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Prophylactic Antioxidant use for the Prevention of Post-Operative Atrial Fibrillation in Cardiac Surgery Patients

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Abstract

Background: Atrial fibrillation occurs in 20-40% of patients following cardiac surgery with extra-corporeal circulation. Among the multiple factors leading to atrial fibrillation, the oxidative stress resulting from the reperfusion of ischemic myocardial tissue has been shown to play a major role. The reactive oxygen species (ROS) generated by the ischemic-reperfusion event results in direct cellular damage, an increased inflammatory response, and an upregulation of apoptotic gene expression. Atrial fibrillation occurs due to the electrical remodeling caused by changes at the cellular level. However, exposure to low to moderate levels of ROS prior to oxidative stress has been shown to be responsible for an upregulation in the expression of endogenous antioxidant enzymes. For this reason, n-3 polyunsaturated fatty acids (PUFA) have been studied and proven to reduce the incidence of post-operative atrial fibrillation (POAF). The use of exogenous antioxidants such as vitamin C and E have also been shown to reduce POAF. Therefore, a combined therapy should result in increased antioxidant reinforcement resulting in a markedly lower occurrence of atrial fibrillation.

Methods: Exhaustive search of available medical literature was conducted using Medline, CINAHL, and Web of Science using the keywords: antioxidants and atrial fibrillation. The results were limited to articles published from 2011 to the present, written in English regarding human test subjects, and directly answering the clinical question. Articles were critically appraised for quality using GRADE.

Results: Two studies met inclusion criteria and were included in this systematic review. A randomized, double blind, placebo controlled trial with 203 participants demonstrated a statistically significant reduction in post-operative atrial fibrillation when n-3 unsaturated fatty acid and vitamins C and E were administered. A second randomized, double blind, placebo controlled trial with 152 participants demonstrated a statistically significant reduction in post-operative atrial fibrillation in patients over 60 years of age with moderate improvement with participants under 60 years after the administration of unsaturated fatty acid and vitamins C and E.

Conclusion: The prophylactic use of antioxidants in cardiac surgery patients has proven to be an effective low-cost low-risk intervention for the prevention of post-operative atrial fibrillation. The indirect effects of n-3 PUFAs brought about the upregulation of endogenous antioxidant enzymes while exogenous antioxidants, vitamin C and E, reduced ROS both by directly scavenging ROS, and down-regulating their production. This readily available treatment would reduce the risk of POAF for on-pump cardiac surgeries resulting in reduced hospital stay, overall costs, and cardiovascular pathology.

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Degree Name
Master of Science in Physician Assistant Studies

Keywords
Antioxidants, atrial fibrillation, n-3 unsaturated fatty acid, ascorbic acid, α-tocopherol

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Prophylactic Antioxidant use for the Prevention of Post-Operative Atrial Fibrillation in Cardiac Surgery Patients

Ross William Davis

A Clinical Graduate Project Submitted to the Faculty of the
School of Physician Assistant Studies
Pacific University
Hillsboro, OR

For the Masters of Science Degree, 2014

Faculty Advisor: Prof. Eric Foote
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

Ross Davis is a native of Michigan. He received a Bachelor of Science degree from Portland State University in 2010. While completing undergraduate studies, he worked as an EMT. He is interested in pursuing a career in emergency medicine.
Abstract

Background: Atrial fibrillation occurs in 20-40% of patients following cardiac surgery with extra-corporeal circulation. Among the multiple factors leading to atrial fibrillation, the oxidative stress resulting from the reperfusion of ischemic myocardial tissue has been shown to play a major role. The reactive oxygen species (ROS) generated by the ischemic-reperfusion event results in direct cellular damage, an increased inflammatory response, and an upregulation of apoptotic gene expression. Atrial fibrillation occurs due to the electrical remodeling caused by changes at the cellular level. However, exposure to low to moderate levels of ROS prior to oxidative stress has been shown to be responsible for an upregulation in the expression of endogenous antioxidant enzymes. For this reason, n-3 polyunsaturated fatty acids (PUFA) have been studied and proven to reduce the incidence of post-operative atrial fibrillation (POAF). The use of exogenous antioxidants such as vitamin C and E have also been shown to reduce POAF. Therefore, a combined therapy should result in increased antioxidant reinforcement resulting in a markedly lower occurrence of atrial fibrillation.

