COMPARISON STUDY; FOR EVALUATION OF DIFFERENT DOSES OF ORAL FLECAINIDE AND SOTALOL AS COMBINATION FOR TERMINATION OF ATRIAL FIBRILLATIOSN

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ABSTRACT

Evaluation the efficacy of oral combinations consists of different doses of flecainide and Sotalol for termination of atrial fibrillation and estimate the effective dose in these combinations. 106 hemodynamically stable adult patients, with atrial fibrillation lasting ≤ 48 hours; randomized into groups to receive treatment as follow: Group **1** (N=28): Intravenous amiodarone. The remaining groups treated by oral combinations as single dose. Group **2** (N=17): Flecainide 100mg-metaprolol 50mg. Group **3** (N=21): Flecainide 100mg - Sotalol 80mg. Group **4** (N=21): Flecainide 100mg - Sotalol 120mg. Group **5** (N=19): Flecainide 150mg - Sotalol 80mg. Groups **3**, **4**, **5** as compared with group 1& 2 had significantly (at $p<0.05$) higher conversions rate at 8 and 24 hours and shorter conversion time. Groups **3**, **4**, **5** as compared with group **1** & **2** had no significant differences in QTc prolongation and P wave. Groups **3**, **4**, **5** as compared with group **1** & **2** had only significant differences (at $p<0.05$) in QRS, PR and heart rate changes as compared with group **2**. Group **4** had the shortest conversion time and greatest declining in heart rate. Flecainide - sotalol combinations made higher conversion rate within shorter time than intravenous amiodarone and flecainide–metoprolol combination. (Flecainide 100mg - sotalol 120mg was most efficient) and their effects on ECG data during treatment was not significantly different from intravenous amiodarone..

Keywords: Atrial fibrillation; Amiodarone; Flecainide; Sotalol; Sinus rhythm.

INTRODUCTION

Most published studies; and even in the clinical practice, for termination of atrial fibrillation and restoring sinus rhythm in patients complaining a symptomatic, paroxysmal or persistent, atrial fibrillation; a loading dose of intravenous antiarrhythmic drugs, have been used, these drugs that widely involved include amiodarone, flecainide, ibutilitde, danderone, propafenone etc.[1] or some time used high loading oral dose of flecainide or propafenone in selected patients; as in pills in pocket approach, for same purpose.[2] Some of these pharmacological approaches may be with low efficacy for conversion to sinus rhythm and/or dangerous side effects, especially if they are used in higher doses or for prolonged time; these adverse effects including ventricular proarrhythmias and non-cardiovascular toxicity. Despite these drawbacks, they are able to restore or maintain sinus rhythm significantly better than placebo.[3] Oral combination of currently available antiarrhythmic drugs may be interesting area which may develop further in the near future; since, combining drugs may allow for lower doses of each drug, and potentially reducing the risk of unwanted side effects while maintaining the same or, due to synergism between the drugs, may improve their

antiarrhythmic spectrum.[4] According to our knowledge, Combination of class IC and Class III was only described in only in very small number of case reports.[5] Both oral Flecainide, a class IC, and Sotalol; Class III antiarrhythmic, are characterized by rapid onset after oral dose, they start to act within 3 hours after single oral dose[6,7] and their duration of action may extend to 24 hours.[8] So they probably suitable to be used as oral combination for termination of symptomatic atrial fibrillation.

Aim of the study is to evaluate the efficacy of Sotalol and flecainide as combination therapy; used orally for termination of atrial fibrillation and estimate the effective dose in the combination through measuring of percentage of conversion, time required for termination of atrial fibrillation and restoring sinus rhythm and their effect on ECG data include P, PR, QRS, QT intervals & heart rate.

METHODS

Patient Selection

Criteria for patients selection were adapted from Johann Reisinger *et al* 2004.

Patients' eligibility

All patients, females and males, have been diagnosed as having atrial fibrillation episodes by cardiologist and admitted to Cardiac care unites for treatment. Patients were considered possible candidates for entry into the study; if they have atrial fibrillation diagnosed by ECG and

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with ventricular rate >70 beats/minute at rest, with age range of 18-90 years old and with highly symptomatic episodes lasting ≤ 48 hours. Concurrent control of the ventricular rate with digoxin, beta-blockers, was permitted in some patients.

