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Original Article

Ibutilide with magnesium for conversion of atrial fibrillation or flutter in rheumatic heart disease patients
Ibutilide with magnesium for chemical cardioversion of atrial fibrillation or flutter

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ABSTRACT

Background: Data on adjunctive use of magnesium with ibutilide for conversion of persistent rheumatic atrial fibrillation and flutter to sinus rhythm is lacking.
Aim: We aimed to study the efficacy of adjunctive supplementation of intravenous magnesium with ibutilide for conversion of persistent rheumatic atrial fibrillation and flutter to sinus rhythm and to define a definite level of serum magnesium which leads to significant increase in rates of such conversion.
Methods and results: This was a prospective study including 33 Rheumatic heart disease patients (13 males and 20 females) with mean age of 49.27 ± 11.4 years and persistent AF or AFl. All patients received intravenous magnesium to raise serum magnesium level in range of 4 mg/dl to 4.5 mg/dl prior to administration of Ibutilide. 25 out of 33 (76%) patients converted to sinus rhythm. Upon univariate analysis, presence of background beta blocker therapy, serum potassium and magnesium at time of Ibutilide injection were found to have significant relation with conversion to sinus rhythm. Upon multivariate analysis serum magnesium level at the time of Ibutilide injection was found to have significant contribution on post injection rhythm reversal (p-value = 0.006).
The level of magnesium at 3.8 mg/dl was found to have maximum sensitivity of 96% and specificity of 62.5% for conversion to sinus rhythm by ibutilide with magnesium (p-value< 0.05).
Conclusions: Ibutilide is highly effective in cardioversion of persistent rheumatic atrial fibrillation/flutter patients. Raising Serum Magnesium levels above 3.8 mg/dl significantly improves efficacy of ibutilide.

1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia associated with an approximately five-fold increase in the risk for stroke and a twofold increase in the risk for all-cause mortality.[1,2] AF is a frequent complication in rheumatic heart disease involving relatively younger population (often in Mitral stenosis patients) and is related to escalation in morbidity and mortality. Patients with mitral valve disease and AF have lower functional capacity, have more severe left ventricular dysfunction and exhibit greater left atrial enlargement as compared to those in sinus rhythm.[3] AF in valvular heart disease almost always progress to chronic AF and more often results in AF related complications.[4] It is

Abbreviations: AF, Atrial fibrillation; AFl, Atrial flutter; AUC, Area under the curve; AR, Aortic regurgitation; AV, Atrio-ventricular; BMV, Balloon mitral valvotomy; DC, Direct-current; ECG, Electrocardiogram; HR, Heart rate; ICU, Intensive care unit; I.V., Intra-venous; LA, Left atrium; Mg^{++}, Magnesium; MG, Mean gradient; MVA, Mitral valve area; MR, Mitral regurgitation; MS, Mitral stenosis; MVD, Mitral valve disease; NYHA, New York heart association; PIRR, Post injection rhythm reversal; QTc, Corrected QT interval; RHD, Rheumatic heart disease; ROC, Receiver operating characteristic; SPSS, Statistical product and service solutions; TDS, Ter die sumendus (three times per day); VT, Ventricular tachycardia.

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typically more difficult to restore sinus rhythm in these patients because of pressure overload of the left atrium.

Ibutilide, an intravenous class III antiarrhythmic agent, which is an IKr-channel blocker and slow inward sodium-channel (INas) enhancer, can convert approximately 45% of patients with atrial fibrillation and 75% with atrial flutter to sinus rhythm but can also induce sustained and non-sustained polymorphic ventricular tachycardia in 1.7% and 2.7–6.7% of patients, respectively.[5,6] Adjunctive use of magnesium seems to enhance the efficacy of ibutilide on conversion rates as well as to prevent TdP associated with ibutilide.[7–10]

Studies relating to ibutilide have either not tested its efficacy in rheumatic atrial flutter/fibrillation of or not commented upon the composition of valvular AF among study subjects.[6,8,11,12] To best of our knowledge ibutilide has not been tried in persistent rheumatic AF especially with magnesium supplementation.

