MEXILETINE AS A STAND-ALONE ANTIARRHYTHMIC AGENT FOR ELECTRICAL STORM AND RECURRENT VENTRICULAR ARRHYTHMIAS

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ABSTRACT:

Objectives: In developing countries like India, patients with ventricular arrhythmias who were treated with antiarrhythmic drugs, in whom catheter ablation or implantable cardioverter-defibrillators (ICDs) were ineffective or contraindicated, are still obscured. Thus we aimed to evaluate the efficacy of mexiletine in patients with ventricular tachyarrhythmias/electrical storm, in whom standard treatment failed to prevent ventricular tachyarrhythmias.

Methods: We performed a prospective, unicentric, observational study in patients with ventricular tachyarrhythmias treated with mexiletine in our institute from January 2019 to March 2021. The study population included all patients presented with recurrent ventricular tachyarrhythmias, with or without ICD.

Results: Among the arrhythmic patients included in the study 20(80%) had monomorphic ventricual tachycardia (VT), 3(12%) had polymorphic VT and 2(8%) patients had ventricular fibrillation (VF). Patients were followed for 12 months, which showed only one patient had an episode of VT after initiating mexiletine **(p<0.001)**. Total number of shocks and ATPs were significantly reduced compared to prior initiation of mexiletine (**p<0.01 & p<0.001**, respectively). Patients treated with mexiletine and both (mexiletine+amiodarone), did not have significant difference when compared to their long term efficacy. Survival analysis showed that the patients treated with mexiletine had increased survival rate compared to patients who were treated with other antiarrhythmic drugs.

Conclusions: The study indicates that treatment with mexiletine may be effective and safe in patients with ICD and frequent ventricular arrhythmias and ICD shocks, regardless of the aetiology of heart disease.

Keywords: Mexiletine, Antiarrhythmic, Ventricular arrhythmia, Cardioverter-defibrillator, Amiodarone.

1. INTRODUCTION:

Ventricular fibrillation or symptomatic sustained ventricular tachycardia has a high risk of recurrence of arrhythmia, which is often fatal [1]. In 1996, the implantation of a defibrillator was reported to improve survival in patients with coronary heart disease, reduced ventricular function, unsustained ventricular tachycardia, and inducible ventricular tachycardia [2]. Cardioverter-defibrillator (ICD) is implanted in high-risk patients who have recurrent ventricular tachycardia/ventricular fibrillation (VT/VF) and risk of sudden cardiac death [3]. An increase in number of ICD implantation has resulted in increase in survival years for the patients. The underlying structural heart disease deteriorates over time and is susceptible to cardiac arrest due to recurrent ventricular tachycardia and ventricular fibrillation [4]. Electrical storm is defined as three or more episodes of VT/VF or device therapy (including ATP and Shock) during 24 hours period and is reported to occur in 10- 20% of patients with ICD [5,6]. Catheter ablation may not be readily available or ineffective due to comorbid features. Combination of anti-arrhythmic drugs is used in most cases [7,8].

Class Ib antiarrhythmics are widely prescribed to treat patients with VT/VF [9]. Amiodarone is the most commonly used drug but its side-effects and proarrhythmic effects make it ineffective in some patients and led to discontinuation [10]. Mexiletine, a class Ib drug preferentially inhibit the late component of the Na+ current (INa) and shorten the action potential duration and prolong the effective refractory period, thereby reducing the risk of arrhythmia, which could be an important therapeutic option in reducing the recurrence of electrical storms [11,12]. In this study we assessed the efficacy and tolerance of mexiletine in patients with recurrent ventricular tachyarrhythmias in whom other standard therapies had failed.

2. MATERIALS & METHODS:

Study design:

A prospective, unicentric, observational study, was conducted in patients presented with/without ICDs treated with mexiletine for recurrent ventricular arrhythmias (VT/VF) at PSG Hospitals, Coimbatore, Tamil Nadu. This study was approved by the Institutional Human Ethics Committee and was carried out according to the rules of the Declaration of Helsinki.

Study population:

The study population included all patients presented with recurrent VT/VF, with or without ICD, under the Department of Cardiology, PSG hospitals from 2019 to 2021.

