"Mesodiencephalic" modulation in the treatment of diabetic neuropathy

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Abstract

OBJECTIVE: Aim of the study was to verify the efficacy of "mesodiencephalic" modulation (MDM), as named by the commercial promoters, in reducing symptoms accompanying painful diabetic neuropathy and in improving mental health.
METHODS: 32 patients with type 1 and 2 diabetes mellitus, with painful neuropathy, were enrolled in the prospective, double-blind, placebo-controlled, cross-over study. The modulation was performed using MDM electrotherapeutic device (ZAT a.s), sham modulation was used as a placebo. Pain relief (visual analogue scale-VAS; total symptom score-TSS) and changes in mental state (Beck Depression Inventory-BDI-II; OSWESTRY and SF-36 questionnaires) were evaluated.
RESULTS: The study was completed by 30 patients. Pain evaluation: VAS: pain relief was statistically insignificantly higher after real (R) compared to sham (S) modulation (−0.7 vs. −0.3; p=0.06), effect of both modulations was equal after 1 month (−0.4 vs. 0.0; p=0.46). TSS: the effect of R and S modulation did not differ immediately after the procedure (−1.3 vs. −1.0; p=0.27), nor after 1 month (−1.5 vs. −0.34; p=0.9). Psychological tests: according to SF-36, the physical health improved considerably after R compared to S (2.5 vs. −2.0; p<0.01), however, changes in the mental health were equal (−1.5 vs. 0.0; p=0.78). Oswestry (0 vs. 0; p=0.95) and BDI-II (−0.5 vs. −1.0; p=0.42) were comparable after R and S modulation. Order of the procedures (R vs. S) did not affect results.
CONCLUSION: The study did not demonstrate any positive effect of MDM on painful diabetic neuropathy compared to placebo, relative to pain or mental state evaluations. The study emphasizes the need of using placebo-controlled studies, especially when testing a new analgesic drug or a method for pain modulation.

Abbreviations:

BDI-II	- Beck Depression Inventory
DBS	- deep brain stimulation
DC	- direct current
DN	- diabetic neuropathy
MCS	- motor cortex stimulation
MDM	- mesodiencephalic modulation
NNT	- number needed to treat
PNS	- peripheral nerve stimulation
R	- real
S	- sham
SCS	- spinal cord stimulation
SF-36	- the SF-36 questionnaires
TSS	- total symptom score
VAS	- visual analogue scale

Glycosylated hemoglobin in mmol/mol IFCC

ORIGINAL ARTICLE

INTRODUCTION

Diabetic neuropathy (DN) is a chronic complication, which can be diagnosed in up to 50% of patients with diabetes. Approximately 11% of type 1 diabetics and 32% of type 2 diabetics suffer from the painful type. The pain usually accompanies the symmetrical form, but it can be present even in the rarer focal form (Boulton *et al.* 2005). At present, there exists no other causal treatment of diabetic neuropathy than pursuit of tight glycemic control. If, however, DN is accompanied by pain, symptomatic treatment also must be employed. According to recent recommendations, derivates of pregabalin or gabapentin and duloxetine are used for the treatment of neuropathic pain (Tesfaye *et al.* 2010). In most cases, monotherapy is not sufficient. Studies from recent years have had to admit that analgesic treatment is unsuccessful in up to 40% of patients regardless of the combinations of the abovementioned derivates (Tölle *et al.* 2006). Chronic neuropathic pain leads to mood deterioration, sleep disturbance and wasting of energy needed for work and physical activity. It restricts social activities of patients and thus contributes to the deterioration in their quality of life (O'Connor 2009; Galer *et al.* 2000; Benbow *et al.* 1998). Thus it is no wonder that various, even non-pharmacologic, methods are being tested in an effort to offer some relief for this painful condition. Non-pharmacologic treatment includes: water (whirlpools, baths, etc.), light (biolamps, laser, infrared light, etc.), electric current and magnetic field (neuromodulatory methods). Other methods include non-traditional or oriental medicine (acupuncture, acupressure, etc.) (Abuaisha *et al.* 1998; Walker 2001).

The aim of the presented study was to verify the efficacy of a little known neuromodulatory method referred to by Russian authors as "mesodiencephalic" modulation (MDM).

Fig. 1. Position of the modulating electrodes.

