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Is Sotalol A Better Choice Over Metoprolol for Atrial Fibrillation Prophylaxis Post Coronary Artery Bypass Graft Surgery?

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Abstract

Background: Atrial Fibrillation (AF) is the most common arrhythmia post Coronary Artery Bypass Graft surgery (CABG). Up to 50% of patients who undergo a CABG procedure will have AF. Metoprolol, a conventional beta-blocker, has been the drug of choice for AF prophylaxis. Sotalol, also a beta-blocker, with class III antiarrhythmic effects, could possibly provide a better prophylaxis intervention of AF post CABG surgery.

Methods: The focus of this study was to review clinical trials on the comparison between sotalol and metoprolol. A thorough review of clinical trials within the last twelve years, pertaining to sotalol versus metoprolol and sotalol versus placebo, were carefully selected and analyzed. Double-blinded and randomized clinical trials of metoprolol and sotalol were identified by systematic literature search using Medline, CINAHL, Medscape, and MD consult search engines.

Results: Based on the five clinical trials analyzed, atrial fibrillation incidences were lowest in the sotalol groups (as low as 12.5 %) versus metoprolol groups (19%), and placebo groups (18%). Data gathered also demonstrates sotalol and metoprolol reducing hospital length of stay to at least half a day when compared to placebo.

Conclusion: Metoprolol and Sotalol both reduce the risk of post-operative AF, sotalol having a greater efficacy than metoprolol in reducing the rates of AF post CABG surgery. It is shown however, that sotalol has added adverse effects from its class III antiaryhtmic effects in addition to its beta blocking side effects. There is some evidence, although not significant, that both drugs reduce hospital length of stay (LOS) when compared to placebo, however, there is no marked difference between the two groups, sotalol and metoprolol.

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School of Physician Assistant Studies

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Faculty Advisor: James Ferguson, PA-C

Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC

Biography

Felipson Ramos was born in Pangasinan, Philippines. He moved to Guam, USA at the age of seven. After finishing high school in Guam, he enlisted in the Guam Army National Guard to serve as a Combat Medic, while maintaining his full time college status at the University of Guam. Due to an unfortunate accreditation probation of the University of Guam, he moved to Oregon to continue and pursue his bachelor's degree in Biology/Chemistry. Felipson continued to be involved in healthcare by working as a Certified Nursing Assistant and a caregiver for people with developmental disabilities while completing his Bachelors degree. Prior to his acceptance to PA school, Felipson worked two years in a Biomedical Research Laboratory at the Oregon Health Science University and also was also closely involved with clinical research conducted at the Emergency Department at OHSU. Currently Felipson is a Health Professional Scholarship Program recipient with the United States Air Force. He will be serving as an Air Force Physician Assistant after graduation.

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Table 1. Summary of AF in Sotalol when compared to metoprolol and placebo in five clinical trials.

List of Abbreviations

AF.....	Atrial Fibrillation
ACC.....	American College of Cardiology
CABG.....	Coronary Artery Bypass Graft
ECG.....	Electrocardiogram
ICU.....	Intensive Care Unit
NSR.....	Normal Sinus Rhythm
AV.....	Atrioventricular

Abstract

Background: Atrial Fibrillation (AF) is the most common arrhythmia post Coronary Artery Bypass Graft surgery (CABG). Up to 50% of patients who undergo a CABG procedure will have AF. Metoprolol, a conventional beta-blocker, has been the drug of choice for AF prophylaxis. Sotalol, also a beta-blocker, with class III antiarrhythmic effects, could possibly provide a better prophylaxis intervention of AF post CABG surgery.

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Conclusion: Metoprolol and Sotalol both reduce the risk of post-operative AF, sotalol having a greater efficacy than metoprolol in reducing the rates of AF post CABG surgery. It is shown however, that sotalol has added adverse effects from its class III antiarrhythmic effects in addition to its beta blocking side effects. There is some evidence, although not significant, that both drugs reduce hospital length of stay (LOS) when compared to placebo, however, there is no marked difference between the two groups, sotalol and metoprolol.

