A DOUBLE-BLIND RANDOMIZED PLACEBO CONTROLLED TRIAL

OF MAGNESIUM OXIDE FOR ALLEVIATION OF CHRONIC

LOW BACK PAIN

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ABSTRACT

This double-blind randomized placebo controlled trial used a pre-test/post-test control group design. Sixty adults patients complaining of chronic low back pain (greater than six months) were recruited from a free standing major metropolitan pain center. Half of the patients received an oral 800mg magnesium oxide supplement and half received an oral placebo every day for a two-month trial period. Laboratory analysis of serum total magnesium, serum ionized magnesium, and sublingual (tissue) magnesium levels (Exatest, ICD Inc.) were performed before and after the trial. All patients were asked to assess their pain and various quality of life indicators using a 10 point Likert Scale before and after the trial. In the magnesium treated group starting pain scores reported a mean of 6.6 (SD$\pm$2.0) and post study pain scores were reported with a mean of 6.4 (SD$\pm$1.7). There were no significant changes in pre or post study magnesium levels in the treatment group. Total serum and serum ionized magnesium levels correlated ($p < .001$), but no significant correlation ($p = .828$) was noted between total serum and sublingual (tissue) magnesium levels. The average diastolic blood pressure in the magnesium treated group decreased significantly (5.9mmHg; $p = .040$). Surprisingly, the total serum magnesium levels increased by 0.05mM/L in the placebo group. Although these data do not support the hypothesis that oral magnesium oxide supplementation can reduce chronic pain, compliance was not confirmed, so replication of this study with a more controlled patient population may be beneficial. As magnesium levels did not rise significantly, a higher dose or a more absorbable magnesium chelate might be more effective. A magnesium wasting effect of orally administered magnesium oxide may also need to be considered.

KEY WORDS: magnesium oxide, chronic low back pain, magnesium levels.

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PREFACE

This research was conducted to provide information about the effects of using magnesium in the treatment or management of chronic pain. Chronic pain is often difficult to manage in the clinical setting. Although there are many different medical and surgical interventions available, health care providers still are not able to answer all the questions related to this issue. This study is an attempt to create yet another option for patents with chronic pain in hopes of improving their quality of life.

ACKNOWLEDGEMENT

CHAPTER I: INTRODUCTION

Background

The role of magnesium in the management of pain has been disputed for many years. Early in the twentieth century, a narcotic action of magnesium sulfate was described by practitioners. This debate continued on how magnesium may play a part in analgesia and anesthesia throughout these early years.   Somjen, Hilmy, and Stephen (1966), in a study attempting to use magnesium as an anesthetic, determined that magnesium alone did not provide anesthesia or analgesia in a dose that was safe for use in humans.

Over the years, it has been shown that magnesium has many purposes throughout the body. Magnesium ranks fourth in order of importance regarding cations found within the body. It is the second most important intracellular cation and is responsible for the activation of over 300 enzyme systems. Many of these enzyme systems are involved in energy metabolism (James, 1991).

One of the important actions of magnesium that relates to this study is the regulation of calcium access into the cell and the actions of calcium inside the cell. The influx of calcium inside the depolarized presynaptic cell allows for exocytosis of neurotransmitter onto the postsynaptic cell. This sequence of events allows the action potential to travel across cells (Rhoades & Tanner, 1995). Magnesium activates pumps on the cell membrane that extrude calcium from the cytosol of the cell (James, 1991). It also inhibits the entrance of calcium into the cell by binding on certain receptor sites (Foster & Fagg, 1987). Due to the unique actions of magnesium in biologic systems, it

has been given the nickname of nature s own physiologic calcium channel blocker (Iseri & French, 1984).

For the purposes of this study, the actions of magnesium on the N-methyl-D-aspartate (NMDA) receptor channel will be examined closely. The NMDA receptor channel is embedded in the cellular membrane in central nervous system tissue. When activated or open, this channel allows for the influx of sodium and calcium into the cell and the efflux of potassium out of the cell (Foster & Fagg, 1987), thereby resulting in cellular depolarization. According to Smith (1996), when magnesium ions are present, the NMDA receptor channel is closed. When the NMDA receptor channel is closed, small membrane depolarizations have little or no effect on the cell. Magnesium therefore reduces neuronal activity.

Antagonistic effects at the NMDA receptor channel can prevent induction of central sensitization due to peripheral nociceptive stimuli (Woolf & Thompson, 1991). It has been shown that calcium channel blockers also have antinociceptive effects (Wong, Dey, Yarmush, Wu, & Zbuzek, 1994).

Purpose of the Study

Studies assessing the effects of magnesium during attacks of acute pain have focused primarily on the use of magnesium in the treatment of migraine headaches and immediate postoperative pain. The effects of magnesium on patients experiencing chronic pain are not well documented and little research is available on this topic. Therefore, the purpose of this study is to evaluate the effects of magnesium on patients experiencing chronic low back pain and add to the current literature.

Primary Research Question

Does magnesium given to patients experiencing chronic low back pain reduce the

level of pain and improve quality of life?

Secondary Research Questions

1. Do quality of life or pain scores correlate with serum or tissue magnesium

    levels in patients experiencing chronic low back pain?

2. Can two months of oral supplemental magnesium oxide significantly raise

    ionized serum or tissue magnesium levels?

Conceptual/Theoretical Framework

The conceptual framework for this study is based on two theories. The first is

Abdellah s typology of 21 nursing problems and the second is the physiological action of

magnesium at the NMDA receptor channel. The application of these two theories to the

problem of chronic pain provides a better understanding of this topic.

Abdellah s Typology of 21 Nursing Problems

Abdellah developed a problem-solving method to resolve issues related to nursing

(Abdellah, Beland, Martin, & Metheney, 1960). The typology of 21 nursing problems

was developed to create a body of knowledge for the nursing profession. She developed

three major concepts in her methodology of health care (Dycus, McClure, Schnmeiser,

Taggart, & Yancey, 1994).

These concepts are nursing, nursing problems, and problem solving. Nursing, the

primary component of Abdellah s work, is a service provided to society. The profession

of nursing is based upon art and science and provides people with specific or general

directions to achieve health. Health can be defined as a state in which the individual has

no unmet needs and does not anticipate any new or have any actual impairments (Dycus et al., 1994).

The second major concept presented by Abdellah is the nursing problem. Nursing problems are consistent with nursing functions or goals. The problems can be overt or covert and can be identified and solved through the professional functions of the nurse (Falco, 1994).

Problem solving is the last major concept of Abdellah s framework. This is the process of identifying the problem, selecting data, formulating a hypothesis, testing the hypothesis, and revising the hypothesis. Nurses must use this approach to solve problems in order to render professional quality nursing care (Dycus et al., 1994).

Along with these three major concepts, Abdellah et al.(1960) described 21 nursing problems that focus on the physical, biological, and socio-psychological needs of individuals. Nurses can use this problem list as a basis for organization of the problem-solving approach (Falco, 1994). For the purposes of this study, three of these 21 problems will be applied to the problem at hand: (a) to maintain good hygiene and physical comfort, (b) to facilitate the maintenance of nutrition of all body cells, and (c) to facilitate the maintenance of fluid and electrolyte balance.

NMDA Receptor Channel Physiology

Glutamate and aspartate are excitatory amino acids (EAAs) found in the mammalian brain. They are found widely distributed throughout the brain and spinal cord. Glutamate and its receptors (GluRs) are best known. When these receptors are stimulated, membrane depolarization occurs or a G-protein system is initiated causing activation or inhibition of cAMP. The type of effect in the second situation depends on

the type of neuron (excitatory or inhibitory) where the action is taking place (Smith, 1996).

The NMDA receptors are found throughout the brain and especially in the telencephalic structures. The hippocampus is heavily represented by NMDA receptors. The NMDA receptor is sensitive to voltage across the membrane in which it is embedded. This fact creates a hybrid channel. The channel is ligand operated, yet sensitive to voltage (Smith, 1996).

The voltage dependent opening of the NMDA receptor is affected by the presence of magnesium ions. When magnesium ions are present, the NMDA receptor is closed. When the NMDA receptor is closed, small membrane depolarizations have little or no effect. The magnesium blockade of the NMDA receptor channel is overcome when the cell membrane is depolarized 30mV from the resting state. At this point, the NMDA receptor begins to open. The larger the cell membrane depolarization; the more NMDA receptors open. This situation is similar to the voltage-gated sodium channel. More channels open with a larger depolarization (Smith, 1996).

According to Smith (1996), the most important ion to pass through this channel is calcium. It should be noted that sodium and potassium ions also pass through this channel. The entrance of calcium ions into the cellular cytosol is physiologically and biochemically significant. Calcium ions are important intracellular second messengers in synaptic transmission.

When the voltage across the cell membrane has been reduced enough to overcome the magnesium blockade on the NMDA receptor, the positive feedback created tends to keep the channels open. This results in a long lasting response. This magnesium

mediated voltage dependence of the NMDA channels is important for synaptic

physiology (Smith, 1996). When magnesium levels are low, these channels may not be

adequately blocked and a smaller cell membrane depolarization could open the NMDA

channels. This effect could lead to easier facilitated cellular depolarization.

It is also important to note that if NMDA receptors are activated by an EAA, the

inflow of calcium ions could open nearby calcium-dependent potassium gates found in

some neural membranes. This outflow of potassium ions would assist in repolarization of

the cell membrane. The repolarization could assist in regaining the magnesium blockade

of the NMDA receptor. At this point, the inflow of calcium would be stopped and the

remaining cytosolic calcium would be bound. Outward flow of potassium would also

stop. Hence, the cell membrane would be ready for another series of depolarization and

repolarization (Smith, 1996).

<div align="center">Variables</div>

The major variables identified in this study are:

1.   Independent Variables:

    (a)   Treatment: magnesium supplement

    (b)   Placebo: receiving no treatment

    (c)   Ionized serum or tissue magnesium levels

    (d)   Amount of pain medication used (measured in morphine

        equivalents)

2.   Dependent Variables:

    (a)   Pain (as measured by a 10 point numeric pain intensity scale)

    (b)   Quality of Life (as measured by a quality of life scale)

(c)   Ionized serum or tissue magnesium levels

3.   Demographic variables include age and gender of patients.

4.   Extraneous variables include the prescribed treatment for low back pain.

Conceptual and Operational Definitions

The following terms have been conceptually and operationally defined for the

purposes of this research project:

Magnesium

A cation found predominantly intracellularly within the body. Operational

definition: Normal adult levels of total magnesium range between 1.3-2.1mEq/L or 0.65-

1.05mM/L (Fischbach, 1992).

Placebo group

Group of patients complaining of chronic low back pain receiving placebo.

