ORIGINAL ARTICLE

Clinical Efficacy and Safety of Ibutilide in Cardioversion of Atrial Fibrillation or Flutter in Indian Patients: A Multicenter Study

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Abstract

Aim and background: To assess the efficacy and safety of Ibutilide infusion for cardioversion of atrial fibrillation (AF) or flutter (AFL) to sinus rhythm.

Materials and methods: This open-label, multicenter phase IV study was conducted at six sites across India. The study enrolled 120 patients (108 with AF, 12 with AFL), each receiving up to two, 10-minute intravenous doses of 1.0 mg Ibutilide. The primary endpoints were the proportion of patients achieving cardioversion and the mean time taken to achieve cardioversion. Secondary endpoints included the proportion of patients maintaining sinus rhythm at 24 hours and the incidence of adverse events.

Results: The cardioversion rate at 4 hours post-Ibutilide infusion among 120 patients was 65.83% ($n = 79$), with an average conversion time of 35.12 ± 36.71 minutes. At 24 hours, 85 patients (70.8%) had successful cardioversion, with a mean time of 107.24 minutes. The majority of patients (71.76%) had achieved cardioversion within 30 minutes. Of the 85 patients who achieved successful conversion, 82 (68.3%) maintained sinus rhythm at 24 hours. A total of 66 patients (55%) achieved cardioversion with the first bolus whereas 19 (15.8%) needed a second bolus. Atrial fibrillation patients had a higher conversion rate (75%) compared to AFL patients (33%). A total of 10 adverse events were recorded in eight patients (6.67%), including nausea, headache, palpitations, and bradycardia. Three severe cardiac events, one case of ventricular tachycardia, and two of tachycardia necessitated discontinuation of Ibutilide. No fatalities or serious adverse events (SAE) were reported.

Conclusion: Ibutilide was found to be effective and well-tolerated for rapid restoration of sinus rhythm in patients with AF or AFL.

Clinical Trial Registry of India: CTRI/2018/01/011248.

Keywords: Atrial fibrillation, Atrial flutter, Cardioversion, Ibutilide.

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Highlights

Ibutilide infusion was effective and well-tolerated for cardioversion of atrial fibrillation (AF) or flutter (AFL), achieving a 65.83% conversion rate at 4 hours and 70.8% at 24 hours. Adverse events were minimal, with no fatalities or serious adverse events (SAE) reported.

Introduction

In clinical practice, AF and AFL are among the most commonly diagnosed cardiac arrhythmias, often resulting in severe complications such as stroke and cardiac dysfunction. These conditions lead to greater healthcare expenditures and higher mortality rates. Recent global epidemiological data have reaffirmed that AF is a worldwide epidemic with substantial long-term health implications.[1] Studies conducted in India have shown significant variations in the prevalence of AF, ranging from 0.1 to 1.6%.[2] The geriatric population is particularly vulnerable, as these conditions are often referred to as the "diseases of the elderly."[3]

The elevated heart rate and irregular rhythm caused by uncoordinated atrial activation in AF can lead to severe hemodynamic distress.[4] Cardioversion is commonly performed to alleviate symptoms and prevent adverse effects in patients with compromised cardiovascular function. Timely conversion helps to avoid electrical remodeling and minimizes the chances of embolic events from intra-atrial thrombi. Current pharmacologic agents for conversion have variable efficacy and safety concerns. Therefore, an effective, rapidly acting, and safe pharmacologic alternative would be highly beneficial for both patients and healthcare providers.[5]

Ibutilide, the first 'pure' antiarrhythmic agent, received USFDA approval in 1995 and was subsequently authorized in India in June 2016 for the management of AF or AFL.[6] *In vivo*, Ibutilide injection enhances both atrial and ventricular refractoriness and prolongs the length of the action potential in isolated adult cardiac myocytes—class III electrophysiologic effects.

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Research shows that Ibutilide extends the repolarization phase by promoting a gradual inward flow of sodium ions. This mechanism contrasts with most class III antiarrhythmics, which typically work by blocking outward potassium currents.

