Research Report

Intravenous Metoprolol Versus Diltiazem for Rate Control in Atrial Fibrillation

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Abstract

Background: Currently, it remains unclear whether β-blockers or nondihydropyridine calcium channel blockers are preferred for the acute management of atrial fibrillation (AF). **Objective:** The objective of this study was to compare the efficacy and safety of intravenous (IV) metoprolol and diltiazem for rate control. **Methods:** This was a single-center, retrospective cohort study of patients who presented to the emergency department between 2015 and 2019 with AF with rapid ventricular rate (RVR) and received IV metoprolol or diltiazem. The primary outcome was the percentage of patients who achieved rate control (defined as heart rate $<$ 100 beats per minute). Secondary outcomes included time to rate control, percentage of patients requiring additional agents for rate control, and incidence of cardioversion, bradycardia, and hypotension. **Results:** A total of 200 patients were included in this study. Rate control was achieved in 35% and 41% of the metoprolol and diltiazem groups, respectively ($P = 0.38$). Mean time to rate control was not significantly different between the metoprolol and diltiazem groups (35 vs 21 minutes, $P = 0.23$). One patient developed hypotension, no patient developed bradycardia, and 4 patients required electric cardioversion. No adverse events were observed in patients with ejection fraction ≤40%. **Conclusion and Relevance:** There was no difference in the achievement of rate control between IV metoprolol and diltiazem. This is the largest study to date comparing the two classes of agents for acute rate control in AF. No patient-specific factors were identified that would influence the preferential use of one medication over the other.

Keywords

arrhythmias, calcium channel blockers, β-adrenergic blockers, antiarrhythmics, cardiology

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia. At least 5 million people in the United States currently live with AF, and 1 in 4 individuals will develop AF by the age of 40.[1,2] The AF accounts for approximately 600 000 emergency department (ED) visits, 450 000 hospitalizations, and 22 000 deaths annually in the United States.[3] Patients with AF have a 5-fold higher risk of developing cardioembolic stroke, 3-fold higher risk of developing heart failure (HF), and 2-fold higher mortality rate.[4-6]

To date, it remains unclear which first-line rate control agent is preferred in the acute management of AF with rapid ventricular rate (RVR). The 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society (AHA/ACC/HRS) guideline recommends using either a β-blocker or nondihydropyridine calcium channel blocker for rate control in hemodynamically stable patients, without a preference for one class over the other.[7] The 2019 AHA/ACC/HRS guideline update did not provide additional guidance on agent selection.[8] The 2020 European Society of Cardiology (ESC) guideline recommends both classes as first-line agents in patients with an ejection fraction (EF) ≥ 40%.[9] Furthermore, studies comparing intravenous (IV) metoprolol and diltiazem have yielded inconsistent findings regarding the preferred agent in addition to limitation in sample size and design.[10-17] Therefore, this study aimed to further compare the efficacy and safety of IV metoprolol and diltiazem for rate control and to add to the existing literature.

Methods

Study Design

This was a single-center retrospective cohort study of adult patients who received IV metoprolol or diltiazem for the

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treatment of AF with RVR within the ED during 2015-2019. The study site is a 685-bed academic-affiliated medical center with more than 110 000 ED visits annually. This study was approved by the Community Medical Centers' Institutional Review Board.

Patient Selection

Patients were included if they were 18 years or older, presented to the ED between 2015 and 2019 with AF with RVR, and received either IV metoprolol or diltiazem within 1 hour. The AF with RVR was defined as electrocardiogram (ECG)-confirmed AF with HR $>$ 120 beats per minutes (bpm). Patients who were pregnant, incarcerated, or had an implanted pacemaker or cardioverter-defibrillator were excluded. As the study was retrospective in nature, treatment was not standardized or guided by a study protocol. A system-generated report identified patients who received the study medications during the study period and patients' medical records were reviewed in chronological order. Demographic and clinical data were collected using a standardized data collection tool by 2 of the study investigators with a Cohen's kappa coefficient of 0.9.

