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TRANSDERMAL MAGNESIUM SPRAYS FOR MYOFASCIAL PAIN RELIEF AND FACILITATION OF AUTONOMOUS TWITCH ELICITATION WITH ELECTRICAL TWITCH-OBTAINING INTRAMUSCULAR STIMULATION (ETOIMS)

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ABSTRACT

Introduction: ETOIMS optimally relieves denervation supersensitivity related myofascial pain when autonomous muscle twitches can be elicited focally or remotely at involved trigger points. **Aim:** To provide objective evidence that autonomous twitch elicitation with ETOIMS is best facilitated with concomitant transdermal magnesium sulfate (MgSO4) spray rather than magnesium chloride (MgCl) or using only faucet-water. **Methods and materials:** An 83 year old mildly hypertensive patient with refractory migraine and persistent pain had 3 consecutive ETOIMS therapy trials (N=40/trial) with faucet-water wetted electrodes only or with trans-dermal spray supplementation using MgCl or MgSO4. Pain scores, blood pressure (BP) and pulse/heart-rate were recorded before and immediately after each treatment alongside highest level of clinically elicitable twitch-forces/session and number of muscles with autonomous twitches. For MgSO4 sessions (N=30), the patient also measured onset BP and heart-rate/pulse immediately on sitting down, as well as after sitting for 10 minutes without spray and 10 more minutes with MgSO4 spray applied once to paraspinal and limb muscles. **Results:** ETOIMS results for eliciting autonomous twitches with MgCl spray were equivalent to using faucet-water. One way ANOVA comparisons showed that using MgSO4 significantly increased number of muscles with autonomous twitches and reduced pain and heart-rate/pulse. Twitch-forces (TWF) between the three groups did not differ. MgSO4 spray alone was also able to reduce the systolic BP within 10 minutes. **Conclusions:** MgSO4 showed the best capacity to potentiate ETOIMS pain relief effects probably through better skin absorption and vasodilation made possible through skin hydration and iontophoresis effects that enabled autonomous twitching.

KEYWORDS:

INTRODUCTION

Electrical Twitch-Obtaining Intramuscular Stimulation (ETOIMS) is an innovative surface electrical stimulation system for managing persistent myofascial pain, a global public health disease. Stimulation of myofascial trigger points (MTrPs) provide objective evidence of denervation supersensitivity (DS) in multiple myotomes as cause, aggravation and maintenance of chronic pain associated with spondylotic radiculopathies.[1.2] ETOIMS uses faucet-water soaked cotton electrodes for stimulating MTrPs. MTrPs are the skeletal muscle motor points and represent the skin area above the muscle where the motor threshold is the lowest for a given electrical input. It differs from the anatomical definition of the motor entry point which is the actual location where the motor branch of a nerve enters the muscle belly.[3] Single muscle contractions (twitches) can occur on MTrP stimulation using minimum intensity and short-duration electrical pulses.[4] Anatomically the area where terminal motor nerve fibres are dense is termed the motor end-plate zone. The neuromuscular junction (MTrP) is the site most susceptible to acute ischemia.[5]

To achieve optimal pain relief with ETOIMS, the ultimate goal is to induce large force autonomous twitch elicitation at ischemic MTrPs.[1.2] Autonomous twitches fatigue when the twitch-cascade ends and MTrPs with DS in the motor end-plate zone become temporarily refractory to further stimulation. Twitches exercise and stretch muscles at the MTrP, restore circulation to the ischemic area and provide neuromuscular re-education resulting in the reduction of muscle hypertonia.[1.2]

Autonomous twitch generation is best likened to that of cardiac dysrhythmias.[6]

When performing surface electrical stimulation, the key barrier for adequate stimulation of neuromuscular tissue is skin impedance. Impedance is the measure of a material's opposition to flow of alternating electric currents of various frequencies and reflects the clinical status of the tissue under study.[7]

Internal factors that influence skin impedance are the chemical composition of the skin, including water and electrolyte content, blood supply, state of innervation by the autonomic nervous system and the emotional state of the test subject, The effect of body fat and water content on skin impedance can be related to body composition and nutritional state. External factors that influence skin impedance are the environment such as room temperature and humidity.