This results in a prolonged duration of atrial and ventricular action potentials and refractoriness. These properties are thought to play a crucial role in its antiarrhythmic effect.[7]

Ibutilide has demonstrated superior efficacy compared to other antiarrhythmic agents in managing acute-onset AF and AFL, achieving a success rate of 75–80%. It is both safe and effective for managing AF in patients following cardiac surgery. Additionally, Ibutilide is highly effective in treating accessory pathway-mediated AF, achieving a conversion rate of up to 95%. Pretreatment with Ibutilide can enhance the effectiveness of transthoracic defibrillation and reduce the energy required for electrical cardioversion, whether using monophasic or biphasic shocks. When Ibutilide is used as pretreatment before electrical defibrillation, the conversion rate reaches 100%, compared to a 72% conversion rate without pretreatment.[8–10]

Due to limited awareness of Ibutilide's efficacy and safety profile among physicians and the scarcity of Indian studies validating its use, this research aimed to examine the clinical outcome and risk profile of Ibutilide in Indian patients.

Materials and Methods

Design and Settings

An open-label, multicenter, and prospective phase-IV study was conducted in Indian patients with AF/AFL. After receiving the approval from Drug Controller General of India (DCGI), the study was conducted on 120 patients at six geographically diverse sites across India between March 2018 and October 2021. The study received approval from the institutional Ethics Committee (IEC) at each respective site. The study adhered to Schedule Y and the New Drugs and Clinical Trials Rules, 2019. It also followed the Ethical Guidelines of Indian Council of Medical Research (ICMR) 2017, the International Council for Harmonization (ICH) E6 (R2) Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki (Brazil 2013), and other applicable guidelines. The study was prospectively registered (CTRI/2018/01/011248) in the Clinical Trial Registry of India.

Study Population

The study inclusion criteria were: Patients with 18 years and above with sustained AF or AFL lasting between 1 hour to 90 days or patients developing AF or AFL since 1–7 days post-cardiac surgery included. Patients with QTc 440 ms or less on a 12-lead electrocardiogram (ECG), hemodynamic stability (systolic blood pressure between 90- and 105-mm Hg, and diastolic blood pressure ≥60 mmHg), no structural heart disease, and a ventricular rate >60 bpm were enrolled. Informed consent from each participant was obtained before their inclusion in the study.

Participants were excluded from the study if they had: Hypersensitivity to Ibutilide injection or its components, including sulphonamides or sulfa drugs; sinoatrial node disorder, advanced AV blocks or torsades de pointes (TdP); documented atrial clot formation; severe anemia (Hb < 8.0 gm/dL); grade III or IV congestive heart failure; Serum potassium levels <3.5 mEq/L or serum magnesium levels <1.5 mEq/L; severe liver, blood, endocrine, kidney, gastrointestinal, neurological, psychiatric, or any disorders that may affect the study. The study did not include any women who were nursing or pregnant.

Clinical Assessment

An initial clinical evaluation was conducted for all patients, which included obtaining a patient history, comprehensive physical assessment, 12-lead cardiac monitoring (ECG), pulse-oximetry, routine blood chemistry tests, echocardiography, and chest X-ray. Patient demographics were recorded and continuous ECG monitoring was performed. Before administering Ibutilide, intravenous repletion of serum potassium and magnesium levels was carried out if the values were found to be below normal.

Interventions

A total of 120 enrolled patients received two Ibutilide infusions, each lasting 10 minutes, with a 10-minute interval between the two administrations. Patients weighing 60 kg or more received one vial of 1 mg/10 mL infusion. Patients weighing less than 60 kg received 0.1 mL/kg (0.01 mg/kg of Ibutilide) per infusion. If the arrhythmia did not resolve within 10 minutes after the initial infusion, a second 10-minute infusion of the same dosage was given after the first infusion was completed.

Ibutilide injection was diluted in 50 mL of 0.9% sodium chloride before infusion. One 10 mL vial (containing 0.1 mg/mL Ibutilide) was added to a 50 mL infusion bottle, resulting in a final concentration of approximately 0.017 mg/mL Ibutilide.

In patients who had cardiac surgery, one or two infusions of 0.5 mg (or 0.005 mg/kg for those weighing <60 kg) were given to terminate the arrhythmia.

The Ibutilide infusion was promptly discontinued either upon the termination of arrhythmia or if there was ventricular tachycardia or significant QTc prolongation. Patients were monitored for at least 4 hours after infusion, or as long as the QTc interval had reverted to its original levels before treatment. If AF or AFL persisted for >48 hours, anticoagulation therapy with IV heparin (according to an accelerated protocol) was initiated before attempting cardioversion, or patients were given adequate oral anticoagulant therapy for at least 2 weeks before receiving Ibutilide (to achieve an INR between 2 and 3).

