

SPECIFIC BIOCHEMICAL CHANGES IN CIRCULATING LYMPHOCYTES FOLLOWING ACUTE ABLATION OF SYMPTOMS IN REFLEX SYMPATHETIC DYSTROPHY (RSD): A PILOT STUDY

A. D. Ericsson¹, C. F. Hazlewood², M. Markov³, and F. Crawford⁴

Institute of Biologies Research, 6560 Fannin, suite 720, Houston TX 77030 Email: ade@rxibr.com USA; 2Research Consultants International, P.O. Box 130282 The Woodlands TX 77393-0282 USA Email: carltonh@s\vb\bellnet? Research International, Buffalo, 135 Arielle Court, Suite E, Buffalo NY 14221 USA Email: msmarkov(a)1aol.com, and 4SpectroCell Labs., 7051 Portwest Drive, Suite 100, Houston, Texas 77024 Email: fcrawford@spectracell.com

Abstract

A new approach of using electromagnetic fields (EMF) for therapeutic purposes, which is linked to its potential systemic effect, has been developed. In order to prove the efficacy of this approach an objective measure of the efficiency of EMF therapy was deemed necessary. In the present study, ten patients with RSD were clinically evaluated. Lymphocytes isolated from circulating blood were cultured before and after therapy with EMF. The metabolic uptake for specific biochemical energy and nuclear turnover compounds were determined in the cultured cells that were taken before and after exposure of the uninvolved limb to an electromagnetic device (TheraMag™). A conventional visual analogue scale (VAS) technique was used to evaluate the intensity and level of pain before and after EMF exposure. The increase in the flexibility of contractures and the reduction swelling of the affected extremity following exposure were monitored by clinical evaluation. Utilizing the objective method of radio labeled molecules, protein-free media, cultured and stressed lymphocyte cultures were found to have significantly elevated fructose, serine, glycine, and calcium cellular metabolic uptake ($p < 0.01$) following exposure to EMF. These findings are in concert with the new hypothesis that, with relief of pain, lymphocytes are predominately altered in their cell cycle from M phase to S phases associated with increased structuring of intracellular water. It is postulated that these changes also reflect a fundamental shift in production of Th1 T lymphocytes to Th2 T lymphocytes, by means of the effect on gating of tRNA mechanisms. A consideration of the basic understanding of the role lymphocytes may be inferred from this preliminary study. A review of the literature on the theoretical and therapeutic use of magnetic fields in humans is provided in an attempt to understand the relevance of magnetic therapy in specific pain syndromes.

INTRODUCTION

Background Information on Reflex Sympathetic Dystrophy.

Reflex Sympathetic Dystrophy (RSD) is a relatively rare phenomenon in medicine. It is to be differentiated from Causalgia, Sudek's Atrophy or Shoulder-Hand Syndrome, as RSD refers to a group of specific symptoms and signs that may follow relatively minor musculo-skeletal or peripheral nerve injuries.

RSD is identified as having three stages:

Stage I: the acute phase is when a patient may complain of severe pain, which seems out of proportion to the extent of injury. The affected extremity may be hot or cold, edematous (swollen) and may exhibit early skin and hair changes. The skin often has a shiny or glistening appearance and the hair may change in texture and direction of growth.

Stage II: the dystrophic phase is recognized by progression of symptoms with worsening pain and coolness of the extremity. Nails become ridged, cracked and brittle and early bone

demineralization occurs. Loss of hair in the involved extremity, livedo reticularis or cyanosis (purple or blue pattern of the skin) are symptoms which have led to the phrase "hairless, blue agony" to define this stage. Suffering is so great that patients may ask for amputation of the affected limb. In addition there appears flexion contractures of the fingers, hand and wrist, which begin to occur and progress unremittingly.

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Stage III: the atrophic phase is characterized by irreversible tissue damage along with irreversible contractures of the fingers into the palm of the affected hand. The skin is thin and tight, connective tissue is dense and contracted, bone is severely demineralized, and joints are ankylosed. In this stage the extremity is described as a "dead painful limb." See Inhofe and Garcia-Moral (1) for additional information on RSD (which may also be referred to as chronic regional pain syndrome-CRPS).

Therapy for RSD?

The pathophysiologic mechanisms of RSD have been studied extensively, but scientists cannot agree on exactly how the pain and symptoms of RSD occur. The prevailing belief is that there is a self-sustaining imbalance in the nervous system. So the initial injury causes an abnormal firing of sympathetic component of peripheral nerves which causes altered responses in the spinal cord, which then responds abnormally to the sympathetic receptors in the brain stem and cortical influences. (2)

Human Use of Magnetic Fields.

It is becoming clear, to a growing segment of the scientific community that magnetic fields interact with biologic tissues in a beneficial way. Limitations on space, however, do not permit us the luxury of an extensive review. We refer the reader to a number of reviews that cover a large spectrum of the literature on the subject (3-8), and provide a short overview of work with electromagnetic fields.

