The effect of omega-3 fatty-acid supplements on perioperative bleeding following posterior spinal arthrodesis

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Abstract

Purpose To investigate the effect of omega-3 fatty-acid supplements (n-3FA) on bleeding during posterior spinal arthrodesis.

Methods We reviewed all one- or two-level posterolateral lumbar decompression/fusions with or without interbody fusion by five surgeons within 3 years. Patients taking n-3FA preoperatively were matched 1:2 with controls based on procedure, surgeon and operative time. Patients with abnormal coagulation parameters, known bleeding disorders or other medications that could affect surgical blood loss were excluded.

Results Twenty-eight patients met inclusion criteria. The n-3FA and control groups were similar with respect to gender, age, body mass index, operative time, and preoperative use of non-steroidal anti-inflammatory drugs. The n-3FAs were stopped an average of 5.2 days before surgery (range 1–10). Mean estimated blood loss (EBL) was 697 ml in the n-3FA group and 771 ml in the control group ($p = 0.36$). Mean transfused volume of Cell Saver (CS) was 282 ml in the n-3FA group and 321 ml in the control group ($p = 0.30$). A post hoc power analysis showed that the study was powered to detect a minimum difference of

105 ml for EBL and 50 ml for CS. The multivariate generalized estimating equation did not show a significant difference between groups for EBL or CS ($p = 0.35$ and $p = 0.29$, respectively). Secondary outcomes including drop in postoperative hemoglobin, transfusion requirement, complications and surgical drain output were similar between the two groups.

Conclusions The n-3FA use did not contribute to higher perioperative blood loss during spinal arthrodesis.

Keywords Omega-3 fatty acids · Bleeding · Spinal arthrodesis

Introduction

Omega-3 fatty acids (n-3FA) are widely used dietary supplements due to their cardioprotective effects. Their mechanism of action is thought to result from an anti-platelet effect leading to inhibition of vascular thrombus formation [1]. In vivo studies have shown that eicosapentaenoic acid (an n-3FA derivative) competes with arachidonic acid as a substrate for cyclooxygenase (COX). In patients with either a diet high in fish oil or pharmacological intake of n-3FA, eicosapentaenoic acid derivatives are substituted for arachidonic acid derivatives within the phospholipid layer of platelet cell membranes [2–4]. This is hypothesized to result in the reported quantitative decrease in platelet aggregation. Multiple studies have reported increases in bleeding times [5–7] and decreases in platelet aggregation [6, 8, 9] in humans taking n-3FA supplements.

The relationship of this observed increase in bleeding time to clinically significant perioperative blood loss remains poorly understood. Several previous studies have investigated the effect of n-3FA supplementation on

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bleeding after vascular, cardiac and abdominal surgery [9–14] with none of the studies showing a significant increase in perioperative bleeding events.

Bleeding in spinal surgery, however, may not behave in a clinically similar fashion. Bleeding complications in spinal surgery can manifest in several ways including large volumes of blood loss during multi-level spinal arthrodesis leading to hemodynamic instability or small amounts of bleeding leading to an epidural hematoma that compresses the neural elements of the spine. Due to theoretical concerns about bleeding, spinal surgery is frequently cancelled or delayed at our institution if the patient has recently taken an n-3FA supplement. However, there are no previous reports in the spinal arthrodesis literature on which to base clinical decision-making regarding the bleeding risk of n-3FA supplementation during and after spinal arthrodesis. The goal of this study is to retrospectively assess the effect of n-3FA supplementation on perioperative bleeding complications during one- or two-level posterior spinal decompression and instrumented arthrodesis.