Outcome Measures

The primary endpoint was to investigate the proportion of AF and AFL patients achieving cardioversion after intravenous administration of Ibutilide injection and the Time required to achieve cardioversion. Restoration of normal sinus rhythm was confirmed by 12 lead ECG and patients were monitored for 4 hours after Ibutilide administration. If there was no conversion after the second dose of Ibutilide injection, direct current (DC) cardioversion could be attempted at the investigator's discretion if necessary.

The secondary endpoint evaluated the number of patients who remained in sinus rhythm at 24 hours after receiving Ibutilide infusion and adverse events observed during the study period.

Follow-up

Participants remained under observation for up to 24 hours post-drug administration, but no extended follow-up was undertaken.

Statistical Analysis

Qualitative data was represented in the form of frequency and percentage while quantitative data was represented using mean ± SD. Patients achieving cardioversion (sinus rhythm) after intravenous administration of Ibutilide fumarate injection were to be recorded as number and percentage while the mean

time to achieve cardioversion (sinus rhythm) was presented as mean ± standard deviation.

Safety was analyzed based on the number of adverse events observed and the total number of subjects reporting adverse effects. Adverse event reported by the subject was measured in terms of the percentage of subjects reporting side effects. All subjects who experienced any complication of therapy were described and analyzed to ascertain relationships, if any, to the trial center and trial medication.

Results

Baseline Characteristics

In this trial, 120 patients (66 males and 54 females) with a mean age (±SD) of 53.8 (±15) years and presented with recent onset AF or AFL were enrolled. All enrolled patients completed the study and were considered in the final assessment (Fig. 1). Table 1 outlines the demographic profile and baseline characteristics of all 120 enrolled patients. Table 2 indicates the patient's medical history. The majority of patients (*n* = 108) presented with AF, while the remaining 12 had AFL.

Conversion Rates

The cardioversion rate at 4 hours post Ibutilide infusion among the 120 patients of AF or AFL was 65.83% (*n* = 79), with an average conversion time of 35.12 ± 36.71 minutes. At 24 hours, 85 patients (70.8%) had successful cardioversion, with a mean time to achieve sinus rhythm of 107.24 ± 300 minutes (Table 3).

A total of 87 patients (72.5%) received a single vial (1 mg) of Ibutilide fumarate, while the remaining 33 patients (27.5%) needed two vials (2 mg each). Successful cardioversion was achieved with the first bolus in 66 patients (55%) and with the second bolus in 19 patients (15.8%). The success rate was notably greater among AF patients (75%) as compared to AFL (33%), with a *p*-value of 0.0525, as illustrated in Table 4.

We also analyzed the conversion efficacy of Ibutilide in patients with arrhythmias lasting <48 hours, between 48 hours and 7 days, and >7 days. Our findings indicated that patients with arrhythmias lasting more than 7 days also achieved cardioversion with Ibutilide (*N* = 19 patients). Of these 19 patients, 11 achieved cardioversions after the administration of a single vial of Ibutilide injection (Table 5).

Aggregate success rates are presented only for patients who converted to Ibutilide treatment. In patients with AF and AFL, 69.44 and 33.33% of the conversions occurred within 4 hours of Ibutilide administration respectively (Fig. 2). Before the second infusion, 57.40% of conversions were achieved in AF, compared to only 33.33% in AFL.

