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Hemodynamic comparison of intravenous push diltiazem versus metoprolol for atrial fibrillation rate control

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ABSTRACT

Objective: Intravenous push (IVP) diltiazem and metoprolol are commonly used for management of atrial fibrillation (AF) with rapid ventricular rate (RVR) in the emergency department (ED). This study's objective was to determine if there was a significant difference in blood pressure reduction between agents.
Methods: This was a single-center, retrospective study of adult patients initially treated with IVP diltiazem or metoprolol in the ED from 2008 to 2018. Primary endpoint was mean reduction in systolic blood pressure (SBP) from baseline to nadir during the study period. Study period was defined as time from first dose of IVP intervention to 30 min after last dose of IVP intervention or first dose of maintenance therapy, whichever came first.
Results: A total of 63 diltiazem patients and 45 metoprolol patients met eligibility criteria. Baseline characteristics were similar except for initial ventricular rate (VR) and home beta-blocker use. Median dose of initial intervention was 10 [10−20] mg and 5 [5–5] mg for diltiazem and metoprolol respectively. Mean SBP reduction was 18 ± 22 mmHg for diltiazem compared to 14 ± 15 mmHg for metoprolol ($p = .33$). Clinically relevant hypotension was similar between groups 14% vs. 16% ($p = .86$). Rate control was achieved in 35 (56%) of the diltiazem group and 16 (36%) of the metoprolol group ($p = .04$).
Conclusion: IVP diltiazem and metoprolol caused similar SBP reduction and hypotension when used for initial management of AF with RVR in the ED. However, rate control was achieved more often with diltiazem.

1. Introduction

Atrial fibrillation (AF) is a common dysrhythmia that leads to approximately 600,000 emergency department (ED) visits in the United States per year [1]. AF with rapid ventricular rate (RVR) requires prompt management to prevent complications such as hemodynamic instability and left ventricular dysfunction [2]. Non-dihydropyridine calcium channel blockers and beta-blockers are recommended by the 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society (AHA/ACC/HRS) Guidelines as preferred initial rate control options in hemodynamically stable patients without decompensated heart failure or pre-excitation syndromes [3].

Intravenous push (IVP) diltiazem and metoprolol are commonly used for the acute management of AF with RVR in the ED. [2] Several studies have published conflicting results when comparing efficacy between these two medications [4–8]. Therefore, treatment is often guided by provider preferences, patient comorbidities, and home rate control therapies [9].

To the best of our knowledge, no studies have evaluated the incidence of hypotension between IVP diltiazem and metoprolol as a primary outcome. Data regarding hypotension and blood pressure reduction is limited to the reporting of adverse effects and secondary outcomes within currently published literature. Studies suggest systolic blood pressure (SBP) reduction after administration of these agents ranges from 7 to 23 mmHg [4,5]. Due to the amount of conflicting data between IV diltiazem and metoprolol efficacy, research pertaining to the impact of these medications on a patient's hemodynamics would provide insight not yet published in the literature. The objective of this study was to quantify and compare blood pressure reduction between these two agents when used for acute management of AF with RVR.

2. Methods

2.1. Study design

This was a single-center retrospective study of adult patients who received IVP diltiazem or metoprolol for treatment of AF with RVR in the ED from July 1, 2008 to July 1, 2018. It was conducted in a tertiary

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academic medical center with approximately 100,000 annual ED visits. The study was approved by the local Institutional Review Board prior to data collection.

