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Effect of neuromodulation on autonomic dysreflexia in patients with spinal cord injury: Randomized clinical trial

Osama Mohamed Ahmed Abdelrehem

Neurology Department, Faculty of Physical Therapy, Deraya University, Egypt
Corresponding author Email: Osamaabdelrehem83@gmail.com

Nahed Salem

Physical Therapy Department for Neuromuscular Disorders and its Surgery, Faculty of Physical Therapy, Cairo University, Egypt

Enas Elsayed

Neurorehabilitation Department, Faculty of Physical Therapy, Galala University, Suez, Egypt and Physical Therapy Department for Neuromuscular Disorders and its Surgery, Faculty of Physical Therapy, Cairo University, Egypt.

Mohab Darwish

Neurosurgery Department, Faculty of Medicine, El-Minia University, Egypt

Abstract--Background: Autonomic dysreflexia is a common clinical presentation in patients with spinal cord injury (SCI). Objectives: To study the effect of the neuromodulation on autonomic dysreflexia in patients with SCI. Methods: Forty SCI patients from both sexes had participated in this study. They were assigned randomly into two equal groups, (A and B). Patients in group (A); the study group received TENS therapy in addition to selective physical therapy program for AD. Group (B); the control group received the same selective physical therapy program only. Electrocardiogram monitor was used to assess blood pressure, pulse rate variation and ECG device was used to assess heart rate variability before and after eight weeks training period for both groups. Results: There was a statistically significant decrease in all measured parameters of the ECG monitor in both groups (A and B) in favor to group A ($p < 0.05$). Conclusion: Neuromodulation had a beneficial effect on improving autonomic dysreflexia in patients with SCI.

Keywords--spinal cord injury, autonomic dysreflexia, neuromodulation, ECG monitor.

Introduction

According to the National Spinal Cord Injury Statistical Center, there are 12,500 new cases of SCI each year in North America [1]. Cardiovascular autonomic dysfunction is a major problem in SCI, and contributes to the excess cardiovascular mortality in SCI [2]. Up to 90% of patients with cervical spinal or high-thoracic spinal cord injury are susceptible to the disorder. Dysregulation of the autonomic nervous system leads to an uncoordinated autonomic response that may result in a potentially life-threatening hypertensive episode when there is a noxious stimulus below the level of the spinal cord injury. Patients with traumatic spinal injuries with autonomic dysreflexia have a significantly higher death rate than similarly injured individuals without the disorder [3]. Recent studies indicate AD can occur within the first month of injury. typically, first presents within 3–6 months after SCI

Severe spinal cord lesion may disrupt autonomic nervous system functions, such as cardiovascular control and sweating. [4] Autonomic dysreflexia is triggered by stimuli below the level of the SCI that led to unopposed sympathetic activation without supraspinal neurogenic inhibitory signaling, resulting in vasoconstriction and hypertension [5]. Electrical neuromodulation has been found to serve as a useful neuromodulation technique to avoid neuronal dysfunction following SCI, as they can help to train spinal interneuron networks by enhancing afferent inputs. [6] .one of noninvasive neuromodulation is transcutaneous electrical nerve stimulation has shown to be effective in the reduction of sympathetic activity in healthy subjects and individuals with cardiovascular diseases [7]. A widely used noninvasive tool for the assessment of autonomic nervous system activity is analysis of heart rate variability (HRV) [8].

Aim of the study

The purpose of the study was to determine the effect of neuromodulation on autonomic dysreflexia in patients with spinal cord injury.

Methodology

The study was conducted on forty patients suffering from autonomic dysreflexia due to incomplete SCI diagnosed and referred from neurosurgeon. Both Computed tomography scan and MRI was used to confirm the diagnosis. The patients were selected from Outpatient Clinic of Faculty of physical therapy, Deraya University. Patients were randomly divided into two equal groups (Group A) is the study group that was treated by TENS therapy in addition to selective physical therapy program for AD (tilting table and passive movement exercise for lower limb) and Group (B) is the control group that was treated also by the selective physical therapy program (tilting table and passive movement exercise for lower limb) only. Ethical approval was obtained from the Institutional Review Board for Human Subject Research at Cairo University, Cairo, Egypt. Patients were Included if they had the spinal cord injury was traumatic at upper thoracic level from T1-T5 according to ASIA impairment scale.