Operational definition: Adult patients from the Dulles Pain Clinic complaining of chronic

low back pain enrolled in this study and receiving the placebo.

Treatment group

Group of patients complaining of chronic low back pain receiving treatment.

Operational definition: Adult patients from the Dulles Pain Clinic complaining of chronic

low back pain enrolled in this study and receiving oral magnesium supplements.

Pain

A feeling of distress, suffering, or agony. Pain is caused by stimulation of nerve

endings usually due to tissue damage (Miller & Keane, 1983). Operational definition: A

numeric rating scale will determine levels of pain among individuals. The focus of this

study will be related to complaints of pain in the lumbosacral region of the back lasting

greater than six months.

Numeric Pain Intensity Scale (0-10)

A numeric rating scale from 0-10 with equidistant intervals measuring pain.

Operational definition: Scale used to quantitatively evaluate levels of pain.

Numeric Quality of Living Scale (0-10)

A numeric rating scale from 0-10 with equidistant intervals measuring quality of

life. Operational definition: Scale used to evaluate quality of life.

Demographics

No limitations will be placed on patient age or gender. Patients will be excluded

from the study if they (a) are pregnant, (b) are on diuretics, (c) have known renal

dysfunction with a creatinine greater than 1.5, (d) have any known magnesium deficiency

or (e) are receiving a magnesium supplement for another reason.

Assumptions

1.   Chronic low back pain is an undesirable experience.

2.   All patients will supply information to the best of their knowledge and
      ability.

3.   All patients will comply with the prescribed study and low back pain
      treatment protocols.

Limitations

1.   Since all patients will receive a prescribed treatment for low back pain, a
      decrease in pain scores could be attributed to this aspect rather than
      magnesium supplementation.

2.   Psychological effects of participating in a study may influence the reporting

of pain scores.

3.   Laboratory venipuntures may discourage participation in the study.

4.   Pain is difficult to quantify.

5.   Patient compliance in adhering to the prescribed low back pain protocol and

the study protocol could influence the outcome of the study.

6.   Generalizability to the entire population may be difficult to achieve.

Summary

The focus of this study is to assess the effects of increasing magnesium blood

levels in patients experiencing chronic low back pain. Many of the previous studies

found in the literature have focused on the reduction of acute pain with magnesium

supplementation. Since chronic low back pain affects many people, this study could

provide information and further treatment regimens for patients experiencing chronic

pain. Adding to the current medical and nursing literature also benefits other healthcare

providers by creating alternative plans of care for their patients.

CHAPTER II: REVIEW OF THE LITERATURE

Introduction

Over the years, the pharmacological properties of magnesium have not been completely understood and are now becoming appreciated in certain areas of anesthesia practice. One of the main functions of magnesium in the body is to modulate neuromuscular activity of the calcium ion (Iseri & French, 1984). Magnesium ranks fourth in order of importance regarding cations found within the body. It is the second most important intracellular cation and is responsible for the activation of over 300 enzyme systems. Many of these enzyme systems are involved in energy metabolism. Along with these essential enzyme activation functions, magnesium regulates calcium access into the cell and the actions of calcium within the cell. Because of these unique features, magnesium may be regarded as a natural physiologic calcium antagonist (James, 1992).

In the human body, magnesium is passively absorbed primarily in the small intestine (Rhoades & Tanner, 1995). According to Graham, Caesar, and Burgen (1959), less than half of the dietary intake of magnesium is absorbed. A study by Wester (1987) noted that only an average of 35-40% of orally ingested magnesium is absorbed. The majority of orally ingested magnesium is excreted in the feces. Due to this low percentage of absorption, minimum dietary magnesium requirements have been difficult to determine.

Jones, Manalo, and Flink (1967) performed magnesium balance studies on 18 normal and 7 obese adults. They found that a magnesium intake of 0.3 to 0.35mEq/kg/day was adequate to maintain magnesium balance in normal adults. The

obese group required less magnesium to maintain a positive magnesium balance.

According to Durlach (1989), the current recommended dietary amount of magnesium is

6mg/kg/day. Durlach also pointed out that an absolute magnesium requirement is not a

valid concept when assessing magnesium deficiency. Individual genetic and

environmental differences should be considered when determining the nutritional

requirements of magnesium.

Once absorbed by the small intestine, the kidney regulates magnesium excretion

from the body. Wester (1987) reports that only about 3-5% of filtered magnesium is

excreted in the urine. According to Quamme and Dirks (1986) and Wester (1987), the

proximal tubule is responsible for the reabsorption of approximately 20-30% of

magnesium. Sixty-five percent of the filtered magnesium is reabsorbed in the thick

ascending limb of the loop of Henle. Diuretics or other medications that affect these

areas of the nephron decrease renal reabsorption of magnesium and can lead to a

magnesium deficit.

The Clinical Relevance of Magnesium

The role of magnesium in the field of anesthesia has not always been clear.

Somjen, Hilmy, and Stephen (1966) attempted to provide complete anesthesia to two

surgical candidates with parenteral administration of magnesium alone. During the

experiment, it was noted that the patients appeared anesthetized, but upon emergence, the

patients were able to remember details and felt pain during the surgery. Many prior

experiments using magnesium for anesthesia had been performed on animals; therefore,

without intelligent conversation and recollection, the appearance presented by the two

patients during the magnesium anesthetic experiment could have been mistaken for a

general anesthesia effect. In a study by Aldrete, Barnes, and Aikawa (1968), dogs were used as to evaluate the anesthetic effects of magnesium. These researchers confirmed the pseudo-anesthesia state produced with serum magnesium concentrations greater than 12 mEq/L. Further observation and monitoring suggested that magnesium did not have direct general anesthetic properties and the sleep-like state was attributed to cardiac depression and hypoxia.

When providing inhalation anesthesia, Thompson, Moscicki, and DiFazio (1988) found that with plasma magnesium levels of 7-11 mg/dl, the minimum alveolar concentration (MAC) of halothane could be reduced approximately 20% in female rats. When plasma magnesium levels were increased greater than 11 mg/dl, a reduction of up to 60% MAC occurred. This study documents the significant anesthetic benefit of magnesium when used in conjunction with proven anesthetic agents. According to James (1992), magnesium can be regarded as a central nervous system depressant. Anticonvulsant properties were documented in patients with pregnancy induced hypertension in this study.

Magnesium has been alluded to as nature s physiological calcium blocker (James, 1992). This concept can be applied in anesthesia practice with neuromuscular blocking agents and analgesics. Ghoneim and Long (1969) found that magnesium potentiated the neuromuscular blockade produced by d-tubocurarine, decamethonium, and succinylcholine. One of their proposed mechanisms of the lengthened blockade was due to a decrease in the amount of acetylcholine liberated from the motor nerve terminals. Magnesium is known to block the influx of calcium into the cell body (James, 1992). This action would account for the decreased amount of acetylcholine in the synaptic cleft.

The influx of calcium allows for the release of acetylcholine from the synaptic vesicles within the cell body (Rhoades & Tanner, 1995). A study by Fuchs-Buder, Wilder-Smith, Borgeat, and Tassonyi (1994) assessed the use of magnesium in conjunction with the nondepolarizing muscular blocking agent, vecuronium. These researchers noted that magnesium pretreatment prior to administration of vecuronium increased the potency and lengthened the neuromuscular block provided by this drug.

The use of calcium channel blocking agents in combination with analgesics has also been extensively researched. Miranda and Paeile (1989) reported a minireview of the interactions between calcium channel blockers and analgesics. In a metaanalysis of several studies, they concluded that calcium channel blockers and related drugs were found to possess analgesic effects due to the antinociceptive effect associated with calcium channel blockade.

In a study by Santillan, Maestre, Hurle, and Florez (1994), nimodipine, a calcium channel blocker, was administered to cancer patients chronically treated with morphine for pain control. Daily morphine consumption was assessed in these patients. During this study, nimodipine reduced the daily dose of morphine in 16 of the 23 patients studied. In those 16 patients, the total daily oral dose of morphine was reduced from 282.6 mg (+/-47.7 mg) to 158.7 mg (+/-26.2 mg). The use of nimodipine also lowered the daily doses of morphine by 1-5 mg/day in three of the patients who were receiving intrathecal morphine. These findings supported the concept that interfering with calcium regulated mechanisms could modify chronic opioid effects and could decrease morphine tolerance.

Contreras, Tamayo, and Amigo (1988) assessed the effects of morphine-induced

analgesia and tolerance in mice receiving calcium channel blockers. It was noted that the

calcium channel blockers, when given alone, did not alter the reaction time to thermal

stimulation. However, the analgesic effects of morphine were significantly prolonged

with the concurrent administration of diltiazem, flunarizine, nicardipine, and verapamil.

These drugs also decreased the intensity of tolerance to morphine. The authors reported

that nifedipine induced an antagonistic effect when administered in conjunction with

morphine.

On the contrary, Wong, Dey, Yarmush, Wu, and Zbuzek (1994) demonstrated

positive effects with nifedipine-induced analgesia in rats. These researchers found that

when nifedipine was given epidurally at doses of 5 µM or greater, antinociceptive

properties were evident. This information suggests that nifedipine can produce spinal

analgesia. The researchers conclude that further testing regarding side effects and

neurotoxicity needs to be conducted before application of this type of analgesia in the

clinical setting.

Wilder-Smith, Hoffmann, Borgeat, and Rifat (1992) further examined the analgesic

effects of magnesium. These researchers compared intraoperative analgesic

supplementation with magnesium versus fentanyl. Postoperatively, the group treated

with magnesium required significantly less narcotic pain medication. Howell, Gambling,

Pavy, McMorland, and Douglas (1995) compared the effects of fentanyl and morphine as

analgesics in patients post-Caesarean section. Although this study did not specifically

include magnesium as an indirect variable, the researchers noted that two patients who

were receiving magnesium sulphate for pre-eclampsia required the least amount of

opioids in this study. The authors attribute this as a synergistic effect of the magnesium with opioids and suggest further study in this area.

Two significant contributions to the magnesium/analgesia debate provide interesting findings. Tramer, Schneider, Marti, and Rifat (1996) performed a randomized, double-blind study on 42 females undergoing elective abdominal hysterectomies with general anesthesia. Half of the patients each received a total of 13 grams of intravenous magnesium sulfate, while the control group received saline intravenously. All of the patients received the same postoperative patient controlled analgesia and instructions. In this study, the treatment group utilized significantly fewer narcotics for postoperative pain control and reported a better quality of sleep without adverse effects. A comparable study by C. H. Wilder-Smith, Knopfli, and O. H. Wilder-Smith (1997) produced the opposite effects. These researchers enrolled 24 females undergoing elective hysterectomy procedures utilizing general anesthesia. In this study, each patient in the treatment group received a total of 1.2 grams of intravenous magnesium laevulinate, while the control group received saline intravenously. The patients in both groups reported similar pain scores. These data may demonstrate the dose/effect relationship of magnesium.