The clinical advantage of maintaining patients in sinus rhythm following corrective procedures for mitral valvular disease has been demonstrated in a few studies.[13–16] We aimed to study the efficacy of adjunctive supplementation of intravenous magnesium with ibutilide for conversion of persistent rheumatic atrial fibrillation and flutter to sinus rhythm and to define a definite level of serum magnesium which leads to significant increase in rates of such conversion.

2. Methods

Patients: 33 patients satisfying the inclusion and exclusion criteria and having given an informed consent to participate in the study were selected for the study. The study was duly approved by institute ethical committee.

2.1. Inclusion criteria

- Rheumatic valvular heart disease
- Persistent (defined as sustained palpitations or documented arrhythmia by 12 lead ECG, for more than 7 days) atrial fibrillation or flutter
- QTc intervals $\leq$440 ms
- Stable hemodynamics
- Serum magnesium and potassium levels within the normal range

2.2. Exclusion criteria

- Paroxysmal atrial fibrillation
- History of myocardial infarction within the previous 30 days
- Polymorphic ventricular tachycardia
- Hyperpyrexia, Thyrotoxicosis
- Symptoms of congestive heart failure
- Bradycardia
- Known ibutilide hypersensitivity

2.3. Protocol

The primary end point in this study was rate of conversion of atrial fibrillation and atrial flutter (AFl) to normal sinus rhythm. All patients underwent initial clinical assessment that included taking a clinical history, complete physical examination, 12-lead electrocardiogram (ECG), pulse-oximetry, standard blood biochemistry measurements, echocardiography, and chest radiography. All patients were given oral anticoagulation for 21 days prior to attempting cardioversion with ibutilide and underwent transesophageal echocardiography before ibutilide administration.

All patients received intravenous magnesium with an objective to raise serum magnesium level in range of 4 mg/dl to 4.5 mg/dl. Intravenous magnesium was given in dose of 2 g i.v. thrice daily for 3 days to attain desired serum levels. A bolus dose of magnesium (4 mg) was given 2 h before ibutilide injection (Fig. 1). Our goal was to maintain high serum magnesium concentration before injecting ibutilide to assess the additional cardioversion efficacy of magnesium in patients receiving ibutilide.

Ibutilide was given as an intravenous infusion of 1 mg over a 10-min period. A second 1-mg dose was given after the first dose if the arrhythmia persisted. Patients were continuously monitored throughout the dosing period and for 6–8 h thereafter in ICU setup.

2.4. Follow-up

Patients were monitored for following 24–48 h, but no long-term follow-up was conducted.

2.5. Statistical analysis

The data was collected using a structured questionnaire. Data entry and analysis was done on SPSS version 22.0. Categorical variables were expressed as proportion and percentages. Quantitative variables were expressed in mean ± standard deviation and median (interquartile range). Univariate analysis in form of Chi-square test for categorical variable and *T* test for quantitative variables was done to explore the association of factors with rhythm conversion. To compare median across the groups, Mann-Whitny *U* test was conducted. Statistical significance was defined at a *p* value of less than 0.05. Binary logistic regression using Forward Conditional method was applied by including factors from univariate analysis (with *p*-value <0.20). Independent factors like serum magnesium level at time of Ibutilide injection, serum potassium level at the time of injection, beta blocker usage, and left atrial size were included in the model. ROC curve was plotted using SPSS version 22.0 between serum magnesium level at time of admission, serum magnesium level at time of ibutilide injection and conversion of arrhythmia. The area under curve and cut-off point of magnesium at maximum sensitivity and specificity was determined.

3. Results

3.1. Baseline characteristics

33 patients (13 males, 20 females) were enrolled in the study with mean age 49.27 ± 11.40 years [mean age (male) 45.77 ± 9.83 years, mean age (female) 51.55 ± 11.99 years]. Mean Body mass index of the study participants was 23.16 ± 1.92 kg/m^2. Out of 33 patients 25 patients were having rheumatic MS, 6 patients with rheumatic MR and 2 patients with rheumatic AR + MR. Among 25 Mitral stenosis patients 19 were suffering from progressive MS (mean MVA = 1.86 cm^2) and 6 from severe MS (mean MVA = 1.23 cm^2). Seven patients were post-BMV status (Table 1).

