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Effect of High-Power Laser Therapy on Modified Total Neuropathy Score in Patients with Chemotherapy Induced Peripheral Neuropathy

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Abstract

Background: Peripheral neuropathy is a common problem among cancer patients receiving chemotherapy. Chemotherapy-Induced Peripheral Neuropathy (CIPN) may have a significant negative impact on the Quality of Life (QOL) and treatment outcome. Studies showed that High Power Laser Therapy (HPLT) has an effect on peripheral neuropathy.

Aim of Study: To investigate the effect of high-power laser therapy on modified total neuropathy score in patients with chemotherapy induced peripheral neuropathy.

Patients and Methods: Thirty patients with CIPN, the patients were assigned randomly into two equal groups, study and control groups. The study group were received HPLT with routine medical treatment for 3 days/week for 6 weeks, the control group were received sham laser with routine medical treatment, CIPN was graded according to the modified Total Neuropathy Score (mTNS) to assess the severity of CIPN pre and post-treatment.

Results: There was significant decrease of the mean values of mTNS only on the study group. After HPLT, there was a significant decrease in the mean of neuropathy from 11.6±.96 before HPLT therapy to 7.8±1.26 after HPLT (p<0.0001). The mean difference was 3.26 and the percentage of change was 29.48 (p=0.0001).

Conclusion: The results suggest that the use of HPLT has a significant effect on mTNS in patients with CIPN.

Key Words: *Laser therapy – Chemotherapy-induced peripheral neuropathy – Cancer.*

Introduction

CHEMOTHERAPY-Induced Peripheral Neuropathy (CIPN) can be a severe side effect often associated with several chemotherapeutic agents including the platinum agents, taxanes, vinca alkaloids, thalidomide, and bortezomib. CIPN is often dose dependent and progressive while receiving and after such treatment **[1]**.

The symptoms of CIPN are varied and presentation varies from sensory neuropathy which is the most frequent type of CIPN, primarily affecting patients treated with taxanes (docetaxel and paclitaxel), platinum derivatives (oxaliplatin, cisplatin and carboplatin), vinca alkaloids (vincristine, vinblastine and vinorelbine), thalidomide and bortezomib **[2]**. To mixed sensorimotor neuropathy and less commonly, pure motor neuropathy **[3]**.

In severe cases; pain, sensory changes and weakness associated with CIPN can lead to dose reductions, changes in chemotherapy protocols, or termination of a therapeutic agent. The morbidity associated with CIPN can lead to pronounced alterations in quality of life and independent performance of activities of daily living **[4]**.

Increasing study of non-pharmacologic therapies has revealed multiple strategies with potential efficacy in reducing the burden of CIPN. Photo Biomodulation (PBM) employs non-ionizing, high power, laser light therapy and has been shown in pre-clinical and small trials to improve neural function **[5]**.

The present study was planned to investigate the effect of HPLT on treating CIPN in cancer patient due to various malignancies.

Material and Methods

The study was conducted in Kasr Al-Aini Hospital in center of Clinical Oncology and Nuclear Medicine, in the period from November 2018 to December 2019.

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Thirty patients with CIPN were carefully examined and referred by their oncologists. All patients were randomly assigned into two equal groups: Group A (study group): Patients in this group received HPLT in addition to routine medical treatment. Group B (control group): Received sham laser in addition to the same routine medical treatment. All patients received 3 sessions per week for six week, the duration of each session was 30 minutes. All patients included in this study were on chemotherapy from at least one cycle as a treatment of malignant tumor with peripheral neuropathy, the patients included in the study with mild to moderate neuropathy according to mTNS. Patients were excluded from the study if they had: Patients who had history of any other neuropathy as diabetic neuropathy, unstable medical condition during chemotherapy, patients who are starting new therapy or dose modification during study period, morbid obesity body mass index >40%, history of non-surgically repaired nerve compression injuries such as carpal tunnel, brachial plexopathy, spinal stenosis, and spinal nerve root compression, history of central nervous system primary or metastatic malignancy. mTNS was used to assess the severity of CIPN pre and post-treatment for both groups. There was two constructs should be considered when assess neuropathy: Neuropathy signs (altered vibratory and pinprick sensation, diminished reflexes, and muscle weakness) and symptoms (numbness, tingling, and neuropathic pain). Total Neuropathy Score (TNSr) and its modifications such as TNSr, the TNSc and the mTNS are the most commonly used tool can be used to measure these constructs. It includes 6 items graded from 0 to 4 according to the patients' symptoms, the total grade from 0 to 24. The higher grade the worse neuropathy. It graded as mild (1:9), moderate (10:19) and (20:24) severe **[6]**.