Outcomes

The primary outcome was the percentage of patients who achieved rate control (defined as HR $<$ 100 bpm within 2 hours of medication administration). Secondary outcomes included time to rate control, percentage of patients requiring additional agents for rate control, and incidence of cardioversion, bradycardia (defined as HR $<$ 60 bpm), and hypotension (defined as a systolic blood pressure [SBP] $<$ 90 mm Hg requiring the administration of vasopressors). A subgroup analysis was performed to evaluate the incidence of adverse effects in patients with reduced EF (defined as EF $\leq$ 40%).

Prior to admission medications, past medical history, and need for electric cardioversion were obtained from physician progress notes and discharge summaries. Laboratory values and vitals were obtained from the results section and vitals flowsheet within the patient's medical record, respectively. The presence of valvular heart disease and EF were obtained from echocardiograms performed within 1 year of the admission. The medication administration record was reviewed to determine medication doses, administration times, and the use of additional medications.

Analysis

Based on the results from prior studies, a sample size of at least 194 patients equally distributed between the study arms was needed to achieve a power of 80% to detect a difference in the number of patients who achieved rate control.[13,16] Continuous data were assessed using the Mann-Whitney *U* test. Nominal data were assessed using the Pearson χ^2 test or the Fisher exact test. Statistical significance was determined with a *P*-value $<$ 0.05.

Results

Of the 508 patients screened, 308 were excluded and 100 patients were included in each study arm. The most common reasons for exclusion were no AF on ECG (n = 194), presence of an implanted defibrillator or pacemaker (n = 34), and no ECG (n = 33). Although past medical history was not significantly different between the groups, prior to admission rate control medications were (Table 1). In comparison with IV metoprolol, significantly more patients in the diltiazem group were not on any rate control medication prior to admission (10% vs 37%, $P < 0.001$). Patients were significantly more likely to receive IV metoprolol if they were on a β-blocker prior to admission. Similarly, patients were significantly more likely to receive IV diltiazem if they were on a nondihydropyridine calcium channel blocker prior to admission. More than half of the total population had a history of HF and approximately half was EF $\leq$ 40%. There were no significant differences between the groups in these values.

Overall, rate control was achieved in 35% and 41% of the metoprolol and diltiazem groups ($P = 0.38$), respectively (Table 2). There were no significant difference between the groups in the number of doses received to achieve rate control. Within the diltiazem group, the initial fixed doses were similar between those who achieved rate control and those who did not (median [interquartile range, IQR]: 10 [10-18] vs 10 [10-15] mg, respectively, $P = 0.65$). In addition, within the diltiazem group, there was no significant difference in the initial weight-based dose received between those who achieved rate control and those who did not (median [IQR]: 0.16 [0.12-0.23] vs 0.14 [0.11-0.2] mg/kg, respectively, $P = 0.37$). Similarly, within the metoprolol group there were no significant differences in the initial fixed and weight-based doses received between those who did and did not achieve rate control. Time to rate control was not significantly different between the metoprolol and diltiazem groups (median [IQR]: 35 [13-56] vs 21 [11-58] minutes, respectively). The median postintervention heart rate in the metoprolol and diltiazem groups was 86 (IQR 78-96) and 90 (IQR 86-97) bpm, respectively ($P = 0.044$).

Rates of electric cardioversion, hypotension, and bradycardia were not significantly different between the groups (Table 3). Five patients received both a β-blocker and nondihydropyridine calcium channel blocker during the study time period. None of these patients achieved rate control or experienced an adverse event. No adverse events were observed in any of the patients with EF $\leq$ 40%.

Table 1. Baseline Characteristics.

	Metoprolol (n = 100)	Diltiazem (n = 100)	*P*-value
Age, years (IQR)	64 (55-73)	66 (56-75)	0.28
Female, n (%)	38 (38)	49 (49)	0.12
Baseline heart rate, beats per minute (IQR)	148 (135-159)	150 (141-162)	0.31
Prior to admission medication, n (%)			
None	10 (10)	37 (37)	<0.001
β-blocker	88 (88)	56 (56)	<0.001
Nondihydropyridine calcium channel blocker	2 (2)	13 (13)	0.003
Digoxin	11 (11)	5 (5)	0.12
Amiodarone	4 (4)	1 (1)	0.17
Other	5 (5)	0 (0)	0.06
Past medical history, n (%)			
Hypertension	84 (84)	75 (75)	0.12
Diabetes	35 (35)	36 (36)	0.88
Heart failure	57 (57)	51 (51)	0.50
Heart failure with ejection fraction ≤ 40%	24 (42)	27 (53)	0.26
Valvular heart disease	10 (10)	6 (6)	0.30
Stroke, transient ischemic attack, or thromboembolism	12 (12)	17 (17)	0.65
Vascular disease	37 (37)	25 (25)	0.067
Urine drug screen positive for amphetamine, cocaine, or phencyclidine, n (%)	5 (5)	5 (5)	>0.5

Interquartile range (IQR).

