Spring 2022

THE EFFECTS OF FLOATATION-REST ON CORTISOL LEVELS OF PATIENTS WITH GLIOBLASTOMA GRADE IV: A CONCEPTUAL FRAMEWORK

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by

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Submitted to the School of Honors Committee

in partial fulfillment

of the requirements for University Honors Scholars

Southeastern University

2022

Acknowledgement

I would like to give a big thank you to my thesis advisors, professor Wendy Berry and Dr. Melba Horton, who guided me in my pursuit for a subject matter that is really important to me. I would also like to acknowledge my family, especially my cousin Javier Gonzalez, an angel guiding me every day. His battle with glioblastoma encouraged me to seek out an alternative pain management for those with glioblastoma. I am forever grateful for all the support and inspiration that you all have given me.

Abstract

Glioblastoma is reported to be the most aggressive and common brain tumor in adults (Davis, 2016). To help alleviate pain in patients with glioblastoma, floatation-REST (Restricted Environmental Stimulation Technique) is proposed. Such therapy has been shown to benefit chronic tension headaches, muscle tension, and other stress-related pain conditions (Feinstein, 2018). The magnesium and sulfate components of Epsom salt combined with controlled warm water allow the muscles and joints to relax. Studies show that magnesium targets the Adrenocorticotropic Hormone (ACTH) produced by the Anterior Pituitary Gland which in turn affects cortisol hormone levels to activate the body's immune defenses and eliminate the cause of pain and possible tissue recovery. This study aims to develop a conceptual framework that can be used to determine the possible effect of floatation-REST on cortisol levels of patients with glioblastoma for pain management.

KEY WORDS: glioblastoma, cortisol, cancer, hormone, sensory deprivation tank, floatation-REST, pain relief

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Introduction

Cancer has become increasingly prevalent in society today. The origins of the mutations that lead to different cancers are caused by a variety of factors. Among these are environmental, genetic, and lifestyle factors (Blackadar, 2016). Each factor can cause different types of cancers such as lymphoma, lung cancer, breast cancer, melanoma, and much more (Siegal, 2020). To counteract the high mutated disease, scientists with the help of advanced technology have come a long way to finding and defeating cancer altogether (Siegal, 2020).

In an evaluation of cancer patients, the 5-year survival rate of patients in the United States between 2009 and 2015 proved to be 67% overall across ethnicities, ages, genders, and different types of cancers (Siegal, 2020). One particular cancer though has not been as prominent to treatment as the others, is glioma. Glioma is a type of cancer that comes in many forms such as astrocytoma and oligodendroglioma (Zong, 2012). These different types of glioma are created by an overproduction of a particular glial cell. The overgrowth of oligodendrocytes, cells used to create myelin for axons, creates a tumor called oligodendroglioma. On the other hand, astrocytoma is caused by astrocytes which are cells used to do a variety of tasks. Some include synaptic support and control of the blood-brain barrier. A sub-type of astrocytoma is glioblastoma. Glioblastoma is the most common malignant brain tumor today (Thakkar et al., 2014). As neural stem cells and multipotent progenitor cells generate lineage-restricted progenitor cells that then create neurons and glial cells (astrocytes and oligodendrocytes), the complexity of the cancerous origin is difficult to identify (Zong, 2012).

Presently, glioblastoma has had a low-survival rate as treatments to cure or resect the cancer have not been successful (Davis, 2016). Despite many advancements in cancer treatment, the aggressiveness of glioblastoma, as well as the location of the tumor has made the survival rate decrease in percentage (Davis, 2016). Therefore, it has come to attention that patients with glioblastoma should be able to live a more fulfilled life with a decrease of pain and stress. Thus, the issue at hand provides a list of questions that need to be answered:

1. What therapies are currently used to alleviate pain or stress in general?
2. Would floatation-REST be well suited for alleviating pain in patients with glioblastoma?
3. Do patients live longer if the immune system is not compromised by cancer and pain/stress?

Many patients with glioblastoma do not live past five years of prognosis (Davis, 2016). Thus, it is important to find a therapy that improves their quality of life while advancements in technology are still being developed. Patients should not have to continuously rely on medication to alleviate symptoms such as pain. Holistic therapies should be researched and considered as alternatives to those medications.

Glioblastoma is an aggressive brain tumor that has had a low survival rate. The overproduction of astrocytes in the central nervous system has caused treatment to be difficult, as the nervous system is crucial to functions. Hence, a non-pharmacological modality is needed to alleviate symptoms, such as pain and stress in patients with glioblastoma. Altogether, the hope is to find an alternative pain management therapy for patients with glioblastoma in order to improve their quality of life.

Methodology

The following thesis is an extended literature review fabricated by a multitude of current and historical peer reviewed articles discussing glioblastoma, current cancer treatments, alternative pain therapies, and the systems of the human body. The information obtained was used to discuss the pathology and characteristics of glioblastoma and provide alternative pain therapies, specifically the utilization of floatation-REST therapy. Additional literature was further gathered to design an experiment utilizing floatation-REST to test the current hypothesis that cortisol levels of patients with glioblastoma grade IV will stabilize after being subjected to the floatation-REST by the end of the experiment. Preliminary data gathering was incorporated into the experimental design in order to recognize current treatments used by oncologists, and their perception of alternative pain therapies, but more specifically, the utilization of floatation-REST and the effects of magnesium in the treatment. The experiment was designed with alterations to the testing parameters following the review of limited current studies that involve floatation-REST. This information was collected primarily through databases such as PubMed and PMC using key words such as 'glioblastoma', 'floatation-REST', 'sensory deprivation tank therapy', 'the endocrine system', and 'magnesium sulfate'. Overall, this methodology functions to inform the reader of the subject at hand with current treatments for patients with glioblastoma grade IV, and viable alternative pain therapies such as the utilization of floatation-REST.

Review of Literature

Glioblastoma is the most common and aggressive brain tumor known today. It has been found that few patients live past five years of diagnosis as a result of its aggressiveness (Davis, 2016). Therefore, the science community is beginning to recognize that alternative therapies are needed to counteract or alleviate some or all the symptoms these patients have (Carlsson, 2014). Patients with glioblastoma have a diagnostic range of symptoms including, but not limited to the following: headaches, muscle tension, muscle loss, and fatigue (Davis, 2016). Following the analysis of a multitude of articles and sources, this literature review covers five general categories: (1) what glioblastoma is and how it is currently treated, (2) different types of pain that are associated with the body and cancer, (3) how cancer as a stimulus affects the endocrine system that gradually affects the rest of the body, (4) various forms of non-pharmacological therapies, (5) the effects of Floatation-REST (restricted environmental sensory therapy) on the body from different studies using different types of patients, and (6) the effects of Epsom Salt (magnesium sulfate) on the body and its various systems. It is critical to understand the importance of each patient’s pain in order to aid them properly. Patients with glioblastoma deserve to live their best quality of life, enjoying time with the people they love. Therefore, decreasing a patient's pain through alternative therapy options is vitally important.

