

Official title: Docosahexaenoic Acid (DHA) For The Treatment of Pediatric Concussion Related to Sports Injury

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Docosahexaenoic Acid (DHA) for the Treatment of Pediatric Concussion Related to Sports Injury

Principal Investigator: Shane Miller, MD

Co-Investigators: Robert Dimeff, MD

1. Introduction and Purpose:

In recent years, media attention has focused on the long-term sequelae of repeated concussive episodes in professional athletes. The growing understanding of the damage done by what was once considered a “ding” during a game or match, and the neurologic consequences of “playing through” or returning to play too soon has led to additional interest in and concern for pediatric athletes (18 or under) who experience sports-related concussions during game or practice play.

Because it has only been in recent years that the full scope of damage done by repeated concussive episodes has come to light, very little research has been done on treatment of concussion in either adults or children. Brain injuries in children can be especially problematic, as the brain may continue to develop until the child reaches the age of 24 or older, so concussion during this time of development may be particularly damaging.

Docosahexaenoic acid (DHA) is an omega-3 fatty acid commonly found in both fish oils and algae. DHA is known to improve development of the eyes and brain in young children. It is thought to be an effective anti-inflammatory and anti-oxidant, and since it occurs naturally and causes very few harmful side effects, it may be a useful compound in the treatment of pediatric concussion.

This is a feasibility trial of DHA for the treatment of sports concussion in a pediatric population. Our primary aim is to determine acceptability of randomization for this compound as well as rate of enrollment given our clinical population. Our secondary aim is to examine preliminary outcomes. We hypothesize that subjects who take 2 g of DHA daily for 3 months will see a shorter time to full recovery and return to play and a shorter time to resolve balance disturbance. These are good, albeit unvalidated, clinical indicators of concussive recovery.

2. Background:

Current estimates suggest that 300,000 to 3.8 million recreation- and sports-related concussions occur each year in the U.S., and that 8.9% of all high school athletic injuries are concussions. Other reports indicate that concussion accounts for 3-5% of injuries in all high school sports, but self-report data suggests a significantly higher incidence of unreported concussion. Additionally, girls have a higher reported rate of concussion than boys in similar sports. The athletes at highest risk of concussion are boys participating in high school football and girls participating in soccer and basketball. Approximately 50% of high school and college football players report experiencing concussion-like symptoms each season. Other high contact sports, such as ice hockey and rugby, also place athletes at risk, but participation in these sports is often limited to club sports, so data are limited. Due to a paucity of data in younger athlete populations, no estimates of concussion rate are available.

Research into this population is complicated by numerous issues, including a parent and athlete perception that it was “just a little bump to the head;” growing competitiveness among younger athletes and athletic organizations; and the under-reporting of injury or symptoms that result from this lack of understanding of the serious nature of concussion, compounded with a desire not to be taken out of play due to the competitive environment. Our understanding of concussion is still somewhat limited, but most sports medicine doctors currently agree that even a minor hit to the head may be a serious concussion, and that rating how serious a concussion is cannot truly be done until well after the injury has occurred. Consequently, the evaluation and management of all concussions must proceed with a very conservative approach.

Omega-6 and omega-3 fatty acids are both required for normal human development. However, it is thought that the omega-3 fatty acids are more beneficial, and in fact there is mounting evidence that omega-3 supplementation, particularly the omega-3 fatty acid docosahexaenoic acid (DHA), may

benefit the heart, triglyceride levels, retinal health, and emotional health. The precise mechanism of action is not known, but there is also evidence that DHA may also have an anti-inflammatory process, as patients with rheumatoid arthritis who took DHA reported shorter durations of morning stiffness and lower levels of NSAID use than patients who did not take it. Omega-6 fatty acids are associated with increased production of inflammatory processes, a necessary and adaptive response to injury in the human body. However, due to the greater consumption of omega-6 than omega-3 in the western diet, it is also thought that this increased consumption of omega-6 may be contributing to increased rates of cancer, allergies, and other immune dysfunction disorders. Omega-3 supplementation may have a perceived anti-inflammatory effect not because of actual anti-inflammatory processes, but by competing for receptors for the omega-6 fatty acids, thus slowing down the inflammatory processes.

