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The Effectiveness of Transcutaneous Electric Nerve Stimulation (TENS) in The Management of Painful Diabetic Peripheral Neuropathy (DPN)-A critiquing

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Abstract:
Background: *The peripheral neuropathy is one of the common complications of type II diabetes mellitus along with other complications and affects both somatic and autonomic nervous system. The pharmacological treatment of diabetic peripheral neuropathy is mainly directed for symptom control with varying extent of the effectiveness. TENS is a less expensive, non-invasive procedure useful in neuropathic pain; however, the literature evidence for its effectiveness is inconclusive and contradictory. This article aimed for a critical analysis of the available evidence on the application of TENS for the clinical treatment of painful diabetic peripheral neuropathy patients.*
Methodology: *An electronic search was carried out for the relevant literature published during the period of 2009 to 2014 in the databases. The selected evidence evaluated for quality and level of evidence using SIGN critiquing tool and Harbour and Miller 2001 hierarchy of evidence respectively.*
Results: *Identified five relevant pieces of evidence for critical analysis. Three of them were systematic reviews, one randomized controlled trial and one observational study.*
Conclusion*: The majority of the evidence recommends the use of TENS therapy for the management of painful diabetic peripheral neuropathy. However, it is limited with short duration of trial period and lack of standardization of TENS therapy for the condition.*
Keywords:*TENS, Electrotherapy, Neuropathic pain, Diabetic neuropathic pain.*

I. Introduction

The peripheral neuropathy is one of the common complications of type II diabetes mellitus along with other complications affecting 60-70% of diabetic patients in varying extent from mild to severe forms (Charnogursky et al., 2014). As a heterogeneous disorder with complex pathophysiology, diabetic peripheral neuropathy (DPN) affects both somatic and autonomic nervous systems (Singh et al., 2014). The clinical symptoms are characterized with burning, tingling (pins and needles or paraesthesia) sensation, and shooting (like electric shock), or lancinating (stabbing) type of pain (Singh et al., 2014). The currently using pharmacological treatment of diabetic peripheral neuropathy is mainly directed for a symptom control rather than a curative therapy and the extent of the effectiveness varies in different patients (Brilet al., 2011; Charnogurskyet al., 2014). The National Institute for Health and Clinical Excellence (NICE) guidelines recommends the use of tricyclic antidepressants, selective serotonin and norepinephrine reuptake inhibitors, anticonvulsants, opioid agents and topical medications such as lidocaine patch and capsaicin for the pharmacological treatment of neuropathic pain. However, these agents are only able to partially control the symptoms, and they may cause serious adverse effects, which is a major role for the discontinuation of drug therapy in these patients (Charnogurskyet al., 2014). In addition to these complications of drug therapy, the limited availability of evidence, the low degree of cost-effectiveness and the little improvement in physical functioning limits the use of the pharmacological agents (Brilet al., 2011). On this context, it is logical to consider other effective treatment modalities such as TENS and electrotherapy for the management of painful diabetic peripheral neuropathy.

TENS is a less expensive, widely used non-invasive procedure for the management of painful conditions, and it carries low incidence of complications(Tashani and Johnson, 2009). A modulation of gate-control of pain process (Melzack and wall, 1965) at the spinal level has been hypothesized as a mechanism for the analgesic effect of the TENS. It is also suggested that the modulating effect of TENS on the descending spinal inhibitory mechanism of pain and the application of TENS releases the endogenous opioids and affects the metabolism of other neurotransmitters such as GABA (Gamma Amino Butyric Acid), acetylcholine, serotonin, noradrenaline and adenosine (Tashani and Johnson, 2009), which may alter the pain experience at the spinal level. However, different kinds of literature provide an inconclusive and contradictory results on the effectiveness of TENS in the management of painful peripheral diabetic neuropathy. Therefore, it is relevant to

carry out a critical appraisal of available evidence on the application of TENS for the clinical treatment of painful diabetic peripheral neuropathy patients.

II. Literature Search Strategy

An electronic search was carried out for the relevant literature published during the period from 2009 to 2014 in the databases of COCHRANE Review, MEDLINE Ovid (from1996 to 2014 November 25), CINAHL PLUS, Scopus and EMBASE. The following search terms such as "Transcutaneous Electric Nerve Stimulation" "TENS" "pain" "Diabetic neuropathy" "diabetic peripheral neuropathy" were used along with appropriate boolean operators AND or OR. The search was limited for the articles, in English language and human adults. Also used forward as well as backward chaining for the relevant articles cited in retrieved publications. The primary screening identified 33 related articles and after an initial reading of title and abstract for relevant articles and avoiding duplication, retrieved eight articles for critical reviewing. Three articles were excluded from the analysis, as they were not acceptable according to SIGN checklist criteria for analysis of the internal validity of the evidence. Three of the selected literature are systematic reviews (2 of them with meta-analysis and one systematic review), one randomized controlled trial and one observational study. Figure (1) shows the flow chart of the literature search and Table (1) describes the features of the evidence that is selected for critical analysis.