Exclusion criteria:

- Patients with ventricular arrhythmias discharged against medical advice.

Patient selection:

Total 30 patients were enrolled in the study. Among the enrolled patients, who were ineligible for catheter ablation and patients who were started on mexiletine before Amiodarone were excluded (n=5). Remaining 25 patients were included in the study, which had recurrent VT/VF and electrical storm events. Electrical storm was defined as three or more episodes of ventricular arrhythmias including Anti-tachycardia pacing (ATP) and Shocks from ICDs over 24 hours period.

Drug intervention and follow up:

All patients received adequate Beta blockers, Antiplatelets therapy, ACE inhibitors/ARBs, Minerelocorticoid receptor antagonist according to underlying structural heart disease. The dose of amiodarone after loading dose was started with 200mg daily and increased up to 400mg daily upto maximum of 1600 daily. Oral Mexiletine was started after loading and maintenance dose of intravenous Lidocaine infusion which was given for 24 hours. Maintenance dose of Mexiletine was 200 mg (maximum dose of 1200mg/day) twice daily after adequate control of ventricular arrhythmias. Patients were followed up for 12 months, where heart rate, heart rhythm, QRS morphology, QTc interval, VT morphology and heart failure symptoms were recorded during every clinic visit. Amiodarone dose was reduced to 100 to 200 mg per day maintenance dose or stopped completely in patients who developed side effects due to amiodarone therapy.

Typical ICD settings for primary and secondary prevention due to VT/VF:

Detection criteria for slow VT was programmed 20 beats less than the slowest VT and for fast VT and VF detection zone was set at 181bpm and 220 bpm respectively. For slow VT zone more ATPs were programmed and for fast VT/VF zone more shocks with single ATP before maximum shock. ICD programming was changed according to electro physiologist discretion.

Statistical analysis:

Continuous variables were expressed as mean±standard deviation (SD) or median and Interquartile range. Categorical variables were presented as the percentage of total patients. Association between groups in categorical variables (before and after mexiletine treatment) was analyzed by paired t-test. Kaplan-Meier estimator is used to analyze the 12 months survival rate between two groups (Mexiletine vs other Anti-arrhythmic drugs). All statistical analysis was performed using IBM SPSS Statistics software (version 24.0; IBM Corp., USA).

3. RESULTS:

Patient characteristics:

A total of twenty five patients were included in the study, who presented with recurrent ventricular arrhythmia and electrical storm which included recurrent ICD therapies including shock and ATP therapies. In which most of the patients were male (84%), where their mean age was 68.7±14.1 years. Among the arrhythmic patients included in the study 20(80%) had monomorphic VT, 3(12%) had polymorphic VT and 2(8%) patients had VF. The most common co morbidities among the population were heart failure (68%) and smoking (56%). Patients other baseline characteristics are summarized in Table 1.

Adding mexiletine to the study population had no significant difference in QRS complex (p 0.704), QTc interval (p 0.941) and PR interval (p 0.174). Blood investigations like serum creatinine, SGPT and SGOT showed no significant change after adding mexiletine. But there was a significant dose reduction in usage of Amiodarone after starting mexiletine **(p<0.05)**. (Table: 2)

Specifications for VT/VF:

To classify the type and number of VT/VF events, the following rules were used:

1. **Monomorphic:** Single morphology.
2. **Polymorphic:** More than one morphology with varying cycle length.

Based on these specifications, before mexiletine 20(80%) patients had monomorphic VT, 2(12%) patients had polymorphic VT and 2(8%) patients had VF. (Table: 1)

Long term efficacy of Mexiletine:

Patients were followed for 12 months, which showed only one patient had an episode of VT after initiating mexiletine **(p<0.001)**. Total number of shocks and ATPs were significantly reduced compared to prior initiation of mexiletine (**p<0.01 & p<0.001**, respectively). (Table: 3)

Long term efficacy of Mexileine with Amiodarone:

Patients who were treated with both mexiletine and amiodarone (n=15) were followed for 12 months and their efficacy was compared. Among 15 patients, only 1(7%) patient had experienced VT **(p<0.001).** There was a significant reduction in total number of shocks and ATPs (among these patients (53% vs. 13%, **p<0.05** & 80% vs. 13%, **p<0.001**, respectively)

(Table:3). Patients treated with mexiletine and both (mexiletine+amiodarone), did not have significant difference when compared to their long term efficacy.