Another extensively investigated clinical problem related to magnesium research is migraine headaches. Altura (1985) hypothesized that migraine attacks could be prevented if magnesium blocked the entry of calcium into cerebral vascular smooth muscle. In a study by Mauskop, B. T. Altura, Cracco, and B. M. Altura (1992), the researchers assessed total serum magnesium, serum ionized magnesium levels, percent ionized magnesium levels, ionized calcium levels and the ionized calcium:ionized

magnesium ratio in patients with various headache syndromes. The patients were divided into two groups according to the symptomatology of their headaches, that being continuous or intermittent. The researchers found total serum magnesium to be normal in both groups. In the group of patients with intermittent headache complaints, serum ionized magnesium levels of 0.556 mM/L (+/-0.009) were significantly lower than the control group of 0.59 mM/L (+/-0.005), even though their total serum magnesium levels of 0.836 mM/L (+/-0.012) were higher than the control group of 0.81 mM/L (+/-0.008). These data clearly indicate that total serum magnesium levels, alone, may not be an accurate measure when assessing magnesium balance.

Mauskop, B. T. Altura, Cracco, and B. M. Altura (1995) conducted a similar study while assessing total serum magnesium, serum ionized magnesium, serum ionized calcium, and ionized calcium:ionized magnesium ratios. In this study, the researchers administered one gram of magnesium sulfate intravenously to patients with various types of headache complaints. Thirty-two (80%) of the 40 patients experienced complete pain relief within 15 minutes of the infusion. In 18 (56%) of these patients, this pain relief lasted over 24 hours. Sixteen of the 18 patients were noted to have low serum ionized magnesium levels while all of the patients had normal total magnesium levels (0.7-1.05 mM/L). The normal range for ionized magnesium levels used in this study was 0.55-0.66 mM/L. These data emphasize the need to assess ionized magnesium along with total magnesium levels in the clinical setting.

The use of intravenous magnesium supplementation has been demonstrated to have an effect in controlling headaches; however, others tested the effects of oral magnesium administration for pain control. Peikert, Wilimzig, and Kohne-Volland (1996) created a

placebo-controlled, double-blind randomized study to assess the efficacy of oral

magnesium on migraine headache. At initiation of the study, all patients received a

physical exam that included assessing serum potassium, calcium, creatinine, and

magnesium (atomic absorption spectrophotometry) levels. Exclusion criteria were

identified and included pregnancy, nursing, renal dysfunction with serum creatinine

greater than 1.5 mg/dl, ammonium-phosphate-calculus-diatheses, interfering medical

disorders, known allergies, serious psychiatric disorders, substance-abuse, abusive

behavior, and inability to distinguish migraine from other headaches. This study lasted

12 weeks for each patient. The treatment group received daily supplements of 600 mg

(24 mM) magnesium (trimagnesium dicitrate) in the form of a water-soluble granular

powder. The placebo group received a magnesium-free powder.

Sixty-eight (84%) of the 81 patients who started in the study finished according to

plan. Three patients in the study group dropped out due to unwanted gastrointestinal side

effects (diarrhea). One patient in the placebo group dropped out because of lack of

effectiveness in treating the headaches. The other four patients (three placebo and one

treatment group) were lost to follow up. No significant side effects were noted and the

gastrointestinal side effects reversed upon cessation of therapy. The authors of this study

concluded that high-dose oral magnesium was effective in decreasing migraine headaches

with minimal adverse effects. No significant correlation was noted between serum

magnesium levels and the reduction of headaches prior to the study.

<p align="center">The Relationship of Magnesium and Stress</p>

An important clinical aspect of magnesium that is relevant to this research project

is its relationship to stress. According to Durlach (1989), magnesium deficit and the

stress response reinforce each other in a vicious circle. Stress produces magnesium deficit through two neurohumoral mechanisms. First, stress is responsible for opposing magnesium sparing neurohormonal mechanisms. In doing so, large amounts of other catecholamines replace adrenaline, insulin secretion is decreased, and taurine is lost in the urine. Secondly, stress increases urinary excretion of magnesium by increasing secretion antidiuretic hormone, thyroid hormones, and corticoids. In addition to these effects, low serum magnesium allows for a state of increased susceptibility to stress. This creates a vicious circle. According to Seelig (1994), magnesium deficiency intensifies the stress response by allowing an increased release of the stress hormones (other catecholamines and corticosteroids). This response further depletes magnesium levels. The stress response can be activated by various neural and humoral factors like pain, anxiety, acidosis, local tissue factors, and hypoxia (Barasch, Cullen, & Stoelting, 1997).

Weissberg et al. (1991) studied women in their third trimester of pregnancy and during labor, patients with acute medical conditions with and without pain, and patients with and without pain admitted to surgical units. Serum magnesium levels showed an inverse relationship with reported pain in this study. These researchers attributed the decrease in serum magnesium to an increased urinary loss and a shift of the magnesium cation into the intracellular compartment. Sanchez-Capuchino and McConachie (1994) conducted a similar study assessing the effect of major gastrointestinal surgery on serum magnesium. This research also documents a statistically significant reduction of serum magnesium levels in patients after major surgery. The stress response to major surgery could attribute to this reduction in magnesium levels.

Abraham, Schaoul, Schimonivitz, Eylath, and Weinstein (1980) measured serum magnesium levels in patients with acute medical and surgical conditions and in women before and during childbirth. Their findings were relevant in that serum magnesium levels fell significantly when there was pain associated with the presenting condition. There was no correlation with the severity or type of illness involved. Another interesting finding was that magnesium levels did not decline in the seven patients presenting for elective surgery under local anesthesia.

<center>Magnesium and the NMDA Receptor</center>

The NMDA receptor channel is embedded in the cellular membrane. This channel when activated or open allows for the influx of sodium and calcium into the cell and the efflux of potassium out of the cell (Foster & Fagg, 1987). In other words, this channel plays a role in cellular depolarization. According to Smith (1996), when magnesium ions are present, the NMDA receptor channel is closed. When the NMDA receptor channel is closed, small membrane depolarizations have little or no effect on the cell.

Antagonistic effects at the NMDA receptor channel can prevent induction of central sensitization due to peripheral nociceptive stimuli (Woolf & Thompson, 1991). It has been shown that calcium channel blockers also have nociceptive effects (Wong, Dey, Yarmush, Wu, & Zbuzek, 1994). Magnesium is known to have antagonistic effects at the NMDA receptor channel and has been labeled as a natural physiologic calcium channel blocker.

Smith (1996) reports that the NMDA receptor is sensitive to voltage across the membrane in which it is embedded. This fact creates a hybrid channel. The channel is ligand operated, yet sensitive to voltage. According to Dickenson (1990), the NMDA

receptor at rest is blocked by magnesium which is removed by depolarization and

provides a mechanism that allows neuronal activity to be switched from low to high

levels when the block is relieved. This aspect of the NMDA receptor is consequential

providing that pain sensations are not a fixed system, but rather capable of plasticity.

Reynolds (1990) reported that inappropriate activation of the NMDA receptor is

controlled by the magnesium blockade when the cell is at rest.

According to Smith (1996), the most important ion to pass through the NMDA

channel is calcium. It should be noted that sodium and potassium ions also pass through

this channel. The entrance of calcium ions into the cellular cytosol is physiologically and

biochemically significant. Calcium ions are important intracellular second messengers in

synaptic transmission. According to Ascher and Nowak (1987), NMDA agonists open

cationic channels in magnesium free solutions. With the addition of magnesium to the

solution, the NMDA-induced currents are diminished. This blockade of the channel by

magnesium is voltage dependent and is removed by depolarization of the cell.

When the voltage across the cell membrane has been reduced enough to overcome

the magnesium blockade on the NMDA receptor, the positive feedback created tends to

keep the channels open. This results in a long lasting response. This magnesium

mediated voltage dependence of the NMDA channels is important in the regards for

synaptic physiology (Smith, 1996). When magnesium levels are low, these channels may

not be adequately blocked and a smaller cell membrane depolarization could open the

NMDA channels. This effect could lead to easier facilitated cellular depolarization.

Magnesium Oxide Use in Patients with Chronic Pain

As evident in this literature review, extensive research has been conducted with magnesium in patients complaining of acute pain or various headache syndromes. The majority of this research reflects a positive outcome with the utilization of magnesium to decrease or alleviate pain. The present gap in our anesthesia knowledge base is the lack of this application to individuals experiencing chronic pain.

Abdellah et al. (1960), in a problem solving approach toward patient care, dedicated physical comfort as a priority for nursing care. According to Abdellah, fluid and electrolyte balance and the nutritional status of all body cells also should be closely examined when organizing health care needs of the patient. These are roles assumed by anesthesia providers when a patient presents for anesthesia-related health care needs, in this instance, pain management.

Low back pain is an extremely common, nonfatal health problem worldwide. According to Simpson, Edmondson, Constant, and Collier (1997), chronic low back pain causes 2-5% of adults to seek medical attention or take time off from work. Chronic low back pain often affects people between 35 and 45 years of age. The average patient has complained of intermittent pain for over 10 years. Severity of the pain usually varies, but most patients are able to localize their pain. Due to the chronicity of the pain, many patients have sought numerous treatments with minimal to no relief (Long, BenDebba, & Torgerson, 1996). These data demonstrate a need for further study.

Summary

Clinical studies, such as Weissburg et al. (1991), show that many patients under stress often demonstrate low serum magnesium levels. Magnesium is an important

electrolyte within the body and is responsible for activating over 300 enzyme systems,

many of which are involved in energy metabolism at the cellular level (James, 1992).

Woolf and Thompson (1991) affirm that the magnesium blockade of the NMDA receptor

may play an important function in depressing the interpretation of the pain sensation.

Current research demonstrates that by increasing magnesium levels acute pain and

headaches may be reduced or alleviated. These facts provide relevancy when applying

Abdellah s problem solving technique in caring for the patient with chronic low back

pain (Abdellah et al., 1960). Further research of magnesium oxide use in the clinical area

could possibly enhance quality of life and alleviate chronic low back pain for many

people.

CHAPTER III: METHODS

Research Design and Procedures

Three research questions were proposed relating to the use of magnesium for the alleviation of chronic low back pain. In order to answer these questions efficiently, an experimental design was used in this study. According to Burns and Grove (1997), experimental designs examine the relationship between two or more variables. All extraneous factors that may influence the dependent variables must be eliminated or controlled in order to evaluate the influence of the independent variables.

