the treatment and week six of the treatment patients' severance of pain within the group and across the group. Alpha level was set at 0.05.

VI Results:

Physical attributes of those that participated are presented in table 1; there was no appreciable difference in the values of outcome measures before the treatment between the two groups ($p > 0.05$).

E.

Table 1: Physical Characteristics of Participants and Independent t-test

VARIABLES	TENS (× ± S.D)	TUS (× ± S.D)	t-value	P
Age (YRS)	64.25±8.42	60.50± 11.03	0.540	0.608
Height (Cm)	1.70±0.21	1.74±1.03	0.328	0.754
Weight (Kg)	80.00±4.39	99.50±35.03	1.104	0.312
BMI ($Kg/m^{2)}$	28.68±7.31	33.31±12.30	0.621	0.557
Waist circumference (cm)	94.25±5.12	108.75±22.20	1.273	0.250
Hip circumference (cm)	91.00±4.00	103.75±22.18	1.131	0.301
WHR	1.04±0.01	1.05±0.02	0.851	0.427

Key: x ---mean value; S.D ---- standard deviation; WHR ---- waist circumference to hip circumference ratio

Improvements were noted in the disability scores of TENS group after six weeks of treatment ($p = 0.035$)

TABLE 2: REPEATED MEASURE ANOVA FOR PAIN INTENSITY AND DISABILITY FOR GROUP A (TENS)

PAIN INTENSITY (PI)	× ± S.D	F	P
PIR			
Pre treatment	6.50± 1.73		
3rd Week	4.75 ± 2.36	3.472	0.036*
6th week	3.00 ± 1.41		
PIM			
Pre treatment	18.50 ± 9.47		
3rd Week	14.00 ± 8.49	4.758	0.028*
6th week	8.25 ± 4.42		
DISABILITY			
Pre treatment	60.50 ± 20.62		
3rd Week	51.75 ± 10.20	5.001	0.035*
6th week	40.00 ± 0.00		

Key: pain at rest =PIR, pain during movement =PIM

However there was no significant improvement on pain intensity and disability score in TUS group (p> 0.05).

TABLE 3: REPEATED MEASURE ANOVA FOR PAIN INTENSITY AND DISABILITY FOR GROUP B (TUS)

PAIN INTENSITY (PI)	MEAN ± S.D	F	p
PIR			
Pre treatment	7.00±1.41		
3rd Week	5.50± 2.65	0.844	0.461
6th week	5.50±1.29		
PIM			
Pre treatment	24.25±5.32		
3rd Week	18.00±7.11	1.458	0.283
6th week	18.75±4.11		
DISABILITY			
Pre treatment	58.00±12.00		
3rd Week	47.00±18.35	0.840	0.463
6th week	44.00±16.65		

Key: pain at rest= PIR, pain during movement= PIM

Following six weeks of treatment, comparison of the groups showed significant differences across the three domains evaluated i.e pain at rest (PIR), pain during movement (PIM) and disability. Post-hoc analyses showed that group A (TENS) was more effective than TUS (table 4).

TABLE 4: COMPARISON OF OUTCOME MEASURES IN TENS AND TUS GROUPS

PAIN INTENSITY (PI)	TENS	TUS	F	P
PIR	**MEAN ± SD**	**MEAN ± SD**		
Pre treatment	6.50±1.73[a]	7.00±1.41[a]		
3rd Week	4.75±2.36[b]	5.50±2.65[c]	2.252	0.050*
6th week	3.00±1.42[d]	5.50±1.29[e]		
PIM				
Pre treatment	18.50±9.47 [a]	18.00±7.11[a]		
3rd Week	14.00±8.50 [b]	24.25±5.32[c]	2.502	0.045*
6th week	8.25±4.42[d]	18.75±4.11[e]		
DISABILITY				
Pre treatment	69.50±20.69[a]	68.00±12.00[a]		
3rd Week	51.75±10.21[b]	47.50±18.35[c]	2.126	0.040*
6th week	40.00±0.00 [d]	44.00±16.65 [e]		

Key: pain at rest= PIR, pain during movement= PIM. . *Post hoc analysis: means (a, b, c, d, e) with the same alphabet are not significantly different but means of different alphabet are significantly different. PI: Pain intensity SD: Standard deviation*

5. DISCUSSION

Hemiplegic shoulder pain can delay rehabilitation and functional reintegration; hence the need for relief. The research was designed to examine the similarities in the effectiveness of TENS and therapeutic ultrasound in the management of hemiplegic shoulder pain.