Kaplan-Meier analysis was used to project the survival of patients treated with mexiletine versus other antiarrhythmic drugs. This showed a significant number of patients treated with mexiletine had increased survival rate compared to patients who were treated with other antiarrhythmic drugs.

Table: 1 Baseline characteristics

Variables	tients (%) :25)
Age (years)	68.7±14.1
Gender (male)	21 (84)
Comorbidities	
Diabetic	3 (12)
Hypertension	2 (8)
Obese	1 (4)
Smoker	14 (56)
Heart failure	17 (68)
Ischemic Heart Disease	18 (72)
Non ischemic cardiomyopathy	
DCM	2 (8)
RCM	1 (4)
Type of Arrhythmias	
Monomorphic VT	20 (80)
Polymorphic VT	3 (12)
VF	2 (8)
NYHA functional class	
I	15 (60)
II	8 (32)
III	2 (8)
IV	0
Hospitalization for ACS	12 (48)
Hospitalization for ICD shocks	15 (60)
Baseline rhythm	
Sinus rhythm	10 (40)
AF	9 (36)
Pace rhythm	6 (24)
QRS morphology	
Narrow QRS	4
LBBB	12
RBBB	9
QRSd (ms)	151±1.7
QTc (ms)	450±2.3
PR interval (ms)	200±2
LV EF (%)	40±15
Other Antiarrhythmic drugs	
Amiodarone	15 (60)
Beta blocker	20 (80)
Sotalol	2 (8)
Lidocaine	5 (20)
Phenytoin	2 (8)

DCM: Dilated cardiomyopathy, RCM: Restrictive cardiomyopathy, VT: Ventricular tachycardia, VF: Ventricular Fibrillation, NYHA: New York Heart Association, ACS: Acute Coronary Syndrome, ICD: Implantable Cardioverter-defibrillator, AF: Atrial Fibrillation, LBBB: Left Bundle Branch Block, RBBB: Right Bundle Branch Block, LVEF: Left ventricular Ejection Fraction.

Table 2: Comparison of ECG, LFT, Renal function and Amiodarone dose before and after Mexiletine

bles	?	e
QRSd (ms)		.2
QTc (ms)	.3	
PR interval (ms)		
Serum creatinine (mg/dl)	75	62
SGPT	3.2	2.3
SGOT	22	7.6
Amiodarone dose (mg)	06.9	

SGPT: Serum Glutamic-Pyruvic Transaminase, SGOT: Serum Glutamic-Oxalacetic Transaminase

Table 3: Efficacy of Mexiletine with other Antiarrhythmic drugs, long term effects (12 months)

Long term effects in patients treated with Mexiletine (n=25)			Long term effects in all patients treated with Mexiletine+Amiodarone(n=15)		
Events	Before Mexiletine	After Mexilet	p value	Before Mex+Amio	After Mex+Amio	p value
VT/VF episodes	25 (100)	1 (4)	**0.000**	15 (100)	1 (7)	**0.000**
Total shocks	10 (40)	0	**0.003**	8 (53)	2 (13)	**0.011**
Total ATP	25 (100)	2 (8)	**0.000**	12 (80)	2 (13)	**0.000**
Electrical storms	2 (8)	0	0.161	1 (7)	0	0.327