2.2. Patients

All patients who were ≥18 years old and received IVP diltiazem or metoprolol during an ED encounter were eligible for inclusion. All unique patient encounters were assigned a numeric identifier. At this time, each encounter's corresponding treatment intervention was known. Using a random number generator, patient encounters were then randomly selected and screened against exclusion criteria until the a priori sample size was met for each treatment arm, or until all available patients were screened. In the setting of patients with multiple ED encounters, only the first randomly selected encounter was reviewed. Patients were excluded for the following: indication other than AF with RVR (ventricular rate (VR) ≥ 120 beats per minute (bpm) on electrocardiogram (ECG)), known pregnancy, incarceration, rate or rhythm modifying interventions prior to administration of study medication, extreme dosing of study intervention (metoprolol <2.5 mg or > 5 mg, diltiazem <10 mg or > 25 mg), myocardial infarction during admission, SBP < 90 mmHg immediately prior to study intervention, fever (≥ 38 °C) before study intervention, no documentation of blood pressure after study intervention, or contraindication to diltiazem or metoprolol (decompensated heart failure, sick sinus syndrome, atrioventricular block, pre-excitation syndrome).

2.3. Outcome measures

The primary outcome of this study was the mean reduction in SBP from baseline to nadir between those who received IVP diltiazem or metoprolol during the study period. Baseline vitals were considered those documented immediately prior to intervention. Study period was defined as the time from the first IVP dose of diltiazem or metoprolol to 30 min after the last IVP dose or initiation of a secondary intervention, whichever came first. Secondary interventions included oral and maintenance infusions of rate or rhythm modifying medications as well as electrical cardioversion.

Secondary outcomes during the study period included a composite of clinically relevant hypotension (SBP < 90 mmHg, new vasopressor requirement, or fluid bolus during the study period) and achievement of rate control (VR < 100 bpm, conversion to normal sinus rhythm, or VR < 120 bpm if a 20% reduction from baseline occurred). Additionally, mean reduction in SBP from baseline to nadir was assessed during an extended study period. The extended study period was defined as time from the first IVP dose of diltiazem or metoprolol to 6 h after the last IVP dose. The extended study period excluded patients who received multiple classes of rate or rhythm modifying medications and those who received electrical cardioversion.

2.4. Statistical analysis

Due to lack of published literature, a sample size was calculated based upon what the authors considered to be a clinically significant difference in blood pressure reduction. It was estimated that a sample size of 63 patients per group would provide 80% power to detect a 10 mmHg difference in SBP reduction between groups. Analysis was performed with Minitab 18.1 statistical software 2018 (State College, PA). All outcomes were tested for normality using the Anderson-Darling test. Continuous data were reported as median and interquartile range [IQR] if non-normally distributed or mean ± standard deviation if normally distributed. Statistical significance was evaluated with an a priori significance value of $p < .05$. T-test and Mann Whitney U test were utilized for continuous data that was normally and not normally distributed respectively. Categorical data was reported as frequencies and percentages (%) and evaluated with the chi square test.

3. Results

From July 1, 2008 to July 1, 2018, 2164 encounters were identified in which adult patients received one dose of IVP diltiazem ($n = 1707$) or metoprolol ($n = 457$) in the ED. Of these encounters, only 596 were screened against exclusion criteria due to meeting the a priori sample size in the diltiazem arm ($n = 1125$) and duplicate encounters ($n = 443$). All metoprolol encounters were reviewed but the a priori sample size was never met. Only 108 patients of the original cohort were included in the study of which 63 received diltiazem and 45 received

