

## Original Research Article

# Intravenous ibutilide versus intravenous amiodarone for post-operative management of atrial fibrillation following coronary artery bypass grafting: a prospective randomized controlled double blinded trial

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## ABSTRACT

**Background:** Increased incidence of post-operative atrial fibrillation (POAF) is responsible for more post-operative complications, length of hospital stay and subsequent higher costs of hospitalization. This study was done to compare the efficacy and safety of ibutilide versus amiodarone for treatment of POAF following coronary artery bypass grafting (CABG).

**Methods:** In this prospective, randomized, double blind controlled study, 60 patients posted for CABG developing POAF, divided randomly into 30 patients each in groups A and group I. Group A received IV amiodarone at 3 mg/kg over 20 minutes and group I received IV ibutilide at 0.01 mg/kg over 10 minutes (weight <60 kg) or 1 mg over 10 minutes (weight >60 kg). Patients underwent standard anesthetic technique and monitoring for CABG. All the demographic data, hemodynamic data were recorded in a structured manner.

**Results:** Ibutilide showed significantly faster resolution of AF at 12.47±5.3 versus 22.9±7.68 minutes by amiodarone (p=0.000). Ibutilide was found to have significantly higher incidences of recurrence at 23.3% versus 0% by amiodarone (p=0.0048). Ibutilide showed significantly lesser hypotension 0% versus 26.67% with amiodarone (p=0.002).

**Conclusions:** This study concluded that ibutilide was found to be better suited to treat POAF patients, who underwent CABG; due to its early and efficient resolution and reduced risk of hypotension.

**Keywords:** Post-operative atrial fibrillation, Amiodarone, Ibutilide, Coronary artery bypass grafting

## INTRODUCTION

Increased incidence of POAF is responsible for more post-operative complications, length of hospital stay and subsequent higher costs of hospitalization.<sup>1</sup> POAF is the most common arrhythmia encountered after isolated CABG surgery, with an incidence of 20-40%.<sup>2</sup> POAF

tends to occur within first 3 days after CABG surgery.<sup>3</sup> The most consistent predictor for the development of POAF is advanced age. In addition other risk factors for the development of POAF have been identified as a previous history of AF, male gender, decreased left ventricular ejection fraction, left atrial enlargement, valvular heart surgery, chronic obstructive pulmonary

disease, chronic renal failure, diabetes mellitus, rheumatic heart disease, obesity has also been shown to be an independent predictor of new onset AF in general population and in cardiac surgery patients.<sup>4</sup> With increasing number of elderly and high-risk patients undergoing cardiac surgery and CABG, there is a need to elucidate the long-term influence of POAF, given that there are already known associations with comorbidities including heart failure, stroke, prolonged hospital stay and cost.<sup>5</sup> Even after cardioplegia, the atrium still maintains residual electrical activity which results in varied degrees of ischemia despite the adoption of myocardial protection measures. Such incisions associated with the atrial ischemia arising from the surgical procedure and from the underlying cardiopathy give rise to abnormalities in atrial conduction, in refractoriness and in the triggering factors such as ectopic atrial beats.<sup>6</sup>

Amiodarone class III antiarrhythmic drug is approved for life threatening ventricular tachyarrhythmia and atrial arrhythmias. It has also significant class I, class II and class IV activity. The drug has demonstrated safety in patients with structural heart disease and severe left ventricular hypertrophy but it does carry a risk of hypotension, phlebitis and infusion with the iv form, abnormalities in thyroid function, elevated hepatic enzyme levels and severe pulmonary fibrosis.<sup>7,8</sup>

Ibutilide is also a class III antiarrhythmic drug used for acute termination of atrial tachyarrhythmias. It affects not only atrial and ventricular myocardium but also the atrioventricular node, His-Purkinje system and accessory pathway. It is seen that efficacy of ibutilide is higher than that of intravenous amiodarone, though in studies the superior efficacy was seen in atrial flutter (AF) while similar efficacy was seen for AF.<sup>9</sup> Ibutilide and amiodarone had comparable conversion rates at 4 hours and ibutilide was also found to be superior in terms of hemodynamic and systemic side effects. Hypotension was seen more often in patients receiving amiodarone.<sup>10</sup>

Recent studies have shown that ibutilide is better tolerated by patients in whom beta blockers are contraindicated and has better cardioversion potential when coupled with other antiarrhythmic agents or electrical cardioversion. Vernakalant, the relatively atrial selective antiarrhythmic agent is being compared to amiodarone and ibutilide as a more recent alternative for chemical cardioversion.<sup>11</sup> This study was designed to compare the efficacy and safety of ibutilide versus amiodarone for treatment of POAF following CABG.