There are five essential elements in experimental research. These elements include (a) random sampling, (b) manipulation of the independent variables by the researcher, (c) control of the experimental situation with the use of a comparison or control group, and (d) random allocation to experimental or control groups, and (e) masking of the intervention through placebo. Rigid control of the situation in which the study is conducted should be maintained to prevent uncontrolled and extraneous factors from affecting the dependent variables (Burns & Grove, 1997). The conceptual and operational definitions described in Chapter I were utilized to maintain consistency throughout the study.

This study was a double-blind randomized placebo controlled trial using a pre-test/post-test control group design. The patients were randomized upon acceptance into the study according to a schedule provided by the Blaine Company, Inc. (Burlington, Kentucky). The company also supplied the magnesium and placebo. This enabled the researcher, as well as the study participants, to remain blind as to who was receiving magnesium and who was not.

Prior to initiation of the study, informed consent and a thorough history and physical were obtained from all patients. During the history and physical exam, all patients were asked to assess their pain and various quality of life indicators using a 0-10 Likert Scale (see Appendix A). A previously created data collection tool was utilized for obtaining this information (see Appendix A). Reliability and validity of the data collection forms was assessed by subject matter experts.

All patients had the same panel of prestudy laboratory values performed. These included sublingual magnesium levels and serum levels for (a) sodium, (b) potassium, (c) creatinine, (d) ionized magnesium and (e) total magnesium. Less than 20 milliliters of blood was collected from each patient at the initial visit. The prestudy aspect of data collection is an important element in this study. Altura, Wilimizig, Nyulassy, and Altura (1994) found that in patients who received oral magnesium supplementation the serum ionized magnesium and percent ionized magnesium levels rose significantly, but total serum magnesium levels were not affected.   Altura, Shirey et al., (1994) also found that ionized magnesium levels were typically 71% of the total magnesium value, but that it varied from person to person. These researchers determined that ionized magnesium cannot be predicted from total magnesium values.

Sublingual magnesium levels were also obtained from each patient to assess the relationship between sublingual magnesium levels and serum magnesium levels. The validation of a direct measure of ionized magnesium levels has a useful role to play in the patient care setting. Haigney et al. (1995) found that levels of sublingual epithelial cell ionized magnesium correlated with levels of atrial tissue ionized magnesium, however there was no correlation with total serum magnesium levels. Sublingual tissue

magnesium levels were obtained using energy dispersive X-ray analysis (EXA Test) (IntraCellular Diagnosics, Inc., 1991). This test is specific for total cellular magnesium concentration.

Therapy was initiated after obtaining the laboratory data. Randomly assigned patients received either placebo or 800 mg of magnesium oxide on a daily basis. According to Durlach (1989), the recommended dietary amount of magnesium has been set at 6 mg/kg/day in developed countries. An average 70 kg person should therefore receive 420 mg of magnesium per day. The 800 mg dose prescribed in this study allowed for dietary supplementation of magnesium.

This regimen continued for two months. At the end of the two month trial, all patients were asked to return the empty study drug pill container. All patients were medically monitored according to standards already in place at the Dulles Pain Management Center. The use of prescribed pain medication/narcotics during this time frame continued without change in the patients prescribed plan of care.

After the elapsed time of two months on the magnesium/placebo trial, all patients were debriefed, and poststudy laboratory values were collected. These laboratory studies consisted of the same set of prestudy lab tests and the amount of blood drawn from each patient did not exceed 20 milliliters. Laboratory equipment and analysis for the study was provided by the Clinical Center of the National Institutes of Health. All patients were asked to reevaluate their pain and quality of life on the scales used to obtain initial measures.

Sample

Sixty patients treated at the Dulles Pain Management Center (Centerville, Virginia) comprised the study sample. With the randomization table provided by the Blaine Company, Inc., 30 patients received placebo and 30 patients received magnesium oxide. This sample provided an acceptable power of .80 at an alpha of .05 in a two sided test of significance, since a moderate effect size was expected to be obtained (E. Levine, personal communication, April 15, 1998).

Exclusion criteria for this study were developed and consisted of: (a) patients with known renal dysfunction and/or with creatinine levels greater than 1.5 mg/dl, (b) pregnant women, (c) patients receiving diuretic therapy, (d) patients with known magnesium deficiency, (e) patients who have been prescribed or are taking magnesium for another reason, and (f) patients who are currently taking tetracyclines. All patients were closely assessed for these criteria during their history and physical exam and throughout the study.

Measurement

Validity of an instrument is an evaluation of the extent to which the instrument accurately measures the study variables. Subject matter experts evaluated the study instruments for content validity prior to initiation of the study. Reliability, the consistency of measurement, was tested using the test-retest method. The evaluations of the instruments were be analyzed using the Statistical Package for the Social Sciences (SPSS) (1997). A correlation coefficient of .80 and greater indicates a high level of reliability; therefore, a reliability coefficient of at least .80 was used as the standard (E. Levine, personal communication, April 15, 1998).

Protection of Human Rights

The Internal Review Board (IRB) from the Uniformed Services University of the Health Sciences reviewed the content of this study. The IRB also was available to provide answers to patients who had questions or concerns that they were unwilling to convey to the researcher. After obtaining IRB approval, informed consent was obtained from all patients in the study. Strict adherence of exclusion criteria was maintained to prevent any untoward effects. Patients were informed of their rights to discontinue participation in the study at any time.

The benefits to the patient significantly outweighed the risks when participating in this study. There was minimal risk to patients of this study. Magnesium oxide is poorly absorbed in the gastrointestinal tract (Graham et al., 1959; Wester, 1987). The majority of orally ingested magnesium is excreted in the feces. Due to this fact, it would be very difficult to achieve toxic dosages of magnesium in the blood stream using the oral route of magnesium administration. In a study by Peikert, Wilimzig, and Kohne-Volland (1996), 43 patients received 600 mg of magnesium daily with minimal adverse effects. Diarrhea was the most frequent adverse effect and resolved with the cessation of treatment.

Data Analysis

The data collected from the patients were analyzed using the SPSS. Demographic data were collected and all study variables were summarized in frequency distributions, means, standard deviations, and standard errors. The independent variables, including serum ionized magnesium, total serum magnesium, and sublingual magnesium levels, were analyzed in relationship to the dependent measures of pain and quality of life

indicator pre and post scores. Paired t-tests were be used to analyze the data for

statistical significance in the difference in mean scores between the treatment and control

groups. The alpha level was set at .05.

Summary

The planned methodology of this pre-test/post-test clinical trial research was

carried out at the Dulles Pain Management Center. A randomized double blind approach

was used to assess the effects of magnesium supplementation in sixty patients

experiencing chronic low back pain. The patients were enrolled in study for a two-month

period. These patients were asked to rate their pain and quality of life at the beginning

and end of the study. Laboratory data were also collected at the beginning and end of the

study. The obtained data were analyzed using SPSS (1997).

CHAPTER IV: ANALYSIS

Presentation, Analysis & Interpretation of Data

One primary and two secondary research questions were presented at the beginning of this project. Each of these questions will be presented and answered according to data obtained from this study.

The study sample initially consisted of 60 volunteers from a free-standing pain center located in a major metropolitan area. Each of these volunteers was complaining of chronic low back pain (defined as greater than six months in duration). The exact pathophysiology of the back pain was not defined. Baseline laboratory data and demographic data were collected on each volunteer after obtaining informed consent and prior to enrollment in the trial. Each volunteer was also asked rate their low back pain and quality of life on the data collection sheet (see Appendix A).

Study design consisted of a randomized placebo controlled trial; therefore, the researcher and the volunteers did not know whom received placebo or magnesium oxide tablets. The volunteers were instructed to take two tablets daily for two months. The control group received a placebo and the treatment group received 800 mg magnesium oxide on a daily basis. Upon completion of the two month trial, similar laboratory data were collected from each volunteer. Volunteers were asked to rate the intensity of their low back pain and quality of life on the data collection sheet (see appendix A).

Study Sample

The initial study sample consisted of 21 males and 39 females (see Table 1). The majority of the volunteers were Caucasian. The ages of the volunteers ranged from 27 to 60 years old, with a mean age of 45 years.

Upon completion of the two-month trial, the control group and the treatment group were identified. Forty-three volunteers completed the two-month trial, 20 in the treatment group and 23 in the control group (see Table 1). Ten people dropped out of the placebo group and seven dropped out of the treatment group. Two people dropped out of the treatment group due to complaints of diarrhea that immediately resolved after stopping the study drug. The others dropped out for reasons unknown or not specifically related to the study.

Table 1.

Study Participants Grouped by Gender

	Male	Female
Total Initially	21	39
Treatment Group	7	23
Control Group	14	16
Completed Trial	14	29
Treatment Group	4	16
Control Group	10	13

Analysis

Pre-study reported pain scores were similar in both treatment and placebo groups.
The mean average pain score for both groups prior to beginning the two month trial was
6.6(SD±1.9). After completion of the two month trial, the average pain score reported in
the magnesium treated group was 6.4(SD±1.7) a difference from the initial pain score of
—0.2, with a p value of .479. The placebo group reported an average post study pain
score of 6.0(SD±1.9), a difference of -0.6 with a p value of .029. This value does
indicate statistical significance at the .05 level using a t test of the significance between
means. The difference between treatment and control groups of 0.4 was not statistically
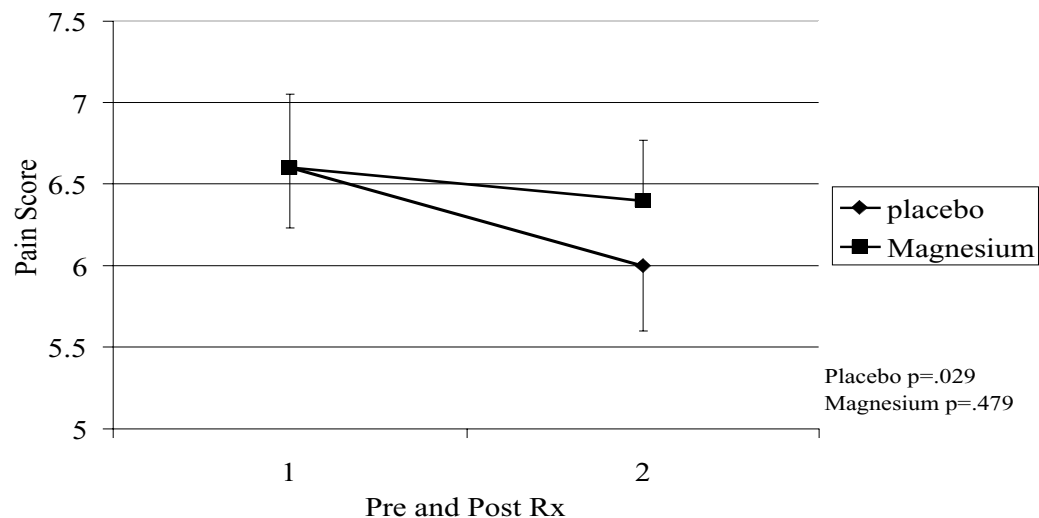significant at the .05 level (p=.525) (see Figure 1).