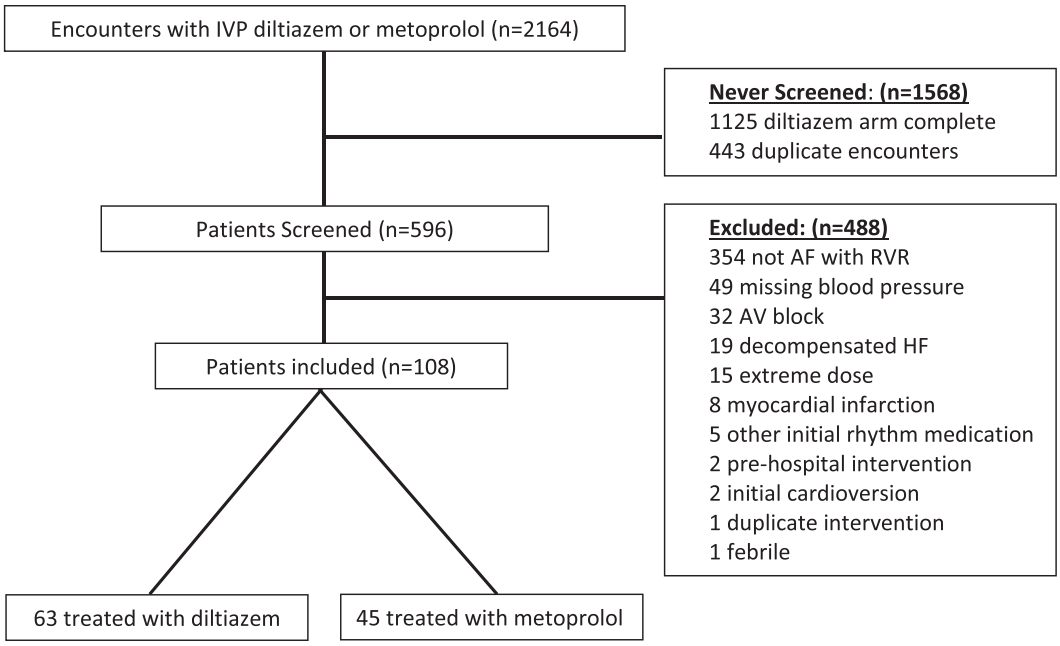

Fig. 1. Study flow diagram. AF: atrial fibrillation; AV: atrioventricular; HF: heart failure; IVP: intravenous push; RVR: rapid ventricular rate.

metoprolol. The most common reasons for exclusion were treatment for an indication other than AF with RVR ($n = 354$) and lack of blood pressure documentation after intervention ($n = 49$). Other reasons for exclusion are further summarized in Fig. 1.

Baseline characteristics were similar between groups with the exception of mean (±SD) baseline VR (diltiazem 146 ± 15 bpm vs. metoprolol 138 ± 13 bpm; $p = .003$) and home beta-blocker use (diltiazem 38 (60%) vs. metoprolol 43 (96%); $p < .01$) as summarized in Table 1. Characteristics of study interventions and ED disposition are described in Table 2. The initial median (IQR) diltiazem and metoprolol doses were 10 [10–20] mg and 5 [5–5] mg, respectively.

Primary and secondary outcomes are summarized in Table 3. The primary outcome, mean SBP reduction from baseline to nadir, was 18 ± 22 mmHg compared to 14 ± 15 mmHg for diltiazem and metoprolol patients ($p = .33$), respectively. The composite of clinically relevant hypotension was also similar between diltiazem and metoprolol patients (9 (14%) vs. 7 (16%); $p = .86$). However, more patients receiving diltiazem obtained rate control (35 (56%) vs. 16 (36%); $p = .04$). SBP reduction from baseline to nadir during the six hour extended study period was 33 ± 20 mmHg for diltiazem and 26 ± 15 mmHg for metoprolol patients ($p = .13$).

Only 13 diltiazem patients (21%) received a weight-based dose 0.2–0.3 mg/kg similar to what is recommended by current AF guidelines [3]. Of these patients, the mean SBP reduction was 25 ± 21 mmHg, 2 (15%) met the composite outcome of clinically relevant hypotension, and 11 (85%) obtained rate control. Forty-nine patients (78%) were given an initial dose <0.2 mg/kg. They had a mean SBP reduction of 15 ± 22 mmHg, 7 (14%) experienced the composite outcome of clinically relevant hypotension, and 23 (47%) achieved rate control. The incidence of rate control was higher in patients who received guideline recommended weight-based diltiazem compared to those who received <0.2 mg/kg of diltiazem initially ($p = .02$). Other outcomes were not statistically different between diltiazem dosing subgroups.

