Novel venous thromboembolic disease (VTED) prophylaxis for total knee arthroplasty—aspirin and fish oil

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Background: Despite the demonstrated success of multiple anticoagulation therapies for post-operative prophylaxis of thromboembolic disease in lower extremity arthroplasties, each modality comes with a unique set of limitations. Thus, the ideal anticoagulation medication which provides adequate therapy with minimal cost, complications, or added patient work is yet to be defined. One promising novel thrombophylactic supplement is fish oil, as many preliminary clinical trials have demonstrated a protective effect of fish oil against thrombosis in multiple clinical settings. In addition, others have demonstrated synergistic effect when combined with aspirin. However, there are paucity of studies that compared combined aspirin and fish oil therapy for venous thromboembolism prophylaxis with other pharmacological agents, especially in the field of orthopaedics. Therefore, this study evaluated: (I) risk of post-operative deep vein thrombosis (DVT) and pulmonary embolism (PE), and (II) bleeding complications; among patients who had primary total knee arthroplasty (TKA) and received one of the following regimens: (i) 325 mg aspirin and mechanical pulsatile stocking; (ii) rivaroxaban; or (iii) 325 mg aspirin and 1,000 mg fish oil.

Methods: This was a 6-year prospective study analyzing the postoperative thromboembolic prophylaxis received by patients who underwent primary TKA. Patients who had a previous history of thromboembolic disease were excluded from the study due to an increased risk of recurrent clot formation. A total of 850 patients were enrolled. A total of 300 patients enrolled between October 2011 and June 2013 received 325 mg aspirin and mechanical pulsatile stocking, while 250 patients enrolled between June 2013 and December 2014 received rivaroxaban. A total of 300 patients enrolled between January 2015 and July 2017 received 325 mg aspirin and 1,000 mg fish oil. Major venous thromboembolic events (VTEs) and bleeding complications within the first 90 days post-operatively were recorded in each cohort. The odds ratios (ORs) and 95% confidence intervals (CIs), for thromboembolic and bleeding events were calculated and compared between the aspirin and fish oil cohort vs. aspirin and pulsatile stocking cohort, and aspirin and fish oil cohort *vs.* rivaroxaban cohort. A P value of <0.05 was used to determine statistical significance.

Results: A total of 25 DVT events were recorded including 1 of 300 (0.33%) in the aspirin and fish oil cohort, 22 of 300 (7.33%) in the aspirin and pulsatile stocking cohort and 2 of 250 (0.8%) in the rivaroxaban cohort. When comparing ORs, patients who received aspirin and fish oil demonstrated significantly lower risk for thromboembolic events when compared to the aspirin and pulsatile stocking group (OR: 0.045; 95% CI: 0.0061–0.3394; $P<0.05$). When compared to the rivaroxaban cohort the ORs did not differ significantly (OR: 0.416; 95% CI: 0.0376–4.6223; $P>0.05$). In addition, no PE events were recorded in any of the cohorts. When compared to rivaroxaban, the fish oil and aspirin cohort demonstrated significantly lower incidence

of bleeding episodes (1 of 300, 0.33% *vs.* 30 of 250 patients, 12%; OR: 0.0278; 95% CI: 0.0038–0.2051; P<0.05). No bleeding events were recorded in the aspirin and pulsatile stocking cohort.

Conclusions: This study demonstrated the potentially synergistic anti-thromboembolic effect of aspirin and fish oil in the prevention of post-operative venous thromboembolism in primary TKA patients. Based on the results from this study, the authors conclude that the combination of aspirin and fish oil maybe an excellent thromboprophylactic modality for patients to use after TKA. These results warrant further, larger prospective studies analyzing the use of fish oil supplements in VTE prophylaxis.