Figure 1.

Pre and Post Trial Reported Average Pain Values

Each patient enrolled in the study continued the narcotic pain regimen prescribed by a physician from the pain management center. In an attempt to control for this variable, each of the patient s prescribed medications was converted to an equal value of orally administered morphine in a milligram per hour (mg/hr) basis. Within the magnesium treated group, the mean average amount of orally consumed morphine equivalents prior to the study was 4.57 mg/hr. Upon completion of the two month trial the mean average consumed was 5.63 mg/hr. A paired t test on this increase in consumption of 1.06 mg/hr resulted in a p=.094, which indicates a modest trend toward significance in the difference of these values. The control group demonstrated an increase consumption of 1.01 mg/hr (p=.015) of morphine equivalents during the two month trial.

Statistical analysis was also performed separately by gender for each group. Within the magnesium treated group, the mean average pre-study pain score for males was 6.0 (SD ±2.2) and for females was 6.8 (SD ±2.0). While there was a reported decrease of —0.3 (p=468) in average pain post study scores in the female treatment group, the clinical significance of this decrease is questionable. The reported pain scores for men in the treatment group remained the same over the two month period. An interesting observation in the control group was that both the men and women reported decreased pain scores after the two month trial (see Figure 2 and Figure 3).
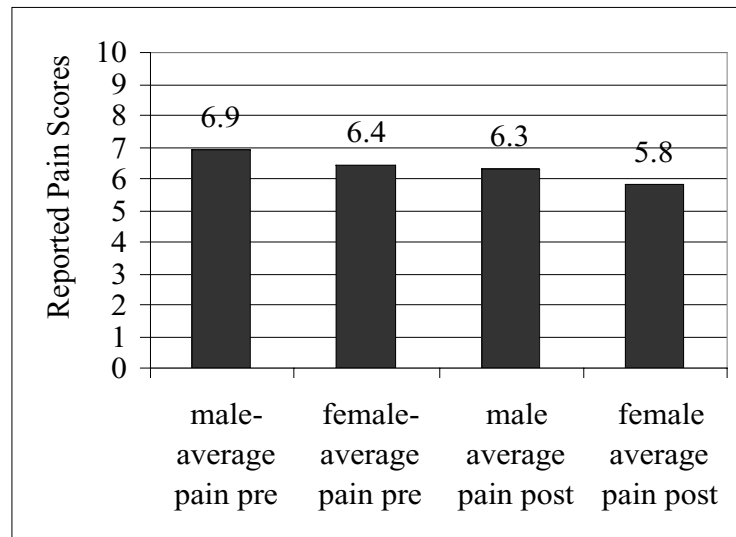
Figure 2.

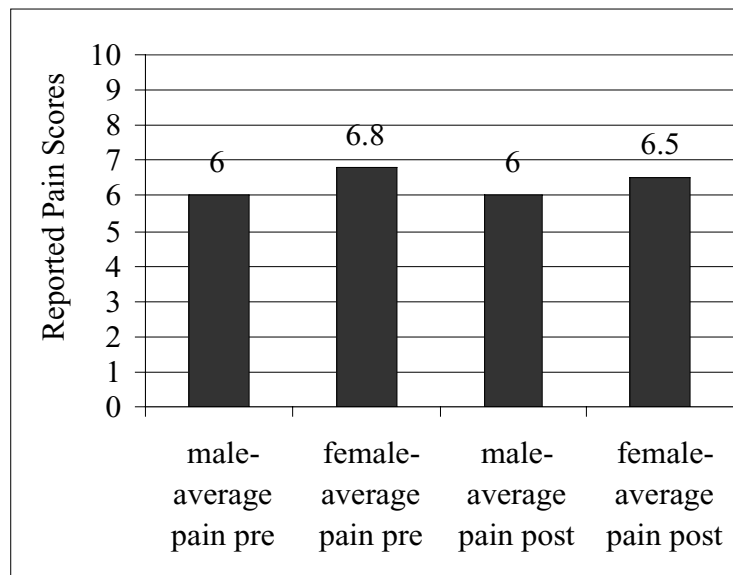**Treatment Group Average Pain Scores Pre and Post Two Month Trial**

Figure 3.

Control Group Pain Scores Pre and Post Two Month Trial

The effects of pain on the individual s mood, general activity, enjoyment of life were some of the quality of life indicators that were assessed. These indicators remained unchanged in both groups before and after the trial.

The first secondary research question was: Do quality of life or pain scores correlate with serum or tissue magnesium levels in patients experiencing chronic low back pain? Total serum magnesium levels, serum ionized magnesium levels, and sublingual (tissue) magnesium levels were collected before and after the two-month trial. According to the data obtained in this trial, simple correlation calculations between average post study pain scores and total serum magnesium demonstrate that the correlation between these variables was not statistically significant (p=.282; r=-.26) as was the difference between average post study pain scores and serum ionized magnesium (p=.77; r=-.07). The difference between average post study pain scores and sublingual (tissue) magnesium levels did reach statistical significance at the .05 level (p=.04; r=-.474). This indicates a correlation between sublingual magnesium levels and pain.

The final research question was: Can two months of oral supplemental magnesium oxide significantly raise ionized serum or tissue magnesium levels? (see Figures 4 through 9) Initially, the control group and the treatment group were compared. Within the control group prior to participation in the trial, a mean ionized magnesium level of .546 mM/L was noted. After the two-month trial, this level declined to .543 mM/L. Paired t-tests confirmed a p of .638, indicating that this value did not statistically change after two months of participation in the study. The treatment group started with an ionized magnesium value of .537 mM/L that increased to .548 mM/L. This increase in the serum ionized magnesium values did not reach statistical significance with paired t-

tests resulting in a p value of .34. The prestudy average ionized magnesium levels within

the control group and the treatment group were similar, resulting in a difference of 0.009

mM/L. When comparing this difference between groups with an unpaired t test, p=0.5.
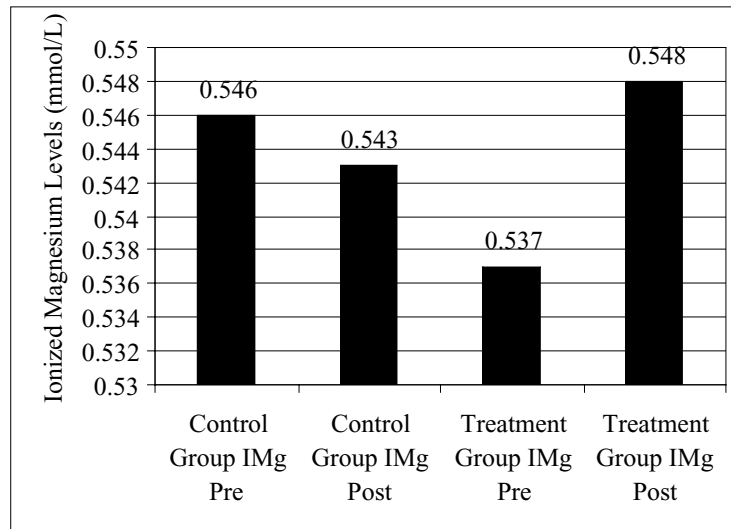
Figure 4.

<u>Ionized Magnesium Levels in the Control and Treatment Groups</u>

After evaluation of the groups as a whole, the males and females were separated

and serum ionized magnesium levels were statistically evaluated. Serum ionized

magnesium levels among men in the magnesium treated group rose from 0.523 mM/L to

0.528 mM/L. Resulting paired t tests indicated a p value .731. Among females in the

magnesium treated group, the serum ionized magnesium levels rose from 0.541 mM/L to

0.553 mM/L. The corresponding p value to this increase was .379.

Figure 5.

Serum Ionized Magnesium Levels within the Treatment Group
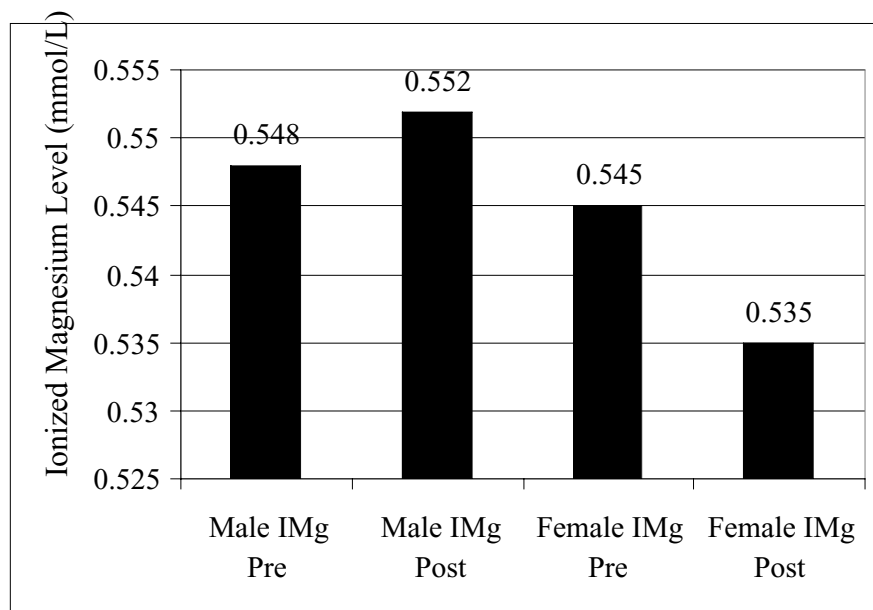
Figure 6.

Serum Ionized Magnesium Levels within the Control Group

Sublingual (tissue) magnesium levels were analyzed pre and post study. The initial mean sublingual magnesium level in the control group was 33.0 mEq/L and after the two-month trial ended with a level of 33.1 mEq/L. Paired t-tests produced a p-value of .898. In the treatment group the starting mean sublingual (tissue) magnesium level was 33.4 mEq/L and decreased to 32.9 mEq/L. The change in these values produced a p-value of .732.