MDM first appeared in the Czech Republic in 2005. According to its author and promoter, Pavlov V. from Russia, it is a non-invasive neuromodulation method, based on the principle of very low transcranial impulses of direct electric current acting transcranially on the "mesodiencephalic" region of the central nervous system. The method was patented in the former Soviet Union in 1990. According to the inventor of the method, DC modulated impulses of electric current, in accordance with the ion and colloidal theory of the internal environment, cause electric polarization, which leads to rearrangement of ion structures, changes in cell membrane function and activation of various structures and biological substrates present in the central nervous system, which leads to endorphin release. Apart of the analgesic effect, a putative positive effect can be found on the immune system of damaged organs or tissues of a patient, where stress reactions and adaptability are balanced. The result is achieved by modulating the stress response, decreasing functional hyperactivity of the hypothalamus and the mesodiencephalic region of the brain, altering microcirculation and elimination of pathologic reactions to allergens (*www.mdmcentrum.com*).

The wide scope of the method across individual medical specialties, including experiments claimed by the distributors, the lack of reputable randomized studies, and queries from our patients regarding commercial advertising for MDM, inspired us to design and test the claims made for the MDM method.

The aim of our prospective, double-blind, cross-over study was to test the efficacy of MDM modulation, in reduction of symptoms accompanying the painful form of DN and to assess changes in the mental health of patients after MDM treatment relative to a placebo (sham modulation).

PATIENTS AND METHODS

Study design

It was a prospective, interventional, placebo-controlled, double-blind, cross-over study. The electrical modulation was performed using MDM 2000/1-set electrotherapeutic device with a BF-type application part (*ZAT a.s., Příbram, Czech Republic*).

We adhered to the procedure and the length of modulation suggested by the promoter of the MDM method, which was also used in two previous Czech studies (Musil *et al.* 2007; Kvapil & Krýšová 2011). The treatment was comprised of 13 thirty-minute procedures. On the first three days of treatment the modulation was applied twice a day and on the remaining days it was applied once per day. The whole treatment thus lasted 10 days. Sham modulation was performed as the placebo. The placebo treatment involved application of the electrodes, initiation of a current that gradually tapered to zero within 1 minute, followed by 29 minutes with no modulation. Technical parameters of the

device: [a] therapeutic intensity of the electrical current was set from 0 to 4 mA, and [b] a maximum (peak to peak) within 8 mA (the standard allows up to 10 mA) according to the tolerance of the patient. Parameters of frequency changed automatically during the course of the treatment. Two electrodes placed in a sagittal plane on the head of the patient were used for the application of rectangular pulse electrical current (230 V, 50 Hz). (Figure 1). During the first 4 days, patients were hospitalized, the rest of the modulations were done using an out-patient regimen. The protocol was administered by someone trained in the technique. Half of the patients initially went through the real treatment (10 days + one month follow-up) which was then followed by the sham treatment (10 days + one month following-up). The other half of the patients had treatments in the reversed order, i.e., sham treatment first, followed one month later by the actual treatment plus one month follow-up. The order was determined by draw. Entry pharmacologic treatment of neuropathic pain or other therapy remained unchanged. Neither the medical doctor performing the evaluation, nor the patients knew which modulation was real (R) or sham (S) (Figure 2).

Patients

In total, we enrolled 32 patients with diabetes mellitus type 1 or 2, older than 18 years, and suffering from DN accompanied by symptoms (pain, burning, stabbing pain, cramps, insomnia for restless legs syndrome, etc.) for at least 6 months. The presence of DN was verified using a simple examination (questionnaire, monofilaments, biothesiometer, Neuropad). Characteristics of the patients are provided in table (Table 1). Contraindications for MDM included metal in the cranial cavity, epilepsy, psychoses and schizophrenia, and also a history of organ transplantation.

Pain assessment

The VAS graphic scale (0–10) was used for pain assessment one week prior to the commencement of the study, daily within the 10-day exposure and for the whole month after each treatment. The evaluation was done by the patients themselves. For the purpose of statistical evaluation we used mean values from the last 5 days prior to study commencement, from the end of the modulation and after one month follow-up. The symptoms were additionally evaluated using the calculation of a Total Symptom Score (TSS) at base-line, after termination of each treatment and after one month follow-up (Ziegler *et al.* 1995).

Psychological tests

Evaluation of mental state and the quality of life was performed at base-line and at monthly intervals after each treatment using the following three psychological questionnaires: Beck Depression Inventory for the adults (BDI-II) (Steer *et al.* 1998), OSWESTRY (life with chronic pain) (Fairbank & Pynsent 2000), SF-36 (two components: physical and mental health)(Ware 2000).

Tab. 1. Characteristics of patients.

