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Low-dose diltiazem in atrial fibrillation with rapid ventricular response

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Background and significance

- Symptomatic patients with RVR during AF require prompt medical management;
- Cardioversion should be considered if symptomatic hypotension,angina, or heart failure

Background and significance

- IV β-blockers or nondihydropyridine calcium channel antagonists : slow the ventricular response to AF.
- Diltiazem : the most common agents.
- Try lower dose of diltiazem to avoid hypotension and found that rapid AF could be controlled effectively,but no published evidence.

Goals of this investigation

- The efficacy and safety of low-dose, standard-dose, and high-dose diltiazem in patients presenting to the ED with rapid AF.

Methods

- Study design
- A retrospective chart review : the efficacy and safety of various doses of diltiazem.
- This study was approved by institutional review board committee of our hospital (B-0906/077-101).

Setting

- 950-bed urban academic tertiary hospital, with an annual ED census of 67 000.
- The study hospital was a paperless institution where all medical records were fully electronic or computerized.

Subjects

- Adult patients older than 18 years with AF with a rapid ventricular response.
- Intravenous boluses of diltiazem.
- Excluded : administered any other medications within 30 minutes.
- Excluded : if body weight was not measured in the hospital.

Measurements and outcomes

- Demographic and clinical data : Electronic medical records
- Clinical information :
  - a prior history of hypertension
  - diabetes mellitus
  - congestive heart failure (CHF)
  - recent medications
  - ventricular function (ejection fraction).

Measurements and outcomes

- Clinical information :
  - Physical findings : vital signs before and up to 30 minutes after the diltiazem bolus injection.
  - Echocardiography.
  - Patients not admitted : ejection fraction within 3 months of the ED visit.
  - Heart function did not undergo echocardiography within 3 months : missing value.

Measurements and outcomes

- Clinical information :
  - Body weights
  - If the body weight was not measured in the ED, values measured on the inpatient ward.

Measurements and outcomes

- Patients were divided into 3 groups according to diltiazem dosage:
  - low dose ($\leq$ 0.2 mg/kg)
  - standard dose (> 0.2 and $\leq$ 0.3 mg/kg)
  - high dose (> 0.3 mg/kg).

Positive therapeutic response

- Any one of the following events within 30 minutes after diltiazem injection:
  - reduction of the lowest ventricular response rate (VRR) to 100 beats/minute or less
  - reduction of VRR by 20% or greater from baseline.

Complication

- Any one of following events within 30 minutes after diltiazem injection:
  - lowest systolic blood pressure (SBP) less than 90 mm Hg,
  - reduction of SBP by 20% or greater from baseline,
  - respiratory failure requiring intubation,
  - cardiac arrest
  - Unstable dysrhythmias requiring emergency interventions(cardioversion ; defibrillation).

Measurements and outcomes

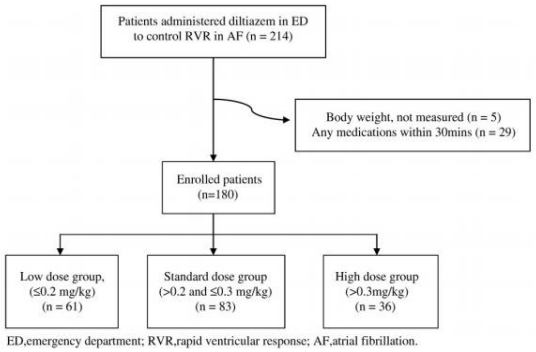
- Continuous variables:
  - lowest SBP : not exceeding 90 mm Hg or greater than 90mmHg
  - lowest VRR : not exceeding 100/min or greater than 100/min
  - (baseline SBP - lowest SBP)/baseline SBP : at least 0.2 or less than 0.2

Measurements and outcomes

- Continuous variables:
  - (baseline VRR - lowest VRR)/baselinen VRR : at least 0.2 or less than 0.2
  - age : exceeding 65 years or greater than 65 years.

Measurements and outcomes

- The outcomes of this investigation:
  - the rate of a successful therapeutic response
  - the rate of any complications.



ED,emergency department; RVR,rapid ventricular response; AF,atrial fibrillation.

Fig. 1 Inclusion and exclusion criteria.