Treatment protocol:

High power laser therapy: Gilliam-arsenide (GA-AS) M6 the multitarget for the MLS®Laser Therapy has the following specifications, multi diode applicator and standard handpiece, wavelengths of 808nm and 905nm. Patients lay in comfortable prone position treatment was divided into two phases scanning and handheld phase at the same time. Treatment was delivered using a Robotized head, scanning phase on (lumbo-sacral" L2 to s2" and whole planter surface of foot), the distance between the laser head and the treated area (height) was fixed accurately at 30cm, the area of treatment X-Y dimensions of the lumbosacral area was marked by four points, one on the L2, one on the S2 and two points laterally to the spine by about 2cm, these areas were exposed to HPLT through a sweeping robotized scanning at an angle of 30±15 for 15min at each part. Before laser application, the target areas were cleaned with alcohol (95%) to minimize any backscatter or reflection from oily skin. The power output 3.3, allow pulsed emissions to achieve peak power of 3* 25 watts, without the risk of thermal damage, frequency 1000HZ, Intensity 100%, for 15 minutes on lumbosacral area and 15 minutes on planter surface of foot, delivered Energy 1762.200 joule. The handheld phase power up to 1.1 frequency 900HZ, intensity 100%, for 15 minutes at popliteal fossa and fibular head for each limb delivered energy 524.160 joule. The same procedures were taken for the control group with the laser device OFF. As there is no heating effect of laser and the patient was lying prone, the patient could not detect if the device was on or off. All patients received routine medical treatment in the form of gabapentin, pregabalin and B12 oral tab or injection. All patients received 3 sessions per week for six weeks (18 total treatment sessions).

Statistical methods:

Descriptive statistics and unpaired *t*-test were conducted for comparison of the mean age, weight, height, BMI and number of chemotherapy cycles between both groups, Chi squared test and Fisher exact test was conducted for comparison of categorical data between both groups. Unpaired *t*-test was conducted for comparison of mTNS between groups.

Paired *t*-test was conducted for comparison of mTNS pre and post-treatment within each group. The level of significance for all statistical tests was set at $p<0.05$. All statistical measures were performed through the Statistical Package for Social Studies (SPSS) version 25 for windows.

Results

This study included 30 cancer patients with CIPN. Subjects demographic data: There was no significance difference between both groups regarding age, weight, height, and BMI ($p>0.05$) as shown in (Table 1).

Sex distribution:

The sex distribution of the study group revealed that there were 11 (73%) females and 4 (27%) males. The sex distribution in the control group revealed that there were 10 (70%) females and 5 (30%) males. There was no significant difference in sex distribution between both groups ($p=0.69$). (Table 2).

Modified total neuropathy score:

Comparisons between groups:

Pre-treatment: There was no significant difference in the mTNS between groups pretreatment (p =0.33).

Post-treatment: There was a significant decrease in the mean values of mTNS of the study group post-treatment compared with that pre-treatment (p=0.0001) and there was no significant difference in mTNS of the control group between pre and post-treatment (p=0.55).

Comparison between groups post-treatment: The mean difference in mTNS between study and control groups post-treatment was –3.06. There was a significant decrease in the mTNS of the study group post-treatment compared with that of control group (p=0.0001).

Table (1): Descriptive statistics and *t*-test for comparing the mean age, weight, height and BMI of the study and control groups.