3.2. Conversion to sinus rhythm

A total of 25 out of 33(76%) patients converted to sinus rhythm after ibutilide injection supplemented with intravenous magnesium as described above. On the basis of conversion to sinus rhythm, the patients were further divided into two groups, Group A which converted to sinus rhythm and Group B which failed to convert. Univariate analysis was undertaken to ascertain

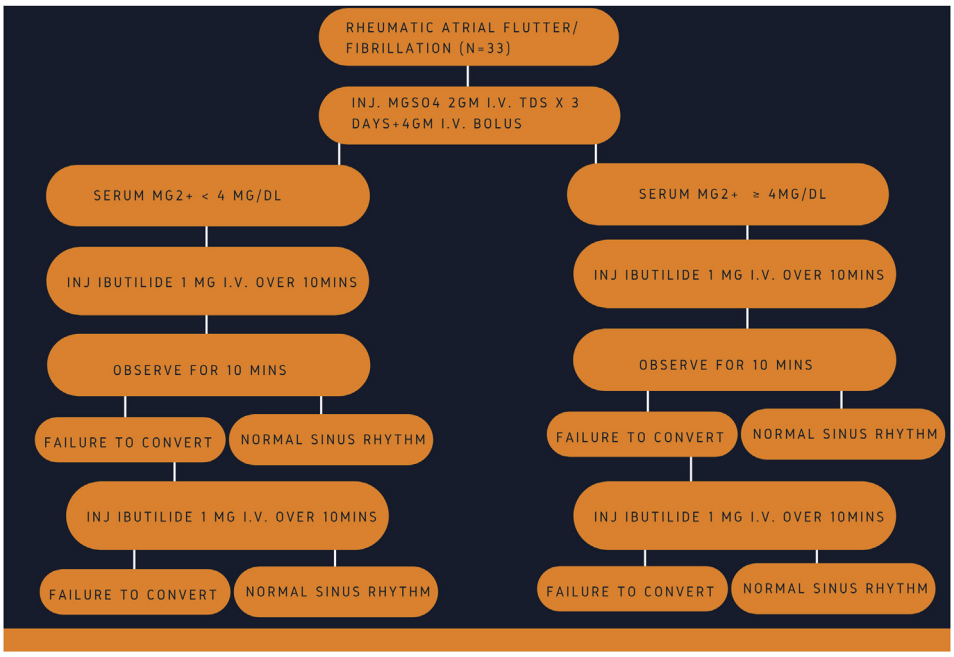

Fig. 1. Administration of Ibutilide and magnesium.

associative factors. Presence of background beta blocker therapy, high serum potassium at time of Ibutilide injection and high serum magnesium at time of Ibutilide injection were found to have statistically significant relation with the sinus rhythm conversion in patients (Table 2).

Patients with serum Mg level of >3.8 mg/dl had statistically significant higher rate of conversion to sinus rhythm as compared to those with serum Mg level of <3.8 mg/dl (88.89% vs 16.67%). None of patients with AF, who did not achieve serum Mg above 3.8 mg/dl, converted to sinus rhythm while 50% of patients of AFl who had low serum Mg converted to sinus rhythm with ibutilide injection. In the group of patients who had achieved high serum magnesium levels,the rates to conversion to sinus rhythm for AF and AFl patients were 86.36% and 100% respectively.

Table 1
Baseline Clinical characteristics.