Glioblastoma: Overview and Current Treatments

Glioblastoma Multiforme (GBM) is a type of tumor located primarily in the brain. Though it is commonly identified in the brain, it can also appear in the spinal cord by traveling through the foramen magnum of the skull and down the posterior **(**Davis, 2016). Researchers discovered that the complicated genetic profiling of GBM is established by a set of three core signaling pathways that are commonly activated. These consist of the tumor protein p53 pathway, the receptor tyrosine kinase/Ras/phosphoinositide 3-kinase signaling pathway, and the retinoblastoma pathway. The use of these pathways allows the tumor cells to escape any cell-cycle checkpoints (Davis, 2016). Despite a number of factors being associated with the cause of cancer development, it is unknown how patients get glioblastoma.

The presentation of glioblastoma at diagnosis can vary depending on the size and location of the tumor. Often, primary malignant glioblastomas occur mainly in adults, suggesting that the cells being affected reside in a full-grown brain (Zong, 2012). In diagnostic imaging, necrosis (dead cells) is the main feature of GBM that automatically makes the tumor a grade IV (Blissitt, 2014). When the tumor becomes grade IV, the survival rate diminishes to 12-15 months (Zong, 2012). Patients demonstrate symptoms of increased intracranial pressure, constant pain, and are more likely to suffer a seizure due to the tumor (Davis, 2016). In addition to these symptoms, the destruction of the brain cells often leads to a deficit in cognitive and emotional function (Zong, 2012). For example, the patient may feel exhausted or anxious as their emotional status is altered. As the tumor encompasses parts of the brain, it is highly likely that the damage of cortical and subcortical areas increases patient behavioral problems. Including the symptoms of the tumor, cancer patients are unable to cope mentally with the thought of having cancer, particularly patients with glioblastoma grade IV who have a definitively low survival rate. They show signs of psychological distress and mood issues such as depression, anxiety, and suicidal thoughts (Boele, 2015). It therefore is important to understand not only the symptoms, whether there are direct effects of the tumor on the brain or a possible psychophysiological condition of the patients.

Treatment of glioblastoma requires a multidisciplinary approach. Current treatment includes maximal surgical resection, radiation, as well as the consumption of oral chemotherapy agent followed by chemotherapy (Davis, 2016). Surgical resection is classified as gross total resection (GTR) and subtotal resection (STR) (Carlsson, 2014). In STR, the tumor is difficult to undergo full resection, as the location of these tumors are around areas that are very important for an individual to function. For instance, a tumor may display itself in the prefrontal cortex, the anterior portion of the brain where critical thinking and personality takes place. If this area is fully resected, the patient may have a personality change. As a result, surgery is not a promising option for patients. An incomplete full resection thus leads to further progression of the tumor as cells remain in the untouched areas. Through the progression of research, there has been an advancement in surgical and preoperative mapping techniques to get better results throughout the years. In the face of all the improvements in technology, it is difficult to determine the normal brain from the tumor (Davis, 2016).

Additionally, another form of treatment following resection is chemoradiation. In this stage of treatment, it has been determined that radiation therapy with TMZ chemotherapy is more effective than radiation therapy alone (Davis, 2016). Although, TMZ is a risk due to this type of chemotherapy potentially damaging the healthy cells in the location being targeted by the radiation (Carlsson, 2014). Many patients will undergo chemoradiation in hopes that the tumor will dissipate, yet despite the long use of treatment, GBM has found its way to resist and progress (Fernandes, 2017).

Currently, there are ongoing clinical trials and research to improve the state of those that are diagnosed with GBM (Carlsson, 2014). For example one treatment includes the use of monoclonal antibodies. The antibodies recognize cell-surface receptors and ligands, hence preventing receptor signaling. Furthermore, the secretion of vascular endothelial growth factor (VEGF) by the GBM is blocked by the antibody being injected thus reducing the size of the tumor (Carlsson, 2014). Ultimately, based on current studies, more research should be done to increase patient's survival rate while also enhancing their quality of life.

Pain and Stress Caused by Cancer

Despite recent advances in comprehending cancer and developing the numerous ways to treat varying types of tumors, the treatment of cancer pain has been slow in progression (Chwistek, 2017). Pain can be produced in any form from body aches and sore muscles to pain induced by cancer. In this case, glioblastoma grade IV comes with chronic headaches and muscle tension in various areas of the body. Because GBM has a low survival rate, it should be important to understand the pain that these patients live through in their daily struggles.

A factor that is manifested by pain or a stimulus is known as a stressor. A stressor is a stimulus that triggers a physiological response often known as stress or anxiety. Those physiological responses are threats to the safety and well-being of the body, which can be pain or non-pain related (Hannibal, 2014). When a foreign stimulus is presented to the body, the amygdala is triggered releasing hormones such as epinephrine and norepinephrine to destroy any foreign invader. The prolonged response then triggers the endocrine system to respond back with a series of regulated hormones, which maintain homeostasis within the body whether it is controlling growth, development, or metabolism (Hiller-Sturmhöfel, 1998). Such functions are produced by the endocrine glands, including the hypothalamus, the pituitary gland, the adrenal glands, the thymus, the gonads, the pancreas, the parathyroid glands, and thyroid glands (Figure 1) (Hiller-Sturmhöfel, 1998).

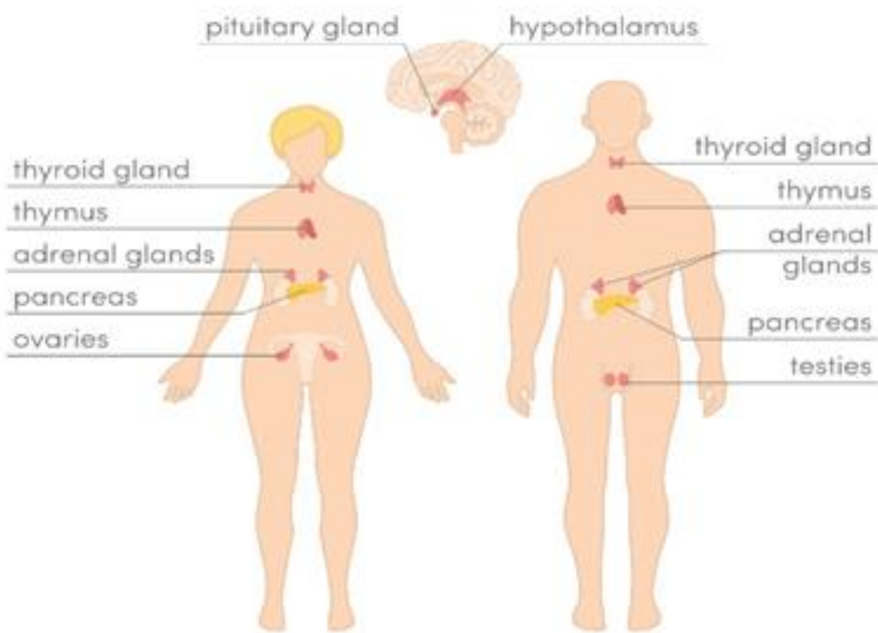


Figure 1. The location of the hormone- producing organs in the body (Maryniack, 2018).