Omega-3 fatty acids, and specifically DHA, are also an essential component of neuronal structures in the brain and are thought to be an essential part of memory and cognition processes. 2006 Dietary Reference Intakes for Omega-3 fatty acids are for 1.1g/day (female adolescents) and 1.6 g/day (male adolescents). These values are based on similar adult values and are minimum recommended amounts, and are specified for alpha linoleic acid, with the recommendation that 10% of these fatty acids be DHA and EPA. Because DHA is necessary for proper function of the brain, and its potential for reducing inflammation and increasing memory, we propose a study to examine the effects of DHA supplementation in adolescents after a concussive sports injury.

The neuroprotective effects of fish oil have been studied and documented in experimental models, however the effects of DHA after TBI have not been studied. To date, there have been no clinical trials investigating the effects of DHA and/or EPA dietary supplementation on the treatment or prevention of TBI. A recent report shows that DHA supplementation for 30 days can reduce axonal injury in brainstem white matter tracts in a rodent head acceleration injury model (Bailes and Mills, 2010).

Several studies have demonstrated the safety of high doses of DHA in children. For example, Sorgi, Hallowell, Hutchins, and Sears (2007) studied the effects of an open-label pilot study with high dose EPA/DHA concentrates on plasma phospholipids and behavior in children ages 8-16 years with attention deficit hyperactivity disorder. Study participants were administered a dose of EPA/DHA concentrate per day based on the ratio of arachidonic acid (AA) to EPA in the isolated plasma phospholipids at 4 weeks. All subjects were initially supplemented with 16.2 g of long-chain omega-3 fatty acids (10.8 g EPA and 5.4 g DHA) per day. After four weeks, if the AA:EPA ratio was below 1.0, the dosage was decreased to 5.4 g EPA and 2.7 g DHA per day. If the AA:EPA ratio was between 1.0 and 1.5 the dosage was decreased to 8.1 g EPA and 4 g DHA per day. The assigned dosage was continued for eight weeks (the duration of the study). Findings suggested that high-dose EPA/DHA supplementation may improve behavior in children with ADHD. No adverse effects on bleeding were reported. One participant reported loose stools when taking the initial dose of 10.8 g EPA and 5.43 g DHA. This was reportedly corrected with a decreased dose.

In a study of the safety of a high-dose of DHA in cystic fibrosis patients, Lloyd-Still et al. (2006) randomized twenty subjects, ages 8 to 20 years old, to receive 50mg/kg/day of DHA (1 to 4.2 g of DHA per subject per day) or placebo for eight weeks. This high dose of DHA was shown to be well-tolerated and safe with no adverse effects.

A study targeting the effect of DHA on deterioration of nutritional status in children with acute lymphoblastic leukemia, in which enrollment is currently ongoing, provides a dose of 100 mg/kg/day DHA, which translates to approximately 5-6 g per day, to children ages 4 to 15 years for a period of three months (NCT01051154).

Furthermore, high doses of DHA are currently being used in adults for sports-related injuries. For example, The Center for the Study of Retired NFL Athletes at the University of North Carolina at Chapel Hill is studying memory and cognition in retired NFL athletes with cognitive impairment. The athletes receive either DHA (2 g per day) or placebo for nine months whilst undergoing intermittent neuropsychological testing. At Virginia Tech, participating adult males currently follow a protocol of 2 grams per day of DHA vs. placebo for a total of 6 weeks during a resistance training and exercise program in a study of inflammation, soreness and strength. And finally, the Texas A&M football program is conducting a study of inflammation, power and cardiovascular risk in their participating players who are randomized to 2 grams per day of DHA or placebo. The study runs from summer training through the end of fall camp.

