Comparison of Rate Control Efficacy between beta-blockers and Calcium Channel Blockers in Patients Hospitalized with Atrial Fibrillation

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ABSTRACT **Background:** Atrial fibrillation (AF) is the most prevalent cardiac arrhythmia. Previous studies showed that rhythm and rate control strategies are associated with similar rates of mortality and serious morbidity. Beta blockers (BB) and calcium channel blockers (CCB) are commonly used and the selection between these two medications depends on personal preference.

Objectives: To compare real-time capability of BB and CCB for the treatment of rapid AF and to estimate their efficacy in reducing hospitalization duration.

Methods: We conducted a retrospective cohort study of 306 patients hospitalized at Soroka Hospital during a 5-year period with new onset AF who were treated by a rate control strategy.

Results: A significant difference between the two groups regarding the time (in hours) until reaching a target heart rate below 100 beats/min was observed. BB were found to decrease the heart rate after 5 hours (range 4–14) vs. 8 hours (range 4–18) for CCB (P = 0.009). Patients diagnosed with new-onset AF exhibited shorter duration of hospitalization after therapy with BB compared to CCB (median 72 vs. 96 hours, P = 0.012) in the subgroup of patients discharged with persistent AF. There was no significant difference between CCB and BB regarding the duration of hospitalization (P = 0.4) in the total patient population.

Conclusions: BB therapy is more potent for rapid reduction of the heart rate compared to CCB and demonstrated better efficiency in shortening the duration of hospitalization in a subgroup of patients. This finding should be reevaluated in subsequent research.

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KEY WORDS: atrial fibrillation (AF), rate control, beta blockers (BB), calcium channel blockers (CCB), hospitalization duration

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice and affected patients are at increased risk for mortality, heart failure, and thromboembolic events [1,2]. AF represents a substantial public health burden with a rapid increase in prevalence with age. U.S. healthcare expenditure on management of AF and its complication is estimated by nearly $16 billion per year [3].

Current therapy for AF is targeted at treating symptoms and reducing the risk of stroke and tachycardia-induced cardiomyopathy [4]. Strategies for acute treatment of AF include rate-control drugs, pharmacologic or electrical conversion for rhythm-control, and prevention of thromboembolic events [3,5–8]. Large scale studies showed that rhythm control approaches have not demonstrated superiority in the incidence of complications, such as hospitalizations, development of heart failure, stroke, and mortality in patients with AF compared with rate control [9]. Thus, rate control is currently the method preferred by most physicians as the initial therapy for patients with new onset atrial fibrillation [10].

A rate control strategy generally uses drugs that prolong the refractory period of the atrioventricular (AV) node, such as beta blockers (BB), non-dihydropyridine calcium channel blockers (CCB), or digoxin. Remarkably, there are no guideline preferences for a particular rate control agent in patients hospitalized due to new onset AF and the initial treatment is based on a physician's experience or the in-hospital treatment policy [8]. The choice between a BB and CCB may be influenced by other underlying factors. For example, CCB may be preferred in patients with obstructive lung disease and BB may used in patients with ischemic heart disease. Neither the use of BB nor the use of CCB is significantly associated with improved survival [11]. Two previous studies examined the efficacy of those two medication groups for treating rapid AF at the emergency department (ED) with inconsistent results [12,13].

The objectives of the present study were to compare the therapeutic efficacy of BB and CCB with regard to the period of time (in hours) before reaching a target heart rate below 100 beats per minute (bpm) in patients with new-onset AF and to evaluate the duration of hospitalization of patients initially treated with either BB or CCB for controlling ventricular response.

PATIENTS AND METHODS

SETTING

Soroka University Medical Center is a tertiary referral center with approximately 1000 beds. It is the only facility serving a metropolitan area of over 700,000 residents in the southern district of Israel. The policy of our emergency and internal medicine departments for patients admitted with primary diagnosis of atrial fibrillation who are eligible for a therapeutic approach of rate control drugs is to use one of two drug types: CCB (non-dihydropyridines, such as verapamil) or BB (e.g., metoprolol, bisoprolol).