To maintain homeostasis and obtain tight control, regulations of bodily functions are achieved by the use of multiple hormones that regulate one another. The cascade of hormones is initiated by the hypothalamus. From the hypothalamus, the releasing hormones are transported via blood to their target glands which in turn influences multiple organs and systems. One mechanism that controls this complex system is called the negative feedback loop. To ensure that there is not an excess of one hormone in the body, the negative feedback loop shuts off the hypothalamic or pituitary hormone release (Hiller-Sturmhöfel, 1998).

The three main glands under focus in this research are the hypothalamus, pituitary, and adrenal glands. The hypothalamus is a region of the brain that controls many functions such as eating and drinking, circadian rhythm, emotional states, blood pressure, and much more. As a result of the hypothalamus being part of the central nervous system, it serves as a bridge between the nervous and endocrine system. For example, the hypothalamus will respond when the brain transmits a nerve impulse affecting external or internal factors that disrupt homeostasis by releasing a series of hormones relative to the function necessary for homeostasis regulation. The gland that receives these hormones is known as the pituitary gland. The pituitary gland is divided into two parts: the anterior pituitary and the posterior pituitary. The anterior pituitary produces hormones such as adrenocorticotropic hormone (ACTH), gonadotropins, thyroid-stimulating hormone, growth hormone, and prolactin. The posterior pituitary stores two hormones that include vasopressin and oxytocin that are produced by the hypothalamus (Hiller-Sturmhöfel, 1998). In need of these hormones, the adrenal gland receives them via a release into the bloodstream in order to reach their target. For example, the adrenal gland releases cortisol to provide a multitude of functions (figure 2) (Hannibal, 2014). Cortisol levels then rise to provide energy to cope with a stress-related stimulus or escape any danger-related situation. If the stimulus is prolonged, cortisol levels will plummet, as the hypothalamic-pituitary-adrenal (HPA) axis ceases to function properly. Through the application of these physiological functions, specifically to patients with glioblastoma, it can be inferred that levels of cortisol will fluctuate as pain can be either chronic or acute.

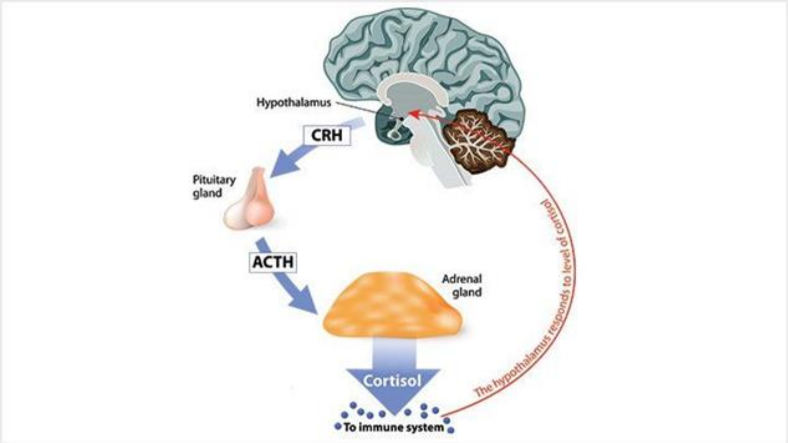


Figure 2: The Negative Feedback Loop of Cortisol Release (Konkel, 2018).

Stress can have a wide variety of effects stretching from brain function to various systems being affected. While analyzing articles about stress, Yaribeygi (2017) found that there is a direct correlation between stress and the body's immune system. The physiological response that the body encounters can lead to an inhibition of the immune system by decreasing the activity of cytotoxic T-lymphocytes and natural killer cells. Therefore, malignant cells such as cancer cells are able to expand with ease (Reiche et al., 2004). Other diseases that have been linked to stress include mental illnesses such as depression and anxiety disorders. When a person is in a state of chronic stress, the neuroimmune axis can be overstimulated causing neuroendocrine/immune imbalances leading to such mental illnesses and more (Mariotti, 2015).

To counteract the symptoms of pain, anxiety, and mood disturbances, there are complementary therapies that are able to help. Such therapies include acupuncture, massage, and other methods. The utilization of massage therapy has demonstrated a slow relief of pain in most patients. Similar to massage, acupuncture through studies has shown promise for pain relief benefits. It has been shown to reduce chronic and acute pain (Deng, 2009). Another form of therapy that has been used to alleviate symptoms of physical and emotional pain is mind-body techniques. This therapy has been found to alter the perception of pain or emotional disturbances (Deng, 2009). Hypnosis and imagery training can reduce the use of analgesic use thus reducing side effects of analgesics. While these therapies have shown to help many patients in studies, there are limitations to all of these therapies. For this reason, floatation-REST (restricted environmental sensory therapy**)** should be considered as an option as well. This type of therapy can reach patients that would not otherwise be reached by the therapies available now.

Floatation-REST as an alternative therapy

Floatation-REST is a type of therapy that involves an enclosed tank which can be easily opened and closed from the inside as seen in figure 3 (Bood, 2009). The individual enters into the tank filled with a minimum amount of water saturated with a high concentration of Epsom salt (magnesium sulfate) (Feinstein, 2018). Because Epsom salt concentrate increases the density of the water, a high salt concentration produces a high enough density giving individuals the ability to float effortlessly. The tank is built to prevent any heat from escaping, as well as any sound or light to enter in order to minimize sensory input (Bood, 2009). This type of therapy has been circulating for more than 50 years, but it has not become popular until recently due to the increased availability of pools and spacious tanks (Feinstein, 2018).

Figure 3: A floatation-REST tank with an optional closed hatch in an enclosed room (Ashland Source, 2020).

As a result of limited studies utilizing isolation tank therapy specifically on patients with glioblastoma, research studying these patients with similar symptoms were analyzed. Initially, a study by Feinstein and his colleagues (2018) determined the effects of floatation-REST on symptoms of anxiety, stress, and depression. Within this study, seventeen patients were selected at random across a variety of anxiety and stress-related disorders. As a point of reference, thirty healthy and non-anxious patients were also selected at random to participate. In the study, the self-reported measurements the authors administered included baseline measures, pre/post-float measures, and follow-up questions. These measurements ensured there was sufficient data to cover all possible questions encompassing the concept of floatation-REST as a possible therapy. Each group participated in the open float pool created by the Laureate Institute for Brain Research to exclude any feelings of claustrophobia. Altogether, the seventeen patients with disorders reported to have a significant reduction in stress, depression, and pain while also improving their mood. Following the completion of the study, it was concluded that the effects of the floatation-REST were greatest concerning the most severely anxious participants (Feinstein, 2018). The results of this article positively display the effects of the floatation-REST on symptoms that negatively affect an individual.

