Title: High Dose Omega-3 Fatty Acids in the Treatment of Sport Related Concussions

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Methods

This study obtained IRB approval prior to enrollment of participants through East Carolina University and Medical Institutional Review Board. The study design was a randomized double-blind placebo-controlled trial using student's T test for analysis of continuous outcome variables. This study was conducted at East Carolina University over a 4 year period. The inclusion criteria for each subject were: must be a NCAA Division I student athlete at East Carolina University, must be 18 years old, have sustained a sport related concussion with the past 24 hours, and have a neurological exam not consistent with concern for an intracranial hemorrhage or other significant pathology. The exclusion criteria for each participant was: a recent prior concussion within the past 30 days, a history of moderate to severe TBI that has required hospitalization or resulted in prolonged signs and/or symptoms (>3 weeks), a known neurological diagnosis associated with impaired cognitive function other than attention deficit hyperactivity disorder or attention deficit disorder, a known allergy to algae, omega-3 fatty acid, or any component of the formulation, a known liver pathology or significantly elevated LFTs (greater than 3 x normal), a current lower extremity injury that will affect postural stability testing, subjects already routinely using omega-3/DHA supplementation, and subjects currently requiring anticoagulants, anti-platelets or any NSAIDs.

Once a student-athlete was diagnosed with a sport related concussion, and met the inclusion and exclusion criteria, the athlete met with the primary investigator and an IRB approved informed consent was obtained. The athlete then was randomly assigned to either high dose omega-3 fatty acid/DHA supplementation or placebo. Demographics of the athlete were obtained and include age, gender, sport, academic year, height, weight, BMI, history of prior concussion, migraines, learning disability, or psychiatric diagnosis. The experimental group was given a standardized dose of 2 grams (4 capsules) of omega-3 fatty acid/DHA for 30 days after onset of concussion. The placebo group was given an equal number of capsules. Both the omega-3 fatty acid/DHA capsules and placebo capsules were donated to East Carolina University for the purpose of this study by DSM Nutritional Products. The omega-3 fatty acid/DHA used in this study was derived from algae and therefore had no fish odor or after taste. The physician and the athletic training staff evaluating and clearing the athlete to return to activity were blinded. Each athlete underwent daily directly observed therapy by certified athletic trainers and daily symptom monitoring using the Symptom Evaluation scale found on the Sport Concussion Assessment Tool 2 (SCAT2). Symptoms were grouped into physical, cognitive, emotional and sleep categories with the total number of symptoms and symptoms severity score calculated for each category and overall.

Both groups underwent standard and usual care for concussed athletes at East Carolina University. East Carolina University employs a regimented return-to-play protocol for every student-athlete that has sustained a concussion (Figure 1). As part of their pre-participation physical, all student-athletes have a baseline computerized neuro-physical postural stability test using Biodex SD/BioSway and a computerized neurocognitive test using ImPact. At the time of

injury, a SCAT2 is administered by a certified athletic trainer, and the student-athlete is withdrawn from participation if they are symptomatic and/or have deficits noted. The same day a concussion is suspected a repeat Biodex postural stability test is administered and the student-athlete is given a detailed information sheet on instructions for monitoring and follow-up. A repeat Impact neurocognitive test is administered within 24 hours after the injury. The student-athlete is then seen and examined by a sports medicine physician to review the results, perform a clinical examination, and confirm the diagnosis. The student-athlete is then evaluated daily with a modified Symptom Evaluation Questionnaire found on the SCAT2 by an athletic trainer. When the student-athlete is asymptomatic with activities of daily living (ADLs) for 24 hours, he/she then begins a non-contact return to play protocol beginning with a supervised cardiovascular challenge. This includes 30 minutes of supervised light aerobic activity on a treadmill or stationary bike. If the athlete is asymptomatic with the cardiovascular challenge, then he/she can progress to noncontact sport specific drills the subsequent day. If the athlete is still doing well, he/she can progress their non-contact training drills and start light resistance training the following day. If the student-athlete remains asymptomatic through the non-contact activity progression, he/she then re-takes the computerized neurocognitive test, postural stability assessment and is re-evaluated by the physician. If the postural stability assessment and neurocognitive test are back to baseline the athlete is then cleared at the discretion of the treating sports medicine physician to return to full unrestricted activity. However, if a student-athlete continues to be symptomatic on day 7 both Impact and Biodex SD/BioSway evaluation will be re-administered. This will be repeated at 14 days and 30 days post-injury if the student-athlete continues to be symptomatic (Figure 1). The primary outcome of the study is the total number of days from onset of concussion it takes for the athlete to return to unrestricted full participation in their respective sport.