Keywords: Fish oil; aspirin; deep vein thrombosis (DVT); total knee arthroplasty (TKA)

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Introduction

A number of pharmacological agents, including warfarin, aspirin, and factor Xa inhibitors, are currently used as postoperative thromboprophylaxis in orthopedic surgery (1-6). Even with these prophylactic modalities, venous thromboembolic events (VTEs) are still the second-most common medical complication after surgery, with some studies reporting VTE rates of up to 14% in some cases (7,8). Furthermore, the logistics of prescribing some of these medications as well as the added patient work involved can also add to the complication of using these medications. Specifically, as a newer therapeutic agent, not all insurance companies cover the full cost of factor Xa inhibitor, which can result in significantly higher, over $5,000, pharmacy costs for patients when compared to other standard of care medications (9). Warfarin, the most commonly prescribed anticoagulant, creates increased work for patients due to its slow onset of action, narrow therapeutic index requiring frequent international normalized ratio (INR) blood draws, and high sensitivity to genetic and environmental factors (10,11). These challenges can potentially result in patient non-compliance and might require meticulous medical supervision to ensure favorable outcomes (12-14), In addition to the rate of VTE, higher costs, and increased patient work, these medications are also not organically produced. Recent studies have reported that nearly 40% of adults in the United States currently use alternative medications and that worldwide, patients generally prefer more natural medications (15,16). An alternative therefore, is to use more natural supplements like fish oil, which has been found to safely contain anticoagulation properties (17,18).

Fish oil is a natural, low-cost supplement that is easily accessible to patients. The oil is derived from oily fish, such as salmon and mackerel, and contains omega-3 fatty acids like eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are known anti-inflammatories (19). Fish oil has also been found to be safe as part of many treatment regimens (20). Multiple reports cite the cumulative cardiovascular benefits of fish oil including a reduction of risk of coronary artery disease, decrease in hypertension, and prevention of certain cardiac arrhythmias and sudden death (21). Some studies have even demonstrated several key antithrombotic properties of fish oil that include a reduction of fibrin and thrombin generation leading to reduced platelet activation and aggregation (22-24). Long-chain polyunsaturated fatty acids of fish oil can also function by competitive inhibition with arachidonic acid for the cyclooxygenase enzyme (25). These thromboprophylactic effects have also been found to be enhanced when fish oil is combined with aspirin (26-28). Therefore, fish oil can be a natural alternative medication, and play a marked role in VTE management in post-surgical patients.

Although there are a number of studies analyzing fish oil in cardiovascular patients, there is currently a paucity of data surrounding the use of fish oil in the orthopaedic population. In particular to VTE prophylaxis in the orthopaedic population, it is not well understood how a fish oil and aspirin combination therapy compares with current leading practices in orthopaedic patients. Therefore, the purpose of this study was to determine the rates of deep vein thrombosis (DVT) and pulmonary embolism (PE) as well as bleeding complications in these patients. Specifically, we compared: (I) DVT and PE rates as well as; (II) bleeding complications, between total knee arthroplasty (TKA) patients who received: (i) 325 mg aspirin and mechanical

pulsatile stocking; (ii) rivaroxaban; or (iii) 325 mg aspirin and 1,000 mg fish oil.

Methods

Patient selection

A prospective, 6-year evaluation of 850 patients who were undergoing TKA by a single orthopaedic surgeon was performed at a high volume academic center. Patients with a history of DVT or PE were excluded from the study due to the marked increase in risk of recurrent venous thromboembolism compared to the general risk of (7% *vs.* 0.1%) (29). Institutional review board approval was obtained prior to the initiation of this study.

Medication cohorts

The 850 patients were consecutively organized into three prophylactic regimen cohorts. A total of 300 patients enrolled between October 2011 and June 2013 received a 90-day dose of 325 mg aspirin and mechanical pulsatile stocking, while 250 patients enrolled between June 2013 and December 2014 received a 4-week dose of rivaroxaban. A total of 300 patients enrolled between January 2015 and July 2017 received aspirin and mg fish oil. The aspirin and fish oil cohort consisted of 300 patients who received a 90-day combination regimen of 325 mg aspirin and 1,000 mg fish oil. The fish oil was available as an over-the-counter medication. Patients were instructed to take 1 concentrated 1,000 mg softgel along with the aspirin after a morning meal.

Postoperative monitoring

Patients were monitored through clinical, laboratory, and imaging diagnostics, assessing for risk of thromboembolic event, including DVT and/or PE, during their 90-day postoperative window. Clinical evaluation was based on patient symptoms including, but not limited to, lower extremity pain, tenderness or swelling, as well as any complaints of chest pain, shortness of breath, or difficulty breathing. Any suspected DVT was evaluated by ultrasonography and laboratory testing checking for D-dimer. Any suspected PE was immediately referred to the emergency department for full evaluation. Any other post-operative complications, such as bleeding, were assessed and managed by the primary surgeon.

