Neuromuscular electrostimulation techniques: historical aspects and current possibilities in treatment of pain and muscle waisting

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Key words

Abstract. Application of electricity for pain treatment dates back to thousands of years BC. The Ancient Egyptians and later the Greeks and Romans recognized that electrical fishes are capable of generating electric shocks for relief of pain. In the 18th and 19th centuries these natural producers of electricity were replaced by man-made electrical devices. This happened in following phases. The first was the application of static electrical currents (called Franklinism), which was produced by a friction generator. Christian Kratzenstein was the first to apply it medically, followed shortly by Benjamin Franklin. The second phase was Galvanism. This method applied a direct electrical current to the skin by chemical means, applied a direct and pulsed electrical current to the skin. In the third phase the electrical current was induced intermittently and in alternate directions (called Faradism). The fourth stage was the use of high frequency currents (called d’Arsonvalisation). The 19th century was the “golden age” of electrotherapy. It was used for countless dental, neurological, psychiatric and gynecological disturbances. However, at beginning of the 20th century electrotherapy fell from grace. It was dismissed as lacking a scientific basis and being used also by quacks and charlatans for unserious aims. Furthermore, the development of effective analgesic drugs decreased the interest in electricity. In the second half of the 20th century electrotherapy underwent a revival. Based on animal experiments and clinical investigations, its neurophysiological mechanisms were elucidated in more details. The pain relieving action of electricity was explained in particular by two main mechanisms: first, segmental inhibition of pain signals to the brain in the dorsal horn of the spinal cord and second, activation of the descending inhibitory pathway with enhanced release of endogenous opioids and other neurochemical compounds (serotonin, noradrenaline, gamma aminobutyric acid (GABA), acetylcholine and adenosine).

The modern electrotherapy of neuromusculo-skeletal pain is based in particular on the following types: transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS or electro-acupuncture) and spinal cord stimulation (SCS). In mild to moderate pain, TENS and PENS are effective methods, whereas SCS is very useful for therapy of refractory neuropathic or ischemic pain. In 2005, high tone external muscle stimulation (HTEMS) was introduced. In diabetic peripheral neuropathy, its analgesic action was more pronounced than TENS application. HTEMS appeared also to have value in the therapy of symptomatic peripheral neuropathy in end-stage renal disease (ESRD). Besides its pain-relieving effect, electrical stimulation is of major importance for prevention or treatment of muscle dysfunction and sarcopenia.

In controlled clinical studies electrical myostimulation (EMS) has been shown to be effective against the sarcopenia of patients with chronic congestive heart disease, diabetes, chronic obstructive pulmonary disease and ESRD.

Introduction

Pain is a constant companion from birth to death in our everyday life [1]. Its prevalence in patients with end-stage renal disease (ESRD) is much higher than in the general population. In the majority of these individuals management of pain is inadequate [2, 3]. This is in particular due
Neuromuscular electrostimulation techniques: historical aspects and effects

Application of electricity for pain relief dates back to antiquity. It is assumed that as early as 9000 BC magnetite and amber (“animated minerals”) were used by Ancient Egyptians for treatment of headaches and arthritis [4]. Also some hints assumes that in the time of Pharaohs the Egyptians were even able to produce electricity from a direct current battery (Ureus battery) [5].

A very effective approach was the contact with electrical fishes. There are hints that the Ancient Egyptians employed the Nile catfish for treatment of severe painful conditions. Their power has been shown in tomb paintings as early as 2750 BC [6]. In a similar manner Hippocrates (420 BC) used the numbing action of the electrical ray fish (black torpedo fish). The Roman physician Scribonius Largus (AD 47) (Figure 1) was the first who, in the Compositiones Medicae, prescribed the direct contact with the ray fish for pain relief in patients with gout, arthritis or headaches [6]. The torpedo fish generates discharges from as little as 8 volts up to 220 volts, depending on the species. The average current is ~50 volts.

