ejpmr, 2021,8(12), 55-63

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

MAGNESIUM SULFATE: ADJUVANT ROLE IN CHRONIC PAIN MANAGEMENT WITHELECTRICAL TWITCH-OBTAINING INTRAMUSCULAR STIMULATION (ETOIMS)

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Article Received on 09/10/2021 **Article Revised on 30/10/2021** **Article Accepted on 19/11/2021**

ABSTRACT

Introduction: ETOIMS optimally relieves myofascial pain when autonomous muscle twitches can be elicited at other distant muscles without direct electrical stimulation of involved trigger points. **Aim:** Use of magnesium sulfate (MgSO4) dermal spray is essential to demonstrate dominant sympathetic nervous system maintenance of pain. **Methods and Materials:** Three patients with chronic pain were treated with ETOIMS for 1 hour every 1-3 days with long-term follow-up. Recorded post and pre-ETOIMS were systolic (SBP), diastolic blood pressure (DBP), and heart-rate (HR). The patients were classified according to the highest grade level of twitch forces (TF) obtainable in any treated muscle. ETOIMS prior to 2018 was performed using plain faucet water for electrical conduction through the skin. In 2018 dermal magnesium sulfate spray was added for ETOIMS. **Results:** Patient with TF3 (that which produces anti-gravity movements) post and pre-ETOIMS with water for conduction, paired T-test showed significant reduction in SDP and HR but not DBP. TF4 and TF5 (forces produce anti-gravity movements with autonomous spreading of stimulation phenomenon ending with slow muscle fatigue and autonomous twitches with fast fatigue, respectively) demonstrated post-treatment reduction of all parameters except HR which increased in TF5. With MgSO4 spray added to ETOIMS for transcutaneous electrical conduction improvement,post and pre-treatment paired T-test for TF3-T5 showed significant reduction in all tested parameters (paired T-test p=0.000) except DBP for TF5. ETOIMS results between the 2 methods, the MgSO4 method showed post-pretreatment difference for TF3 for DBP and HR had higher difference (p=0.000) but no significant changes noted for SDP (p=0.06). For TF4 SBP and DBP values were higher post-ETOIMSwith MgSO4 but HR was lower using MgSO4. TF5 values were increased after MgSO4 treatment for all parameters but HR was slower. Linear regression with ANOVA statistics showed for number of days between treatments, pre and post-treatment differences increased for SDP and DBP but not HR (p>0.05). **Conclusions:** MgSO4 showed the best capacity to potentiate ETOIMS TF probably through better skin absorption, local vasodilation from skin hydration promoting iontophoresis effects. MgSO4 facilitated autonomous twitching with stronger force twitches that affect SBP, DBP and HR more than with using water only.

KEYWORDS: magnesium sulfate dermal spray; blood pressure; heart-rate; muscle twitchforces.

MATERIALS AND METHODS

Three patients are included in this study which started in 2013 and lasted through 2021. The inclusion criteria involves negotiated payment for Electrical Twitch Obtaining Intramuscular Stimulation (ETOIMS) with voluntary commitment for a minimum of twice a week treatmentregimen with 1 hour ETOIMS treatments at an average charge of $2-3/min usually in 60 minute sessions. Our experience is that patients will voluntarily stop treatments once treatments are of no benefit to them but will continue their negotiated payments for treatment if they have pain relief.[1] Only three patients qualified for this study using long-term treatments followed with statistical process control.[2,3]

ETOIMS was performed using a high-voltage powered muscle stimulator with these stimulation parameters 500 microseconds (µs) pulse width, 50-60 milliamps (mA) stimulus strength and 3 hertz (Hz) stimulation frequency.

Statistics was performed using the SPSS program version 12.

TF3 Patient

62 year old male with chronic neck and right upper arm pain after a slip and fall injury. His muscles are tight and

swollen especially in the region of the lower trapezius, between the scapulae down to the lower back. He had no signs of peripheral neuropathy or upper motor neuron involvement.

He started the first round of treatments in 2013 during which he received 173 ETOIMS treatments using water for electrical conduction. No autonomous twitches could be elicited and the highest grade on ETOIMS was TF3 which meant that the treated muscle that twitched was able to lift the limb off the surface of the treatment table in an anti-gravity direction.

He had to discontinue the treatments when he lost his employment. However, he returned to resume with ETOIMS treatments in 2015 at which time he was re-employed.

