Project Title	**Effect of omega 3 fatty acid supplementation in patients with sickle cell anaemia: Randomised, double-blind, placebo-controlled trial**
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Background	Blood cell aggregation and adherence to vascular endothelium, and inflammation play a central role in vaso-occlusive crisis and organ damage in sickle cell disease (SCD). The antiaggregatory, antiadhesive, anti-inflammatory and vasodilatory omega 3 fatty acids, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), are compromised in blood cell membrane of patients with SCD. Hence, it is postulated that amelioration of the abnormality will reduce the incidence of vaso-occlusive episodes.
Aims	To investigate whether supplementation with the omega 3 fatty acids, DHA and EPA, reduces sickle cell crisis.
Patients (Subjects)	Patients with homozygous sickle cell disease (n=140), aged 2 to 24 years, in regular follow-up at the outpatient SCD Referral Clinic, Ibn-Aoaf Paediatrics and Khartoum Teaching Hospitals, Khartoum (Sudan) will be recruited. The patients will be in a “Steady State” defined as the absence of evidence of fever, infection or crisis for longer than four weeks before the start of the study. Phenotypic characteristic will be confirmed with the use of cellulose acetate electrophoresis at pH 8.5. All of the patients will be on regular folate supplement and those under five years on standard oral prophylactic penicillin.
Inclusion and exclusion	• Inclusion - HbSS phenotype; male and female patients; steady state; 2 to 50 years old

criteria	• Exclusion- Other phenotypes; patients in crisis; patients on hydroxyurea treatment; presence of other chronic diseases; blood transfusion in the previous four months; Pregnancy; Previous history of overt stroke
Intervention	The patients, after stratification by age and gender, will be randomly assigned to receive coded and indistinguishable omega 3 (n=70) or placebo (n=70) capsules. Randomisation will be conducted using a sequence of computer-generated random numbers at the Faculty of Life Sciences, London Metropolitan University (UK). The person who will perform the randomisation will have no knowledge about the demographic, clinical or laboratory characteristics of the patients, and staff of the SCD Referral Clinic, investigators and participants will be blinded until the biochemical and clinical outcome data are analysed and the database unlocked. Subsequent to randomisation, the patients will be given, daily, for one year, one (2-4 year old), two (5-10), three (11-16) or four (≥ 17) omega 3 or placebo capsules. The omega 3 capsule contains 277.8 mg DHA and 39.0 mg EPA and the placebo high oleic acid (41%) oil blend placebo capsules. Vitamin E, 1.5mg/capsule, is added to both to prevent peroxidation. Enrolment identification number, gender, residence, ethnicity, weight, height, history of blood transfusion and stroke, number of sickle cell-related hospital admission during the previous year and sickle cell complication data will be collected using a validated structured questionnaire at baseline. Monthly self-assessment health diary will be given to each patient to record on daily pain frequency and severity, pain medication taken and hospitalisation. Name and telephone number of the medical doctor in charge will be given to the patients and their guardians in case they require advice or care outside normal working hours. During each monthly follow-up, the self-recorded health diaries will be reviewed, patients examined thoroughly and the data obtained entered into the database by the same physician. Whole blood, about 10 ml, will be obtained from the patients at recruitment and after one year of intervention for haematological and biochemical analyses.
Compliance	Blood cell DHA and EPA status will be used as objective measure to assess compliance; pre-structured record of daily capsule intake completed by patients.
Endpoints	• Primary - Annualised rates of clinical vaso-occlusive crisis is defined as painful events that lead to hospitalisation. Vaso-occlusive crisis is defined as a painful event characterised by musculoskeletal and/or visceral pain which is usually associated with mild pyrexia and the passage of dark or red urine. • Secondary – Severe anaemia; rate of blood transfusion; school attendance; Hb level and mean cell volume (MCV).
Data analyses	The data will be presented as mean± standard deviation (sd), median and percentile or median and inter-quartile range (IQR). The treatment effects will be compared on the basis of annualised vaso-occlusive crisis rate computed by dividing the total number of crisis experienced by the number of follow up months and multiplication by 12 (A patient who experienced 3 crisis and followed up for 11 months will have a crisis rate of 3.3/year).

	Statistical differences of continuous variables of the two groups will be examined with Mann–Whitney–Wilcoxon or t-test depending on the homogeneity of variance (data distribution). Categorical data differences will be explored with Fisher's exact test for expected frequency of less than five or chi-squared test for five or more. All patients who started the treatment regardless of the duration of supplementation or follow-up period will be analysed. Statistical analysis will be performed with the use of SPSS for Windows, version 17 (SPSS Ltd., Woking, Surrey, UK) and other pertinent data analyses software.
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