Jonsson and Kjellgren (2016) assessed general anxiety disorder (GAD) symptoms before and after the use of floatation-REST therapy. The patients were placed into two groups: a control group and a treatment group. Prior to treatment, questionnaires provided a multitude of measurements such as worry, general anxiety disorder, depression rating, sleep quality, emotional regulation, mindful attention awareness, and the experienced deviation from normal state. The study lasted twelve weeks where the patients were able to float in an isolated tank of water with concentrated Epsom salt. The results demonstrated a positive correlation between the symptoms of the treatment group and the treatment itself. Most of the measurements under analysis decreased in intensity after the use of the treatment tanks, hence providing more support in the utilization of the restricted environmental sensory tanks as a form of therapy for patients with glioblastoma who may experience similar symptoms. The authors also found it interesting that floatation-REST significantly improved GAD symptoms despite the fact that GAD was considered a treatment-resistant disorder (Jonsson, 2016). Overall, this article reinforced the topic at hand regarding the potential positive effects of utilizing flotation-REST therapy in the treatment of the patients experiencing glioblastoma.

Finally, the article by Kjellgren and Westman (2014) evaluated the effects of healthy individuals who participated in floatation-REST. The study randomized sixty-five participants from different business companies into a control group and treatment group. Similar to the previous studies, the participants were given questionnaires measuring psychological and physiological variables before and after the treatments. The study lasted a total of twelve sessions where each session lasted forty-five minutes. At the conclusion of the study, symptoms such as stress, anxiety, depression, and worsened pain decreased while optimism and sleep quality increased within the treatment group. On the contrary, the control group did not show a difference in the observed psychological and physiological measurements after the treatment (Kjellgren, 2014). Thus, this article has proven that those individuals who do not suffer from an illness or a disorder may also benefit from floatation-REST and its positive properties.

All three articles have had similar results in alleviating the patient's conditions, such as a decrease in pain, stress, anxiety, and depression. By utilizing the body-temperature, water, and Epsom salt properties, the muscles relax and all functions of the organ systems return to normal. Body systems such as the endocrine system that were being overused are able to regulate themselves by using negative feedback loop, thus allowing the body to live in homeostasis. For example, the cortisol levels that deal with stress and pain when normalized could result in a decrease in the levels of stress and pain.

Epsom Salt

Epsom salt also known as magnesium sulfate is the main component used in floatation-REST therapy. The high concentration of the salt is what allows individuals to float in the water effortlessly by adding mass to the water without additional volume. In practice, with the addition of water, the Epsom salt dissociates into magnesium and sulfate ions which are able to permeate through the tough layer of skin known as the stratum corneum (Elbossaty, 2018). In a study conducted by Navin Chandrakanth Chandrarasekaran et. al. (2016), magnesium was found to permeate through human skin when applied topically. Before the experiment, the authors postulated that the magnesium ions could potentially move through the pores or the hair follicles through bulk diffusion. The hypothesis was investigated in a number of ways. The authors obtained excised human skin from patients that underwent abdominoplasty. For the first experiment, they applied deionised water and 5 mM $MgCl_2$ solution for 30 minutes at 23-25 ℃ using the upper chamber of a franz cell (Navin Chandrakanth Chandrarasekaran et. al., 2016). Using a Zeiss Primostar microscope and Zeiss AxioCam Erc 5s, the group conducted another experiment to see if $MgCl_2$ permeated through hair follicles by plugging the hair follicles with acriflavine solution. Lastly, they experimented with 52 mM and 1.9 M $MgCl_2$ solutions for 5, 15, and 60 minutes to investigate the effects of concentration and time on the permeation of magnesium. From the experimental results using skin, $MgCl_2$, and indirect staining of magnesium ions, the authors concluded that magnesium is capable of permeating through the epidermis, especially at a faster rate when the hair follicle orifices are open. They also observed a greater influx of magnesium ions within the body when the authors applied an increased concentration of $MgCl_2$ on the skin for 60 minutes.

Another study, “Permeability of Human Skin to Selected Anions, and Cations - In Vitro Studies" by Halina Laudańska el. at. (2002) also examined ion diffusion through the human skin. By using an in-vitro system, the authors were able to evaluate Mg^{2+}, Ca^{2+}, NO_3^-, and SO_4^{2-}. They used skin samples from mammectomized breasts of 27 breast cancer patients that were frozen until utilized. The skin samples were placed in the in-vitro system where an ion chromatography method was used to determine cation and anion levels. Laudańska el. at. (2002) concluded from multiple experiments that magnesium, calcium, sulfate, and nitrate ions are able to permeate through the human skin via various routes of ion penetration.

There are a variety of benefits of Epsom salt. Some of the medical benefits include: body relaxation, pain and muscle relief, improvement of muscle and nerve function, and detoxification effects. Magnesium has been found to be a cofactor in over 300 enzymatic reactions (Gröber, 2015). Some of those reactions are microscopic; however other reactions such as the regulation of muscle contractions and blood pressure provide a much greater reaction (Gröber, 2015). In regards to body relaxation, the magnesium ions control the influx of calcium at the cell membrane while also producing serotonin, a neurotransmitter in charge of positive satisfaction (Grober, 2015). The regulation of calcium through the inhibition of influx can be seen in figure 4.

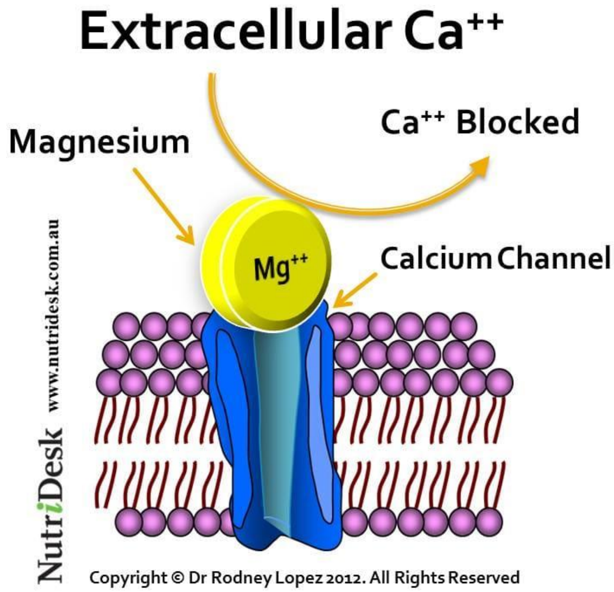


Figure 4: The magnesium ion blocks calcium from entering the cell thus preventing muscle contraction (Lopez, 2012).