He was able to continue working uninterruptedly and his employer negotiated payments for ETOIMS treatments for him. He received 930 ETOIMS hour-long treatments twice aweek using magnesium sulfate spray for electrical skin conduction. He ended his treatmentswhen he retired in 2016.

TF4 patient: 85 year old man with chronic neck pain due to C6 - C7 cervical stenosis, headaches with aura and lower back pain, status post lumbar foramino-laminotomy at L5 - S1 10years earlier. There is ongoing pain down the left lower limb down to the lateral aspect of the left leg. There are no signs of upper motor neuron changes or peripheral neuropathy and the patient is ambulatory and able to perform his activities of daily living without an assistive device.He also has a diagnosis of stiff-man syndrome.

Patient has had no significant pain relief for his severe headaches with pain medications, epidural injections and many other treatments. Neck pain and lower back pain received pain relief when he started ETOIMS in 2015. He undergoes 1 hour ETOIMS twice a week and his treatment results showed presence of TF4 which are described as autonomous twitches with twitch forces that can lift the limb in an anti-gravity fashion and fatigue after 30-60 seconds. Twitches were easy to elicit in bilateral triceps (C7), bilateral quadriceps and bilateral adductor magnus. Most of his muscles were very tight with non-antigravity force twitches. There was mild numbness along the lateral aspect of the left leg along the left L5 dermatome.

For this first round of treatments he had significant pain relief such that he underwent 503 treatments. While ETOIMS was not available during the Covid 19 pandemic he had a spinalcord stimulator inserted in 2020 as a trial for six months but had to be removed ultimately because there was no pain relief for his lower back pain. He then returned for ETOIMS treatments in 2020 by which time ETOIMS was performed using magnesium sulfate spray. Although there was pain relief in his neck and lower back including the legs there was no relief in headache pains. On the second round, he underwent only 44 ETOIMS treatments and discontinued therapy.

TF5 Patient

68 year old female with chronic neck pain due to an auto accident and had been treated with ETOIMS since 2009 to 2012 during which time she received 153 ETOIMS treatments usingwater for electrical conduction.

She was stable and had a good quality of life and was discharged until she presented again in 2021 with severe low back and right lower limb pain after a slip and fall injury that resulted in a left ankle fracture. There is no evidence of peripheral neuropathy or central nervous system disorders.

Six months after the ankle fracture healed she suffered from severe lower back and left lower limb pain lasting four months after vigorous thread mill exercise. She sought and underwent daily 1 hour ETOIMS treatments. All the muscles were so electrically irritable that TF5 were easily obtained. TF5 twitches occurred autonomously not only in the muscles stimulated but would spread to other muscles throughout the body and would fatigue within less than 5 seconds.

RESULTS

TABLE 1: Comparing post-pre treatment results for ETOIMS using water for conduction. Paired T test for TF3 showed reduction in SBP and HR and not DBP. TF4 and TF5 showed significant reductions for after treatment results for all parameters (p=0.000) but with increased HR. Abbreviations : Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP),Heart Rate (HR), Twitch force (TF).

	Tf3 Tx With Water Only (N =173)	Significance Paired T Test	Tf4 Tx With Water Only (N = 503)	Significance Paired T Test	Tf5 Tx With Water Only (N =353)	Significance Paired T Test
SBP (sys blood pressure) BEFORE TX (RANGE)	121 ± 8 (109 to 155)	**P=0.000**	123 ± 7 (109 to 176)	**P=0.000**	120 ± 6 (98 to 124)	**P=0.000**
SBP AFTER TX (RANGE)	121 ± 6 (101 to 146)		120 ± 10 (104 to 172)		119 ± 7 (97 to 137)	
DBP (diastolic blood pressure) BEFORE TX(RANGE)	69 ± 6 (57 to 91)	**P= 0.209**	59 ± 3x (51 to 71)	**P=0.000**	71 ± 7 (60 to 81)	**P=0.000**

DBP AFTER TX (RANGE)	67 ± 5 (56 to 90)		56 ± 5 (45 to 75)		70 ± 4 (61 to 83)	
HR (heart rate) BEFORE TX (RANGE)	81 ± 7 (62 to 104)	**P= 0.000**	65 ± 4 (53 to 78)	**P=0.000**	70 ± 7 (65 to 87)	**P=0.000**
HR AFTER TX (RANGE)	77 ± 6 (59 to 91)		61 ± 4 (50 to 78)		75 ± 10 (56-82)	

Table 2: Comparing post-pre treatment results for ETOIMS using MgSO4 for conduction. Paired T test for TF3-T5 showed significant reduction in all tested parameters (p=0.000) exceptno significant DBP changes for TF5 patient (p>0.05).