Liquids such as faucet water contain high levels of calcium, magnesium, and sodium[8] and these solutes aid in electrical conduction during ETOIMS. Faucet-water has been shown suitable for use as a conductive medium in electrocardiography with equal or better trace clarity than electro-conductive gel and suitable for diagnostic use.[9] Felt-pad electrodes soaked in faucet-water or saline produced the highest mean force and lowest electrical impedance and are excellent choices for single session electrical stimulation. Pre-gelled electrodes produced the lowest force, and they displayed consistently higher electrical impedance in prolonged neuromuscular stimulation with greater average decreases in skin impedance.

For performing ETOIMS, many skin areas need stimulation such that using pre-gelled electrodes with imbedded wires is not practical since such electrodes lose their adhesiveness after stimulation at 3-4 sites. Practical and clinically suitable in ETOIMS for consecutive stimulation to multiple MTrPs throughout the body is the use of cotton electrodes wetted with faucet-water attached to a hand-held bipolar probe. To improve conduction, we have in the past used saturated saline as well as normal saline for ETOIMS twitch elicitation purposes but found faucet-water to be most convenient and advantageous for obtaining good ETOIMS results. [1,2]

Magnesium (Mg) influences nerve conduction, muscular contraction, and cardiac rhythm.[10] We thus explored the use of market available Mg sprays for ETOIMS treatment purposes. Magnesium chloride (MgCl) spray has been found useful for pain relief in fibromyalgia.[11] It is rapidly absorbed through the skin and, therefore, can rapidly increase low or depleted levels of Mg in the body.[12] Yet there are no comparative reports to show if MgCl has the more therapeutic advantage than magnesium sulfate (MgSO4).[13]

MgCl influences cell membrane potential directly, while MgSO4 interferes first with endothelial cells, an intermediary between Mg ions and the membrane of smooth muscle cells. This allows MgSO4 to depolarize smooth muscle cells at a lower threshold than MgCl.[14] This should allow a more therapeutic advantage in dermal spray application of MgSO4.

The anion associated with Mg appears to exert significant influences on micro-vascular reactivity.[15] There are no studies available for skin absorbability of MgCl whereas sulfate (SO4) ions may move across biological membranes including skin.[16] MgSO4 is capable of penetrating through undamaged skin and trans-dermal absorption of MgSO4 increased linearly with solution concentration and skin surface area.[17]

Our aim for this ETOIMS study is to prove that MgSO4 is the better agent over our usual method of using faucet-water or the commonly available MgCl.

PATIENT HISTORY

83-year-old male with serology proven diagnosis of stiff-man syndrome has been managed long-term with ETOIMS for his refractory migraine headaches and persistent myofascial pain. He also has reflux oesophagitis with Barrett's esophagus, generalized osteoarthrosis with past multiple surgeries that include low back, knee, arms, and hands. The only pain medication he could tolerate was Tramadol and has had side-effects with most medications.[2] He receives ETOIMS treatments using faucet-water soaked electrodes twice weekly paying $200/hour fee-for-service since October 8, 2014.

On June 6, 2016, the patient brought in an advertised popular dermal spray of MgCl which he had been using at home to alleviate local leg pain/cramps that regularly occurred every other day**.** The corresponding author used this MgCl spray during ETOIMS treatments to assess its ability to facilitate ETOIMS treatments.