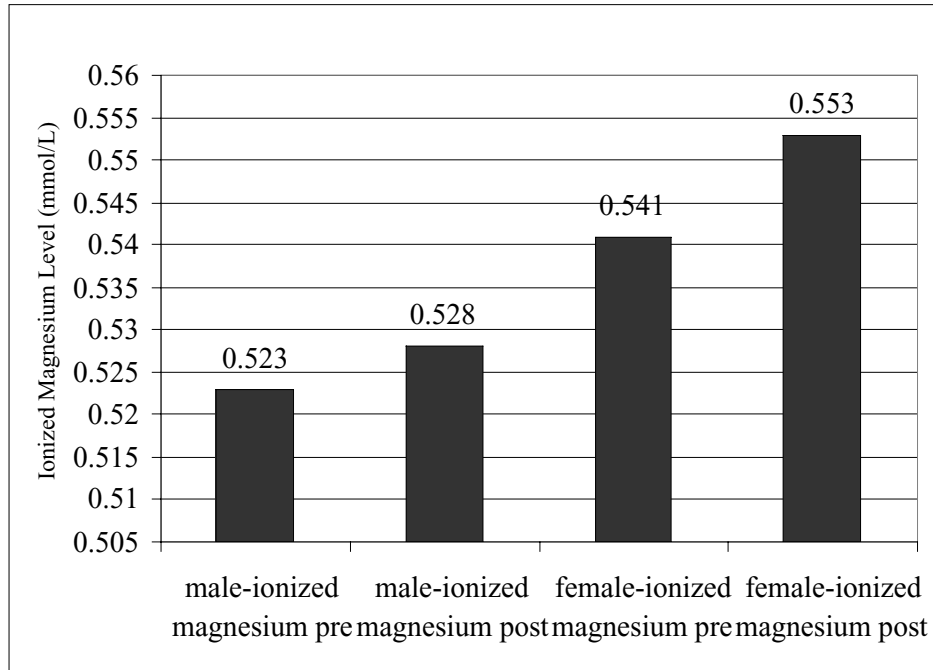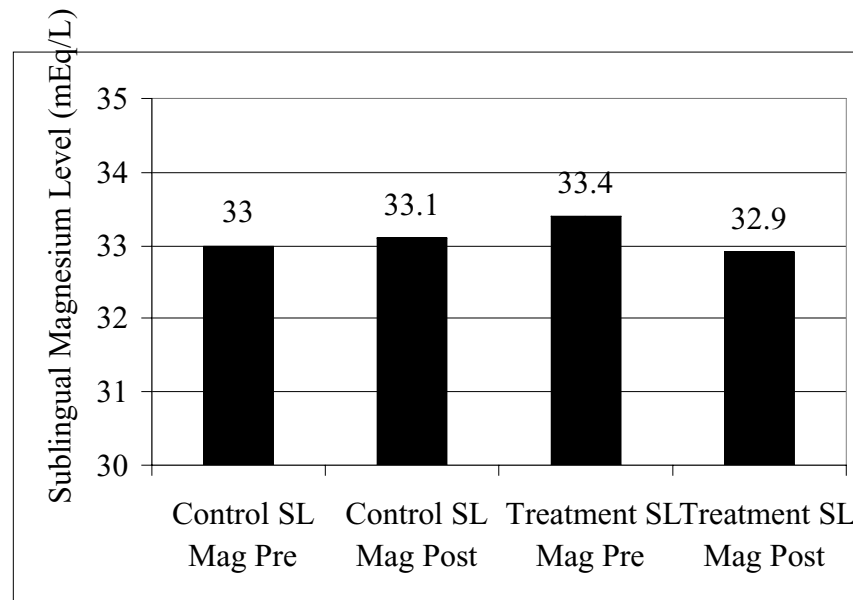**Figure 7.**

Sublingual Magnesium Levels in the Control and Treatment Groups

Again the males and females were separated and group analysis was performed. Sublingual (tissue) magnesium levels decreased from 31.3 mEq/l to 31.0 mEq/l among the men in the magnesium treated group, resulting in a p value of .795. A decrease in sublingual (tissue) magnesium levels among the women in the magnesium treated group was also noted from 33.7 mEq/l to 33.2 mEq/l, which corresponds to the p value of .752.
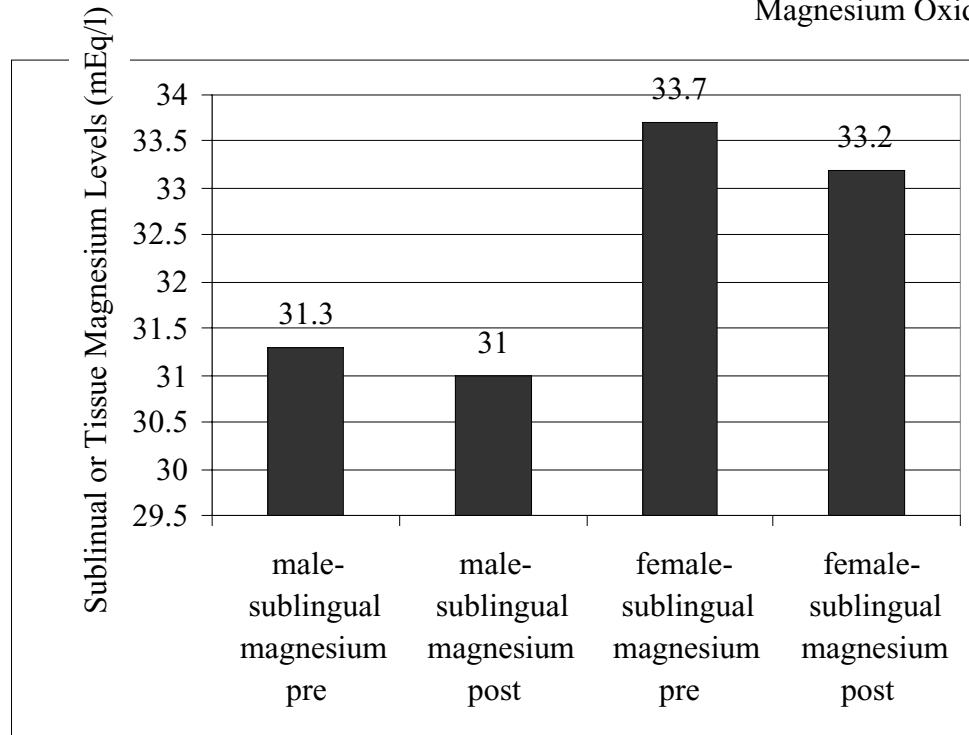
Figure 8.

Sublingual (Tissue) Magnesium Levels in the Treatment Group
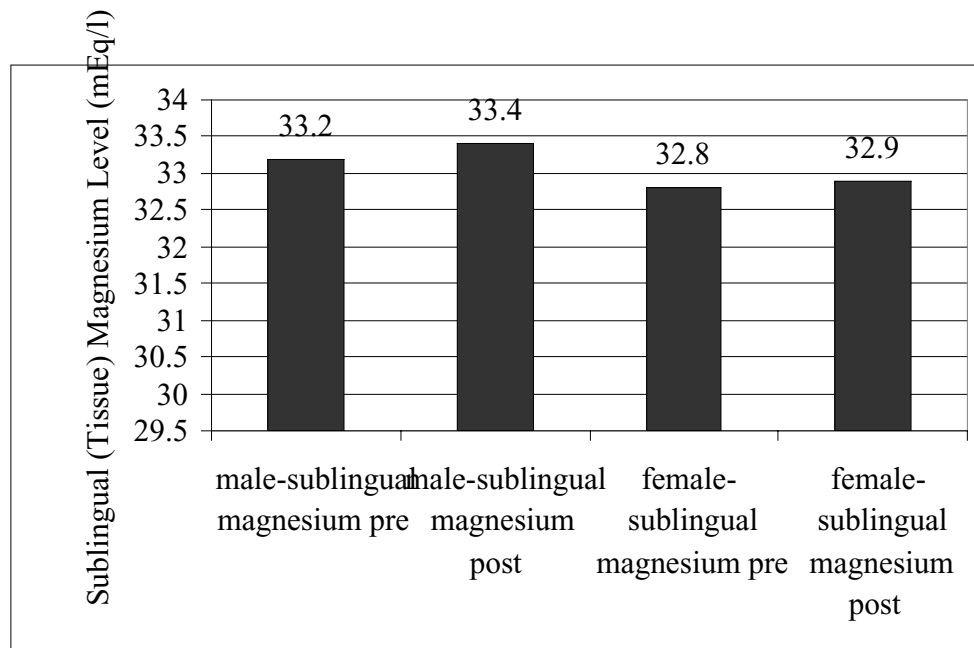
Figure 9.

Sublingual (Tissue) Magnesium Levels in the Control Group

In addition to the data analysis dedicated to the original prestudy research questions, other valuable information was learned during the data analysis. Within the magnesium treated group, paired t-tests indicated a significant decrease (p=.04) in diastolic blood pressure from 85.2 mmHg to 79.4 mmHg (see Figure 10). The average mean diastolic blood pressure decreased 5.9 mmHg in this group. These data support previous findings of magnesium s calcium channel blocking effects.
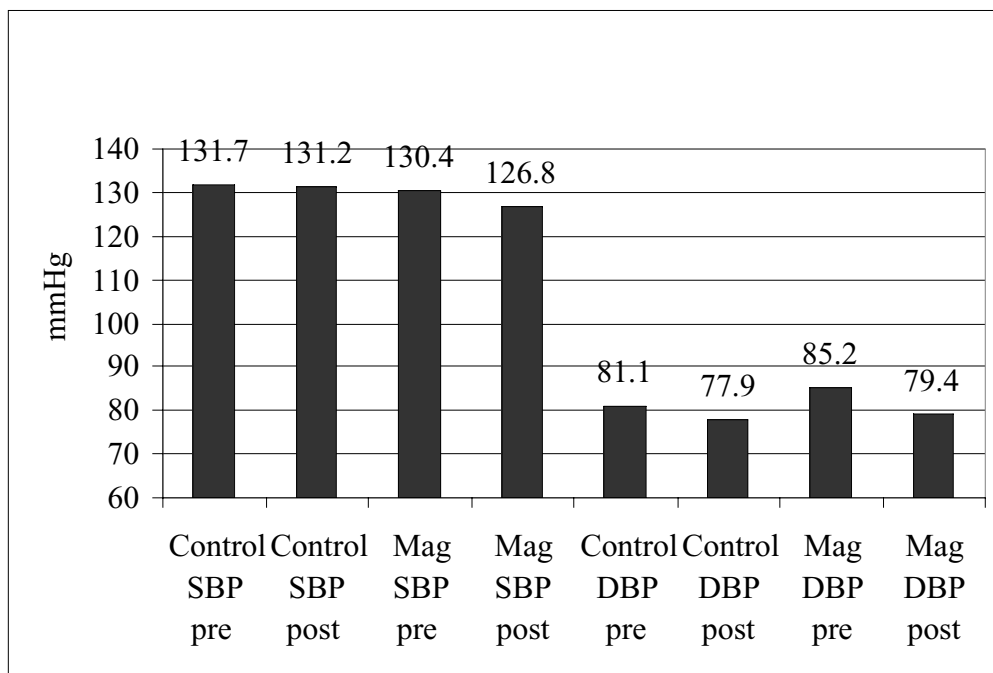
Figure 10.