Regarding dosage, a DRI has not yet been established for DHA. An Acceptable Macronutrient Distribution Range (AMDR) that has been set. The AMDR is the current mean intake in the United States, which for EPA and DHA is approximately 100mg/day, which is much lower than research is recommending. While side effects such as blood thinning may be seen at very high dosages, doses as high as 11.5 mg/kg DHA are recommended to treat asthma symptoms in children, which translates to approximately 575-750 mg/day DHA for an average high school male. Our suggested dose in this protocol is only slightly higher. In adults, recommended doses for preventing blood clots is as high as 6 g fish oil per day, which is approximately 6000 mg DHA per day, more than twice our protocol dose. (<http://www.nlm.nih.gov/medlineplus/druginfo/natural/993.html>). Additionally, the studies we have discussed above show that research has demonstrated - and continues to utilize - high doses of DHA in children and adults safely with minimal or no side effects.

3. Concise Summary of Project:

This is a double-blind, randomized, placebo-controlled feasibility trial of DHA for the treatment of pediatric concussion related to sports-injury. The definition used for concussion is from the Consensus Statement on Concussion in Sport: the 3rd International Conference on Concussion in Sport (*Br J Sports Med* 2009;43:Suppl 1 i76-i84 doi:10.1136/bjsm.2009.058248) and will meet the following criteria:

- a) Direct blow to the head, face, neck or a blow elsewhere on the body with an “impulsive” force transmitted to the head.
- b) Rapid onset of short-lived impairment of neurologic function in one or more of the following clinical domains that resolves spontaneously:
 - 1. symptoms: somatic (eg, headache), cognitive (eg, feeling like in a fog) and/or emotional symptoms (eg, lability).
 - 2. physical signs (eg, loss of consciousness, amnesia).
 - 3. behavioural changes (eg, irritability).
 - 4. cognitive impairment (eg, slowed reaction times).
 - 5. sleep disturbance (eg, drowsiness).
- c) No abnormality on standard structural neuroimaging studies, if such neuroimaging studies are completed for a clinically-indicated reason. Note: neuroimaging is not a part of this study protocol. Study participants will not undergo neuroimaging as part of this study.

Subjects will be randomized in a 1:1 fashion. DHA is an omega-3 fatty acid that occurs naturally in fish oil and algae. There are many dietary supplements containing DHA available in the marketplace. Martek Biosciences provides an algae-based DHA compound which minimizes the side effects of “fishiness” in both flavor and “fish burps.” The DHA produced by Martek Biosciences is also used for many infant formula companies in the US. DHA and identical placebo will be provided by Martek Biosciences.

The DHASCO capsules are supplied as 950 mg capsules with an effective dose of 500 mg DHA per capsule. The placebo capsules are supplied as 950 mg capsules consisting of 475 mg corn oil and 475 mg soy oil. Both DHA and placebo are flavored with sweet orange flavoring and masking agents.

They are supplied in sealed white plastic bottles containing 100-200 capsules per bottle, depending on dose. Each bottle has the lot number stamped on it. The capsules will be stored in a dry, locked compartment at room temperature (60 to 75 F). Martek's Quality Assurance department completes regularly scheduled chemical and long-term stability analyses on each lot of capsules. If shipments will occur during warmer months, arrangements will be made for capsules to be shipped with ice packs or other temporary refrigeration. Capsules will be dispensed to subjects in separate bottles in quantities sufficient to last until their next appointment. Any unused capsules will be returned to the PI or research staff and sent to the pharmacy for destruction in compliance with Children's regulations.

Subjects will be randomized to 2 g of DHA or matched placebo for 12 weeks. In order to achieve this dose of DHA, subjects will receive 2 950 mg capsules twice a day. Subjects who cannot tolerate the divided dose of 2000 mg per day will be discontinued from the study.

Although much of our knowledge of the pathophysiology of concussion comes from animal models, it is believed that the mechanical trauma to the brain causes a sudden disruption in the ionic balances, leading to an increase in calcium and an increase in glucose metabolism as cells try to compensate for the potassium/calcium imbalance. This is followed by a period of decreased glucose metabolism which may last up to 4 weeks in humans, resulting in continued high levels of calcium which interfere with mitochondrial oxidative metabolism. This decrease in mitochondrial oxidative metabolism appears to be biphasic, with improvement seen at 2, followed by a decrease which bottoms out on day 5 and recovers around day 10. Other important aspects of the concussive trauma include free radical production, initiation of inflammatory responses, and altered neurotransmission.

