BONE DENSITY CHANGES IN STROKE PATIENTS

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1. SUMMARY

The goal of this pilot study is to determine the progression of osteoporosis in elderly hemiplegic stroke patients and to test an innovative treatment (functional electrical stimulation, FES) to reduce osteoporosis progression and decrease secondary complications. Presently, the investigators have an NIH grant (#5R01AR40231-02) from the National Institute of Arthritis and Musculoskeletal and Skin Diseases [redacted] to study osteoporosis in spinal cord injured (SCI) subjects. This pilot project will extend our understanding of osteoporosis to the much more prevalent and older population of individuals with stroke. Since stroke affects larger numbers of people, the associated problems and costs are much more widespread than with SCI. For the pilot study, initial bone density measurements of both involved and uninvolved lower extremities and both forearms will be performed on 20 elderly hemiplegic patients within four weeks post-stroke. Baseline neuromuscular examinations will also be performed at this time. Ten of the subjects will be assigned to a treatment program using bouts of repetitive FES-induced contractions of the calf and thigh muscles for six weeks, three times weekly. Scans and neuromuscular examinations will be repeated every two months for up to one year for this experimental group. The remaining ten subjects (control group) will not have FES, and will have repeat evaluations every two months. The non-involved leg will serve as control for the neurologically-impaired leg for all subjects, permitting long term evaluation of osteoporosis changes. This pilot study is expected to provide useful information about osteoporosis in older stroke patients and about a potential technique to facilitate their recovery. This information will permit subsequent grant proposals with widespread clinical applications, not only for the elderly but also for many individuals suffering from disuse osteoporosis.

2. PROTOCOL

Rationale. The number of elderly individuals in the United States is rising faster than at any other time in history due to improvements in medical services and adoption of better life styles (1). With longer life expectancy, health problems and disability are increasingly related to old age. Chronic health problems can have a great impact on normal physical functioning. The chronic problems of the aged include: arthritis, osteoporosis, cardiovascular problems, high blood pressure, and cerebrovascular disease. These conditions exemplify the need for research in health care for the aged.

Stroke or cerebral vascular accident (CVA), can be defined as an interruption in the oxygen supply to the brain resulting from a cerebrovascular lesion (2). Cerebral anoxia (deprivation of oxygen and nutrients to the brain tissue) for more than 5-6 minutes leads to irreversible brain damage. The effects of a stroke may vary from person to person depending on the vessels involved and the amount of brain tissue deprived. CVA can occur at any age, however, individuals over 65 are at substantially higher risk. According to the Department of Health and Human Services 1.7/100,000 people between the ages of 18-44 have the chronic condition classified as cerebrovascular disease. These numbers increase dramatically to 50/100,000 people in the age range of 65-74. Strokes are the leading cause of disability and the third leading cause of death in adults. Annually, 150,000 people die (4) and approximately 3 million in the United States are left permanently disabled as a result of CVA (5). The cost of hospitalization is more than $25 billion (6).

Another disease that affects the aged is osteoporosis, a disease manifested by diminished bone mineral mass and highly associated with increased susceptibility to fracture. The incidence of osteoporosis increases with age. From birth to 20 years of age, bones are in a phase of rapid growth and bone modeling. Bone modeling is the exchange of bone tissue which allows bone growth and skeletal development. The net bone tissue balance during this time is positive because formation exceeds resorption until cessation of growth. After this period, the skeleton is in a constant state of remodeling.

During the process of aging, bone remodeling creates a negative net bone tissue balance where bone resorption exceeds formation. In essence all men and women become osteoporotic if they live long enough. There is no national survey data for osteoporosis and under-reporting of this problem is likely since osteoporosis is often undetected until a fracture occurs. Radiological studies involving women of different ages found that from age 50-59 years, 6.5% of women had osteoporosis (7). There was a dramatic increase to 26% in the prevalence of osteoporosis for the older age range of 70-79 years.