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Acknowledgements

To my parents: Thank you for your endless encouragement and support.
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Table I: GRADE Quality of Assessment and Summary of Findings

List of Abbreviations

AF..............................................................Atrial fibrillation
POAF..........................................................Post-operative atrial fibrillation
ROS..........................................................Reactive oxygen species
NADPH..........................................................Nicotinamide adenine dinucleotide phosphate
eNOS............................................................Endothelial nitric oxide synthase
NO..............................................................Nitric oxide
CAT.............................................................Catalase
GPX.............................................................Glutathione peroxidase
PUFA............................................................Polyunsaturated fatty acids
SOD...........................................................Superoxide dismutase
GRADE..........................................................Grading of Recommendations, Assessments, Development, and Evaluation
EKG..........................................................Electrocardiography
MDA...........................................................Malondialdehyde
EPA..........................................................Eicosapentaenoic acid
DHA..........................................................Docosahexaenoic acid fibrillation
NNT...............................................................Number needed to treat
CRP............................................................C-reactive protein
Prophylactic Antioxidant use for the Prevention of Post-Operative Atrial Fibrillation in Cardiac Surgery Patients

BACKGROUND

Atrial fibrillation (AF) is commonly seen in up to 20-40% of patients following cardiac surgery with extra-corporeal circulation and has been shown to increase the risk of short-term mortality as well as long-term survival rates.\textsuperscript{1-3} The complications surrounding AF can result in costly extended hospital stays as well as increasing the risk of in-hospital mortality.\textsuperscript{4} Modern antiarrhythmic medication and advances in surgical practice have had little effect on the occurrence of post-operative atrial fibrillation (POAF).\textsuperscript{5} Research has shown multiple mechanisms influencing the occurrence of POAF but the specifics remain unclear.

Sources of Reactive Oxygen Species (ROS)

The ischemia-reperfusion event associated with extra-corporeal circulation has been shown to increase the production of reactive oxygen species (ROS), which contribute to a cascade of events leading to electrical and structural remodeling resulting in post-operative atrial fibrillation.\textsuperscript{6,7} The main source of ROS at the moment of reperfusion is from the reactivation of mitochondrial electron transport chain complexes as well as myocardial xanthine oxidase to a lesser extent.\textsuperscript{6-9} The greatest source of ROS in the cardiovascular system is nicotinamide adenine dinucleotide phosphate (NADPH) oxidase found in myocytes.\textsuperscript{10,11} The ROS generated by NADPH are thought to result in an uncoupling of endothelial nitric oxide synthase (eNOS) resulting in increase ROS instead of generation of cardioprotective nitric oxide (NO).\textsuperscript{12} ROS are also generated by
NADPH oxide via neutrophils infiltrating ischemic tissue in the hours following an ischemia-reperfusion event.\textsuperscript{7,13}

**Effects of Reactive Oxygen Species**

Increased ROS activity contributes to the alteration of myocardial electrical conduction by adversely impacting intracellular mechanisms resulting in cell death, altering expression of membrane proteins responsible for cell-to-cell electrical conduction, and increasing the inflammatory response.

