Award Number:W81XWH-10-1-1043

TITLE: FES-Rowing versus Zoledronic Acid to Improve Bone Health in SCI

PRINCIPAL INVESTIGATOR:Leslie R. Morse, DO

CONTRACTING ORGANIZATION: Spaulding Rehabilitation Hospital
Charlestown, MA 02129

REPORT DATE: October 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Marylan 21702-5012

.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE
October 2014

2. REPORT TYPE
Annual Report

3. DATES COVERED
30 SEP 2013 – 29 SEP 2014

4. TITLE AND SUBTITLE
FES-Rowing v. Zoledronic Acid to Improve Bone Health in SCI

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-10-1-1043

5c. PROGRAM ELEMENT NUMBER

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

6. AUTHOR(S)
Leslie R. Morse, DO
E-Mail: lmorse4@partners.org

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Spaulding Rehabilitation Hospital
Charlestown, MA 02129

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

There is no established treatment to prevent bone loss or to induce new bone formation following SCI, although the risk is high in this population of osteoporosis-related bone fracture. This study aims to learn if the severe osteoporosis in lower extremities caused by spinal cord injuries can be slowed or reversed with a combination of an exercise that simulates weight-bearing and a bisphosphonate medication. 70 Individuals with T3-12 spinal cord injuries will be enrolled in a 12-month regime of adapted FES-rowing. Our preliminary study findings demonstrated this exercise led to new bone formation and improved bone micro architecture in the lower extremities of people with SCI. Half of the subjects also receive a bisphosphonate medication known to slow bone loss, but not stimulate bone renewal.

Participant recruitment began in late February, 2011, and was completed in October 2013. We have enrolled 70 subjects, 46 of whom have completed the study.

15. SUBJECT TERMS
SCI, Osteoporosis, FES-rowing, zoledronic acid, exercise, bone health

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON** ~~USAMRMC~~
a. REPORT U	**b. ABSTRACT** U	**c. THIS PAGE** U	UU	9	**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

Introduction

Serious spinal cord injury (SCI) causes osteoporosis in the lower extremities, significantly increasing the risk of bone fracture in this population. However, there currently is no established treatment to prevent bone loss or to induce new bone formation following SCI. The goal of this clinical trial -- *FES-Rowing versus Zoledronic Acid to Improve Bone Health in SCI* – is to develop an evidence-based therapeutic protocol to address a prevalent and significant health issue in this population. A second aim is to better understand the bone biology and bone health of people with serious SCI.The trial calls for 70 subjects with SCI to participate in a 12-month adapted FES-rowing program. Half of the subjects also receive a one-time infusion of zoledronic acid, a bisphosphonate used to treat osteoporosis, usually in older women.

We demonstrated in our preliminary studies that functional electrical stimulation (FES) rowing stimulates bone formation and improved bone micro-architecture in the lower extremity. Bisphosphonate medications slow bone loss but do not stimulate new bone formation. Therefore, combination treatment with a bone-building stimulus (FES-rowing) and a medication that stops bone loss (bisphosphonate) may result in greater improvements in bone compared to either agent alone. We are using DXA and CT bone scans to compare changes in bone density and health pre- and post-rowing and bisphosphonate treatment. The results of this study should provide a better understanding of possible therapies to maintain bone strength among people with SCI.

Body

We received final Department of Defense approval to begin active subject recruiting in February, 2011. In the past year we have focused row training, and data collection. We have completed study enrollment, enrolling 70 subjects. Among the enrolled subjects, 46 have completed end of study testing and 18 have received the zoledronic acid infusion. We expect the remaining 3 active subject to complete the study by the end of this month.

Statement of Work, Task 1: Study preparation, human subjects approval, finalize instruments, procedures, protocols; research coordinators

This task was completed during the first year of the study.

Statement of Work, Task 2: Recruitment and screening

We have reached our subject enrollment goal of 70 and are no longer recruiting or screening potential subjects.