Demographic features	
Age (years)	49.27 ± 11.40
Age (Male)	45.77 ± 9.83
Age (Female)	51.55 ± 11.99
Gender	
Male, n (%)	13 (40)
Female, n (%)	20 (60)
Body Mass Index (kg/m^2)	23.16 ± 1.92
Hypertension, n (%)	2(6)
Antiarrhythmic pre-treatment	
Amiodarone, n (%)	1(3)
Average daily dose (mg)	200
Concurrent therapy for ventricular rate control	
Beta-blocker [Metoprolol, n (%)]	27(82)
Average daily dose (mg)	35
Calcium-channel blocker [Diltiazem, n (%)]	14 (42)
Average daily dose (mg)	99
Echocardiographic parameters	
Size of left atrium (mm)	45.69 ± 6.23
Left ventricular ejection fraction (%)	61 ± 1.79
RHD.MS n (%)	25(76)
Progressive MS (MVA > 1.5 CM^2)	19
Severe MS (MVA ≤1.5 CM^2)	6
RHD.MR n (%)	6(18)
Severe MR	4
Moderate MR	2
Multivalvular RHD n (%)	2(6)
Post-BMV	7 (21)
Biochemistry	
Baseline Serum Potassium (mmol/l)	4.15 ± 0.48
Serum Potassium at time of Ibutilide inj (mmol/l)	4.33 ± 0.37
Baseline Serum Magnesium (mg/dl)	2.11 ± 0.36
Serum Magnesium at time of Ibutilide inj (mg/dl)	4.40 ± 0.79
Electrocardiography	
Resting Heart Rate (per minute)	101.94 ± 19.48
QTc interval, milliseconds (range 385–500)	429.24 ± 18.19

Values in Mean ± Standard deviation, RHD = Rheumatic Heart Disease, MS = Mitral Stenosis, MR = Mitral Regurgitation, MVA = Mitral Valve Regurgitation, BMV = Balloon Mitral Valvotomy, QTc: Corrected QT interval.

3.3. Effect of magnesium on post injection rhythm reversal (PIRR)

Two models were generated in forward conditional binary regression, the second model included both serum magnesium and potassium levels at the time of Ibutilide injection. The model prediction was found to be 87.9%, Nagelkarke R square came out to be 0.60 explaining 60% of variability in PIRR by these predictors. The adjusted Odd's ratio (C.I.) was found to be 0.014 (0.001–0.30) for serum magnesium level at time of injection and 68.5 (0.86–5409.1) for serum potassium level at the time of injection. Serum magnesium level at the time of Ibutilide injection was found to have significant contribution on PIRR (p-value = 0.006).

The AUC (area under curve) was found out to be 0.73 with statistical significance (p-value = 0.047) for serum magnesium level at the time of ibutilide injection in the ROC curve. The level of magnesium at 3.8 mg/dl was found to have maximum sensitivity of 96% and specificity of 62.5%. Thus, it was determined that administration of Ibutilide when serum magnesium is above 3.8 mg/dl has highest rates of conversion to sinus rhythm (Fig. 2). However, the serum level of magnesium at the time of admission had no significant relationship with conversion to sinus rhythm.

3.4. Adverse effects

4 patients (12%) suffered from sustained VT and 2 patients (6%) suffered non-sustained VT, these episodes had no significant relationship with rhythm reversal. One patient suffered from first

Table 2
Univariate analysis for post-injection rhythm reversal.

Factor	Group A Converted to Sinus rhythm (n = 25)	Group B Failed to convert (n = 8)	*p*-value
Demographic features			
Age (Male)	46.56 ± 8.37	44 ± 13.93	0.68
Age (Female)	52.06 ± 11.58	49.5 ± 15.29	0.71
Male, n (%)	9 (36)	4 (50)	0.48
Female, n (%)	16 (64)	4 (50)	
Body Mass Index (kg/m^2)	23.12 ± 2.11	23.27 ± 1.25	0.85
Antiarrhythmic pre-treatment			
Amiodarone, n (%)	1 (4)	0	NA
Average daily dose (mg)	200	NA	
Concurrent therapy for ventricular rate control			
Beta-blocker [Metoprolol, n (%)]	19 (76)	8 (100)	0.19**
Average daily dose (mg)	38.16	28.13	
Calcium-channel blocker [Diltiazem, n (%)]	11 (44)	3 (37.5)	0.37
Average daily dose (mg)	100.91	90	
Echocardiographic parameters			
Size of left atrium (mm)	44.72 ± 5.53	48.75 ± 7.65	0.11
Mitral Valve area*	1.78 ± 0.33	1.48 ± 0.32	0.08
Mean Gradient*	4.79 ± 1.68	6.15 ± 2.77	0.16
Biochemistry			
Baseline Serum Magnesium (mg/dl)	2.12 ± 0.35	2.08 ± 0.40	0.76
	2.12(1.9–2.1)	2.05(1.9–2.27)	0.75
Serum Magnesium at time of Ibutilide inj (mg/dl)	4.56 ± 0.76	3.94 ± 0.73	0.05
	4.50(4.25–4.9)	3.70(3.5–4.7)	0.04
Serum Potassium at time of Ibutilide inj (mmol/l)	4.4 ± 0.34	4.1 ± 0.38	0.04
	4.30(4.2–4.6)	4.20(3.7–4.37)	0.067
Electrocardiography			
QTc interval, milliseconds (range 385–500)	428.64 ± 18.29	431.13 ± 18.98	0.74
Dose of Ibutilide			
1 mg (n)	6 (24)	0	0.12
2 mg (n)	19 (76)	8 (100)	
Polymorphic VT (n)	4 (16)	2 (25)	0.56