According to many recent studies there is a strong correlation between osteoporosis and strokes (8,9,10). It has long been recognized that forces applied to bone by muscles constitute the most important factor in the prevention of disuse osteoporosis (8). Most strokes cause unilateral flaccid paralysis resulting in a dramatic reduction of stress and strain on the affected limb. Disuse osteoporosis occurs as a result of the reduction of normal stress and strain. Forces applied to bone by contracting muscles constitute the most important factor in the prevention of disuse osteoporosis. In a study by Prince *et al.* hemiplegia was found to be associated with excessive bone loss in the paralyzed limb (9). This study confirms the importance of normal function in the maintenance of bone mass. Significant bone loss occurs with reduction in function and increases with the time duration of the disabling disease. Significant osteoporosis is therefore evident both in the elderly and with conditions resulting in reduced mobility due to neurologic disease. Another study conducted by Browner *et al.* revealed a strong relationship between osteoporosis and death from stroke. The investigation examined non-traumatic mortality in elderly women with low bone mineral density and found that diminished bone mineral density at the proximal radius was strongly associated with deaths from strokes (12). Women with bone mineral density at the proximal radius of 1 SD (standard deviation) below the mean were found to be approximately three times more likely to die of stroke than those with bone mineral density of 1 SD above the mean. Both conditions may result from estrogen deficiency. Bone density might be a marker for lifetime exposure to estrogens which are known to slow bone loss after menopause and have been associated with reduced risk of cerebrovascular disease including stroke.

As more information regarding the rate of development of osteoporosis for stroke victims becomes available, intervention programs are becoming more universally accepted. With positive advances in treatment, the myth that the survival of patients with completed stroke is not sufficiently long to justify the great expense and effort of rehabilitation has been disproved. Studies have found that traditional rehabilitation of stroke patients usually is focused on regaining the ability to walk or ambulate (11,12). The most widely practiced therapeutic program for gait improvement includes lower extremity strengthening, range of motion exercises, and gait training with braces or other assistive devices (11). Newer therapeutic approaches include biofeedback and FES which offer specific benefits for many hemiplegics but have not yet been universally accepted. Because FES-induced contractions produce relatively gross movement of muscle groups, it may be more suitable for use on legs rather than arms. Three desirable effects occur simultaneously during FES treatment: 1) the reversal of disuse muscular atrophy of activated muscles, 2) facilitation of movement via the sensorimotor cortex, and 3) possible reduction of bone loss rate. Therapeutic benefit from FES has been shown to be less dramatic if begun a long time after neurologic injury. FES causes muscle contraction due to direct stimulation of motor neurons and specific recruitment of Type II muscle fibers. It has already been stated that the normal function of the affected limb is critical in the maintenance of bone mass. Without Type II muscle fibers, this normal function is impossible. In contrast to voluntary recruitment which activates Type I motor units first, FES selectively activates Type II motor units due to their lower axonal input resistance. According to Kraft and associates, muscle atrophy in chronic stroke patients occurs selectively on Type II muscle fibers (12). A study by [redacted] on FES in disuse osteoporosis found that it provides some type of bone stimulation that improves the osteoporotic state arising from disuse (13). A study by Hangartner *et al.* investigated tibial bone density loss on spinal cord injured patients and found that FES exercise training reduced the rate of bone loss (14). These findings support the potential of FES as a deterrent to bone loss in disuse osteoporosis.

The primary focus of this project is to investigate the relationship of osteoporosis to the disability caused by stroke and the effectiveness of an intervention (FES) in decreasing bone loss in this elderly population. Bone density measurements on elderly patients with hemiplegia following CVA will provide important initial information concerning:

1) the rate of osteoporosis progression with lower-limb paralysis due to stroke;
2) osteoporosis related to age and sex in this patient population;

3) the effects of paralysis vs. immobility and rehabilitation efforts, respectively;
4) the potential treatment (utilizing FES) of stroke patients in order to reduce the rate of osteoporosis progression and decrease secondary complications.