Following reperfusion, increased ROS levels result in direct damage of cellular structures as well as inhibition of intracellular mechanisms. ROS cause mitochondrial dysfunction by opening mitochondrial permeability transition pores. This leads to further increases in ROS, decreases in ATP production, and cardiomyocyte death.\textsuperscript{7,14} ROS also cause sarcoplasmic reticulum dysfunction as well as direct damage to the sarcolemma membrane which results in a Ca+ overload within the cardiomyocyte cytosol.\textsuperscript{7} The highly elevated cytosolic Ca+ levels cause irreversible hypercontracture of the cardiac muscle cell and cell death following reperfusion.\textsuperscript{15} Additionally, ROS have been shown to activate a signaling protein which upregulates the expression of inflammatory cytokines and signals transcription events leading to cardiomyocyte apoptosis.\textsuperscript{3,16,17}

Oxidative stress has also been shown to alter the electrical properties of atrial tissue. ROS expand the expression of conductive proteins beyond the cardiomyocyte gap junctions to the entirety of the cell membrane. This alteration causes multiple cell-to-cell conduction pathways throughout the atrial myocardium, each with varied conduction velocities and resistance properties.\textsuperscript{18} Ion-channel expression is also altered due to ROS which results in decreased refractory time and conduction velocity, increasing the
likelihood of an electrical signal reentering a pathway multiple times. These changes allow the ischemic myocardium to function without adequate metabolic resources but greatly increase the likelihood of sustained atrial fibrillation.\textsuperscript{19}

ROS bring about the inflammatory response by increasing the release of neutrophil chemoattractant cytokines, activating compliment, and upregulating adhesion molecules, which allow neutrophil myocardial infiltration. The recruitment of neutrophils results in further myocyte death through the occlusion of capillaries, increased production of ROS by way of NADPH, and the release proteolytic enzymes.\textsuperscript{20} Rising levels of atrial inflammation have been found to cause increased inhomogeneity of atrial conduction leading to atrial fibrillation.\textsuperscript{21}

Cardiomyocyte death, altered cell-to-cell electrical conduction, and the inflammation response all contribute to changes in the electrical substrate of the atrial myocardium, giving rise to paroxysmal atrial fibrillation, which if persistent, brings about changes in the myocardial structural substrate, making the recurrence of atrial fibrillation even more likely.\textsuperscript{22}

\textbf{The Antioxidant system}

It has been shown that ROS trigger cardioprotective mechanisms at low to moderate levels by activating a signaling protein, resulting in increased expression of endogenous antioxidant enzymes such as catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD).\textsuperscript{3,23,24}

\textbf{N-3 fatty acid}

N-3 polyunsaturated fatty acids (PUFAs) have been found to protect against the effects of ROS. PUFAs increase ROS levels to low to moderate levels, which initiates the
upregulation of endogenous antioxidant enzymes expression, providing decreased vulnerability to ROS at the moment of oxidative challenge. After exposure to ROS generating stress, experimental groups were found to have lower levels of ROS due to a significant upregulation of endogenous antioxidant enzymes. Experimental groups were also found to have higher levels of PUFAs incorporated into myocytes cell membranes, which results in a more fluid membrane less reactive to ROS. In addition, PUFAs effectively reduced the concentration of cytosolic Ca+, which lowers the risk of myocyte hypercontracture and cell death.

**Vitamin C & E**

Exogenous antioxidants also play an important role in lowering oxidative stress. Vitamins C and E in particular have been found to be effective in preventing the formation of ROS through a number of mechanisms.

The properties of Vitamin C and E are complimentary when it comes to the reduction of ROS. Vitamin C is hydrophilic and scavenges the water-soluble components for ROS while vitamin E patrols the lipid-soluble components such as the cell membrane. This differentiation of roles allows for ROS protection throughout the entire cell. Vitamin C has an additional role regenerating vitamin E after oxidation. This action prevents the adverse effects of the vitamin E radical and allows the vitamin to be “recycled” for further ROS scavenging.

NADPH oxidase is the greatest source of ROS in the cardiovascular system. Although the mechanism is not completely known, it is thought that vitamins C and E work to downregulate NADPH oxidase transcription as well as post-transcriptional activity. This leads to decreased superoxide formation and enhanced levels of eNOS.
resulting in increased NO generation.\textsuperscript{28}

Vitamin C has been found to reverse the oxidation of an important cofactor of eNOS while Vitamin E activates an amino acid which initiates eNOS activity. The end result is increased levels of NO which is important for proper endothelial function.\textsuperscript{27} The aim of this review is to evaluate whether a combined therapy should result in increased antioxidant reinforcement resulting in a markedly lower occurrence of atrial fibrillation.