The patient's age was range from 25 to 45 years old, Duration of illness was range from three to twelve months post spinal cord injury The study was conducted on

forty patients suffering from autonomic dysreflexia due to incomplete SCI diagnosed and referred from neurosurgeon. Both Computed tomography scan and MRI was used to confirm the diagnosis. Patients were excluded if they had cardiac pacemaker, pressure sores and ingrown toenails and other gastrointestinal precipitants as appendicitis, esophageal reflux and ulcer erosion. We had also excluded patients with language deficits that impair patient's cooperation and Patients with auditory or visual dysfunction. ECG monitor and Electrocardiogram (ECG) machine evaluation was performed. ECG MONITOR SYSTEM (model mindary imec 10, made in chine) was used to evaluate autonomic balance analysis. This part of the study is intended to present the collected data through measure The measurement was conducted pre-treatment and 8 weeks after application of treatment using in TENS therapy in addition to selective physical therapy program for AD (tilting table and passive movement exercise for lower limb) (Group A) and selective physical therapy program (tilting table and passive movement exercise for lower limb) only in (Group B).

Electrocardiogram (ECG) Device

To measure heart rate variability lead configurations The choice of location on the thorax for the electrodes used to record the ECG is dictated by the type of clinical information required. Since the voltage difference between a pair of electrodes (known as a lead) is only representative of the variations along one axis from the heart there is no three-dimensional activity information in single lead measurements. However, there are standard lead configurations for acquiring 3-D information about the electrical activity of the heart [9].

ECG monitor system (model mindary imec 10, made in china)

Was used to evaluate autonomic balance analysis (MINDARY IMEC 10 DEVISE is a non-invasive, fully automated computer-based system that provides heart rate variability (HRV), blood pressure analysis and pulse wave velocity analysis as a quantitative assessment of the ANS. It was be used to measure HRV, blood pressure and pulse rate.

Therapeutic Procedures

The procedures of treatment applications were achieved as the following:

Group A: Patients in this group received TENS therapy in addition to selective physical therapy program for AD (tilting table and passive movement exercise for lower limb)

Transcutaneous Electrical Nerve Stimulation

It was applied for each patient for 30 minutes, three sessions per week, for eight weeks. Using a TENS current, biphasic, frequency 10 Hz, pulse duration 200 microseconds. Position of patient was side lying position with applying two channels of electrodes paravertebral below T6 spinal level (T6-L1).

Electrode placement

Adhesive electrodes measuring 9x5 cm were used, TENS electrode can be placed over the bilateral paravertebral region in the paravertebral ganglion region (from T6 to L1). Before the application of TENS, the skin site for the current application will be cleaned with alcohol to avoid any barrier conduction of the electrical current. TENS was applied for thirty minutes, being the frequency defined according to randomization. The current was delivered at sensory-level intensity, adjusted every five minutes by the sensory threshold as tolerated by each subject, but with no motor contraction or pain reported. [10]

Preparation of apparatus

Check whether all the knobs are at zero., Checking the pins of the plug and check whether the switch is turned off., Check the insulation of the wire. Check whether the switch in the stimulator is working. Check whether fuse is present in the apparatus; see that it is not blown out. Check whether hand switch for patient's use is intact and is working, correct positioning of the patient.

Instructions to the patient during application:

Be relaxed and don't touch anything around you and don't pull the leads and don't touch the walls or ground, if you feel uneasy switch off from the patients switch.

Duration of treatment

Thirty minutes, three times per week for eight weeks with frequency 10 Hz, pulse duration 200 microseconds. [7]

Group B: The patients in this group received selective physical therapy program (tilting table and passive movement exercise for lower limb) only.