Methods

The operative case logs of five spinal surgeons at a major academic medical center were reviewed for the time period from January 2007 to January 2010. This time period was selected because none of the participating surgeons had significantly altered their surgical technique during this period. Eligible patients must have undergone a one- or two-level posterior spinal decompression and instrumented arthrodesis between L3 and S1 with or without an associated posterior interbody arthrodesis and iliac crest bone graft harvest. Patients who had undergone a prior microdiscectomy were included but all patients with any other prior spinal surgery at the involved or adjacent levels were excluded from this analysis. The operative record was reviewed for each patient and any patient with an intraoperative complication such as an incidental durotomy or nerve root injury was also excluded from the analysis.

Clinical information available for review for all patients included both office charts and hospital records. On the day of surgery, it is our institutional policy for both a nurse and physician's assistant or orthopedic resident to review and record all medications taken prior to surgery and the date of the last dose. This policy explicitly includes both medications and nutritional supplements. Medications or supplements considered to contain n-3FA included: fish-oil capsules, cod-liver oil capsules or cod-liver oil, omega-3 supplements, eicosapentaenoic acid or EPA, and Lovaza (GalaxoSmithKlein, Philadelphia, PA, USA). Patients taking other medications or supplements with known

effects on bleeding were excluded. These medications included but were not limited to: aspirin, clopidogrel, dipyridamole, heparin, enoxaparin, fondaparinux, warfarin [active use with abnormal international normalized ratio (INR)], phenytoin, valproic acid, and ginkgo biloba. The complete physician office note and medical clearance note were also reviewed. Patients with medical disorders that might cause abnormal bleeding were also excluded. These disorders included but were not limited to: hemophilia, Factor V Leiden, prothrombin variants, von Willebrands disease, alcoholism, hepatitis, HIV, ITP, polycythemia vera, myeloproliferative disorders, hematological malignancies, and rheumatological disorders. All patients included in the study had normal preoperative INR, activated partial thromboplastin time (aPTT) and platelet levels.

Based on research which demonstrated a return to baseline bleeding time of 14 days after the last dose of n-3FA [3, 5], 14 days prior to surgery was selected as the time period after which patients taking n-3FA supplements would be included in the experimental group. Patients who had stopped taking n-3FA supplements more than 14 days prior to surgery were excluded.

To further control for potential confounders, each n-3FA patient was matched to two controls who met all of the above criteria and had no history of n-3FA use. Each control was matched such that it was the same surgeon performing the same procedure with as similar an operative time as was possible based on the available patients for comparison. Information obtained from medical records regarding perioperative blood loss included, estimated blood loss (EBL) averaged across surgeon and anesthesiologist estimates, the amount of fluid transfused from the Cell Saver (CS) device (Haemonetics Corp., Braintree, MA, USA), surgical crystalloid and colloid, postoperative drain output, intravenous fluid and transfusion requirements and postoperative complications including re-operation for epidural hematoma and wound infection. All of the above outcomes were determined based on clinical parameters. This study was approved by our Institutional Review Board.

Statistical analysis of the case-control data consisted of descriptive evaluation using means and standard deviations for continuous variables and frequencies and percentages for discrete variables. All potential risk factors were evaluated for a univariate association using Chi-square or Fisher's exact tests for discrete variables and independent samples *t* tests for continuous variables. Unadjusted odds ratios and 95 % confidence intervals were calculated and presented for the discrete variables. A generalized estimating equation, accounting for clustering by surgeon, was used to evaluate the independent association of potential effect of using fish oil on each of the dependent outcomes.

Table 1 Procedures included in the study cohort

Procedure	<i>N</i>
One-level posterolateral fusion (PSF) and decompression (PLD) with posterior lumbar interbody fusion (PLIF)	27
Two-level PSF, PLD and PLIF	18
Two-level PSF and PLD with one-level PLIF	3
Two-level PLD and one-level PSF with PLIF	3
One-level PSF and PLD	9
Two-level PSF and PLD	15
One-level PSF and PLD	9

The listed number included both omega-3 fatty acid and control patients. All procedures occurred at adjacent levels between L3 and S1

All statistical analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

Our review identified 28 patients who had taken n-3FA supplements within 14 days of surgery (mean 5.2 days, range 0–10 days). Seven of these patients were taking Lovaza while the remainders were taking other n-3FA supplements. Each of these patients was matched 1:2 with controls of the same surgeon and same procedure with as similar an operative time as was possible given the available cases for review. A list of procedures included in our cohort is included in Table 1. Reported indications for surgery included spondylolisthesis, spinal stenosis and degenerative disc disease. Descriptive statistics of the n-3FA and control groups as well as univariate comparisons of perioperative blood loss are displayed in Table 2.