	Tf3 Tx With MgSO4 Only (N =939)	**Significance Paired T Test**	**Tf4 Tx With MgSO4 Only (N = 44)**	**Significance Paired T Test**	**Tf5 Tx With MgSO4 Only (N =115)**	**Significance Paired T Test**
SBP BEFORE TX (RANGE)	125 ± 9 (101 to 155)	**P=0.000**	136 ± 6 (124 to 153)	**P=0.000**	119 ± 7 (104 to 144)	**P=0.018**
SBP AFTER TX (RANGE)	119 ± 8 (97 to 172)		128 ± 9 (112 to 153)		118 ± 7 (106 to 144)	
DBP BEFORE TX (RANGE)	68 +6 (56 to 91)	**P= 0.000**	66 ± 4 (56 to 73)	**P=0.000**	71 ± 4 (62 to 85)	**P=0.132**
DBP AFTER TX (RANGE)	64 +12 (64-98)		59 ± 4 (51 to 70)		72 ± 4 (60 to 83)	
HR BEFORE TX (RANGE)	79 ± 7 59-to 109	**P= 0. 000**	59 ± 4 (53 to 70)	**P=0.000**	75 ± 7 (62 to 98)	**P=0.000**
HR AFTER TX (RANGE)	65 ± 11 55 to 108		55 ± 2 (51 to 70)		69 ± 7 (57-88)	

Table 3: Comparing ETOIMS post-pre treatment results between using water or MgSO4for conduction purpose. TF3 independent T test for DBPDIFF AND HR DIFF showed increased difference (p=0.000) for MgSO4 but no difference for SDPDIFF (p=0.06). For TF4, SBPDIFF, DBPDIFF and HRDIFF were increased after ETOIMS with MgSO4compared to water treatment. TF5 values were increased after MgSO4 treatment for SBPDIFF and DBPDIFF but HRDIFF decreased.

Abbreviations SBP and DBP=Systolic andDiastolic Blood Pressure, HR= Heart Rate, DIFF= Difference.

	Tf3 Txs With Water Only	**Tf3 Txs With MgSO4 Spray**	**Independent T Test**	**Tf4 Txs With Water Only**	**Tf4 Txs With MgSO4 Spray**	**Independentt Test**	**Tf5 Txs With Water Only**	**Tf5 Txs With MgSO4 Spray**	**Independent Test**
	(N = 173)	(N = 939)		(N-503)	(N=44)		(N=353)	(N=115)	
Before-After Sbp Diff With Mean And Sd	7 ± 9	6 ± 8	0.06	7 ± 8	9 ± 7	0.042	0.6 ± 6	-1 ± 5	0.005
Before-After Dbp Diff With Mean And Sd	0.4 ± 6	3 ± 4	0.000	4 ± 4	7 ± 4	0.000	0.5 ± 4	-0.4 ±0.3	0.008
Before-After Hr Diff With Mean And Sd	3 ± 5	5 ± 5	0.000	5 ± 4	4 ± 3	0.05	3 ± 6	6 ± 6	0.000

TABLE 4: ANOVA testing of the three TWF groups for SBPDIFF, DBPDIFF and HRDIFF showed the highest F values for SBPDIFF and DBPDIFF response. Smallest F values noted for HRDIFF when ETOIMS is performed using water (p=0.002) for conduction comparedto using MgSO4 for conduction (p=0.02).

ANOVA

4 A. Sbpdiff Using Water Conduction For ETOIMS.

	Sum of Squares	**df**	**Mean Square**	**F**	**Sig.**
Between Groups	8183.077	7	1169.011	22.761	.000
Within Groups	42885.912	835	51.360		
Total	51068.989	842			

ANOVA

4 B. Sbpdiff Using Magnesium Sulfate Spray Conduction For ETOIMS.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	11367.738	5	2273.548	39.441	.000
Within Groups	62889.571	1091	57.644		
Total	74257.309	1096			

ANOVA

4 C. Dbpdiff Using Water Conduction For ETOIMS.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	2495.225	7	356.461	18.375	.000
Within Groups	16198.777	835	19.400		
Total	18694.002	842			