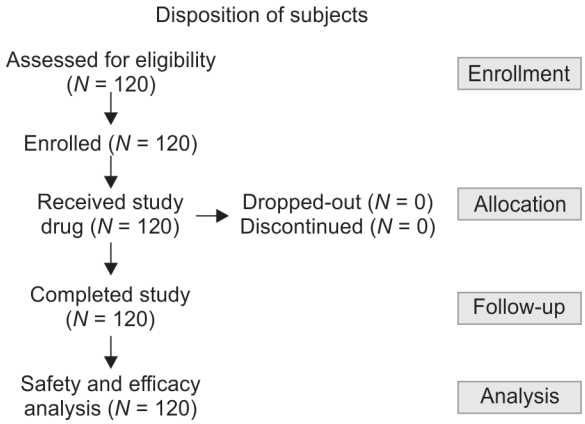

Fig. 1: Flowchart depicting the disposition of the subjects during the study

Table 1: Demographics and baseline characteristics of the patients

Factors	*Values*	
Age (years)	53.80 (±15.63)	
Gender, *n* (%)	54 (45.0%) females and 66 (55.0%) males	
Weight (kg)	65.12 (±10.43)	
Past history of AF/AFL, *n* (%)	24 (20.0%)	
Antiarrhythmic medication used before enrolment, *n* (%)	6 (5.0%)	
Anticoagulant therapy used at enrolment, *n* (%)	109 (90.8%)	
Current arrhythmia duration, *n* (%)	<48 hrs	80 (66.7%)
	>48 hrs to <7 days	16 (13.3%)
	>7 days	24 (20.0%)
Patients' INR between 2 and 3, *n* (%)	15 (12.5%)	
LA diameter (mm) at baseline	38.85 (8.50)	
LVEF (%) at baseline	56.73 (5.06)	
Valvular heart disease at enrolment (12-lead ECG), *n* (%)	28 (23.3%)	
QT interval (ms) at baseline	332.07 (56.28)	
QTc interval (ms) at baseline	433.62 (54.17)	
Vital signs		
SBP baseline (mm Hg)	119.49 (±15.49)	
DBP baseline (mm Hg)	78.56 (±7.70)	
Heart rate (beats/min) baseline (BPM)	111.41 (±28.97)	
Respiratory rate (breaths/min) baseline	18.25 (±1.88)	

Arrhythmia Termination Time

We have observed that cardioversion was achieved by 29 (24.17%) patients within 10 minutes. By 15 minutes, a total of 30 (25.00%) patients had achieved cardioversion, and by 20 minutes, 44 (36.67%) patients had cardioversion. The cumulative % increased to 50.83% (61 patients) at 30 minutes, steadily increasing at 40 minutes post-infusion to 52.50% and 55.83% at 60 minutes. By 90 minutes, 71 (59.17%) patients had achieved cardioversion. Thus, we found that cardioversion was achieved by more than 50% of patients within 30 minutes following the first infusion (Fig. 3).

The mean time for conversion to sinus rhythm among the 85 patients with cardioversion (sinus rhythm), was 107.24 ± 300.00 minutes.

Follow-up through 24 Hours

At the 24-hour assessment, 82 out of the 85 patients who had initially achieved cardioversion (sinus rhythm) with Ibutilide injection maintained it. Thus, three patients did not maintain conversion at 24 hours. Of these, two had AF and one had a 2:1 atrioventricular (AV) block.

Table 2: Medical history of the enrolled patients

Medical history	*n (%)*
Hypertension	49 (40.8%)
Coronary artery disease	10 (8.3%)
Diabetes	10 (8.3%)
Valvular disease	15 (12.5%)
Hypercholesterolemia	5 (4.2%)
Myocardial disease	10 (8.3%)
Post cytomegalovirus infection	1 (0.83%)
Rheumatic heart disease	4 (3.33%)

Table 3: Displays cardioversion rates and mean time to achieve cardioversion at 4 and 24 hours

Cardioversion	*At 4 hrs*	*At 24 hrs*
Cardioversion rate (*n*)	65.83% (79)	70.83% (85)
Mean time to achieve cardioversion	35.12 ± 36.71 min	107.24 ± 300.00 min

Effects on QTc Interval

The QTc interval was significantly prolonged from a baseline of 433.62 ± 54.174 ms (range 320–596 ms) to 451.62 ± 69.046 ms (range 410–507 ms) after Ibutilide infusion ($p < 0.0001$) which returned to baseline at 24 hours. Following Ibutilide infusion, the change in QTc (ΔQTc) was 29.076 ± 73.342 ms (Fig. 4).

Safety Assessments

Adverse events were recorded from the point of intervention to the end of the study period. A total of eight patients experienced 10 adverse events, with five classified as mild, two as moderate, and three as severe, leading to the discontinuation of the drug. The observed adverse events included moderate nausea, mild headache, palpitations, bradycardia, and ventricular tachycardia as mentioned in Table 6. Eight of these adverse events were certainly or possibly related to the investigational drug, Ibutilide. One patient developed polymorphic ventricular tachycardia TdP, which was treated according to the standard protocol and resolved without any sequel. No deaths or SAE were observed throughout the trial.

Discussion

In clinical practice, an intravenously administered antiarrhythmic drug that can consistently and safely restore normal rhythm in recent-onset AF is highly sought after. Quickly restoring sinus rhythm in the early phase can remove the necessity for prolonged antiarrhythmic maintenance and anticoagulation treatments, decrease the risk of AF relapse, reduce the necessity for electrical cardioversion, shorten hospital stays, and lower healthcare costs.[11]

Ibutilide, a "pure" antiarrhythmic agent, is one of the most effective medications in rapidly terminating atrial tachyarrhythmias. It has a rapid onset and a success rate of 55–61% within 90 minutes, outperforming other antiarrhythmic medications. Ibutilide is FDA-approved in the USA; however, its use in India is limited due to restricted availability, skepticism about its association with proarrhythmia, and insufficient awareness among physicians.[11,12] Therefore, this research sought to assess the safety and effectiveness of Ibutilide in reinstating normal heart rhythms in Indian individuals with AF and AFL.