Tilting table

During tilt-table therapy, the patient was gradually accustomed to head-up tilt by incrementally increasing tilt angle over a period of time.[11]. Duration of application was continued for 30 minutes with elevation of the table to 80 degrees. Position of patient was supine lying position then support patient for five minutes then start graduated elevation of table to 70-80- degrees.

Passive movement exercise for lower limb: done passive movement for lower limb (ankle and knee joint), duration 10 minutes, position of patient supine position

Patient education: Patients was instructed to

Sit up as much he can. Loosen any tight clothing or constrictive devices. Check regularly for bed sores or pressure spots on the skin. If an indwelling catheter is present, check it for obstructions.

Follow a regular bowel program.

Results

The purpose of the study was to determine the effect of neuromodulation on autonomic dysreflexia (AD) in patients with spinal cord injury. The current test involved two independent variables. The first one was the tested group; between subject factors which had two levels (group A; the study group that was treated by TENS therapy in addition to selective physical therapy program for AD and group B; the control group that was treated by the same selective physical therapy program only. The second one was the (measuring periods); within subject factor which had two levels (pre and post). In addition, this test involved four tested dependent variables (systolic blood pressure - diastolic blood pressure -pulse rate - heart rate variability). Prior to final analysis, data was screened for normality assumption, homogeneity of variance, and presence of extreme scores. This exploration was done as a pre-requisite for parametric calculations of the analysis of difference. Descriptive analysis using histograms with the normal distribution curve showed that systolic blood pressure, diastolic blood pressure, pulse rate and heart rate were normally distributed. The demographic, medical history and health behavior variables were described using descriptive statistics and all variables were normally distributed. All variables were examined for normality of the distributions at each time period.

General Characteristics of the sample

The findings showed that the mean age of group (A) was 31.15 years and 32.7 years in group (B). There was no significant difference between both tested groups (table 1). The sex distribution of group (A) revealed that there were three females with percentage of 15 % and 17 males with percentage of 85% of the sample. There was no significant difference between both groups in sex distribution ($P<0.05$) (table 1). Moreover, the mean values of the duration of illness distribution group A and B were 7.5 and 7.25 months respectively. There was no significant difference between both tested groups ($P<0.05$) (table 1). Also, the level of injury distribution of group A was T1 (10%), T2 (5 %), T3 (15 %), T4 (20 %), T5 (50 %). In group B, T2 (15 %), T3 (20 %), T4 with reported percentage of 20 %, T5 (45 %). No significant difference between both groups was found ($P<0.05$) (table 1).

Table 1
General characteristic of patients in study and control

Demographic variable	Study group N=20	Control group N=20
	<i>M(SD)</i>	<i>M(SD)</i>
Age	31.15 (4.68)	32.7 (4.49)
Sex		
Female	3 (%15)	3 (%15)
Male	17 (%85)	17 (%85)
Duration of illness	7.5(2.06)	7.25 (2.4)
Level of injury (t1, t2, t3, t4, t5)	(10,5,15,20,50) %	(0,15,20,20,45) %

M: Mean, SD: Standard Deviation

Pulse rate

The findings showed significant difference between the study and control group regarding the Pulse rate mean values before (mean= 99.70 ± 5.768 and 95.85± 12.236 respectively) after treatment (77.50± 9.725 and 89.50± 7.557 respectively) ($p=0.000$ and 0.000 respectively). On the other hand, there was a significant decrease in the Pulse rate mean values after treatment compared to that before treatment in both the study and control groups ($p=0.000$ and 0.000 respectively) (Table 2 and fig 1).