Table 1 Baseline characteristics

	Low-dose group	Standard-dose group	High-dose group	*P* value
	n = 61	n = 83	n = 36	
Age (y)	66.8 ± 13.5	66.7 ± 13.5	72.1 ± 10.7	.129
Male sex, n (%)	27 (44.3%)	40 (48.2%)	15 (41.7%)	.781
Dosage (mg/kg)	0.14 ± 0.04	0.24 ± 0.02	0.34 ± 0.02	
Weight (kg)	63.8 ± 17.1	61.3 ± 11.2	54.6 ± 9.5	.005
PMHx				
HTN, n (%)	36 (59.0%)	35 (42.2%)	18 (50.0%)	.135
DM, n (%)	12 (19.7%)	16 (19.3%)	7 (19.4%)	.956
CHF, n (%)	7 (11.5%)	3 (3.6%)	2 (5.6%)	.167
Hyperlipidemia, n (%)	3 (4.7%)	3 (3.6%)	2 (5.6%)	.873
Medications				
Aspirin, n (%)	13 (21.3%)	14 (16.9%)	8 (22.2%)	.717
Warfarin, n (%)	4 (6.6%)	5 (6.0%)	3 (8.3%)	.897
CCB, n (%)	20 (32.8%)	18 (21.7%)	7 (19.4%)	.217
BB, n (%)	9 (14.8%)	11 (13.3%)	5 (13.9%)	.967
DGX, n (%)	1 (1.6%)	2 (2.4%)	3 (8.3%)	.169
Baseline V/S				
SBP (mm Hg)	132 ± 26	135 ± 29	138 ± 32	.629
DBP (mm Hg)	79 ± 18	78 ± 17	76 ± 22	.779
HR (/min)	139 ± 19	138 ± 21	142 ± 25	.707
RR (/min)	23 ± 5	23 ± 6	23 ± 6	.949
BT (°C)	36.3 ± 0.7	36.4 ± 0.8	36.3 ± 0.6	.934
EF (%)	56 ± 9	56 ± 9	58 ± 11	.774

Continuous data are presented as means and standard deviations and compared with 1-way analysis of variance. Binomial data are presented as the percentage frequency of occurrence and compared with χ^2 test or Fisher exact test. PMHx indicates past medical history; HTN, hypertension; DM, diabetes mellitus; CCB, calcium channel blocker; BB, β-blocker; DGX, digoxin; V/S, vital signs; DBP, diastolic blood pressure; HR, heart rate; RR, respiration rate; BT, body temperature; EF, ejection fraction (percentage).

Table 2 Success and complication

	Low-dose group n = 61	Standard-dose group n = 83	High-dose group n = 36	*P* value
Overall success	43 (70.5%)	64 (77.1%)	28 (77.8%)	.605
Lowest VRR ≤100 (n)	33 (54.1%)	42 (50.6%)	19 (52.8%)	.915
VRR ▽ ≥20% of baseline HR (n)	41 (67.2%)	59 (71.1%)	26 (72.2%)	.837
Percentage reduction of VRR (n)	26.30%	27.90%	29.90%	.588
Overall complication	11 (18.0%)	29 (34.9%)	15 (41.7%)	.025
Lowest SBP <90 (n)	1 (1.6%)	6 (7.2%)	1 (2.8%)	.237
SBP ▽ ≥20%(n)	11 (18.0%)	28 (33.7%)	14 (38.9%)	.047
Percentage reduction of SBP (%)	9.70%	12.60%	13.40%	.369

Binomial data are presented as the percentage frequency of occurrence and compared with χ^2 test or Fisher exact test. ▽ indicates reduction.

Results

- The diltiazem dose increased, the frequency of hypotensive episodes also significantly increased (P = .025)
- No patient receiving any dose of diltiazem had experienced endotracheal intubation, cardioversion, cardiac arrest, or unstable dysrhythmias.

Results

- Complications occurred less frequently :
  - among the low-dose group (OR, 0.41; 95% CI. 0.18-0.90)
  - among patients with an initial SBP between 90 and 140 mm Hg
- CHF was not associated with complications in our study (OR, 0.74; 95% CI,0.19-2.86)
- As a relative contraindication to diltiazem due to its negative inotropic effect.