ANOVA

4 D. Dbpdif Using Magnesium Sulfate Spray Conduction For ETOIMS.

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	7623.800	5	1524.760	77.835	.000
Within Groups	21372.167	1091	19.590		
Total	28995.967	1096			

ANOVA

4 E. Hrdiff Using Water Conduction For ETOIMS (P=0.002 Using Water And P=0.023 Using MgSO4 Spray

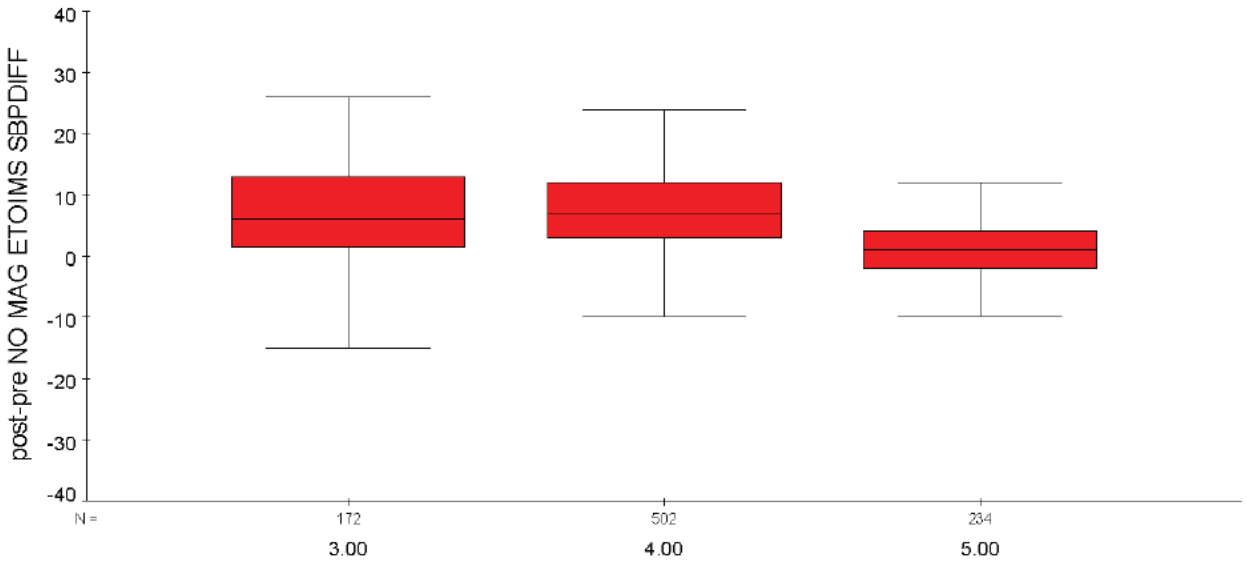
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	535.854	7	76.551	3.220	.002
Within Groups	19852.746	835	23.776		
Total	20388.600	842			