DHA has several important functions in the brain with relatively few side effects, making it a good option for concussion treatment. DHA is helpful in modulating ion channels; higher levels of DHA are associated with higher levels of sodium pump activity, so it is possible that providing DHA post-injury may help the cells reduce the calcium balance more quickly or efficiently. DHA also has an apparent anti-inflammatory action. DHA interferes with the inflammatory arachidonic acid cascade by reducing the affinity of platelet $\text{TxA}_2/\text{PGH}_2$ receptor for its ligand. Additionally, higher levels of DHA in the cerebral cortex cause significantly higher levels of the anti-oxidant enzymes catalase, glutathione and glutathione peroxidase -- resulting in decreased cerebral levels of lipid peroxides. DHA reduces formation of the peroxynitrite free radical and reduces formation of pro-inflammatory cytokines by inhibiting transcription factor $\text{NF-}\kappa\text{B}$ and inducible nitric oxide synthetase. Finally, DHA is highly concentrated in synapses, indicating a role in synaptic signal transduction. DHA appears to address many different aspects of how we believe concussive injury affects the brain.

The primary outcomes of this feasibility trial are to determine the willingness of patients to be randomized, the expected rate of enrollment based on the clinic population, and protocol adherence of enrolled study participants. We anticipate the results from this study will provide data to inform a larger randomized trial of DHA for the treatment of pediatric sports concussion. Secondary outcomes are time to clearance to return to play (in days) and improvement in balance, as assessed by the Balance Error Scoring System (BESS) which is a component of the Sport Concussion Assessment Tool 3 (SCAT-3). Time to clearance to return to play was chosen as a clinically significant measurement for medical professionals in the sports medicine field. The investigators will determine clearance for return to full competitive game play (Stage 6 of graduated return to play protocol) according to Consensus Statement guidelines and following the law in Texas, House Bill 2038. Criteria for return to play include complete clinical recovery from the concussion including returning to baseline symptoms, exam and

neurocognitive function and successful completion of a gradual return to play progression. The BESS was chosen because it is a relatively simple assessment that has been noted by the investigators to be a good predictor of neurological recovery.

In addition to time to return to play and the BESS, the SCAT-3 and Immediate Post Concussion Assessment and Cognitive Testing (ImPACT) computerized neurocognitive testing programs will be used to evaluate recovery. The SCAT-3 is a standardized method of evaluating injured athletes for concussion and can be used in athletes aged from 10 years and older. The ImPACT program is a computerized exam that helps to quantify the degree of symptom, injury, or dysfunction that occurs after a sports related concussion. Although this test is utilized by many professionals, college, and high school sports programs throughout the country, it is unclear if its use contributes to a safer or more expedited return to activity.

Finally, information on side effects will be collected at every visit in order to track the rate and severity of side effects in this patient population.

We plan to enroll 40 subjects for this study, which consists of 20 subjects to be treated with DHA and 20 subjects to be treated with placebo. In order to achieve enrollment of 40 total subjects, we anticipate screening 80 subjects in order to consent 40. Because this is a pilot study, information on early withdrawals is important to us and no extra subjects will be consented due to this. We anticipate that it will take approximately 12 months to complete enrollment, with an additional 3 months for patient follow-up once the last patient has been enrolled. We anticipate that it will take approximately 6-9 months to complete data clean-up, analysis, and manuscript submission for total study duration of 2 years.

Subjects who are non-compliant with the protocol either by not keeping appointments or by not taking study pills as directed may be discontinued from the study. Subjects who do not tolerate the minimum dose of 2000 mg of DHA per day or who experience intolerable side effects will be discontinued. Subjects who choose to withdraw consent will be discontinued early.

4. Study Procedures:

Subjects presenting with a new concussion within 4 days of their initial injury will be identified and screened for eligibility from the investigators' regularly scheduled clinic patients. Once a patient has been identified, the PI or research personnel will approach the family for consent. Patients who choose not to participate will continue to receive clinically indicated care.

Subjects who enroll will complete 5 scheduled visits, although additional visits may be clinically indicated for symptom evaluation and treatment. All assessments done for this study are routinely done as part of the standard clinic visits for concussion at the Sports Medicine Center.