Table 3 Univariate analysis for complications

		Unadjusted OR	95% CI	*P* value
Age (y)	≤65	Reference		
	>65	1.41	0.72-2.75	.306
Sex	Male	Reference		
	Female	1.11	0.59-2.11	.732
CHF	No	Reference		
	Yes	0.744	0.19-2.86	.666
CCB	No	Reference		
	Yes	0.48	0.21-1.09	.08
Baseline SBP	90 < SBP ≤ 140	Reference		
	SBP >140	6	3.00-11.97	<.001
Diltiazem dose	Low	0.41	0.18-0.90	.028
	Standard	Reference		
	High	1.33	0.59-2.96	.486

Table 4 Multivariate logistic regression for complications

		Adjusted OR	95% CI	*P* value
CHF	No	Reference		
	Yes	0.69	0.15-3.18	.636
Baseline SBP	90 < SBP ≤ 140	Reference		
	SBP >140	6.52	3.17-13.42	<.001
Diltiazem dose	Low	0.39	0.16-0.94	.037
	Standard	Reference		
	High	1.5	0.61-3.66	.366

Discussion

- Which loading dose of diltiazem is most appropriate
- American College of Cardiology/American Heart Association/European Society of Cardiology 2006 guidelines:
  - Diltiazem bolus injection of 0. 25 mg/kg over 2 minutes

Discussion

- No published research concerning the safety and efficacy of diltiazem according to dosage
- Our study suggests that lower dosages of diltiazem may be safer than standard dose without interrupting therapeutic efficacy.
- To confirm the safety and efficacy of low-dose diltiazem, randomized controlled studies are necessary.

Discussion

- Prior studies have compared the safety and efficacy of various doses of diltiazem in patients with paroxysmal supraventricular tachycardia (PSVT)
- In one study, patients with PSVT were randomized to receive 1 of 4 doses of diltiazem (0.05, 0.15, 0.25, or 0.45 mg/kg)

Discussion

- Successful therapeutic response : conversion to normal sinus rhythm
- 4 (29%) of 14 patients with 0.05 mg/kg,
- 16 (64%) of 19 with 0.15 mg/kg,
- 13 (100%) of 13 with 0.25 mg/kg,
- 14 (62%) of 17 with 0.45 mg/kg.

Discussion

- The most frequent adverse event was hypotension (SBP < 90 mm Hg), 10 (16%) of 63 patients receiving diltiazem.
- Adverse effects occurred more frequently in the higher-dose groups,
- the difference between groups was not statistically significant.

Discussion

- The optimum dose of diltiazem for PSVT be 0.25 mg/kg
- Low-dose diltiazem could effectively control rapid AF and was less likely to cause hypotension than the standard dose.

Discussion

- Underlying ventricular dysfunction in patients with AF : more susceptible to hypotension after administration of diltiazem.
- Or the small sample size, underpowered

Discussion

- Excluded 29 patients did not make selection bias
- Because there was nearly the same percentage of each dose group in excluded cases (data not shown).

Limitation

- Retrospective nature of this study, multiple potential limitations:
  - selection bias : minimized by the use of an electronic medical record system
  - ascertainment bias
  - Incomplete data documentation and extraction
  - Nonstandardized treatment regimens.

Limitation

- Retrospective nature of this study, multiple potential limitations:
  - Echocardiography was not available in all patients.
  - 160 patients/180 were examined with echocardiography within 3 months of the index visit: failed to identify differences in ventricular function among the groups.

Limitation

- Retrospective nature of this study, multiple potential limitations:
  - Defined a hypotensive episode as a SBP less than 90 mmHg or a reduction from baseline SBP of 20% or greater; the clinical significance of such a decline in SBP in patients with rapid AF is unclear.

Conclusion

- Low dose of diltiazem(< 0.20 mg/kg) :
  - might be as effective as standard dose in patients with rapid AF
  - reduces the rate of hypotension.
- Additional research is necessary to determine the optimal loading dosage,
- Our results suggest that the initial loading dose of diltiazem might be less than 0.20 mg/kg.

Thank you for listening

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A pilot study to develop a prediction instrument for endocarditis in injection drug users admitted with fever

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Introduction

- Injection drug users (IDUs) with fever : endocarditis
- 1980s~1990s criteria to predict endocarditis : poor sensitivity and specificity

Goals of this pilot study

- Frequency percentage of IDUs with fever and no clear source
- Individual clinical criteria and combinations of criteria : discharge diagnosis of endocarditis
  - elements of patient history
  - physical examination findings
  - laboratory tests

Methods

- Study design and setting
  - Retrospective study of all IDUs admitted through the ED, “fever without a clear source ” in 2006 at 3 urban, county hospitals
  - annual ED censuses of approximately 61,000, 72,000, and 102,000 patients

Selection of participants

- H/o injection drug use,
- Older than 17 years,
- Admission from the ED
- ED diagnosis of
  - “rule out endocarditis”
  - “shooter with a fever”
  - “fever without a source”
  - “IDU with fever.