Statement of Work, Task 3: Enrollment, randomization, baseline testing

We have enrolled 70 individuals, 35 in treatment arm and 35 in the rowing only arm. Baseline bone density scanning, blood draws (renal function, vitamin D levels, calcium levels, bone turnover markers), and distribution of calcium and vitamin D supplements have been carried out successfully at the VA Boston Healthcare-Jamaica Plain Campus. Among participants who have been tested as of October, 2014, 36 were found to have a vitamin D deficiency (<than 30ng/ml) and were treated with supplemental vitamin D. No subject has been excluded from participation based on screening blood work (ie renal function has been adequate in all subjects).

Statement of Work, Task 4: 6-month measurements

37 subjects have had their midpoint data collection – bone density scans, as well as blood draws to check vitamin D, renal function, and future analysis of bone turnover markers. 20 subjects have had their 6 month of rowing ct scan of the knee.

Statement of Work, Task 5: FES-row training

38 subjects transitioned from strength-training to active rowing.

Statement of Work, Task 6: Zoledronic acid infusion

Eighteen subjects have received the zoledronic acid infusion at the VA Boston Healthcare-Jamaica Plain Campus. The nurse practitioner who administered the infusion makes follow-up phone calls within 24 hours to check on how the subject is feeling.

Statement of Work, Task 7: 18-month measurements

We have scheduled final testing for the 3 remaining subjects who have completed 1 year of rowing and expect to complete data collection by the end of December, 2014. When testing is complete, we will send 6 month and 12 month blood samples for batch analysis.

Statement of Work, Task 8: Data analysis

We are currently analyzing cross-sectional data collected for the all subjects enrolled, including baseline ct data on 44 subjects and longitudinal ct data on 20 participants who have completed at least 6 months of rowing. Once data collection is complete, we will analyze longitudinal change in bone strength for all participants.

Key Research Accomplishments/Preliminary Findings to Date: We have several interim key research accomplishments based on analysis of baseline and 6 month data.

As of November 2014, we have enrolled 70 participants, 35 to the zoledronic acid infusion arm and 35 to the exercise only arm. Of those enrolled there are 63 males and 7 females. There are 17 motor incomplete injuries and 53 motor complete injures. The mean age was 38.7 (20.73-65.1) and the mean years post injury was 10.39 (0.08-37.5). A total of 59 have had baseline blood work, 60 have had their baseline DXA scan and 45 have had their baseline CT.

Subject Characteristics:

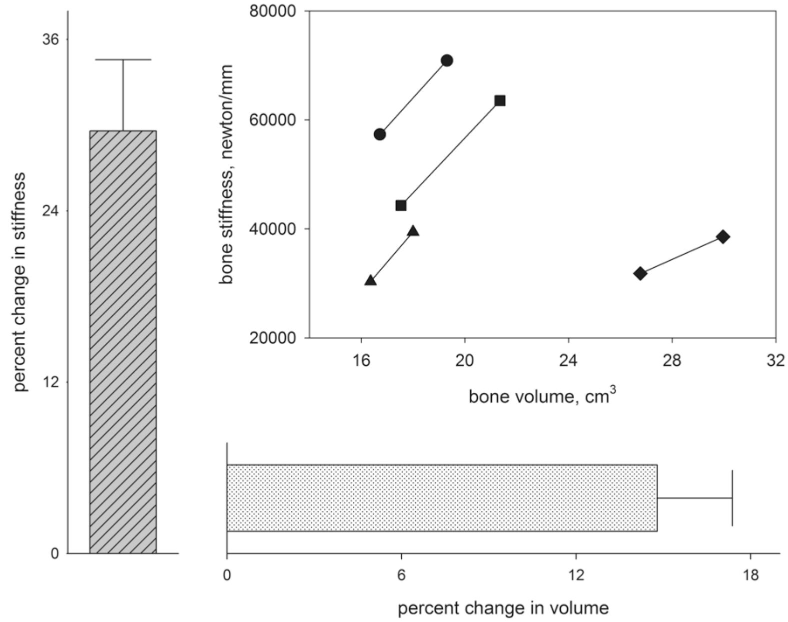
Variable	ZA Infusion and Exercise Arm n=34	Exercise Only Arm n=35
Demographics		
Age (Mean ± SD) [years]	37.2 ± 12.7	40.1 ± 11.3
Age (Range) [years]	20.7-63.5	21.1-65.1
White %	27 (77.14%)	30 (85.71%)
Male %	32 (91.43%)	31 (88.57%)
Duration of SCI (Mean ± SD) [years]	9.93 ± 10.8	10.9 ± 10.5
Duration of SCI (Range) [years]	8.1-46.1	0.13-37.3
Motor Complete Injury %	28 (52.24%)	25 (71.43%)
BMI [Mean ± SD] (kg/m^2)	25.2 ± 5.6	27.5 ± 5.6
Vitamin D (Mean ± SD)	29.6 ± 10.3	26.6 ± 10.6
• Deficient <30 ng/ml	23 (65.71%)	25 (71.43%)
• Sufficient ≥30 ng/ml	12 (34.29%)	10 (28.57%)
Smoking History		
• Current smoker	3 (10.0%)	3 (10.3%)
• Former smoker	8 (26.7%)	8 (27.6%)
• Never smoker	19 (63.3%)	18 (62.1%)