**METHODS**

An exhaustive search of available medical literature was conducted using Medline, CINAHL, and Web of Science using keywords: antioxidants and atrial fibrillation. Articles directly pertaining to antioxidant use for prevention of atrial fibrillation were included. Other eligibility criteria included articles published from 2011 to the present, written in English regarding human test subjects, and directly pertaining to antioxidant use for prevention of atrial fibrillation. Relevant articles were critically appraised for validity using the Grading of Recommendations, Assessments, Development, and Evaluation (GRADE).\textsuperscript{29}

**RESULTS**

The initial result of the search yielded 100 articles for review. After screening results were, a total of two articles met inclusion criteria.\textsuperscript{30,31} Both articles were randomized, double-blind, placebo-controlled trials. See Table I.

**Rodrigo et al (2012)**

This randomized, double-blind, placebo-controlled trial\textsuperscript{30} investigated the effects of PUFA and vitamin C and E on patients scheduled for cardiac surgery with extra-
corporal circulation. The study involved 132 patients admitted for cardiac surgery utilizing extra-corporal circulation at the Cardiovascular Department of the University of Chile Clinical Hospital between July 2007 and February 2009.30

The primary endpoint of the trial was the occurrence of AF anytime following surgery, until discharge from the hospital. An electrocardiogram (EKG) continuously monitored patients following surgery to document any AF. A Holter monitor was used 4 days following surgery. AF lasting at least 1 minute, as documented by EKG or Holter, was considered POAF.30

The secondary endpoints included biochemical evidence of oxidative stress in atrial tissue samples and plasma. Five blood samples were obtained beginning before PUFA supplementation on Day -7 (seven days before the surgery), before administration of antioxidant vitamins on Day -2, before surgery on Day 0, 6–8 hours after surgery on Day +1, and 5 days after surgery on Day +5.30

The right atrial appendage was sampled before starting extra-corporal circulation. Malondialdehyde (MDA) analysis was performed for plasma and atrial tissue, assessing for oxidative stress resulting in lipid peroxidation. Antioxidant enzyme activity was measured on red blood cells and atrial tissue by assessing levels of CAT, SOD, and GSX.30

The eligibility criteria included patients from 30 to 80 years of age with sinus rhythm, scheduled for valve, coronary artery bypass graft, and mixed surgeries. Exclusion criteria included previous cardiac surgery, chronic or paroxysmal AF, other preoperative arrhythmias, advanced pulmonary, and hepatic disease or chronic renal failure (serum creatinine >2.0 mg/dl). Study participants were divided into groups greater
and less than 60 years of age, followed by computer-generated randomization done centrally, unstratified, and block-based.\textsuperscript{30}

Immediately following randomization, treatment consisted of daily doses of n-3 PUFAs (2 g/d) with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in an average 1:2 EPA/DHA ratio. Two days before surgery, vitamin C (1 g/d) plus vitamin E (400 IU/d) were added. This supplementation was administered until discharge from hospital. The placebo group received an equal number of capsules of identical size and color. Participants were admitted two days prior to surgery after five days of n-3 PUFA supplementation through ambulatory administration.\textsuperscript{30}

No significant differences in demographic characteristics, comorbidities, pharmacological treatment, and surgery data were found between participant groups.\textsuperscript{30}

Among the under 60 years groups, twelve out of 40 (30.0\%) patients from the placebo group were found to have POAF while only five out of 40 (12.5\%) patients receiving n-3 and antioxidant vitamin supplementation had an arrhythmic event. This resulted in a relative risk of 0.42, which results in a risk reduction of 58\% and a number need to treat (NNT) of 6. However, the difference in the survival curve was found to be not statistically significant.\textsuperscript{30}

