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***Impact of Yoga and Gentle Massage Practices on
Symptom Management in Patients Undergoing
Hematopoietic Stem Cell Transplantation at the
Hospital Israelita Albert Einstein***

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1. Introduction

1.1 Hematopoietic Stem Cell Transplantation (HSCT)

This project aims to observe the impact of yoga practices on symptom management in patients undergoing Hematopoietic Stem Cell Transplantation (HSCT) at the Israelite Albert Einstein Hospital - Morumbi Unit. The clinical use of HSCT as a new form of cancer treatment was developed by the Fred Hutchinson Cancer Center in Seattle, USA. The first HSCT was performed in 1957, under the direction of Edward Donnall Thomas, MD, who was awarded the Nobel Prize in 1990 for his groundbreaking work (1)(2). HSCT, also known as Bone Marrow Transplant (BMT), began in Brazil in 1979 at the Hospital das Clínicas of the Federal University of Paraná. In 1983, it was implemented in another public service, the National Cancer Institute (INCA) in Rio de Janeiro. In 1987, the Israelite Albert Einstein Hospital was the first private institution to perform HSCT, using a unique type of transplant in Brazil at the time: autologous transplant, with the patient's own frozen marrow. Today, the HSCT unit has performed more than 1,300 transplants, and HIAE is the only hospital in Latin America to obtain FACT (Foundation for the Accreditation of Cellular Therapy) accreditation (1). HSCT is a complex and costly procedure performed only in specialized centers. HSCT has become a standard treatment for many patients with congenital or acquired disorders, malignant or non-malignant diseases, and remains associated with significant morbidity and mortality. It requires a vast network of specialists from various fields of medicine in its process (2)(3). The treatment involves risks, is lengthy, and predisposes the patient to various complications that require rapid management to ensure the life, survival, and quality of life of individuals. In addition to physical problems, emotional and social changes that occur throughout the process must be observed. Special attention should be given to social isolation in the early stages of treatment, as well as feelings of fear and distress that often affect both the patient and their family members (4). This treatment is used to replace the patient's bone marrow when it is defective due to diseases or not functioning properly. There are three types of HSCT:

- **Autologous:** performed with the patient's own cells, collected from the marrow or through peripheral blood, frozen, and stored (cryopreserved). After collection and cryopreservation, the patient undergoes a high-dose chemotherapy regimen, with or without radiation therapy, called conditioning, aimed at eliminating diseased cells, which consequently leads to the destruction of the patient's bone marrow. After conditioning, the previously collected stem cells are thawed and infused into the patient, a process similar to a blood transfusion.
- **Allogeneic:** performed using stem cells from a donor, who can be a relative or not. The degree of compatibility is determined by a set of genes located on chromosome number 6. The analysis is performed in the laboratory, using blood samples from the donor and the patient, known as human leukocyte antigen (HLA) testing. The patient's siblings are the relatives most likely to be 100% compatible. When the marrow donor is a relative, the transplant is called related allogeneic, and when not, it is called unrelated allogeneic. It is also possible to perform a related transplant with 50% compatible donors, known as haploidentical transplantation, usually done through the father or mother.
- **Syngeneic:** The procedure is exactly the same as allogeneic, but in this case, the donor and the recipient are identical twins.

Most transplants are indicated for hematological diseases. Autologous HSCT is usually indicated for Multiple Myeloma (MM) and Lymphomas. It can also be used to treat solid tumors, such as germ cell tumors, Neuroblastomas, Ewing's Sarcoma, and Medulloblastoma. For allogeneic HSCT, the main indications are Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Myelodysplastic Syndromes, and Myeloproliferative Neoplasms. Hematopoietic stem cell transplantation can also be used to treat a variety of non-malignant conditions, such as Severe Aplastic Anemia (SAA), Sickle Cell Anemia, Thalassemia, Hereditary Immunodeficiency Syndromes, and certain metabolic disorders (2)(3). When the bone marrow

starts functioning again (usually around 2 to 4 weeks after cell infusion), it is said to have "engrafted," and the transplant is considered successful. Rigorous medical monitoring remains essential, as complications can still arise even a year after the procedure. New reduced-intensity conditioning regimens have been developed, reducing toxicity, which has expanded the use of HSCT to older patients or those with comorbidities. Over the last two decades, there has been rapid expansion and continuous evolution in transplant protocols, and new indications are constantly being evaluated (5). Complications resulting from HSCT can be divided into three categories, based on time:

1. **Pre-engraftment period:** from the start of the conditioning regimen until neutrophil recovery. Patients may experience pancytopenia, gastrointestinal toxicities, infections (the most common being gram-positive and gram-negative bacteria, herpes, candidiasis, and invasive aspergillosis), and organ dysfunction. Organ failure and even death can occur. The risks vary depending on the type of transplant, the conditioning regimen, the underlying disease, and the recipient's comorbidities.
2. **Early post-engraftment period:** from neutrophil recovery to generally 100 days post-transplant. Acute Graft-Versus-Host Disease (GVHD) can occur early in this post-engraftment period. GVHD occurs when transplanted immune cells recognize the recipient as foreign and mount an immune response, causing the disease. Acute GVHD occurs only in allogeneic transplants and usually affects the skin, gastrointestinal system, and liver; common manifestations include skin rash, watery diarrhea, persistent nausea, vomiting, cholestatic jaundice, and abnormal liver function tests. Systemic corticosteroids are the mainstay of therapy, and severe acute GVHD is associated with worse survival. During this early post-engraftment period, patients remain at risk of infectious complications. Despite neutropenia recovery, cellular immunity remains impaired, and there is a risk of opportunistic infections such as cytomegalovirus and susceptibility to common respiratory viruses like influenza and adenovirus. As a general rule, the presence of GVHD and its treatment entails a higher degree of immunosuppression. Therefore, patients with active GVHD have a higher risk of invasive fungal infections and viral reactivation.
3. **Late post-engraftment period:** typically from day 100 onwards. Chronic GVHD can occur and affect one or more organs (skin is usually the most affected). If the salivary and lacrimal glands are affected, it results in increased dryness. As with acute GVHD, the gastrointestinal tract and liver can be affected. Patients with chronic GVHD experience autoimmune phenomena and more frequent opportunistic infections, reducing their quality of life. Multimodal treatment is often used, but management is usually based on immunosuppression. After HSCT, patients need to receive their primary immunizations again. Throughout the entire post-transplant period, the recurrence of the underlying disease remains one of the leading causes of mortality. Post-HSCT survivors, especially those with chronic GVHD, score lower on measures of quality of life (2).

It is observed that bone marrow transplantation can be a curative option for high-risk cancer patients and other life-threatening diseases. Advances in transplantation have led to an increasing number of long-term survivors, estimated to reach 500,000 in the United States alone by 2030. As overall outcomes and survival after BMT improve, infections remain among the most important causes of late morbidity and mortality, accounting for 7% to 13% of deaths among survivors within 3 years. The entire team must maintain high vigilance for infections in this population and ensure adherence to existing antimicrobial prophylaxis and vaccination guidelines (6).

1.2 Main Symptoms in Patients Undergoing HSCT

The most common symptoms experienced by patients undergoing HSCT include both physical symptoms (fatigue, pain, sleep disturbances, nausea, loss of appetite, drowsiness) and psychological (anxiety, depression) and social symptoms (loneliness, negative self-image, loss