At Visit 1, the patient will sign the consent form and complete the SCAT-3, ImPACT, and concussion assessment questionnaire. The ImPACT computerized test has standardized scores for subjects in the age range for the population and is used clinically to assess neurocognitive deficits after sports concussion. The concussion assessment consists of medical history, symptom assessment, and sports and school activity components. Subjects will be randomized to either DHA or placebo in a 1:1 ratio, and receive enough DHA or placebo capsules to reach the target dose of 2 g of DHA per day (or placebo) until the day of their next appointment. Subjects will be instructed to take 2 capsules at breakfast and 2 capsules at dinner (with food). Subjects will take their first dose in the office to assure their ability to swallow the pills. Subjects will be instructed to bring their pill bottle with any remaining pills with them to their next research visit. This visit will last approximately 90 minutes.

Visit 2 will occur 7 days after enrollment (+/- 2 days). Subjects will complete the SCAT-3 and ImPACT at this visit. Subjects will also be asked if they are experiencing any side effects. At this visit, the research personnel will count how many capsules remain in the bottle, and enough additional capsules will be dispensed to last a week, until the next scheduled visit. This visit will last approximately 90 minutes.

Visit 3 will occur at 2 weeks after enrollment (+/- 2 days). Subjects will again undergo the SCAT-3 and ImPACT, and be asked about side effects. The research personnel will count the capsules returned and the patient will receive enough capsules for another 2 weeks, until their next appointment. This visit will last approximately 90 minutes.

Visit 4 will occur at 4 weeks after enrollment (+/- 2 days). Subjects will complete the SCAT-3 and ImPACT at this visit, and be asked if they are experiencing any side effects. The research personnel will count the capsules returned and the patient will receive enough capsules for another 8 weeks, until their next appointment. This visit will last approximately 90 minutes.

Visit 5/Exit, the final visit, will occur at 12 weeks (+/- 2 days). Subjects will complete the SCAT-3, and ImPACT test. Research personnel will count the capsules returned, and any unused capsules will be stored until the expiration date or end of the study, whichever comes first, then all returned stock will be turned over to the pharmacy for destruction. If subjects choose to withdraw early or are terminated for lack of protocol compliance, they will be asked to return for this final visit. This visit will last approximately 90 minutes.

In addition to the office visits listed above, the patient will be contacted by phone at week 8 to see how the patient is doing, assess study capsule supply, and answer any questions the patient or family currently have. This phone contact will last approximately 5-10 minutes.

Patient participation in this research will last approximately 12 weeks. If patients require additional clinically indicated visits, data from any assessments done during these visits will be collected. Subjects are not responsible for research costs (DHA or placebo capsules), but will be responsible for the portions of their visits that are clinically indicated (Visit 1 ImPACT testing, all SCAT-3, BESS, and concussion assessments, and visit 5 ImPACT testing if clinically indicated). Subjects (or their insurance companies) will be charged for visits that are clinically indicated (i.e., Visits 1-4) but will not be charged for the DHA or placebo capsules, or Visit 5 unless that visit is clinically indicated by the patient's course of recovery.

In addition, subjects who are released to play prior to Visit 4 (4 weeks post-enrollment) will not be asked to return for additional weekly visits, but instead will be asked to complete a symptom questionnaire and answer questions about side effects online via MyChart in lieu of these visits. Once patients have returned to their baseline and are returned to play, there is no need for additional visits for well subjects. As a safety precaution, subjects will fill out symptom questionnaires and a side effects scale so that if a patient does worsen, additional clinical follow-up may be scheduled. This does not place the patient at additional risk, and encourages protocol compliance as subjects will not be required to miss additional school or other activities for appointments that are not clinically necessary. Subjects will receive follow-up phone calls to remind them to complete these forms online. Subjects will still be asked to return for visit 5, but will not be charged for this visit if it is not clinically indicated.

