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Wake Forest School of Medicine

Plastic and Reconstructive Surgery

Radiofrequency Hyperthermia Safety Study (RHySS)

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Background, Rationale and Context

There is increasing evidence that mild hyperthermia (MH) may have a positive effect on wound healing. Currently, MH is clinically used to facilitate recovery from chronic pain and soft tissue maladies, including sports injuries. MH has been used for thousands of years to improve blood flow to tissues and aid lymphatic drainage. MH is commonly employed to augment the delivery of chemotherapeutic agents, for example, the HIPEC procedure. Localized hyperthermia may be classified as mild (T < 45°C) or ablative (T>45°C). The time of application is also critical, with most MT being applied for between 30 and 120 minutes.[1] Although the complete mechanisms are not yet understood, there is substantial evidence that MH may be beneficial in many diseases, including cancer and wound healing.[1,2]

In spite of these observations, MH has been slow to be established, approved and adopted as therapy, possibly due to wide variations in technical specifications of the heating devices, including frequency and duration, recovery time between treatments and the total number of treatments delivered. One of the challenges of applying MH to tissue is that the penetration depth may not be sufficient due to the modality of heating (for example, a heating pad from the drugstore is not efficient at elevating hyperthermia deep into tissue).

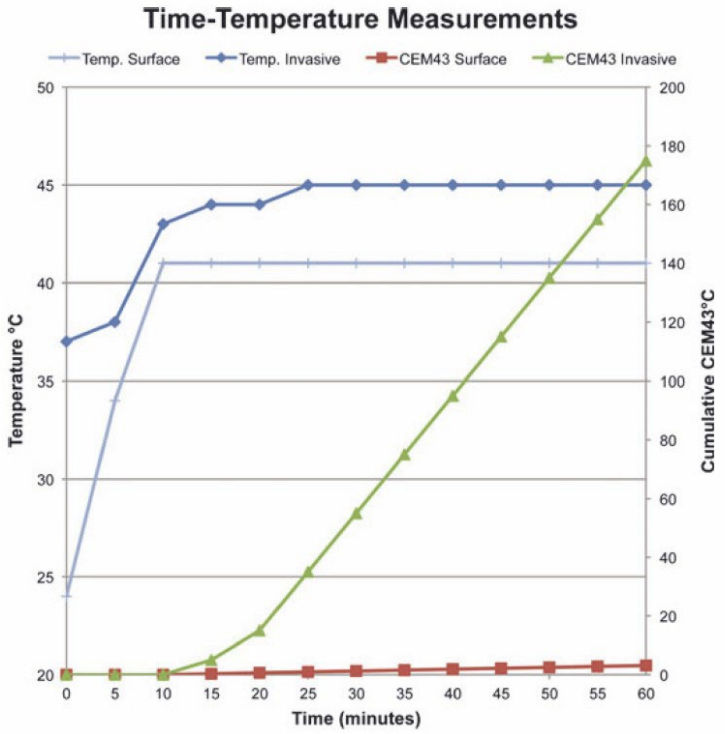
A major benefit of the vast literature on MH is the conclusion that application of MH does not cause any harm. Radiofrequency heating is routinely used clinically, although most often for ablation.[3] Although RF can heat tissue precisely and deeply, its application in MH therapies has been limited due to the need for precise temperature controlling to maintain safe MH over time. There is currently no standard of care for treating specific wound types with MH therapy due to the multiple variables that have been included in previous studies.

One of the challenges has been development of heating devices that can control temperature over time. Within the past few years, Thermofield has developed a novel radiofrequency heating device with temperature control. They have established a set of clinical veterinary guidelines for applying MH for augmenting cancer treatments in animals and have demonstrated safety in these models.[4,5] These guidelines have been utilized by veterinarians for pain and cancer management. In addition to these benefits, some wounds appeared to have better healing. It is hypothesized that MH application should benefit wound healing. The use of superficial hyperthermia for the adjuvant treatment of soft tissue tumors has been used in veterinary medicine.[6] These studies demonstrated improved in outcomes, but hyperthermia devices have are still large and cumbersome to use with adequate precision of heating and temperature control at depth in tissue. Thermofield has collected safety and performance data following the

treatment of >200 canines, 50 cats, and 20 horses with a novel superficial hyperthermia and demonstrated the optimized thermal dosimetry, ease of use, and safety of the system.