During treatments with MgCl spray, his ETOIMS protocol was kept unchanged. He routinely performed 90 minutes of self-treatment as warm-up sessions in order to get optimal pain-relieving results during the 60-minute professional treatments from the corresponding author. On October 19th, 2016 one of his specialist-physicians prescribed him Depakote DR 125 milligrams PO BID for his headaches and Baclofen 10 mg PO BID for muscle hyper-tonicity of the stiff-man syndrome. He took them for 2 weeks, felt dizzy and discontinued these medications. Three weeks later on November 24, 2016, he suffered his 1st ever episode of sudden chest pains, and was hospitalized for 3 days due to non-ST elevated myocardial infarction. He underwent stent placement and an echocardiogram revealed diastolic dysfunction with an ejection fraction of 45–50%.

After 3 weeks recuperation at home, he returned for ETOIMS therapy. His cardiologist advised him to limit ETOIMS sessions to 60 minutes since he will also participate in a cardiac rehabilitation exercise program. Without the benefit of his 90-minute warm-up sessions, the corresponding author was limited to produce similar pain relieving results within a 60-minute professional treatment time-frame on this difficult to manage patient.

Continuing the use of MgCl spray was not an option since no notable changes in clinical results were observed compared to using faucet-water wetted electrodes during ETOIMS (Table 1). To prevent ETOIMS clinical regression, the corresponding author began use of the only available, non-allergenic, non-sensitizing marketed MgSO4 dermal spray beginning December 16, 2016.

MATERIALS AND METHODS

Using an automated sphygmomanometer, patient regularly self-measured and recorded the average of 3 sitting BP and pulse/heart-rate before and immediately post-ETOIMS.

For his 90 minutes warm-up sessions, stimulus parameters were 500µs pulse-width, 40mA stimulus-intensity at 2 Hz. Muscles he could self-treat include trapezius, arm and leg muscles. Professional treatments were applied for 60 minutes using 500µs pulse-width, 60-70 mA stimulus-intensity at 3 Hz frequency.

Autonomous twitches were able to be elicited in muscles such as biceps, triceps, hip flexors and hip adductors with twitch forces (TWF) at Grade 4 of 5 scales.[2] Muscles consistently treated include bilateral paraspinal muscles from C2-S1 levels, trapezius (C3, C4), latissimus dorsi (C6-C8), gluteus maximus (L5-S1) and adductor magnus (L2-S1).[1,2] The dominant roots in these muscles are in shown in parenthesis.

He had 44 sessions of MgCl spray before his heart attack after excluding time period from October 19th, 2016 to November 24, 2016, during which he was on Depakote and Baclofen. These 44 ETOIMS sessions using MgCl beginning June 6, 20, 2016 to October 17, 2016, were compared to 44 consecutive sessions of ETOIMS (using faucet-water) just before using MgCl (December 31, 2015, to June 1, 2016). On using MgSO4 spray he had obvious clinically identifiable increased numbers of muscles that could twitch autonomously. The trial could have been stopped at 30 sessions but we continued to collect data to complete the 44 sessions.

Recorded for all 3 ETOIMS protocols were pain-levels, BP, pulse/heart-rate before and immediately after each treatment, the highest level of elicitable twitch-forces/session in any muscle, the number of muscles that twitched autonomously, session-duration and treatment-intervals.

Twitch-force is graded from 1-5, grade 5 twitch-force (TWF) being strongest. Grade 1 twitches result from focalized, partial contraction of stimulated muscle(s) at MTrP. A stronger twitch force on the electrode overlying MTrP with DS gives an asymmetrical, bouncy feed back on the bipolar probe electrodes overlying that area but will have no movement effects on the joint that this muscle crosses over. Grade 2 twitches additionally show rocking/shaking limb and/or trunk movements from stimulation of MTrPs of deep muscles apposed to bone and joints. The ETOIMS treatments must search to obtain a minimum of such Grade 2 twitches since they indicate that the stimulation has reached the deepest MTrPs and are thus therapeutic. Grade 3 twitches produce antigravity limb movements with MTrP stimulation but fatigue will not occur. Grade 4 twitches can erupt into autonomous twitches that take minutes to fatigue whereas Grade 5 autonomous twitches rapidly fatigue within a few seconds.