In the 18th – 19th centuries, pain treatment by natural electricity was replaced by man-made electricity with invention of electrical devices. According to Turrell [8] the following four phases of electrotherapy have to be mentioned: the first phase was the application of static or atmospheric electricity, called Franklinism. It was characterized by high voltage and low milliampere currents, which were derived from a frictional machine which induced sudden shocks and sparks. The method dates back to the German engineer Otto von Guericke who developed frictional electricity by an electrostatic sulphur sphere in 1672 [9]. Later, the storage of the electrical charge (Figure 2) was made possible by invention of the Leiden jar (the forerunner of the electrical capacitor). The first medical use of static electricity in Europe was performed in 1744 by the German physician Christian Kratzenstein. A few years later (1752), the American scientist and politician, Benjamin Franklin, invented the “Magic Square”, a simple form of a condenser capable of giving strong shocks for treatment of various illnesses [10]. Another approach was the use of a large-sized static-induction machine, the “improved Holtz”, which worked with high power under any weather conditions. In contrast the old-fashioned friction machines did not work in stormy weather or when the atmosphere was damp or humid [11].

The second phase was Galvanic current (around 1800s), which allowed the direct contact of dynamic electricity over the nerves without shocks and sparks. Introduction of “contact electricity” was preceded by the discovery of Galvani (1780) showing that the severed legs of a dead frog kicked outward when stimulated by electrical currents. Galvani’s assumption of “animal electricity” was criticized by Alessandro Volta. He could demonstrate that the electricity leading
to contraction of the frog muscle was not of animal source but of electrochemical origin [10]. Subsequently in 1800, Volta showed that when two dissimilar metals and brine-soaked cloth are placed in a circuit, an electric current could be produced. This discovery resulted in the invention of the voltaic pile – the first form of a battery. Galvanism was used for management of numerous illnesses including depression by placing the voltaic pile on the parietal region of the head (Figure 2) [9].

In 1825, the French physician Jean-Baptiste Sarlandière demonstrated that the effect of Galvanism could be enhanced by use of acupuncture needles leading to the first development of electro-acupuncture. He resumed: “... in my opinion electro-acupuncture is the most proper method of treating rheumatism, nervous afflictions and attacks of gout …” [9]. It should be mentioned that before Sarlandière, the French physician and composer, Hector Berlioz, suggested the combination of classic Chinese method of acupuncture with electrotherapy. He mentioned that “apparently the application of Galvanic shock produced by the voltaic pile heightens the medical effect of acupuncture” [9].

Application of Galvanic current was not without side effects. Its prolonged use led to necrotic changes in the tissues. This damaging action was later employed for destruction of superficial tumors including prostate cancer.

The third phase was the introduction of Faradism. The British scientist, Michael Faraday, in 1832 employed the voltaic pile and discovered that the flow of electricity could be induced intermittently (interrupted) and in alternate directions. Stimulations were performed with a short pulse duration (< 1 millisecond), thereby preventing any risk of tissue damage. The most important promoter of Faradism in the mid 19th century was the French physician, Guillaume Duchenne, (“father of electrotherapy”), who used this technique in particular for muscle stimulation. In 1849 he stated “Faradism is the best form of muscular electricity and can be practiced frequently and for a long time... The results are of highest importance” [8].

The fourth phase was the discovery of high frequency currents by the French physician, Jacques Arsène d’Arsonval, in 1888 who observed that frequencies beyond 5,000 Hz decreased the excitation of muscles [8].

Throughout the 19th century the analgesic effects of electricity were widely popular and enjoyed their “golden age”. Electrotherapy was used for countless dental, neurological, psychiatric and gynecological disturbances. It was even used by quacks and charlatans for enhancing health and beauty with the slogan “vibrate your body and make it well”. With regard to these unserious applications, electricity fell into disregard more and more.

Figure 2. Otto von Guericke’s demonstration of the first electrical machine using friction [9].

Figure 3. Illustration of the voltaic pile, the first battery consisting of copper and zinc, separated by electrolyte solution to increase the conductivity (Adolphe Ganot in Elementary Treatise on Physics: Experimental and Applied 1893).
Another cause of the declined interest was the advance of potent analgesic drugs.

**Modern development of neuromuscular stimulation**

In the second half of the 20th century, the scientific bases of electrotherapy was increasingly elucidated, offering the chance for a rational treatment of various painful conditions. The new techniques included transcutaneous electrical nerve stimulation (TENS), percutaneous electrical nerve stimulation (PENS) and spinal cord stimulation (SCS). In 2005 the so-called high tone external muscle stimulation (HTEMS) was introduced to combat pain. The electrical devices differ in regard to the amplitude (intensity), frequency, duration and pattern of the electrical currents (Figure 4).

