Comparison of Effects of Amiodarone versus Verapamil in Prevention of Atrial Fibrillation Post Coronary Artery Bypass Grafting

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Abstract: Atrial fibrillation (AF) is the most common sustained arrhythmia affecting humans. The initiation of AF may be caused by rapidly firing foci, in the pulmonary vein (s). Although the atrial rate is rapid, the ventricular response depends on atrioventricular (AV) node conduction and the autonomic tone conductivity of AV node. The aim of the present study was to compare to compare effects of amiodarone and verapamil in prevention of atrial fibrillation post coronary artery bypass graft in patients with dilated left atrium. The study was carried out on 300patients after approval of the medical ethical committee of Faculty of Medicine, Ain Shams University and obtaining informed written consent from all studied patients. We have (300) patients undergoing CABG surgery ware included in the study with dilated left atrium (more than 5mm in diameter). Divided into three groups, **Group (A):** Included (100) patients, received IV amiodarone in a dose of 300 mg I V loading dose followed by1200 mg /day by infusion. (50 mg/h)**, Group (B)** included: (100), patients received IV verapamil in dose of 0.6 mg/kg/h I V by infusion, **Group (C)** included (100) patients as a control group and received placebo in the form of equal volume of normal saline 0.9% infusion. These medications were given by IV infusion for 48 hours before surgery. We excluded patients with chronic pre-existing AF or atrial flutter**,** previous cardiac surgery, Patients on pacemaker, Patients on antiarrythmic drugs and Contraindications to any of the medications used in the study. In our study, the rate effects of amiodarone a prevention of atrial fibrillation post coronary artery bypass is 24%. On the other hand, success rate effects of verapamil in prevention of atrial fibrillation post coronary artery bypass is 38%. The results of our study showed the superiority of amiodarone (p-value was significant =0.019) in prevention of atrial fibrillation post coronary artery than verapamil (p-value was significant =0.032). Also The results of our study showed the superiority of amiodarone group (A) (p-value was significant =0.022) in to decrease length of hospital stay significant fewer days than those in the Verapamil group (B) and placebo group (C).

1. Introduction

Atrial fibrillation (AF) was recognized as a major cause of morbidity and mortality after CABG **(Mirhosseini et al., 2013).** The incidence of AF depends on several factors like clinical factors (duration of arrhythmia and co-morbid diseases), type of post-operative monitoring (intermittent or continuous) and changing profile of patients undergoing CABG **(Erdil et al., 2013).**

Although the pathogenesis of AF after open heart surgery is incompletely understood, stimuli & triggers such as pre-existing structural changes of the atria related to hypertension, volume over load, age, atrial ischemia, electrolytes imbalances and pericardial lesions are thought to play a role in the pathogenesis

of atrial fibrillation after coronary artery bypass grafting **(Awer and Weber, 2005).**

Therefore clinical data, ECG changes, echocardiography may be useful in pre-operative stratification of surgical patients for occurrence of post CABG AF. Maintenance of sinus rhythm could be effective in improving the quality of life and heart performance in patients with congestive heart failure (CHF), and also, could decrease the risk of thrombo-embolism and the side effects of long term anticoagulation therapy **(Van Gelder et al., 2010).**

Patients with post-operative AF usually are older, have larger left atrium (LA) dimension, and electro-mechanical delay in atria. Also they have lower left ventricle ejection fraction (LVEF) and longer P-wave

duration. They have smaller A-wave in Doppler echocardiography. It has been shown that the atrial electro-mechanical delay is the best independent factor for predicting the incidence of post-operative AF **(Park et al., 2010).**

Aim of the Work

The aim of this study is to compare effects of amiodarone Versus verapamil in prevention of atrial fibrillation post coronary artery bypass graft in patients with dilated left atrium.

2. Patients and Methods

This study was conducted on (300) patients undergoing CABG surgery with dilated left atrium (more than 5mm in diameter).

Patients randomized divided into three groups:

Group (A): including (100) patients, received IV amiodaronein a dose of 300 mgI V loading dose followed by1200 mg /day by infusion. (50 mg/h).