Thermofield has developed a lightweight, portable radiofrequency heating system that can apply heat topically with a controlled feedback loop to maintain a specific temperature.[7] This development is critical to ensure that there is no burning of the skin during the applied heating. Having a feedback loop such that the applied heating is consistent over time is also vital for the future development of standardized MH treatments, and such a feature has not been available until now. Applications of MH to the skin for heating of underlying tissues needs consistent, safe, temperature application in order to demonstrate the full spectrum of clinical utility. Thermofield has developed an appropriate device that may be beneficial in aiding multiple disease and the first step is to demonstrate that it may be applied safely in healthy individuals with intact skin. This device has not yet been approved by the FDA for the treatment of any disease, although similar heating devices have been approved for elevating tissue temperature and providing temporarily relief of pain and stiffness associated with arthritis. In this clinical trial we propose to demonstrate the safety and good tolerability of the Thermofield device. This information will be used for a future clinical trial for application of FDA approval.

To validate the thermal field generated by our hyperthermia system, we used both non-invasive and intratumoral thermocouples in spontaneous canine tumors. The non-invasive surface thermocouple incorporated into the multilayer antenna construct allows for thermal measurements in the central/surface portion of the electric field. Feedback from the surface thermocouple was used to control power output, automatically achieving and maintaining programmed target temperatures. Intratumoral thermocouples were placed parallel to the surface at a depth of approximately 4cm through the central portion of the electric field. Digital readouts were continuously monitored during therapy and used for thermal dose calculations.



A time-temperature profile from a single 60-minute treatment is shown above. Thermal doses were expressed in the equivalent number of minutes. Exposure to 43°C intratumoral temperature is achieved as previously described [34]. Actual temperature measurements are shown on the left axis, while cumulative equivalent minutes at 43°C (CEM43°C) are shown on the right axis. A thermal gradient of 3–4°C is seen between non-invasive and invasive temperature measurements resulting in a significant difference between CEM43°C as determined from non-invasive and invasive measurements. Times to reach effective surface treatment temperatures of ≥39°C ranged from 6 to 15 minutes Intratumoral temperatures averaged 3-5 °C higher than surface temperatures, documenting a relative skin-sparing effect. These data show that this method of thermometry considerably reduces the risk of thermal burns. There was no observed skin toxicity for surface treatment temperatures of ≤41°C (intratumoral temperatures ≤45 °C).

Objectives

Primary: To demonstrate that application of the Thermofield temperature controlled radiofrequency device is safe for dermal application for generating elevated temperatures.

Secondary: To ensure that participants will adhere to a weekly MH program.

Methods and Measures

Design

This study will include 20 healthy subjects with intact skin on their lower legs that meet inclusion criteria below. Participants will serve as their own control, by heating one leg and not the other. The radiofrequency device consists of a 4 by 6 inch heating pad connected to a temperature controller. The pad will be applied to the back of the leg (calf). The other leg will receive a pad, but radiofrequency will not be applied (no heating).

At the first visit, subjects will be asked to fill out a healthcare questionnaire. If patients meet the inclusion criteria they will also be asked to provide their date of birth for access to their medical records, if associated with Atrium Health Wake Forest, can be reviewed to ensure that the participant does not have underlying health concerns that could lead to vascular or skin compromise. With each weekly treatment, subjects will be evaluated to assess how their legs feel on a scale of 1-10, with 1 being no discomfort and 10 being intense pain. Their legs will be photographed before and after radiofrequency MH to examine any visible changes to the tissue. Study team will then use a PeriScan PIM 3 System Laser Doppler scanning for blood perfusion before the Thermofield treatment. The radiofrequency will be set to achieve 40°C/104°F) and maintain this temperature consistently during the application time. This temperature is mild and may feel like a drugstore heating pad. The device will be turned on on one leg and will remain off on the other. The time for the heating will be 40 minutes, during which participants will remain in a reclined position, with their legs elevated. The device takes approximately 7 minutes to achieve a tissue temperature of 40.0°C, with a goal temperature of 40°C, or an average between 39.7 and 40°C. The treatment time with consistent temperature application will be 33 minutes. Study team will then use a PeriScan PIM 3 System Laser Doppler scanning for blood perfusion after the Thermofield treatment ends. Study team will take thermal imaging photographs of the treatment area following each treatment.

