Supplementation of Omega-3 Fatty Acids Does Not Reduce the Incidence of Thrombosis

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Introduction

Introduction: Thromboses are more likely to occur with End-Stage Renal Disease patients in their vascular access which can cause increased morbidity and mortality. **Objective:** The purpose of this study was to investigate the effects of orally administered over-the-counter (OTC) n-3 fatty acid supplements on primary patency of polytetrafluorethylene (PTFE) grafts. **Design:** The study was conducted using a triple-blind, permuted-block randomized and placebo controlled experimental design. Central Texas Nephrology Associates related dialysis clinics with patients who needed a new PTFE graft based on physician diagnosis were recruited for the study. Patients (N=34) were followed prospectively for 8-months after being placed into an n-3 fatty acid or control group and monitored for primary patency as the primary outcome variable. Primary patency is defined as patients having avoided either a placement of a new graft or angioplasty due to a thrombosis in the vascular access of the draining vein. **Results:** The n-3 fatty acid group had a mean PTFE graft primary patency rate of 254.2 days (SEM=51.8), while the control group had a mean PTFE graft primary patency rate of 254.1 days (SEM=34.6) revealing no significant difference in survival time between groups [Log-Rank (.7451), Wilcoxon (.4221) and -2Log (LR) (.5883)] using Kaplan-Meier and Cox proportional hazard method. There were no significant differences in the covariates with the exception of small LDL. **Conclusions:** There were no significant differences in primary patency rates between groups suggesting the OTC supplement may have not had enough DHA and EPA to elicit a response of decreased endothelial hyperplasia.

Introduction

Various complications of vascular access dysfunction have been identified in the literature with thrombosis being the most common reoccurring problem. Stenotic lesions caused by progressive neointimal hyperplasia at the venous anastomosis or outflow system have been identified as the major cause of access thrombosis. Moreover, vascular access dysfunction has been identified as a predictor of morbidity in End-Stage Renal Disease (ESRD) patients. Study authors report that more than 75% of access grafts will develop a thrombosis in the first year of placement. Adding to this problem is the increasing use of polytetrafluorethylene (PTFE) grafts which have become the most common hemodialysis access used in the United States and is associated with access dysfunction. The purpose of this study was to investigate the effects of orally administered OTC n-3 fatty acid supplements on primary patency of PTFE grafts.

Experimental Design

Participants

- ESRD patients (N=34) 18 years of age and older were recruited for the study
- Participants were informed as to the experimental procedures and signed informed consent statements in adherence with the human subjects guidelines with Baylor University

Study Protocol

- The study was conducted using a triple-blind, permuted-block randomized and placebo controlled experimental design.
  - Participants were placed into an omega-3 fatty acid group (n=14) or control group (n=15).

Methods

The study was conducted using a triple-blind, permuted-block randomized and placebo controlled experimental design. After initiation of graft placement, patients were randomly placed, based on the four-block permuted design, into an n-3 fatty acid (experimental) or control (corn oil [n-6]) group. Patients in the experimental group consumed two 1-gram softgel capsules of fish oil concentrate with each meal or six capsules (6 grams) per 24 hours. The control group consumed two 1-gram softgel capsules of corn oil with each meal or six capsules (6 grams) per 24 hours, following the same protocol as the n-3 fatty acid group. Graft clotting that occurred within those seven days was more than likely due to technical errors in graft placement. Waiting until seven days before study initiation allowed clotting and graft failure from technical errors to occur. Patients would then have a new graft placed, followed by a seven day waiting period and study initiation. Additionally, all patients consumed vitamin supplements which contained 15 mg of B_6, 12 mg of B_{12}, and 2.5 mg of Folic Acid. Two surgeons who were responsible for 95% of graft placements, with another four surgeons performing the remaining 5% of graft placements.