There was no significant difference in physical characteristics of subjects in both groups; it implied that it was the intervention that resulted in to the observed changes in the study. Our findings showed that TENS was effective in relieving HSP, this corroborates previous studies

which showed that TENS was effective in relieving HSP (19). Leandri et al., comparing high and low intensity TENS discovered that with high intensity treatment of TENS, there were notable improvement of movement of shoulder joint when it was done passively especially in all range of motion at the shoulder joint (19). Satisfactory relief of pain was also obtained with patients who received treatment with high intensity TENS (19). Transcutaneous electrical nerve stimulation (TENS) has been reported to be an effective nonpharmacological intervention that stimulates descending inhibitory systems in the central nervous system which activate the complex neuronal network and thereby reduces hyperalgesia (20)

Large diameter afferent fibers are stimulated by the application of TENS (21,22). Hyperalgesia is been produced from the body when the central nervous system received the stimulus, the stimulus then hindered the descending inhibition system hence hyperalgesia.

A study of patients with fibromyalgia revealed a restoration of modulation of pain with a measure of central inhibition by TENS (23). More so, there was an hyperalgesia effects of TENS by both peripheral and central mechanism.

The reduction of hyperalgesia could be explain thus; in the spinal cord, there was a blockage of μ opioid receptors by low frequency (LF) electrical stimulator machine, not only this, the current also inhibition of transmission at the synaptic cleft of the ventrolateral PAG (24,-26). More so, there were blockage of GABAA, serotonin 5-HT2A and 5-HT3, again, at the spinal cord, there were receptors named muscarinic M1 and M3 receptors which are associated with release of serotonin, all these were been prevented by the stimulation of LF TENS (27-29). In addition, research has shown that low frequency electrical stimulation reduces pain by a process of abasing the activities of dorsal horn neuron, the mechanism was through the inhibitory pathway which descend from the central nervous system involving the PAG-RVM, opioid GABA, serotonin and muscarinic receptors (29)

. Considering the site of stimulation, high frequency (HF) and low frequency TENS was found to be effective. Literature reported that there was a reduction of substance P by HF TENS; substance P was found increased in animals after injury to the tissues at dorsal region of the root of ganglia neurons (30). Analgesia, produced by LF has been shown to be prevented by the blockage of peripheral opioid receptors, but not by HF TENS (31,32). On the other hand, the excitability of the peripheral nociceptors might be altered in order to reduce the input from the afferent nerves to the central nervous system

Comparatively, pain intensity (at rest and during movement) was significantly different in both TENS and ultrasound groups at baseline, third and sixth weeks. Participants in the TENS group improved better than their counterparts in TUS group; this supported the work of Moniruzzaman et al., (33)

Our result revealed that US has effect in the reduction of Hemiplegic Shoulder pain, though the effect was not significant from the result. One of the methods of operation of US is through phonophoresis. The process that drives in

drug in to the skin by waves of Ultrasound (34). Being reported by Kanikkannan et al., the process of phonophoresis entails pushing in of the light drug molecule via the skin to the tissues through the US energy (35). US used for treatment purposes disturbs the cell fluid, though very difficult to separate by creating a mixture of sound wave and continuous flow [36]. Ultrasound produces a process called acoustic, this is the wave by sound that mobilizes ions and minute molecules within the tissues from one place to the another [36]. A cell comprises of small organs and molecules in various sizes floating either in the interstitial fluids or located on the same sport. A streamline motion of fluid is created by a pushing force of wave from the ultrasound machine, the force usually create a mechanical pressure that moves the organs and molecules along a streamline around the cell membrane which is termed continuous flow or streaming (36). Further to the effect of PUS is a process called cavitation which is the disturbance of cell fluid; the surrounding cell fluid is forced to vibrate on receiving the sound wave (37). Couple with cavitation, there is a feature of thinning and reduction in size of cells caused by the movement of the sound wave in the cell; due to this event, the minutes globe-shaped air filled films present in the cells increase in size and shrink, cell structure may be injured during the process This may explain how the US produces a relief of pain in patient with HSP

In conclusion, this study showed that TENS was more efficacious than therapeutic ultrasound in the management of hemiplegic shoulder pain.

Limitation: One of the limitation was the financial constraints on the part of patients; most of them have to pay out of pocket so their regularity in terms of clinic attendance was affected. The study had a time lag for completion there for there was no follow up after the completion to study the sustainability of the success of the patients.

Recommendation: We propose that further studies could incorporate the follow up of the patients to evaluate the sustainability of the effects of TENS and TUS in the management of HSP.

Acknowledgement: I wish on behalf of all the author to acknowledge the assistance of Dr O.B Oyelese, Director Physiotherapy Services, Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife for allow the research conducted in his Department

Authors Contribution: Ojoawo A.O conceived and designed the study. He did the analysis, interpreted the data and critically read the manuscript for publication.