The study of osteoporosis in hemiplegic stroke patients will add new dimensions to research in aging by providing information about the osteoporosis which occurs following a type of paralysis/immobility common to the elderly. Stroke in older females occurs quite frequently, compounding an already existing bone loss problem (i.e. post-menopausal osteoporosis) with that related to paralysis/immobility. Severe osteoporosis can markedly increase medical complications and patient care costs. In addition, the hip fracture which often occurs with stroke and osteoporosis is associated with high mortality rates. Prevention of osteoporosis is important for the elderly since the process cannot be reversed once it has taken place. If the FES intervention is successful, the older individual will not have to suffer the consequences of osteoporosis following stroke. If bone integrity can be preserved during the time of disuse (the flaccid stage), later recovery will be more effective since the osteoporosis process would have been prevented. The potential for improved quality of life and rehabilitation in patients with strokes makes this study important as a tool for future development.

Objectives. To achieve the goal of studying the progression of osteoporosis in elderly hemiplegic stroke patients, the following objectives will be accomplished:

1) recruit a group of 24 elderly hemiplegic stroke patients within four weeks of their CVA;
2) perform initial CT scans on the involved and uninvolved lower limbs and forearms for baseline bone density measurements;
3) perform neuromuscular examinations at the time of CT scans in order to determine the degree of flaccidity/muscle function recovery.
4) perform an innovative treatment program of FES on the involved lower limb for six weeks for the experimental subject group (n=12).
5) perform follow-up CT scans for comparison of the rates of osteoporosis progression in both experimental and control groups.

Subjects. The study will document bone density loss in both legs of 20 elderly hemiplegic patients for up to a one year period post-stroke. Approximately 24 recent stroke patients (male and female) will be recruited, screened, and entered into the protocol, which allows for 4 subject drop-outs. Prior to participation, potential subjects will be informed about the study in accordance with the Institutional Review Boards of Wright State University and participating medical centers. Entry criteria will include: 1) stroke resulting in flaccid paralysis of one lower extremity, 2) typically, age 55 to 75 years, and 3) available for first bone measurement no later than 4 weeks after stroke. Area hospitals, including USAF Medical Center, Wright-Patterson Air Force Base, will assist in recruiting participants for the study as long as the patients are transportable. [redacted], will serve as the project's medical facility investigator for the USAF Medical Center, Wright-Patterson Air Force Base. Generally, all stroke patients with flaccid paralysis of one leg will be accepted if medically stable enough for bone measurements. The exact characteristics of the hemiplegia will be assessed by neurologic examination. Medical screening will ensure the patient's safe participation in the study, particularly transfers to the bone scanner in the early stages after injury. Subjects will be assigned to either the experimental or control group. Experimental subjects will participate in the FES treatment program along with routine rehabilitation. Control subjects will be matched to the experimental subjects for neurological involvement as closely as possible.

Data Collection Protocol. Procedures will include measurement of bone density at the distal end of both tibias and both forearms (distal radius) as soon as possible following stroke for baseline osteoporosis level. After the initial measurement, scans will be performed every two months for both the experimental and control groups for one year post-stroke. The scans will include the uninvolved leg and forearm to evaluate the progression of osteoporosis without immobility. In order to obtain information about the expected changes in the degree of flaccidity/muscle function recovery which occur following stroke, neurological and functional assessments will be performed at the time of the scans. Since recovery after stroke is highly variable, these assessments will enable documentation of the relationship between muscle flaccidity/recovery vs. changes in the degree of osteoporosis.

Measurements. Bone density will be monitored in all patients using the specially-designed CT scanner (OsteoQuant) at Miami Valley Hospital. The OsteoQuant is a special CT scanner based on the translate-rotate principle and optimized for the measurement of cross-sections up to 200 mm diameter. The radio-active isotope ^{125}I is used as the radiation source instead of an X-ray tube. This guarantees a very stable energy spectrum in a range most suitable for an optimum contrast between bone and soft tissue at the size of the legs and arms. Sixteen detectors measure the transmitted photons and a VAX 8200 from Digital Equipment Corporation with an FPS 5000 array processor from Floating Point Systems are responsible for image reconstruction and evaluation (16). These measurements involve very low radiation levels and are considered to be safe.