Undesirable side-effects: Hypertonic muscles are recognized when TWF is weak and MTrPs difficult to find. Thus when performing repeated stimulation of available MTrPs, the probe needs to be lifted after every 2-4 twitches to prevent direct muscle stimulation by the other electrode which may not over an MTrP. This prevents intra-treatment and post-treatment pain.

RESULTS

There were significantly more muscles that could twitch autonomously ($p=0.00$) on using MgSO4 spray during treatment. See the video for simultaneous autonomous twitching of 4 limbs and trunk and compare with previous published report and video on same patient.[2]

Serum Mg levels showed no differences between using faucet-water and MgCl for ETOIMS but increased with MgSO4 (table1).

MgSO4 was also able to further reduce SBP within 10 minutes of self-spray compared to SBP after quiet sitting for 10 minutes without spray (Table 2).

One way ANOVA comparisons showed no difference in SBP between the 3 treatments but DBP reduction achieved with faucet-water was better than MgCl and as effective as MgSO4. Pulse/heart-rate was effectively reduced only by MgSO4. No TWF changes noted. Linear regression results for pain scores before and after ETOIMS showed best results with MgSO4 (Figs 1-2). Spearman analysis showed a negative correlation between pain level and the number of muscles that could twitch autonomously (Fig.3).

Patient’s leg cramps reduced in frequency from alternate days while using MgCl to 1 episode/3-4 weeks since using MgSO4 spray.

Statistics: SPSS v12 software package was used for analysis.

Table 1: Comparison table for ETOIMS treatments using MgSO4, MgCl and faucet-water for conduction.

	MgSO4 vs MgCl for conduction N=44 vs N=44	**MgSO4 vs faucet-water for conduction N=44 vs N=44**	**MgCl vs faucet-water for conduction N=44 vs N=44**
Pain Score (no) (P) 95% CI	3.7+0.1 vs 3.9+0.1 **0.00** 3.7-3.8 vs 3.8-3.9	3.7+0.2 vs 3.9+0.1 **0.00** 3.7-3.8 vs 3.9-4.0	3.9+0.1vs 3.9+0.1 0.06 3.8-3.9 vs 3.9-4.0
Systolic Blood Pressure (P) 95% CI	123+6 vs 122+5 1.00 121-125 vs 121-125	123+6 vs 121+4 0.37 121-125 vs 120-122	123+5 vs 121+4 0.98 121-125 vs 120-122
Diastolic Blood Pressure (P) 95% CI	58+4 vs 60+3 **0.00** 56-59 vs 59-61	58+4 vs 58+3 1.00 56-59 vs 57-59	60+3 vs 58+3 **0.001** 59-61 vs 57-59
Pulse- Presuure (P) 95% CI	66+5 vs 63+4 **0.01** 64-67 vs 61-64	66+5 vs 64+5 0.25 64-67 vs 62-65	63+4 vs 64+5 0.49 61-64 vs 62-65
Pulse (P) 95% CI	58+6 vs 64+4 **0.00** 57-60 vs 63-65	58+6 vs 65+4 **0.00** 57-60 vs 64-67	65+4 vs 65+4 1.00 64-67 vs 64-67
	MgSO4 vs MgCl for conduction N=44 vs N=44	MgSO4 vs faucet-water for conduction N=44 vs N=44	MgCl vs faucet-water for conduction N=44 vs N=44
Muscles that twitched autonomously (no) (P) 95% CI	11+2 vs 6+0 **0.00** 10-12 vs 6-6	11+2 vs 6+0 **0.00** 10-12 vs 6-6	6+0 vs 6+0 1.00 6-6 vs 6-6
Session-duration (min) (P) 95% CI	60+0 vs 150+2 **0.00** 60-60 vs 150-151	60+0 vs 150+2 **0.00** 60-60 vs 150-151	150+2 vs 150+2 1.00 150-151 vs 150-151
Treatment interval (days) (P) 95% CI	4+2 vs 4+1 0.95 3-5 vs 3-4	4+2 vs 4+2 1.00 3-5 vs 3-5	4+2 vs 4+2 1.00 3-4 vs 3-5
Serum Magnesium (mg/dl) Normal is 1.8-2.5	2.4 (15/2/17) vs 1.9 (25/11/16)	2.4 (15/2/17) vs 2.0 (15/3/16)	1.9 (25/11/16) vs 2.0 (15/3/16)

