Randomized Study of Early Intravenous Esmolol Versus Oral Beta-Blockers in Preventing Post-CABG Atrial Fibrillation in High Risk Patients Identified by Signal-Averaged ECG: *Results of a Pilot Study*

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Background: Patients with prolonged signal-averaged ECG have four times higher risk for development of atrial fibrillation (AF) after coronary artery bypass surgery (CABG). Incidence of AF is reduced, but not eliminated by prophylaxis with beta-blockers. The limitations of prophylaxis with oral beta-blockers may be related to the delayed effect of oral therapy. We performed a pilot study of the efficacy of early intravenous esmolol and an oral beta-blocker regimen for prevention of postoperative AF.

Methods: Fifty patients referred for CABG and considered to be at high risk for postoperative AF on the basis of prolonged signal-averaged ECG P wave duration > 140 ms were randomized to receive either a 24-hour infusion of esmolol 6-18 hours after CABG, at an average dose 67 ± 7 μg/kg/min, followed by oral beta-blockers versus oral beta-blockers only beginning on postoperative day 1.

Results: Seven of 27 patients (26%) in the esmolol group and 6 of 23 patients (26%) in the oral beta-blocker group developed postoperative AF, P = NS. The mean time of onset of AF (2.7 ± 0.5 vs 2.7 ± 0.3 postoperative day, P = NS) and the median duration of AF (10 [2192] vs 7 [1.16] hours, P = NS) were similar between the two groups. Eleven (41%) patients treated with esmolol developed adverse events (hypotension: 8, bradycardia requiring temporary pacing: 2, left ventricular failure:1 patient) as compared to only one patient (4%) in the beta-blocker group who developed hypotension, P = 0.006.

Conclusions: This randomized controlled pilot study suggests that intravenous esmolol is less well tolerated and offers no advantages to standard beta-blocker in preventing AF after CABG.

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atrial fibrillation; prevention; signal-averaged ECG; coronary artery bypass grafting; esmolol; beta adrenergic receptor antagonists

Postoperative atrial fibrillation (AF) is the most frequent complication of coronary artery bypass surgery occurring in 25-40% of patients.[1] It is associated with an increased risk of thromboembolic complications, worsening congestive heart failure, prolonged hospital stay and increased costs.[1,2] Risk

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factors include prior AF, advanced age, male gender, postoperative beta-blocker withdrawal, and prolonged P wave duration on signal-averaged (SA) ECG.[3-5] The likelihood of experiencing AF after cardiac surgery is increased almost fourfold if SAECG is prolonged.[4] The peak incidence of AF is on the second postoperative day with 73% of arrhythmia episodes occurring between postoperative days one and three.[1]

The beneficial role of beta-blockers for the prevention of postoperative AF has been extensively studied.[6,7] Randomized studies suggest that oral beta-blockers reduce the incidence of postoperative AF by nearly 50%.[7,8] Despite the dramatic risk reduction, a substantial number of patients treated with beta-blockers after coronary artery bypass surgery develop AF. Patients receiving oral beta-blockers may not experience the full benefit of early beta blockade, as the initiation of treatment is often delayed, dose titration is gradual, and therapeutic levels may not be consistently achieved as a result of the variation in absorption of medication.[9] This is likely to be especially true in clinical practice relative to the strict protocols of clinical trials. Therefore, by the time patients achieve significant beta blockade, most AF will have already occurred and the therapeutic benefit lost.

Esmolol hydrochloride is an intravenous $\beta 1$ selective adrenergic receptor antagonist. It has been successfully used perioperatively for treatment of hypertension and rate control of atrial tachyarrhythmias.[10-12] Due to its rapid onset of action and short half-life, esmolol can be easily titrated to achieve optimal levels of beta-blockade. Intravenous esmolol can be started within hours after surgery and transitioned to oral beta-blocker therapy at the appropriate time later in the hospital course.

We hypothesized that intravenous esmolol administered early after coronary artery bypass surgery would be more effective than a standard oral beta-blockers regimen for the prevention of AF in patients at high risk, as determined by SAECG. A randomized clinical trial was designed to test this hypothesis; we report the results of the pilot investigation.