Among the over 60 year groups, 10 out of 35 patients (28.5\%) from the placebo group experienced POAF while only two of 37 (5.4\%) patients receiving supplementation experienced AF. This resulted in a relative risk of 0.19, which results in a risk reduction of 81\% and a number need to treat NNT of 5. Among patients over 60 years, there was a statistically significant difference (log-rank \(P = 0.0076\)). GSX activity in atrial tissue prior to surgery was higher in patients over 60 years who received the antioxidant
supplementation compared with the other participant groups (P < 0.05). Following surgery, patients with POAF showed higher plasma MDA levels and lower atrial GSX activity compared with those who did not present post-operative AF (P < 0.01).^{30}

The authors of this study mention interest experimenting with increased vitamin C administration to not only decrease ROS production, but to also improve ROS scavenging. Future studies involving an increased PUFA exposure before surgery would be useful in determining its ability to generate a greater antioxidant response.^{30}

Rodrigo et al (2013)

The Randomized Controlled Trial to Prevent Post-Operative Atrial Fibrillation by Antioxidant Reinforcement trial^{31} investigated the effects of PUFA and vitamin C and E administration on reducing the incidence of post-operative atrial fibrillation among cardiac surgery patients with extra-corporeal circulation.^{31}

The study enrolled 307 patients who were admitted to the University of Chile Hospital and San Juan de Dios Hospital for cardiac surgery between February 2010 and December 2011.^{31}

The primary outcome was the occurrence of POAF anytime following surgery until discharge from the hospital. Patients were continuously monitored electrocardiographically for the first 24 to 48 hours following surgery and then monitored via Holter monitor until the fourth post-operative day. EKG-confirmed AF lasting at least one minute was documented as POAF.^{31}

The secondary outcomes included blood inflammation indexes and oxidative stress-related biomarkers in the atrial tissue and/or plasma. Blood samples were drawn at
a fasting state on the day of enrollment (day -7), 5 days after n-3 PUFAs administration (day -2), 15 min before beginning extra-corporeal circulation (time 0), 6 to 8 h after surgery (day +1), and post-operative day 5 (day +5). Right atrial appendage samples were collected before extra-corporeal circulation.\textsuperscript{31}

Eligibility criteria required patients 18 years of age or older, scheduled for coronary artery bypass graft, valve surgery, or mixed, all in sinus rhythm. Patients were excluded for previous history of any arrhythmia, previous myocardial infarction, current use of amiodarone or sotalol, severe congestive heart failure (New York Heart Association class III or IV), presence of prosthetic valves, congenital valvular disease, or left atrial diameter > 50 mm. Patients were also excluded for conditions associated with oxidative stress or inflammation such as chronic rheumatic or neoplastic diseases, liver insufficiency, severe chronic kidney disease (serum creatinine > 2.0 mg/dl), and recent infections. Patients receiving nonsteroidal, anti-inflammatory drugs, corticosteroids, antioxidant vitamins, or fish oil supplements 3 months prior to surgery were also excluded from the study.\textsuperscript{31}

Treatment began 7 days prior to surgery with 2g of n-3 PUFAs daily initiated immediately after central, nonstratified block based, computerized randomization. The formulation contained EPA and DHA acids in a 1:2 EPA:DHA ratio. Two days before surgery, vitamin C (1 g/day) plus vitamin E (400 IU/day) were added. The whole supplementation regimen continued until hospital discharge. The placebo group received capsules indistinguishable from those of the treatment group.\textsuperscript{31}

The participant groups were comprised of 203 patients with comparable baseline characteristics. POAF was documented in 10 of the 103 patients (9.7%) in the
experimental group and 32 of the 100 patients (32%) in the placebo group (RR 0.28, 95% CI 0.14-0.56, p < 0.001, NNT=4.7 (95% CI: 3.3 to 11.4). Thirty patients (71.4%) developed AF between the second and third post-operative days belonged mostly to the placebo group (24 of 30 patients (80%), log-rank test p < 0.001). The placebo patients had 3.62 times more risk for POAF at any day compared with the supplemented patients (HR 3.62, 95% CI 1.78-7.36, p < 0.001).³¹