Age (years)	62±7.2
Diabetes duration (years)	16.75±8.8
Duration of DN duration (years)	5.3±5.2
OAD only treatment	9/32
Insulin pump treatment	7/32
Other medications for DN	11/32
Analgesics use	8/32
Nephropathy	6/32
Retinopathy	10/32
Macroangiopathy	13/32
Alcohol abuse	1/32
Smoking	5/32

(mean ± SD)
OAD - oral antidiabetic drug, DN - diabetic neuropathy, Other medications for DN (pregabalin, gabapentin)

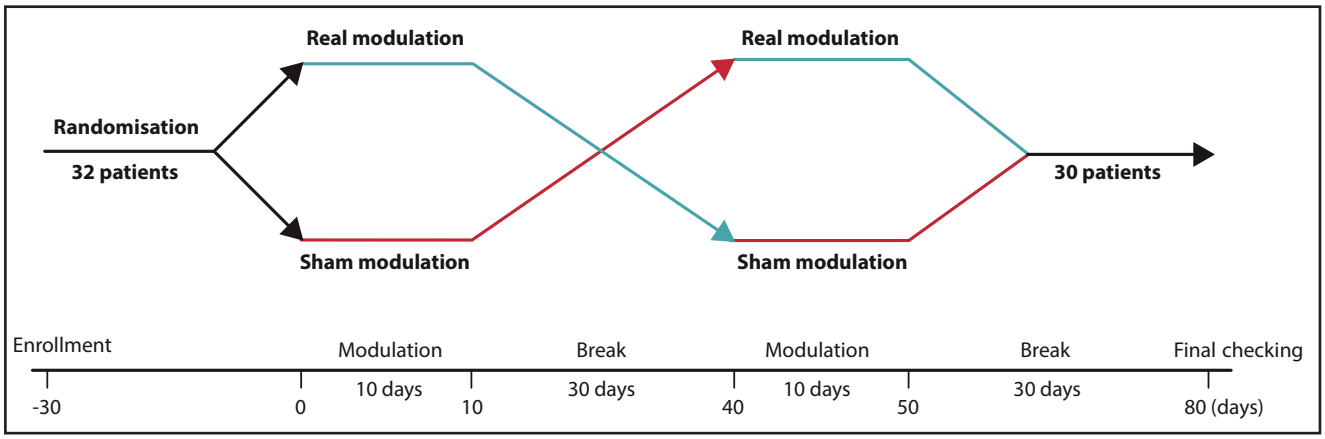

Fig. 2. Study design.

Statistics

Basic statistical methods were used for group characteristics. Data normality were tested by skewness and curtosis criteria. The paired Wilcoxon test and the Friedman test were used for comparison within one method scope, the Mann-Whitney test was used for effect comparisons of real and sham modulation.

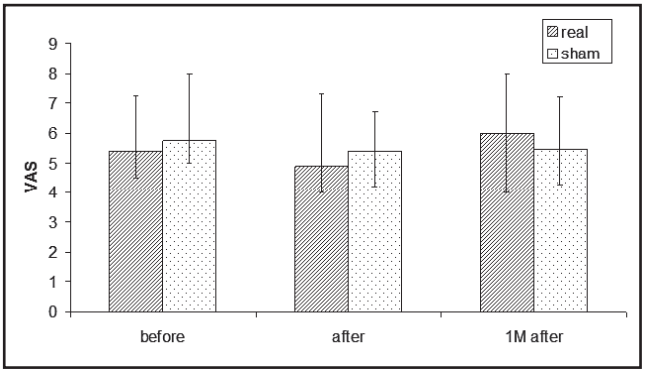

Fig. 3. Evaluation of pain before and after modulation (Visual analogue scale-VAS).

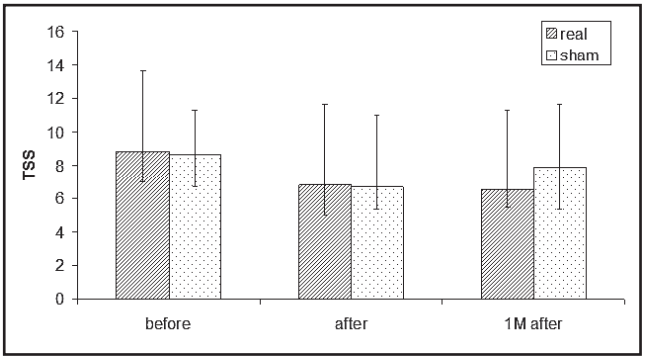

Fig. 4. Evaluation of pain before and after modulation (Total symptome score-TSS).