Baseline Bone Density/Incidence of Osteoporosis at the Hip: We scanned at traditional bone density sites (femoral neck, total hip and radius) as well as SCI specific skeletal sites (distal femur and proximal tibia) as these are the sites were fractures are most common within the SCI population. For subjects age 50 or older, T-score was used to classify hip bone density (total hip and femoral neck) according to the World Health Organization (WHO) definitions of normal (T-score ≥-1), osteopenia (T-score <-1 and >-2.5) and osteoporosis (T-score ≤-2.5). For subjects under the age of 50, Z-score was used to classify hip bone density as normal (Z-score >-2) or as lower than expected for age and sex (Z-score ≤ -2). A total of 30.0% of the participants were classified as having osteoporosis/BMD lower than expected for age. Four participants had no hip data available for analysis due to contracture and 3 are pending DXA scans.

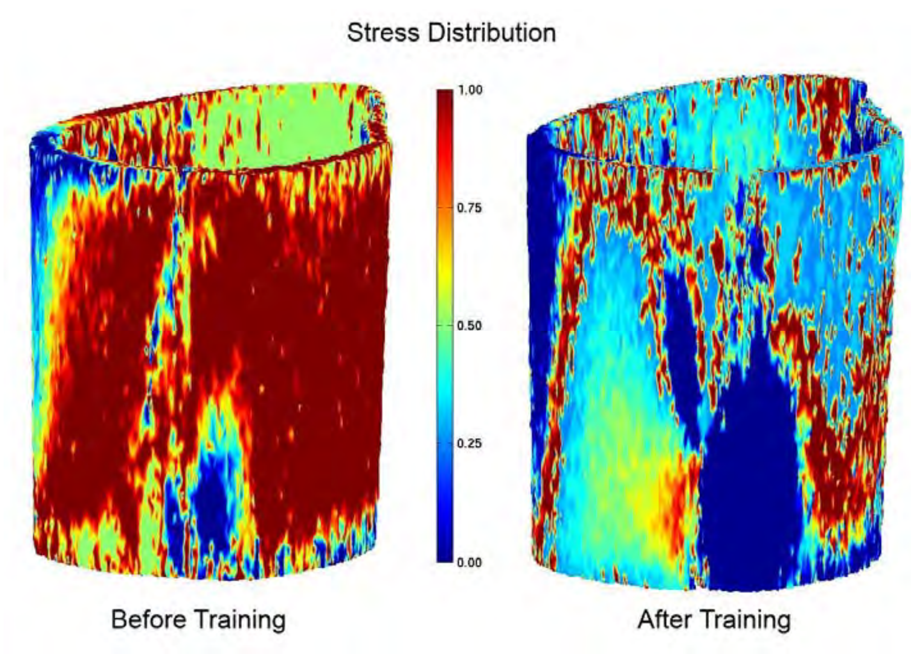
Bone Mineral Density (Mean ± SD) (Range) [g/cm^2]		
SCI Specific Sites		
• Distal femur	0.756 ± 0.24	0.715 ± 0.25
• Proximal tibia	0.795 ± 0.30	0.733 ± 0.26
Traditional Sites		
• Femoral Neck	0.859 ± 0.21	0.795 ± 0.23
• Total Hip	0.834 ± 0.23	0.780 ± 0.23
• Radius	0.980 ± 0.09	0.985 ± 0.08
Osteoporosis status		
• Normal	9 (25.7%)	7 (20.0%)
• Osteopenia	12 (34.3%)	9 (25.7%)
• Osteoporosis/BMD lower than expected for age	9 (25.7%)	12 (34.3%)
• No hip BMD available	5 (14.3%)	6 (17.1%)