Methods of measurement, data collection, and outcome measures

- 12 candidate prediction criteria, derived from review of past studies and from investigator consensus :
  - H/o endocarditis
  - H/o HIV-positive
  - T > 38.8°C
  - HR > 100 beats/min
  - Heart nurnur
  - skin infection (-)

Methods of measurement, data collection, and outcome measures

- 12 candidate prediction criteria, derived from review of past studies and from investigator consensus :
  - Pneumonia on chest x-ray
  - Hyponatremia
  - Thrombocytopenia
  - Leukocytosis
  - Hematuria/Pyuria
  - ESR

Methods

- Abstracted the following outcome data from inpatient records:
  - Echocardiogram
  - Blood culture results
  - Hospital length of stay
  - Discharge diagnoses.

Methods

- Endocarditis : Modified Duke Criteria & discharge diagnosis of endocarditis

Duke's Criteria (Modified)		ACC Guidelines
Major Criteria	**Minor Criteria**	**Indications for Surgery in Native Valve Endocarditis**
Sustained bacteremia by an organism known to cause endocarditis	**Predisposing conditions:** intravenous drug use, diabetes, indwelling venous catheters, hemodialysis, diabetes	**Class I: Surgery indicated in:** 1. Patients with valvular stenosis or regurgitation resulting in heart failure 2. Patients with aortic or mitral regurgitation with hemodynamic evidence of elevated LV end-diastolic or left atrial pressures, or moderate or severe pulmonary hypertension 3. Patients with infective endocarditis caused by fungal or highly resistant organisms 4. Patients with infective endocarditis complicated by heart block, annular or aortic abscess, or destructive penetrating lesions
Echocardiographic evidence: vegetation, abcess, prosthetic dehiscence	**Vascular phenomena:** septic arterial or pulmonary emboli, Janeway lesions, mycotic aneurysms	
	Immune phenomena: Osler's nodes, (+) Rheumatoid factor, Osler's nodes, Roth spots	
New valvular regurgitation	**Fever**	**Class IIa: Surgery reasonable in:** 1. Patients with infective endocarditis who present with recurrent emboli or vegetations despite antibiotic therapy
	Blood cultures positive for organisms not meeting major criteria	**Class IIb: Surgery can be considered in:** 1. Patients with mobile vegetations greater than 10mm.

Results

- 11,980 screened ED charts, 236 met inclusion criteria.
- The κ statistic for inter-abstractor agreement was 0.82 (95%CI, 0.74-0.90).

Table 1 Subject characteristics

Description	Total responders, no. (%)	Mean (SD) [a]
Sex		
Male	154 (65.3)	
Female	82 (34.7)	
Age		43.7 (11.3)
Race/ethnicity		
White	98 (41.5)	
African American	68 (28.8)	
Hispanic	42 (17.8)	
Asian/Pacific Islander	5 (2.1)	
Other	17 (7.2)	
Unknown	6 (2.6)	
Hospital survival		
Yes	225 (95.3)	
No	11 (4.7)	
Hospital length of stay, d		9.4 (9.6)

[a] n = 236.

Results

- 20 (8.5%) subjects were diagnosed with endocarditis.
- 18 : positive blood cultures.
- 16 : echocardiographic evidence of endocarditis.

Results

- 2 : negative blood cultures
  - treated with antibiotics prior to their blood cultures and had vegetative lesions on their echocardiograms.