Table 2
Comparison between study and control groups regarding pulse rate before and after treatment

Pulse rate	Study group (Mean ± SD)	Control group (Mean ± SD)	P
Pre	99.70 ± 5.768	95.85± 12.236	.000
Post	77.50± 9.725	89.50± 7.557	.000
P	.000	.001	

* $p < 0.05$. ** $p < 0.01$

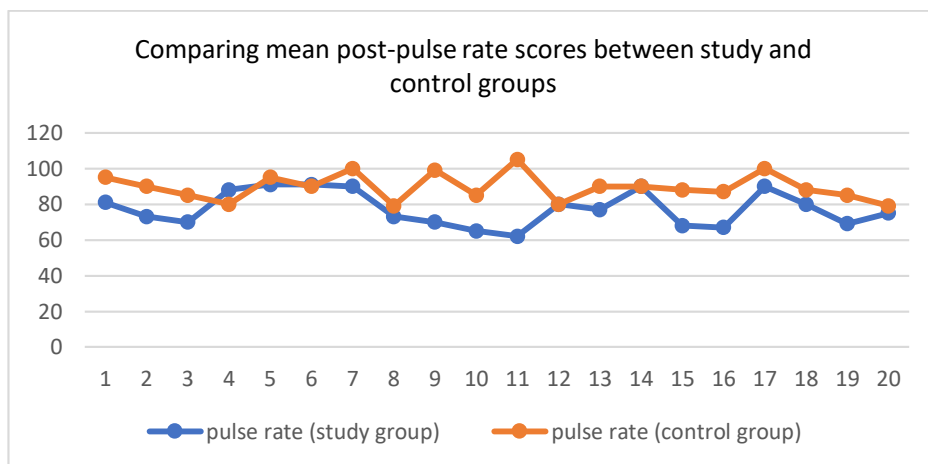


Fig 1. Comparing mean post-pulse rate scores between study and control groups

Heart rate

The results revealed a significant difference between the study and control group regarding the heart rate mean values before (mean= 66.00 ± 21.374 and 67.50± 23.368 respectively) after treatment (20.00 ± 20.520 and 60.00± 22.243 respectively) ($p=0.000$ and 0.000 respectively). In addition, there was a significant decrease in the heart rate mean values after treatment compared to that before treatment in control group ($P<0.05$). (Table 3 and fig 2).

Table 3
Comparison between study and control groups regarding heart rate before and after treatment

Heart rate	Study group (Mean \pm SD)	Control group (Mean \pm SD)	P
Pre	66.00 \pm 21.374	67.50 \pm 23.368	.000
Post	20.00 \pm 20.520	60.00 \pm 22.243	.000
P	.000	.000	

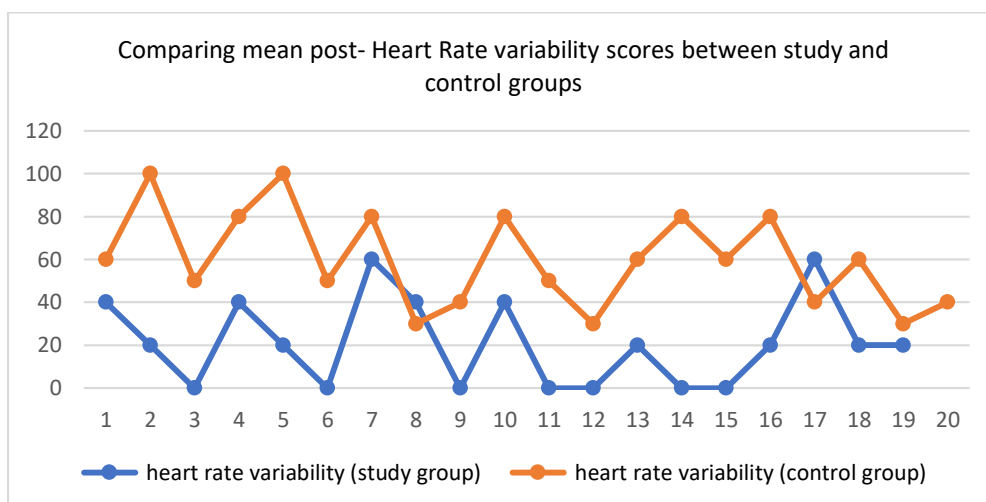


Fig 2. Comparing mean post-Heart rate scores between study and control groups

Blood pressure (systolic)

In the study group, a significant difference was found between the study and control group regarding the blood pressure (systolic) mean values before (mean= 143.85 \pm 7.506 and 143.00 \pm 6.358 respectively) after treatment (116.20 \pm 9.666 and 137.10 \pm 5.628 respectively) ($p=0.000$ and 0.000 respectively). In addition, there was a significant decrease in the blood pressure (systolic) mean values in study group compared to control group (table 4 and fig 3).