Statistical Analysis

Survival analyses were based on the Kaplan-Meier and Cox proportional hazard method with stratification based on treatment group. The tests used to measure equality over strata were Log-Rank, Wilcoxon, and -2Log(LR). A sample size > 25 was chosen to ensure power >80% based on formulas published by Freedman where alpha = 0.05 (one-tailed test), the average primary patency rate for untreated PTFE grafts in a 12-mo follow-up period is 30% ($P1$= 0.3), and treatment improves the survival rate to 75% ($P2$ - $P1$ = 0.45). A Student's t was calculated to ascertain the differences in the number of months on dialysis. A one-sample Kolmogorov-Smirnov test for normality was calculated for tHcy to test for a normal distribution. Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC).

Results

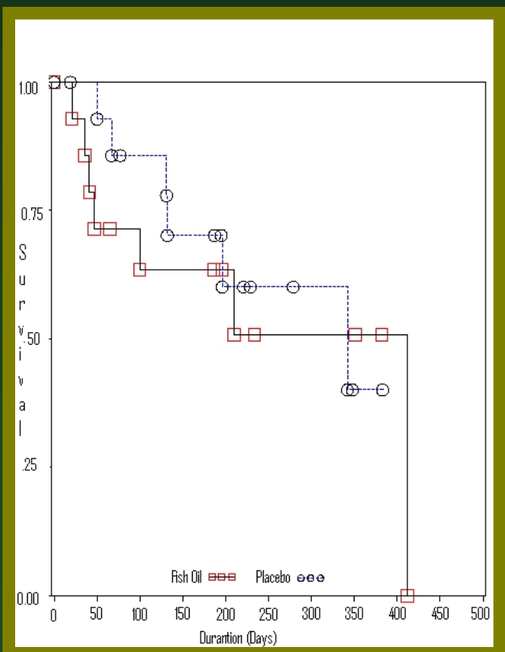
There were no significant differences in the covariates used in the Kaplan-Meier and Cox proportional hazard methods with the exception of small LDL. The n-3 fatty acid group had mean PTFE graft primary patency rate 254.2 days (SEM=51.8), while control group had mean PTFE graft primary patency rate of 254.1 days (SEM=34.6). The n-3 fatty acid group (n=14) had seven patients clot or require angioplasty and seven that did not clot**,** while the control group (n=15) had six patients clot or require angioplasty and nine that did not clot. The tests of equality over strata used were Log-Rank (.7451), Wilcoxon (.4221) and -2Log (LR) (.5883) revealing no significant differences in survival time. There were no significant differences in months on dialysis between groups (t = .607, p = .556). Kolmogorov-Smirnov test of normality revealed a normal distribution.

Conclusions

The results of this study reveal that the daily administration of 6 grams of n-3 fatty acids containing 160mg of EPA (.96g/day) and 100mg of DHA (.6g/day) started within seven days of a new PTFE graft placement had no effect on the duration of primary patency when compared to patients who received 6 grams per day of corn oil. Therefore, the reason for this non-significant result may be found in the dose-response relationship as the present study used approximately 55% of EPA and 62.5% of DHA than in a previous study The present study participants may have not had sufficient levels of EPA and DHA in the periphery, due to less in the supplements than the supplements used by Schmitz et al. (2002) to alter cell membrane phospholipids levels and inhibit the creation of inflammatory cell cytokines, including tumor necrosis factor, and cell hyperplasia in the intimal lining of the vein at the venous anastomosis. It is unknown if the differences between the two groups would have been different if the grafts that required angioplasty had been allowed to progress to a clotting event. Additionally, though the supplements were quality controlled by the manufacture prior to shipping, OTC supplements can have significant variation in their content. Due to the impossibility of quality checking each individual supplement, the amount of DHA and EPA could have varied and thereby decreased the likelihood of a significant change in clotting between groups.

Tables/Figures

Figure 1: Kaplan-Meier Survival Analysis for a new PTFE graft in patients followed for eight months in a fish oil group (n=14) or placebo group (n=15).



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