Results

- Best screening performance :
  - absence of skin infection
  - tachycardia
  - hyponatremia
  - pneumonia on CXR
  - history of endocarditis
  - thrombocytopenia
  - heart murmur

Results

- No diagnostic utility :
  - Temperature higher than 38.8˚C
  - Leukocytosis
  - Hematuria/pyuria
  - HIV positive

Table 2 Screening performance of individual ED clinical criteria for the prediction of endocarditis in injection drug users admitted with fever

Criterion	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	Diagnostic odds ratio (95% CI)
High fever (temperature >38.8°C)	35 (19-56)	69 (68-71)	10 (5-51)	92 (90-95)	1.21 (0.47-3.09)
History of endocarditis	40 (17-68)	74 (72-77)	12 (5-21)	93 (91-96)	1.93 (0.55-6.88)
HIV-positive	23 (8-49)	69 (67-71)	6 (2-13)	91 (90-94)	0.66 (0.19-2.34)
Tachycardia (heart rate ≥100 beats/min)	75 (54-89)	40 (38-41)	10 (8-12)	95 (90-98)	1.99 (0.72-5.44)
Heart murmur	44 (25-65)	68 (66-70)	12 (7-18)	93 (90-95)	1.68 (0.65-4.36)
Absence of skin infection	70 (49-85)	51 (49-52)	12 (8-14)	95 (91-97)	2.42 (0.92-6.32)
Leukocytosis (WBC count >11.7)	53 (32-72)	56 (54-57)	10 (6-13)	93 (90-96)	1.39 (0.56-3.47)
Thrombocytopenia (platelet count <150)	26 (12-47)	83 (81-85)	12 (6-22)	93 (91-95)	1.71 (0.60-4.87)
Hyponatremia (serum Na <136)	59 (37-78)	58 (56-59)	10 (6-13)	95 (92-97)	1.94 (0.73-5.11)
Pyuria/Hematuria (UA WBC or RBC >5)	30 (11-59)	61 (60-64)	6 (2-12)	91 (90-95)	0.68 (0.18-2.54)
Pneumonia on chest radiograph	35 (19-55)	77 (76-79)	13 (7-20)	93 (91-95)	1.84 (0.71-4.73)

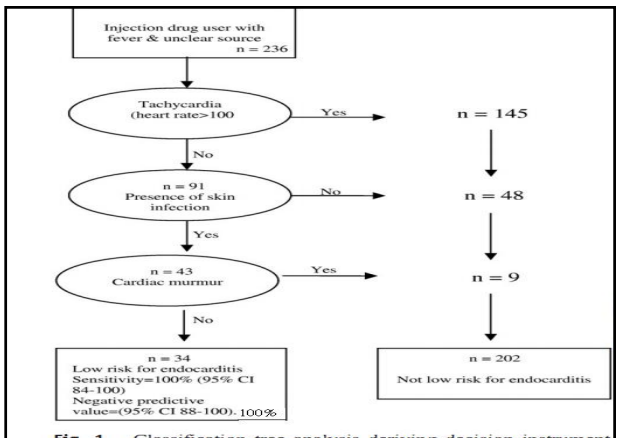

Fig. 1 Classification tree analysis deriving decision instrument for low risk of endocarditis in injection drug users with fever and

Discussion

- Partitioning generates the tree : High sensitivity and negative predictive value
- Allow for safe discharge of as many as 20% of patients.

Discussion

- An early diagnostic evaluation strategy :
  - Absence of skin infection
  - tachycardia
  - hyponatremia
  - pneumonia on CXR
  - history of endocarditis
  - thrombocytopenia
  - heart murmur

Discussion

- A low endocarditis risk ,Transthoracic echocardiography (TTE) :
  - Discharge of IDUs with fever.
- PCR analysis : detect bacteremia before growth of organisms from blood cultures, 86.7% sensitivity.

Limitations

- Most important limitation :
  - the retrospective design, limited the collection of data
- A prospective study that is currently underway will allow for larger sample size, more complete data collection, and external validation.

Limitations

- A reliable prediction instrument for endocarditis may not completely ensure safe discharge from the ED.
- An instrument may nevertheless help guide evaluation testing and strategy in all such patients — clinicians evaluating a patient deemed to have a very low risk for endocarditis may forego echocardiography

Conclusions

- The best ED-derived predictors of endocarditis in febrile IDUs:
  - Absence of skin infection,
  - Tachycardia,
  - Hyponatremia,
  - Pneumonia on CXR,
  - H/o endocarditis,
  - Thrombocytopenia
  - Heart murmur.

Conclusions

- Low percentage of IDUs admitted with fever and an unclear source are ultimately diagnosed with endocarditis.
- Overall subjective physician clinical evaluation was not found to accurately predict endocarditis.
- Single criterion is insufficiently sensitive to rule out endocarditis.

Thank yor for listening