Table 2. Achievement of Rate Control.

	Metoprolol (n = 100)	Diltiazem (n = 100)	*P*-value
Overall rate control, n (%)	35 (35)	41 (41)	0.38
One dose, n (%)	18 (18)	28 (28)	0.09
Dose, mg (IQR)	5 (5-5)	10 (10-18)	—
Weight-based dose, mg/kg (IQR)	0.06 (0.05-0.07)	0.16 (0.12-0.23)	—
2 doses, n (%)	13 (13)	11 (11)[a]	0.66
3 doses, n (%)	3 (3)	1 (1)	0.31
4 doses, n (%)	1 (1)[b]	1 (1)	>0.5
Time to rate control, minutes (IQR)	35 (13-56)	21 (11-58)	0.23

Interquartile range (IQR).
[a]Two patients were initiated on a diltiazem infusion.
[b]Patient was initiated on an esmolol bolus and infusion.

Discussion

To our knowledge, this is the largest study to date comparing IV metoprolol and diltiazem for rate control in AF. Our study found no difference in achievement of rate control between the 2 medications, which supports guidelines' recommendations to select either agent.[7-12,14,15,17] To date, only 2 previously published studies comparing IV metoprolol and diltiazem have found IV diltiazem to be the preferred medication.[11-17] However, the efficacy endpoint used in these 2 studies likely influenced their findings. Nicholson et al and Fromm et al defined rate control as HR < 100 bpm within 30 minutes, whereas in this study, rate control was defined as HR < 100 bpm within 2 hours.[13,16] The shorter time frame utilized in the Nicholson et al and Fromm et al studies may have reduced the number of patients who achieved rate control after receiving metoprolol. In comparison with IV metoprolol, IV diltiazem has a faster onset of action (3 vs 10 minutes after drug administration, respectively).[18,19] McGrath et al found a higher percentage of patients who achieved rate control with diltiazem within 1 hour, but no difference at 2 hours.[11] In our study, the time to rate control was not significantly different between the

Table 3. Adverse Events.

	Metoprolol (n = 100)	Diltiazem (n = 100)	*P*-value
Cardioversion, n (%)	1 (1)	3 (3)	0.31
Hypotension, n (%)	1 (1)	0 (0)	>0.5
Bradycardia, n (%)	0 (0)	0 (0)	>0.5

groups and the median time to rate control in the metoprolol and diltiazem groups was 35 and 21 minutes, respectively.

The median initial dose of diltiazem administered in this study was 0.15 mg/kg, which is lower than the guideline recommendation of 0.25 mg/kg.[7,9] However, the lower diltiazem dose administered in our study aligns with other studies' dosing and is not expected to have influenced our study findings.[12-15] Diltiazem's efficacy does not appear to be dose-dependent, but its safety does. Three studies comparing IV diltiazem and metoprolol did not demonstrate greater success with diltiazem doses of 0.24-0.32 mg/kg.[20-22] Ross et al and Ward et al compared low-dose IV diltiazem (0.13-0.14 mg/kg) with the recommended dose of 0.25 mg/kg and found no difference in the number of patients who achieved rate control.[20,21] Lee et al compared 3 different diltiazem doses (0.14, 0.24, and 0.34 mg/kg) and also found no difference in the number of patients who achieved rate control, but found significantly higher rates of hypotension with escalating doses (18%, 34.9%, and 41.7% respectively, $P = 0.025$).[22] Therefore, based on our findings and those of other studies, a diltiazem dose lower than that recommended by guidelines may be given with similar efficacy outcomes and lower risk of adverse events.