Baseline Vitamin D Status: Of those tested, 36 were found to have a vitamin D deficiency (<than 30ng/ml) and were treated with supplemental vitamin D. After completing the round of repletion, 14 had corrected vitamin D levels greater than 30 ng/ml. After repletion, everyone takes a standard dose of vitamin D and calcium. The average vitamin D value was 28.1 ng/ml (std=10.48, range 7-58.7).

Improvements in Bone Stiffness: 26 subjects have completed rowing (13 ZA infusion and 13 rowing only). We performed finite element analysis to calculate changes in bone volume and bone stiffness in response to rowing. A 3D model of the proximal tibia was created from the volumetric CT images. A 10 mm section of the proximal tibia was segmented from the surrounding tissue by thresholding followed by region growing. The model was meshed with tetrahedral elements and linear elastic material properties for bone were assigned to the model (Young's Modulus, E, of 17kGPa and a Poisson's ratio of 0.3). After boundary conditions were assigned, the bottom of the tibia was fixed in space and the top was compressed by 0.1 mm in axial direction. Stiffness was determined by recording the sum of the reaction forces of all elements and dividing it by the displacement (k=F/x). We observed increases in bone volume and in bone stiffness (14.8% +/- 2.6 and 29.6% +/- 5.0, respectively) due to row training.



FES rowing results in increased tibial bone volume and stiffness. Bone stiffness was plotted as a function of volume for four SCI subjects (●, ■, ▲ and ◆) after 6 months of row-training. Rowing increased stiffness and volume in all four subjects**.**



FES rowing improves tibial stress distribution. This image demonstrates the change in stress distribution in response to the same axial force (10 kN) at the tibia in the same subject before and after FES-row training. Stress values are normalized to 0 - 1 (0: blue, no stress to 1: red, max stress). The overall stiffness of the bone (i.e., its ability to withstand axial compression) was improved by almost 50%, from ~43 to ~64 kN/mm). This indicates improved bone strength and better stress distribution.

Adiponectin as a marker of bone strength and fracture history in motor complete SCI: We explored the association between circulating adiponectin levels and bone strength in 27 men who had completed baseline testing. Plasma adiponectin levels were quantified by ELISA assay. Axial stiffness and maximal load to fracture of the distal femur were quantified via finite element analysis using reconstructed 3D models of volumetric CT scans. We also collected information on timing, location, and cause of previous fractures. Axial stiffness and maximal load were inversely associated with circulating adiponectin levels (R^2=0.32, *p*=0.002; R2=0.33, p=0.002) after adjusting for injury duration and lower extremity lean mass. In individuals with post-SCI osteoporotic fractures, distal femur stiffness (*p*=0.01) and maximal load (*p*=0.005) were lower and adiponectin was higher (*p*=0.04) than those with no fracture history. Based on these findings, strength estimates may improve fracture risk prediction and detection of response to osteogenic therapies following spinal cord injury. Furthermore, our findings suggest that circulating adiponectin may indeed be a feasible biomarker for bone health and osteoporotic fracture risk in individuals with motor complete spinal cord injury. These findings will were reported in a recent publication (Adiponectin is Associated with Bone Strength and Fracture History in Paralyzed Men with Spinal Cord Injury. Osteoporos Int. 2014 Nov;25(11):2599-607).