Table 4: Cardioversion after first and second bolus ibutilide injection

		No. of patients who achieved cardioversion		
Total number of patients		*After administration of one dose of ibutilide*	*After administration of two doses of ibutilide*	*Total*
Atrial fibrillation	108	62	19	81 (75%)
Atrial flutter	12	4	NA	4 (33%)
Total	120	66 (55%)	19 (15.8%)	85 (70.8%)

Table 5: Duration of arrhythmias and conversion efficacy of ibutilide

		No. of patients who achieved cardioversion		
Duration of arrhythmias	*N*	*After the first dose of ibutilide*	*After the second dose*	*Total*
<48 hrs or >48 hrs to <7 days	96	55	11	66
>7 days	24	11	8	19
Total	120	66	19	85

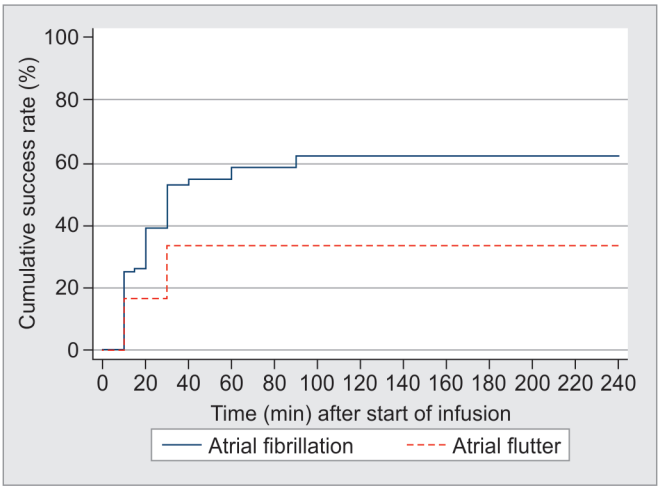

Fig. 2: Cumulative success rates (%) in atrial flutter and fibrillation based on time after the start of the Ibutilide infusion

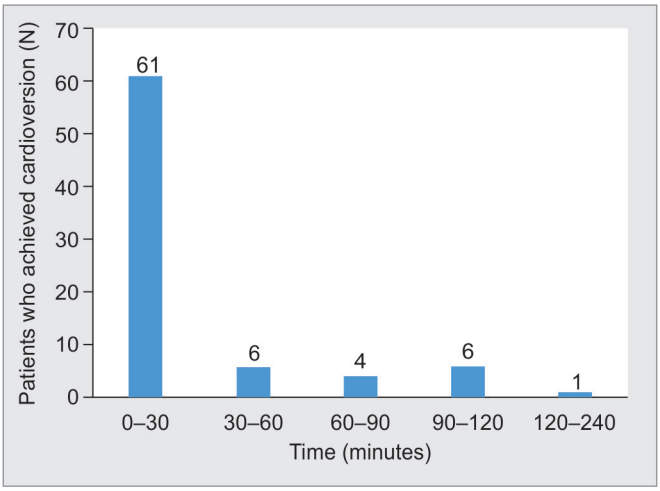

Fig. 3: Time for cardioversion following Ibutilide fumarate injection

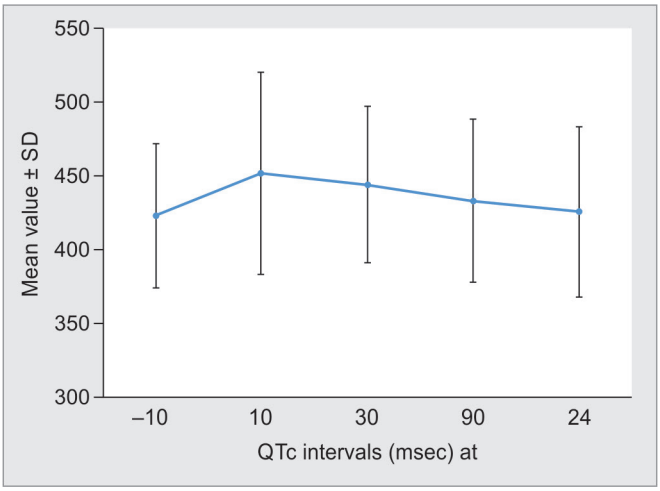

Fig. 4: QTc interval before and after Ibutilide administration

Intravenous Ibutilide successfully restored sinus rhythm in 70.83% of patients with AF and AFL, with sinus rhythm maintained in all but three cases within the post-dose monitoring phase of 24 hours. Rapid cardioversion with Ibutilide was achieved in an average of 107.24 minutes, with 70% of patients achieving conversion within the first 30 minutes. Notably, one-fourth of patients converted within just 10 minutes, highlighting Ibutilide's rapid antiarrhythmic action, which can be particularly advantageous in patients with unstable hemodynamic conditions compared to other agents like amiodarone.[13]