Tab. 2. Evaluation of pain.

	real modulation			sham modulation		
	before	after	1M after	before	after	1M after
visual analogue scale						
average	4.4	3.8	4.0	4.3	4.0	4.1
SD	1.4	1.7	2.1	1.9	1.7	1.8
1q	3.2	2.8	2.0	2.9	2.4	2.6
median	4.5	4.0	4.0	5.0	4.2	4.3
3q	5.4	4.9	6.0	5.8	5.4	5.5
total symptome score						
average	6.9	5.1	5.2	6.6	5.1	5.7
SD	2.8	2.7	3.0	2.8	2.9	2.9
1q	4.8	3.0	2.9	4.7	3.3	3.7
median	7.0	5.0	5.5	6.7	5.3	5.3
3q	8.8	6.8	6.5	8.7	6.7	7.9

The study was approved by the Ethics committee of the Teaching Hospital in Plzen, CZ. A signed informed consent was required prior to enrollment in the study.

RESULTS

Basic characteristics of the two groups are provided in Table 1. A total of 32 patients were selected for the study. The group included 21 men and 11 women, 27 patients with type 2 diabetes and 5 patients with type 1 diabetes. Two patients did not finish both treatment methods and were excluded for the statistical evaluation. Glycosylated hemoglobin (mmol/mol IFCC) was checked before R and S modulation (R 61.1±19; S 58±14.7). Its level did not differed significantly.

The main results are presented in Figures 3 and 4 and Table 2 and 3 (median and interquartile range):

Pain evaluation

The VAS decrease after real modulation (R) was statistically insignificantly higher than after sham modulation (S) (−0.7 vs. −0.3; p=0.06), after 1 month the effect of both modulations was equal (−0.4 vs. 0.0; p=0.46). The TSS effect of R or S modulation did not differ immediately after either treatment (−1.3 vs. −1.0; p=0.27) nor 1 month after treatment (−1.5 vs. −0.34; p=0.9).

Psychological tests

The SF-36, which assayed the physical health component improved considerably after real modulation in comparison with sham modulation (2.5 vs. −2.0; p<0.01), however, the change in mental health was equal after both modulations (real and sham) (−1.5 vs. 0.0; p=0.78). Tests for evaluation of daily functioning and life with chronic pain (Oswestry) (0.0 vs. 0.0; p=0.95) as well as the BDI-II (depression scale) (−0.5 vs. −1; p=0.42) after R and S modulation were comparable. The order of the treatments (R vs. S) did not influence the results.

DISCUSSION

MDM and pain

Our study demonstrated that MDM produced statistically significant pain relief and the effect persisted for one month. However, similar curves for pain relief were also observed for sham modulation. This confirms the strong effect of a placebo, which itself is capable of pain "treatment". The placebo effect is the subject of an increasing number of studies. A placebo can increase opioid levels and the placebo effect can be blocked by naloxone administration (Rokyta *et al.* 2012). On the other hand, it is necessary to realize that a specific substance may appear to have an effect or to have a better effect provided the patient is properly informed about its administration and expects a benefit or some positive effect. This means that the placebo effect also applies to specific treatments.

The majority of traditional and alternative treatment methods function based on the placebo effect. The degree of the effect depends on the patient's faith in the technique. When testing the analgesic effect of a new drug or a new treatment method against a placebo, the threshold for the new substance or the treatment is set fairly high and it must exceed the placebo effect by 50%. The NNT (number needed to treat) definition must be used; this means that the percentage of patients, in whom the drug produces the desired effect, must be 50% higher than the percentage of those in which the treatment was ineffective. In acute pain, an even stricter criterion of efficacy (60–70%) is used (Moore et. al. 2003). The role of placebo is important particularly with regard to pain relief. The placebo effect is usually considerably shorter than the effect of an active substance. In our case the fading of the effect of real and sham modulation was identical. It is very important, relative to effect, that patients and providers believe in the positive effects offered by the alternative method.

The quality of the study was demonstrated by the fact that only 9 of the 32 enrolled patients were able to identify the order of the treatments. Results of our study are not in agreement with a similar study performed in the Czech Republic in 2005/2006. It was also a randomized placebo-controlled cross-over study, which found the method had a positive effect on neuropathic pain relief in 23 patients (Musil *et al.* 2007). How is it possible that the results of the Czech studies differ so much and how is it possible that some patients did not react to the placebo effect at all, while having a positive response to real modulation? The answer seems self-evident; patients in the earlier study were somehow able to differentiate which modulation was real and which was sham. It is acknowledged that patients who know or think they know which drug administration is the control always reacts better than those who do not know which administration is the control, even in cases where the active drug is presented as the control (Benedetti *et al.* 2003). This has also been shown in animal trials (Benedetti 2012).