## METHODS

This study was conducted at Geetanjali medical college and hospital, Udaipur from February 2019 to July 2020 only after obtaining approval from institutional ethics committee. A total of 60 patients posted for CABG developing POAF were included in study. Patients BMI

>35 kg/m<sup>2</sup>, ASA grade >4, age >75 years, with significant left ventricular dysfunction (left ventricle ejection fraction <30%), renal function tests significantly deranged (eGFR <60ml/min/1.73 m<sup>2</sup>), liver function tests significantly deranged (SGOT/SGPT >150 IU/l), combined operations (CABG with valvular disease operations), pre-existing rhythm abnormalities, known hypersensitivity to the study drugs, medical conditions precluding the use of the study drugs were excluded from the study.

64 patients (including dropouts) were randomly divided into 2 groups of 30 each using a computer-generated randomization schedule of 32 each. Total 60 patients were statistically analyzed after withdrawal of 4 patients in this study. Blinding was achieved by preparing the drug in 50 ml D5 to keep a constant volume of 50ml. The anesthesiologist preparing the drug and administering it and doing the data recording were separate from the anesthesiologist compiling the data.

Group A (n=30) patients were given 3 mg/kg over 20 minutes of amiodarone, or group I (n=30) patients were given 0.01 mg/kg over 10 minutes of ibutilide (<60 kg), Patients given 1 mg over 10 minutes of ibutilide (≥60 kg).

Written informed consent was taken from all patients and all patients were subjected to thorough pre-anesthetic evaluation. Patients were kept nil orally eight hours prior to surgery. Two 18 gauge cannula were inserted, arterial line for IBP monitoring and central venous cannulation was done for CVP monitoring and cardiac support. Anesthetic and surgical techniques were standardized.

Balanced anesthesia technique was used with injection midazolam 1.5-2 mg, injection fentanyl 3-5 mcg/kg, injection etomidate 0.1 mg/kg and after induction the patient was intubated with non-depolarizing muscle relaxant injection vecuronium at 0.1 mg/kg and maintained with O<sub>2</sub>, air and isoflurane. Perioperative monitoring included ECG, temperature, invasive blood pressure (IBP), central venous pressure (CVP), SpO<sub>2</sub>, EtCO<sub>2</sub>, urine output, length of hospital stay.

All patients were monitored postoperatively in terms of ECG, IBP, CVP, SpO<sub>2</sub>, at the time of drug administration for up to 4 hours, then every 12 hourly up to 3 days from the time of drug administration. Further interventions like incremental doses, electrolyte correction and cardioversion were recorded when required. All the demographic data, hemodynamic data were recorded in a structured manner. Vital parameters like heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SPO<sub>2</sub>, CVP and rhythm, at 2 minute intervals for 10 minutes and then 10 min intervals till 30 min, then at 30 minute intervals till 240 minutes, followed by 12 hourly intervals for 3 days were recorded. Specific investigations like SGPT, SGOT,

serum bilirubin, estimated glomerular filtration rate (eGFR) were done. Patients were monitored for 3 days to assess for hemodynamic variables, adverse effects and recurrence of arrhythmias. Monitoring included ECG, IBP, CVP, SpO<sub>2</sub>. In case of resistant POAF the patient was administered rescue anti arrhythmic in the form of an incremental dose of the same drug (1st line), bradyarrhythmias-pacing, tachyarrhythmias-magnesium supplementation and xylocard infusion, VPCs-serum electrolytes correction, administration of metoprolol (oral or IV), unstable tachyarrhythmias-cardioversion, which were all recorded.

**Statistical analysis**

Categorical variables were summarized as frequency and percentage and were analyzed using the Chi square test.

Continuous variables were summarized as mean and standard deviation and t test was used. A p<0.05 was taken as statistically significant.

**RESULTS**

There was no statistical significance in demographic data between the two groups (Table 1).

The HR normalization was found significant at the time of resolution of AF (p<0.05). Ibutilide showed significant resolutions around the 6 and 10 minutes mark, majority of amiodarone resolutions and subsequent HR normalization was seen around 20 minutes (Figure 1). Baseline blood pressure (SBP, DBP and MAP) after drug administration and at different time intervals were insignificant in the two groups (p>0.05).

