

EXTRACORPOREAL SHOCKWAVE THERAPY AND PLACEBO CONTROL FOR INSOMNIA WITHIN DIABETIC NEUROPATHYEngi E. Sarhan^{1*}, Nermeen Bleedy², Sally Mosad Kamar³, Nesma EM. Barakat⁴, Shaimaa E Salem⁵, Amr Ali Ali Elkhodary⁶¹Lecturer of Physiotherapy for Neurology and Its Surgery, Faculty of Physical Therapy, Kafrelsheikh University, Egypt; ²Physical Therapy Department, College of Applied Medical Sciences, Jerash University, Jerash, Jordan; ³Lecturer in Physical Therapy Department for Integumentary Disorders, Faculty of Physical Therapy, Kafrelsheikh University, Egypt; ⁴Lecturer of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Kafrelsheikh University, Egypt; ⁵Lecturer of Physical Therapy in Basic Science Department, Faculty of Physical Therapy, Cairo University and Al Ryada University for Science and Technology, Egypt; ⁶Lecturer of Physical Therapy for Internal Medicine and Geriatrics, Faculty of Physical Therapy, Kafrelsheikh University, Egypt**Abstract****Purpose:** To allocate the influence of extracorporeal shockwaves on insomnia in comparison to placebo control in patients with a complaint of diabetic neuropathy. **Methods:** According to inclusion and exclusion items of the study, one hundred twenty six patients participated randomly into two equal groups, (study group) was the extracorporeal shockwave (ESW) group; (control group) was placebo receiver one. Both groups had been treated once a week for three months. **Results:** Outcomes established that patients in the study group had improved in foot neuropathic pain and insomnia severity; there were a significant difference between groups ($p > 0.05$).**Conclusion:** ESWT could be recommended for rehabilitation to improve the diabetic neuropathic foot pain and the severity of insomnia.**Keywords:** Extracorporeal Shockwave Therapy. Diabetes Mellitus Type 2. Neuropathic Pain. Insomnia**Introduction**While someone struggles with falling asleep or waking up in the early morning three times per week or more in a single month, he/she has insomnia¹. Nowadays, many in the general population are facing sleep disorders. Insomnia (chronic difficulty sleeping with or without repetitive waking up early) is the most recurrent sleep disorder (30–40%)². Diabetes mellitus affects 415 million people live with the disease, with a 5% annual increase, resulting in at least half a billion people living with the disease in 2045³. The most prevalent complication of diabetes is poly-neuropathy (symmetrical diminished followed by loss of sensation in the extremities, whichManuscrito recibido: 09/12/2023
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starts in the longer nerves and distally)⁴. Unfortunately, more than half of diabetic patients have diabetic polyneuropathy⁴. An abundance of adult patients with diabetic neuropathy (DN) have insomnia, A marked number of DM patients suffer from insomnia, with a prevalence of 39% due to many smitten body functions (neurologic, metabolic, and endocrine) leading to pain, burning sensation, uncomfot and tingling due to atherosclerosis of the micro-vessels (vasa nervosa) of nerves, causing chronic nerve inflammation². Blockade of diabetic neuropathy is necessary to recover from insomnia³. Extracorporeal shockwave therapy (ESWT) is considered a non-invasive intervention that overcomes DN via controlling pain and stimulating healing⁵. It is characterized by a wide range of acoustic energy. Waves, focused or radial. Its energy flux density unit is (EFD, MJ/mm²)⁶. Consequently, the ESWT scope is from (0.001 to 0.5 MJ/mm²)⁶. ESWT has a small single pulse width of 0–30 ms, a wide frequency (0–20 MHz), and a high pressure amplitude (0–120 Mpa)⁶. All of the previous mentioned features affect nociceptive impulses via gate control theory, change the chemical medium around the nerve, demean inflammatory mediators, and eliminate free nerve ending irritation⁶. It is predicted that ESWT has a fluffy effect on the affected nerves, increasing expression of activating transcription factor 3 (ATF-3) and of growth-associated phosphoprotein 43 (GAP-43) in dorsal root ganglion neurons (reaching cell body also)⁷. Wu Y T and his colleagues excluded that, shockwave therapy of radial form could subside pain and enhance range of motion of hand joints in those cases of peripheral neuropathy (carpal tunnel syndrome)⁸. On the other hand, these resulting insomnia symptoms lead to a deterioration of glucose tolerance and insulin sensitivity³. Jung H.L and Sung H.C deduced that ESWT relieves pain from peripheral nerve degeneration (sciatic nerve), encourages muscle power, and overcomes hypertonia⁹. Samantah B.J et al concluded that sleep manifestations are very common in diabetic patients, having a bad influence on health outcomes. They found that management of the sleep disturbance could stop diabetes's progressive course, which will ultimately promote general health and life quality¹⁰. A safe, long-term effective and convenient-cost modality of treatment is extracorporeal shockwave therapy (ESWT), which has been estimated for improvement of the symptoms of insomnia in DN patients due to its regenerative biological influence⁴. Improvement in DN depends on controlling neuropathic pain. ESWT controls it via conjugation of integrin molecules (growth cone on nerve axon membrane) with a lot of

extracellular molecules, production of Schwann cells in the degeneration site and stimulation of macrophages¹⁰.**Patients and methods****Participants**