Numerous studies have been conducted where it has been shown that magnetic fields interact with biological tissues by initiating physiological changes that heal some health conditions. (5, 7-15). Even though the mechanisms are unclear, controlled clinical studies are appearing in the scientific literature, which indicate therapeutic value. Static, as well as, time-variable electromagnetic fields have been applied with apparent success in the management of pain in a variety of orthopedic conditions, most commonly traumatic bone fractures or surgical osteotomies (6,8). In addition, the enhancement of wound healing following treatment with low frequency, low energy pulsed electromagnetic fields concentrated on non-union fractures (16-18) and the closure of chronic skin wounds (19-21) have been reported for some time.

Furthermore, thousands of patients have been exposed to electromagnetic fields throughout the world without deleterious effects being reported. (22) In addition, the World Health Organization has reported that "the available evidence indicates the absence of any adverse effects on human health due to exposure to static magnetic fields up to 2T" (23,24). To the best of our knowledge, scientific studies involving the use of magnetic fields have not been reported on RSD patients.

Electromagnetic device (TheraMag™).

The portable TheraMag™ device is capable of producing EMF in the range of 0-200 mT. For this study, the unit was operated at 100 mT, for one hour. The coil of wire is wound around the cylindrical opening in the middle front and produces a homogenous electromagnetic field, which bathes the hand or forearm of the patient when inserted into the unit. The FDA classifies this type of medical device as low risk, and does not require formal IDE application. (25).

DESCRIPTION OF THE STUDY

Ten patients were evaluated by one of the investigators (neurologist) who determined if each of the patients met the criteria of reflex sympathetic dystrophy or neurogenic pain of peripheral nerve origin. Only patients with classic symptoms of reflex sympathetic dystrophy symptoms were included in this study, and those with peripheral nerve injury, which had resulted in a neurogenic pain pattern, were excluded. For eligibility in this study, patients must have exhibited specific, localized pain and sympathetic changes limited to one or more extremities. Pain proximal to the involved extremity was permitted as inclusion, however, general myofascial pain syndromes (in

which patients have pain over much of their body) were excluded. The purposes of this study was thoroughly explained to the patients and the study conducted only after the appropriate medical informed consent was read and signed by both the patient and the principal investigator.

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Each patient, following evaluation and consent approval, ranked their pain on the VAS, had a baseline whole blood sample taken, and the hand and forearm of the uninvolved limb placed in the TheraMag Device for 1 hour. After conclusion of this therapy, each patient was evaluated for relief of pain, clinical signs and an additional whole blood sample taken. The collected samples were delivered to SpectraCell Laboratories identified by random number, thus blinded to the laboratory.

SpectraCell Studies.

Based upon the previously mentioned research that T lymphocytes were altered in stages of development when pain syndromes were relieved, using magnetic therapy was encouraging. It was concluded that these changes may become an objective measurement of pain (26).

SpectraCell Laboratories, has developed a process in which white blood cells (T lymphocytes) are cultured in a sera free medium and the metabolic turnover rates are identified biochemically utilizing an uptake mechanism employing radioactive thymidine (27-29). Following complete medical evaluation at baseline whole blood sample was taken for the SpectraCell analysis. Each culture cell represented over 500 individual counts; therefore, the standard deviation is small. Each individual was his own control as the T cell cultures were taken before and after relief of pain (using TheraMag™ Device in RSD patients). The following cellular metabolites were analyzed:

1. Vitamins: B1 (thiamin), B2 (riboflavin), B3 (niacinamide), B6 (pyridoxine), B12 (cobalamin), biotin, folate and pantothenate.
2. Minerals: Calcium, magnesium and zinc (possibly ferritin)
3. Aminoacid and fatty acids: asparagines, cysteine, glutathionine, glutamine, serine, homocysteine, choline, oleic acid and inositol.
4. Glucose/insulin metabolism: Insulin and fructose

Following complete medical evaluation at baseline, a whole blood sample was taken for SpectraCell analysis. It is believed that analysis of an individual's white blood cells before and after treatment with the TheraMag device would make it possible to quantify the pain process in an objective manner as well as define the biochemical process that may be related to the alterations in phase shift as previously noted. If this could be established, then a quantitative measurement for pain may not only be established and available for usage by the medical community of pain management.

Measurement of Pain in RSD/CRPS Patients.

Each patient was evaluated medically and neurologically, clinically scored, read and then signed a consent form for inclusion into the study. This approach allowed a comparison between objective and subjective measures. According to the medically evaluated VAS scores before and after EMF therapy, the exposure resulted in an overall pain reduction, reduction in edema and dramatic relaxation of the extremity. Also, following the 1 hr therapy with the TheraMag device, each patient was scored clinically and neurologically and a repeat whole blood sample was taken for SpectraCell analysis.

RESULTS

Ten patients with RSD (age 21-70) have been recruited. The average immediate clinical improvement in pain was from VAS score of 8.5 (10 maximum) to VAS score of 1.1 (0-total pain free). Clinical evaluation revealed that muscle strength was measurably improved, edema reduced, and the flexion contractures reduced in the most severe cases of RSD. All subjects tolerated the procedure well. Several interesting clinical observations were made which are worth noting:

1. There was a marked redness of the opposite extremity than that placed in the TheraMag™ Device after about 15-20 minutes (indicating what appears to be cross reflex).
2. Each patient experienced for a slight euphoria followed by drowsiness during the course of

therapy for 1 hour.