Is Sotalol A Better Choice Over Metoprolol for Atrial Fibrillation Prophylaxis Post Coronary Artery Bypass Graft Surgery?

Introduction

There are four standard oral drugs administered to patients post CABG surgery. These oral drugs include statins (eg simvastatin), ACE Inhibitors (Lisinopril), Aspirin, and a Beta Blocker (Metoprolol), and are usually administered once patients are off the ventilator, weaned off inotropic support, and when they are able to take oral medications without complications. Low dose metoprolol usually begun 12 to 24 hours after surgery is the preferred drug of choice in most physician groups for post AF prophylaxis. Other groups use sotalol to prevent atrial fibrillation post CABG surgery. Is use of metoprolol or sotalol to reduce rates of AF a personal preference or does one have a more therapeutic efficacy and safety over the other?

AF is a common arrhythmia post Coronary Artery Bypass Graft surgery. It is more prevalent in men and with increasing age. Age has been identified as one of the most powerful contributing risk factors for AF after cardiac surgery.¹ Other risk factors include a previous history of AF, mitral valvular disease, particularly mitral stenosis, increased left atrial size or cardiomegaly, long bypass and aortic cross-clamp times, previous cardiac surgery, chronic obstructive pulmonary disease, and obesity.^{2,3}

AF is characterized by disorganized atrial electrical activity and progressive deterioration of atrial electrochemical function. The disturbance of normal atrioventricular synchrony can result in a 15% to 25% reduction in cardiac output, with the incidence most commonly found in the third or fourth day post surgery, and recurrence is common.³ Of the patients destined to experience postoperative atrial fibrillation, approximately 90% will do so by the end of the sixth postoperative day.² Post surgical AF is associated with increased mortality and morbidity, due to the high risks of thromboembolic events. The disruption of electromechanical function in AF leads to blood stasis and

therefore, promotes the development of thrombus, most commonly in the left atrial appendage. The thrombotic clot may be dislodged and cause a stroke.

AF occurs frequently post CABG in 15-40% of patients.² AF post CABG is probably related to the combination of atrial trauma, atrial stretch, atrial ischemia, epicardial inflammation, hypoxia, acidosis, electrolyte disturbances, and electrophysiologic changes that accompany sympathetic nervous system discharge.⁸ If prophylactic drug therapy is not initiated, it could lead to devastating consequences which include discomfort/anxiety, hemodynamic deterioration, stroke, exposure to the risks of antiarrhythmic treatments, prolongation of hospital stay, increased healthcare costs, and death.²

A meta-analysis conducted by Crystal analyzed 52 randomized trials (controlled by placebo or routine treatment) of beta-blockers and sotalol in their effectiveness for prevention of post CABG atrial fibrillation.¹ Twenty seven trials that evaluated beta-blockers for prevention of postoperative AF reduced the percentage of patients with AF from 33% in the control group to 19% in the beta-blocker group. There were 8 trials that were reviewed in this meta-analysis that looked at sotalol for prevention of postoperative AF. Sotalol reduced the percentage of patients with AF from 37% in the control group to 17% in the sotalol group. There were 4 trials that were looked at that compared sotalol versus conventional beta-blockers. In the studies examined, sotalol reduced the percentage of patients with AF from 22% in the other beta-blocker group to 12% in the sotalol group. Both conventional beta-blockers (-0.66 days) and sotalol (-0.40 days) did not significantly effect hospital length of stay. Based on 12 trials that were reviewed that looked at postoperative stroke, with or without treatment, the incidence of stroke was 1.2% in the treatment group and 1.4% in the control group.