Results

A total of 62 student-athletes were enrolled and completed the study. 7 student-athletes were excluded from the analysis secondary to return to play greater than 30 days. Of those 7 student-athletes 6 were in the DHA cohort and 1 was in the placebo cohort. 55 student-athletes (33 male and 22 female) were used in the analysis. The demographics of the DHA cohort were: 19.7±1.4 years of old, 60.9% male, 39.1% female, and a BMI of 27.7±6.1. The demographics of the placebo cohort were: 19.9±1.4 years of age, 59.4% male, 40.6% female, and a BMI of 28.3±6.1. There was no statistically significant difference in age, gender, BMI, and sports distribution in the DHA vs the placebo cohort. Direct observed therapy of the intervention lead to a compliance rate of 84.2% in the DHA cohort and 83.0% in the placebo cohort. A previous history of concussion prior to the study was recorded and there was no statistical difference between the cohorts with the DHA cohort at 47.8% and the placebo cohort at 50%. The initial SCAT2 symptom severity score, an indicator of concussion severity, was recorded. The DHA cohort's initial SCAT2 symptom severity score was 42.7±27.9 compared to the placebo cohort's initial SCAT2 symptom severity score of 49.9±26.6. Despite the placebo cohort's higher symptom

severity score this was not statistically significant. The primary outcome of this study was the number of days that the athlete required to return to play. The DHA cohort's return to play was 11.0±4.8 days [95% CI 9.1,13.0] and the placebo cohort's return to play was 11.9±5.4 days [95% CI 10.0,13.8], with a P value of 0.558 (Figure 2). The effect size was calculated to be 0.16 and a post hoc power analysis was calculated to be 0.09.