Magnesium not only plays a role in body relaxation, it also inhibits nerve receptors linked to the area of pain and regulates the release of neurohormones in order to relieve pain or muscle tension. To improve the function of nerves and muscles, inflammatory responses such as a release of pro-inflammatory proteins decrease due to the cellular magnesium increasing in the body. Lastly, the sulfate ions in Epsom salt are used to help the body pump heavy metals and toxins out. In order for the body to be able to perform the task, cells need energy (ATP) to be able to pump out the toxins. As a result, Magnesium assists in the generation of energy in the cells (ATP) (Elbossaty, 2018). Therefore, the individual is able to de-stress, relax, and feel energized after a session in the flotation-REST therapy.

Magnesium is a very important factor that can affect the body greatly, such as affecting cortisol and the hypothalamic-pituitary-adrenal axis. One study by Sartori (2012) assessed how important magnesium deficiency was on the HPA axis. Through research by Sartori, it has been found that magnesium controls the productivity of the HPA axis (Murck and Steiger, 1998). This raised the question regarding the correlation between the two variables. They split mice into two groups: a control and an experimental. The experimental group received a magnesium deficient diet as well as either desipramine or paroxetine via drinking water while the control group received a normal magnesium-based diet. At the end of the 12-week study, the results displayed the magnesium deficient mice having an increase in the ACTH hormone as compared to the control group. This outcome is due to the increase of transcription of the prepo-CRH in the paraventricular hypothalamic nucleus (PVN) (Sartori, 2012). Furthermore, the increase of the ACTH hormone proves that magnesium does play a role in the activity of the HPA axis thus demonstrating that magnesium can inhibit the overall production of cortisol.

Proposal

The objective of this proposed study is to investigate the effects of floatation-REST on cortisol levels in patients with glioblastoma grade IV. Floatation-REST has been shown in the previous studies to have beneficial effects on the human body. Such treatment has been shown to benefit chronic tension headaches, muscle tension, and other stress-related pain conditions. Based on the results of these studies and the research gathered, it is hypothesized that the patients using floatation-REST with Epsom salt will have a stabilization in cortisol levels and decreased pain than the control group.

Experimental Design

Preliminary research

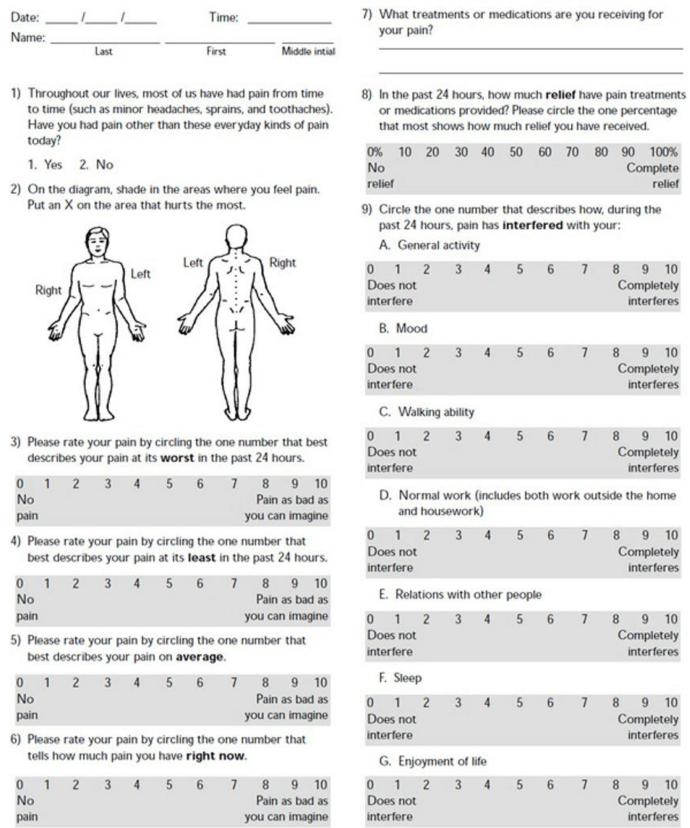
Data will consist of analyzed online surveys from licensed oncologists in order to gather medically-based information regarding their professional opinions on alternative pain therapy, specifically floatation-REST. Thirty Florida licensed oncologists will be selected via a convenient sampling, non-experimental design with the assistance of a local hospital. A PowerPoint detailing floatation-Rest research will be provided as the study intervention. This intervention will demonstrate the potential effectiveness of floatation REST as a pain management treatment alternative for patients with glioblastoma grade IV. The PowerPoint will also provide specific details regarding the connection between magnesium sulfate utilized in floatation-REST and the inhibition of pain. Cortisol will also be highlighted as a biomarker, indicating that the magnesium sulfate in floatation-REST was effective at reducing pain. The data for this study will be collected from a combination of survey and interview questions via Qualtrics. All oncologists will receive a mix-methods questionnaire that contains seven questions and an informative PowerPoint via email. Of those seven questions, four questions are survey questions that include the use of the Likert scale. In order to obtain concrete data and see patterns within the results, all participants will receive the same questions and PowerPoint that can be observed in Appendices A and B. The results of the survey will help the researchers determine which oncologists will be interested in co-investigating this study, as well as aid in the recruitment of patients with glioblastoma grade IV.

Participants

Inclusion criteria include patients with glioblastoma grade IV between the ages of 30 - 48 with their physician's approval from various hospitals in Florida. Fifty participants will be recruited to volunteer using resources from the affiliated oncologists on the research team. These participants will be randomly assigned between the experimental and control groups. The former will consist of 25 participants receiving floatation-REST with Epsom salt and the latter will consist of 25 participants using floatation-REST without Epsom salt.

Measures

Each patient will have their plasma cortisol levels measured and pain evaluated using the Brief Pain Inventory scale before and after floatation-REST for 60 minutes. The plasma cortisol levels will serve as a biomarker to indicate whether the physiological response to pain has reduced after the utilization of floatation-REST thus giving unbiased results. Each test will be administered at a local Labcorp. As for the Brief Pain Inventory scale, it is a self-administered questionnaire that identifies pain intensity and pain interference as seen in figure 5 (Poquet et. al., 2016). The questionnaire will serve as a second metric that will help determine whether floatation-REST is effective at reducing pain.



Date: ____ /____ /____ Time: __________
Name: ______________ ______________ ________
Last First Middle intial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

1. Yes 2. No

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

Right Left Left Right

3) Please rate your pain by circling the one number that best describes your pain at its **worst** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **least** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on **average**.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tells how much pain you have **right now**.