METHODS

Patient Eligibility

This open-label randomized controlled study was approved by the Human Investigation Committee at St. Luke's-Roosevelt Hospital Center. Consecutive patients referred for elective coronary artery bypass surgery without concomitant valve replacement at St. Luke's-Roosevelt Hospital Center were screened for clinical eligibility.

Patients who were in sinus rhythm on a preoperative electrocardiogram were further screened with a SAECG of the P wave. Acquisition and analysis of the P wave SAECG has been described previously in detail.[4] Briefly, an orthogonal lead arrangement similar to QRS acquisition was used. The QRS complex was used as a trigger, but fiducial point was shifted to the extreme right of the 300 ms window, exposing the P wave and the PR segment. P wave complexes were matched to a sinus P wave template selected by the operator, and automatically rejected if they did not match the template with 99% correlation. A high pass filter of 29 Hz was applied to the averaged output and the result was subsequently amplified to facilitate identification of low amplitude components. The vector sum of each of three leads was computed and the P wave duration was manually measured. Patients whose P wave duration on a SAECG exceeded 140 ms represented a high risk population for postoperative AF[4] and were considered eligible for the study.

Patients were excluded from randomization if they had a history of AF, severe congestive heart failure due to left ventricular systolic dysfunction, symptomatic COPD requiring inhaled beta-agonists, bradycardia less than 45 beats/min in the absence of a pacemaker, or were taking class I or III antiarrhythmic agents. Informed consent was obtained prior to surgery. Patients were reevaluated after surgery and were enrolled in the study if they were deemed to be hemodynamically stable for infusion of intravenous esmolol (SBP $>$ 100 mmHg, no clinical signs of CHF).

Treatment and Follow-up

Patients were randomized to treatment with intravenous esmolol or standard oral beta-blocker therapy. Intravenous esmolol was initiated within 6 to 18 hours of arrival to the recovery room after surgery. Patients received a bolus of esmolol 0.5 mg/kg over 5 minutes, followed by a continuous infusion of esmolol initiated at a rate of 0.05 mg/kg/min and titrated to achieve a heart rate of 55 to 65 beats/min and systolic blood pressure greater than 100 mmHg. The esmolol infusion was continued for up to 24 hours. Following the esmolol infusion, patients were treated with oral propranolol. The first dose of propranolol was adminis-

Table 1. Clinical and Surgical Characteristics of Study Population

	Esmolol, n = 27	Oral BB, n = 23	P Value
Age, years	65.7 ± 1.5	64.3 ± 2.0	ns
Male	16 (59%)	18 (78%)	ns
Diabetes mellitus	7 (26%)	7 (30%)	ns
Hypertension	15 (56%)	15 (65%)	ns
CCSC angina class	3.0 ± 0.2	2.8 ± 0.3	ns
Prior MI	12 (44%)	8 (35%)	ns
LV ejection fraction, %	49 ± 3	49 ± 3	ns
Preop BB use	19 (70%)	10 (44%)	ns
SAECG P-wave duration, ms	158 ± 2	154 ± 2	ns
Aortic cross clamp time, min	69 ± 8	64 ± 7	ns
Number of grafts	3.3 ± 0.2	3.9 ± 0.2	0.02
Heart rate, bpm	86.7 ± 2.2	89.3 ± 2.0	ns
SBP, mmHg	117.9 ± 1.8	114.5 ± 1.5	ns
Postoperative LOS, days	8.0 ± 0.5	7.3 ± 0.3	ns

BB = beta-blockers; CCSC = Canadian Cardiovascular Society Classification; LOC = length of stay; LV = left ventricle; MI = myocardial infarction; Preop = preoperative; SAECG = signal-averaged electrocardiogram; SBP = systolic blood pressure.

tered 30 minutes before discontinuing the esmolol infusion. The dose of propranolol was titrated to achieve systolic blood pressure > 100 mmHg and a heart rate of 60 beats/min.