Metoprolol is a Class II beta-blocker. This drug is commonly used to treat hypertension, chest pain or pressure, migraine headaches, performance anxiety, tachycardia, and for cardiac rhythm control. Metoprolol blocks the effect of catecholamines on B₁- receptors decreasing AV node conduction by prolonging the PR interval. Since metoprolol is a cardiac B₁ receptor blocker, it does

not exhibit any membrane stabilizing or intrinsic sympathomimetic activity. Beta-blockers have been extensively studied over the years for postoperative atrial fibrillation. It is reported that beta-blockers should reduce the incidence of AF to 12% to 16% after CABG surgery alone. Metoprolol will also reduce ventricular rate when AF occurs.¹

Sotalol, in addition to being a beta-blocker, has Vaughan-Williams Class III antiarrhythmic effects and appears to be effective in suppressing both supraventricular and ventricular arrhythmias. Sotalol is commonly used to treat tachycardia or fast heart beat. Sotalol antagonizes effects of the sympathetic nervous system. It allows prolongation of electrical conduction in the atrial muscle, the ventricular muscle, and the atrioventricular accessory pathways in both the antegrade and retrograde directions. Unlike metoprolol, sotalol has both beta1 and beta 2 receptor blocking properties. Previous studies show sotalol has effectively prevented postoperative AF compared with placebo.^{4,5}

Materials and Methods

A comprehensive literature search was compiled of the most recent studies on atrial fibrillation prophylaxis using Ovid, Cinahli, medscape, uptodate, and MD consult. Keywords that were used to search for appropriate articles included Sotalol vs Metoprolol, post CABG atrial fibrillation prophylaxis, and atrial fibrillation prevention post CABG. Guidelines from the American College of Cardiology, American Heart Association, North American Society of Pacing and Electrophysiology were also carefully and thoroughly scanned for relevant articles. No language restrictions were applied. Earliest data included on this study dated back to 1998 with the most recent clinical trial study dating to 2004. Both double-blinded and non-blinded studies were included. In addition, all studies included had a Jaded score of at least 3. In all the studies that were reviewed the primary outcome measure was incidence of postoperative AF. Results that were excluded were in clinical trials that compared other beta-blockers (carvedilol) and amiodarone with sotalol and placebo.

Results

A total of 5 published articles from 1997 to 2004 on the pharmacological prevention of postoperative AF with metoprolol and sotalol were used in this article. (see Table 1) Each article was graded using the Jadad scale. All studies included patients undergoing CABG surgery and had very similar on-pump time for the treatment population and placebo (controlled) population for each clinical trial. Most patients were male. All trials used continuous ECG monitoring or holter recordings to detect AF patients in the ICU.^{7,5,4} In the Evrard and Parikka study more than half of the patients were on beta-blockers preoperatively. All 5 studies excluded patients with severely decreased left ventricular function. In addition, patients having had a previous history of CABG surgery or atrial fibrillation were excluded. Five articles were randomized trials and two of those were both randomized and double blinded.

Evrard took 206 patients and randomized them to a sotalol group (n=103) and control group (n=103) in which patients received beta-blockers or no antiarrhythmic drugs on the first CABG postoperative day until discharge.⁴ There was approximately 16% AF occurrence in the sotalol group and 48% in the control group. There was 1 death in each group, 1 of ischemic event in the sotalol group and 1 of pulmonary infection in the control group. Adverse effects from the sotalol group that lead to discontinuation of treatment, were observed in 8 patients and were related to asthma in 3, mild heart failure in 2, and reduction in cardiac index in 1. Torsades de Pointes, a rare but serious adverse effect of sotalol, was not observed in either group.

Gomes analyzed 85 patients who underwent CABG surgery and were randomized to either receive sotalol or placebo before the surgery and who continued to receive the drugs for four days postoperatively.⁵ AF was significantly lower in patients on sotalol (12.5%) as compared with placebo (38%). There was significant bradyarrhythmia and hypotension (5%) from drug withdrawal on sotalol

and none in placebo. There was no difference in the sotalol group and placebo group in terms of reducing hospital length of stay.