Analysis of Evidence in patients with diabetic peripheral neuropathy for the efficacy of TENS to reduce pain:

In a systematic review with meta-analysis of randomized controlled trials, Stein et al.,(2013), evaluated and compared the effectiveness of the TENS and electromagnetic field use on the pain and measured the improvement of sensitivity in patients with painful diabetic peripheral neuropathy with placebo and other interventions. The authors carried out this systematic review in accordance with Cochrane collaboration and statement for systematic review and Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA), with the search for evidence in electronic databases such as Medline, LILACS, PEDro, EMBASE and Cochrane central register using predefined search terms and without language restriction. The features of the studies included for analysis are shown in Table:2. The total sample size from the studies was 173 with 96 patients in the TENS arm. The main outcome of the evaluation was pain relief with secondary outcomes of sensitivity and length of treatment. The investigators assessed the extent of bias involved in the analyzed studies and mentioned in the table, which increases the internal validity of the article. Of these reviewed articles, six of them used TENS as a treatment modality, which is the focus of this assignment. Five articles compared TENS with placebo and one study compared it with high-frequency muscle stimulation for its effectiveness. The included articles used different methodologies of TENS in treatment (see table 1), and this lack of uniformity further reduces the validity of the article. The meta-analysis of articles of placebo-controlled trials showed improvement in pain measurement (VAS) with a significant difference between intervention group and control group (p-value of 0.01, CI: 95% standard mean difference of -0.44 within the range of -0.79 to -0.09). The short-term effectiveness was assessed with a sub-analysis of four studies with treatment period of 2,4, and 6 weeks, which showed improvement in pain (p-value =0.03 under CI: 95% standard mean difference of -0.54 within the range of -1.02 to -0.06), however, two studies with longer treatment period of 12 weeks were without significant reduction in pain with p value= 0.14 (with CI: 95% standard mean difference of -0.47 within the range of -1.10 to -0.16). This data questions the long-term efficacy of the TENS in pain relief with DPN. Overall, this study was conducted with a well-designed methodology with high degree rigor and internal validity. However, the main drawbacks involved with this evidence such as multi-focused assessment with different modalities of treatment, lack of uniformity in methods of treatment and a small number of patients in the included study trials affects negatively on the validity and reliability of the results. Finally, the publication bias involved with this meta-analysis could have been reduced with funnel plot test.

Jin et al (2010) carried out a meta-analysis of RCTs with the aim to evaluate the effectiveness of transcutaneous nerve stimulation on diabetic peripheral neuropathy. Two investigators independently carried out the literature search in databases such as PubMed, EMBASE, Cochrane central register of controlled trials, CINAHL, and other relevant search engines. The literature search was based on pre-defined inclusion and exclusion criteria. The discrepancies between the investigators were resolved by consensus or third author adjudication. The use of Cochrane Handbook for Systematic Reviews of Interventions guidelines as a reference for this meta-analysis increased the validity and reliability of the article. The results of this article are expressed as relative risk ratio under 95% confidence interval and consideration of p value <0.05 as significant, favoured the reliability and validity of the data. The authors used the CONSORT statement for the assessment of study quality and baseline characteristics, which enhanced the validity and reliability of the evidence and analyzed three RCTs with total 78 patients. The baseline parameters were comparable among both groups of patients (see Table 3). However, the number of patients in placebo TENS group were less in all three studies and the pain

reduction is expressed in standard mean difference (SMD). The small number of selected articles for analysis and the difference in the trial duration in studies also affected the reliability of the evidence (see Table 3). The reduction in mean pain score was significantly greater in TENS group than in placebo group with SMD of 5.37 at 4th week (95% CI, -6.97 to -3.77) and SMD 1.01 at 6th week (95% CI, -4.02 to 0.73). The overall neuropathic symptoms were improved with TENS therapy with a weighted mean difference (WMD) of 0.18 with 95% CI(-0.32 to -0.0521). One of the studiesanalyzed and evaluated the effect of TENS on sensory nerve thresholds and found improvementsin the heat, cold, and heat-pain perception with TENS therapy. Even though, this rigorously conducted meta-analysis shows a therapeutic benefit of TENS therapy in diabetic peripheral neuropathy, the small number of the analyzed trials and the difference in trial duration reduced the reliability of the data produced by this article.