Patients randomized to standard beta-blocker therapy were started on oral beta-blockers at the discretion of the patient's cardiologist. Metoprolol was preferred at a dose of ≥ 50 mg/day. Routine preoperative and postoperative care was not altered.

The primary endpoint of the study was the development of AF lasting longer than 30 minutes. AF was defined by the absence of P waves and presence of fibrillatory waves in the isoelectric portion of the ECG. The duration of AF was recorded as was the postoperative day on which it occurred. Secondary endpoints included the development of treatment adverse effects: hypotension with systolic blood pressure less than 90 mmHg, symptomatic bradycardia or congestive heart failure.

Patients were transferred to the open heart recovery room following surgery and monitored by telemetry continuously for the first 72 hours. Telemetry was then discontinued at the discretion of the patient's cardiologist.

Statistical Analysis

The efficacy of intravenous versus oral beta-blockers in prevention of AF after CABG has not been previously compared. We estimated that 181 patients were needed in order to demonstrate a 50% reduction in the primary endpoint with an alpha level at 0.05 and a beta level of 0.20. An interim analysis was planned after enrollment of 50 patients in order to review the incidence of study endpoints and to confirm sample size calculations. Provision was made to terminate the study if study treatment was associated with significant adverse effects, or if the primary endpoint could not be met with planned or augmented sample sizes. All data were analyzed on an intention to treat basis. Statistical analysis was performed using the statistical package SPSS version 9.0. The Student's two-tailed *t*-test for independent samples was used to test for group comparisons involving normally distributed continuous variables, and a Mann-Whitney U test for nonnormally distributed continuous variables. The chi square test was used for group comparisons involving categorical outcomes. A bootstrap analysis was done to determine the largest probable difference between the control group and the esmolol group.[13] Results for continuous variables are reported as mean ± standard error of the mean, unless otherwise noted. The alpha level for statistical significance for all comparisons was 0.05.

RESULTS

Clinical and Surgical Characteristics of the Study Patients

Fifty patients were enrolled in the study. The baseline clinical characteristics of study groups are described in Table 1. Patients randomized to standard beta-blocker treatment received a greater number of bypass grafts than patients randomized

Table 2. Characteristics of Patients with Atrial Fibrillation Compared with Those Who Maintained Sinus Rhythm

	Atrial Fibrillation n = 13	Sinus Rhythm n = 37	P Value
Age, years	69.4 ± 2.2	63.4 ± 1.4	0.03
Male	10 (77%)	24 (65%)	ns
Diabetes mellitus	1 (8%)	13 (35%)	ns
Hypertension	8 (62%)	22 (60%)	ns
Prior MI	7 (54%)	13 (35%)	ns
Ejection fraction	51 ± 4	49 ± 2	ns
Preop BB use	11 (85%)	18 (49%)	0.047
Aortic cross clamp time, min	79 ± 8	63 ± 7	ns
Number of grafts	3.8 ± 0.3	3.5 ± 0.2	ns
Postoperative LOS, days	8.6 ± 0.6	7.3 ± 0.3	0.016

BB = beta-blockers; LOC = length of stay; MI = myocardial infarction; Preop = preoperative; SAECG = signal-averaged electrocardiogram.

to esmolol (3.9 ± 0.2 vs 3.3 ± 0.2, P = 0.02). There were otherwise no significant differences in the baseline variables and operative course for the two groups of patients.

Study Treatment

Of 27 patients randomized to treatment with esmolol, 22 received a 24-hour esmolol infusion. Five patients had esmolol infusion discontinued 2 to 10 hours after its initiation due to development of significant treatment side effects. The mean administered dose of esmolol was 67 ± 7 μg/kg/min, and the average maximum dose was 89 ± 10 μg/kg/min. Twenty patients (74%) subsequently received propranolol, at a dose of 58 ± 5.4 mg/day and 7 patients (26%) received metoprolol, at a dose of 110 ± 19 mg/day.

Patients randomized to standard beta-blocker treatment were started on oral beta-blockers on postoperative day 1. Nineteen patients (83%) received oral metoprolol at a dose of 74 ± 4.9 mg/day. One patient (4%) received propranolol 40 mg/day. Three patients (13%) were not administered beta-blockers at the discretion of patient's cardiologist. None of the three developed postoperative AF.