Data analysis

The number of thromboembolic events and bleeding complications in each cohort were recorded during the 90-day postoperative window. The data was initially collected in the patient's medical record and later deidentified and exported to a Microsoft Excel spreadsheet (Microsoft Office 2013, Microsoft Corporation, Redmond, Washington, USA). In order to measure the association between VTE and bleeding events to medication cohort, the odds ratio (OR) and 95% confidence interval (CI) for VTE and bleeding events were calculated between all three cohorts (30). Statistical analyses were performed SPSS Version 23 (International Business Machine Corporation, Armonk, New York, USA). A cutoff P value of <0.05 was set to determine any statistical significances between the results.

Results

Overall outcomes of venous thromboembolism (DVT and PE)

A total of 25 patients (3%) had a reported venous thromboembolism complication of DVT. Only 1 patient (0.33%) in the combined aspirin and fish oil cohort experience DVT. A total of 22 patients (7%) experienced DVT who were in the aspirin and pulsatile stocking cohort. In the rivaroxaban cohort, 2 patients (1%) also experience DVT. Significantly fewer patients in the combined aspirin and fish oil cohort had a reported DVT ($P<0.05$). No patients had a reported outcome of PE in any cohort.

OR and CIs for venous thromboembolism (DVT and PE)

Based on the OR, patients in the combined aspirin and fish oil cohort had a significantly lower risk for developing a thromboembolic event when compared to patients in the aspirin and pulsatile stocking cohort (OR: 0.045; 95% CI: 0.006–0.339; $P<0.05$). There was no significant difference in OR between the combined aspirin and fish oil cohort and the rivaroxaban cohort (OR: 0.416; 95% CI: 0.038–4.622; $P>0.05$).

Overall bleeding complications

Overall, 31 patients (4%) had reported bleeding complications. Only 1 patient (0.33%) in the combined aspirin and fish oil cohort had a bleeding complication.

This patient was diagnosed with hemarthrosis, which required the discontinuation of fish oil. After the stoppage of fish oil, the patient continued to have an uneventful and successful postoperative recovery. A total of 30 patients (12%) in the rivaroxaban cohort experienced bleeding complications. Two of these patients (7%) required a return to the operating room for hematoma evacuation. After their re-operation, both patients continued to have an uneventful and successful postoperative recovery. The remaining 28 rivaroxaban cohort patients were all managed non-operatively by the primary surgeon and remained on their current regimen. The occurrence of bleeding complications was significantly lower for patients in the combined aspirin and fish oil cohort than it was for patients in the rivaroxaban cohort (P<0.05). No patients in aspirin/pulsatile stocking cohort sustained a bleeding episode. No other surgical or medical complications were reported.

OR and CIs for bleeding complications

Based on the OR, patients in the combined aspirin and fish oil cohort had a significantly lower risk for developing bleeding complications when compared to patients in the rivaroxaban cohort (OR: 0.028; 95% CI: 0.004–0.210; P<0.005).

Discussion

Despite multiple available thromboprophylaxis modalities, VTE is still the second-most common surgical complication, with rates up to 14%, in patients undergoing major orthopaedic surgery (7,8,31). Although several agents, including warfarin and factor Xa inhibitors, have shown clinical success (1,2,4), each medication has its shortcomings, driving the continued search for an ideal anticoagulant. One alternative to current therapies might be the addition of fish oil, a natural and low-cost supplement with demonstrated antithrombotic properties, to the current anticoagulation modalities. Therefore, the purpose of this study was to determine the rates of DVT, PE, and bleeding episodes in patients receiving regimens of aspirin/fish oil, aspirin/pulsatile stockings, or rivaroxaban. At 90 days post-operatively, we found that patients on combined aspirin and fish oil (0.33%) had significantly fewer thromboembolic events than patients who were using aspirin and pulsatile stockings (0.8%) as well as patients who were taking rivaroxaban (7%) (P<0.05). Furthermore, patients who were taking combined aspirin and fish oil (0.33%) had significantly fewer reported bleeding complications than patients taking rivaroxaban (12%) (P<0.05). Therefore, based on these results, the combined effects of aspirin and fish oil can provide patients adequate, if not superior, therapeutic anticoagulation.