Table 4
Comparison between study and control groups regarding blood pressure (systolic) before and after treatment

Blood pressure (systolic)	Study group (Mean \pm SD)	Control group (Mean \pm SD)	P
Pre	143.85 \pm 7.506	143.00 \pm 6.358	.000
Post	116.20 \pm 9.666	137.10 \pm 5.628	.000
P	.000	.000	

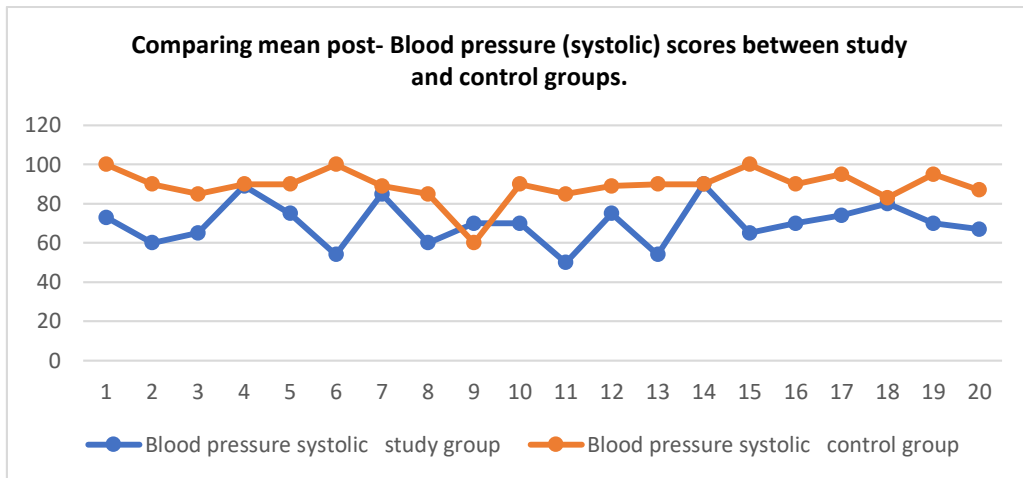


Fig 3. Comparing mean post- Blood pressure (systolic) scores between study and control groups

Blood pressure (diastolic)

The findings showed a significant difference between the study and control group regarding the blood pressure (diastolic) mean values before (mean= 93.60 ± 7.789 and 93.60 ± 8.592 respectively) after treatment (69.80 ± 11.077 and 89.15 ± 8.493 respectively) ($p=0.000$ and 0.000 respectively). On the other hand, there was a significant decrease in the blood pressure (diastolic) mean values after treatment compared to that before treatment in both the study and control groups ($p=0.006$ and 0.006 respectively) (Table 5 and fig 4).

Table 5
Comparison between study and control groups regarding blood pressure (diastolic) before and after treatment

Blood pressure (diastolic)	Study group (Mean \pm SD)	Control group (Mean \pm SD)	P
Pre	93.60 ± 7.789	93.60 ± 8.592	.006
Post	69.80 ± 11.077	89.15 ± 8.493	.006
P	.000	.000	