STUDY POPULATION

This study is a retrospective cohort type, which comprised 306 patients who were hospitalized at Soroka during a 5-year period with a primary diagnosis of new onset AF and no other diagnosis during their hospitalization that could lead to the appearance of AF (e.g., fever) and who were treated with an initial rate control from one of the two drug classes. Patients who were treated with pharmacological or electrical cardioversion were excluded from the study. Patients with known heart failure, asthma, chronic obstructive pulmonary disease, or ischemic heart disease were also excluded from the study. We collected data from several databases, including reports from Soroka computerized databases to determine the sample population. We also collected patient data including symptoms, demographics, diagnoses and tests, reports from release of patient hospitalization, patients' pulse during hospitalization and while in the ED, initial drug treatment, and the patient's initial vital signs.

STATISTICAL ANALYSIS

The patients were divided into two groups based on their exposure to a rate control drug (either CCB non-dihydropyridines or BB). For statistical analysis, the patient population was further divided to three groups differentiated by patient response to treatment and patient condition on discharge (spontaneous cardioversion, induced cardioversion, or atrial fibrillation).

The primary outcome was a measurement and comparison of hospitalization length of patients with a first event of AF admitted to Soroka, who received either BB or CCB to control their heart rate. Secondary outcomes were comparison of therapeutic efficacy with respect to the time measured until reaching pulse below 100 beats per minute (bpm)and hospitalization length. Further sub analysis was conducted according to age group and sex. The time was measured from the arrival of the patient and opening of a file in the ED to the time specified in the internal medicine ward chart that the pulse had decreased consistently (at least two consecutive measurements) to below 100 bpm.

We compared patient characteristics and outcomes using either chi-square or Fisher's exact tests for categorical variables, and either the *t*-test or Mann-Whitney U test for the continuous variables. The data collected in the study were summarized in frequency tables, summary statistics, confidence coefficients and standard *P* value.

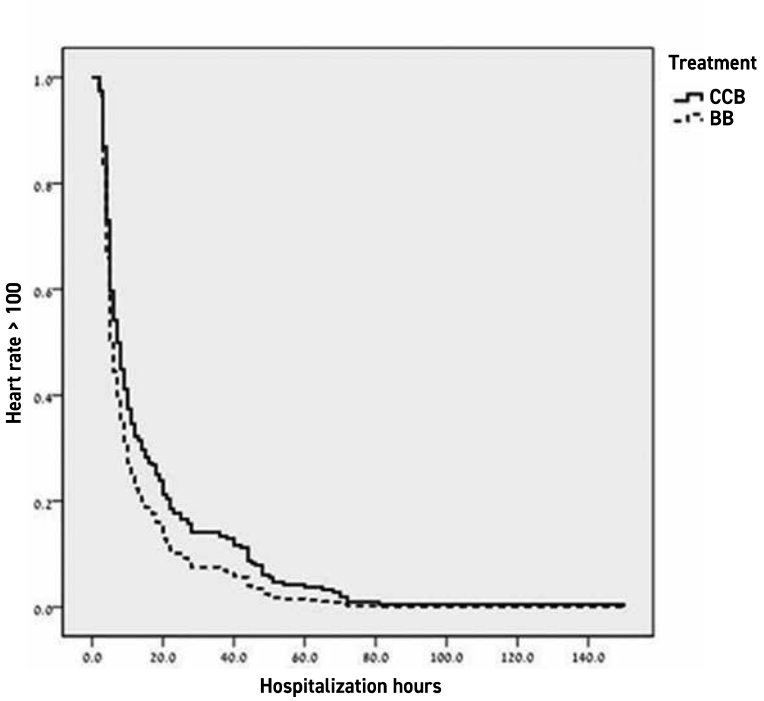
Analysis of primary outcome, length of hospitalization, was performed using Mann Whitney test for independent variables divided into age groups and sex. For secondary outcome analysis, comparing the time before reaching a pulse < 100 bpm, measured in hours, among patients treated with BB and patients treated with CCB, was performed using Kaplan Meier test. Multivariate analysis (Cox regression model) was used to adjust for possible confounders that may affect reaching a pulse < 100 bpm or achieving a sinus rhythm, in both study groups. Results were presented as hazard ratios (HRs) with 95% confidence intervals (95%CI) and mean ± standard deviation (SD).