The Auer study was a randomized, double blinded trial with a sample size of 253, in which patients undergoing CABG received either metoprolol (n=62), amiodarone plus metoprolol (n=63), and sotalol (n=63) to assess which drug is superior to placebo (n=65).⁶ Although amiodarone was included in this study, for the purposes of sotalol versus metoprolol, amiodarone results were not specifically considered in this review. In this particular study, patients who were receiving sotalol significantly reduced the frequency of AF (20/63 31.7%) compared to patients taking placebo (53.8%). Metoprolol alone also reduced rates of AF (25/62 40.3%). There were more adverse effects of nausea, dyspepsia in the sotalol group (28.6%) than metoprolol (19.4%). There was a higher incidence of bradyarrhythmia in the metoprolol group (16.1%), sotalol (12.7%), and placebo (3.1%). There was no significant difference between the length of stay of the placebo group compared to the treatment groups. Patients who had postoperative AF had a significantly longer hospital stay when compared to those without AF (14.9 +/- 5.7 vs 10.6 +/- 3.6).

The Pfistere ME study, also a double-blinded and randomized clinical trial, looked at a total of 255 patients who undergone CABG surgery.⁹ Patients were randomized to a sotalol group (n=126) and placebo, controlled group (n=129) prior to surgery. The low dose sotalol group reduced the rates of AF to 26 % compared to the placebo group at 46%. Also found in the study was the reduction of heart rate (74 +/- 12 beats/min) in the sotalol group from (85 +/-15 beats/min) in the placebo group. Hospital length of stay was also reduced to almost half a day (10.0 +/- 4.0 days versus 10.4 +/-3.2 days). Approximately 5.6% in the sotalol group and 3.9% in the placebo group had side effects to treatment. The most common adverse effect experienced by both groups were bradyarrhythmias (3.2% in sotalol and 1.6% in placebo). Other side effects included hypotension, dizziness, nausea, vomiting, and headaches, there were, however, no significant difference between the treatment group and control group.

The Parikka study was a randomized comparison study of the efficacy between metoprolol and sotalol in the prevention of postoperative atrial fibrillation.⁷ To examine whether sotalol, a beta-blocker with class III antiarrhythmic effects, is superior to metoprolol, 191 patients undergoing CABG surgery were randomized to a sotalol group (n=93) and a metoprolol group (n=98) postoperatively. AF was seen in 32% of the metoprolol group and 16% in the sotalol group. Ventricular rate did not differ in the two study groups; in the sotalol group (127 +/- 32) and the metoprolol patients (129 +/-29).

Discussion

Although there have been numerous studies on the prevention of post CABG atrial fibrillation, the primary goal of this study is to look at the effectiveness of sotalol versus the effectiveness of the popular metoprolol in reducing the rates of atrial fibrillation. Recent studies suggest that prevention of AF not only prevents incidences of serious health consequences, but also reduce cost. Prevention of atrial fibrillation is a worthwhile goal.

Currently, the standard therapies for atrial fibrillation prevention are beta-blockers, like metoprolol, sotalol, and amiodarone, magnesium, and atrial pacing; all which have proven successful in reducing AF. The studies above suggest sotalol to be superior to metoprolol by at least 10%.^{1, 6, 7} Sotalol however, has a potential to create proarrhythmic effects counterbalancing possible superior efficacy. One of the main reasons to use prophylactic therapy to prevent AF is to reduce hospital length of stay, and in turn, cost of care. Although the difference between metoprolol and sotalol is insignificant in reducing hospital length of stay, the Crystal study demonstrates pharmacologic treatment to reduce length of stay by at least half a day.¹

The Evrard study looked at the safety and efficacy of low dose sotalol in not only preventing supraventricular arrhythmias but also ventricular arrhythmias.⁴ According to the results of the Evrard study, prophylactic use of sotalol reduces the occurrence rates of AF by up to 67%. It is still unclear if

this reduction is from sotalol's beta blocking effect or in combination with its antiarrhythmic effects. Some concerns of the study are that only patients whose arrhythmias lasted long enough to be recorded were documented. Short period supraventricular arrhythmias may have been missed.