Abbreviations: MgSO4= magnesium sulphate; MgCl= magnesium chloride; CI= confidence intervals; p=significance < 0.05; vs= versus

Table 2: Comparison table for effects on blood pressure and heart rate/pulse of immediate sit, quiet sit for10 minutes before MgSO4 spray and 10 minutes after sitting with spray on compared to effects of ETOIMS using spray.

	Immediately after 10 min quiet sitting vs after 10 more minutes sit (no spray) n=30	**After 10 minutes sit (no spray) after 10 minutes sit (with spray) n=30**	**After 10 minutes sit with spray vs after 60 minutes ETOIMS with spray n=30**
Systolic Blood Pressure (mm Hg) CI (P)	123+5 vs 115+7 5 to 10 **0.000**	116+7 vs 113+5 0 to 5 **0.05**	113+5 vs 115+4 0 to 4 0.06
Diastolic Blood Pressure (mm Hg) CI (P)	56+4 vs 54+4 0 to 3 **0.02**	54+4 vs 54+4 -2 to 2 0.97	54+4 vs 51+2 -1 to -3 **0.002**
Pulse- Presuure (mm Hg) CI (P)	67+6 vs 61+3 4 to 8 **0.000**	61+6 vs 59+4 0 to 5 **0.05**	61+6 vs 63+5 2 to 7 **0.001**
Pulse (no) CI (P)	56+3 vs 55.4 0 to 2 0.06	55+4 vs 55+3 0 to 1 0.84	55+3 vs 54+3 0 to -1 0.19

Abbreviations: MgSO4= magnesium sulphate; MgCl= magnesium chloride; CI= confidence intervals; p=significance < 0.05; vs= versus

DISCUSSION

Surface electrical stimulation and skin impedance

The high impedance to electrical stimulation of non-hydrated skin is from the stratum corneum. The lipid milieu of skin provides capacitive contribution (ability to store and gradually release electrical charge) that resist homogenous and uniform electrical flow.

Skin capacitance increases as skin hydration increases. Therefore, chronic neuromuscular stimulation such as functional electric muscle stimulation of 30 minutes to many hours, could modify the skin under the electrodes and can cause electrochemical burns.[18] Similarly nonlinear electrode–tissue impedance occurs with transcutaneous electrical stimulation from the presence of skin, fat, nerves, and muscles between stimulation electrodes.

Electrochemical burns are not a concern in ETOIMS since stimulation to each MTrP is about 1-5 seconds and performed with wet cotton electrodes that do not have embedded wires. The probe is constantly moved to relocate and re-focus stimulation to the MTrP of interest that has moved such that even with repeated stimulation of 1-5 minutes in a motor end-plate zone, the same MTrP in the same zone cannot be re-stimulated repeatedly. MTrPs do not remain in the same location but rather move by about 2–3 cm as the joint is flexed and extended (due to muscle lengthening/shortening).[19]

Impedance falls when skin hydration improves from an increase in local ion concentrations that load the skin with additional charge-carriers. This occurs during the first few postnatal months when an increase in skin hydration results from the greater functional maturity of eccrine sweat glands. Acute changes in electrodermal responses are modified by transdermal water movement as in sweating, as influenced by the autonomic nervous system.[20]

A fall in skin impedance that occurs with pain is unrelated to stable factors, such as body fat, muscle or cell mass but results from a rapid movement of water and ions in and around the skin. Our study also confirms that obtaining local and remote autonomous twitches on using faucet-water, MgCl and MgSO4 is probably related to lowering of skin impedance from skin hydration. This phenomenon occurs usually in the latter part of the treatment session after multiple muscles had been stimulated repeatedly. This allows transmission of greater current intensities throughout a stimulation pulse enabling electrical conduction to reach susceptible local and/or remote MTrPs with DS.