In this study, 55% of patients achieved conversion with the first dose of Ibutilide, a result comparable to findings in other adult studies using the drug.[14–16]

Ibutilide is generally reported to be more effective for treating short-duration arrhythmias, particularly AF.[17,18] However, our study revealed a higher success rate in patients with AF (75%) compared to those with AFL (33%). This contrasts with other studies that have found Ibutilide to be more effective for AFL.[16,19,20] This discrepancy may be influenced by the predominance of AF cases in our study and the relatively small sample size.

Ellenbogen et al.[15] stated that AF of brief duration is more likely to achieve normal rhythm conversion with Ibutilide. However, our study found that some patients with arrhythmias lasting more than seven days converted to normal heart rhythm after a single infusion. This suggests Ibutilide's potential efficacy in persistent arrhythmias, further large-scale clinical trials are required to validate the study results. This suggests that Ibutilide is effective in persistent arrhythmias and that its efficacy is not affected by the time of AF onset.

Despite differences in study designs, our study's 70.8% successful cardioversion rate for Ibutilide monotherapy is among the highest reported.[8,15,21,22] We observed a better conversion rate compared to the study by Delle Karth et al.,[23] which reported a cumulative conversion efficacy of 56.8%. Additionally, Bickford et al.[21] found a conversion rate of 75% in a study of 81 cancer patients, which closely aligns with our results.

Ibutilide elevated the QTc interval in all patients, though TdP was noted in just one patient within the first two hours after infusion. Consequently, careful monitoring is crucial for all patients during and up to 4 hours following Ibutilide administration. We reported three severe adverse effects, leading to the suspension of Ibutilide use. No proarrhythmia-related deaths have been reported with Ibutilide. The drug causes few non-cardiovascular adverse events like nausea, and headache and has insignificant hemodynamic effects.

The study's limitations include a small number of patients and the lack of a comparative control group. Furthermore, no subsequent assessments were carried out to determine the long-term preservation of sinus rhythm or time of recurrence of arrhythmia.

Pharmacological cardioversion in symptomatic patients with recent-onset AF improves quality of life and reduces hospitalizations, making it a cornerstone of emergency management.[24,25] Our data suggest that under controlled conditions, Ibutilide serves as an alternative to traditional cardioversion methods, especially when immediate termination is necessary. Ibutilide may be advantageous as it eliminates the need for sedation and the inherent risks associated with anesthesia. It acts quickly, attaining a high success rate in converting arrhythmias within the first hour of intravenous infusion. Torsades de Pointes is a primary concern when using Ibutilide; nevertheless, the current study demonstrates that the occurrence of this issue is minimal, and Ibutilide can be administered with confidence in the critical care environment.

Table 6: Summary of adverse events reported during the study

S. no.	*No. of adverse events*	*Adverse events*	*Severity*	*Relationship with study drug*
1	1	Headache	Mild	Unlikely
2	2	Bradycardia	Mild	Possible
3	1	Palpitation	Mild	Possible
4	1	Ventricular tachycardia	Severe	Certain
5	1	Tachycardia	Moderate	Probable
6	1	Nausea	Moderate	Certain
7	1	Tachycardia	Severe	Certain
8	1	Headache	Mild	Possible
9	1	Tachycardia	Severe	Certain

Conclusion

Ibutilide is both effective and well-tolerated for the rapid termination of AFL and AFL in Indian patients. Due to its ease of administration, effectiveness, and relative safety, Ibutilide could be a highly appealing treatment option for both patients and physicians.

Clinical Significance

Ibutilide infusion effectively restored sinus rhythm in patients with AF or AFL, achieving a 65.83% cardioversion rate within 4 hours, with a favorable safety profile and no fatalities.

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Availability of Data and Materials

The data set used in the current study is available on request from the corresponding author.

Ethics Approval

The trial was approved by the IECs of the respective sites.

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