VT/VF: Ventricular tachycardia/ Ventricular fibrillation, ATP: Anti-tachycardia pacing.
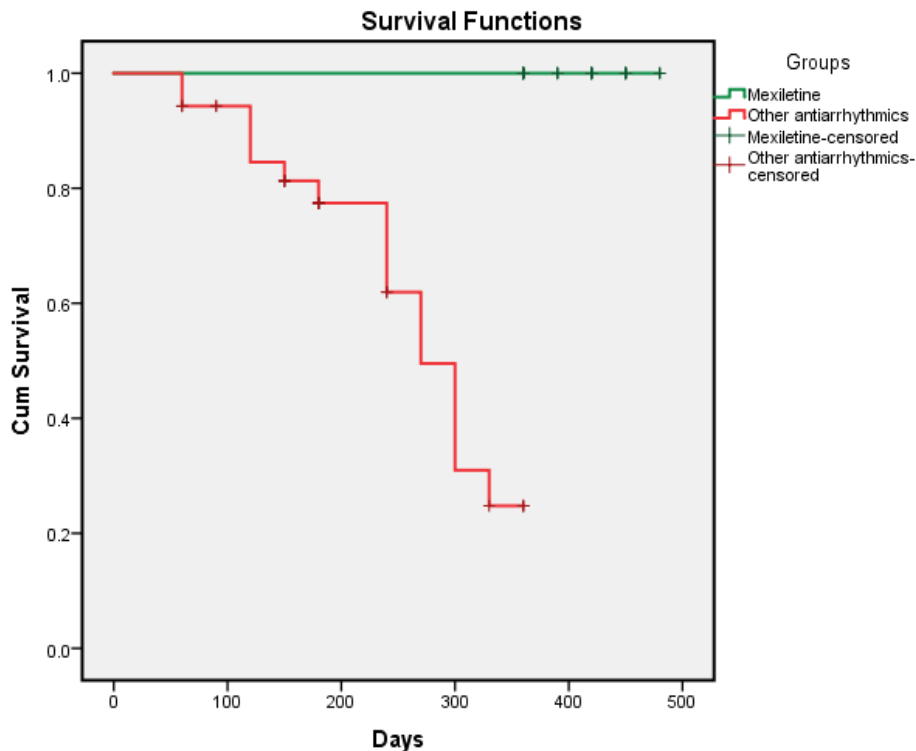

Fig 1: Survival analysis: Patients treated with Mexiletine vs other Antiarrhythmic drugs (Kaplan-Meier analysis)

4. DISCUSSION:

Recurrent episodes of ventricular arrhythmias are clinically important and difficult to treat. Evidence for antiarrhythmic drugs use in patients with an ICD who develop frequent venricular arrhythmias or electrical storms is very limited. Intravenous

followed by oral amiodarone together with beta‑blocker therapy has been shown to be successful as a short‑term management of electrical storm and possibly results in long‑term outcomes similar to those in patients not experiencing ventricular arrhythmias episodes [13-15].

Our study is a prospective, unicentric, observational study to evaluate the efficacy of mexiletine in the reduction of ICD shocks in patients suffering from electrical storm. Most of the previous studies on the efficacy of antiarrhythmic drugs in patients with an ICD mainly focused on patients who have not yet had therapy from their ICD or just had a few VT/VF events while being treated with an ICD [7].

In the total cohort of 25 patients, adding mexiletine to amiodarone or to other antiarrhythmic drugs was effective in reducing the number of VT/VF episodes and ATPs. This was similar to a study which showed mexiletine to be effective as an adjutant therapy to amiodarone in reducing the total and appropriate ICD shocks and ES episodes [13].

In our study, we present long-term efficacy of mexiletine treatment in a patients with recurrent polymorphic VT and VF with frequent ICD shocks (including VT storm). Our study is concordant with previous studies showing that treatment with mexiletine is safe and sufficiently tolerated [8]. The percentage of patients with mexiletine intolerance was low.

5. CONCLUSIONS:

The study indicates that treatment with mexiletine may be effective and safe in patients with ICD and frequent ventricular arrhythmias and ICD shocks, regardless of the aetiology of heart disease. Mexiletine is a sufficiently tolerated antiarrhythmic drug in short-term treatment of ventricular tachyarrhythmias in the studied population. Unfortunately, in developing countries like India, mexiletine is not readily available on the market. In India, the necessity of drug import with time-consuming formal procedures limits its use.

6. DISCLOSURE OF FUNDING: Nil
7. DISCLOSURE OF ANY CONFLICT OF INTEREST: Nil
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