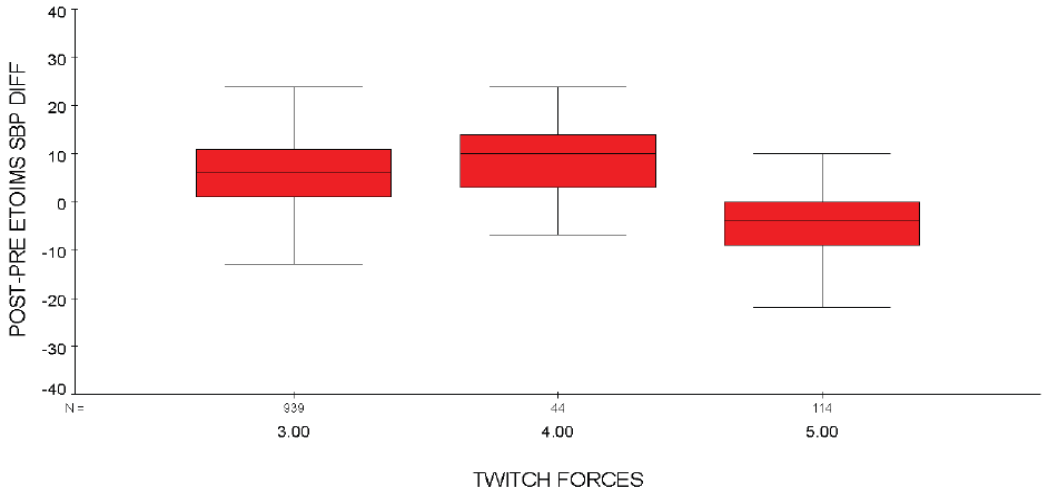
ANOVA

4 F. Hrdiff Using Magnesium Sulfate Spray Conduction For ETOIMS

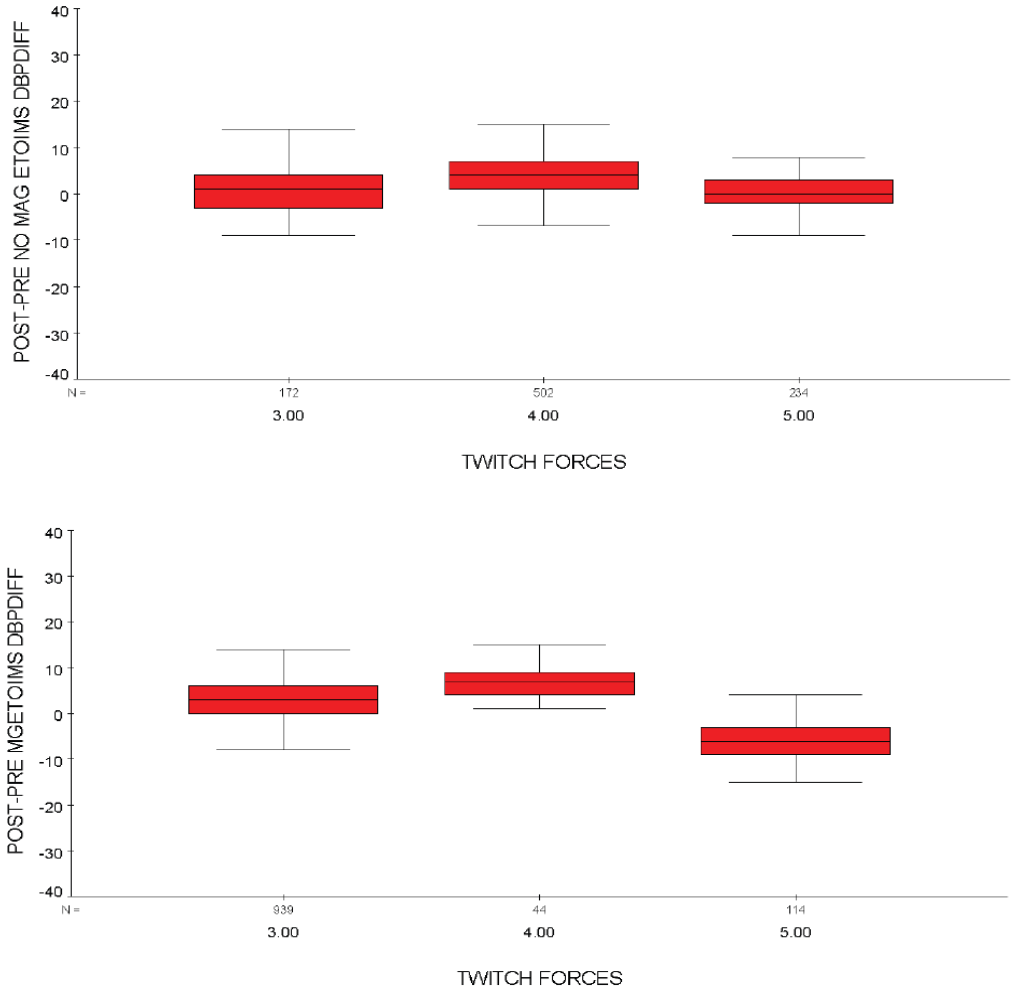
	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	375.779	5	75.156	2.624	.023
Within Groups	31251.926	1091	28.645		
Total	31627.705	1096			

5. Linear regression with ANOVA showed effect of days between treatments on SDBPDIFF P=0.000), DBPDIFF (p=0.007) but not HRDIFF(p>0.05).