	Study group $\bar{X} \pm SD$	Control group $\bar{X} \pm SD$	MD	*t*-value	*p*-value	Sign
Age (years)	53.53±12.14	52.46±9.98	1.07	0.26	0.79	NS
Weight (kg)	66.2±4.36	67.46±5.02	–1.26	–0.73	0.46	NS
Height (cm)	161±2.72	160.66±4.63	0.34	0.24	0.81	NS
BMI (kg/m^2)	25.54±1.61	26.17±2.18	–0.63	–0.89	0.37	NS

$\bar{x}$: Mean. *t*-value : Unpaired *t*-value.
SD : Standard Deviation. *p*-value : Probability value.
MD : Mean Difference. NS : Non Significant.

Table (2): The frequency distribution and chi squared test for comparison of sex distribution between study and control groups.

	Study group	Control group	χ^2-value	*p*-value	Sig
Females	11 (73%)	10 (70%)	0.15	0.69	NS
Males	4 (27%)	5 (30%)			

$\chi 2$: Chi squared value. *p*-value: Probability value.
NS: Non Significant.

Table (3): Mean mTNS pre and post-treatment of the study and control groups.

mTNS	Pre $\bar{X} \pm SD$	Post $\bar{X} \pm SD$	MD	% of change	*t*-value	*p*-value	Sign
Study group	11.06±0.96	7.8±1.26	3.26	29.48	12.25	0.0001	S
Control group	10.66±1.23	10.86±1.35					
MD	0.4	–3.06	–0.2	1.88	–0.61	0.55	NS
t-value	0.99	–6.4					
p-value	0.33	0.0001					
Sig	NS	S					

$\bar{x}$: Mean. *p*-value : Probability value.
SD : Standard Deviation. S : Significant.
MD : Mean Difference. NS : Non Significant.

Discussion

The present study was conducted to investigate the effect of HPLT on CIPN, thirty cancer patients 21 females and 9 males with age range from 25 to 60 years diagnosed by the stuff of clinical oncology to have CIPN participated in this study; they were recruited from the outpatient clinic of Al-Kasr Al Aini Hospital in the Center of Clinical Oncology and Nuclear Medicine and assigned equally into two groups (study and control group). All patients were given chemotherapy (Cth) in the form of taxenes and platinum agents with treatment cycles ranged from 4 to 12 cycles. Laser treatment included 30 minute sessions 3-times weekly for 6 weeks.

The modified total neuropathy score was used to assess the incidence and severity of peripheral neuropathy pre and post-treatment betwwwn both groups.

The results of our study showed that, the study group who received HPLT had a statistically significant difference regarding the severity of neu-

ropathy according to mTNS (0.001) compared to the control group (0.45) who received sham laser, as the reduction of mTNS in study and control groups was 29,48% and 1.88% respectively from baseline to 6 weeks after beginning of treatment which was clearly detected clinically. These results comes in agreement with the findings of Argenta et al., 2017 **[5]**, who enrolled 70 cancer patients with CIPN in his study and found that photobiomodulation therapy was very effective and well tolerated low-toxicity treatment for such patients which significantly reduced the clinical manifestations of CIPN compared to sham therapy and that nearly 90% of patients experienced significant improvement in mTNS scores that begins within weeks of starting treatment and lasted for at least 10 weeks after the conclusion of therapy.

Also results of our study agreed with Yamany & Sayed, 2012 **[7]**, who found that laser therapy could be an effective therapeutic modality in the treatment of painful neuropathy for its ability to modify pain, foot skin microcirculation and some electrophysiological parameters of peripheral nerve function. And as because the typical etiology of peripheral neuropathic pain starts with injury to the peripheral nerve, the great majority of researches done in the treatment of neuropathic pain is focused predominantly on nerves themselves.

It was also mentioned by Rochkind, 2009 **[8]**, that direct laser irradiation therapy to the spinal cord improves the recovery of the corresponding injured peripheral nerves, which suggests that laser phototherapy accelerates and improves the regeneration of the injured peripheral nerve.