Sample size calculations were predicated on finding a difference of one hospitalization day between the two groups tested. We used the following assumptions: mean hospitalization length for patient with atrial fibrillation is about 4 days, the ratio between patients receiving CCB and those receiving BB is 2:1, and $\alpha = 0.05$ double sided, power = 80%. Based on these assumptions, the sample size calculation with non-parametric correction showed that it was necessary to test 306 patient records (two-sided Mann Whitney test). $P < 0.05$ represented statistically significance. All *P*-values were rounded to two decimal places. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software (SPSS, IBM Corp, Armonk, NY, USA).

Table 1. Hospitalization characteristics divided by pharmacological treatment (beta blockers or calcium channel blockers)

	Patients treated with calcium channel blockers (N = 143)	Patients treated with beta blockers (N = 163)	All patients (N=306)	*P* value
Age, years (mean ± standard deviation)	65.72 ± 13.74	67.19 ± 13.36		0.35
Sex: male	52 (37.1%)	59 (36.6%)		0.92
Admission pulse (mean ± standard deviation)	125.29 ± 16.87	122.85 ± 18.45		0.23
Spontaneous cardioversion during hospitalization (group 1)	83 (58%)	88 (54%)	171 (56%)	
Induced cardioversion with sinus rhythm at discharge (group 2)	13 (9.1%)	11 (6.7%)	24 (7.8%)	
Atrial fibrillation at discharge (group 3)	47 (32.9%)	64 (39.3%)	111 (36%)	

Figure 1. Achieving a pulse under 100 bpm, with comparison between two pharmacological strategies, BB and CCB
BB = calcium channel blockers, CCB = calcium channel blockers



RESULTS

PATIENT POPULATION AND TREATMENT CHARACTERISTICS

The study comprised 306 patients with a primary diagnosis of AF who were treated with a therapeutic approach with a heart rate control drug from one of two drug types: CCB (verapamil) or BB (metoprolol, bisoprolol). The population was divided into three main groups, which was differentiated by the patient's response to treatment and the patient's condition on discharge. The comparison is listed in Table 1.

PROCEDURAL OUTCOMES

There was not a statistically significant difference between the two groups in terms of length of hospitalization (P = 0.4), as seen in Table 2. However, focusing on group 3, in which patients were discharged home with AF, which comprised approximately 36% of the patient population, we found a preference for a BB over CCB treatment, especially due to a 24-hour shorter length of hospitalization (P = 0.012). No other groups demonstrated a significant difference.

As shown in Table 2, elapsed time (measured in hours) from arrival at the ED and receiving medication for lowering heart rate to reaching a pulse under 100 bpm was significantly low-

Table 2. Comparison of duration of hospitalization and of the time (in hours) before achieving a pulse lower than 100 beats per minute between the two treatment groups according to rhythm at discharge and according to sex and age groups