In a systematic review, Pieber et al (2010) analyzed the efficacy of different types of electrotherapy including TENS for the management of painful diabetic peripheral neuropathy. The authors included studies which investigated different electrotherapeutic methods for analysis and this caused loss of specificity of intervention which affected the validity of the evidence. A comprehensive literature was carried out by two investigators independently using predefined key words according to inclusion and exclusion criteria. This reduced the risk of bias and enhanced the internal validity and rigor of the study. However, the use of a single database for literature search and limiting the articles to English and German languages caused publication bias.

The selected articles allowed for grading according to guidelines adapted from GRADE working group. This process of quality of evidence assessment enhanced the rigor of the study and raised the reliability. Out of 15 selected articles, 4 studies (see table 4) used TENS as an intervention for the treatment of DPN with total 135 patients. 108 (80%) patients out of 135 showed significant improvement in pain score after TENS therapy. In another study by Reichstein et al (2005), TENS therapy was compared with high-frequency external muscle stimulation and found that TENS was inferior to produce symptom relief in DPN. Another article by Kumar et al (1998) analyzed the combination of TENS and amitriptyline therapy for DPN patients in a placebo-controlled randomized trial and found the combination is superior to TENS alone with 85% of symptomatically improved patients. In short, this evidence recommends TENS for the management of painful diabetic peripheral neuropathy as adjuvant therapy.

Gossrauet al(2011) conducted a randomized single blinded placebo controlled trial to find out the effectiveness of micro-TENS in reducing neuropathic pain in patients with diabetic peripheral neuropathy. This article carries an acceptable grade of study methodology supported the rigor and internal validity of the article. However, it is not clear about the method of randomization and allocation concealment used. The authors used specified method of electric neuronal stimulation and standardized instruments such as Pain Disability Index (PDI), Neuropathic Pain Score (NPS) and Centre for Epidemiologic Studies Depression Scale (CES-D), for the measurement of outcome. The use of standardized measurement tools in the trial improved the reliability of the results as it favors reproducibility. The research data was analyzed by using Statistical Software Package for Social Sciences (SPSS) with the t-test. The total sample size was 41 with 22 patients in the active treatment arm and 19 patients in placebo group. There was no dropout from the trial. The basic characteristics of enrolled patients were equally distributed among both groups and nullified the effect of confounding factors on the treatment outcome. The total duration of the study was 4 weeks and patients were followed up during 1 month of the post-trial period. There was no significant difference in neuropathic pain score between active and placebo group ($p>0.5$) after treatment. The pain disability index and CESD scale were similar in both groups after trial and during the follow-up period ($p>0.5$). The evidence concluded showed no significant difference between placebo group and treatment group.

In an observational study,Moharic and Burger (2010) measured the extent of the improvement in small fibre function in diabetic peripheral neuropathy patients with TENS therapy. The authors enrolled the patients who fulfilled at least two items of Michigan Neuropathy Screening Instrument (MNSI) criteria, and used a standard method of Quantitative sensory testing (QST) to detect sensory abnormalities in the neurons. For comparison, the investigators obtained the normative data from age-comparable normal healthy volunteers using the same measurement procedures and instruments. In this evidence, the authors restricted the use of other therapeutic methods and drugs for neuropathic pain but allowed tricyclic antidepressants and selective serotonin reuptake inhibitors. The permission of these drugs during trial period might have affected the results, as these drugs have a neuro- stimulating effect. Thermal and pain thresholds were measured using Marstock method, vibratory perception threshold with Vibratory Sensory Analyzer 3000 and static touch threshold with von Frey's hair. The total number of patients enrolled was 46, with 25 males and 21 females. The duration of diabetes and pain had great variation ranging from 2 to 36 years and 0.5 to 20 years respectively. This wide difference in basic data also might have influenced the result of this study. The intervention was carried out for 3 weeks with the application of TENS therapy for 3 consecutive hours daily. The patients were followed up for 1 month after treatment. The data analysis with SPSS15.0.1.1 for windows with a prefixed significant level of 5% showed two significantly changed measurements from baseline. The threshold for cold sensation is increased significantly

($p<0.0001$) on thenararea.Baseline line: Mean value 4.1 interquartile range (IR) of 13.6 to post treatment result-Mean 13.2 (IR 15.9) and one month post treatment 15.9(IR 12.0)]. The threshold for heat pain on thenar area reduced from baseline significantly ($p<0.0001$). [Baseline value: Mean 47.4 (IR 7.9), post treatment Mean 45.0 (IR 8.2), one-month post treatment Mean 44.5 (IR 10.0). There were no significant differences in other measurements and the article concluded that TENS did not have a significant effect on perception activity of C, A-delta and A-beta sensory fibres in diabetic peripheral neuropathy patients.