3. There was a detectable, but slight, drop in postural (standing) blood pressure following conclusion of therapy that lasted from 30-60 seconds.
4. Often, 60% of the patients, experienced some form of slight chest discomfort during the course of the therapy.
5. After 60 minutes a profound diuresis invariably resulted associated with the therapy.

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Test	Before	After	After-Before
Bl		101.8	3
B2	98.8	49.4	-5.1** 0.7
B3	54.5	100	1.2
B6	99.3	68	1.6
BI2	66.8	7.4	
	9	28.4	-7.6**
Folate	36	J8	4.8
Pantothe.	18.8	92.4	0.1
	92.3	38.4	6.1**
Biotia	32.3	93	10.5*
Serine	82.5	100.2	2.7
Glycine	97.5	32.6	-0.9
Asn/Gln	33.5	71.4	-5.9**
Chollne	77.3	112.8	
Inositol		99.2	2
	110.8	98.2	30.2*
Insulin	69	110	4.9**
Fructose	93.3		0.8
Calcium	110.8		1
Zinc	104.8		1.3
Magnes.	81.3		5.7**
Clulatam.	96.5		
Cysteine			

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DISCUSSION

It is well documented that tissue and cellular water are highly organized relative to bulk water and in many disease states there is a disordering of cellular and tissue water structure. It has been postulated that the magnetic moment of the water hydrogen ions may be coupled with the electrical dipole moment of the water molecules. We speculate that, in addition to the known effect of magnetic fields on water, there could be a change in the conduction properties of sub-varieties of peripheral nerves and perhaps other structures and, as a consequence, improve function. In our thinking, the organization of water in space and time is of fundamental importance, and relates, in ways not fully understood at the present time, to the mechanism of action of magnetic fields living systems, organs, tissues, cells, subcellular organelles, and molecules. In addition, evidence is accumulating that the objectification of pain is an obtainable goal in the near future. Therefore, the discussion is divided into these two subdivisions. Objectification of Pain.

A demonstration of changes in the physical state(s) of water in various phases of the cell cycle has been reported (30,31). It was concluded that cell water was most organized in the S-phase and the least organized in the M-phase. A relief from chronic pain was associated with changes in the cell cycle of human T lymphocytes. From these cell culture studies (30), coupled with the findings in the human lymphocyte study, it seems reasonable to conclude that the physical properties of cellular water may correlate with the degree of chronic pain experiences by a human. Such possibilities led to the proposal of a three-part pain mechanism hypothesis (26). If one assumes that these phase specific changes are reflected in the physical properties of water, as shown by cultured T lymphocytes, then these cells may provide a window in which to monitor the level of pain that the human is experiencing. At this juncture, we are compelled to ask the question: Is it possible that the physical state of water in living cells may be "coupled" in some way with relief of pain? Certainly, other investigators have proposed the potential therapeutic effects of magnetic fields in pain syndromes. (32-34). That structuring of cellular water plays a role in health and disease has been well known (30,31,33,35-43).

Mechanism of Action.

Although we cannot offer an exact mechanism(s) for the immediate pain relief observed in our study patients, the effect could result from a local or direct change in pain receptors'. Vallbona and Richards did list many speculations regarding the possible mechanism of action. (7) A number of testable mechanisms have been proposed including a reversible contraction-relaxation cycle in connective tissue (44). Curiously, additional immunological information has demonstrated that memory T lymphocytes appear to remember the exact anatomical site where they encountered an antigen that is produced when injury has occurred (45,46). These memory T cells represent about 10-15% of all circulating T cells in the peripheral blood, and although they share some common features (chemokine receptors), their T cell antigen receptor specificities are quite heterogeneous. These T cells, either CD4 or CD8 lymphocytes, once activated, are capable of producing either Type-1 (TH1) T cell cytokines (interferon gamma, interleukin 2, and lymphotoxin) or Type-2 (TH2) T cell cytokines (interleukin 4, 5, 10 and 13) (47,48). These cytokines all appear to mediate a response by NF-kB activation in the receptor cells, which, in turn causes the typical inflammatory response (49). It appears that specific activation of types of T cells by antigen and the subsequent release of Type-1 (TH1) or Type-2 (TH2) T cell cytokines as well as perhaps other effector molecules (peptides) will result from the pain and inflammatory syndrome. An introduction to recent work in this area may be found elsewhere (50). Finally, we suggest the consideration that at a cellular level the mechanism is proposed to include an induction effect on the iron response elements within each cell. A method of translational regulation is the binding of repressor proteins. This mechanism is the regulation of the synthesis of ferritin, a protein that stores iron within the cell. The translation of Ferritin mRNA is regulated by the supply of iron: more ferritin is synthesized if iron is abundant. This regulation is mediated by a protein, which, in the absence of iron binds to a sequence called the iron response element (IRE) in the 5' untranslated region of the Ferritin mRNA, blocking its translation.

In no way can we offer final resolution to these different possibilities, but do hope they will provoke inquiry.

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