5. Criteria for Inclusion of Subjects:

1. Male or females age 14-18 inclusive
2. Diagnosed with concussion due to sports-related injury. Concussion is defined as:
 - a) Direct blow to the head, face, neck or a blow elsewhere on the body with an “impulsive” force transmitted to the head.
 - b) Rapid onset of short-lived impairment of neurologic function in one or more of the following clinical domains that resolves spontaneously:
 - i. Symptoms: somatic (eg, headache), cognitive (eg, feeling like in a fog and/or emotional symptoms (eg, lability).
 - ii. Physical signs (eg, loss of consciousness, amnesia).
 - iii. Behavioral changes (eg, irritability).
 - iv. Cognitive impairment (eg, slowed reaction times).
 - v. Sleep disturbance (eg, drowsiness).
 - c) No abnormality on standard structural neuroimaging studies, if such neuroimaging studies are completed for a clinically-indicated reason. Note: neuroimaging is not a part of this study protocol. Study participants will not undergo neuroimaging as part of this study.
3. Concussion within 4 days of enrollment
4. Presenting for treatment to the Sports Medicine Center at Children's Medical Center

6. Criteria for Exclusion of Subjects:

1. Subjects not actively participating in an organized sport at time of enrollment
2. Subjects who received a concussion from an event other than playing a sport (motor vehicle accident, fall, etc.)
3. Subjects who participate in or received a concussion during participation in motorized sports (i.e., motocross, dirt biking, jet skiing, etc.)
4. Subjects with radiographic evidence of traumatic brain injury (i.e., skull fracture, intracranial hemorrhage, cerebral contusion, etc).
5. Subjects with a prior diagnosed concussion in the previous 6 months.
6. Pregnant women.
7. Subjects sensitive to aspirin
8. Subjects diagnosed with high blood pressure and currently being treated with blood pressure medications
9. Subjects allergic to soy bean oil or corn oil.
10. Subjects currently taking fish oil or DHA supplements.

7. Sources of Research Material:

Data collected for this research will come from the SCAT-3, concussion assessment questionnaire, ImPACT testing results, and the medical record. All of the assessments used for this research are routinely collected during regular clinic visits for pediatric concussion subjects. As such, there is no additional burden on patients or families for time to complete assessments. Data will be prospectively collected, after consent and enrollment, from both patient medical records and directly from patients.

8. Recruitment Methods and Consenting Process:

Patients will be recruited from the population presenting to the Sports Medicine Center located at Children's Medical Center. Patients will be recruited from all clinical locations including Dallas, Legacy, and Southlake. All eligible patients will be patients of the investigators, as they are the primary physicians at the Sports Medicine Center.

Each morning, the patient schedule will be reviewed by research personnel and any new potential concussion patients identified. A HIPAA waiver will be obtained for the purposes of screening so that researchers may pre-screen based on any history provided (i.e., mechanism of injury, MRI/CT results, allergies on file, date of injury if available) and age.

Once identified, patients will be seen for their regular appointment. If a diagnosis of concussion is made, either the investigator or the research coordinator will approach the family in the exam or consultation room to ascertain if there is interest in the research study. The informed consent form will be fully explained to both the parent and the child, and if, after reading the consent form and considering the study, the family wishes to participate, both parental consent and child assent will be obtained. Non-English speaking subjects may be consented using the Spanish short form and an interpreter.

All information gathered during the screening process will be either destroyed upon screen failure or the patient's choice not to participate, or stored in the patient's research file. Paper files are stored in a locked filing cabinet in a locked, restricted access room. Electronic files will be stored in RedCap, which is a secure data capturing web-based application. The login is password protected and the study can only be accessed by approved study members. . In order to ensure the privacy of patients during consent, the researchers will speak to the families in either a private exam room or a private consultation room.

Although patients may be approached to participate by the treating physician, it will be made clear to both the patient and the family that participation is voluntary and that the decision not to participate does not impact their level of care at the Sports Medicine Center or Children's Medical Center. There is no monetary incentive for participation in this study, and the assessments are the same as the routinely used assessments for this clinic. None of the investigators has a financial interest in Martek Biosciences, nor is Martek Biosciences providing any monetary funding for this research.

As mentioned previously, children will be required to provide written assent before participating in this research. The inclusion criteria for this study includes only children older than 10. Children who are 18 at the time of their appointment may provide informed consent for themselves.