III. Conclusion

Envisaging the principles of evidence-based medicine, a critical appraisal of five relevant articles was carried out to find out the effectiveness of TENS therapy in the management of painful diabetic peripheral neuropathy. The selected articles were critically analyzed for validity and reliability using the SIGN criteria and graded based on the criteria of Harbour and Miller Hierarchy of Evidence 2011. All the analyzed systematic review articles recommended the use of TENS for the management of painful diabetic peripheral neuropathy; however, the main short coming of them was the short duration of the studies. A three weeks randomized controlled trial could not find any difference between the intervention group and placebo in diabetic peripheral neuropathy patients and an observational study showed improvement in cold and heat -pain threshold with TENS. In summary, the majority of the analyzed contemporaneous evidence recommends the use of TENS therapy for the management of painful diabetic peripheral neuropathy. However, the use of different methods of TENS therapy and the short duration of the trials limit the validity of this recommendation. Therefore, it is advisable to have long-term studies with a standardized methods in the application of TENS for painful diabetic peripheral neuropathy.

Table. 1: Features of the evidence selected for critical analysis

Authors & Year	**Method of Study**	**Hierarchy of Evidence** (Harbour and Miller 2001)	**Grade based on SIGN criteria**	**Comments**
Stein C. et al., 2013	Systematic review with meta-analysis	1-A	High Quality (++)	As the majority of SIGN criteria met by this article with little risk of bias. Use of TENS improved the symptoms of DPN patient significantly. The article favours the use of TENS for the painful diabetic peripheral neuropathy
Jin D et al., 2010	Systematic review with meta-analysis	1-A	High Quality (++)	Reviewed only 3 articles and find out significant improvement in pain and other subjective symptoms in DPN patients.
Pieber K. et al., 2010	Systematic review	2++A	Acceptable (+)	Small number of studies analysed. Recommends use of TENS in DPN patients for the symptomatic improvements and long-term therapy for maintenance of effect
Gossrau G. et al., 2011	Randomised, single blind, controlled study	1-	Acceptable (+)	The article proved that there is no difference in between treatment group and placebo group.
Moharic, M and Burger, H. 2010	Observational study-cohort study	2+	Acceptable (+)	3 week of application of TENS in DPN patients improved the heat and cold pain threshold and the article recommends long-term therapy with TENS for beneficial effects

SIGN- Scottish Intercollegiate Guidelines Network, Transcutaneous Electric Nerve Stimulation, DPN- Diabetic Peripheral Neuropathy.

Table 2: The characteristics of studies (using TENS) included by Stein, C. et al., 2013 pp. 97-98.

Author(s)	Year of study	Number of patients n(n1 in TENS/ n2 Comparator)	Features of TENS
TENS versus Placebo			
Cheing and Luk	2005	19 (10/9)	Pulse=200, frequency =100Hz, adjusted intensity for tingling sensation
Forst, et al	2004	19 (12/7)	Pulse=280, frequency =4Hz, individual intensity between 5-70 mA
Gossrau, et al	2011	40 (21/19)	Pulse=30-40, frequency =2Hz
Kumar, et al	1998	23 (14/9)	Pulse=400, frequency =2-70Hz, intensity<35mA
Kumar and Marshall	1997	31 (18/13)	Pulse=400, frequency =2-70Hz, intensity<35mA
TENS versus High Frequency Muscle Stimulation			
Reichstein, et al	2005	41 (21/20)	Pulse=400, frequency =180Hz, voltage=<35V, intensity =20-30mA

Table 3:The characteristics of studies analysed by Jin. et al., 2010 pp. 12

Author(s)	Year of study	Number of patients n(n1 in TENS/ n2 Placebo)	Duration of treatment
Kumar et al	1997	31 (18/13)	4 weeks
Kumar et al	1998	23 (14/9)	4-20 weeks
Forst et al	2004	24 (13/11)	12 weeks

Table 4:The characteristics of studies analysed by Pieber et al 2010 pp. 291

Author(s)	Year of study	Study design	Number of patients / duration of study	Commends
Kumar & Marshall	1997	Randomised controlled	31/ 4 weeks	Significant therapeutic effect with TENS in DPN compared to placebo
Kumar et al.,	1998	Randomised controlled	26/ 12 weeks	Combination of TENS with amitriptyline was more effective than TENS alone
Julkaet al.,	1998	Retrospective analysis	54/ 1.7 years	Continuation of treatment prolonged the therapeutic effect in DPN
Forstet al.,	2004	Randomised double blind	24/ 12 weeks	Significant improvement in pain VAS score and NTSS-6 score.
Reichstein et al.,	2005	Randomised controlled	41/3 days	Compared TENS with high frequency external muscle stimulation. Found TENS inferior in amelioration of pain and symptoms of DPN. Short period of intervention.

TENS- Transcutaneous Electrical Neuronal Stimulation, DPN- Diabetic Peripheral Neuropathy, VAS- Visual Analogue Scale, NTSS-6- New Total Symptom Score.

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Figure 1:The flow chart of studies included for review