Figure 1: East Carolina University Concussion Management Standardized Protocol

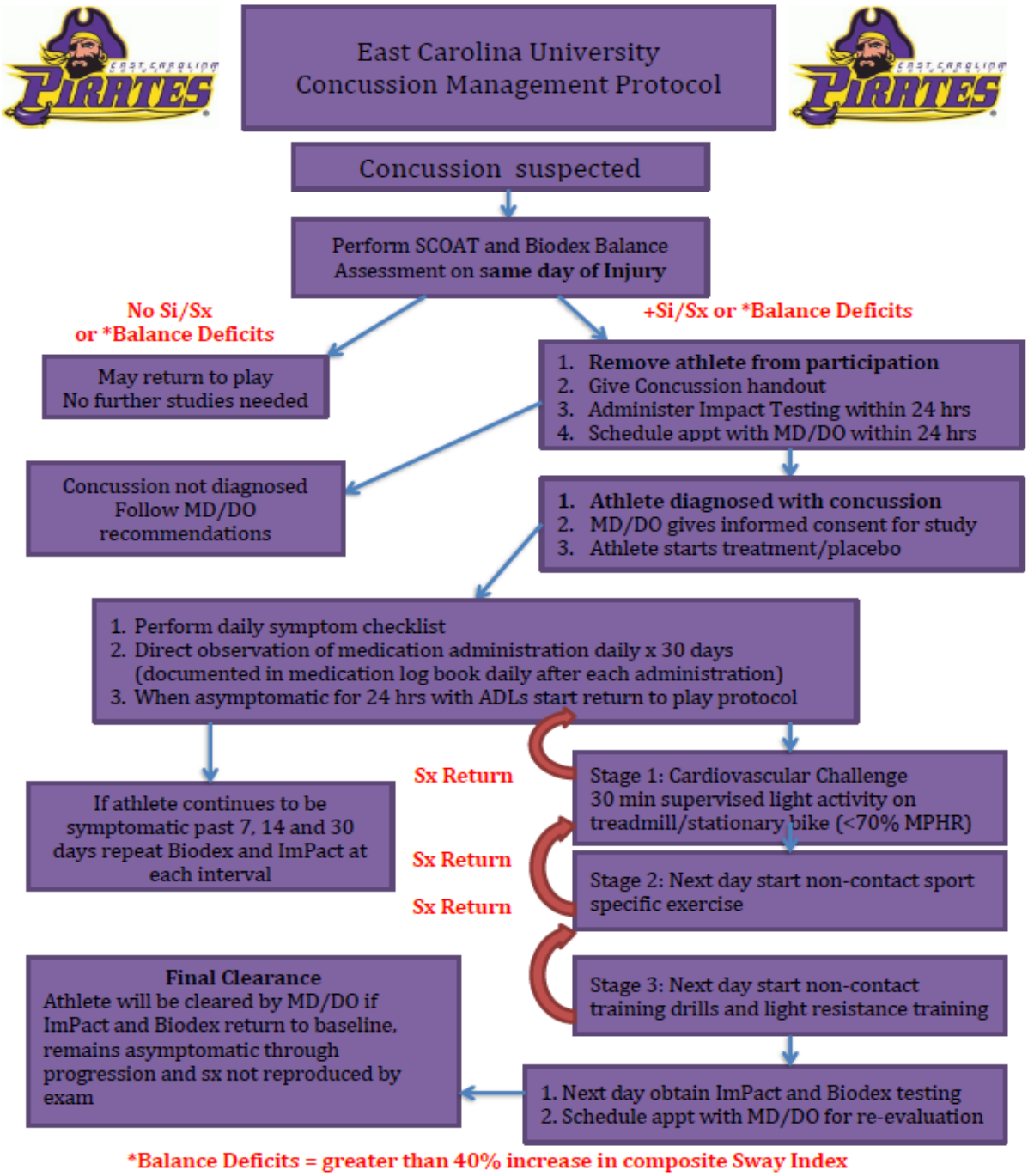

Figure 2: Results

	DHA (n= 23)	Placebo (n=32)
Age (years)	19.7 ± 1.4	19.9 ± 1.4
Gender (male: female)	60.9%: 39.1%	59.4%: 40.6%
BMI (kg/m²)	27.7 ± 6.1	28.3 ± 6.1
Compliance	84.20%	83.02%
History of Concussion	47.8%	50%
SCAT2 Symptom Severity Score	42.7±27.9	49.9±26.6
Return to Play (days) (P=0.558)	11.0 ± 4.8 [95% CI 9.1,13.0]	11.9 ± 5.4 [95% CI 10.0,13.8]

East Carolina University

Informed Consent to Participate in Research

Information to consider before taking part in research that has more than minimal risk.

Title of Research Study: High Dose Omega-3 Fatty Acids in the Treatment of Sport Related Concussions

Principal Investigator: Joseph Armen DO

Institution/Department or Division: Department of Family Medicine and Sports Medicine, Brody School of Medicine

Address:1001 East 5th Street, Greenville, NC 27858

Telephone #: 252-737-2593

Researchers at East Carolina University (ECU) study problems in society, health problems, environmental problems, behavior problems and the human condition. Our goal is to try to find ways to improve the lives of you and others. To do this, we need the help of volunteers who are willing to take part in research.

Why is this research being done?

The purpose of this study is to evaluate if Brain Armor, a high-dose omega-3 fatty acid supplement, gives added benefit and improve recoverability to athletes who have sustained a concussion. Omega-3 fatty acids is an oil commonly found in fish, there is a growing body of evidence that omega-3 fatty acids have antioxidant and anti-inflammatory properties and can improve brain function. A concussion is a self-limiting head injury in which a direct or indirect blow to the head causes functional problems without any structural brain damage. The purpose of this study is to determine if omega-3 fatty acids' antioxidant and anti-inflammatory properties can improve symptoms of a concussion and improve brain function. A potential benefit of this study is to reduce the length of time recovering from a concussion and potentially reducing the incidence of post-concussion syndrome.

Why am I being invited to take part in this research?

You are being invited to take part in this research because you are National Collegiate Athletic Association (NCAA) Division I athlete who has sustained a concussion within the last 24 hours. If you volunteer to take part in this research, you will be one of 100 people to do so.

Are there reasons I should not take part in this research?

You should not volunteer for this study if you are less than 18 years of age. You must not have a history of: 1. Have a recent prior concussion within the past 30 days. 2. Have a history of

moderate to severe concussion that has required hospitalization or result in prolonged signs/symptoms (greater than 3 weeks). 3. Have a known neurological problem associated with trouble thinking or focusing other than Attention Deficit Disorder or Attention Deficit and Hyperactivity Disorder (ADD/ADHD). 4. Already routinely using omega-3/Docosahexaenoic Acid (DHA) supplementation. 5. Have a history of allergy to algae (common water plant), omega-3 fatty acid, or any component of the formulation. 6. Currently on any blood thinners such as Coumadin, aspirin, or Plavix, if you are on an anti-inflammatory (ie Motrin, Aleve) you will be asked to stop that medication. 7. If you have known liver problems with significantly elevated liver enzymes. 8. A current lower extremity injury that will affect postural stability testing (balance testing).