4. Discussion

This study did not demonstrate a difference in mean SBP reduction or incidence of hypotension between IVP diltiazem and metoprolol. Despite commonly using diltiazem dosing lower than recommended by AF guidelines, rate control was obtained more frequently in patients given diltiazem than those who received metoprolol [3]. However, the lower dosing of diltiazem used at our institution may have impacted primary and secondary outcomes. To date, one medication is not considered superior as several studies have published conflicting results comparing the efficacy of IVP diltiazem and metoprolol [4-8]. Furthermore, current AF guidelines do not recommend one medication over the other [3]. This study is unique in its evaluation of the hemodynamic impact of these two agents as a primary outcome and can therefore help optimize the management of AF with RVR in the ED.

Several small studies have compared SBP reduction and incidence of hypotension between diltiazem and metoprolol as secondary outcomes. Both Demircan and Fromm et al. evaluated hypotension defined as SBP < 90 mmHg 20–30 min after intervention [4,6]. While neither study found a difference in hypotension between diltiazem and metoprolol, Demircan and colleagues reported a trend toward greater reduction in SBP in those who received metoprolol (diltiazem 15.5 mmHg versus metoprolol 22.3 mmHg; $p > .05$) [4]. Scheuermeyer et al.

Table 1
Baseline patient characteristics.

Variable	Diltiazem ($n = 63$)	Metoprolol ($n = 45$)	p-Value
Age, mean ± SD	68 ± 13	64 ± 11	0.15
Male, n(%)	32 (51)	23 (51)	0.97
Weight (kg), mean ± SD	90.6 ± 29	87.1 ± 26	0.51
Body mass index (kg/m^2), mean ± SD	31 ± 9	30 ± 8	0.35
Past medical history, n (%)			
Atrial fibrillation	38 (60)	39 (87)	0.095
Congestive heart failure	20 (32)	16 (36)	0.68
Home medications, n (%)			
Amiodarone	1 (2)	1 (2)	1
Beta-blocker	38 (60)	43 (96)	< 0.01
Calcium channel blocker	18 (29)	8 (18)	0.2
Digoxin	2 (3)	3 (7)	0.4
Baseline VR[b] (bpm), mean ± SD	146 ± 15	138 ± 13	0.003
Baseline SBP[c] (mmHg), median [IQR]	137 [125–148]	132 [119–140]	0.25
Baseline SBP[c] <120 (mmHg), n (%)	9 (14)	12 (27)	0.11
Pre-intervention fluid bolus,[a] n (%)	12 (19)	13 (29)	0.2

[a] One-time fluid of ≥250 ml within 30 min before intervention.
[b] VR: ventricular rate.
[c] SBP: systolic blood pressure.

Table 2
Interventions and disposition.

Study period interventions	Diltiazem	Metoprolol
Dose 1	n = 63 (100)	n = 45 (100)
Actual dose (mg), median [IQR]	10 [10–20]	5 [5–5]
Weight-based dose (mg/kg), median [IQR]	0.14 [0.11–0.19]	0.06 [0.05–0.07]
Dose 2	$n = 16$ (25)	n = 17 (38)
Actual dose (mg), median [IQR]	10 [10–15]	5 [5–5]
Weight-based dose (mg/kg), median [IQR]	0.14 [0.11–0.18]	0.05 [0.05–0.06]
Dose 3	$n = 0$ (0)	n = 11 (24)
Actual dose (mg), median [IQR]	–	5 [5–5]
Weight-based dose (mg/kg), median [IQR]	–	0.06 [0.05–0.07]
Extended study period interventions[a]	Diltiazem ($n = 44$)	Metoprolol ($n = 27$)
Transitioned to infusion alone, n (%)	28 (64)	0 (0)
Transitioned to infusion and oral, n (%)	2 (5)	0 (0)
Transitioned to oral alone, n (%)	5 (11)	7 (26)
No further rate or rhythm intervention, n (%)	9 (20)	20 (74)
Disposition	Diltiazem (n = 63)	Metoprolol (n = 45)
Admission, n(%)	51 (81)	34 (76)
ED length of stay (minutes),[b] median [IQR]	293 [221–434]	374 [257–559]

[a] Patients were not evaluated for the extended study period if they received cardioversion or a different class of rate or rhythm control medication from original intervention.
[b] Emergency department (ED) length of stay defined as first intervention to ED discharge or transfer to floor, whichever came first.