**Table 1: Comparison of demographic data in the two groups.**

Demographic variables	Group I	Group A	P value
	Mean±SD (n=30)	Mean±SD (n=30)	
Age (years)	62±6.86	62.8±9.03	0.701
Height (cm)	166.8±6.96	166.37±5.51	0.790
Weight (kg)	68.76±10.59	66.93±8.42	0.463
BMI (kg/m <sup>2</sup> )	24.67±3.12	24.18±2.87	0.532

**Table 2: Comparison of rhythm in two groups.**

Rhythm at different time intervals	Group I (n=30)			Group A (n=30)			P value
	AF	Sinus	Total	AF	Sinus	Total	
Baseline	30	0	30	30	0	30	NA
2 min	30	0	30	30	0	30	NA
4 min	30	0	30	30	0	30	NA
6 min	30	0	30	30	0	30	NA
8 min	22	8	30	30	0	30	0.002*
10 min	18	12	30	30	0	30	0.000*
20 min	4	26	30	19	11	30	0.000*
30 min	0	30	30	3	27	30	0.076
40 min	2	28	30	2	28	30	NA
50 min	1	29	30	0	30	30	0.313
60 min	1	29	30	0	30	30	0.313
90 min	0	30	30	0	30	30	NA
120 min	1	28**	30	1***	29	30	0.601
150 min	0	30	30	0	30	30	NA
180 min	1	29	30	0	30	30	0.313
210 min	1	29	30	0	30	30	0.313
240 min	1	29	30	0	30	30	0.313
12 hours	1	29	30	0	30	30	0.313
24 hours	0	30	30	0	30	30	NA
36 hours	0	30	30	0	30	30	NA
48 hours	0	30	30	0	30	30	NA
60 hours	0	30	30	0	30	30	NA
72 hours	0	30	30	0	30	30	NA

\*significant, \*\*1 incidence of SVT in group I, \*\*\*shows recurrence and hypotension in group A at 120 minutes, AF-atrial fibrillation, NA-not applicable.

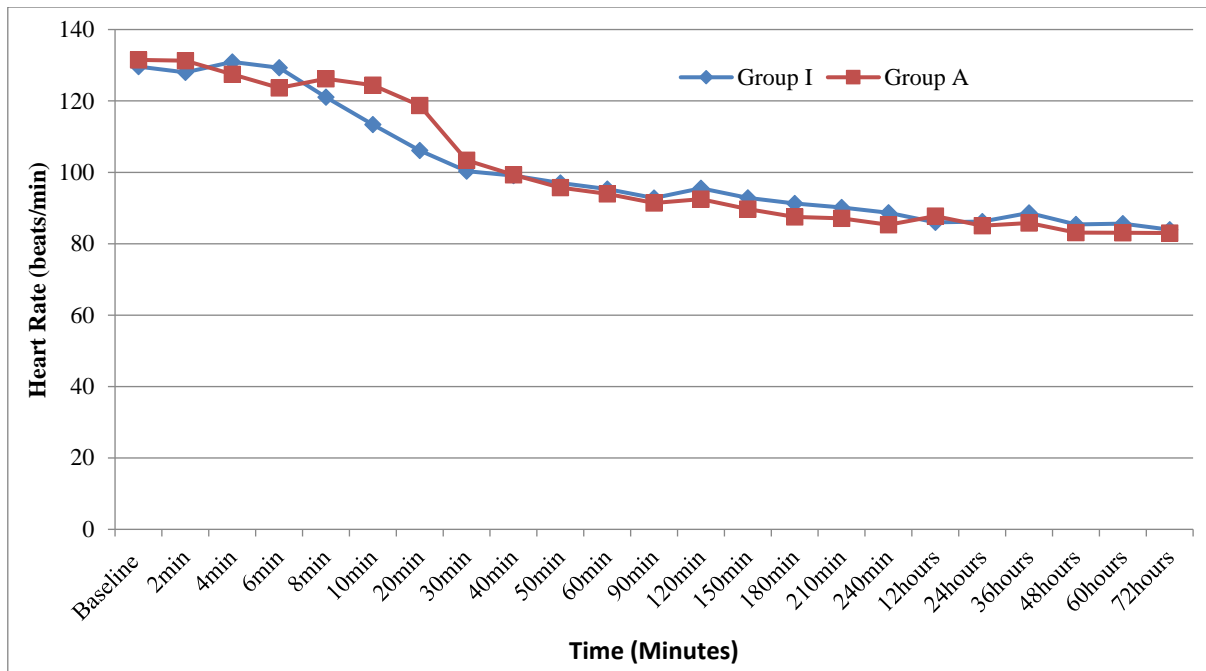


Figure 1: Comparison of heart rate between the two groups.

Table 3: Comparison in both the groups in terms duration of AF, incidence of recurrence and hypotension.