Pain in bone and joints has been shown to reduce skin impedance.[21,22] However, acute cold pain increases skin impedance. Joint pain is a common manifestation in patients with persistent pain.[23] To obtain pain relief with ETOIMS, it is thus necessary to obtain TWF2-5 that moves joints since it indicates that electrical stimulation reached MTrPs of deepest muscles that lie apposed to joints.[1,2]

Iontophoresis using surface electrical stimulation

Conventionally, iontophoresis employs direct current (DC) but can have side effects such as pain and burns. Treatment effect tended to appear sooner when alternating current (AC) iontophoresis was combined with administration of anticholinergic drugs than when using only AC iontophoresis in treating palmoplantar hyperhidrosis.[20]

Application of an iontophoretic current causes skin impedance to decrease sharply. The applied field can induce conformational changes in lipid/protein molecules, forcing them to adopt high, energy conformations that facilitate charged ion transport. This enlarges pre-existing channels. Also, the decrease in impedance may be due to re-orientation of lipids or keratin bundles in stratum corneum and formation of transient conduction channels. Additionally, ion concentration in resistive pathways may rise sharply, increasing the number of charge carriers that reduce impedance. However, once the external field is removed, the system begins to relax and the majority of current-induced transient pathways disappear.

AC iontophoresis in human epidermal membrane causes lipid lamellae electroporation in stratum corneum leading to a constant state of pore induction. Pore enhancers reversibly reduced AC voltage required to sustain this action.[24] Compared to conventional DC iontophoresis, square-wave AC and pulsed DC were of equal or less magnitude during low/moderate voltage iontophoresis for pore induction and sustaining new pores.[25]

The voltage used In AC iontophoresis for the treatment of palmoplantar hyperhidrosis was 20-40 volts at high frequencies of 4.3 kHz, and in DC iontophoresis, stimulus current used was 5-10 mA.[20] ETOIMS system (constant current, 400-volt device with MTrP stimulation technique) employs an average stimulus amplitude of 40-60 mA, a pulse width of 500 µs at 2 Hz. Increasing current density caused an even greater reduction in value of the skin impedance and slowed the rate of recovery. Thus, the ability to obtain autonomous twitches in ETOIMS is probably from using stronger voltage and current since the maximum frequency used is only 3 Hz.

Tissue mobilization and drug retention in skin

With MTrPs massage, dialysate lactate concentration and blood flow increased at MTrPs.[26] Studies measuring permeation rates directly through human and animal skin ex vivo showed rubbing increased flux, reduced skin impedance and increased drug retention in the skin.[27]

Active movements associated with twitches from stimulation of MTrPs in ETOIMS produce single muscle contractions. The immediate contractions with stretch relaxation are therefore more specific and effective than passive tissue mobilization movements of manual massage. The relatively higher serum levels of Mg on using MgSO4 than that obtained with using faucet-water or MgCl during ETOIMS may reflect better skin absorption with MgSO4. This may be related to increased active blood flow to muscle and skin during ETOIMS induced active exercise complemented by ionophoresis (Table1).