MDM was well accepted by our patients. The fact that the patients gained free access to a method that is otherwise costly surely had a positive effect (at the time when the study was conducted, the cost of the technique was approximately equal to the average monthly wage in the Czech Republic (25000 CZK). Furthermore, there was a very friendly atmosphere potentiated by the positive attitude of the assistant, who herself was a fan of the method.

Pain, depressive behavior and the quality of life are tightly connected and influence each other like points of a triangle. Chronic pain, intensity rather than duration, negatively influences the mental state of patients. It is acknowledged that neuropathic pain leads to a deteriorationin the quality of life. Depression can also reduce the effect of analgesics and equally lead to a deterioration in the quality of life. Patients are able to tolerate chronic pain better after treatment for and improvement in their level of depression. It can even change the assessment of the same pain (Schmader 2002; Quattrini & Tuesday 2003; Sullivan *et al.* 2002). To identify and exclude such possible interferences in our study, we included simple questionnaires to observe the extent of depression (BDI-II), evaluation of life with chronic pain (OSWESTRY) and the SF-36 questionnaire, where a patient evaluates their physical and mental health separately. The only statistically significant difference in the whole study was found in the evaluation of the SF-36 questionnaire, but only in the physical health assessment part. Real modulation was able to significantly improve the patient's evaluation of their physical health relative to sham modulation ($p<0.01$). The result was surely influenced by the fact that the entry values of physical health differed significantly before real and sham modulation (30.5 vs. 37; $p<0.05$). Patients reported worse physical health before real modulation. In spite of the fact that physical health improved after R modulation, this phenomenon did not reflect in the interpretation of pain relief. The evaluation of mental health was equal after both modulations (real and sham). Tests for assessment of daily activity and life with chronic pain (Oswestry) were not affected by R vs. S modulation. The depression scale (BDI-II) improved after sham modulation ($p<0.05$), but the changes in the BDI-II was comparable and statistically insignificant relative to type of modulation. Again, this demonstrates how sham modulation was able to influence the mental state of a patient in a positive way.

MDM and other neuromodulatory methods

Neurostimulation and other neuromodulatory methods have an established place in the treatment of neuropathic pain. They are techniques where pain transmission is modulated without damaging nerves or nerve structures. Neuromodulation can be divided into three types; chemical, electric and electromagnetic (Cruccu *et al.* 2007). In the first case, the modulation is achieved by medication (opioids or anesthetic agents) administered to neuraxial structures. In the latter cases, the effects of exactly defined electric or electromagnetic fields are used. Neuromodulatory techniques act at the level of peripheral nerves, ganglia and skeletal muscles (peripheral nerve stimulation, PNS), or at epidural level in a region of cerebral cortex (motor cortex stimulation, MCS) or spinal cord (spinal cord stimulation, SCS). Some methods affect even deep cerebral structures (deep brain stimulation, DBS). Methods can be non-invasive or invasive, which require implantation of stimulatory electrodes. The principle of action behind neuromodulatory methods cannot be always clearly defined. In the past, the gate control theory of pain was suggested as the most likely mechanism; however, it was subject to debate during its development and was later even questioned by its original proponent, professor Melzack. It proposes the effect of spinothalamic

conduction blockage, activation of supraspinal mechanisms, blockage of supraspinal sympathetic mechanisms and activation of release of various mediators and neurotransmitters, in particular GABA and its receptors. The methods were documented experimentally, but also clinically using histochemical, biochemical, neuroanatomical and imaging (PET and functional MRI) methods (Rokyta & Hakl 2011). Based on the declared depth of MDM modulation from proponents, MDM nearly corresponds to DBS or MCS. However, is it possible to compare these methods to MDM? They are invasive methods which are employed in cases of unbearable pain after failure of all other available methods. Electrode implantation (epidural in the case of the motor cortex and spinal cord modulation, and stereotactic to deep cerebral structures in cases of deep brain modulation) are very complicated procedures, performed under general anesthesia and only in specialized centers for pain treatment with neurosurgery departments. Deep brain stimulation is also used for treatment of extrapyramidal movement disorders, e.g. in Parkinson disease.