9. Potential Risks:

Burping or fishy after-taste have been infrequently reported. In clinical studies with DHASCO, these mild gastrointestinal side effects may be reduced by taking capsules with food. Other mild gastrointestinal symptoms such as diarrhea have been reported infrequently, but the incidence of these AEs is not different from that observed in subjects receiving placebo. DHA supplementation may result in modest elevations of LDL-C and non-HDL-C in some individuals. However, the increased level of LDL-C was associated with a shift of lipoprotein particle size toward larger, less atherogenic subfractions. In summary, adverse event monitoring revealed an excellent safety and tolerability profile for DHASCO.

There are no known serious side effects from taking DHA. However, based on the experiences of 379 men and women, both children and adults, the following side effects occurred at a greater rate than in placebo and in greater than 2% of participants: burping (17.7%), headache (8.97%), bad taste in the mouth (7.65%), back pain (3.43%), abdominal distension (2.11%), and weight increase (2.11%).

Patients taking placebo may also experience side effects. These side effects occurred more frequently than DHA and in greater than 2% of participants, and are based on the experiences of 200 men and women, both children and adults, who took placebo during clinical trials of DHA: diarrhea (10%), flatulence (excessive gas; 8.5%), common cold (7%), upper respiratory infection (6%), upset stomach

(4%), nausea (3.5%), rash (3.5%), increased blood triglycerides (3%), frequent bowel movements (2.5%), cough (2.5%), stomach flu (2%), influenza (2%), and contact dermatitis (2%).

10. Subject Safety and Data Monitoring:

All patients will receive standard clinical treatment for concussion. Participation in this study does not preclude additional treatment for concussion as indicated, including, but not limited to, additional medications for headache, referrals for neurological or neuropsychological consultations, or other medications or consultations as deemed clinically appropriate. Patients with no diagnostic imaging studies for the current concussion who are later referred for imaging and found to have radiographical evidence of acute traumatic brain injury may continue on the study, but will also be referred for appropriate care as necessary based on imaging (i.e., referrals to neurology, neurosurgery, etc, as clinically indicated).

The PI will monitor the safety of this protocol by reviewing adverse events. The patient or patient guardian(s) may request removal from the study, and this request will be honored.

In addition, a data safety monitoring board consisting of Dr. Pam Okada, a pediatric emergency medicine physician at Children's Medical Center, and a second Children's Medical Center physician appointed by Drs. Okada and Miller. The Board will meet to review protocol compliance and safety data at the 50% and 100% enrollment points. An additional meeting will be triggered by any patient experiencing a severe adverse event. Statistics and reports will be prepared by a staff statistician.

11. Procedures to Maintain Confidentiality:

Any information obtained in connection with this research that can potentially identify a subject will remain confidential and be disclosed only with the permission of the subject or his/her parents or guardians. Data forms will be kept in locked file cabinets. Subject data will be entered into a password-secured database that can be accessed only by the investigators. Data will be deidentified at the time of data analysis, and In order to maintain confidentiality, each subject will be given a unique identification number. Keys linking subject names with identification numbers will be kept in a locked file within the Sports Medicine Center at TSRH. Information will be disclosed in a de-identified manner to the following study members: pharmacy staff and data analysis personnel. Collected information will be used exclusively in the context of this study.

12. Potential Benefits:

Patients who receive DHA may experience a faster recovery from concussion and a quicker return to play time, or they may experience no benefit. This study may inform future treatment studies for pediatric concussion, which could benefit future pediatric concussion patients.

13. Biostatistics:

This will be a pilot study with 20 patients in each arm. The data will be used to estimate between- and within-patient components of variation and preliminary effect sizes in order to design a definitive study. Descriptive statistics including mean, median, range, and standard deviation will be calculated for global variables. Comparative data analysis will include t-tests and for continuous variables, with Chi-Square analysis conducted for nominal data where appropriate. P-values less than 0.05 will be considered statistically significant. The primary outcome of time to clearance to return to play and the secondary outcome of BESS scores will be analyzed using t-test for continuous variables.

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