The average heart rate on the first postoperative day was significantly lower in the esmolol group as compared with the standard beta-blockers group (80.0 ± 1.9 vs 91.0 ± 2.0 beats/min, P < 0.001).

Study Endpoints

Thirteen patients (26%) developed postoperative AF 2.7 ± 0.3 days after surgery. Older patients and those who used beta-blockers preoperatively were more likely to develop AF after surgery (Table 2). Postoperative AF was associated with significantly longer postoperative length of stay (Table 2). Three patients had symptoms during AF: two patients complained on shortness of breath, and one patient (in the oral beta-blockers group) sustained an embolic stroke.

Seven patients (26%) in the esmolol group and 6 patients (26%) in the oral beta-blockers group developed AF after CABG, P = NS (Table 3, Fig. 1). The postoperative day of onset of AF and the median duration of AF were also similar in the two groups (Table 3). Two patients in the esmolol group had AF lasting longer than 24 hours. One patient underwent medical cardioversion with procainamide (duration of AF, 192 hours), the other was discharged from the hospital in AF (duration of AF, 168 hours). Patients randomized to esmolol had lower ventricular rates at the onset of AF as compared with patients receiving standard oral beta-blockers (130 ± 8 vs 160 ± 8 beats/min, P = 0.02).

Eleven patients (41%) in the esmolol group developed significant side effects during treatment as compared to only one patient (4%) randomized to standard beta-blocker treatment, P = 0.006 (Table 3, Fig. 1). Eight patients (30%) in the esmolol group experienced hypotension, four of whom required discontinuation of esmolol infusion, and two who required subsequent use of vasopressors. Three of the eight patients with hypotension had esmolol infusion held for 1 hour. Two patients in the esmolol group required transvenous pacing for symptomatic bradycardia on postoperative day 3 and 8, respectively. Both of them had beta-blockers discontinued. One patient developed left ventricular failure during esmolol infusion, requiring discon-

Table 3. Study Endpoint Results

	Esmolol n = 27	Oral BB n = 23	P Value
Postop AF	7 (26%)	6 (26%)	ns
Postop day of AF	2.7 ± 0.5	2.7 ± 0.3	ns
Duration of AF, hours[a]	10 (2,192)	7 (1.6)	ns
Heart rate during AF, beats/min	130 ± 8	160 ± 8	0.02
Patients with treatment adverse events[b]	11 (41%)	1 (4%)	0.006
Hypotension, SBP < 90 mmHg	8	1	0.03
Bradycardia requiring pacing	2	0	ns
LV failure	1	0	ns

[a] Median (Min, Max), [b] Some patients had more than one side effect.
AF = atrial fibrillation; LV = left ventricle; Postop = postoperative; SBP = systolic blood pressure.

tinuation of esmolol and administration of intravenous inotropes.

One patient in the oral beta-blocker group (4%) experienced hypotension and required temporary use of vasopressors on postoperative day 1.

DISCUSSION

This study demonstrates that the early administration of intravenous esmolol is not superior to standard oral beta-blockers in preventing AF after CABG. In addition, intravenous esmolol did not alter the day of onset of AF or the duration of AF. Intravenous esmolol was associated with significantly higher incidence in treatment adverse effects, especially hypotension. Although patients in the esmolol group did have significantly lower heart rates on postoperative day 1, consistent with higher levels of beta-blockade, they did not experience clinical benefit.

The study was terminated when the interim analysis revealed significantly greater incidence of adverse effects in the group receiving esmolol, and the lack of any reduction in AF incidence. Based on the observed AF incidence of 26% in the present study, 320 patients would have needed to be recruited in order to test for the anticipated 50% reduction in the primary endpoint.