In spite of the fact that DBS is a globally known method, mechanism of its action is still being discussed. Some hypotheses support the idea that electrical stimulation produces depolarization that disables the stimulated structures. Alternatively, the existence of distant inhibitory circuits, where the inhibitory synaptic mediator, GABA, is used for transmission of stimuli, has also been suggested. An explanation based on brain MRIs was also suggested based on observations of increased metabolism of cerebral tissue surrounding the electrodes and explained by local excitation. It can affect even distant cerebral nuclei connected to the basal ganglia system (Houdek *et al.* 2007; Rokyta & Hakl 2011). Repetitive transcranial magnetic stimulation is a non-invasive method, which uses precisely targeted magnetic stimulation, which induces electrical current changes in cortical areas involved in pain processing (Fricová *et al.* 2009).

How can it be possible that a direct current, as stated by the author of the method, acts transcranially precisely on the mesodiecephalic region? PET or functional MRIs of the brain would be an easy way to verify this claim. Another unsolved question is why direct current is used.

We believe that MDM cannot be compared to the neuromodulatory methods mentioned above. In studies by Russian authors, MDM is compared to transcranial neuromodulation with the potential to affect deep structures of the diencephalon via an "electric signal", which selectively activates central regulatory systems (Karev *et al.* 2002). Unfortunately, the conclusion that the "mesodiencephalic" region is stimulated seems to be very speculative.

The method was brought to the Czech Republic by Doctor Pavlov V. from Russia. Despite being patented in Russia in 1990, supporting studies have generally not successfully crossed Russian borders. Abstracts of some studies are accessible through PubMed, while some articles are in Russian only. The above mentioned studies suggest a wide scope for MDM, while presenting few clear facts and little peer reviewed evidence. MDM in conjunction with psychotherapy, for example, was used for smoking cessation (Rassulova *et al.* 2010). MDM associated with laser therapy was used after hemihepatectomy in early the post-operative period (Goädenko *et al.* 2009). Another use of MDM was demonstrated in a group of drug addicts, where MDM was used together with other detoxification treatments (Badalian *et al.* 2008). A study with a similar target group dealt with MDM in the course of rehabilitation of patients after acute neurotropic drug intoxication complicated by toxic encephalopathy (Krasil'nikov *et al.* 2005). MDM has even found use in patients with irritable bowel syndrome (Efendieva & Gusakova 2008). In another older study, MDM was reported to affect the immunity of an organism relative to infections. It is suggested that it influences immunocompetent blood elements during mixed viral-bacterial infections. The immunomodulatory affect was found to be increased in ten patients with lacunar tonsillitis, who underwent MDM in comparison with ten patients without modulation. The effect is explained by the exposure of a subpopulation of lymphocytes to electromodulation (Grishchenko & Grishchenko 1996). In light of all its other proclaimed affects; it is not surprisingly that MDM has been reported to positively affect even speech and hearing disorders. MDM was used on 665 patients in a center for speech and hearing disorders. Regardless of the diagnosis, 6–7% of the patients improved, 5% significantly even 1–2 weeks after treatment termination, while 2.7% needed repeat modulation (Grishchenko *et al.* 1995). Some studies remained at the level of an experiment. Oxidative stress and cell metabolism in preparations from the small intestine of rats, which when exposed to hemorrhagic shock, showed a positive response, as presented by the authors, after only one exposure to MDM, thanks to normalization of intracellular energy metabolism in the mitochondria of the cell preparations (Titova *et al.* 2000). Pavlov V. made repeated presentations in the Czech Republic, in which he documented a case-study of a patient after an acute coronary syndrome, where the ST segment of their ECG normalized immediately after a single MDM treatment (www.mdmcentrum.com).

At present, the promoters of the MDM method in the Czech Republic focus on women with infertility problems, which include their partners, and men with erectile dysfunction. Case-studies that claim MDM was curative in the healing of unsolvable diabetic foot syndrome are also being presented (Záhumenský 2012).

Nonetheless, none of these studies offer any evidence that the "mesodiencephalic" cortex is actually being stimulated. Considering the width of the spectrum of MDM effects, it seems quite dubious that any "mesodi-

encephalic" stimulation is actually taking place. A final observation is that the majority of the MDM studies were published in journals without an impact factor, and some of the Czech studies have only been published in popular (non-peer) magazines.

CONCLUSIONS

Pharmacologic and non-pharmacologic treatment of neuropathic pain is based on influencing, modulation of transmission and interpretation of pain. Our study did not demonstrate any positive effect of MDM on painful diabetic neuropathy via any of the methods used for pain assessment (VAS, TSS). Pain assessment improved statistically insignificantly only in the VAS immediately after real modulation in comparison with sham modulation. However, one month later, the VAS values were comparable between real and sham modulation. The assessment using TSS did not differ immediately after termination of modulation nor a month later (based on a comparison of absolute numbers or differences). Similarly, the psychological tests did not prove any advantage of MDM relative to placebo. Our study underlines the importance of using placebo-controlled trials, especially in the area of testing new analgesic drugs or other methods used for pain modulation. In contrast to testing drugs that affect other parameters (e.g. blood pressure), when it comes to pain relief, placebos have been shown to offer very strong competition even to active substances.