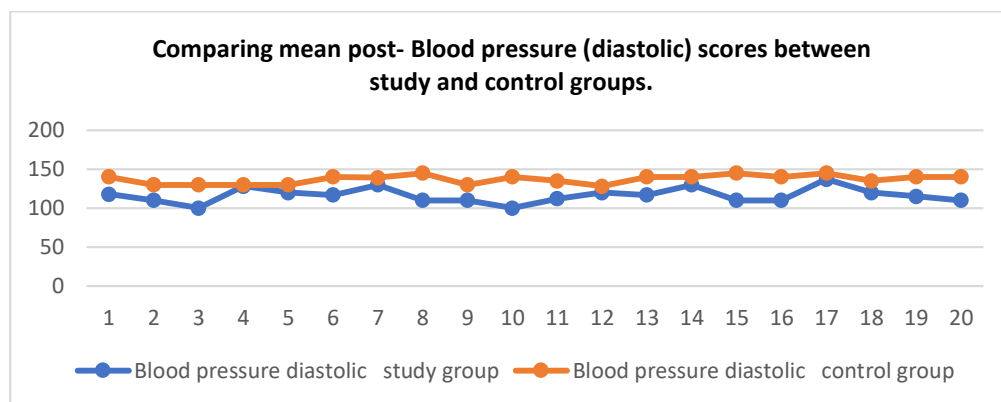


Fig 4. Comparing mean post- Blood pressure (diastolic) scores between study and control groups

Correlations

The Pearson correlation coefficient was performed between age, level of injury and its relationship with pulse rate ($r = 0.18$, $p < 0.05$, $r = 0.31$ $p < 0.05$) as it was found that there is significant correlation between them. Moreover, The Pearson correlation coefficient was performed between age, level of injury and its relationship with blood pressure (diastolic) ($r = 0.27$ $p < 0.05$, $r = 0.16$ $p < 0.05$). There was significant correlation between them. Also, The Pearson correlation coefficient was performed between age, level of injury and its relationship with blood pressure (systolic) ($r = 0.41$, $p < 0.05$, $r = 0.03$ $p < 0.05$) as it was found that there is significant correlation between them. The Pearson correlation coefficient was performed between age, level of injury and its relationship with heart rate ($r = 0.017$, $p < 0.05$, $r = 0.23$ $p < 0.05$) as it was found that there is significant correlation between them.

Discussion

The study was conducted to investigate effect of the neuromodulation on autonomic dysreflexia in patients with SCI. Forty patients from both sexes were included and were divided into two equal groups (A and B). Group (A) received TENS therapy in addition to selective physical therapy program for AD while patients in group (B), the control group, was treated by the selective physical therapy program only. The treatment duration lasted for eight weeks; three times per week. All patients were assessed before and after the treatment program by using Electrocardiogram (ECG) device and ECG monitor system measurement. The parameters that were investigated in this study were; blood pressure, pulse rate, heart rate variability. The present study showed significant decrease in study group in all variables.

It has been observed that, upon applying TENS in the cervicothoracic ganglion region. The cervicothoracic ganglion or stellate ganglion, whose predominant action is sympathetic activity, is a confluence of nerves located in the posterior cervical region at the junction of the lower and upper thoracic cervical ganglia. Also, Mannheim et al. demonstrated that low-frequency electrical stimulation

applied to the suprathoracic lymph node region produced an anti-ischemic effect by reducing myocardial oxygen demand due to the reduction in the afterload resulting from a reduction in BP. In turn, observed that TENS applied to the suprathoracic ganglion region during exercise might be associated with decreased peripheral and central BP in healthy young people, a response indicated by significant changes in heart rate variability (Vilela-Martin et al, 2016)

The Pearson correlation coefficient was performed between age, level of injury and its relationship with pulse rate it was found that there is significant correlation between them in the results of study this is agreed with Wang et al. (2000) who found age dependency of heart rate variability, blood pressure variability and baroreflex sensitivity to compare the cardiovascular autonomic regulatory function between young and middle-aged male subjects and to assess the effects of aging. They concluded that in the middle-aged, both HRV and BRS are reduced and the correlations between HRV indices and BRS are not existent. Hypertension is due to a derangement of sympathetic and parasympathetic cardiovascular regulation is one of the most widely accredited and tested hypotheses in cardiovascular research. In animal models of hypertension, both an increased sympathetic nerve activity and a reduction of vagal cardiac tone associated with and responsible for the appearance and maintenance of high blood pressure (Giuseppe et al., 2014)