The measurement procedure requires the scanning of 6 to 10 cross-sections, 2mm apart from each other. Each cross-section is evaluated separately by finding the outer contour of the bone. A certain number of pixel-wide shells is then pealed off until 40 to 60% of the cross-sectional area is left. This is the region of interest (ROI) for averaging trabecular bone density (TBD). The outer boundary of the ROI is chosen in a way to make sure that no part of the cortex is included. The obtained TBD values of all sections are then correctly averaged to produce a mean TBD for the volume of interest.

Treatment. FES will be administered via surface electrodes to the quadriceps, hamstrings, tibialis anterior and gastrocsoleus muscle groups of the involved lower limb. With the patient lying supine, isometric co-contractions of all four muscle groups will be induced with a 1.5 s on / 1.5 s off duty cycle. The stimulation pulses are abruptly turned on and off in order to produce a strong impact loading on the bones, and to simulate the stress on the bone which naturally occurs as muscles voluntarily contract. This is considered safe since the degree of osteoporosis immediately following stroke would be low. The stimulator provides biphasic rectangular pulses of 0.3 ms duration at a frequency of 35 Hz. The current output will be adjusted to obtain vigorous contractions of all muscles. This is done by increasing the stimulation current until no further increase in muscle contraction can be observed. The maximum current amplitude is 150 mA. The FES treatment will be applied during 45 minute sessions, 3 times per week for a 6 week period of time. This duration and frequency of training has been shown to be adequate for re-building muscle strength in other neurologically impaired subjects several years after injury (17). This will not alter their normal therapeutic treatment but rather be in addition to it. For those participants who have or develop lower limb sensation, current parameters will be adjusted to obtain the best muscle contractions possible within the patient's tolerance.

Analysis. The experimental design with treatment of only the involved leg permits subjects to serve as their own control. The neurologically-matched control group will enable the assessment of the FES intervention effect on bone density in stroke patients. Measurements of bone density will be analyzed for each patient separately. By comparing the first measurement (baseline/reference) with all subsequent measurements, they can be expressed as a percentage change relative to the baseline. Using the non-involved leg as a control for the neurological-impaired (paralyzed) leg permits a better understanding of osteoporosis changes in comparison to the innervated functional leg which is highly utilized in rehabilitation activities. Comparisons will also include differences in post-stroke osteoporosis progression between pre- and post-menopausal patients, and correlational analysis of the relationship of age to osteoporosis progression.

Resources. This interdisciplinary study includes the participation of faculty from many different departments and clinicians from many different area hospitals. The principal investigator, [redacted] Ph.D., P.T., (Research Associate Professor of Rehabilitation Medicine and Restorative Care, Research Associate Professor of Orthopedic Surgery) from Wright State University's Institute for Rehabilitation Research and Medicine (IRRM) desires to establish new directions in the rehabilitation problems of geriatric populations. She will generally coordinate the pilot study, interacting regularly with co-investigators and collaborating physicians as well as with the research personnel, and be responsible for all FES treatments, evaluations, and data analysis. [redacted] Ph.D., (Associate Professor of Biomedical Engineering and Medicine) will be responsible for measurements by the CT scanner. [redacted], MD., (Professor and Chair of Neurology) will supervise the neuromuscular physical exam. Bone scanning equipment and analysis software are available through the

Biomedical Imaging Laboratory at MVH. The stimulator equipment and technical support are available through the IRRM. Equipment and techniques required for this project have already been developed and established from previous work, reducing the costs for this pilot study.

The larger Dayton community will also be involved in this project. Clinicians at area hospitals, including USAF Medical Center, Wright-Patterson Air Force Base, Miami Valley Hospital (MVH), St. Elizabeth Medical Center, Dayton VAMC, Greene Memorial Hospital, Middletown Regional Hospital, and Good Samaritan Hospital and Health Center, will assist in recruiting participants for the study. [redacted], M.D., will serve as the Medical Facility Investigator for USAF Medical Center, Wright-Patterson Air Force Base. Only those patients who are able to go to MVH for the bone scan measurements will be recruited. Students participating in the study will gain experience in elderly patient problems and relations, FES techniques, bone density measurements, and statistical analysis of the data. This will reinforce their basic science knowledge and provide relevant clinical applications.

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