A study sample of 126 patients (80 males and 46 females) (66 Rt foot and 69 Lt foot) were recruited from outpatient clinic of Kafrelsheikh University hospital and enrolled according to their eligibility to participate in this study. All patients are suffering from insomnia and diabetic neuropathic pain.

They all included in the following criteria, All patients diagnosed with neuropathic foot due to diabetes mellitus (DM) type II (HBA1C was less than 7.5) and insomnia (according to the insomnia severity index). The BMI of all patients was class II (25-30). The patients' ages ranged from 40 to 60 years old.

Patients with some conditions had been excluded as follows: Other neurological conditions include neuropathy caused by drug or alcohol abuse and sensory impairments caused by lumbar disc prolapse for focusing on neuropathy in diabetic patients. Deformities (Charcot foot) that might interfere with the results. Complaining of nephropathy Patients with clotting disorders as ESWT affects circulation directly. Corticosteroids six months before the recruitment period to be sure that the effect of our treatment. Also, we excluded patients those are suffering from associated psychological disorders such as depression to keep them co-operative with us in the study period. Patients suffering from obstructive sleep apnea did not share in this study to avoid bias that originates from other sleep disorders. Anyone who has received ESWT previously for any reason for blinding reason. Finally, patients who are suffering from diabetic foot ulcers couldn't be included.

All participants (males and females) had been checked corresponding to inclusion and exclusion criteria. Whole, competent patients signed an evident consent form before their participation in this study. All participants had been chopped randomly and equally [1:1] (simple randomization) into two groups: study group (1) and control group (2).

Ethical committee of faculty of physical therapy Kafrelsheikh University approved the protocol of this study. The Guidelines of Declaration of Helsinki on the conduct of human research 1975 are the guidelines that this study based on.

Instrumentation

Assessment tools

Each patient (in both groups) had been evaluated before the intervention and after 3 months (the treatment end point) by the same therapist using:

Diabetic neuropathy-4-score questionnaire (DN-4) (Figure 1) which is a scale of 4 questions, including 10 sub-questions with a score of 10, if patient's score is ≥ 4 , the diagnosis is DN (as a primary outcome) ¹¹.

Insomnia Severity Index (ISI) (Figure 2) which is a 7-item self-reported questionnaire to measure the quality, intensity, and influence of insomnia (final score is explicated as follows: 0-7 no insomnia, 8-14 mild insomnia, 15-21 moderate insomnia and 22-28 severe insomnia) (as a secondary outcome) ¹².

Treatment tools

The model of ESWT equipment that we used is EMS-SWISS DOLORCLAST MASTER. Radial pressure wave - Swiss made from the inventors of radial shock wave therapy. FDA approved. Features of it as follows: Colour touch screen display, easy to master with its preset protocols, accurate manual settings, pressure ramp-up and energy density display. It can Inform the patients using treatment pictures, videos and method details. Also can Track clinical results by recording patient's data. The Specifications of this ESWT machine are: Frequency range: 1 - 20 Hz, in 1Hz increments, air pressure range: 1.5 - 4 bar (increment of 0.1 bar) and impulse range: 500 - 10000 (increment of 500 impulses).the machine included: Swiss DolorClast® Master console, evo Blue® handpiece, contact gel, trolley cart and external compressor (Figure 3).

Therapeutic procedures

Patients in group 1 was in a relaxed supine lying position and received the application on the mid-dorsum of the foot with parameters of 1000 impulses (0.08 mJ/mm, 2.4 Hz) ¹³. Patients in group 2 received ESWT placebo treatment that is installed on the equipment's software (provided just sounds without any real parameters). Accordingly, all patients in both groups received treatment once a week for a three-month long period by the same therapist. We achieved double blind control as follows: informed the patient and therapist that the treatment will be to prevent diabetic foot ulcer.