0 1 2 3 4 5 6 7 8 9 10
No pain — Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

8) In the past 24 hours, how much **relief** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10 20 30 40 50 60 70 80 90 100%
No relief — Complete relief

9) Circle the one number that describes how, during the past 24 hours, pain has **interfered** with your:

A. General activity

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

C. Walking ability

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

D. Normal work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not interfere — Completely interferes

Figure 5: The following Brief Pain Inventory Scale short form questionnaire is given to the patients to assess their pain intensity and pain interference. There are a total of nine questions with subsections within question nine (The University of Texas MD Anderson Cancer Center, 2022).

Floatation tanks

The parameters of this study are built on prior research established by the multiple studies evaluated in the literature review. In this study, the floatation tank will be 8 ft. long and 4.5 ft. wide. One tank will be filled with 10 inches of water saturated with Epsom salt (magnesium sulfate), while another tank will be filled with water and no Epsom salt. The water temperature will be held at a constant temperature of 35 °C. The tanks will be held in quiet rooms in order to block out any sound or disturbances. When participants enter the tank, participants are encouraged to close the hatches of the tank. Latches are available inside the tank if participants would like to exit the tank. A blue LED light will also be available to participants if they need it, but they are encouraged to leave the lights off.

Procedure

The experiment will take place between 1 PM and 5 PM. Before entering the tanks, each patient will have their blood drawn to test cortisol levels and fill out a brief pain inventory scale form. Patients will be randomly assigned to the experimental group and control group evenly. The experimental group will consist of a tank with Epsom salt. The control group will consist of a tank with no Epsom salt. Following 60 minutes, each patient will exit the tank and plasma cortisol levels will be obtained via blood draw and recorded. Patients will end their session by filling out a brief pain inventory scale form. This study will be done 3x a week for 4 weeks and the data will be statistically analyzed using SAS software.

Future Implications

Due to limited studies, there are many unanswered questions. Though the studies proved to show a positive correlation between the utilization of floatation-REST and a reduction in negative symptoms similar to patients with glioblastoma, there were no studies done regarding the therapy and patients with glioblastoma. For that reason, a study has been proposed to close the gap in research. Once the proposed study is completed, there are a few different implications that could arise. These implications could include expanding the participant pool to further analyze the effectiveness of floatation-REST. Future research should assess different times a person floats, as this could affect their cortisol levels. Lastly, various concentrations of Epsom salt can be evaluated to determine the effectiveness of this therapy.

Conclusion

Despite initial maximal resection and multimodal therapies, less than 5% of patients with glioblastoma survive five years after prognosis (Davis, 2016). Patients cope with symptoms including headaches, muscle loss, depression, pain, and mood changes (Davis, 2016). These symptoms may result from a variety of causes, such as the cancer, pharmacological therapies, or the medication prescribed to alleviate the initial symptoms. Therefore, it has come to my attention to find an alternative non-pharmacological pain management that can give patients with glioblastoma a more fulfilled life with a decrease of pain and stress.

Currently, there are non-pharmacological therapies that have shown to help cancer patients in alleviating pain. Because these therapies have been proven to have limitations, floatation-REST should be considered as a viable option. By using this modality, patients who would otherwise avoid current therapies are able to receive the assistance they need. Due to limited public exposure on floatation-REST, there have been no studies dedicated to see its effect on patients with glioblastoma. For this reason, this extended literature review proposes a conceptual framework for a future study to determine the effectiveness of floatation-REST on cortisol levels of patients with glioblastoma grade IV. This study will then evaluate the current hypothesis; patients with glioblastoma grade IV in the experimental group that includes floatation-REST and Epsom salt will have a normal range of cortisol levels as compared to the control group. If this proposal were to be conducted and show similar results to previous studies, this non-pharmacological pain therapy can be utilized as an option for pain management.

Appendices

Appendix A

Questionnaire

1. What forms of non-pharmacological pain therapy do you prescribe/ recommend to patients with glioblastoma grade IV?

2. Based on your professional opinion, are current pain therapies effective at controlling pain in patients with glioblastoma?

Strongly Disagree	Disagree	Agree	Strongly Agree

3. Based on the PowerPoint of floatation-REST as a pain therapy for patients with glioblastoma, would you recommend this therapy to patients?

No	Probably Not	Probably Yes	Yes

4. If this study were to be conducted in the future, would you participate in a study transforming this conceptual idea into research-based evidence in the future?

No	Probably Not	Probably Yes	Yes

5. In the event there is a study on this floatation-REST, how likely is it that you would recommend it for non-pharmacologic pain therapy for patients with glioblastoma?

Very Unlikely	Unlikely	Likely	Very Likely

6. If very unlikely and unlikely, please describe the reasons why you would not prescribe/recommend this pain therapy for patients with glioblastoma?

7. Based upon the PowerPoint lecture, please describe:
    a. Strengths
    b. Weaknesses

Appendix B

Figure B1

Introduction

Glioblastoma is the most aggressive and common brain tumor in adults. Five years after a prognosis, less than 5% of patients survive (Davis, 2016). Some symptoms include headaches, muscle loss, depression, and mood changes (Davis, 2016). In previous studies, it was found that floatation-REST (sensory deprivation tank therapy) has had beneficial effects on different stress-related and pain-related conditions in the body (Feinstein, 2018). Those conditions release cortisol, a stress hormone necessary to cope with a provoking stimuli (Hannibal, 2014). This therapy being studied uses Epsom salt (magnesium sulfate) to help the body maintain its homeostasis while assisting in the relaxation of the patient, thus decreasing any pain. Therefore, this reduction or relief of overall pain intensity can possibly help people feel better.

Objectives

The purpose of this experiment is to collaborate with physicians specifically oncologists and physical therapists in helping future patients alleviate emotional and physical pain.