The n-3FA and control groups were similar with respect to gender, age, body mass index (BMI), preoperative laboratory studies and operative time. Preoperative use of non-steroidal anti-inflammatory drugs (NSAIDs) was similar in the two groups. NSAIDs used in the cohort included ibuprofen, naproxen, celecoxib, etodolac and meloxicam. In the n-3FA group, four patients had taken at least one dose of an NSAID within 7 days prior to surgery versus six patients in the control group. One patient in the control group had stopped warfarin 7 days prior to surgery and had a normal preoperative INR.

The primary outcome measures for this study were EBL and CS. Mean EBL was 697 ml in the n-3FA group and 771 ml in the control group ($p = 0.36$). Mean CS was 282 ml in the n-3FA group and 321 ml in the control group ($p = 0.30$). A post hoc power analysis showed that the study was powered to detect a minimum difference of 105 ml for EBL and 50 ml for CS. Secondary outcomes including change in postoperative drop in hemoglobin, transfusion requirement and surgical drain output were similar between the two groups. There were no epidural hematomas or wound infections requiring a return to the operating room in this cohort. Multivariate analysis using a generalized estimating equation, similarly, did not show a significant difference between groups with respect to EBL or CS ($p = 0.35$ and $p = 0.29$, respectively). The results of multivariate analysis are shown in Tables 3 and 4.

Discussion

There is little evidence in the surgical literature to guide decision-making regarding the cessation of n-3FA supplements around the time of spinal surgery. This is the first

Table 2 Descriptive statistics and univariate analysis of perioperative blood loss

	n-3FA	Control	<i>p</i> value
Gender	71 %	59 %	0.68
Age	61 (range 44–85)	56 (range 35–79)	0.06
Body mass index	27.3 (range 20.9–37.5)	28.3 (range 16.9–40.4)	0.35
Preoperative INR	1.00 (0.05)	1.00 (0.06)	0.67
Preoperative aPTT	27.0 (2.7)	27.3 (3.0)	0.57
Preoperative platelet level	260 (57.7)	259 (71.0)	0.92
Operative time (min)	220 (39.8)	230 (47.3)	0.34
Estimated blood loss	697 (397.6)	771 (340.4)	0.36
Transfused volume of Cell Saver	282 (126.5)	321 (169.2)	0.30
Surgical drain output through POD2	647 (333.2)	595 (264.5)	0.44
Transfusion requirement (in units of packed red blood cells)	0.89 (1.03)	0.69 (0.92)	0.37
Drop in hemoglobin preop to POD1	2.7 (1.1)	2.5 (1.2)	0.57
Drop in hemoglobin preop to POD2	3.2 (1.2)	3.0 (1.3)	0.63

The omega-3 fatty-acids group (n-3FA) includes 28 patients and the control group includes 56 patients unless otherwise specified. Values are listed as mean (standard deviation) unless otherwise specified. All volumes are in mL
POD postoperative day

Table 3 Generalized estimating equation of the correlation of omega-3 fatty-acids supplement (n-3Fa) use with estimated blood loss (EBL)

	Parameter estimate	95 % CI lower	95 % CI upper	<i>p</i> value
Intercept	771.13	681.55	860.70	
n-3FA	−74.11	452.30	941.74	0.349

Table 4 Generalized estimating equation of the correlation of omega-3 fatty-acids supplement (n-3Fa) use with transfused volume from the Cell Saver (CS)