Values in Mean ± Standard deviation, QTc: Corrected QT interval, * in mitral stenosis patients only, **Fisher exact test.

degree AV block during administration of ibutilide which subsequently improved. Although these events were numerically more in group of patients with high serum magnesium but it was not statistically significant. Interestingly five out of these six patients received a total 2 mg of intravenous dosing. All sustained episodes were easily reverted with 50 J biphasic shock and 4 patients (66%) out of them converted to sinus rhythm.

4. Discussion

In this study we evaluated the efficacy of Ibutilide along with magnesium in rheumatic heart disease patients with persistent AF/AFl for achieving sinus rhythm and to find a definite level of serum magnesium at which this effect is maximum. We had chosen this subset of patients with AF/AFl because not only these are frequent complications in rheumatic heart disease patients, but also the conversion/maintenance of sinus rhythm is also difficult due to structural abnormalities and presence of unhealthy substrate. The benefit of restoring sinus rhythm are not clear in rheumatic heart disease patients who are haemodynamically stable and those who do not require valvular surgery. However, studies have shown benefit in terms of functional class, quality of life and exercise capacity on achievement of sinus rhythm in valvular AF.[4]

For persistent AF, cardioversion success rates in the range of 60% have been reported with flecainide, propafenone and amiodarone.[17,18] Newer class III agents such as intravenous ibutilide and intravenous or oral dofetilide are most effective in atrial flutter and fibrillation of recent onset but have not been tested in persistent rheumatic AF.

CRAAFT trial was a prospective study of 144 RHD patients, comparing rate control (using Diltiazem) Vs rhythm control (Amiodarone versus placebo) in AF. This trial besides demonstrating a mortality benefit with rhythm control also showed an improvement in NYHA class, quality of life and exercise capacity on achievement of sinus rhythm. In this trial conversion rates were 38/43 (88.4%) with amiodarone (along with DC cardioversion), however cardioversion only with amiodarone was in 9 (20.9%) patients.[19] As compared to CRAAFT our cardioversion rates were 88.89% with pharmacotherapy (without cardioversion) only when serum magnesium levels were raised above 3.8 mg/dl.

In a study by M K Das et al conversion rates by Ibutilide in AF of recent onset (24 h) was only 30% (9/30 patients) in the presence of an enlarged left atrium (LA $\geq$ 5 cm) and 37.7% (23/61 patients) in the presence of mitral valve disease (MVD), whereas the conversion rates were 82.5% (33/40 patients) in the absence of MVD and 85% (29/34 patients) in the absence of both enlarged LA and MVD ($p = < 0.001$),[20] however we could achieve almost similar rates of conversion (88.89%) to sinus rhythm with MVD using ibutilide and serum magnesium above 3.8 mg %.Most studies on Ibutilide on AF in the past have either not included the valvular heart disease patients or have not mentioned about the composition of valvular heart disease patients.[6,8,11,12,21]

While some of the previous studies on non-valvular AF of more than 30 days duration have demonstrated a success rate of around 45%,[6,21] in our study 6 out of 7 (86%) patients with AFl and 19 out of 26 (73%) patients of AF converted to sinus rhythm with intravenous Ibutilide, the better results are supposedly due to magnesium supplementation in our study group. Role of magnesium in increasing the efficacy of ibutilide has been established in previous studies.[8–10,12,22] However, information on a definite level of serum magnesium, which results in significant increase in efficacy of ibutilide to convert AF to sinus rhythm is scant.