of control and privacy). The most prevalent symptoms include pain (particularly musculoskeletal pain), fatigue, and sleep difficulties (7)(8)(9). These symptoms, along with the physical isolation of patients during hospitalization (an average of 3 to 4 weeks), can contribute to a decline in quality of life and mood (10). Joint Commission International, the American College of Physicians, the National Comprehensive Cancer Network (NCCN), and the American Society of Clinical Oncology (ASCO) recommend a combination of pharmacological and non-pharmacological modalities in the management of pain, one of the most common, costly, and feared symptoms in cancer patients. Integrative Medicine therapies are non-pharmacological interventions, and evidence is growing regarding the use of mind-body practices (such as yoga, meditation, tai chi chuan, relaxation), acupuncture, massage therapy, and music therapy in managing pain for these patients (8). Although pain-related symptoms are not well-described in patients undergoing HSCT, evidence suggests that most of the pain in these patients is correlated with mucositis, GVHD, vascular necrosis, arthralgias, myalgias, and muscle cramps (9). If pain is exacerbated by anxiety, fear, depression, sleep disturbances, or psychological distress, mind-body therapies and therapeutic massage should be considered (8). It is noted that pain increases during hospitalization (11). Fatigue is characterized by a chronic and intense feeling of tiredness, which is not typically associated with stress and does not decrease with rest. On a physical level, fatigue manifests as bodily tiredness and lack of strength, on an emotional level as depressed motivation and mood, and on a cognitive level as difficulty concentrating (12). Fatigue is one of the most common concerns of HSCT survivors, affecting adult patients undergoing both allogeneic and autologous transplants to a high degree. The level of fatigue increases during hospitalization and usually remains with the highest post-transplant scores compared to other symptoms, although it gradually decreases to pre-transplant levels over time (9)(11)(13). Gielissen et al. demonstrated that 35% of transplant patients (both allogeneic and autologous) still had severe fatigue one year after the transplant (14). In most studies, factors associated with fatigue include younger age and chronic pain for all patients, and specifically, female sex and chronic GVHD in allogeneic recipients (15). Fatigue represents a high risk for the development of clinical depression and anxiety (12). Understanding of this issue is still limited in pediatric survivors (9). Loss of appetite, as well as nausea/vomiting, are symptoms with the highest increase before transplant and during hospitalization. They gradually and continuously decrease after discharge (11). Sleep-related problems also worsen during hospitalization, improve after discharge, but remain as a persistent symptom at a high level, although not surpassing the level of fatigue. Dyspnea should be considered a moderate but persistent problem, in which patients experience shortness of breath or difficulty breathing. Patients report lower levels of physical capacity during hospitalization, and scores usually improve to pre-transplant levels after one year. Fatigue, dyspnea, and insomnia are symptoms that persist and should therefore be considered persistent problems after HSCT, with scores above the general population (11). Physical recovery usually occurs earlier than emotional recovery in transplant patients (16). It is well-documented that being diagnosed and treated for cancer is a challenging experience, associated with high levels of stress and suffering. Stress remains high in 22% to 43% of long-term HSCT survivors, due to various factors such as difficulty living with uncertainties, fear of recurrence, anxiety and depression, loneliness, memory problems, financial concerns, and somatic worries (9)(17). Risk factors do not consistently vary by gender, age, or time since transplant, but stress appears to be higher for patients treated with prednisone, those with chronic GVHD, lower family income, greater physical limitations, higher level of education, or lower social support (9)(16)(17). Caregivers should be trained to provide better support and meet the needs of patients, as well as to learn how to better communicate their own needs. Ineffective and low-quality social support often increases the stress and suffering of the patient. Good communication between the multiprofessional team and caregivers/family members can improve the quality and quantity of support and meet the specific needs of each patient (17). With advances in reduced-intensity conditioning and supportive care in hematopoietic cell transplantation, few studies report clinically significant rates of Post-Traumatic Stress Disorder (PTSD) symptoms and associated risk factors (18). HSCT can be considered a traumatic event, defined according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), as exposure to "death, threat of death, or actual serious injury" and can encompass "a sudden, catastrophic

event" due to a medical occurrence. Thus, transplantation has the potential to lead to a diagnosis of PTSD in patients and their informal family caregivers. A broader approach is needed to screen for stress problems in cancer patients, taking into account the psychological history of the patients (18)(19). It is observed that PTSD affects 5% to 28% of these adult patients, but symptoms are likely underdiagnosed or diagnosed as depression or anxiety (9)(18). Interestingly, the number of studies reporting positive psychological benefits from cancer diagnosis and treatment has been increasing (20). In HSCT survivors, few studies have examined Post-Traumatic Growth (PTG): positive psychological change experienced as a result of exposure to traumatic or highly challenging events, and even fewer have considered evaluations of spirituality in this population (9). PTG is associated with a greater appreciation of life, better relationships, existential growth, increased self-confidence, and self-esteem. Possible mediators of PTG include social support, proactive guidance from the healthcare team, support groups, expressive writing, cognitive-behavioral therapy, and meditation, among others, which can serve as methods to enhance PTG (9)(21). In a recent study (2021) conducted by Maya Corman et al. that analyzed PTG five months after HSCT, they reported that the experience of this treatment seems to be more related to psychological decline after transplantation than to PTG (22).

This comprehensive review provides valuable insights into the challenges and symptoms faced by patients undergoing Hematopoietic Stem Cell Transplantation (HSCT). It highlights the multifaceted nature of the physical, psychological, and social issues encountered during this complex medical procedure. Understanding these challenges is crucial for healthcare providers to improve the care and quality of life for HSCT recipients. Additionally, the discussion of potential complementary therapies, such as yoga and mind-body practices, underscores the importance of holistic approaches to managing the symptoms and improving the overall well-being of these patients.

2. OBJECTIVE

This project aims to analyze the impact of yoga and gentle massage practices on symptom management in patients undergoing Bone Marrow Transplantation.