Table 3
Primary and secondary outcomes.

Outcome	Diltiazem (n = 63)	Metoprolol (n = 45)	p-Value
SBP[a] reduction from baseline to nadir during study period (mmHg),[b] mean ± SD	18 ± 22	14 ± 15	0.33
SBP[a] reduction from baseline to nadir during extended study period (mmHg),[c] mean ± SD	33 ± 20	26 ± 15	0.13
Hypotension composite, n (%)	9 (14)	7 (16)	0.86
Fluid bolus	7 (11)	7 (16)	
Nadir SBP[a] < 90 mmHg	2 (3)	0 (0)	
Vasopressor addition	0 (0)	0 (0)	
Rate control composite, n (%)	35 (56)	16 (36)	0.04
VR[d] < 100 bpm	22 (35)	10 (22)	
VR[d] < 120 bpm if 20% reduction	13 (21)	6 (13)	
Conversion to normal sinus	4 (6)	2 (4)	

[a] SBP: systolic blood pressure.
[b] Study period was defined as the time from the first IVP dose of diltiazem or metoprolol to 30 min after the last IVP dose or initiation of a secondary intervention, whichever came first.
[c] The extended study period was defined as the time from the first IVP dose of diltiazem or metoprolol to 6 h after the last IVP dose. There were only 44 patients in the diltiazem group and 27 patients in the metoprolol group in this period.
[d] VR: ventricular rate.

additionally looked at fluid boluses as a marker of hypotension when comparing calcium channel blockers (CCBs) to beta-blockers (BBs) for treatment of AF with RVR. No difference in bolus requirements was found. However, in contrast to findings by Demircan et al. there was a trend toward greater SBP reduction in patients who received CCBs (CCB 12.1 mmHg versus BB 7.4 mmHg; 95% CI = −0.5-7.1) [5].

The current study evaluated hypotension by comparing absolute SBP reduction at 30 min and six hours after treatment initiation as well as a composite including factors such as vasopressor or fluid bolus initiation. Despite using multiple definitions for hypotension and examining a longer time window than previous studies, the authors were unable to find a statistically significant difference in hypotension or SBP reduction between groups. However, the small subgroup of diltiazem patients (n = 13) given an initial 0.2–0.3 mg/kg dose had larger SBP reduction at 30 min than metoprolol patients (25 vs. 14 mmHg). Common institution utilization of diltiazem doses <0.2 mg/kg may have blunted SBP reduction compared to metoprolol. Degree of mean SBP reduction was greater for diltiazem and metoprolol patients at six hours (33 vs. 26 mmHg) compared to 30 min (18 vs. 14 mmHg). There was also a trend toward increased SBP difference between groups at 6 h (7 mmHg; p = .13) compared to 30 min (4 mmHg; p = .33). This is likely due to larger utilization of secondary interventions in the diltiazem group such as transitioning to an infusion and/or oral therapy during the extended study period (Table 2).

The dosing of diltiazem in our study should be considered before interpreting any results. The median initial diltiazem dose was 10 [10–20] mg or 0.14 [0.11–0.19] mg/kg. While lower than the 0.25 mg/kg dose recommended by the 2014 AHA/ACC/HRS guidelines, these lower fixed doses of diltiazem have been studied in the ED and are common practice at our institution [3,10,11]. Two retrospective studies reported similar rate control and a trend toward less SBP reduction when using lower diltiazem doses. Lee et al. found that diltiazem doses of 0.14 mg/kg compared to 0.24 mg/kg provided similar rate control within 30 min (43 (70.5%) vs. 64 (77.1%) patients; p = .605) and percent SBP reduction (9.7% vs. 12.6%; p = .369) [10]. Similarly, Ross et al. concluded that rate control was achieved for 155 (60.8%) versus 138 (68.7%) patients given a fixed 10 mg diltiazem dose compared to 0.2–0.3 mg/kg diltiazem, respectively (p = .082). The small subgroup of patients within our study given a diltiazem dose of 0.2–0.3 mg/kg (n = 13) had a trend toward higher SBP reduction at 30 min with higher incidence of rate control than those who received lower doses of <0.2 mg/kg (n = 49). Institutions that utilize weight-based dosing may see larger SBP reduction with or without higher incidence of rate control.