None of the previous studies have defined a definite level of serum magnesium above which conversion rates significantly

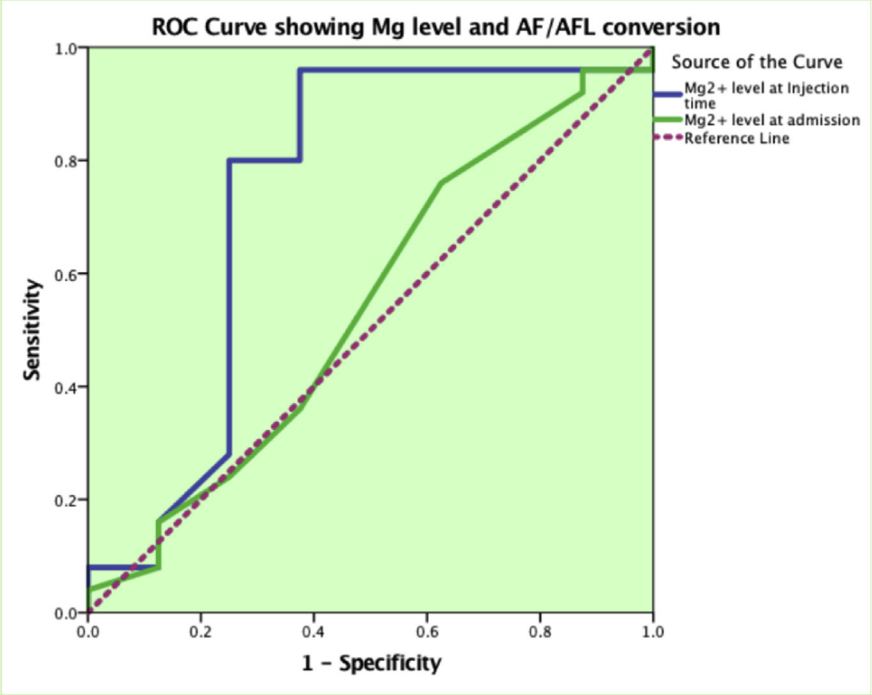

Fig. 2. ROC Curve showing Mg^{++} level and AF/AFl conversion.

increased specially in rheumatic heart disease patients. We tried to define a definite serum level of magnesium which may be helpful in achieving maximum conversion rate. We found that the serum level of magnesium at 3.8 mg/dl was having maximum sensitivity of 96% and specificity of 62.5%. Thus, it was determined that administration of Ibutilide when serum magnesium is above 3.8 m mg/dl has highest rates of conversion to sinus rhythm. All of the patients with AFl who achieved magnesium level above 3.8 mg/dl and 86.3% patients of atrial fibrillation who achieved magnesium level above 3.8 mg/dl were converted to sinus rhythm.

The risk of torsade's de pointes with ibutilide was approximately 7–8% in study by O Viktorsdottir et al[11] In our study 12% patients had sustained VT and 6% had non-sustained VT. Although these events were numerically more in group of patients with high serum magnesium but it was not statistically significant.

We recruited relatively young patients of RHD with persistent AF/AFl and found very encouraging results in terms of high rate of conversion to sinus rhythm with ibutilide administration, especially when serum magnesium levels are above 3.8 mg/dl. Interestingly all patients with atrial flutter whose serum magnesium was more than 3.8 mg/dl converted to sinus rhythm. Upon multivariate analysis serum magnesium at the time of ibutilide administration was only significant factor predicting PIRR.

4.1. Limitations

This study is limited by the fact that number of patients was less and there was no control arm. No follow-up study was conducted to assess maintenance of sinus rhythm. We did not assess the reasons as to why despite the same protocol of Magnesium administration, the levels achieved at the time of cardioversion were highly variable among the patients.

5. Conclusions

Ibutilide is effective in cardioversion of rheumatic heart disease patient. Raising serum magnesium above 3.8 mg/dl by intravenous supplementation before administration of ibutilide is very effective in chemical cardioversion of rheumatic AF/AFl and this combination can be used in rheumatic heart disease patient for cardioversion in ICU setup efficiently.

Declaration of competing interest

All authors have nothing to declare.

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