Although the Gomes study demonstrated marked reduction in AF on study patients on low to moderate doses of sotalol, there were some limitations in the study. The study reports unclear results either coming from sotalol's beta-blocking activity or from its class III antiarrhythmic effects on the effects of its reduction of AF. The authors formulate two explanations for the side effects of sotalol in their study: 1) the high adrenergic state, and the use of inotropes in the postoperative state, may have accounted for an absence of significant bradycardia and bradycardia related torsade de pointes type of ventricular tachycardia; 2) the dosages of sotalol utilized in this study may have been too low.⁵

The double blinded randomized study conducted by Auer, presented data that showed a trend in favor of sotalol over metoprolol in high-risk patients, however, it had some limitations of its own. It is difficult to conclude that sotalol is statistically significantly superior to metoprolol due to the fact the population used in this study were AF high risk patients. Approximately 44.7% of the subjects included in the study had concomitant valve surgery in addition to CABG surgery. The results were obtained from a high-risk population with a very high proportion of patients undergoing surgery for heart valve disease and should not be directly extrapolated to a population with a different baseline risk profile.⁶ This study includes patients that were taking preoperative B-blockers. It has been shown that use of preoperative beta-blockers could significantly reduce AF postoperatively, although they were closely spaced out between sotalol (n=25) and metoprolol (n=24).¹ The results may have been skewed due to beta-blockers showing marked reduction in post CABG surgery AF, compared to those were not receiving treatment preoperatively.

Another study demonstrating the superior efficacy of sotalol in reducing AF post CABG surgery, when compared to placebo, was the Pfisterer ME study. The study however included patients who were on preoperative beta-blockers that had to discontinue their medications prior to surgery. The

discontinuation of preoperative beta-blocking medication in some patients may have lead to an increased rate of supraventricular arrhythmia. Again in this study, use of continuous ECG monitoring was not accomplished, and thus short episodes of atrial fibrillation may have been missed.

The Parrika study, is a unique clinical trial in that it takes sotalol and directly compares its efficacy to metoprolol. The results suggest sotalol's superiority over metoprolol in the prevention of postoperative AF. The study did not include side effects, if any, experienced by study participants. Also excluded from the study, were patients lost to follow up and there was no placebo control group. Unlike other studies examined, the Parrika clinical trial examined sotalol's ability to prolong repolarization even with modest doses, suggesting the specific class III effect of sotalol is present.⁷ The study was not designed to compare AF prophylactic therapy with a controlled placebo group and thus the success rates of sotalol or metoprolol were not compared to those of a non-treatment group. Sotalol demonstrates higher efficacy in prolonging repolarization than with metoprolol, however, because of a lack of a control group, it is difficult to quantify actual prolongation percentage to a non-treatment group. Another concern arises from the arrhythmia documented only in patients who again had arrhythmias that lasted long enough to be recorded. The shorter arrhythmia periods may have been missed.

Low to moderate doses of sotalol is an effective prophylactic drug in the prevention of atrial fibrillation post CABG surgery. Sotalol is especially effective in patients who are at high risk of AF. What is needed, is a study designed to measure every subject using a holter monitor post CABG to prevent missing short AF durations. Furthermore, since there is an increased risk of bradyarrhythmias and hypotension with sotalol, a large clinical trial should be conducted to assess at what sotalol dose has the largest rates of adverse effects.

Conclusion

The American College of Cardiology (ACC) rates Sotalol, a class B prophylactic drug due to its potential side effects and metoprolol a class A. Based on the literature review sotalol is a very reasonable prophylactic drug of choice, especially for patients at high risk (eg. history of AF, heart valve surgery) of atrial fibrillation or who have contraindications to beta-blockers. In addition, the results of the literature review support the recommendations by ACC of the use of conventional beta-blockers (metoprolol) as a standard prophylactic drug of choice for stable and no known history of AF in patients undergoing CABG surgery. Future studies and possible standard guidelines are needed to address when to administer sotalol over metoprolol to further reduce the rates of post surgical AF.

Table 1 Summary of AF in Sotalol when compared to metoprolol and placebo in five clinical trials.

Author	Published	Study Type	Metoprolol AF %	Sotalol AF %	Placebo AF %
Auer J.	2004	Randomized	40.3%	31.7%	53.8%
Evrard,P.	2000	Randomized	Not tested	16%	48%
Gomes, J.A.	1999	Randomized, double blind	Not tested	12.5%	18%
Parikka, H.	1998	Randomized	32%	16%	Not tested
Pfisterer ME	1997	Randomized, double blind			

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