Ibraheem Saheed Areoye: Collected the data, supplied part of the literature and did the skeletal write up

Adepoju F.A. Supplied the part of the literature and did part of the skeletal write up.

Conflict of interest: No conflict of interest from the authors

Ethical approval: Ethical approval was obtained (ERC/2015/12/02) from Ethic and Research Committee, Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife. Nigeria

Funding/Support: No funding or support was received for the study.

Informed Consent: A copy of the consent form was provided for each subject. For those that did not understand the English language, the content of the consent was interpreted into the Yoruba language for a better understanding. Each subject then signed the form before the commencement of the study.

REFERENCES

1 Kaplan MC. Hemiplegic shoulder pain--early prevention and rehabilitation. *West J Med*.,1995;162(2):151–152.

2 Harrison RA, Field TS: Post Stroke Pain: Identification, Assessment, and Therapy. *Cerebrovascular Diseases,* 2015;39:190–201

3 Leandri, PC, Corrieri N, Rigardo S. Comparison of TENS treatments in hemiplegic shoulder pain. *Scand J Rehab Med*., 1990 22: 69-72

4 Murie-Fernández M, Carmona M, Iragui V, Gnanakumar, Meyer M, Foley N, Teasell R. Painful hemiplegic shoulder in stroke patients: causes and management. *Neurología.,* 2012; 27:234—44

5 Van Ouwenaller C, Laplace PM, Chantraine A: Painful shoulder in hemiplegia. *Arch Phys Med Rehahil.*, 1986. 6:23-36,

6 Ancliffe J. Shoulder pain in hemiplegia: incidence and influence on movement and recovery of function. *Proceedings 3rd International Physiotherapy Congress.* Hong Kong, 1990: 187–92.

7 Walsh K. Management of shoulder pain in patients with stroke. *Postgrad Med J.,* 2001;77: 645–649

8 Yu DT, Chae J, Walker ME, Hart RL, Petroski GF. Comparing stimulation-induced pain during percutaneous (intramuscular) and transcutaneous neuromuscular electric stimulation for treating shoulder subluxation in hemiplegia. *Arch Phys Med Rehabil.,* 2001; 82(6):756-60.

9 Yu DT, Chae J, Walker ME, Fang ZP. Percutaneous intramuscular neuromuscular electric stimulation for the treatment of shoulder subluxation and pain in patients with chronic hemiplegia: a pilot study. *Arch Phys Med Rehabil.*, 2001; 82(1):20-5

10 Daniëlle AW.M.van der WindtaGeert J.M.G.van der HeijdenbSuzanne G.M.van den Bergc Gerbenter Rietd Andrea F.de WinteraLex M.Boutera .Ultrasound therapy for musculoskeletal disorders: a systematic review. *Pain,* 1999, 81, (3) 257-271

11 Lindsay DM, Dearness J and McGinley CC. Electrotherapy usage trends in private physiotherapy practice in Alberta. *Physiotherapy Canada,* 1995; 47: 30- 34

12 Ter Haar G, Dyson M and Oakley E. The use of ultrasound by physiotherapists in Britain. *Ultrasound Med Biol.* 1985; 13: 659-663.

13 Rosner, B. Fundamentals of biostatistics 5th ed. Pacific Grove, Calif: Duxbury, 2000; 308.

14 Roach, K. E., Budiman-Mak, E., Songsiridej, N., & Lertratanakul, Y. Development of a shoulder pain and disability index. *Arthritis & Rheumatism*, 1991; 4(4), 143-149.

15 Kitchen S, Bazin S. Electrotherapy: evidence based practice. 11th ed. Edinburgh: Churchill Livingstone; 2002.

16 Ansari NN, Ebadi S, Talebian S, Naghdi S, Mazaheri H, Olyaei G, Jalaie S. A randomized, single blind placebo controlled clinical trial on the effect of continuous ultrasound on low back pain. *Electromyogr Clin Neurophysiol* 2006;46:329 -336.

17 Durmuz D, Akyol Y, Cengiz K, Terzi T, Cantu¨rk F. Effects of therapeutic ultrasound on pain, disability, walking performance, quality of life, and depression in patients with chronic low back pain: a randomized, placebo controlled trial. *Turk J Rheumatol* 2010;25:82-827

18 Ebadi SN, Ansari N, Soofia N, Shohre JM, Sadat HB, Maurits W, van Tulder, et al. The effect of continuous ultrasound on chronic non-specific low back pain: a single blind placebo control randomized trial. *BMC Musculoskelet Disord* 2012;13: 192.