Role of Magnesium ions in cardiovascular and neuromuscular excitability

Magnesium deficiency increases muscle tone and increases sensitivity to stimulatory agonists. Low intracellular Mg leads to increased contractility to a given stimulus and reduced ability to recover from contraction, making it prone to tetany or painful spasms. Mg is necessary for normal muscle contraction and relaxation. Muscle cramps can often be reversed with the addition of Mg. During training and competitions, swimmers found an 86% reduction in muscle cramps after only three days of Mg supplementation.[28]

Blood pressure reduction occurs when augmented with Mg due to its effects on N-methyl-D-aspartate as well as from inhibiting norepinephrine release. This occurs through blocking N-type calcium channels at peripheral sympathetic nerve endings[29] supporting Mg's role in regulating calcium in microvascular muscle cells.[15] A large review of ninety population samples and subgroups points to a negative association between dietary Mg intake and BP. Mg supplementation appears to achieve a small but clinically significant reduction in BP.[30]

Mg prevents the release of pre-synaptic acetylcholine from both sympathetic and neuromuscular junctions which explains why Mg supplements are able to relax muscle spasms and reduce pain. Mg also plays a role in reducing hypertension similar to that noted in our patient. Mg deficiency contributes to hypertension through an increase in angiotensin II-induced plasma aldosterone concentration, production of thromboxane and vasoconstrictor prostaglandins and insulin resistance that increases vascular tone. Mg supplementation reduces the pressor effect of angiotensin II and stimulate the production of vasodilator prostaglandin and also influence the release of nitric oxide and its effects on vascular tone.[30]

The anion associated with Mg appears to exert significant influences on the microvascular reactivity of microscopic arterioles and venules. In rat experiments, topical application of MgCl and MgSO4 attenuated contractile responses to epinephrine and barium chloride on both arterioles and venules. MgSO4 can reverse vasoconstriction in a number of vascular beds with *in-vitro* and *in-vivo* studies, which indicates that MgSO4 may have therapeutic benefit in conditions associated with vasospasm.[31]

Following MTrP massage therapy significant decrease in heart-rate, SBP, DBP was found due to the significant increase in parasympathetic activity.[32] However, this was not reproduced in other studies which showed that massage type and areas massaged were the main factors affecting change in BP. Increases in BP were noted for potentially painful massage techniques, including trigger point therapy. Meta-analyses demonstrated that massage combined with antihypertensive drugs may be more effective than antihypertensive drugs alone in lowering both SBP and DBP. Safety of massage in hypertension however, is still unclear.[33]

Our study clearly shows that MgSO4 spray alone can significantly reduce SBP safely and efficaciously. Use of MgSO4 further augments ETOIMS effects in reducing BP and pulse/heart-rate (Figures1-3 and Tables1-2). The massage studies were short term of 4-12 weeks but our study was over 66 weeks where findings are very unlikely to have occurred by chance.

Chronic widespread pain in rats shifts the cardiac sympathovagal balance towards sympathetic predominance and decreases spontaneous baroreflex sensitivity.[34] ETOIMS reduces sympathetic tone evidenced as a reduction in BP.[2] The increase in parasympathetic tone occurs on stimulating trapezius and sternocleidomastoid muscles supplied by accessory nerve whose cranial portion is part of the vagus nerve. Vagal stimulation with ETOIMS occurs in the region of carotid baroceptors whose increased sensitivity alleviates pain.[35]

Skin pH is 3.8 and the brand of MgCl spray used in this study had pH similar to that of faucet-water which is 7.0. This may have contributed to the similarity in clinical results between using faucet-water and using MgCl (Table 1). Additionally, sodium and calcium solutes in faucet-water were probably factors that contributed to the better ability of faucet-water in the reduction of DBP better than MgCl and as good as MgSO4. The MgSO4 spray that we used has a pH similar to that of skin pH and together and with added property of the SO4 ion[13-15] gave superior results in twitch elicitation.