Also, Sartori S.A. et al., supported current results as they concluded that low frequency TENS decreases sympathetic nervous system activity and increase parasympathetic nervous system when applied on the paravertebral ganglionic region in hypertensive patients, however, the blood pressure did not change when high frequency TENS applied. (Sartori S.A. et al.,2019) The sympathetic nervous system has a critical role in maintenance of arterial blood pressure; regulation of regional blood flow. (Shouman, K et al,2019) This support with this study suggested that transient changes in blood flow caused by low- and high-frequency TENS may not be related to changes in sympathetic activity. Previous studies that investigated vasoconstriction with electrical stimulation of cut nerves, and vasodilatation at the nerve section, found that sympathetic fibers exerted a tonic, vasoconstrictor effect (Parati et al., 2012).

The results improving systolic blood pressure and heart rate on study group after application of TENS this agree by Furthermore, Campos et al., concluded that TENS seems to promote a discrete reduction in SBP, DBP and HR in healthy subjects. Therefore, these results agreed with current study in presence of some difference as our subjects were hypertensive patients. (ZAHRA et al., 2019). Martin et al. (2016) [13] , agreed with current study, as they concluded that TENS causes a reduction of blood pressure after applying of TENS for 30 minute for 30 days on patients which their age ranged from 40 to 70 years. These changes in the vascular tone caused by TENS might stem from the interaction of the endothelial cell layer and physical or chemical stimuli that share a functional antagonism with the sympathetic nervous system in maintaining blood vessel tone, by the release of substances that affect the vascular tonus. The process of regulatory blood pressure depends on the interaction of several regulatory mechanisms such as the autonomic system, hormonal mechanisms,

autoregulatory mechanisms and intrinsic physical regulatory mechanisms. (Waghmare et al., 2016)

These results supported by Amaral Sartori. et al (2018) who reported that TENS has also shown to be effective in the reduction of sympathetic activity in healthy subjects and individuals with cardiovascular diseases. In healthy subjects, sympathetic activity decreases after low-frequency TENS. In addition, patients with hypertension show a reduction of blood pressure (BP) through blood pressure measurement after low frequency TENS and, in heart failure patients, TENS decreases sympathetic activity [8]. However, the positive effects of TENS have not been uniformly reported: some researchers found that TENS was not effective to lower arterial pressure in patients with hypertension (Amaral Sartori do et al., 2018)

Also, Hsiu et al (2011) [12] stated that acupuncture stimulation decreased the heart rate and dilated terminal vessels by decreasing sympathetic activity. However, they did not assess terminal circulation directly, and the vasodilatory effect of acupuncture was assessed only at the acupoint areas. Our results show that to improve peripheral circulation, the application of sympathetic ganglion stimulation was more effective than stimulation at acupuncture points. Overall, the results of this study show that the application of low-frequency TENS at the thoraco-lumbar sympathetic ganglions improved peripheral blood circulation. (Kamali et al., 2017).

Another possible TENS application area that can affect heart rhythm is the back area. This area is the paravertebral ganglion area where the sympathetic nerve innervation of the heart, adrenal gland and vessels is located. In the study of Cinara et al., they hypothesized that TENS application to this area may cause sympathetic modulation and a decrease in circulating catecholamine levels. (Erol et al., 2021). The results of this study are not agreed by Sanderson et al. showed a decrease in sympathetic activity after TENS use, and Buonocore et al. showed that there was no change in autonomic nerve control of the heart. This shows that a definite judgment cannot be made about the effect of TENS on heart rate changes through sympathetic and parasympathetic modulation. (Erol, et al., 2021). The results of this investigation suggests that low frequency TENS may be a noninvasive, non-pharmacological approach to reduce sympathetic modulation. We recognize one limitation of the present study: we did not perform direct measurements of sympathetic nervous system by assessment of muscle sympathetic nerve or by evaluation of plasma catecholamine, which should be conducted to clarify the effects of TENS on sympathetic outflow (Stein, et al., 2011).

Conclusion

It can be concluded that neuromodulation have a beneficial effect on improving autonomic function in patients with SCI; so it is recommended to be added to the physical therapy program for such patients.

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