Comparison	Group I (n=30)	Group A (n=30)	P value
Duration of AF in minutes (mean± SD)	12.47±5.3	22.9±7.68	0.000*
Incidence of recurrence (%)	7 (23.3)	0	0.0048*
Incidence of hypotension (%)	0	8 (26.67)	0.002*

\*Significant.

There was early normalisation of rhythm in the group I, showing significant evidence (p<0.05) of resolution of AF at 8 to 10 minutes as compared to 20 minutes with amiodarone (Table 2).

Duration of AF in group I was significantly lower than in group A (12.47±5.3 versus 22.9±7.68 minutes) (p=0.000). Successful conversion after single dose was observed in 23 of the 30 patients in group I. Recurrences observed were limited to the group I. The number of recurrences was statistically significant (p<0.05). Only a single episode of recurrence was observed in 7 of the 30 patients in the ibutilide group and was resolved after repeat of a single dose of the same drug. Group A showed no recurrences. Incidence of hypotension was seen to be as high as 26.67% in group A and was observed to be statistically significant (p=0.002) (Table 3).

**DISCUSSION**

In present study age, weight, height and ASA were comparable among the two groups and were statistically insignificant (p>0.05), which were comparable to other studies.<sup>12,13</sup>

In present study the baseline heart rate and heart rate at different time intervals were insignificant except at the 6,

10 and 20 minutes. At 6 minutes the heart rate comparison between group I and group A were observed as significant (p=0.028). In group I vs group A the heart rate at 10 minutes 113.37±11.79 versus 124.43±15.72, showed significant slowing down and stabilization of heart rate (p=0.003). This reduction of heart rate was also observed by Schwartz et al who reported a 20% decrease in heart rate a few minutes after starting an ibutilide infusion.<sup>14</sup>

In Bernard et al study, the heart rate declined significantly (p=0.001) with both drugs before conversion. The antiarrhythmic efficacy and safety of amiodarone and ibutilide have been compared by Bernard et al but not directly with a bolus dose.<sup>12</sup> Ibutilide a class III antiarrhythmic agent was a potent blocker of the rapid component of the cardiac-delayed rectifier potassium current and also activated the slow inward sodium current. Thus a bolus dose of ibutilide had a rapid effect on treating arrhythmias like recent onset AF. In group I versus group A however at 20 minutes the mean heart rate was 107.07±10.25 versus 118.7±14.18 showing significant normalisation (p=0.000) of heart rate in group A as compared to group I. Bernard et al found that though hemodynamic changes showed no significant differences in heart rate between the ibutilide and amiodarone groups.<sup>12</sup>

Amiodarone was a class III antiarrhythmic agent (K<sup>+</sup> channel blocker), but in acute therapy had a class I, II and IV action, leading to blocking of both Na<sup>+</sup>, Ca<sup>++</sup> channels and beta blockade. The major effect of class III antiarrhythmic potential of amiodarone was seen in chronic therapy where it caused inhibition of outward potassium currents, resulting in a prolongation of action potential duration (APD), not only in atrial and ventricular muscles but also in the SA and AV nodes.

Mithcell et al in The Papabear trial (prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement or repair) looked into preoperative use of amiodarone for prevention of arrhythmias and they observed bradycardia in 17/299 patients treated with amiodarone as compared to 6/302 treated with placebo. There was significant incidence of bradycardia warranting a stoppage or change in ongoing treatment regimen.<sup>15</sup>

Patel et al in a meta-analysis noted that bradycardia was more observed in the case of postoperative use of amiodarone and not in the preoperative and postoperative setting. Dosing >1 g/day was observed to be responsible for higher incidence of bradycardia compared to ≤1 g.<sup>16</sup> In the present study no such bradycardia was noted with amiodarone, which could be due to the absence of chronic therapy with amiodarone as used orally in this study for 13 days preoperatively in cardiac patients and use of a fixed dose of 3 mg/kg as a bolus and not exceeding 1 g/day in any patient.

In this study the baseline blood pressure (SBP, DBP and MAP) after drug administration and at different time intervals were insignificant in the two groups (p>0.05). The incidence of hypotension was more in group A (26.6%) than in group I (0%). This was managed by fluid bolus and minimal cardiovascular supports. Hypotension in amiodarone group had also been reported by other studies.<sup>12,16</sup> Hypotension from amiodarone was well documented because of its negative inotropic and chronotropic properties and its peripheral vasodilating effects.

