



THE BAROMEDICAL RESEARCH FOUNDATION

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RESEARCH STUDY OVERVIEW

HYPERBARIC OXYGEN RADIATION TISSUE INJURY STUDY “HORTIS”

Objectives

The principle objective of this research is to more precisely determine the degree of benefit that hyperbaric oxygen therapy affords in the treatment of late radiation tissue injury.

The study has eight components. Seven involve evaluation of established radionecrosis at varying anatomic sites (mandible, larynx, skin, bladder, rectum, colon, and GYN). The eighth will investigate the potential of hyperbaric oxygen therapy to prophylax against late radiation tissue injury.

This study will also generate more precise “Benchmarking” data as to the complications associated with hyperbaric exposure, including incidence and degree of morbidity.

Background and Rationale

Radiation therapy is a key component of the control and eradication of malignant disease. Adequate tumorcidal doses may, however, result in damage to surrounding healthy tissue. Therapeutic radiation injuries to non-target tissues can be divided into acute, sub-acute, and delayed complications.⁽¹⁾ Acute injuries are considered a direct cellular toxicity, self-limiting, and in most cases successfully managed symptomatically. Sub-acute injuries are typically identifiable in only a few organ systems, e.g., radiation pneumonitis. These, too, are generally limited but occasionally evolve to late complications. Late changes occur several months to many years after completing radiotherapy.

The etiology of radiation's late effects to normal tissue (LENT) varies somewhat between organ systems. Its hallmark, however, is one of culminating in an obliterative endarteritis, and local hypoxia.

The incidence of LENT is related to both total radiation exposure⁽²⁾ and the length of time a patient is out from completing radiotherapy.⁽¹⁾ The higher the dose, the longer the interval from exposure, the greater the risk. In many cases, resulting radionecrotic lesions seriously impair form and function, and require extensive surgical correction or repair.^(3,4) Such surgery is fraught with complications,^(3,4) hence the inclusion of a "prophylactic" hyperbaric oxygen arm. A disturbing degree of mortality further complicates the development of LENT.^(3,5)

Hyperbaric oxygen has been utilized in the treatment of radiation tissue injury for several decades.^(6,7) Most of the supportive basic science and clinical evidence stems from the management of mandibular osteoradionecrosis.^(8,9) More recently, the use of hyperbaric oxygen has been extended to other anatomic sites.^(10,11,12,13) This expanded use is based, in large part, on a presumed common underlying pathophysiology of LENT, regardless of its anatomic location. Supportive clinical evidence for these other sites is limited, however, and in need of a greater degree of scientific scrutiny.

Study Type

HORTIS has been developed as a multi-center study of international participation, involving a randomized, double blind, placebo-controlled clinical trial, with patient cross-over option.

Patient Eligibility

Patients will be eligible to enter the HORTIS trial if they have a history of exposure to therapeutic radiation, and have developed clinically manifest late radiation tissue injury (HORTIS I-VII).

A separate group of patients are eligible to be enrolled if they have likewise been irradiated, have not developed clinically manifest radionecrosis, and face surgical intervention within or through a previously radiated portal (HORTIS VIII).

Patients would be considered ineligible if they are considered to be at specific risk for hyperbaric-hyperoxic related complications.

Treatment Plan

Patients will be initially randomized to receive either oxygen at 2.0 atmospheres absolute (ATA), or air at 1.0 ATA.

The therapeutic algorithm is personalized to each patient's degree of response at specific points during their course of hyperbaric exposure. The total number of exposures will vary from between 20 and 40.

Following a 30-day observation/"wash out" period, the allocation assignment will be opened. Patients randomized to the 1.0 ATA air group will be offered the opportunity to cross-over to the 2.0 ATA oxygen arm. The offer is mandatory, not so the requirement of the patient to cross-over. A therapeutic algorithm identical to the first randomization will be undertaken during any subsequent cross-over phase.

Data Collection

Data will be entered into a central electronic HORTIS database, accessible via the Internet. Database access is password protected. Clinicians approved as HORTIS investigators will be granted controlled access. The randomization sequence will be revealed at the time of initial entry of background patient information.

HORTIS investigators will be responsible for entering all required data. **Assessment** of change, and clinical outcomes, will be determined by each patient's referring/specialty physician, who will remain blinded as to the initial randomization sequence. Such determinations will be undertaken using standardized forms provided by The Baromedical Research Foundation. All such documents become a part of the Medical Record.

Once the electronic database record has been "Finalized", the information contained therein cannot be altered ("corrected") by the treating physician. Should an error in data entry occur, or previously unattainable information become available, a formal correction request must be transmitted to the HORTIS Principle Investigator, in care of The Baromedical Research Foundation.

Requested changes will be approved, or otherwise, by the HORTIS Principle Investigator, in his capacity as guarantor of study integrity. A Quality of Life

questionnaire will compliment the clinical data by providing patient-specific impressions of the value of this therapy.

Data Analysis

All data analysis will be undertaken in Columbia, South Carolina, by faculty and graduate students at the Biostatistical Department, The School of Public Health at The University of South Carolina, USA. These biostatisticians will have “download only” access to the database, with no capability to alter the collected data.

Statistical procedures used in the analysis of data will include simple tests of two proportions (comparing the proportion that heal in the treatment and control groups); chi-square tests of independence when the outcome is classified into more than two levels, and multiple logistic regression, to adjust for other (demographic) factors when comparing the two groups.

All analyses will be performed using statistical programs in SAS.

Publication

The results of HORTIS research will be published in “English-speaking” specialty journals specific to the anatomic sites/medical specialties involved. A separate paper is planned for each of the eight HORTIS arms. Papers will be submitted for publication once a mean follow-up of approximately 12-18 months has been achieved. A follow-up report will be generated at a mean follow-up of 4-5 years.

Each center contributing patients to the database will have a local Principle Investigator identified. Each local P.I. will feature in the author listing, as appropriate (number of patients referred, and any additional contributions to the manuscripts development and review). All other local investigators (treating hyperbaric physicians and referring specialists) who have likewise contributed will be recognized where appropriate (author listing, or within the “Acknowledgements” section).

For further information on Project HORTIS, please contact The Baromedical Research Foundation.

References

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