Oxidative stress, resulting in lipid peroxidation, was assessed through levels of MDA levels in blood and atrial tissue on the day of surgery (time 0). Following 5 days of n-3 PUFA administration, the MDA levels increased by 59.6% as compared to baseline values (p < 0.01) and were 45.6% greater than placebo baseline values (p < 0.01). There was no significant difference in MDA levels at time 0 after the addition of antioxidant vitamins. Following surgery (day +1), the placebo group had MDA levels 3.7-fold and 3.5-fold higher than baseline levels (day -7) and pre-operative (time 0) respectively (p < 0.01) and 47.5% higher MDA levels than the supplemented group post-operative levels. The supplemented group exhibited a 2.8-fold and 2.2-fold increase in plasma levels of MDA compared to the baseline (day -7) and pre-operative (time 0) values, respectively (p < 0.01). The supplemented group presented 26.1% lower MDA levels (p < 0.01) in atrial tissue on the day of surgery compared with the placebo group. Patients with POAF had markedly higher levels of atrial MDA (4.47 vs. 3.85 mmol/mg protein; p < 0.01) at the time of surgery when compared to patients with sinus rhythm.³¹

Following surgery (day +1), the placebo and supplemented groups both presented with higher serum high-sensitivity C-reactive protein (CRP) levels at 3.6-fold and 2.2-fold greater levels than the pre-operative values (p < 0.01). However, the supplemented
group displayed CRP levels 35.4% less than those of the placebo group (p < 0.05). After 5 days of n-3 PUFA treatment (day -2), the leukocyte count in the supplemented group was 32.5% higher than the baseline values (p < 0.05). Following surgery (day +1), the placebo and supplemented groups exhibited a 73.8% and 36.2% increase in leukocyte count, respectively, compared with preoperative levels (p < 0.05). The supplemented group had a leukocyte count 22.2% lower than that in the placebo group (p < 0.05).31

The activity of antioxidant enzymes CAT, SOD, and GSX in the atrial tissue of the supplemented patients was 24.0%, 17.1%, and 19.7% higher than the placebo group values on the day of surgery (p < 0.05). Furthermore, the expression levels of endogenous antioxidants levels in the supplemented group revealed 52.9%, 42.5%, and 34.5% higher levels, respectively, compared with the placebo group (p < 0.01).31

The atrial tissue of patients with POAF exhibited a 115.5% higher p47-phox NADPH oxidase subunit protein expression and 65.8% higher mRNA levels compared with patients in sinus rhythm (p < 0.05). Furthermore, protein expression and mRNA levels were 41.3% and 36.4% lower in the supplemented group than the respective placebo group values (p < 0.05).31

The authors felt that their study was limited in that the population showed a male predominance and included younger patients compared other related studies. They also mentioned a broader study of n-3 PUFA is warranted due to the likelihood of additional beneficial effects outside of a reduction of oxidative stress and inflammation response. Additional monitoring beyond the fourth post-operative day would have been useful in revealing asymptomatic AF occurring beyond the fourth post-operative day.31
DISCUSSION

Antioxidant reinforcement presents a cost effective and safe method of preventing post-operative atrial fibrillation by upregulating the expression of endogenous antioxidant enzymes while providing exogenous antioxidants for direct ROS scavenging and the increase of cardioprotective molecules such as nitric oxide while minimizing the expression of ROS producing molecules and inflammatory response.

Rodrigo et al (2012) initial study demonstrated that supplemented patients over age 60 were five times less likely to develop post-operative atrial fibrillation follow surgery (RR=0.42, RRR=58%, NNT=6). Although not statistically significant, supplemented patients under age 60 were still twice less likely to develop POAF. The difference is thought to be due to the elder patients being less resilient to the oxidative challenge posed by PUFA supplementation, generating increased ROS levels which would then increase the priming of the expression of endogenous antioxidant enzyme prior to surgery. Accordingly, only supplemented participants over 60 years were found to have elevated GSX activity on the day of surgery. Higher levels of GSX were found in patients without POAF while increased MDA levels, evidence of lipid peroxidation, were found in patients suffering from POAF.