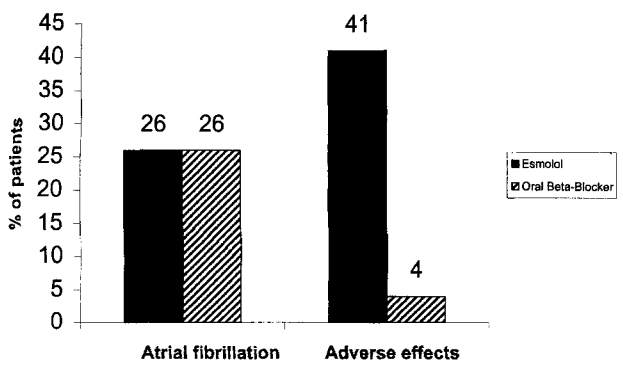

Figure 1. Study endpoint results.

The incidence of postoperative AF in our study population was 26%, which is higher than demonstrated in previous beta-blocker trial treatment groups, for example 8.7% and 9.8% reported in the meta-analyses by Andrews et al.[6] and Kowey et al.,[7] respectively. This is not unexpected as patients included in our study represented a high risk population for postoperative AF as defined by prolongation of signal-averaged P wave > 140 ms.[4,5] The risk for postoperative AF in this group is almost four-fold higher as compared to patients with P wave duration < 140 ms on SAECG.[4]

To our knowledge this is the first randomized trial comparing intravenous beta-blockers to oral beta-blockers in the prevention of postoperative AF. Abel et al.[14] randomized 50 patients to treatment with intravenous propranolol, which was started intraoperatively and continued at 2 mg every 4 hours, or no postoperative beta-blockers. Intravenous propranolol reduced the incidence of AF from 36% in the no-treatment group to 14.6% in the propranolol-treated group (P < 0.05). A trend towards more frequent adverse effects in the treatment group was also noted. Four patients developed intraoperative or early postoperative hypotension or bradycardia requiring pacing and were excluded from the study. The treatment group also required more inotropic support during the first 24 hours postoperatively than the group not receiving beta blockade. In another study, White et al. concluded that intravenous timolol starting 6 hours postoperatively was effective for preventing postoperative atrial arrhythmia as compared to no-treatment controls.[15] No significant morbidity was associated with the use of timolol in this group of

patients, however these patients all had left ventricular ejection fraction greater than 40%.

Hypotension is a common complication during the widely accepted esmolol dosing regimen used in the present study. However, the 30% incidence in hypotension in the present study was higher than previously reported. Although Gray et al.[10] reported asymptomatic hypotension in 54% of patients treated for supraventricular tachyarrhythmias after cardiac surgery, requiring cessation of therapy in 8%, they used a higher (139 ± 83 μg/kg/min) mean esmolol infusion rate. Ko W-J et al. suggested that the myocardium immediately after surgery is more susceptible to depression by beta-blockers because of the effects of surgical damage, hypothermia, and cardioplegic solutions.[11] They used esmolol at 73 ± 42 μg/kg/min for rate control of postoperative supraventricular arrhythmia, and none of 11 patients experienced the side effect of hypotension.[11]

Study Limitations

The planned number of patients was not recruited, as the study was terminated early. It is possible that the finding of no difference between the study groups could have occurred due to random sampling of two populations which differ from one another. We subsequently performed the bootstrap analysis[13] to determine how large a population difference would be tenable with finding of no difference in the primary endpoint in the current sample of patients. Based on the observed 26% incidence in AF in oral beta-blockers group, a finding of no difference was possible (i.e., $P > 0.05$) if the incidence of AF in the population treated with esmolol were 18.5% or higher. This indicates that population incidence in postoperative AF in patients treated with intravenous esmolol could be lower by 7.5% or less as compared to patients treated with oral beta-blockers only. This would represent a decrease by only 29% relative to the control group. The estimated number of patients needed to detect a 29% reduction in the incidence of AF would be 508 per group, alpha = 0.05, power = 80%. A study of this size was unjustified as the incidence of adverse effects (41%) in patients receiving esmolol was much higher than a small possible clinical benefit.

CONCLUSION

This randomized pilot study demonstrated that intravenous esmolol is less well tolerated and offers no advantages to delayed oral beta-blockers regimen in preventing AF after CABG. A large-scale trial is unwarranted.

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