Group (B): including: (100) patients received IV verapamil in dose of 0.6 mg/kg/h I V by infusion.

Group (C) including: (100) patients as a control group and received placebo in the form of equal volume of normal saline 0.9% infusion.

These medications were given by IV infusion for r48 hours before surgery.

Exclusion criteria:

1- Patients with chronic pre-existing AF or atrial flutter.

2- Previous cardiac surgery.

3- Patients on pacemaker.

4- Patients on antiarrythmic drugs.

5- Contraindications to any of the medications used in the study.

All the patients will be subjected to the following:

1-   Consent:

A full-detailed written informed consent for participation in the clinical trial.

2-   History taking:

A full-detailed of Personal history, Present history, Past history and history previous treatment Were taken.

3-   Examination and investigations:

A. Full clinical examination:

B. Investigations:

Follow up evaluation performed every day from day of admission to seven days post operative.

Perioperative investigations:

- Electrocardiogram.

- Echocardiography with its findings about left atrial size, regional wall motion abnormalities and global systolic function (pre and post operative)

- Serum level of Na and K till discharge.

Methods:

• **Incidence of occurrence of AF post-operative till discharge.**

• **Echocardiography:**

○ Left atrial dimension by:

- Left atrial size

- Left atrial volume index (LAVI) {calculated by dividing LA volume by body surface area of subject}. **(Maheshwari et al., 2012)**

○ Left ventricular ejection fraction.

○ Regional wall motion abnormalities.

Ethical Consideration

All the patients included in this study signed an informed consent, having a confidentiality about their condition and will be informed about any possible hazards. Also, the patients have the right to go out from the study at any time taking in mind that they will continue to receive the same needed treatment.

Analysed Items:

▪ Incidence of occurrence of A F postoperative till discharge which is primary end point

▪ Day of onset of AF during hospital stay

▪ Length of hospital stay

▪ outcome of patient in the study due to AF (die or improved)

▪ Incidence of cerebrovascular stroke

▪ Complications of drugs

Statistical analysis:

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean±standard deviation (SD). Qualitative data were expressed as frequency and percentage.

3. Results

The following table shows no statistically significant difference between groups according to demographic data.

Table (1): Comparison between groups according to demographic data.

Demographic Data	Group (A) (N=100)	Group (B) (N=100)	Group (C) (N=100)	F / X²#	P-value
Age Mean±SD	55.34±5.79	54.44±6.05	54.56±5.83	0.688	0.503
Sex Female Male	25 (25.0%) 75 (75.0%)	27 (27.0%) 73 (73.0%)	28 (28.0%) 72 (72.0%)	0.239#	0.888

F: ANOVA test; χ^2: Chi-square test
    This table shows no statistically significant difference between groups according to demographic data (table 1)
    This table shows no statistically significant difference between groups according to risk factors.

Table (2): Comparison between groups according to risk factors.

Risk factors	Group (A) (N=100)		Group (B) (N=100)		Group (C) (N=100)		Chi-square test	
	No.	%	No.	%	No.	%	χ^2	p-value
DM	66	66.0%	69	69.0%	69	69.0%	0.276	0.871
Dyslipidia	75	75.0%	73	73.0%	77	77.0%	2.241	0.538
Family H	30	30.0%	41	41.0%	36	36.0%	0.312	0.468
Smoking	63	63.0%	65	65.0%	62	62.0%	2.304	0.553
HTN	73	73.0%	67	67.0%	70	70.0%	1.065	0.256

x^2: Chi-square test; p-value >0.05 NS;
N.B:DM: (diabetes mellitus), HTN: (hypertension) and family H: (family history) (Table 2)

    This table shows no statistically significant difference between groups according to anthropometric measurements.

Table (3): Comparison between groups according to anthropometric measurements.