Change in Blood Pressure within Both Groups

Also important in assessing magnesium levels in the clinical setting is the

correlation between the serum ionized, total, and tissue levels. In this trial there was a

very strong correlation of the total serum and serum ionized magnesium levels

($r=.896; p<.001$). (see Figure 11 and Figure 12). Total serum magnesium levels were not

significantly correlated to sublingual (tissue) magnesium levels ($r=.055; p=.828$).
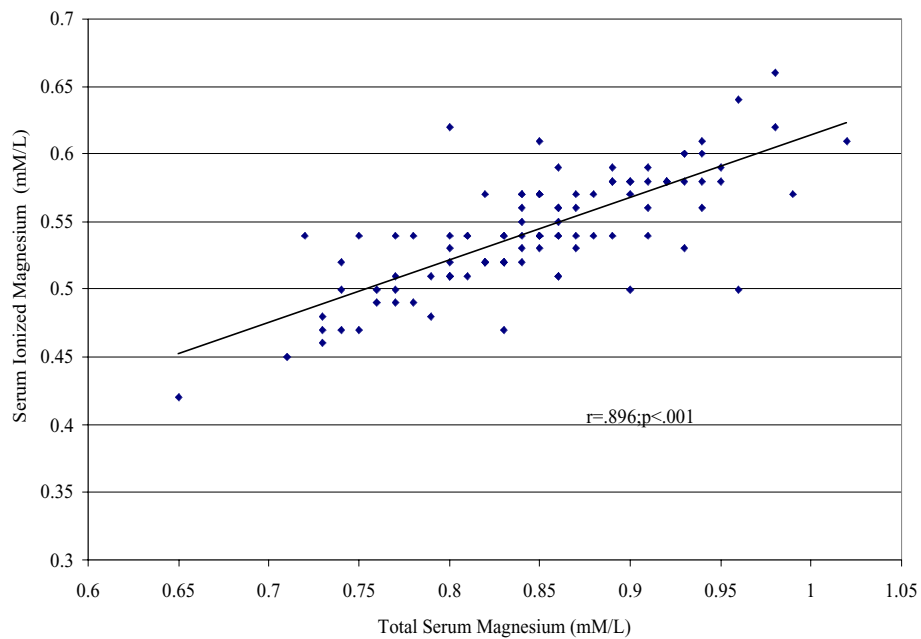
Figure 11.

<u>Correlation of Serum Ionized and Total Serum Magnesium Levels</u>
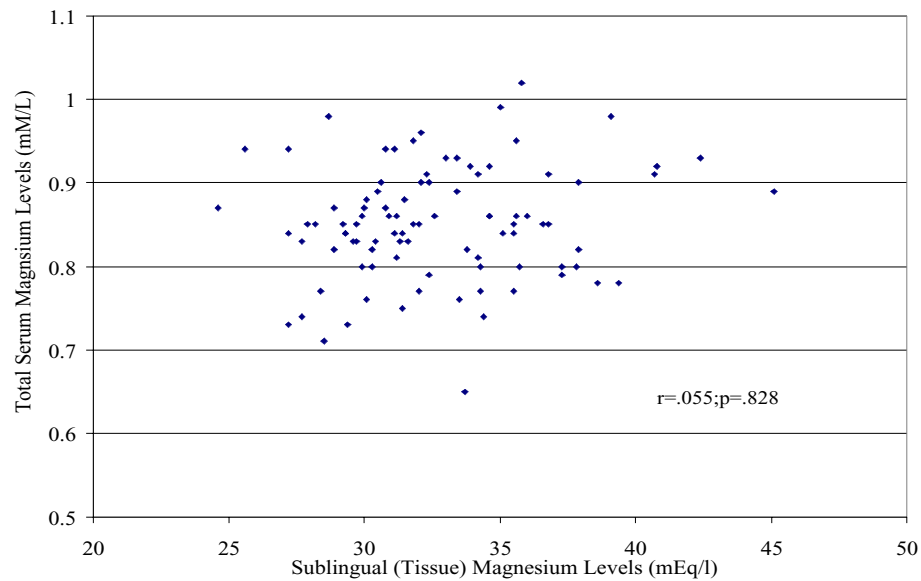
Figure 12.

Correlation of Sublingual (Tissue) and Total Serum Magnesium Levels

Interpretation of Data

Unexpected results were obtained at the completion of this trial. The original

hypothesis was that magnesium supplementation would decrease the complaints of

chronic pain and improve quality of life. This hypothesis was not supported by these

data. Possible reasons for these findings include the following.

The sample contained more females than males. The chronic pain response may

significantly differ in males and females and this may have affected the study findings.

The concurrent analgesic regimen was not controlled in this trial. Therefore, patients

continued to take their prescribed medications, and sometimes the regimen was altered or

changed according to their needs during the two-month trial. To have attempted to

control this variable by withholding prescribed medications from the study participants would be unethical.

For purposes of this study, each patient continued the narcotic pain regimen prescribed by a physician from the pain management center. Each of the patient s prescribed medications (see Appendix A) was converted to an equal value of orally administered morphine in a milligram per hour (mg/hr) basis using a conversion chart obtained from the world wide web (Purdue Pharma L.P., 1997). The mean average consumption of morphine equivalents increased 1.06 mg/hr within the magnesium treated group. A paired t test on this increase in consumption resulted in a p value of .094, which indicates a trend toward an increase in narcotic consumption in this group.

In the control group, the mean average narcotic consumption increased 1.01 mg/hr (morphine equivalents). When comparing this difference the p=.015, which indicates a significant statistical difference. Therefore, this group consumed more narcotics on a daily basis at the end of the two-month trial.

The difference in narcotic consumption was also compared between the two groups. Prior to enrollment in the study, the average narcotic consumption in the control group was 8.01 mg/hr of morphine equivalents and the magnesium group consumed and average of 4.57 mg/hr. An unpaired t test of these values resulted in a p of .064, which indicates a strong trend toward a significant difference in narcotic consumption between the two groups. After the two month trial, the mean average narcotic consumption in the control group was 9.02 mg/hr and in the magnesium treated group was 5.63 mg/hr (morphine equivalents). This unpaired t test produced a p of .091, which is also represents a trend toward a significant difference in narcotic consumption.

The age range of participants in this trial was 26 to 60 years. The pain response may differ across the age span. In addition, pain and quality of life are subjective and difficult to measure accurately.

This study assessed low back pain, but the exact nature of the pain was not defined. The pain response could present differently for different pathophysiology. For example, the pain response from spinal stenosis may be quite different from the response from a herniated disk, but both disease states are classified as low back pain .

As with any prescribed regimen, patient compliance is an important factor in assessing outcomes. Patients with chronic pain present interesting and challenging issues related to compliance in the clinical setting. The lack of an acceptable euphoric effect from magnesium oxide may have decreased compliance. Compliance in this study may have been a significant factor that was difficult to control. .

Serum ionized or sublingual (tissue) magnesium levels did not show a significant increase in the treatment group after the two month trial. This could be attributed to the poor oral absorption of magnesium. Although magnesium oxide is one of the most commonly prescribed magnesium supplements, it is the least soluble oral magnesium preparation and this could have had a significant impact on absorption during this trial. According to Klein (1994), magnesium oxide has poor bioavailability. When administered at therapeutic doses a cathartic effect may result. Further magnesium loss may then occur.

CHAPTER V: SUMMARY

Conclusions

The initial hypothesis that chronic pain could be reduced and quality of life could

be improved with oral supplementation of magnesium oxide is not supported by the

results of this two month clinical trial. A randomized placebo-controlled design left the

researcher and the patients blinded during the two month regimen. This design controls

for the bias of extraneous variables.

It was hypothesized that if magnesium levels were low, then pain scores would be

high. The data collected do not completely support this hypothesis. Quality of life scores

and pain scores were not significantly related to serum or tissue magnesium levels.

A significant correlation was not found between serum ionized magnesium levels

and pain scores or total serum magnesium levels and pain scores. On the other hand, a

modest correlation ($p=.04$, $r=-.474$) was noted when comparing sublingual (tissue)

magnesium levels and pain scores. This information could prove beneficial in the clinical

setting when caring for patients with chronic pain.

Finally, oral supplementation of magnesium oxide did not produce a significant

increase in serum ionized or sublingual (tissue) magnesium levels. There are several

possible reasons for these results. First, as previously mentioned, oral magnesium is

poorly absorbed within the gastrointestinal tract. In fact, the majority of orally ingested

magnesium is excreted in the feces. Secondly, patient compliance with this regimen is

questionable. Finally, patients with chronic pain often require a multi-faceted plan of

care. These factors either alone or in combination could explain the lack of a significant

increase in the magnesium levels in the treatment group. Thus, since magnesium levels

did not rise significantly, it is difficult to state that the supplementation of magnesium is not beneficial to the patient with chronic pain.

Although the magnesium levels did not significantly rise in the treatment group, there was an increase of 0.011 mM/L in ionized magnesium levels. This small increase could account for the decrease in diastolic blood pressure (5.9 mmHg) noted in the treatment group. This response is consistent with the known physiology of magnesium and its effect on smooth muscle.

When assessing concurrent narcotic consumption in the treatment group, an increase of 1.06 mg/hr (morphine equivalents) was noted. Although the corresponding p value of .094 does not reach statistical significance, it is evident that this group consumed more narcotics on a daily basis at the end of the two-month trial. Despite an increase in narcotic consumption and magnesium supplementation, the reported pain scores in the treatment group increased.

The control group actually reported a statistically significant decrease in pain over the two-month trial. One possible explanation for this could be related to the consumption of narcotics in addition to the placebo. The mean average narcotic consumption in the control group increased 1.01 mg/hr (morphine equivalents), which resulted in a p value of .015. This calculated p value indicates a significant increase in narcotic consumption and could explain the decrease in reported pain.