**Transcutaneous electrical nerve stimulation**

TENS is currently the most frequent form of non-pharmacological pain management. It is based on the observation by Wall and Sweat in 1967 [12] that an electrical stimulation with 100 Hz applied on the skin surface resulted in a dramatic relief of pain. TENS consists of a battery-powered portable electric unit with electrodes applied to the skin, delivering electrical impulses to the underlying nerve fibers. Different kinds of frequency modes are: high frequency (HF-TENS > 50 Hz), low frequency (LF-TENS < 10 Hz) and variable frequency (VF-TENS) [13]. The intensity is usually adjustable. After application of HF-TENS intensity is generally low (low pulse amplitude), associated with a non-painful feeling of tingling. On the other hand, application of LF-TENS is associated with a high intensity (high pulse amplitude) resulting in strong, but mostly comfortable muscle twitching. Pain relief after TENS may be rapid, but initially the effects are not long-lasting.

PENS (acupuncture-like TENS) combines the effect of both LF- TENS (usually 2 pps and high intensity) and acupuncture-like needle probes leading to a transcutaneous hyperstimulation [15]. Administration is performed over muscles, acupuncture and trigger points. In general about ten 32 gauge needle probes are used [16].

Spinal cord stimulation (SCS) is an invasive method. The electrode is implanted in the epidural space and exerts pulsed electrical signals directly to the spinal cord. The electrical pulse generator is placed in the lower abdominal area. In 1967, the dorsal horn of the spinal cord was stimulated for the first time by Shealy and Mortinor [17]. In the following years, its marked effects led to the development of implanted electrodes with a modern radiofrequency receiver. SCS is indi-
cated to control severe chronic pain, which is unresponsive to other kinds of therapy.

Potential mechanisms involved in the analgesic action of electrical stimulation

In 1965 Melzack and Wall [18] developed the Gate Control Theory of Pain. The authors suggested that “the substantia gelatinosa in the dorsal horn acts as a gate control system, which modulates the synaptic transmission of nerve impulses from peripheral fibers to the central cells.” According to this hypothesis the small nociceptive A-δ and C fibers hold the hypothetical gate in a relative opened position, while stimulation of the large mecanoreceptive A-β fibers (which are stimulated by touch, pressure or vibration) close the gate and inhibit the pain transmission to the brain. Because small nociceptive fibers are characterized by a higher threshold of action than the large mecanoreceptive fibers, the selective stimulation of the latter ones can prevent or reduce pain transmission (Figure 5). The concept of Melzack and Wall led to the application of gentle electrical stimulation to electrode taped to the skin, the later called TENS [19]. In line with the concept of the gate control mechanisms, TENS application in cats reduced the activity of dorsal horn cells which was evoked spontaneously or noxiously [20].

Besides the segmental inhibition of pain in the dorsal horn, Melzack and Wall also suggested that an activation of descending pain inhibitory mechanisms is implicated in the analgesic action of electricity. The role of this pathway was underlined by two observations: first, the analgesic action of HF-TENS was partly reduced by cutting of the spinal cord (spinalization), which removes the descending inhibitory components [21] and second, the analgesic effect of TENS outlasts the time of stimulation by several hours, implicating the involvement of extra-segmental factors [13].

The descending pathway originates in the midbrain and starts in the periaqueductal grey (PAG), which sends projections to the rostral ventral medulla (RVM), followed by projections to the spinal dorsal horn [22, 23]. TENS-induced activation of PAG and RVM is involved in the reduction of hyperalgesia in arthritic rats [22]. Of particular importance is the enhanced release of endogenous opioids and serotonin, which act through the PAG-RVM pathway [24]. In the spinal fluid of arthritic rats LF-TENS enhanced the levels of μ-opioids, while HF-TENS increased the δ-opioids concentrations. Pre-treatment of these rats with the μ-opioid receptor antagonist, naloxone, blocked the effect of LF-TENS, while the δ-opioid receptor antagonist, naltrindole, prevented the action of HF-TENS [25]. Furthermore in humans, HF- and LF-TENS application is associated with enhanced levels of β-endorphin, both in spinal fluid and blood plasma [26, 27].