There are some limitations to this study. The number of patients enrolled in this study may be too small to definitively conclude the additive efficacy of fish oil in VTE prevention and low rate of bleeding complications, since the rate of occurrence of these events is very small in patients who are taking aspirin. Still, this study provides data on 850 patients who were enrolled without any lapses in patient follow-up. Nevertheless, based on the findings from this study, we encourage other hospitals and academic centers to perform similar studies in large number to help verify the findings from this study. In addition, the lack of blinding in this study may have introduced some degree of bias. However, the aspirin and pulsatile stockings cohort as well as the rivaroxaban cohort provided duel control cohorts to which the aspirin and fish oil cohort was compared, thus helping reduce any potential for bias.

Several studies have also examined the clinical benefits of fish oil with similar results. In a randomized clinical trial involving 201 patients, Lok *et al.* (32) discovered that patients receiving fish oil capsules experienced half as many thrombosis events across a 12-month span compared to those taking a placebo (1.71 *vs.* 3.41 events per 1,000 access days, P<0.001). Andrioli *et al.* (33) performed a randomized prospective trial on 60 patients who took fish oil, soy lecithin, nothing (control) and found significant reductions in platelet adhesion in subjects receiving fish oil (P<0.005), indicating a biochemical role of fish oil in platelet adhesion and eventual blood clot formation. Furthermore, Hansen-Krone *et al.* (34) studied the incidence of venous thromboembolism related diseases in 23,621 participants and stratified the events based on fish oil consumption in the cohort. Weekly fish intake ≥3 times correlated with a 22% lower risk of venous thromboembolism when compared with fish consumption at 1–2 times weekly. [multivariable hazard ration (HR): 0.78; 95% CI: 0.60–1.01; P=0.06]. Also, those who consumed additional fish oil supplements demonstrated even lower rates of venous thromboembolism with 48% lower risk than those who consumed fish 1–2 times weekly and did not use fish oil supplements (HR: 0.52; 95% CI: 0.34–0.79; P=0.002). In addition, Engstrom *et al.* (35) found that the combination of fish oil and 37.5 mg aspirin led to a larger reduction of pro-aggregatory thromboxane A2 (TXA2) (62% *vs.* 40%) and

smaller reduction of anti-aggregatory prostacyclin PGI2 and PGI3 (33% *vs.* 55%), thereby inhibiting platelet build-up and the formation of inter-arterial thrombi.

In contrast to our study, other studies have found limited or no advantages of fish oil in relation to cardiovascular effects or thromboembolism. In a randomized control trial Poppitt *et al.* (36) analyzed 102 patients who were randomized to either 3 g/day of fish oil or placebo for 12 weeks. Although the group concluded there was no effect of 12 weeks of treatment on any lipid, inflammatory, or hemostatic biomarkers, the authors acknowledge the lack of cardiovascular improvement in these patients to be potentially due to insufficient dosage. Additionally, the patients studied were being managed after a stroke, not after an orthopaedic procedure.

Conclusions

This study highlights the synergistic thromboprophylactic properties of combing aspirin and fish oil. The combined use of aspirin and fish oil demonstrated superiority over the multimodal treatment of aspirin and pulsatile stockings with regard to DVT and PE occurrence and rivaroxaban with regard to the number of significant bleeding episodes. Future studies should build on the findings from this study, and should include larger sample sizes to support these findings. Nevertheless, based on the results from this study, the authors conclude that the combination of aspirin and fish oil is an excellent thromboprophylactic modality for patients to use after TKA.

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None.

Footnote

Conflicts of Interest: PM Bonutti: Joint Active Systems Inc., Stryker, Zimmer; MA Mont: AAOS, Cymedica, DJ Orthopaedics, Johnson & Johnson, Journal of Arthroplasty, Journal of Knee Surgery, Microport, National Institutes of Health (NIAMS & NICHD), Ongoing Care Solutions, Orthopedics, Orthosensor, Pacira, Peerwell, Performance Dynamics Inc., Sage, Stryker: IP royalties, Surgical Techniques International, TissueGene; M Chughtai: DJ Orthopaedics, Sage Products, Stryker; FR Kolisek: DJ Orthopaedics, Ortho Tech Review, Orthopaedic Knowledge Online Journal, Orthopedics, Stryker. The other authors have no conflicts of interest to declare.

Ethical Statement: Institutional review board approval was obtained prior to the initiation of this study.

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