According to G. Wang & Industries, 2004 **[9]**, who mentioned that, different hypothesis have also been suggested to support laser biostimulation increasing ATP synthesis by the mitochondria and oxygen consumption on the cellular level, which may result in muscle relaxation, increasing serotonin and endorphins, promotion of anti-inflammatory mechanisms through reduction of prostaglandin synthesis, improving local circulation.

This explanation was also confirmed with the findings of Wang et al., 2014 **[10]**, who mentioned that in vitro studies phototherapy can stimulate Schwann cell proliferation, the principal glial cells of the peripheral nervous system secrete neurotrophic factors that promote the regeneration of the peripheral nerve.

Most of clinical studies showed significant results of laser therapy in treating neuropathic pain, among this studies there was a very rare studies didn't present significant effect of laser therapy on pain, our results contradicted with Zinman et al., 2004 **[11]**, performed a study Low Level Laser Therapy (LLLT) with wavelength of 950nm in 50 patients with diabetic polyneuropathy, who were placed in a control group and in a treated group. When the treated group was compared to the control group, no statistically significant improvement was observed, however, when the pain before and after treatment were compared, a significant decrease in VAS in the treated group was found.

Also our results can be confirmed by Vasquez et al., 2013 **[12]**, regarding mTNS as a method of evaluation in our study since there is a high prevalence in CIPN in cancer patients treated with neurotoxic chemotherapy regimen they stated that it provided a clinically applicable, sensitive screening tool for CIPN in that it detected even mild levels of CIPN, and displayed no floor effect which proved useful in clinical practice as they included in their study patients aged between 18 and 75 years of age who had completed more than 3 cycles of neurotoxic chemotherapy regimens: Paclitaxel or docetaxel and stated that it is, a useful tool for research in this area, and for physiotherapy assessment, and could be recommended for clinical use. They also stated that there is a dearth of research into CIPN itself and that the use of comprehensive and clinically relevant screening tools such as the mTNS adding in the relationships between CIPN and function.

Conclusion:

According to the results of this study, the use of HPLT in the treatment of CIPN in cancer patients receiving conventional chemotherapy is well tolerated and results in improvement of neuropathic pain.

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تأثير العلاج بالليزر عالى القوة على مقياس عد مجموع نقاط الإصابة بالإعتلال العصبى الناتج عن العلاج الكيميائى

الهدف من البحث: تهدف هذه الرسالة إلى تحديد تأثير العلاج بالليزر عالى القوة على مقياس عد مجموع نقاط الإصابة بالإعتلال الناتج عن العلاج الكيميائى.

تم إجراء هذه الدراسة على ثلاثين مريضاً من مرضى السرطان الذين يعانون من إعتلال الأعصاب الطرفى الناتج عن العلاج الكيميائى وتم تقسيم المرضى إلى مجموعتين متساويتين مجموعة الدراسة (١٥ مريض) والتى تلقت علاج بالليزر عالى القوة ومجموعة ضابطة (١٥ مريض) والتى تلقت علاج بالليزر الزائف عالى القوة وكانت مدة العلاج ٣٠ دقيقة ٣ مرات إسبوعياً لمدة ٦ آسابيع متتالياً.

طرق التقييم: خضع المرضى فى المجموعتين إلى قياس شدة الإصابة بالإعتلال العصبى الطرفى نتيجة العلاج الكيميائى عن طريق مقياس عد مجموع نقاط الإصابة بالإعتلال العصبى mTNS قبل وبعد العلاج.

نتائج البحث: أوضحت المعالجة الإحصائية للنتائج وجود تغيير واضح ذو دلالة إحصائية على شدة الإعتلال العصبى الطرفى فى مجموعة الدراسة عن المجموعة الضابطة بعد العلاج.

الخلاصة التى يمكن إستنتاجها: يعتبر العلاج بالليزر عالى القوة من الوسائل العلاجية المفيدة لتقليل شدة إعتلال الأعصاب الطرفى الناتج عن العلاج الكيميائى.