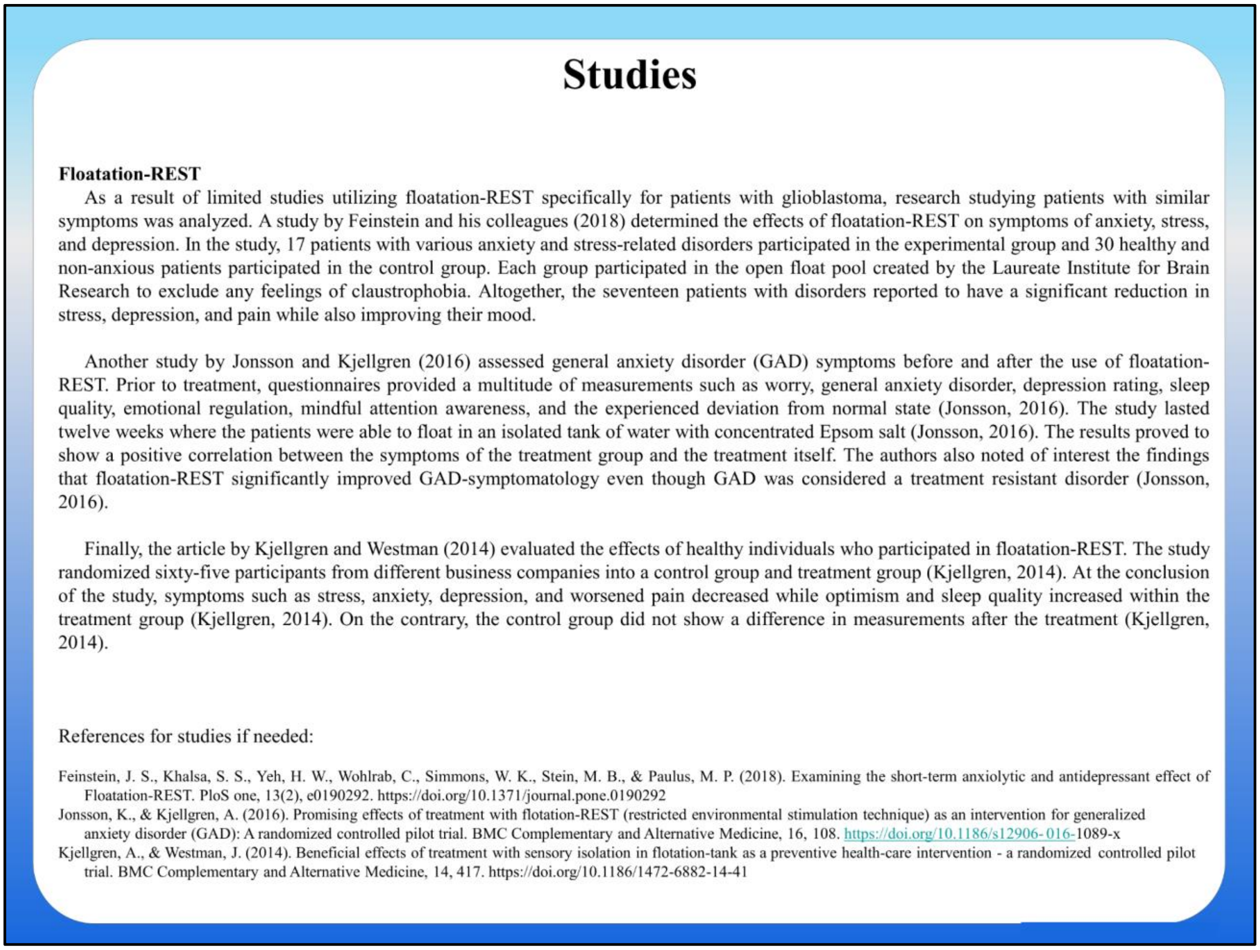
Hypothesis

Patients with glioblastoma in the experimental group that includes sensory deprivation tank therapy and Epsom salt will have a normal range of cortisol levels as compared to the control group.

Figure 1. Image of a sensory deprivation tank ready for use.

Figure 2 and 3: Epsom salt

Figure B2



Studies

Floatation-REST

As a result of limited studies utilizing floatation-REST specifically for patients with glioblastoma, research studying patients with similar symptoms was analyzed. A study by Feinstein and his colleagues (2018) determined the effects of floatation-REST on symptoms of anxiety, stress, and depression. In the study, 17 patients with various anxiety and stress-related disorders participated in the experimental group and 30 healthy and non-anxious patients participated in the control group. Each group participated in the open float pool created by the Laureate Institute for Brain Research to exclude any feelings of claustrophobia. Altogether, the seventeen patients with disorders reported to have a significant reduction in stress, depression, and pain while also improving their mood.

Another study by Jonsson and Kjellgren (2016) assessed general anxiety disorder (GAD) symptoms before and after the use of floatation-REST. Prior to treatment, questionnaires provided a multitude of measurements such as worry, general anxiety disorder, depression rating, sleep quality, emotional regulation, mindful attention awareness, and the experienced deviation from normal state (Jonsson, 2016). The study lasted twelve weeks where the patients were able to float in an isolated tank of water with concentrated Epsom salt (Jonsson, 2016). The results proved to show a positive correlation between the symptoms of the treatment group and the treatment itself. The authors also noted of interest the findings that floatation-REST significantly improved GAD-symptomatology even though GAD was considered a treatment resistant disorder (Jonsson, 2016).

Finally, the article by Kjellgren and Westman (2014) evaluated the effects of healthy individuals who participated in floatation-REST. The study randomized sixty-five participants from different business companies into a control group and treatment group (Kjellgren, 2014). At the conclusion of the study, symptoms such as stress, anxiety, depression, and worsened pain decreased while optimism and sleep quality increased within the treatment group (Kjellgren, 2014). On the contrary, the control group did not show a difference in measurements after the treatment (Kjellgren, 2014).