The time it takes for the radiofrequency device to ramp to the set temperature is usually about 7 minutes, although varies slightly from patient to patient. This study has had an incidence of sensitivity to the heat and development of a first degree burn and tenderness at the site of the application, following the second treatment. In order to be more vigilant in patient pain levels during the ramp time, and to minimize any tenderness or burn, patients will be asked what their pain level is every minute during the ramp time. If they have a pain level of 5 (on a scale of 1 to 10, with 10 being the highest) the device settings will be modified as follows. Normally, the device operates in a continuous wave mode with no time for thermal relaxation of the tissue. However, the applied energy can be modulated using a pulsatile mode, to provide RF energy at 2 pulses per second, which reduces the energy input; however, the set temperature can still be achieved, although it may take 1 or 2 minutes longer. If the patient has discomfort in pulsatile mode, that is at a pain level of 5 or higher, the treatment will be stopped and they will be excluded from the study. These changes were developed through discussions with the sponsor and evaluation in a laboratory setting at Wake Forest. Documentation of pain during the temperature ramp time will be documented and included with the study records.

Subjects will receive weekly treatments for 4 weeks, and will be re-evaluated 4 weeks after the last treatment to assess any tissue changes that continue after the treatments have concluded. Subjects will be excluded from the study if they develop any kind of intolerance to the MH treatment, like increased pain or

unexpected skin changes. If they receive a significant injury or wound that is not due to the study, such that the skin of the lower leg is no longer intact, they will be excluded from the study. Only one patient at a time will be treated until they conclude the 4 week treatment period.

Setting
Study will take place in the Wake Forest University Plastic Surgery clinic area

Subjects selection criteria

Inclusion Criteria

- 18 yo or older
- Healthy
- 20<BMI<40

Exclusion Criteria

- Pregnant, nursing or child bearing potential
- Active infections of the skin in the lower leg
- Open or healing wounds on the lower leg
- Autoimmune disorder
- 40<BMI <20
- History of blood clots
- History of lower limb edema
- Tattoos and metal hardware in the leg

Sample Size

Samples size is 20 subjects

Interventions and Interactions

- Informed consent
- Medical history
- Health and healthcare questionnaires
- Height and weight
- Use of Laser Doppler scanning for blood perfusion
- Radiofrequency treatment
- Use of thermal imaging photographs
- Measuring the circumference of the calf

Outcome Measure(s)

Primary endpoints:
- Safety

Secondary endpoint:
- Subject tolerability of the treatment time and weekly application

Analytical Plan
Results will be analyzed initially using descriptive statistics. Comparison between treated and untreated limbs will be done using chi square tests for proportions, and t-tests or ANOVA procedures for continuous variables. The input data will be based on the comfort scale analyses.

Human Subjects Protection

Subject Recruitment Methods
Subjects will be recruited using fliers posted at Wake Forest Baptist Medical Center. Subjects will be identified based on the inclusion and exclusion criteria through phone discussions, prior to their first visit. All subjects fitting the described inclusion and exclusion criteria will have the ability to enroll in the study. The sponsor will receive no information about the subjects prior to their consenting for the study, so there is no concern of confidentiality/privacy protection before ascertaining desire to participate.

Informed Consent
Signed informed consent will be obtained from each subject. Informed consent will be obtained after the study has been fully explained to each subject and all questions and concerns have been properly addressed. The investigators or a member of the study team will obtain informed consent. Informed consent will take place in a private examination area of Plastic and Reconstructive Surgery clinical areas.
After signing the ICF, the subject will be given a signed copy.

Confidentiality and Privacy
Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed three years after closure of the study, and the data files will be deleted, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring
The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Reporting of Unanticipated Problems, Adverse Events or Deviations
Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

References
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[4] R.J. MacKay, Treatment options for melanoma of gray Horses, Veterinary Clinics: Equine Practice. 35 (2019) 311–325.
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[6] S.M. Gillette, M. Dewhirst, E. Gillette, D. Thrall, R. Page, B. Powers, S. Withrow, G. Rosner, C. Wong, D. Sim, Response of canine soft tissue sarcomas to radiation or radiation plus hyperthermia: a randomized phase II study, International Journal of Hyperthermia. 8 (1992) 309–320.
[7] G. Clark, T. Otten, Apparatus and method for hyperthermic treatments, (2017).

Appendix

1. Copies of each questionnaires or surveys that will be used
2. Consent form