Serotonin exerts its analgesic action supraspinally and spinally, depending on the activated receptor type and the used dose [28]. Correspondingly, in brain homogenates its concentration was elevated. The effect of HF-TENS is enhanced by application of serotonin and reduced by its depletion. Norepinephrine is antinociceptive in the PAG-RVM pathway and in the spinal dorsal horn by activating α2-adrenoceptors [29]. In the analgesic action of electricity, adenosine is implicated via activation of purinergic (adenosine) receptors at peripheral and spinal sites [30].
An important factor in TENS-induced analgesia is the neuroinhibitory transmitter GABA as shown in arthritic rats. HF-TENS enhanced the release of GABA in the deep dorsal horn of the spinal cord and both HF- and LF-TENS reduced the hyperalgesia by activation of spinal GABA-A receptors [31].

Moreover, SCS produces in the dorsal horn an augmented release of acetylcholine, indicating an activation of the cholinergic system in the analgesic effect [32].

In arthritic rats HF-TENS, but not LF-TENS, lowered the levels of some excitatory amino acids such as glutamate and aspartate in the dorsal horn [33].

TENS also reduces the production of substance P in this region [34]. Several lines of evidence suggest that the motor-cortex excitability can be modulated by peripheral nerve stimulation with LF- and HF-TENS [35].

Daily administration of TENS is followed by an analgesic tolerance at the spinal opioid receptor as early as on the 4th day [36]. Recent data suggest that this tolerance can be delayed or prevented by simultaneous activation of μ-opioid and δ-opioid receptors. Therefore, either a mixed frequency (HF- and LF-TENS at the same session) or an alternating frequency (HF- and LF-TENS) applied separately on alternating days) should be used [37].

Circulatory effects of electrotherapy

According to laser Doppler investigations, TENS application in healthy volunteers stimulates the peripheral microcirculation [38], potentially contributing to the analgesic action of TENS. In diabetic neuropathy, a relationship between capillary abnormalities and severity of neuropathy has been observed [39]. In these patients TENS-induced vasodilation is associated with the enhanced microcirculation and increased endoneural blood flow [40]. Electrotherapy, in particular in the form of SCS, enhances the blood flow in ischemic peripheral vascular and coronary heart disease [41]. The vasodilation may be induced by release of vasoactive substances such as calcitonin gene-related peptide and possibly nitric oxide (NO) [42, 43, 44]. In certain conditions an inhibition of sympathetic afferent activity may contribute to vasodilation [45].

Clinical trials of various types of electrotherapy

Transcutaneous electrical nerve stimulation

The effectiveness of TENS was shown in many clinical studies. However, in numerous investigations evidence of TENS was inconclusive due to short-comings of the randomized clinical trials (RCTs), among others due to poor classification of the patient groups and lack of standardization of the therapy etc. Moreover, the possibility of tolerance to TENS has to be considered in the case of negative results. In diabetic polyneuropathy three RCTs were performed with positive results. In the first placebo-controlled RCT of 31 patients with type II diabetes, TENS improved the painful distal polyneuropathy significantly [46]. The same authors likewise demonstrated that TENS in combination with amitriptyline appears to be “a useful adjuvantive modality” [47]. In a third RCT of a German research group, the effect of TENS was significant [48].

Analgesic effects of TENS have also been reported in pain caused by knee osteoarthritis [49], which was not confirmed in a recent RCT [50]. In the treatment of lower back pain beneficial effects of TENS have been reported [51]. However, according to Cochrane database the treatment with TENS for lower back pain seems not to be effective [52]. TENS was shown to be beneficial for pain caused by renal colic in the emergency care unit [53]. These data correspond to an experimental visceral model of renal pain in cats, induced by occlusion of the ureter or renal artery [54]. Moreover, after various surgical procedures the analgesic effects of TENS seem to be significant [55].

Intermittent use of TENS is recommended for patients with acquired polycystic kidney disease (APKD), who frequently suffer from chronic dull acting pain due to enlargement of the cysts [56]. In cancer-related pain intermittent use of TENS is still insufficient (Cochrane review) [57].
Interestingly, TENS was reported to be beneficial in severe angina pectoris [58]. In another study LF-TENS lowered the blood pressure [59]. It was even successfully applied in a small group of patients with therapy-resistant hypertension, as documented by 24-h blood pressure measurements [60]. This effect appears to be partly due to inhibition of the central sympathetic activity. Recently, the blood pressure lowering actions of TENS could not be confirmed [61].