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Figure B3

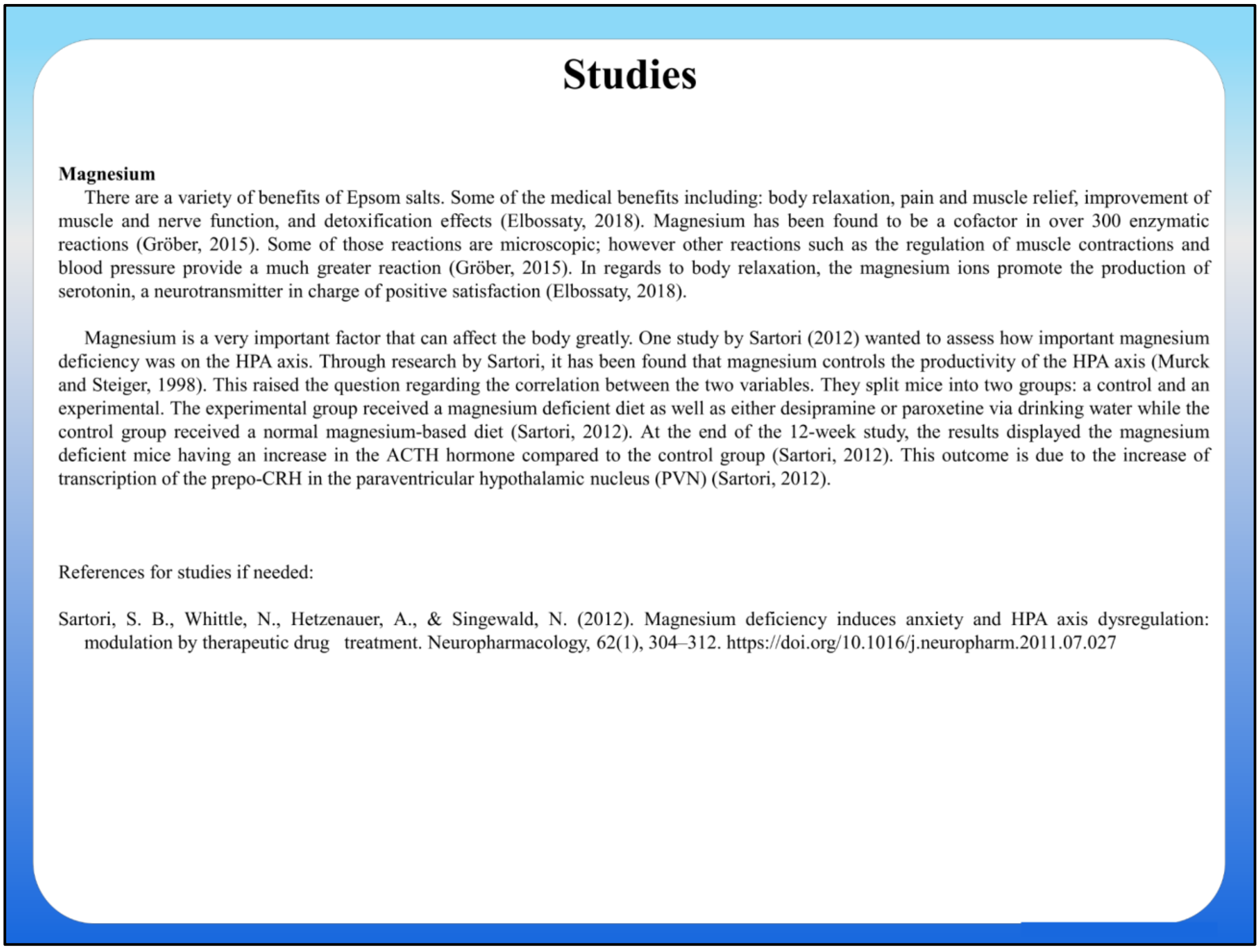
Studies
Magnesium
There are a variety of benefits of Epsom salts. Some of the medical benefits including: body relaxation, pain and muscle relief, improvement of muscle and nerve function, and detoxification effects (Elbossaty, 2018). Magnesium has been found to be a cofactor in over 300 enzymatic reactions (Gröber, 2015). Some of those reactions are microscopic; however other reactions such as the regulation of muscle contractions and blood pressure provide a much greater reaction (Gröber, 2015). In regards to body relaxation, the magnesium ions promote the production of serotonin, a neurotransmitter in charge of positive satisfaction (Elbossaty, 2018).
Magnesium is a very important factor that can affect the body greatly. One study by Sartori (2012) wanted to assess how important magnesium deficiency was on the HPA axis. Through research by Sartori, it has been found that magnesium controls the productivity of the HPA axis (Murck and Steiger, 1998). This raised the question regarding the correlation between the two variables. They split mice into two groups: a control and an experimental. The experimental group received a magnesium deficient diet as well as either desipramine or paroxetine via drinking water while the control group received a normal magnesium-based diet (Sartori, 2012). At the end of the 12-week study, the results displayed the magnesium deficient mice having an increase in the ACTH hormone compared to the control group (Sartori, 2012). This outcome is due to the increase of transcription of the prepo-CRH in the paraventricular hypothalamic nucleus (PVN) (Sartori, 2012).
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Figure B4

Conceptual Methodology for Future Research-Based Evidence

Participants:

- Patients diagnosed with Glioblastoma grade IV ranging from the ages of 30 - 48 from various hospitals in Florida will be randomly selected to volunteer.

Materials:

- Sensory deprivation tanks along with Epsom salt will be obtained for the experiment.
- Plasma cortisol tests from local Labcorp

Procedure:

- Before entering the tanks, each patient will have their blood drawn to test cortisol levels.
- Patients will be randomly assigned to the experimental group and control group. The experimental group will enter a tank with Epsom salt. The control group will enter a tank with no Epsom salts.
- Following 60 minutes, each patient will exit the tanks and plasma cortisol levels will be obtained via blood drawn and recorded.

Analysis of Results:

- After four weeks of recording cortisol levels 3x times a week, we will be able to determine the effectiveness of the sensory deprivation tanks based on the comparison of cortisol levels before and after the treatment.

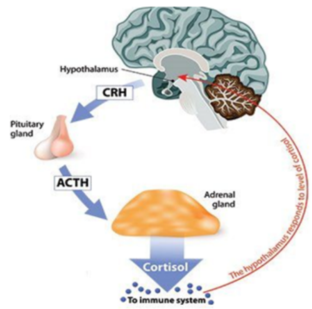

Figure 3. Image of the brain sending signals to the adrenal gland to release cortisol

Figure B5

Anticipated Outcomes

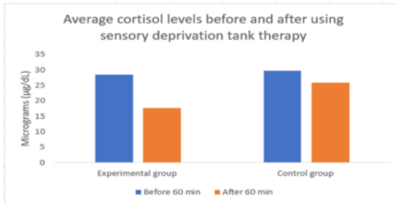

Figure 3: This graph represents the mean data accumulated before and after 60 minutes in the sensory deprivation tank.

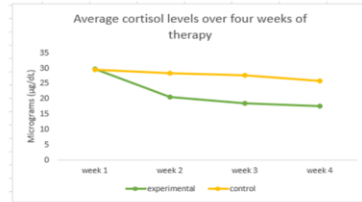

Figure 4: The graph represents the mean cortisol levels recorded over a period of 4 weeks.

Discussion

The anticipated results from the experiment suggest that the Epsom salt involved in sensory deprivation tank therapy stabilizes cortisol release. In this particular case with patients with glioblastoma, chronic headaches should decrease as the Epsom salt combined with warm water will decrease the inflammation. Magnesium from Epsom salt produces serotonin decreasing stress levels and aids in the production of energy for cells (ATP) which in hand increase muscle strength (Gröber, 2015).

Due to a decrease in stress as well as balance cortisol levels, patients will feel more relaxed with less muscle tension and pain (Kjellgren, 2001). Magnesium also plays a vital role in relaxation, as it is controls calcium influx at the cell membrane (Gröber, 2015). Epsom salt also has the benefit of detoxifying the body of toxins and heavy metals with the sulfate ions it contains (Elbossaty, 2018). In conclusion, future studies expanding on sensory deprivation tank therapy will prove the effectiveness of the therapy.

Figure B6

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Figure B7


Acknowledgements
College of Natural & Health Science
Special thanks to the following for the support provided for this project:
• Southeastern University
• Dr. Melba D. Horton
• Professor Wendy Berry
• SEU School of Honors
• Dr. Graham Greene of Lakeland Regional Health
• Dr. Andrew Bugajski of Lakeland Regional Health

Figure B8

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