Anthropometric measurements	Group (A) (N=100)	Group (B) (N=100)	Group (C) (N=100)	ANOVA	
				F	p-value
Weight (kg)	81.02±6.69	81.01±5.91	79.90±5.86	2.073	0.281
Height (cm)	172.66±4.73	172.50±4.12	172.96±4.37	1.478	0.719
BSA (m^2)	1.97±0.09	1.98±0.08	1.96±0.08	0.676	0.510
SBP (mmHg)	132.94±8.63	133.60±9.19	132.30±10.27	1.748	0.354
DBP (mmHg)	79.70±6.45	81.65±8.17	80.00±6.07	2.278	0.104

F-ANOVA test; p-value >0.05 NS
N.B: Body surface area (BSA), (SBP) Systolic blood pressure measures and (DBP) diastolic blood pressure measures.

    Blood pressure was done in prerogative, operative and postoperative period, table show average result.

    This table shows no statistically significant difference between groups according to LAD, LA size, LAVI and EF%.

Table (4): Comparison between groups according to LAD, LA size, LAVI and EF%.

	Group (A) (N=100)	Group (B) (N=100)	Group (C) (N=100)	One Way ANOVA test	
				F	P-value
LAD (cm)	5.22±0.19	5.23±0.18	5.23±0.19	0.101	0.904
LA size (mL)	81.26 ±2.25	81.32±2.21	81.32±2.26	0.024	0.976
LAVI (mL/m^2)	41.16±1.71	41.21±1.21	41.31±1.03	0.321	0.725
LVEF%	47.81±5.65	47.65±5.64	48.40±5.37	0.506	0.603

N.B: LAD (left atrial diameter), LA size (left atrial size), LAVI (Left atrial volume index) and LVEF% (Left ventricular ejection fraction)

    This table shows statistically significant difference between groups according to, length of hospital stay, but no statistically significant K and Na level during hospital stay.

Table (5): Comparison between groups according to other parameters.

	Group (A) (N=100)	Group (B) (N=100)	Group (C) (N=100)	ANOVA F	p-value
Length of hospital stay in days	4.03±1.23‡	4.72±1.70	4.80±1.84	2.325	0.022*
Na peak (mEq/L)	143.98±1.11	142.96±9.94	144.32±0.76	1.493	0.226
Na min (mEq/L)	135.55±0.97	134.67±10.11	135.23±1.15	0.570	0.566
K peak (mEq/L)	4.73±0.20	4.73±0.19	4.74±0.11	0.879	0.407
K min (mEq/L)	3.65±0.25	3.63±0.18	3.59±0.07	2.091	0.107

F-ANOVA test; p-value >0.05 NS ‡ Significant difference between group B and C
N.B: Na (max) maximum, Na (min) minimum, K (max) maximum and K (min) minimum.

The patients in the amiodarone group (A) were hospitalized (length of hospital stay) for significantly fewer days than those in the placebo group **(C)** and Verapamil group **(B)**

There was no statistically significant difference between both groups in regard to drug related complications**.**

Table (6): Complications of therapy in Amiodarone group (group A) and verapamil group (group B)

		Complications	
		Group A	Group B
No complications	N	85	93
	%	82%	93%
Bradycardia	N	5	3
	%	5%	3%
Hypotension	N	5	3
	%	5%	-
Phlebitis	N	4	1
	%	4%	1
Thyroid dysfuction		**1**	-

In group A, 85 patients had no complications, while 5 patient had bradycardia, 5 patients had hypotension,4 patients had phlebitis and 1 patient had thyroid dysfunction.

In group B, 93 patients had no complications while 3 patients had bradycardia, 3paient had hypotension and 1 patient had philibitis.
This table shows statistically significant lower incidence of AF occur in group (A) than group (B) and group (C)

Table (7):   Comparison between groups according to AF, outcome, day of AF and CVS.