Metoprolol dosing used in this study should also be assessed in light of previous literature. Metoprolol was given almost uniformly as a fixed 5 mg IVP dose corresponding to a weight-based dose of 0.06 [0.05–0.07] mg/kg. This dosing strategy matches guideline recommendations and common practice but is lower than the weight-based metoprolol dose of 0.15 mg/kg (max 10 mg) occasionally used in previous AF studies [3,4,6]. Use of a fixed metoprolol dose in our study may have led to reduced efficacy and smaller SBP reduction compared to these previous studies. However, the diltiazem and metoprolol dosing within our study aligns with common practice making results generalizable to many institutions.

Although our results suggest higher rate control with diltiazem versus metoprolol, diltiazem dosing as well as variables beyond dosing may have impacted this exploratory outcome. Incidence of rate control was higher in the diltiazem patients despite having a higher baseline VR than the metoprolol cohort (p = .003). However, incidence of rate control was much higher within the subgroup of patients given weight-based diltiazem dosing suggesting that efficacy may be significantly altered by dosing strategy. In addition, 96% of the patients who received metoprolol were on a beta-blocker at home. These patients may have been susceptible to reduced rate control with IVP metoprolol. Kuang et al. found that patients on chronic beta-blockers were less likely to achieve rate control with IVP metoprolol than those who were beta-blocker naïve [12]. This in conjunction with using guideline recommended fixed-dose metoprolol (rather than weight-based) may explain why rate control in the metoprolol group was lower than the 42–62% reported in previous studies [6-8]. It could be hypothesized that higher incidence of rate control with IVP diltiazem compared to metoprolol led to faster ED disposition as seen by shorter ED length of stay (Table 2).

5. Limitations

There are several limitations to the current study that should be acknowledged. Common limitations of a retrospective, single-center study design include provider bias of patient and medication selection, as well as documentation errors and omissions. Providers may have chosen a certain medication and dose based on patient presentation and practice familiarity. As previously mentioned, dosing strategies used in our study may have altered the severity of SBP reduction, incidence of hypotension, and frequency of rate control. In the current study, continuous vital sign monitoring was not available and repeat ECGs were often not captured during the study period. Incidence of hypotension and rate control may have been different than documented. Accuracy of hemodynamic data collection relied on timely charting of medication administration and vital signs. Missing blood pressure documentation was a large source of patient exclusion and occurred primarily in those who received metoprolol. Documentation could have been completed less frequently in patients that were perceived to be more stable. Patient baseline characteristics including comorbid conditions and home medications relied on availability of diagnoses codes and home medication lists. Home medication compliance was not assessed. Lastly, power was not reached due to inability to meet the a priori sample size for the metoprolol arm. Metoprolol was only used in about 20% of all encounters revealing low representation of metoprolol treatment in the cohort. In addition, exclusion due to missing vital signs and extreme dose of intervention was more prevalent in the metoprolol arm.

6. Conclusion

When used for treatment of AF with RVR, IVP diltiazem and metoprolol resulted in similar SBP reduction and incidence of hypotension. However, more patients treated with diltiazem achieved rate control within 30 min than metoprolol. Prospective studies comparing various dosing approaches of diltiazem to metoprolol are warranted.

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Declaration of Competing Interest

No listed authors have any conflict of interest related to the subject matter in this manuscript.

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