In present study duration of AF was noted to be shorter in the group I (12.47±5.3) versus in group A (22.9±7.68). This earlier resolution with ibutilide was also similarly observed by Ellenbogen et al. In a dose dependent study to find efficacy of ibutilide for rapid termination of atrial fibrillation, mean time of termination to be from 19±15 minutes, with a range from 3 to 70 minutes noted.<sup>17</sup> In Kafkas et al study the mean time to arrhythmia termination was significantly shorter with ibutilide than with amiodarone for AF (53.4±25.8 versus 492±186 min, p=0.000).<sup>13</sup> The longer duration for termination of AF may be attributed to use of study drug in recent onset AF rather than in cardiac surgery, where rate control drugs like oral amiodarone or beta blockers were used pre operatively. Hongo et al has shown matching conversion times to our study, the with a mean conversion time of

25±14 min using ibutilide to convert AF to SR.<sup>18</sup> Vanderlugt et al observed in their study that increasing dose of ibutilide showed decrease in time taken to resolution, with 1 mg showing a mean time of 23 minutes. The range however they noticed was 3 to 90 minutes which coincided with present study of early resolution.<sup>19</sup> Schwartz et al found resolution time 16±11 minutes comparable to our findings of duration of AF.<sup>14</sup>

In present study atrial fibrillation was successfully converted to normal sinus rhythm in group I versus group A in 76.7% versus 73.3% of cases. This rate of conversion was comparable to the study by Kafkas et al where ibutilide versus amiodarone could convert atrial fibrillation at a rate of 77% versus 69%.<sup>13</sup> Bernard et al noted conversion rates to be lower with ibutilide and amiodarone (45% versus 50%) in recent onset AF in non-cardiac surgery patients.<sup>12</sup> Incidence of recurrence was in present study was 23.3% noted with ibutilide which were treated by repeating same dose. In 26.7% of amiodarone patients there was persistence of AF past 25 minutes and hence same dose of drug was repeated leading to resolution thereafter.

Bernard et al reported a recurrence rate of 55% with ibutilide and 35% in amiodarone group. This was due to the short half-life of 4-6 hours of ibutilide which had been used in conjunction with oral beta blockers to retain sinus rhythm post conversion.<sup>12</sup> Vanderlugt et al reported a conversion rate of 78% for atrial flutter and 44% for atrial fibrillation, this was due to the repeated dose model used by them, where total dose was not given to all patients according to the groups they were randomized into.<sup>19</sup> Schwartz et al tested the electrophysiological effects of ibutilide and noticed a 35% conversion rate in randomly chosen 20 patients.<sup>14</sup> Hongo et al noted in their study conversion rate of 47.9% with AF converted to SR after ibutilide. This lower conversion rate may be due to use of ibutilide in the treatment of recent onset or persistent AF, where no pre-treatment by beta blockers or oral amiodarone was ongoing and hence conversion rates were lesser, while 73.9% with AFL converted to SR after ibutilide with a mean conversion time of 20±12 min.<sup>18</sup> Ibutilide had been shown to have a rapid conversion of AF and with good success and been shown to have better action with other antiarrhythmic drugs and electrical cardioversion. Vanderlugt et al observed that combining digoxin with ibutilide lead to higher (65%) conversion rate when given concomitantly. They also observed a lower joules requirement during electric cardioversion in patients with failures of ibutilide versus placebo therapy (225 J versus 300 J).<sup>19</sup>

Adverse events like hypotension and a single isolated incident of SVT were observed in present study. In Patel et al meta-analysis, they had noted significant (p=0.003) incidence of nausea with amiodarone therapy. It was seen to be dose independent and was related more to the oral route of administration with an OR of >1 in all the studies referred. With IV use of amiodarone nausea was not

observed which matches with the findings of our study.<sup>16</sup> Kafkas et al observed a 3.8% occurrence of polymorphic ventricular tachycardia (Torsades de pointes) using ibutilide which were electrically terminated.<sup>13</sup> The rate of giving ibutilide has been associated with higher incidence of polymorphic ventricular and monomorphic ventricular tachycardia, which was also observed by Vanderlugt et al where they noted 4 episodes of Torsades de pointes in the 1 mg dose group that were attributed to diminished left ventricular function and electrolyte imbalance. The other adverse effects like nausea, constipation, hypotension, bradycardia were insignificant in their study as compared to placebo group matching our findings in the current study.<sup>19</sup>

## CONCLUSION

This study concluded that the efficacy of both drugs in converting AF to normal sinus rhythm is comparatively equal. However, due to significantly higher incidence of hypotension and time to resolution of AF, amiodarone is less preferable to treat AF as compared to ibutilide. Ibutilide was observed to resolve AF significantly earlier, hence reducing the risk of post-operative complications of cardiac surgery. However, significant incidence of recurrence was seen with ibutilide, but showed more efficacy when repeated, hence making ibutilide more preferable to treat post-operative atrial fibrillation.

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