**Percutaneous electrical nerve stimulation**

In a sham-controlled cross-over study, PENS lowered pain from diabetic peripheral neuropathy and improved the physical activity of the patients. Also mental components of the SF-36 showed improvements compared to sham [62]. In another sham-controlled crossover study in patients with lower back pain PENS was more effective than TENS [16]. It is also reported that PENS is effective in post-herpetic neuropathy, severe sciatica and lower back pain (among others due to bone metastasis).

**Spinal cord stimulation**

The efficacy of SCS in neuropathic pain of diabetic patients has been demonstrated in a prospective randomized controlled multicenter trial with a 24-month follow-up [63]. It is well established in the treatment of failed back surgery syndrome (FBSS) and the complex regional pain syndrome (CRPS) [64, 65]. In an earlier study in patients with multiple sclerosis, SCS improved the spasticity [66].

SCS was very successful in patients with severe intractable angina pectoris (unsuitable for coronary artery bypass grafting – CABG or percutaneous laser revascularization). Results showed improvements in chest pain, less ST segment depression, augmented myocardial blood flow and enhanced exercise capacity [67]. Notably, SCS was as effective as CABG surgery [68]. Its beneficial long-term actions on angina pectoris were recently confirmed [69].

Also in patients with ischemic peripheral artery disease (unsuitable for vascular reconstruction) SCS was successfully applied [70]. It markedly alleviated pain and delayed or even prevented amputations [71]. In dialysis patients with critical lower limb ischemia (Leriche-Fountain Stage 3 or 4), SCS dramatically improved pain and quality of life [72]. The benefits persisted for up to 6 – 12 months and are also attributed to an improved microvascular blood flow of the legs [73].

However, SCS does not come without complications: The device fails in 3 – 4% of the cases, and 3 – 5% of the patients develop infections [74]. Most frequently, the external electrode is either dislocated or broken (11 – 36%).

In recent animal models of Parkinson’s disease, SCS restored the locomotion [75]. Conceivably, it could be helpful also in patients suffering from severe Parkinson’s disease, who are currently treated with the more invasive electrical deep brain stimulation.

**High tone external muscle stimulation**

HTEMS is a new device for pain treatment. With this method a continuous scan of the carrier frequency, varying in short intervals between 4,096 and 32,786 Hz, is applied. The amplitude and frequency are modulated simultaneously. In a short-term comparative study (3 consecutive days for 30 min) between TENS and HTEMS in painful diabetic polyneuropathy, HTEMS was nearly three times more effective than TENS in relieving pain symptoms and discomfort [76]. The analgesic action was recently confirmed and extended [77]. In a prospective uncontrolled study (twice weekly 60 min sessions, for 4 weeks) in 92 Type 2 diabetic patients with peripheral neuropathy, a marked improvement of pain and of sleeping disturbances was observed in 73% of the patients.

Our group investigated in a pilot study the effect of HTEMS in dialysis patients with symptomatic peripheral polyneuropathy (25 patients with diabetic and 15 with uremic peripheral polyneuropathy) [78]. Electrodes were placed on the femoral muscles. The patients were treated intradialytically for up to
Neuromuscular electrostimulation techniques: historical aspects and effects

60 min, three times a week. After a period of 1–3 months, more than 70% of the patients reported a significant improvement of neuropathic symptoms and sleep disturbances (Figure 6) [78]. In a subgroup of 12 dialysis patients with diabetic polyneuropathy, the effect was followed for 12 months [79]. In these individuals the beneficial action of HTEMS remained significant as compared to baseline with exception of sleeping disorders.

It is well known that placebos are very effective in the treatment of pain. However, their effects diminish with repeated administration. Therefore, the persistence of the analgesic action of HTEMS over a period of one year is a strong indicator of the impact of this kind of therapy. Meanwhile, the efficacy of HTEMS in dialysis patients with peripheral neuropathy has been confirmed and extended [80].

According to recent studies of our group, HTEMS treatment of painful neuropathy in dialysis patients is associated with an improvement of some components of Short Form of the SF-36 questionnaire [81].