FES-rowing and aerobic capacity: We hypothesized that hybrid Functional Electrical Stimulation Row Training (FES-RT) would improve aerobic capacity but that it would remain strongly linked to level of spinal cord lesion due to limited maximal ventilation. We studied 14 participants with complete SCI T3_T11, >2 years post-injury, aged 21-63 years after six months of FES-row-training. We found that FES-row training significantly increased VO_2peak and Vepeak (both $p<0.05$). Prior to FES-row training, there was a close relationship between level of spinal cord injury and VO_2peak (adj $r^2=0.40$, $p=0.009$) that was markedly reduced after FES-row training (adj $r^2=0.15$, $p=0.10$) . In contrast, the relationship between level of injury and $V_E$peak was comparable before and after FES-RT (adj $r^2=0.38$ vs. adj $r^2=0.32$, both $p<0.05$). Therefore, we conclude the increased aerobic capacity reflects more than increased ventilation; FES-row training effectively circumvents the effect of the spinal cord injury on peak aerobic capacity by engaging more muscle mass for training, independent of level of injury.

Reportable Outcomes

Publications

Taylor JA, Picard G, Porter A, **Morse LR**, Pronovost M, Deley G. Hybrid FES exercise training alters the relationship between spinal cord injury level and aerobic capacity. Arch Phys Med Rehabil. 2014 Nov;95(11):2172-9.

Tan C, Battaglino R, Doherty A, Gupta R, Lazzari A, Garshick E, Zafonte R, **Morse LR.** Adiponectin is Associated with Bone Strength and Fracture History in Paralyzed Men with Spinal Cord Injury. Osteoporos Int. 2014 Nov;25(11):2599-607.

Awards

Best Paper Award, Fellow category, 2015 Annual meeting of Association of Academic Physiatrists (Saeed Alzahb, MD)

National and International Presentations

Exercise Program for Spinal Cord Injury Based on Hybrid Functional Electrical Stimulation Row Training, Oral Presentation, 62nd Annual ACSM Meeting, 6th World Congress on Exercise is Medicine® and World Congress on the Basic Science of Exercise Fatigue

Maximal Ventilation Limits Increased Aerobic Capacity with Hybrid Functional Electrical Stimulation Exercise Training in High Spinal Cord Injury, Oral presentation, 2015 Annual Association of Academic Physiatrists

Circulating Adiponectin Levels are Negatively Associated with Bone Strength in Males with Motor Complete SCI, Oral presentation, American Spinal Injury Association Annual Meeting, 2014

Bone Regenerative Effects of FES-Rowing, American Spinal Injury Association Annual Meeting, 2013

Effect of a Regular Rowing Exercise Program on Maximal Exercise Capacity in Spinal Cord Injury (SCI), Oral presentation, American Spinal Injury Association Annual Meeting, 2012

FES-rowing improves bone micro architecture and strength in the paralyzed lower extremity, Poster Presentation, 2012 Annual ISCoS meeting

Bone Regenerative Effects of FES-Rowing, Oral Presentation, First Annual Symposium on Regenerative Rehabilitation, McGowan Institute for Regenerative Medicine, University of Pittsburgh, 2011

Conclusion

We have ended the fourth year of the study with great success in testing. We anticipate completion of data collection by December 2014 and will focus on data cleaning and analysis. We have disseminated our work at national and international conferences with good reception and have published preliminary findings in 2 recent publications.

References
Not applicable

Appendices
None