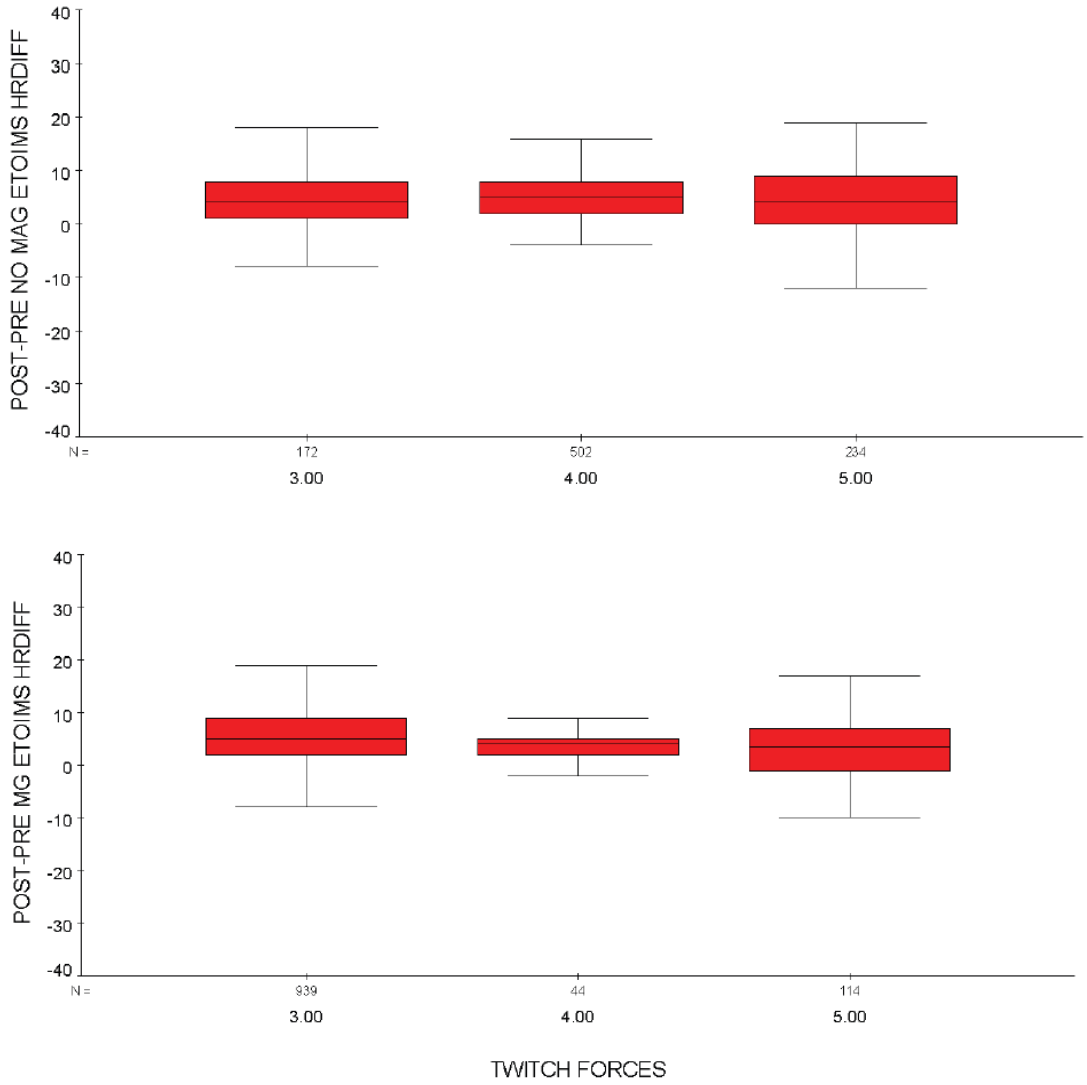




GRAPH 1: Boxplot showing post and pretreatment SBPDIFF on ETOIMS using (top graph) water for conduction and (bottom graph) MgSO4 for conduction for Twitch Forces 3 to 5. Twitch Forces 3&4 had reduced Systolic Blood Pressure after ETOIMS treatment with water and magnesium sulfate. Twitch Force 5 had post-pre Systolic Blood Pressure reduced with water treatment increased with magnesium sulfate treatment due to higher force twitches withmore vigorous exercise effects using magnesium sulfate.



GRAPH 2: Boxplot showing post and pretreatment DBPDIFF on ETOIMS using water for conduction (top graph) and MgSO4 for conduction (bottom graph) for Twitch Forces 3 to 5. Twitch Force 3&4 had reduced Diastolic Blood Pressure after ETOIMS treatment with water and magnesium sulfate. Twitch Force 5 had post-pre Diastolic Blood Pressure decreased with water treatment and increased with magnesium sulfate treatment due to higher force twitcheswith more vigorous exercise effects on using magnesium sulfate.