		Patients treated with beta blockers N=163	Patients treated with calcium channel blockers N=143	*P* value
Mean hospitalization duration, hours (quarters range)	Spontaneous cardioversion during hospitalization (group 1)	46 (26–65)	42 (27.5–67.5)	0.92
	Induced cardioversion with sinus rhythm at discharge (group 2)	66 (30–124)	47 (36–104.75)	0.40
	Atrial fibrillation at discharge (group 3)	72 (46–97)	96 (69–143)	0.012
	All patients	51 (30–74.5)	55.5 (31–93.5)	0.4
Mean hospitalization duration, hours (quarters range), for men by age	< 65	46 (26–74)	41 (26–74.5)	0.59
	65–75	44 (27–73)	68 (44.25–167.25)	0.14
	75+	63.5 (31.75–118.25)	51 (27–92)	0.57
Mean hospitalization duration, hours (quarters range), for women by age	< 65	45.5 (29.25–54.25)	45 (32.5–67)	0.73
	65–75	62 (44–95)	77 (44.5–88.5)	0.55
	75+	61 (48.5–91.5)	74 (44.5–112)	0.27
Median time before achieving a pulse lower than 100 beats per minute, hours (range)	Spontaneous cardioversion during hospitalization (group 1)	5 (3.75–10)	6 (4–9)	0.161
	Induced cardioversion with sinus rhythm at discharge (group 2)	6.5 (3.75–29.25)	7 (5–17.5)	0.78
	Atrial fibrillation at discharge (group 3)	8 (4–18)	18 (7–40)	0.001
	All patients	5 (4–14)	8 (4–18)	0.009
Average pulse at discharge ± standard deviation		69.1 ± 12.5	72.27 ± 12.1	0.026

er by 3 hours with BB treatment, 5 hours (range 4–14) vs. 8 hours (4–18), $P = 0.009$). When stratified into 3 groups by heart rhythm at discharge, this result is only significant for patients without sinus rhythm at discharge ($P = 0.001$).

Average pulse at discharge was significantly lower for patients treated with BB compared to those patients treated with CCB (69.1 ± 12.5 vs. 72.27 ± 12, $P = 0.026$, respectively). Table 3 presents the multivariate analysis (Cox regression model) for achieving a pulse < 100 bpm. BB therapy was independently associated with a decreased time period to get to the target heart rate (heart rate 1.32, $P = 0.018$), adjusted for age, sex, and first pulse measurement in ED (hazard ratio of 0.99, $P = 0.41$; 1.13, $P = 0.35$; 0.99, $P = 0.19$, respectively).

Table 3. Cox regression model examining possible confounders affecting the achievement of a pulse under 100 bpm

		Hazard ratio	95% confidence interval		*P* value
			lower	upper	
Research group	CCB	1			
	BB	1.32	1.05	1.66	0.018
Average age		0.99	0.98	1.00	0.41
Sex, male		1.13	0.87	1.47	0.35
Admission pulse		0.99	0.98	1.00	0.19

BB = calcium channel blockers, CCB = calcium channel blocker

DISCUSSION

AF is the most common cardiac arrhythmia seen in clinical practice and is a leading cause of mortality, heart failure, and thromboembolic events [1,2]. Lack of clinical consensus and defined treatment protocols for the management of new-onset AF may result in prolonged length of hospital stay, increased hospital costs, and hospital readmission. The optimal heart rate during AF is yet unknown, although rate control is currently considered to be a first-choice therapy in many patients with AF. Nevertheless, while several trials such as RACE [9] and AFFIRM [14] found that there was no evidence of a reduction in morbidity or mortality and no quality-of-life improvements in patients with tight versus lenient rate control [15], the ACC/AHA/ESC recommendations for rate-control therapy still consider a favorable heart rate target 60–80 bpm at rest and 90–120 bpm during moderate exercise.

Previous studies demonstrated inconsistent results regarding the efficacy of BB and CCB mainly in the ER. Fromm et al [12] found an advantage of diltiazem over metoprolol. This small prospective study included patients with known and new onset AF. The study was stopped due to the efficacy demonstrated, so it is hard to conclude from that study about other populations and about the safety profile of both medication groups. At our medical center the only option for intravenous (IV) CCB is verapamil, which was not included in the Fromm study [12]. Another study by Atzema and colleagues [13] showed no significant difference between BB to CCB regarding success rate for achieving target heart rate but found lower hospitalization rate after the use of BB. In a multicenter retrospective study, they tested all types of BB and CCB, but the main medications used were metoprolol IV and bisoprolol orally in the BB group and diltiazem for the CCB group. A similar safety profile was demonstrated for both groups. An interesting tendency of physician toward CCB was demonstrated. This tendency was demonstrated in previous survey, which demonstrated a preference of CCB over BB in the United States and Canada, while the opposite is true in the United Kingdom and Australia [8].