2.1 Primary Objective

- To analyze the effects of yoga and/or gentle massage practices + standard treatment versus standard treatment alone on symptom management in patients undergoing Hematopoietic Stem Cell Transplantation, assessed by the Edmonton Symptom Assessment Scale (ESAS). Primary Outcomes
- To analyze changes in ESAS in the domains of fatigue, pain, nausea, anxiety, and well-being before and after each of the 8 sessions.

2.2 Secondary Objectives

- To analyze changes in the Quality of Life Scale during HSCT;
- To analyze changes in the Religiosity Scale during HSCT;
- To analyze the subjective experience of the patient during HSCT;
- To analyze patient satisfaction during HSCT. Secondary Outcomes
 - Changes in the Quality of Life Scale at 2 time points: upon admission and on Day 21 or at discharge (whichever occurs first);
 - Changes in the Religiosity Scale at 2 time points: upon admission and on Day 21 or at discharge (whichever occurs first);

- Open-ended question about the subjective experiences of patients undergoing HSCT on Day 21 or at discharge (whichever occurs first);
- Questions about patient satisfaction during HSCT on Day 21 or at discharge (whichever occurs first).

2.3 Hypothesis The practice of yoga and gentle massage combined with standard treatment is superior to standard treatment alone in symptom management in patients undergoing HSCT.

3. METHOD

3.1 Population The study will be conducted at the Albert Einstein Israelite Hospital - Morumbi Unit, with patients admitted to the Oncology and Hematology Center for Bone Marrow Transplantation. Only after obtaining Informed Consent (ICF) acceptance, the patient's clinical and sociodemographic variables during hospitalization will be extracted from the electronic medical record of the institutional database: age, gender, month/year and type of transplant, conditioning intensity, donor type, cell source, and underlying disease.

3.1.1 Inclusion Criteria

- Adults aged 18 and older;
- Admitted to the HIAE, eligible for Bone Marrow Transplantation;
- Patients who speak and read Portuguese.

3.1.2 Exclusion Criteria

- Patients with hearing impairment;
- Patients previously diagnosed with psychiatric disorders: schizophrenia.

3.2 Experimental Design This is a prospective open-label randomized study evaluating the practice of yoga and gentle massage combined with standard treatment versus the use of standard treatment alone.

3.3 Sample Size The sample will consist of a total of 40 patients for this study. Based on a pilot sample (N = 40) with only one session of yoga + gentle massage, an improvement of 1.58 points (SD = 1.58 points) in fatigue was observed. Aiming to find an average difference of at least 1.5 points between the intervention group (yoga + gentle massage + standard treatment) and the control group (exclusive standard treatment) over 8 proposed sessions, with 80% power and 95% confidence, a sample of 18 patients in each group would be required. Since, in addition to fatigue, other parameters such as pain, nausea, anxiety, and well-being will be evaluated, we will use a sample of at least 20 patients per group to also account for these parameters, totaling at least 40 patients in the study.

3.4 Randomization Randomization will be performed according to the randomization block generated by Excel and will be carried out using the REDCap tool. Thus, upon accepting participation in the protocol, each patient will receive an individual number that will be included in this randomization block, with the sequence of their participation in the protocol predetermined by the Excel table to be inserted into REDCap and randomized according to parameterization, stratified by age groups: 18 to 30 / 31 to 50 / 51 to 65 / over 66 years 18 to 40 / 41 to 60 / above 61 years and by type of transplant: autologous, allogeneic, and umbilical cord.

3.5 Training Program During the HSCT period, patients will be randomized into two groups:

- Group A (control): standard treatment
- Group B (intervention): yoga or gentle massage plus standard treatment

The intervention sessions will be verbally conducted by integrative therapists from the Integrative Medicine Team, hired by the Oncology and Hematology Center of HIAE, all with

postgraduate degrees in Yoga (Institute of Teaching and Research in Yoga - IEPY) and in Integrative Health Bases and Well-being (Albert Einstein Institute of Teaching and Research - IIEP). Group B (intervention) will receive a total of 8 individual integrative practice sessions at the bedside, each lasting 15 to 20 minutes, with 2 sessions per week during the following periods: • from admission until Day 0 • until Day 7 • until Day 14 • until Day 21 or discharge. The therapist will choose the integrative practices that best suit the patient for each session, according to their psychophysical state and presented symptoms, as there are many variations during HSCT. Group A (control) will receive 8 visits from integrative therapists who will remain in the patient's room, able to interact but without offering integrative practices, during the same period described above. After Day 21, these patients will also receive 8 integrative practice sessions at the bedside or in the Integrative Medicine room. If any patient from this group needs to receive Integrative Medicine care, they will receive it and be withdrawn from the study.