Electrical muscle stimulation for prevention and treatment of muscle wasting

In 1988 Gibson et al. [82] postulated that in rheumatic arthritis the motor fibers should be stimulated electrically in order to prevent muscle atrophy and to restore muscle function. In a subsequent study, TENS was associated with increased muscle function as evaluated by a Hand-Grip test [83]. In the last decade further developments led to functional electrical stimulation (FES), in particular in patients with spinal cord damage.

An important indication for electrotherapy is sarcopenia which is defined as loss of muscle mass and weakness. Sarcopenia is a frequent complication in ESRD, chronic heart failure, diabetes mellitus, obesity, cancer and old age. It is a critical factor in normal daily activity and associated with a high risk for falls and fractures with enhanced morbidity and mortality. Myopathy typically affects the proximal muscles of the thighs, while peripheral neuropathy causes muscle loss of the lower legs [84]. The most important causes of sarcopenia in ESRD are uremic toxins, deficiency of vitamin D and of carnitine, secondary hyperparathyroidism, poor nutritional state, vascular ischemia, metabolic acidosis, muscle unloading due to physical inactivity and immobilization, and enhanced insulin resistance [85].

In the therapy of sarcopenia, besides correction of the altered biochemical parameters, physical exercise is of fundamental importance [86], in particular with regard to an improved insulin resistance [87]. However, training is often difficult to realize due to severe co-morbidity conditions. In these individuals electrical myostimulation (EMS) might be an alternative, as it mimics various effects of active exercise. EMS (20 Hz) increases muscle oxidative capacity [88] and enhances glucose disposal [89]. In paraplegic patients, EMS of the paralyzed muscles (3 days per week for 8 weeks) enhanced expression of the GLUT-1 and GLUT-4 transporters, oxidative capacity, and insulin sensitivity [90].

In the past several years EMS has proven quite effective in the treatment of sarcopenia of patients with chronic heart failure. In a randomized clinical trial TENS (low frequency) of the upper legs for 10 weeks (2 times for 2 h per day) enhanced the peak exercise capacity and oxygen consumption considerably, while the corresponding values in the Sham TENS group remained un-
changed [91]. Similar results were obtained in another randomized study of home-based EMS of the legs and conventional bicycle exercise training in chronic heart failure [92]. Also in patients with chronic obstructive pulmonary disease application of EMS improved muscle function significantly [93].

Recently, in a randomized trial in ESRD patients, the effect of intradialytic EMS (frequency of 10 Hz) of leg extensors was investigated and compared to both intradialytic active exercise training (on a bicycle ergometer) and to an untreated control group of dialysis patients [94]. After 20 weeks EMS exerted pronounced effects on functional muscle capacity and mental components of quality of life. In many aspects, EMS was comparable to the group performing active exercise [94]. Interestingly, intradialytic EMS was associated with an enhanced removal rate of urea and inorganic phosphate. The effect was comparable to the group performing intradialytic active exercise.

Up to now the effects of intradialytic HTEMS on muscle function have not been investigated. However, some patients reported spontaneously about an improved strength of the legs and an easier stair-climbing after long-term HTEMS. Moreover, there are data that HTEMS improves the insulin resistance which is an important risk factor of muscle wasting. In a study in obese diabetic individuals, daily application of HTEMS (1 h) for 6 weeks ameliorated the elevated HbA1c levels and lowered the body weight [95], suggesting an improved insulin resistance.

Currently, there are only few contraindications for electrotherapy. These include active bacterial infection, presence of a pacemaker or cardiac defibrillator, pregnancy, recent fractures, acute thrombosis and epilepsy.

Summarizing, in the last decades electro-neuro-muscular stimulation improved the therapy of various kinds of pain and sarcopenia and was associated with the reduction of needed medications. In the case of HTEMS despite the current lack of RTCs, the available clinical data support its benefits. In particular in ESRD patients its application during dialysis has the advantage that the patients do not need any extra time for this treatment.

Conflict of interest

A.H. received lecture honoraria from gbo. The other authors declare no conflict of interest.

References

Neuromuscular electrostimulation techniques: historical aspects and effects


Heidland, Fazeli, Klassen et al. S22


Neuromuscular electrostimulation techniques: historical aspects and effects