GRAPH 3: Boxplot showing post and pretreatment on Heart Rate Difference (HRDIFF) on ETOIMS using (top graph) water for conduction and (lower graph) MgSO4 for conduction for Twitch Forces 3 to 5. All Twitch Forces 3-5 had reduced Heart Rate after ETOIMS treatment with water and increased with magnesium sulfate. See Table 3 for statisticalsignificant differences with independent T-tests.

DISCUSSION

The principal cause of pain in 85% of patients visiting a tertiary pain clinic has a myofascial origin. The root cause is multifocal neuromuscular ischemia at myofascial trigger points from muscle tightening and shortening following spondylotic radiculopathy induced low-grade partial denervation. Chronic refractory myofascial pain (CRMP) is a neuromusculoskeletal disease needing management innovations.[3] Using Electrical Twitch-Obtaining Intramuscular Stimulation (ETOIMS), we provide objective evidence of denervation supersensitivity (DS) in multiple myotomes as origin, aggravation and maintenance of CRMP. This study underscores our previous findings that ETOIMS is safe and efficacious for long-term use in CRMP using statistical process analysis.[1,3]

Our intention with this study is to be able to demonstrate that physiological parameters such as blood pressure and heart rate can be used as diagnostic and prognostic factors in the treatment of neuromusculoskeletal pain. Others have also reported on reduction of blood pressure changes with decrease of procedural and neuromuscular pain.[4,5] We propose that changes in blood pressure and heart rate can be used to demonstrate that they are useful as pain indicators and changes as response to pain relief occurs with ETOIMS.

Within 6–8 days of denervation, supersensitivity (DS) develops due to acetylcholine (Ach)receptor increase and decrease in acetylcholinesterase activity.[6] DS can also occur in a prolonged conduction block.[7] Twitches exercise and stretch individual muscles promoting local blood flow specifically to that muscle. Rat skeletal muscle experiments show that twitch contractions from 1 Hz stimulation increase muscle blood flow by 240%.[8] ETOIMS twitches can identify DS objectively and aids clinical differentiation of normal condition from partial

denervation of spondylotic radiculopathy.[9-10] Force, firing pattern, ease/difficulty of twitch elicitation of deep myofascial trigger points (MTrPs) can objectively show the presence of DS.

Grade 1 twitches result from focali**z**ed, partial contraction of stimulated muscle(s) at myofascial trigger points (MTrPs). A stronger twitch force on the electrode overlying MTrP in DS gives an asymmetrical, bouncy feedback on the bipolar probe with 6 inches (15 cm) separation between the positive and negative poles of the wetted surface electrodes. Grade 2 twitches additionally show rocking/shaking limb and/or trunk movements from stimulation of MTrPs of deep muscles directly attached to the bone and joint.

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

Radiological and other imaging studies cannot identify MTrPs dysfunction. Electromyography and nerve conduction studies, is mainly useful for diagnosis and prognosis of demyelination/conduction block, axonal degeneration/ denervation and neuromuscular transmission problems. ETOIMS, however, has the capacity to provide instantaneous diagnosis, treatment, prognosis and preventive feedback in real time as frequently as needed over the persistent pain patient's lifetime.[10]

Muscle cramps: Repetitive lumbar-injury is common in individuals engaged in long-term performance of repetitive occupational/sports activities involving the spine. Prolonged cyclic loading induces imperceptible spinal creep, reduces muscular activity/stability and triggers muscle spasms. Dysfunctional end plates exhibiting increased acetylcholine release may be the starting point for abnormal regional contractions as the neuromuscular junction is the site most susceptible to acute ischemia, essential for formation of MTrPs.[9,10] Cramps have a peripheral origin in distal intramuscular branches of nerves. Passive muscle stretching that lengthens cramped muscle can abruptly interrupt cramps.[10] Applying ETOIMS to acutely cramped muscle effectively stretches and lengthens shortened muscle fibers at cramped areas through active twitch contractions and immediate twitch relaxation in responsive MTrPs.

Chronic pain management is difficult since there are no easy or useful clinical parameters that can be utilized for follow-up of the results on long-term noninvasive treatments. Resting SBP with short-term pain reduction, demonstrates SBP-related hypoalgesia. We used measurement of blood pressure and heart rate as parameters useful as signs for presence of and relief of pain in all 3 patients with different twitch forces for long-term management of chronic pain. We were able to demonstrate that ETOIMS alone using water for conduction was able to reduce SBP, HR and DBP except for DBP in patient with TF3. The increase in HR for TF5 is due to the strong exercise effects of TF5. Muscles of TF3 patient are more tight than those of TF4 and TF5 patients enough that autonomous twitches could not be elicited in TF3 patient(TABLE1).