In our study, we compared the antiarrhythmic therapeutic effectiveness of BB and CCB regarding the period (in hours) before reaching a target heart rate below 100 bpm and evaluated the duration of hospitalization of patients initially treated with either BB or CCB for controlling ventricular response. We included only patients with newly onset AF and no other diagnosis prior to or during the hospitalization to isolate the influence of BB or CCB on our study population, which might confound the results. To the best of our knowledge, no previous studies tested hospitalization itself and not solely the ED.

According to our results, BB therapy is more potent for rapid reduction of heart rate compared to CCB ($P = 0.009$) [Table 2]. The most robust response was observed in the subgroup of patients who were admitted and discharged with AF ($P = 0.001$). This significant effect indicates that in the absence of contraindications, BB yields the most preferred alternative for a rapid reduction of the heart rate and potentially reduces tachycardia-induced symptoms related to AF. Accordingly, BB may also be recommended as a first-line therapeutic management approach for new-onset AF in the presence of warning signs for hemodynamic compromise. Moreover, these findings may be further utilized clinically for additional benefits such as enhanced quality of life and improved prognosis.

New onset AF often spontaneously reverts to normal sinus rhythm. Our results are in accordance with other reports illustrating that most patients with new-onset AF will revert spontaneously to normal sinus rhythm [16,17]. Yet, like other studies, more than 1/3 of our cohort did not convert spontaneously to sinus rhythm. As shown in Table 1, we stratified the total patient population into three groups according to the response to rate-control treatment from admission to discharge (with respect to heart rhythm status). While no significant effect was observed in the total patient population with regard to length of hospital stay ($P = 0.4$) [Table 2], the use of BB has been shown to be superior to CCB with a beneficial effect in shortening the duration of hospitalization in the subgroup of patients admitted with AF

without return to normal sinus rhythm at discharge ($P = 0.012$) [Table 2]. Considering the prevalence of AF, the total economic burden is enormous [3]. Whether diagnosed with paroxysmal, persistent, or permanent AF in a post-discharge surveillance, our results imply that patients with diverse forms of chronic AF would be likely to benefit from reduced morbidity and mortality attributed to excess length of hospital stay [18,19] with a favorable decline in medical care expenditure and reduction of public health costs [20,21]. In our study, we showed promising results, which is a preview to a bigger prospective study in the treatment of atrial fibrillation in the ED. These results also emphasize the need for a better characterization and differentiation of patients more likely to respond favorably to BB therapy (i.e., patients with a high risk for AF at discharge).

LIMITATIONS

The retrospective nature of the study from a single center precludes follow-up data from other public health records. Thus, no clinical information is available beyond hospital discharge regarding the post-intervention period in the community. The acute treatment of AF includes intravenous administration of BB or CCB with a subsequent oral maintenance therapy. Hence, hospital discharge records tend to under-report the exact dosage of drugs used to control the ventricular response in rate control protocols. To address this problem, we analyzed the data irrespective of the dose administered, thus the possibility of dose-response relationships relative to the pharmacologic effects has not been reported.

CONCLUSIONS

In the clinical setting of new-onset AF, BB displayed higher potency in attaining a desirable heart rate goal and in shortening hospital stay for a considerable subgroup of patients. These outcomes bear a potential implication for the acute treatment of tachycardia-induced symptoms and should be taken into clinical consideration. The inconsistency between previous studies and our results, which support some of the findings but are inconsistent with most, strengthens the need for further studies in this area. These findings are intriguing for a preliminary randomized, controlled prospective study for validation of our results and determination of BB capacity to enhance quality of life and improve prognosis in patients coping with cardiac arrhythmia.

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