To demonstrate the analgesic effect of any method, pain relief must exceed that of the placebo by more than 50% (Moore *et al.* 2004). The MDM method did not even approach this value. Neuropathic pain treatment is very difficult and often unmanageable. Assuming that an alternative method does not put the health of patients at risk, there is no reason to discard it. It depends solely on the patient, which method they prefer. The faith of the patient strengthens the placebo effect and all alternative methods that are based on it. The provider of the alternative method should, however, adhere to the code of ethics when dealing with the patient.

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REFERENCES

1 Abuaisha BB, Constanzi JB, Boulton AJM (1998). Acupuncture for the treatment of chronic painful diabetic neuropaty: A long-term study. Diabetes Res Clin Pract. **39**: 115–21.
2 Badalian AV, Gol'dfarb IuS, Luzhnikov EA, El'kov AN, Krasil'nikov AM (2008). Problem in the rehabilitation of patients with acute chemical poisonings in the toxicological hospital. Anesteziol Reanimatol. **Nov–Dec**(6): 39–41.
3 Benbow SJ, Wallymahmed ME, MacFarlane IA (1998). Diabetic peripheral neuropathy and quality of life. QJM. **91**: 733–7.
4 Benedetti F (2012). Placebo responses in animals. Pain.**153**: 1983–4.
5 Benedetti F, Pollo A, Lopiano L, Lanotte M, Vighetti S, Rainero I (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. J Neurosci.**23**: 4315–23.
6 Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, Malik RA, Maser RE, Sosenko JM, Ziegler D (2005). Diabetic neuropathies. A statement by the American Diabetes Association. Diabetes Care. **28**: 957–962.
7 Cruccu G, Aziz TZ, Garcia-Larrea L, Hansson P, Jensen TS, Lefaucheur JP, Simpson BA, Taylor RS (2007). EFNS guidelines on neurostimulation therapy for neuropathic pain. European Journal of Neurology.**14**: 952–970.
8 Efendieva MT, Gusakova E (2008). Clinico-physiological rationale for the use of the mesodiencephalic modulation in combination with synobiotics in the irritable bowel syndrome. Vopr Kurortol Fizioter Lech Fiz Kult. **Mar–Apr**(2): 25–8.
9 Epifanov VA, Korableva NN, Zhuravleva NV (1999). The correction of the cardiovascular system changes in patients with the spastic form of infantile cerebral palsy in the chronic residual stage by means of mesodiencephalic modulation Vopr Kurortol Fizioter Lech Fiz Kult. **Jan–Feb**(1): 15–8.
10 Fairbank JCT, Pynsent PB (2000). The Oswestry Disability Index. SPINE. **25**: 2940–2953.
11 Fricová J, Klírová M, Šoš P, Tišlerová B, Masopust V, Hakl M, Rokyta R (2009). Repetitive transcranial stimulation in chronic neuropathic pain. Pain Practice. **9**(suppl. 3): 38.
12 Galer BS, Gianas A, Jensen MP (2000). Painful diabetic polyneuropathy: Epidemiology, pain description,and quality of life. Diabetes Res Clin Pract.**47**: 123–8.
13 Goädenko VS, Seraia EV, Chzao AV, Lapshin VP, Zhuravel' SV, Chugunov AO, Andretseva OI, Riumin AO(2009). Laserotherapy and mesodiencephalic modulation after hemihepatoectomy in the early postoperative period. Vopr Kurortol Fizioter Lech Fiz Kult. **Jan–Feb**(1): 39–40.
14 Grishchenko AV, Berdina ES, Tavtin IuK, Karev VA (1995). Experience in treating logopedics patients by mesodiencephalic modulation. Vopr Kurortol Fizioter Lech Fiz Kult. **Mar–Apr**(2): 29–31.
15 Grishchenko SV, Grishchenko AV(1996). Effect of mesodiencephalic modulation on peripheral blood immunocompetent cells in viral-bacterial infections. Vopr Virusol. **41**(1): 16–8.
16 Houdek M *et al.* Neuromodulace, nakl. Grada Publishing a.s. 2007; 296 pp, ISBN 978-80-247-0429-6.
17 Karev VA, Dotsenko VI, Voloshin VM, Tavtin YK (2002). Mesodiencephalic Modulation (Transcranial Stimulation of the Brain) in Neurology and Psychiatry. Biomedical Engineering. **36**: 314–318. (Translated from Meditsinskaya Tekhnika 2002; **36**: 16–20)
18 Krasil'nikov AM, Gol'dfarb IuS, Lapshin VP, Shipilov IV, Lezhenina NF,Sukhodolova GN, Epifanova NM, Kukshina AA, Badalian AV (2005). Transcranial electrical stimulation in the treatment of toxicohypoxic encephalopathy at the early stage of inpatient rehabilitation. Anesteziol Reanimatol. **Nov–Dec**(6): 9–11.
19 Kvapil M and Kryšová A (2011). Vliv mesodiencefalické modulace na kožní mikrocirkulaci (The influence of mesodiencephalic modulation on skin microcirculation). Diagnóza. **4**: 36–38.
20 Moore A, Edwards J, Barden J, McQuay H (2003). Bandolier's Little Book of Pain. Oxford University Press.
21 Musil F, Šmahelová A, Zadák Z, Sobotka L (2007). Použití MDM k zmírnění jevů diabetické polyneuropatie (Mesodiencephalic modulation to ease the symptoms of diabetic neuropathy- a cross-over study). Prakt. Lék. **87**: 664–667.
22 O'Connor AB (2009). Neuropathic pain: quality-of-life impact, costs and cost effectiveness of therapy. Pharmacoeconomics. **27**: 95–112.
23 Quattrini C, Tesfaye S (2003). Understanding the impact of painful diabetic neuropathy. Diabetes Metab Res Rev. **19** (suppl 1): S2–8.
24 Rassulova MA, Safonova OV, Ksenofontova IV, Firsova LD(2010). Complex treatment of tobacco dependence by means of psychotherapeutic correction in combination with mesodiencephalic modulation in patients with chronic diseases of digestive organs. Vopr Kurortol Fizioter Lech Fiz Kult. **Nov–Dec**(6): 18–21.