Sample size and data analysis

According to the results of a pilot study that we performed, the mean and standard deviation of DN-4 were 4.78 ± 1.9 and 2.6 ± 1.58 for group 1 and group 2. As a result, we used the G*power software to compute the sample size (n) for two independent means with an alpha error of 0.05 and a power of 95%: n = 126 for both groups, 63 for each. Regarding this study, we decided to perform: a-Chi Square Analysis Test for demographic data (sex) and an independent t-test for age, illness duration, and daily times of hypoglycemic drug intake. b- A parametric one-tailed t-test (for comparing means of DN-4 and ISI score in both groups). A paired t-test was for intra-group but an independent t-test was for inter-groups (before intervention and after). The significance level was 0.05 (p value) and the confidence interval is 95%.

| | | |
|--|---------|--------|
| Interview questions for the patient: | | |
| Question 1: Does your pain have one or more of the following characteristics? | | |
| | Yes (1) | No (0) |
| 1. Burning | | |
| 2. Cold is painful | | |
| 3. Electric shocks | | |
| Question 2: Is the pain associated with one or more of the following symptoms in the same area? | | |
| | Yes (1) | No (0) |
| 4. Tingling | | |
| 5. Pins and needles | | |
| 6. Numbness | | |
| 7. Itching | | |
| Examination of the patient: | | |
| Question 3: Is the pain located in an area where the physical examination had one or both of the following characteristics? | | |
| | Yes (1) | No (0) |
| 8. Hypoaesthesia to touch | | |
| 9. Hypoaesthesia to pinprick | | |
| Hypoaesthesia: decreased sensitivity | | |
| Question 4: In the painful area, can the pain be caused or increased by: | | |
| | Yes (1) | No (0) |
| 10. Brushing | | |
| Total score = | | |
| Total score ≥ 4 : 90% probability of neuropathic pain. | | |

Figure 1. Diabetic neuropathy -4-score questionnaire (DN-4).

Name: _____ Date: _____

- Please rate the current (i.e., last 2 weeks) **SEVERITY** of your insomnia problem(s).

| | | | | | |
|------------------------------|------|------|----------|--------|------|
| | None | Mild | Moderate | Severe | Very |
| Difficulty falling asleep: | 0 | 1 | 2 | 3 | 4 |
| Difficulty staying asleep: | 0 | 1 | 2 | 3 | 4 |
| Problem waking up too early: | 0 | 1 | 2 | 3 | 4 |
- How **SATISFIED**/dissatisfied are you with your current sleep pattern?

| | | | | | |
|----------------|---|---|---|---|-------------------|
| Very Satisfied | 1 | 2 | 3 | 4 | Very Dissatisfied |
| 0 | | | | | |
- To what extent do you consider your sleep problem to **INTERFERE** with your daily functioning (e.g. daytime fatigue, ability to function at work/daily chores, concentration, memory, mood, etc.).

| | | | | |
|------------------------|----------|----------|------|-----------------------|
| Not at all Interfering | A Little | Somewhat | Much | Very Much Interfering |
| 0 | 1 | 2 | 3 | 4 |
- How **NOTICEABLE** to others do you think your sleeping problem is in terms of impairing the quality of your life?

| | | | | |
|-----------------------|--------|----------|------|----------------------|
| Not at all Noticeable | Barely | Somewhat | Much | Very Much Noticeable |
| 0 | 1 | 2 | 3 | 4 |
- How **WORRIED**/distressed are you about your current sleep problem?

| | | | | |
|------------|----------|----------|------|-----------|
| Not at all | A Little | Somewhat | Much | Very Much |
| 0 | 1 | 2 | 3 | 4 |

Guidelines for Scoring/Interpretation:
 Add scores for all seven items (1a+1b+1c+ 2+3+4+5) = _____
 Total score ranges from 0-28
 0-7 = No clinically significant insomnia
 8-14 = Subthreshold insomnia
 15-21 = Clinical insomnia (moderate severity)
 22-28 = Clinical insomnia (severe)

Figure 2. Insomnia Severity Index (ISI).



Figure 3. Swiss DolorClast® shock wave machine.

Results

Demographic data

Table 1 showed the mean \pm SD age of group 1 and 2. There was no significant difference between both groups in the mean age ($p = 0.599$). Also, there was no significant difference in sex distribution between groups ($p = 0.459$). Also there was non-significant difference between illness duration ($p = 0.681$) and daily times of hypoglycemic drug intake between both groups ($p = 0.681$).

Table 1. Comparison of subject characteristics between group 1 and 2.

| | Group 1 | Group 2 | t value | P value |
|---|-----------------|------------------|----------------|---------|
| Age | 50.78 \pm 4.8 | 51.24 \pm 4.90 | 0.5279 | 0.599 |
| Illness duration | 8.38 \pm 2.51 | 8.56 \pm 2.24 | 0.4117 | 0.681 |
| Daily times of hypoglycemic drug intake | 1.67 \pm 0.57 | 1.62 \pm 0.49 | 0.5041 | 0.6151 |
| Sex | 38/25 | 42/21 | χ^2 value | 0.459 |
| Male/female | | | 0.548 | |