	Group (A) (N=100)	Group (B) (N=100)	Placebo (N=100)	Test F/χ2#	p-value	Post Hoc analysis by LSD P1	P2	P3
AF#	24 (24.0%)	38 (38.0%)	42 (42.0%)	7.889#	0.019*	0.032*	0.007*	0.564
Outcome# Died Improve	6 (6.0%) 94 (94.0%)	5 (5.0%) 95 (95.0%)	7 (7.0%) 93 (93.0%)	0.355#	0.837	--	--	--
onset of AF occurrence in days	3.17±1.01	2.97±0.79	3.34±1.17	1.314	0.273	--	--	--
C.V.S#	3 (3.00%)	4 (4.00%)	4 (4.0%)	0.000#	1.000	--	--	--

NB:C.V.S: Cerebrovascular vascular strok.
P1: Difference between amiodarone and verapamil
P2: Difference between amiodarone and placebo
P3: Difference between verapamil and placebo
F-ANOVA test; #x^2: Chi-square test; p-value >0.05 NS; *p-value <0.05 S

Twenty four patients of group (A) developed atrial fibrillation post operative compare to thirty eight patients of group (B) and forty two patients for group (C) that showed lower incidence of AF in group (A) than group (B) and group (C). and lower incidence of AF in group (B) than group (C). The difference between three groups was statistically significant.

The outcome of the study death occurred in six patients of group (A) while of group (B) death occurred in five patients and for group (C) death occurred seven patients. difference of three groups regards to number of patient died was statistically in significant.

The mean day of onset of AF during hospital stay was of group (A) was 3.17 ±1.01 %, while that for group (B) was 2.97 ±.79 % and for group (C), were 3.34 ±1.17 %, The difference between three groups was statistically insignificant.

Three patients of group (A) developed cerebrovascular (C.V.S). Postoperative compare to four patients of group (B) and fort patients for group (C). The difference between three groups was statistically significant.

Discussion

In our study, we investigated the efficacy of two commonly used drugs to assess the effects of amiodarone versus verapamil on prevention of atrial fibrillation (AF) post coronary artery bypass graft (CABG) in patients with dilated left atrium.

This study showed a significant reduction in the incidence of postoperative AF in both the amiodarone group (24)%, and the verapamil group (38)% in comparison to the placebo group (42)%.

These results were comparable to the results of **many researchers as Kirolos et al,2017, Alcalde et al., Daoud et al. and Ferraris et al**.

These results were comparable to the results of **Kirolos et al. 2017**. In his research 1457 patients underwent cardiac surgery,722 patients of them received prophylactic amiodarone and 735 patients received BB mostly metoprolol. His results showed a significant decrease in the incidence of AF in the Amiodarone group (p=0.029) which is compatible with the result of our study, which showed also a significant decrease in the incidence of AF in the amiodarone group post cardiac surgery.

On the Other hand, Many researchers as **Kirolos et al.** investigated the prophylactic beta-block therapy in prevention of AF post CABG. This research using beta-adrenergic blockers have demonstrated prophylactic benefit against postoperative AF. However, the drawback of the studies that investigated prophylactic beta-blocker therapy is the exclusion criteria. In most trials, the factors calling for exclusion

have included a history of asthma, chronic obstructive lung disease or diabetes mellitus requiring medical therapy. These characteristics requiring exclusion are common among patients undergoing cardiac surgery thus limiting the clinical utility of prophylaxis with beta-blocker **(Emile and Daoud et al., 1997)**.

Amiodarone was well tolerated and did not increase the risk of intraoperative or postoperative complications. Also, amiodarone therapy was not associated with proarrhythmic or serious adverse reactions, even among patients with severe coronary and valvular heart disease. Among the patients who had atrial fibrillation, amiodarone reduced the ventricular rate more significantly than did placebo **(Emile and Daoud et al., 1997)**.

Prophylactic verapamil has been reported safe and effective in the prevention of postoperative atrial dysrhythmias after cardiac operations **(Meinertz et al, 1991)**.

Also These results were compatible with results of **Alcalde et al., 2006,** in this double-blind, randomized study, 93 patients underwent to cardiac surgery.46 patients of them received prophylactic amiodarone while 47 patients consisted the placebo group. The study showed a significantly less incidence of AF in the Amiodarone group (p=0.027), which is similar with the results of the current study that also showed significantly less incidence of AF in the Amiodarone group.