The comparison of narcotic consumption between the two groups produced interesting data. The control group started the study consuming more narcotics (3.44 mg/hr morphine equivalents) than the treatment group. The unpaired t test resulted in a p of .064, which indicates a strong trend in the difference in narcotic consumption between

the two groups. This pattern was also evident at the completion of the two-month trial

where the control group was consuming 3.69 mg/hr more morphine equivalents than the

treatment group. This resulting unpaired t test p value=.091, which again indicates a

trend toward a difference in the narcotic consumption between the groups. Despite

randomization efforts, the narcotic consumption was quite higher in the control group

which could account for the decrease in their pain scores.

Recommendations

The replication of this study would be best performed on a larger sample with a

more defined pain pathophysiology. This would eliminate some of the possible

confounding variables present in this study. The volunteers will probably need to remain

on a prescribed pain therapy in addition to the study drug, but this therapy could be better

defined at the beginning of the two month trial. Ideally, all patients should be on the

same therapy in order to control confounding variables. It is important to maintain the

randomization of patients, but in order to generalize this study to a larger population, a

more diverse ethnic population is necessary while incorporating a wide range of ages.

Comparisons could then be made among different age groups. It would also be desirable

for the composition of the treatment and control groups be equalized for gender and age.

Compliance is a difficult issue to control at any time, but the possibility of offering

some reward at the completion of the study may enhance compliance. Magnesium

supplementation does not produce any sort of euphoric response upon ingestion or

immediately decrease pain. Since the patients may not recognize an obvious decrease in

their pain, a monetary or other reward may entice them to continue with the study

protocol.

Another important aspect that should be considered in future research is the bioavailability of the magnesium preparation being prescribed. Other oral magnesium preparations offer higher solubility in sustained release forms. According to Klein (1994), these sustained released forms may offer three advantages: (a) reduced nausea and diarrhea, (b) avoidance of the bolus effect and thereby reducing the amount of magnesium lost in the urine, and (c) the delayed release may provide better absorption in the distal intestine.

Although data obtained in this study do not support the proposed hypotheses, valuable information was obtained. Further questions have also been formulated and this new information can be applied to future research projects. Chronic pain can be very difficult to manage in the clinical setting. It is important that health care professionals continue to seek other options for patients experiencing chronic pain in hopes of improving their quality of life.

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APPENDICES

Appendix A: Data Collection Tool from Dulles Pain Management Center

Appendix B: Informed Consent Form

Appendix A

Data Collection Tool from Dulles Pain Management Center

Patient_____Date_____Time_____
1. CHIEF COMPLAINT: (what hurts??)_____

2. <u>Current Level of Pain</u>   0=No Pain   10=Horrible pain
_____ On average (0-10)   _____least pain (0-10)   _____most pain (0-10)
3. Rate the Effect of Pain on your Life. Select a Number between 0 and 10.
0=no problem   5=some problems   10=lots of problems
                    <u>When you take your meds</u>   <u>Without meds</u>

	When you take your meds	Without meds
General activity (0-10)	_____	_____
Mood (0-10)	_____	_____
Walking ability (0-10)	_____	_____
Work routine (0-10)	_____	_____
Relations with other people (0-10)	_____	_____
Sleep (0-10)	_____	_____
Enjoyment of Life (0-10)	_____	_____
Ability to concentrate (0-10)	_____	_____
Appetite (0-10)	_____	_____

4. Is your pain in the same location as at the prior visit? ( ) Yes   ( )No_____
5. Is your level of pain   _____greater _____less _____about the same?
6. Do you have any new medical issues since the last visit? [ ]No [ ]Yes(please describe)

7. What Medications do you currently take for your pain?

Drug	Strength	Total per day	Drug	Strength	Total per day
Dilaudid	4mg/8mg	_____	Percocet		_____
Lorcet	10/650	_____	Percodan		_____
Lortab 7.5/500	10/500	_____	Norco 10		_____
Methadone	10mg	_____	Roxicoone	5mg	_____
MS Contin	15mg 30mg	_____	Vicodin		_____
MSIR	15mg 30mg	_____	Vicodin HP		_____
Oxy-IR	5mg	_____	Vicodin ES		_____
Oxycontin	_____	_____	Valium		_____
Duragesic	_____	_____	Cloindine		_____
Klonopin	_____	_____			

Other:_____
8. Circle any of the following symptoms that may be side effects of your medications?
Nausea   dizziness   constipation   emotional irritability   diarrhea
swelling or edema   depression   skin rash   sweating   irregular menses
Difficulty urinating fatigue   itching   decreased potency   insomnia
withdrawal symptoms
other:_____
For CLINICAL USE ONLY: VITAL SIGNS: BP_____P_____R_____SaO2____

[ ]Diane Allen, RN   [ ]Roger Hall, RN   [ ]Bonnie King

Appendix B

Informed Consent

Informed Consent Form

Research Study

A RANDOMIZED PLACEBO CONTROLLED TRIAL OF MAGNESIUM OXIDE FOR ALLEVIATION OF CHRONIC LOW BACK PAIN

Introduction

You are being asked to take part in a research study. This study will be under the direction of Dr. John P. McDonough, CRNA, Ed.D., Dr. Joseph Statkus, Dr. Mark Haigney, Dr. Eugene Levine, and Jeffrey L. Schrader, 1LT, SRNA, AN. Before you decide to be a part of this research study, you need to understand the risks and benefits so that you can make an informed decision. This is known as informed consent. This consent form provides information about the research study. Once you understand the study and the tests it requires, you will be asked to sign this form if you desire to participate in the study. Your decision to participate is voluntary, meaning that you are free to choose to take part in the study.

Description of Purpose and Procedure

The Department of Nurse Anesthesia of the Uniformed Services University of the Health Sciences is carrying out this research study to assess the effects of a dietary additive in patients with chronic low back pain. This additive is a naturally occurring mineral that is found in many different foods. Adding this mineral to your diet has been shown to decrease intense episodes of pain. Approximately sixty volunteers will be asked to participate in this research study. After you consent to participate in this study, some laboratory information will be obtained from your blood and we will ask you to rate your back pain and quality of life on the provided forms.

You will then be placed in either the treatment or placebo group. The

treatment group will receive the supplement (800mg of magnesium oxide). This dosage is similar to that found in an over-the-counter magnesium supplement. The placebo group will receive a pill without the mineral supplement. The pills must be taken as instructed over a two-month period. Neither you nor the researchers will know which group you are assigned. This information is withheld from us because of the study s design. This aspect of the study is very important in order to assess the difference in the supplement levels in your blood without bias.

After the two-month period of taking the pills, we ask that you return your empty pill container to us because it will have your identification on the label. We will perform the same lab tests as before. After the lab work, you will be asked to rate your back pain and quality of life on the provided forms.

Possible Benefits

The benefits of this study are that a better understanding of chronic pain management may be learned and you may directly benefit with the reduction of your pain. Previous studies have shown a reduction of pain with the use of this supplement. There is no cost to participate in this study and the laboratory work will be provided free of charge.

Possible Risks

This dietary supplement has very minimal side effects since it is a naturally occurring mineral found in our routine daily food intake. A very low risk of diarrhea is associated with taking this mineral, but this side effect is usually only associated with taking extremely large doses. There is a possibility of a bruise and slight pain at the time the blood samples are taken.

<u>Confidentiality</u>

The results of this research study will be given to the sponsor and may be asked for

by the Food and Drug Administration (FDA) or by the United States Department of

Health and Human

Services. In addition, the Institutional Review Board at the Uniformed Services

University of the Health Sciences may see your records. Except for those people, records

from this study will be kept private unless required by law. Your name will not appear

on any documents removed from The Dulles Pain Management Center.

<u>Right to Withdraw from the Study</u>

Your participation in this study is entirely voluntary and you may withdraw from

the study at any time. Your care and relations with the faculty, staff and administration at

the Uniformed Services University of the Health Sciences or with the doctors and nurses

at The Dulles Pain Management Center will not be changed in any way if you decide to

stop the study. You should let the doctor in charge of the study know if you decide to

stop the study. You will be asked to visit the study site and return the study drug if you

decide to stop the study early. You will be told if there is any new information about the

research study, as it is ongoing, that may cause you to change your mind about

continuing your participation in the study. You are not waiving any of your legal rights

by signing this form. The doctor in charge of the study may stop the study at any time,

without your approval, if it is in your best interest.

<u>Research Related Injury</u>

This study should not entail any physical or mental risk beyond those described

above. We do not expect complications to occur, but if, for any reason, you feel that

continuing this study would constitute a hardship for you, let us know immediately. The

Department of Defense (DoD) will provide medical care at government facilities for any

members eligible for DoD care for injury or illness resulting from participation in this

research. Such care may not be available to other research participants, except in the

event of an emergency. Compensation may be available through judicial avenues to non-

active duty research participants if they are injured through the negligence (fault) of the

Government. You should not expect anyone to pay you for pain, worry, lost income, or

non-medical care costs that occur from taking part in this research study.

Questions

    If you have any concerns or questions, call 1LT Jeff Schrader at (301) 515-6232

(day or night) or Dr. John McDonough, CRNA, Ed.D. at 301-295-6565 (daytime only),

chair of my thesis committee. If you have any questions about your rights as a research

subject, you should call the Director of Research Programs in the Office of Research at

the Uniformed Services University of the Health Sciences at (301) 295-3303. This

person is your representative and has no connection to the researchers conducting this

study.

    By signing this consent form you are agreeing that the study has been explained to

you and that you understand this study. You are signing that you agree to take part in this

study. You will receive a copy of this consent form.

    If you have any questions at any time, please ask them. If at any time you believe

you have suffered an injury or illness as a result of participating in this research project

you should contact the Office of Research Administration at the Uniformed Services

University of the Health Sciences, Bethesda, MD 20814 at (301) 295-3303. This office

can review the matter with you, can provide you information about your rights as a subject, and may be able to identify resources available to you. Information about judicial avenues of compensation is available from the University s General Counsel (301) 295-3028.

I understand that I may revoke my consent, and withdraw from the study without bias at any time during the course of this research study. I do hereby volunteer to participate in this research study. The implications of my voluntary participation: the nature, duration and purpose; the methods and means by which it is to be conducted; and the inconveniences and hazards to be expected have been thoroughly explained to me. I have been given the opportunity to ask questions concerning this study, and any such questions have been answered to my full and complete satisfaction.

_____/_____   _____/_____/_____
                      Participant (PRINT/SIGN)   Date

I certify that the research study has been explained to the above individual, by me, and that the individual understands the nature and purpose, the possible risks and benefits associated with taking part in this research study. Any questions that have been raised have been answered.

_____/_____   _____/_____/_____
                      Witness (PRINT/SIGN)   Date

_____/_____   _____/_____/_____
                      Investigator (PRINT/SIGN)   Date