3.5.1 Yoga Yoga sessions will be conducted at the patient's bedside, in a supine or sitting position, using one or more of the following techniques: gentle stretches (asanas), guided relaxation (savasana), deep and slow diaphragmatic breathing (pranayama), and meditative exercises focusing on natural breathing or visualizing a place that brings well-being (dhyana). Based on these techniques, the integrative therapist will choose what best suits the patient for each session, according to their psychophysical state and presented symptoms, as there are many variations during HSCT. Non-violence (ahimsa) as a basic and essential principle of yoga practice will be reiterated in each class to encourage participants to be gentle with themselves and accept possible limitations.

3.5.2 Massage Gentle massage involves gentle touches, using light pressure, mainly with the palm, with a slow and steady rhythm over the entire body. It can be performed over clothing and even over the sheet and blanket. The sequence of light touches begins at the head, moving down the right shoulder, arm, forearm, and right hand; thigh, knee, leg down to the right foot, where it will be gently massaged on the back, fingers, and sole of the right foot. Afterward, the therapist's hands move up in the reverse sequence on the left side of the patient's body, finishing again at the head. The action of this technique is on the skin and not on the muscles. Sensory information from this gentle touch on the epidermis activates the Relaxation Response in the Autonomic Nervous System, increasing the stimulation of the PNS and decreasing the excitement of the SNS.

3.6 Assessments The scales and questionnaires will be digitally administered through the REDCap Einstein platform. Only the Qualitative Report will be provided in printed form for the patient to describe their experience. All these documents are available in the appendices of this project.

3.6.1 Edmonton Symptom Assessment Scale - ESAS-Br The Edmonton Symptom Assessment Scale - ESAS-Br will be used before and after each of the 8 sessions in both groups, assessing the domains: pain, fatigue, nausea, anxiety, and well-being.

3.6.2 Functional Assessment Cancer Therapy - Bone Marrow Transplantation Quality of Life Scale - FACIT-BMT The Functional Assessment Cancer Therapy - Bone Marrow Transplantation Quality of Life Scale - FACIT-BMT will be used at two time points: upon admission and on Day 21 (or at discharge).

3.6.3 Duke Religious Index - DUREL The Duke Religious Index - DUREL will be applied at two time points: upon admission and on Day 21 (or at discharge).

3.6.4 Qualitative Report The Qualitative Report will be handed to the patient in printed form on Day 21 (or at discharge), using an open-ended question for the patient to describe: "What was your experience with Integrative Medicine like?"

3.6.5 Patient-Reported Experience Measures (PREMs) To assess patient satisfaction and experience, the Patient-Reported Experience Measures (PREMs) will be applied on Day 21 (or at discharge).

3.7 Statistical Analysis The qualitative characteristics of patients will be described according to groups using absolute and relative frequencies, and associations with the groups will be verified using chi-square tests or exact tests, while quantitative characteristics will be described according to groups using summary measures (mean, standard deviation, median, minimum, and maximum), and group comparisons will be made using t-Student tests or Mann-Whitney tests depending on the probability distribution of the data. Mean changes in each ESAS domain over the 8 therapy sessions will be calculated, and group means on the scales will be compared using t-Student tests or Mann-Whitney tests. The analyses will be performed using IBM-SPSS software for Windows version 22.0, tabulated using Microsoft-Excel 2010 software, and tests will be conducted at a 5% significance level.

4. ETHICAL ASPECTS This project will be submitted for review to the Research Project Management System of the Albert Einstein Israelite Hospital (HIAE), the institution hosting the Einstein Family Dayan - Daycoval Oncology and Hematology Center. Subsequently, it will be submitted to the Brazil Platform and the institutional Research Ethics Committee. All patients will sign the Informed Consent Form because it involves human subjects.

5. RISKS AND BENEFITS

5.1 Risks The expected risks, if any, for the procedures of this study (yoga and gentle massage) and for responses to research questions are minimal. Given that the topic of integrative practices would not put subjects at risk of health, criminal or civil liability, or be detrimental to their financial situation, employability, educational advancement, or reputation. Although we consider the risks of participation in this study to be low, we will ensure that any situation is handled sensitively and empathetically. If any discomfort arises during the study, it may be discontinued.

5.2 Benefits As this is a randomized study, participants may not directly benefit from the proposed research; however, others may benefit from the knowledge gained in this study.

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