19 Leandri M, Parodi CI, Corrieri N, Rigardo S. Comparison of TENS treatments in hemiplegic shoulder pain. *Scand J Rehabil Med*. 1990;22(2):69-71.

20 Vance, Carol GT Dailey, Dana L Rakel, Barbara A and Sluka Kathleen A Using TENS for pain control: the state of the evidence. *Pain Manag.* 2014, 4(3): 197–209.

21 Levin MF, Hui-Chan CW. Conventional and acupuncture-like transcutaneous electrical nerve Stimulation excite similar afferent fibers. *Arch. Phys. Med. Rehabil.*, 1993;74:54–60. [PubMed] [Google Scholar]

22 Radhakrishnan R, Sluka KA. Deep tissue afferents, but not cutaneous afferents, mediate TENS-induced antihyperalgesia. *J. Pain.*

2005;6:673–680. [PubMed] [Google Scholar]
••

23 Dailey DL, Rakel BA, Vance CG. Transcutaneous electrical nerve stimulation reduces pain, fatigue and hyperalgesia while restoring central inhibition in primary fibromyalgia. *Pain*. 2013; 154:2554–2562. [PMC free article] [PubMed] [Google Scholar]

24 DeSantana JM, da Silva LF, De Resende MA, Sluka KA. Transcutaneous electrical nerve stimulation at both high and low frequencies activates ventrolateral periaqueductal grey to decrease mechanical hyperalgesia in arthritic rats. *Neuroscience.* 2009;163:1233–1241

25 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;298:257–263. [PubMed] [Google Scholar]

26 Sluka KA, Deacon M, Stibal A,. Spinal blockade of opioid receptors prevents the analgesia produced by TENS in arthritic rats. *J. Pharmacol. Exp. Ther.* 1999;289:840–846. [PubMed] [Google Scholar]

27 Maeda Y, Lisi TL, Vance CG, Sluka KA. Releaes of GABA and activation of $GABA_A$ receptors in the spinal cord mediates the effects of TENS in rats. *Brain Res.* 2007;1136:43–50. [PMC free article] [PubMed] [Google Scholar]

28 Radhakrishnan R, King EW, Dickman JK, Herold CA, Johnston NF, Spurgin ML, Sluka KA. Spinal 5-HT(2) and 5-HT(3) receptors mediate low, but not high, frequency TENS-induced antihyperalgesia in rats. *Pain.* 2003 Sep;105(1-2):205-13. doi: 10.1016/s0304-3959(03)00207-0.

29 Sluka KA, Lisi TL, Westlund KN. Increased release of serotonin in the spinal cord during low, but not high, frequency TENS in rats with joint inflammation. *Arch. Phys. Med. Rehab.* 2006;87:1137–1140. [PMC free article] [PubMed] [Google Scholar]

30 Rokugo T, Takeuchi T, Ito H. A histochemical study of substance P in the rat spinal cord: effect of transcutaneous electrical nerve stimulation. *J. Nippon Med. Sch.* 2002;69:428–433. [PubMed] [Google Scholar]

31 Sabino GS, Santos CM, Francischi JN, de Resende MA. Release of endogenous opioids following transcutaneous electric nerve stimulation in an experimental model of acute inflammatory pain. *J. Pain.* 2008;9:157–163. [PubMed] [Google Scholar]

32 Santos CM, Francischi JN, Lima-Paiva P, Sluka KA, Resende MA. Effect of transcutaneous electrical stimulation on nociception and edema induced by peripheral serotonin. *Int. J. Neurosci.* 2013;123(7):507–515. [PubMed] [Google Scholar]

33 Moniruzzaman M; Salek AKM; Shakoor MA, Bahadur Ali Miah Md; Moyeenuzzaman Md: Effects of therapeutic modalities on patients with post-stroke shoulder pain. *Mymensingh Medical Journal* 2010 19(1): 48- 53

34 Asano J, Suisha F, Takada M, Kawasaki N, Miyazaki S. Effect of pulsed output ultrasound on the transdermal absorption of indomethacin from an ointment in rats. *Biol Pharm Bull* 1997;20:288-291.

35 Kanikkannan N, Kandimalla K, Lamba SS, Singh M. Structure-activity relationship of chemical penetration enhancers in transdermal drug delivery. *Curr Med Ch* 2000;7:593-608.

36 Nyborg WL. Ultrasonic microstreaming and related phenomena. *Br J Cancer Suppl* 1982;5:156-160.

37 Wilkin LD, Merrick MA, Kirby TE, Devor ST. Influence of therapeutic ultrasound on skeletal muscle regeneration following blunt contusion. *Int J Sports Med* 2004;25:73-77.