The median initial dose of metoprolol administered in this study was 5 mg, which is consistent with guideline recommendations and the dose most commonly administered in other studies.[7,9-15] Unlike diltiazem, few studies have evaluated the effects of varying metoprolol doses. In the Fromm et al and Demircan et al studies, patients received up to 10 mg (0.15 mg/kg) of metoprolol or diltiazem 0.25 mg/kg.[16,17] The Fromm et al study showed that diltiazem was preferred to metoprolol, but the Demircan et al study showed no difference. The hypotensive rates associated with the higher dose of 10 mg were up to 17.9% and comparable with common dose of 5 mg (up to 23.5%).[10-17] Based on these findings, it may be reasonable to administer a metoprolol dose larger than that recommended by guidelines without an increased risk of adverse events. However, this suggestion should be evaluated in future studies.

Unlike the AHA/ACC/HRS guideline, the 2020 ESC guideline recommends to consider combining a β-blocker and a nondihydropyridine calcium channel blocker in patients who have failed rate control with a single agent.[7-9] Concurrent administration of the 2 medications may lead to further atrioventricular node inhibition and rate control, but can potentially lead to complete heart block and hemodynamic compromise. In our study, 5 patients received both IV metoprolol and diltiazem. Although none of these patients achieved rate control or experienced an adverse event, conclusions regarding the safety and efficacy of this approach cannot be elicited from our small sample size. Approximately half of our patients who received diltiazem were reportedly taking a β-blocker prior to admission, whereas only 2 patients who received metoprolol were reportedly taking a nondihydropyridine calcium channel blocker prior to admission. The half-life of extended release diltiazem is 4 to 10 hours, whereas the half-lives of metoprolol tartrate and succinate are 3 to 4 and 3 to 7 hours, respectively.[19,23,24] Due to their half-lives, it is possible that prior to admission medication concentrations may have been present at levels significant enough to interact with the study drug. In our study, only 1 person in the total population experienced hypotension and no one experienced bradycardia, suggesting that one's prior to admission medication should minimally influence which medication they receive in the ED. However, caution should still be exercised when administering a medication from a different class as this approach has demonstrated rates of hypotension up to 14%.[10,13,14]

Contrary to guideline recommendations, our findings suggest that diltiazem may be considered for acute rate control in patients with reduced EF. The 2013 American College of Cardiology Foundation and American Heart Association (ACCF/AHA) HF and 2014 AHA/ACC/HRS guidelines recommend against the use of nondihydropyridine calcium channel blockers in patients with reduced EF due to the potential for hemodynamic compromise resulting from decreased contractility and cardiac output.[7,8,25] However, this recommendation may not be applicable to the acute management of AF because it was based on studies of chronic diltiazem use that found myocardial depression in patients with AF.[26-28] More than half of our study population had a history of HF, with approximately half having an EF $\leq$ 40%. No adverse events were observed in any of these patients. Similarly, in the Hirschy et al study, the rates of bradycardia and hypotension observed in patients with reduced EF who received IV diltiazem were 0% and 3%, respectively.[14] The rates of hypotension associated with IV diltiazem in patients without reduced EF are 0% to 39.3%.[10-17] These findings suggest that IV diltiazem may be considered in patients with reduced EF, but this suggestion requires further investigation.

This study has several limitations. This was a single-center retrospective study. Compliance to home medication and the time from last dose were not obtained. Therefore, our suggestion that one's prior to admission medication should minimally influence which medication they receive in-house is hindered by the omission of these data. Our suggestion regarding the use of IV diltiazem in patients with

reduced EF is limited by our small sample size. We did not follow patients after 2 hours of medication administration and cannot comment on the efficacy of the interventions in maintaining rate control. In addition, we did not evaluate the AF etiology and are unable to discern the influence of precipitating factors on patient outcomes. Finally, hypotension was defined as SBP < 90 mm Hg requiring the administration of a vasopressor which is not consistent with the definition used in other studies. Therefore, our data may have underreported the true incidence of hypotension, but this definition was selected to only identify clinically relevant hypotension.

Conclusion and Relevance

Our study confirms that both IV metoprolol and diltiazem are appropriate agents to use for acute rate control. No patient-specific factors were identified that would influence the preferential use of one medication over the other. In addition, within the limitations of this study, our findings suggest that patient's prior to admission medication should minimally influence the selection of rate control agents in the ED and that diltiazem may be administered to patients with reduced EF in the setting of acute AF.

Declaration of Conflicting Interests

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