Using MgSO4 showed similar results for all three twitch forces except for DBP in TF5 patient which did not show any difference (TABLE 2). The inability to reduce diastolic pressure of TF5 may relate to ongoing tightness of muscles due to presence of acute pain having sustained a new injury with exacerbation of lower back pain for which the TF5 patient needed recurrent and ongoing ETOIMS treatments. This indicates ETOIMS use of magnesiumsulfate had an effect on the autonomic nervous system. However, using MgSO4 had more difference than using ETOIMS water for pre and post-treatment comparisons. The TF5 exercise effects were stronger and faster and hence the heart rate slowed down to compensate. The muscle relaxation effects of MgSO4 become more evident for SDPDIFF, DBPDIFF AND HRDIFF by observing the boxplots for TF3, TF4 and TF5 (Graph 1 and 2).

When the number of days between treatments is increased, it is best to perform ETOIMS-MgSO4 since there is greater sympathetic activation from the presence of pain which is a stressful condition. We used the statistical process control (SPC) method that obviates the need for cost-prohibitive, time-consuming randomized control trials (RCTs). SPC results cannot occur by chance and were thus able to expeditiously and inexpensively obtain valuable clinical information on MGSO4 effects on BP and HR.

With use of MGSO4 spray, the elevation of SDP, DBP is partly due to hypersensitivity and increased reactivity of the sympathetic and parasympathetic nervous system. In the presence of chronic pain and in very painful areas that they might be transiently activated duringtreatment.

MGSO4 spray can reduce BP, which may relate to its muscle relaxant effects.[11-14] As the areas over upper sternocleidomastoid originating at the mastoid process and entire trapezius muscles are routinely sprayed and ETOIMS treated, reduction of noxious input probably occurred to the spinal accessory nerves from reduced intramuscular tension. These 2 muscles are supplied by the spinal accessory nerve whose cranial portion is part of the vagus nerve also responsible for baroreflex sensitivity. We have had prior experience with reduction of HR in management ofmyofascial and neuropathic pain using ETOIMS on these 2 muscles.[1,3,10] We therefore infer that the reduced HR pre and post MGSO4 applications are not solely due to reduction of

sympathetic activity but that there is increased activity of parasympathetic system.[10,15-17]

Different from the common inexpensive, low cost MGSO4 crystals called Epsom salt, is that the MGSO4 spray we used was formulated with pharmaceutical grade MGSO4 used intravenously in hospitals, during surgery[18.19], and in control of hypertension of pre-eclampsia/eclampsia.[19] MGSO4 can also be used as an analgesic.[20-22] Our studies have previously shown that the effectsof magnesium sulfate is far superior to that of Magnesium chloride.[12] Our pure MGSO4 in the dermal spray dries rapidly after application within 1-2 minutes and for that reason the spray is only applied immediately before treating that specific area to make the skin soft and moist allowing the twitches to be easily elicited which gives a massage effect to underlying muscles.

As MGSO4 spray mode of action is fast acting within a few seconds , it is time efficient, easy to apply and is generally convenient to use.

ETOIMS therapy alongside active, targeted individual muscle exercise that stimulates MTrPs intrunk, spine and limb muscles. Acute pain relief and follow-up ETOIMS to those with neuromuscular disorders or frequent muscle cramps with pharmaceutical grade MGSO4 is more effective for use to prevent prolonged rehabilitation, loss of valuable downtime anddisabilities. Premature return to full activity due to an underestimated injury can thus be avoided.

CONCLUSIONS

ETOIMS is a unique and highly valuable clinical tool that can objectively quantify the presence of neuromusculoskeletal pain/discomfort and gives valuable information on the connection between sympathetic nervous system and pain. It has the capacity to provide simultaneous real time diagnosis, treatment, prognosis and prevention of persistent pain. ETOIMS aids potential prevention (pre-rehabilitation), simultaneous diagnosis, treatment (rehabilitation) and prognosis in real time for acute and CRMP management and ETOIMS effects are potentiated with combined use of pharmaceutical grade magnesium sulfate.

ACKNOWLEDGEMENTS: J.S. Andrews and D.V. Neuhauser for introducing this topic to the chief author together with the use of statistical process control.

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