25 Rokyta R, Hakl M. Neuromodulace. pp 89–102. In: Hakl M at al. Léčba bolesti, Mladá Fronta a.s., Praha, 2011.
26 Rokyta R, Kršiak M, Kozák J. Bolest. Učebnice algeziologie (2012). 2. Ed., Tigis Praha.
27 Schmader K (2002). Epidemiology and impact on quality of life of postherpetic neuralgia and painful diabetic neuropathy. Clin J Pain. **18**: 350–4.
28 Steer RA, Kumar G, Ranieri WF, Beck AT (1998). Use of the Beck Depression Inventory-II with Adolescent Psychiatric Outpatients. Journal of Psychopathology and Behavioral Assessment. **20**: 127–137.
29 Sullivan SD, Lew DP, Devine EB, Hakim Z, Reiber GE, Veenstra DL (2002). Health state preference assessment in DPN. Pharmacoeconomics. **20**: 1079–89.
30 Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, Lauria G, Malik RA, Spallone V, Vinik A, Bernardi L, Valensi P; Toronto Diabetic Neuropathy Expert Group (2010). Toronto Diabetic Neuropathy Expert Group. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. **33**: 2285–93.
31 Titova GP, Popova TS, Poryadkov LF, Solov'eva GI, Fedichkina TV, Tropskaya NS,Grishchenko AV (2000). Effect of mesodiencephalic modulation on small intestinal mucosa after masive blood loss in rats. Bull Exp Biol Med. **130**: 1058–62.
32 Tölle T, Xu X, Sadosky AB (2006). Painful diabetic neuropathy: a cross-sectional survey of health state impairment and treatment patterns. J Diabetes Complications. **20**: 26–33.
33 Walker S (2001). A nurse-led acupuncture service for painful diabetic neuropathy: 2. J Diabetes Nurs. **5**: 59–62.
34 Ware JE (2000). SF-36 Health Survey Update. SPINE. **25**: 3130–9.
35 www.mdmcentrum.com
36 Záhumenský E (2012). Mesodiencefalická modulace jako podpůrná léčba nehojící se diabetické ulcerace. (Mesodiencephalic modulation as a supporting treatment for unhealing diabetic ulcerations) Kazuistiky v diabetologii. **10**: (suppl. 2), S31.
37 Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schütte K, Gries FA (1995). The ALADIN Study Group. Treatment of symptomatic diabetic peripheral neuropathy with the antioxidant a-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). Diabetologia. **38**: 1425–1433.