Role of magnesium ions in pain relief

The MgSO4 solution that we used was made with medical grade MgSO4 that has United States Food and Drug Administration approval for IV administration (PQ Corporation, PA, USA). It is used in treating hypertension and seizures of eclampsia.[36] It is also used intravenously in lowering BP in emergency department patients and found as effective as antihypertensives.[37]

Mg can induce antinociceptive effects in central and visceral pain tests and available data indicate the potential use of these cheap adjuvants in pain therapy.[28,38] Meta-analysis study has shown that peri-operative intravenous MgSO4 reduces opioid consumption, and pain scores in the first 24 h postoperatively, without serious adverse effects.[39] MgSO4 applied intramuscularly to the operative region was found to be more effective on postoperative analgesia than systemically administered Mg.[40] It has also been shown that a 2-week intravenous MgSO4 infusion followed by 4 weeks of oral magnesium oxide/gluconate can reduce pain intensity and improve lumbar spine mobility during a 6-month period in patients with refractory chronic low back pain with a neuropathic component.[41]

These different routes of application showed that magnesium sulfate has a role in pain therapy whether it is given through intravenous, intramuscular or oral routes. Studies for MgCl, on the other hand, have shown that when given as an intravenous bolus there is an insignificant reduction in pain in the area of allodynia. When used as a dermal spray MgCl has been found to be useful in improving the quality of life of patients with fibromyalgia.[11] However, over a 4-week study of 40 patients, there was a 22.5% drop-out due to skin irritation. Although the brand of MgCl spray that we used here had no skin irritation effects over the course of 24 weeks, the clinical results were no different from that of using faucet-water.

On using MgSO4 dermal spray over a similar time course, not only were there better clinical results but there were also no signs of skin irritation or skin sensitization effects. This was reproducible with repeated insult patch test studies on 51 subjects who were challenged with MgSO4 spray patches soaked with 0.2 ml of MgSO4 for 24 hours of application 3 times/week. After the supervised induction period, there was a challenge phase 2 weeks later using the same protocol at a virgin test site adjacent to the original induction patch site. The results showed no signs of primary or cumulative irritation and/or allergic contact sensitization.[42]

There are no previous reports on the use of non-allergenic, non-sensitizing MgSO4 dermal spray for pain relief and our study is the first of its kind for use as a most efficacious and safe adjuvant in myofascial pain therapy especially when used in combination with ETOIMS. Our patient was able to discontinue the low dose BP medication he has been on since his myocardial infarction due to better pain control with ETOIMS facilitated with transdermal MgSO4. The MgSO4 spray alone may be used to complement management of hypertension or to decrease blood pressure acutely before oral BP medications take effect in hypertensive patients. This method can be very useful especially when the patient sprays and rests for >10 minutes since the combination of rest and transdermal MgSO4 can reduce BP by 5-15 mm (table 2). MgSO4 spray is also useful in the treatment of muscle cramps. The pharmaceutical grade quality of MgSO4 used is our study may be responsible for the difference in findings between MgCl and MgSO4 effectiveness.

MgSO4 allows depolarization of smooth muscle cells at a lower threshold than for MgCl. Sulfate ions significantly influence microvascular reactivity[15] and absorption through the skin may take place under appropriate circumstances.[16] Sulfate ions may move across biological membranes by means of specific transporters and MgSO4 is capable of penetrating through undamaged skin. It has also been shown that transdermal absorption of MgSO4 increased linearly with solution concentration and skin surface area.[17] All these properties of MgSO4 become more effective when used together with ETOIMS due to the added benefit of iontophoresis.

LEGEND FOR VIDEO

Autonomous twitch phenomenon seen in the latter part of a 60 minute ETOIMS treatment session after multiple muscles had been stimulated repeatedly during the same session.

LEGENDS FOR FIGURES

Figure 1: Linear regression analysis of pain scores immediately before and after ETOIMS.

Figure 2: Linear regression analysis of pulse/heart-rate immediately before and after ETOIMS.

Figure 3: Correlation between pain scores immediately before and after ETOIMS to numbers of muscles with autonomous twitches.

The authors report no conflicts of interest for use of Magnesium products. The corresponding author is the sole inventor of ETOIMS and holds patents for the bipolar probe and electrodes.

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