Effect of treatment on DN-4 and ISI

Paired t test revealed that, there was significant difference in mean value of DN-4 in group 1 before and after treatment ($t = 10.3$) ($p = 0.0001$) (CI=0.95)

and also extremely statistical significant difference in mean values of ISI in group 1 before and after treatment ($t = 11.15$) ($p = 0.0001$) (CI=0.95). according to group 2 we neither detected significant difference in mean values of DN-4 before and after treatment nor detected in mean values of ISI ($t = 0.87$) ($p = 0.3868$) (CI= 0.95), ($t = 1.9565$) ($P = 0.0549$) (CI= 0.95). Table 2

By fulfillment of independent t-test we concluded that, for group 1 and 2 there was no significant difference between DN-4 mean values nor ISI mean values before treatment ($t = 0.7728$) ($p = 0.4411$) (CI= 0.95), ($t = 1.2367$) ($p = 0.2185$) (CI= 0.95).

On the other hand there was an extremely statistically significant difference in

Table 2. DN-4 and ISI values before and after treatment in both groups.

| | G1 | G2 | P value |
|-------------|--------------|--------------|---------|
| DN-4 before | 6.48, ±1.51 | 6.73, ±1.71 | 0.4411 |
| DN-4 After | 4.9, ±1.99 | 6.48, ±1.72 | 0.0001* |
| P value | 0.0001* | 0.3868 | |
| ISI before | 16.67, ±4.17 | 17.62, ±4.78 | 0.2185 |
| ISI after | 14.29, ±4.89 | 17.1, ±5.29 | 0.0018* |
| P value | 0.0001* | 0.0549 | |

mean values of DN-4 between group 1 and 2 after treatment ($t = 4.3541$) ($p = 0.0001$) ($CI=0.95$). As for the ISI mean values of group 1, 2 after treatment we found a very statistically significant between them ($t = 3.1818$) ($p = 0.0018$) ($CI=0.95$) (Table 2).

Discussion

This study has been take place to illustrate the difference between ESWT and placebo control in the treatment of insomnia in diabetic patients those are suffering from neuropathy. Our findings illustrated that in the study group there is significant difference in the severity of insomnia and in neuropathic foot pain according to ISI and DN-4scoring after intervention in comparison to pre-treatment (0.0001), (0.0001). This is perhaps due to the physiological effect of shock wave therapy intra and extracellular effects, such as protein synthesis, pain relief, re-vascularization, cellular proliferation, neuro and chondroprotection leading to tissue renewal and improving functions of injured tissues and relaxation so, causing improvement of sleep quality. Our findings are harmonious with Claudio and his colleagues, they extrapolated that ESWT is a regenerative relaxing medical technique for treatment of many soft tissue injuries¹⁴.

In control group there is no significant difference in level of insomnia according to ISI scoring (0.054) and in neuropathic pain according to DN4 scoring (0.386) after treatment in comparison to pre-treatment. We estimated that the cause of this minimal change is that placebo analgesic and relaxing effect is linked to endogenous opioid system via psychological mechanisms verbally induced expectancies, cued and contextual conditioning and social learning. This finding is on the same track with Colloca et al. who concluded that placebo causes lowering in some brain area activity as prefrontal, thalamus, anterior cingulate cortex and insula. It also involves the descending pain modulating system causing some sort of analgesia¹⁵.

On the opposite side, Nalan et al. concluded that, the ESWT does not seem to be of higher effect either in pain relief or enhancing body functions at least for three months follow up¹⁶.

By comparing between study and control group we concluded that there is significant difference in reducing insomnia severity and neuropathic pain after treatment (0.001) (0.0001). This is may be due to ESWT can elevate permeability of cells, activates cellular division and accelerates rate cytokine production. Sensitive cells to mechanical stimulation as macrophages can be activated by shock waves. ESWT is estimated producing shear force that stimulate capillary inner walls. Cells in those walls (endothelial and smooth muscle cells) were responding to this shearing stress by releasing nitric oxide and vascular endothelial growth factors resulting in improving blood flow and relaxing blood vessels as immediate effect and stimulates angiogenesis as long lasting stimulation effect (delayed effect). Our results are consistent with results of Anna et al. as they concluded that, extracorporeal shock waves therapy improves nitric oxide synthase production of growth factors and thus has immediate and prolonged effect on chronic pain and normal functions¹⁷.

Limitations of the study

- Self-reported data as ISI and DN-4 are subjective and depending on each patient.
- Lack of prior research studies on this topic

Conclusion

Application of ESWT was significantly effective in decreasing insomnia severity and neuropathic pain in diabetic patients those suffering from neuropathy. The percentage of group (A) improvement is about 80% over group (B).

Author's contributions

All of authors were fully involved in drafting this article and approved the submission of the final version for publication.

Ethical approval

Ethical approval was gained from the scientific research ethical committee of physical therapy faculty, Kafr-elsheikh University (No P.T/NEUR/1/2023/23)

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Declaration of competing interest

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