	Parameter estimate	95 % CI lower	95 % CI upper	<i>p</i> value
Intercept	321.10	279.13	363.07	
Fish oil	−39.21	167.22	396.55	0.290

study to examine the effect of n-3FA supplements on perioperative bleeding during spinal arthrodesis. We found no difference between the n-3FA and control groups with respect to bleeding-related parameters including: EBL, CS, change in hemoglobin, transfusion requirement, and drain output. There was no difference with respect to bleeding complications including re-operation for epidural hematoma or postoperative surgical site infection.

There are several limitations inherent within our experimental design. The first is the heterogeneous nature of n-3FA supplementation. Since n-3FA has been classified as a dietary supplement by the Food and Drug Administration, n-3FA is loosely regulated in comparison to therapeutic drugs [15]. Consequently, n-3FA supplements are likely a heterogeneous group of products with variation in formulation, concentration and dosing. In vivo studies have demonstrated that the anti-platelet effects of n-3FA are dose dependent [16–18]. In 2004, the FDA responded to increasing recognition of the use of these agents for cardioprotective purposes by allowing producers of n-3FA supplements to advertise their products with a qualified health claim that use of these supplements may reduce incidence of coronary heart disease, which may have contributed to their increasing popularity [19]. There is unavoidable variability of the interval between patients' last dose of their n-3FA supplement and spinal arthrodesis within our cohort. This variability does, however, reflect the clinical scenario facing spinal surgeons.

A second limitation is the imprecise nature of surgeon or anesthesiologist EBL. We have attempted to compensate for this by the addition of objective measures. The Cell Saver device is able to filter and centrifuge suctioned blood and irrigant to a consistent hematocrit level for re-transfusion. As such, the amount of fluid generated by the Cell Saver is a more objective assessment of intraoperative blood loss than surgeon's estimate. However, blood loss in

lap pads and to sources other than the Cell Saver confounds this estimate. Another limitation is that all of our secondary outcomes were determined based on clinical parameters, which introduces unavoidable variability into these measures. Finally, our study was not powered to detect a significant difference between groups with respect to the rate of reoperation for infection or epidural hematoma.

A strength of this study is the matching technique that minimizes variability due to surgical technique and operative time as much as possible.

One previous study has investigated the effect of n-3FA supplementation on perioperative bleeding during spinal decompression surgery and several studies have investigated this topic at surgical sites other than the spine [20]. Similar to our results, these studies found no increased risk of bleeding complications, blood loss or transfusion requirements associated with n-3FA therapy. Despite citing the lack of convincing evidence that n-3FA administration is associated with increased risk of bleeding during and after surgery, Bays [21] cautiously endorsed stopping n-3FA supplements 5–7 days prior to surgical procedures. Although conservative recommendations based on likely clinical effect are prudent when no clinical information is available, our developing understanding of the risk associated with n-3FA suggests that the theoretical bleeding risk from these supplements may not manifest itself in actual clinical practice. There may be situations where continuation of n-3FA therapy is beneficial. Similar to n-3FA, aspirin has well-demonstrated cardioprotective effects as well as bleeding concerns due to its anti-platelet effects. A recent randomized clinical trial demonstrated that in high-risk patients undergoing non-cardiac surgery, the group that was continued on aspirin through the perioperative period had lower incidence of major cardiac adverse events than placebo without a difference in bleeding complications [22]. Further studies should focus on the interaction of n-3FA with other commonly used anti-platelet agents preferably in a setting where the dosage of the supplement is better controlled. A focus on cases with larger expected blood loss, such as spinal deformity, may better demonstrate the effect of this supplement on surgical blood loss. Ultimately, the value of this study is that it does not demonstrate a safety issue that would prevent future studies designed to assess the risk/benefit ratio of n-3FA supplements during spinal surgery.

Conflict of interest None.

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