Also, these results were compatible with the results of with **Daoud et al., 1997.** In this double-blind, randomized study, 64 patients were given amiodarone before elective cardiac surgery while 60 patients were the placebo group. the Postoperative atrial fibrillation occurred in 16 of the 64 patients in the amiodarone group (25 %) and occurred in 32 of the 60 patients in the placebo group (53 %). these results were compatible with our results, that showed significantly less incidence of AF in the Amiodarone group post CABG surgery.

Also These results were compatible with results of **Kerstein, et al. 1999**, where 51 patients scheduled for CABG were randomly selected for participation in the amiodarone administration trial. IV amiodarone, was administered before the operation for 48 h, while 92 patients received the conventional medical therapy during the same period. The primary end point of this study was the incidence of postoperative atrial fibrillation compared to the control group undergoing CABG during the same time.

AF occurred in 3 of 51 patients in the amiodarone group, compared to 24 of 92 patients in the control group, showed significantly less incidence of AF in the Amiodarone group, which is compatible with current study that showed significantly less

incidence of AF in the Amiodarone group post CABG surgery.

Also our study showed a significant reduction in the incidence of post operative AF in verapamil group by (38%) in comparison to the placebo group. Which is in compatible with **Ferraris et al. 1987.** In this study patients were divided into two groups, group (A) which included 53 patients which were given verapamil hydrochloride and group (B) which included 56 patients which were the placebo group in order to test the efficacy of verapamil in preventing postoperative atrial fibrillation.

In group (A) Postoperative atrial fibrillation occurred in 10 of the 53 (19 %) while in the group B Postoperative atrial fibrillation occurred in 20 of the 56 (36%), these results are compatible with the results of our current study which also showed significantly less incidence of AF in the Verapamil group than placebo group post CABG surgery.

In our study, The patients in the amiodarone group were hospitalized for significantly fewer days in comparison to the placebo group (p value = 0.022) which is compatible with **Daoud et al. 1997** study that showed that, patients in the amiodarone group were hospitalized for significantly fewer days than those in the placebo group (6.52.6 vs. 7.94.3 days, P=0.04), which is compatible with the current study.

Also our study was in compatible with **Alcalde et al. 2006**, in which the amiodarone group were hospitalized for significantly fewer days than those in the placebo group, which is compatible with the current study, that also showed hospitalization for significantly fewer days in amiodarone group than placebo group.

Also These results were compatible with results of **Stamou et al. 2006**, In his work the amiodarone group were hospitalized for significantly fewer days than those in the placebo group (p 0.01), these results were compatible with our results that showed hospitalization for significantly fewer days in amiodarone group than placebo group.

In the current era of reduced health-care funds, shortened hospital stay favorably affects the relative risk/benefit ratio for cardiac operations, and also, reduces the use of hospital resources, and therefore lowers the cost of care.

Conclusion
From the present study we conclude that:
▪ Intravenous infusion of amiodarone as well as Intravenous Verapamil can be successfully used in prevent of AF post CABG.
▪ This study showed a significant reduced in incidence of post operative AF in amiodarone group than in verapamil group.

▪ Amiodarone significantly decrease in length and cost of hospitalization.
▪ Prophylactic amiodarone used inpatients undergoing open-heart surgery was well tolerated and significantly reduced the incidence of postoperative atrial fibrillation, as well as the length and cost of hospitalization in comparison to verapamil and placebo groups.

Recommendations
From the present study we recommend that:
▪ Intravenous infusion of Amiodarone preoperative can be used as antiarrhythmic drug for prevention of AFpost CABG in patient with dilated left atrium.
▪ Amiodarone has the advantages over verapamil in prevention of AF post CAGB.
▪ Dilated left atrium is an important Predictors for occurrence of AF post CABG.
▪ Prevention of AF post CABG decrease length of hospital stay after operation and prevent other complications e.g. stroke.
▪ Proper control of hypertension and diabetes decrease of postoperative complication in CABG patients.
▪ Good Control of elyctrolytes perioperatively prevent occurrence of postoperative complications in CABG patients.
▪ Lift atrium dimensions should be evaluated in all preoperative in patient with CABG.
▪ Appropriate clinical guidelines must be established that Intravenous infusion of Amiodarone preoperative can prevent AF in patients planned for CABG operation.

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