This study clearly demonstrates the benefits of prophylactic supplementation in patients over 60 years (RR=0.19, RRR=81%, NNT=5). However, limitations were present which would be beneficial to explore in the future. Increasing PUFA exposure time prior to surgery may have a marked benefit for all patients, especially those under 60 years. Although more resilient to the oxidative stress provided by the PUFAs, additional exposure could result in great upregulation of endogenous antioxidant enzymes. It would
be worthwhile to explore whether or not increase Vitamin C and E levels would result in greater ROS scavenging in addition to down-regulation of ROS production.

In the Rodrigo et al (2013) study, antioxidant reinforcement was shown to have a 66% reduction in POAF across all age groups using the same treatment protocol as the previous study (RR 0.28, 95% CI 0.14-0.56, p < 0.001, NNT=4.7 (95% CI: 3.3 to 11.4). Increased ROS levels were documented two days prior to surgery indicating that an oxidative challenge had been elicited due to PUFA administration. Following surgery, inflammation, assessed through leukocyte and CRP levels, and oxidation markers, assessed through atrial and plasma MDA levels, were less markedly elevated in the supplemented group. Endogenous antioxidant enzymes, CAT, SOD, GSX, as well as mRNA expression, were elevated among the supplemented participants. Furthermore, decreased levels of protein and mRNA expression of the NADPH oxidase were noted in the supplemented group, which likely resulted from Vitamin C and E down-regulation. It was also noted that levels of atrial xanthine oxidase were no significantly different in the supplemented or placebo groups, they were markedly higher in patients with POAF.

EPA and DHA were administered in a 1:2 EPA:DHA ratio based on previously successful trials. An even greater result in the prevention of POAF was documented in this trial as compared to previous studies, which is likely due to the addition of vitamin C and E. The mechanisms behind the effectiveness of the 1:2 EPA:DHA ratio are still unknown as is the entirety of the benefits of resulting from PUFA administration.

Although the efficacy of antioxidant reinforcement has been clearly demonstrated further exploration would be useful. The lack of significant affect demonstrated among the under 60 years test group in the Rodrigo and colleagues 2012 trial could be due to
the younger patients’ resilience to the n-3 PUFA oxidative stress. Perhaps longer periods of PUFA exposure before surgery would result in a greater endogenous antioxidant enzyme response. The effects prolonged PUFA exposure along with increased vitamin C and E doses would also worth exploring among all future participants. A longer follow-up period would also be beneficial in that the occurrence of asymptomatic POAF could have gone unnoticed in studies following discharge. Future studies would also benefit from a larger participant pool to compare a large population with a broader spectrum of ages, ethnicities, and cardiovascular pathology.

CONCLUSION

The prophylactic use of antioxidants in cardiac surgery patients has proven to be an effective low-cost low-risk intervention for the prevention of post-operative atrial fibrillation. The indirect effects of n-3 PUFAs (1:2 EPA:DHA ratio) brought about the upregulation of endogenous antioxidant enzymes while exogenous antioxidants, vitamin C and E, reduced ROS both by directly scavenging ROS, and down-regulating their production. This readily available treatment would reduce the risk of POAF for on-pump cardiac surgeries resulting in reduced hospital stay, overall costs, and cardiovascular pathology.

Further research is still warranted to determine the effects of additional n-3 PUFA exposure and increased levels of antioxidants vitamin C and E as well as increased follow-up screening for adverse cardiovascular events. The exact mechanisms at work behind antioxidant reinforcement have yet to be fully understood. In particular, the effects n-3 PUFAs administered were thought to extend beyond those related to oxidative stress and inflammation. Larger studies with a more varied patient demographic would
provide a clearer picture of the patient population that stands to benefit from antioxidant reinforcement as well as serving to refine methods to provide greater protection.
References


**Table I. Characteristics of Reviewed Studies**

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### [Outcome #1]

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### [Outcome #2]

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