What other choices do I have if I do not take part in this research?

You can choose not to participate, at which point you will undergo East Carolina University's standard return to play protocol and still receive the standard of care in the treatment of concussions.

Where is the research going to take place and how long will it last?

The research procedures will be conducted at Ward Sports Medicine Building. Once identified as a potential subject it will take about 30 minutes for informed consent and medication dispensing. You will then follow a standard return to play protocol with East Carolina University Sports Medicine staff.

What will I be asked to do?

You are being asked to do the following:

After you sign this consent form, you will be randomly assigned, by sealed random envelope, to either Brain Armor or placebo. You are being asked to be compliant with medication administration and recommendations given by the team physician and athletic training staff. You will undergo standard and usual care for concussed athletes at East Carolina University. Demographics of the athlete will be obtained which include: age, gender, sport, academic year, height, weight, Body mass index, history of prior concussion, and history of learning disability or psychiatric diagnosis.

What possible harms or discomforts might I experience if I take part in the research?

It has been determined that the risks associated with this research are potential adverse drug reactions that can be experienced with omega-3 fatty acids or with the placebo, such as rash or hives. If this occurs you need to contact the primary investigator immediately and discontinue the medication. More common side effects include gastrointestinal upset, heartburn or nausea.

What are the possible benefits I may experience from taking part in this research?
We do not know if you will get any benefits by taking part in this study. A potential benefit of this study is to reduce the length of time recovering from a concussion and potentially reducing the incidence of post-concussion syndrome.

Will I be paid for taking part in this research?

We will not be able to pay you for the time you volunteer while being in this study.

What will it cost me to take part in this research?

It will not cost you any money to be part of the research.

Who will know that I took part in this research and learn personal information about me?
To do this research, ECU and the people and organizations listed below may know that you took part in this research and may see information about you that is normally kept private. With your permission, these people may use your private information to do this research:

- Any agency of the federal, state, or local government that regulates human research. This includes the Department of Health and Human Services (DHHS), the North Carolina Department of Health, and the Office for Human Research Protections.
- The University & Medical Center Institutional Review Board (UMCIRB) and its staff, who have responsibility for overseeing your welfare during this research, and other ECU staff who oversee this research.
- Additionally, the following people and/or organizations may be given access to your personal health information and they are: Joseph Armen DO.

How will you keep the information you collect about me secure? How long will you keep it?

All data will be kept for a minimum of 6 years. For this particular study, you will be assigned a case number that is random and cannot be traced back to you by anyone other than the principal researcher. All computer files are securely on remote departmental folder within Piratedrive. All paper files will be kept in Joseph Armen's office in ECU Student Health Center, room 150.

What if I decide I do not want to continue in this research?
If you decide you no longer want to be in this research after it has already started, you may stop at any time. You will not be penalized or criticized for stopping. You will not lose any benefits that you should normally receive.

Who should I contact if I have questions?
The people conducting this study will be available to answer any questions concerning this research, now or in the future. You may contact Joseph Armen DO 252-737-2593, 7 days a week between 9 am and 5 pm.

If you have questions about your rights as someone taking part in research, you may call the UMCIRB Office at phone number 252-744-2914 (days, 8:00 am-5:00 pm). If you would like to

report a complaint or concern about this research study, you may call the Director of UMCIRB Office, at 252-744-1971.

Is there anything else I should know?

N/A

I have decided I want to take part in this research. What should I do now?

The person obtaining informed consent will ask you to read the following and if you agree, you should sign this form:

- I have read (or had read to me) all of the above information.
- I have had an opportunity to ask questions about things in this research I did not understand and have received satisfactory answers.
- I know that I can stop taking part in this study at any time.
- By signing this informed consent form, I am not giving up any of my rights.
- I have been given a copy of this consent document, and it is mine to keep.

_____ _____

Participant's Name (PRINT) **Signature** **Date**

Person Obtaining Informed Consent: I have conducted the initial informed consent process. I have orally reviewed the contents of the consent document with the person who has signed above, and answered all of the person's questions about the research.

_____

Person Obtaining Consent (PRINT) **Signature** **Date**

_____

Principal Investigator (PRINT) **Signature** **Date**

(If other than person obtaining informed consent)