Patients' exclusion criteria

- Clinical signs of congestive heart failure (New York Heart Association functional class >II)
- Unstable angina pectoris, and acute myocardial infarction within the last 8 weeks
- Hypotension (systolic blood pressure <100 mmHg)
- Severely Asthmatic or with sever COPD
- Any previously documented atrio-ventricular or intraventricular conduction disturbances and conduction blocks or any other rhythm disturbances or patient with pace maker)
- Recent anti-arrhythmic therapy (treatment with class I or III antiarrhythmic within the previous 48 hours or amiodarone within the 6 months)
- Compromised renal function (i.e., serum creatinine >2.5 mg/dl), hepatic insufficiency, uncorrected hypo or hyperkalemia
- Pregnancy and lactation
- Age <18 or >90 years

Collection of Data

Complete medical history, physical examination, routine laboratory results, 12-lead electrocardiogram, and an echocardiogram were obtained at baseline evaluation. Cardiac rhythm was monitored continuously for 24 hours after starting medication.

Patients' allocation and drugs administration

Total number of Patients met criteria was 106, (age 56 ± 1.3 years, range 18-90 years) from two hospitals' Cardiac care units, namely; Al Sadir teaching hospital and Basra general Hospital. Those patients were randomly allocated to groups (by simple randomization); each group would receive the recommended treatment as follow:

Group1 (N=28): Intravenous amiodarone as bolus then maintenance Amiodarone was given as beginning as a loading dose of 150mg as intravenous infusion over 10 minutes then followed by then 1 mg/min (360mg) for next 6 hours, then 0.5 mg/min (540mg) for 18 hours or change to oral dosing. Remaining groups treated by single dose oral combinations as fellow.

Group2 (N=17): Flecainide 100mg and metoprolol tartrate 50 mg tablet.

Group3 (N=21): Flecainide 100mg tablet and Sotalol 80 mg tablet.

Group4 (N=21): Flecainide 100mg tablet and Sotalol 120 mg tablet.

Group5 (N=19): Flecainide 150mg tablet and Sotalol 80 mg tablet.

All doses in flecainide - sotalol combination are less than loading dose of individual drug reported in many published studies. Flecainide used in combination with metoprolol for ventricular rate control, to avoid suspected harmful effect of flecainide induced 1:1 AV conduction; which may convert atrial fibrillation episodes to dangerous ventricular tachycardia or flutters; and to distinguish, whether the effect of sotalol in the combinations is attributed to its beta blocker effect, or due to class III effect. All patients received low molecular heparin (enoxaparin 2000 – 6000 IU Subcutaneously) to reduce risk of thromboembolism.

All actions were done under supervision of authorized staff in CCU units of two Hospitals and under agreement of ethical and scientific committees of Basra Health head office - Ministry of health; number, 2026 in December; 31 2013, in addition to the agreement of each individual patient and committees in college of pharmacy - Baghdad university and college of medicine - Basrah university.

Patients groups were not significantly different in age, gender ratio, and ratio of concomitant diseases and drugs. Also they are not significantly different in ECG data include QRS, QTc and heart rates prior starting treatment. Patients' base line data are summarized in the table **1.**

Table 1. Patients' baseline data

Treatment Group / Patient selection criteria	Intravenous Amiodarone group N=28	Flecainide 100mg + metoprolol 50mg group N=17	Flecainide 100mg + Sotalol 80mg group N=21	Flecainide 100mg + Sotalol 120mg group N=21	Flecainide 150mg + Sotalol 80mg group N=19
Age (years)	59.4 ± 2.9	50.8 ± 2.9	57.9 ± 2.7	55.3 ± 2.1	57.1 ± 3.6
Age Range	23 - 90	34 - 76	32 - 83	36 - 75	23 - 90
Men/women	13/15	8/9	11/10	9/12	9/10
Duration of Atrial fibrillation episode (average) hours	11.8 ± 1.46	11.5 ± 1.2	13.4 ± 1	15.0 ± 1.4	13.8 ± 1.5
Paroxysmal Atrial Fibrillation	19 (67.86%)	9 (52.94%)	15 (71.4%)	10 (47.6%)	11 (63.16%)
Persistent fibrillation	8 (28.57%)	6 (35.3%)	4 (19.1%)	8 (38.1%)	4 (21.05%)
Permanent atrial fibrillation	1 (3.57%)	2 (11.76%)	2 (9.5%)	3 (14.3%)	3 (15.79%)
Concomitant diseases*					
Hypertension	18 (64.3%)	10 (58.8%)	15 (71.4%)	14 (66.7%)	13 (68.4%)
Ischemic heart disease	14 (50%)	3 (17.6%)	6 (28.6%)	5 (23.8%)	7 (36.8%)
Heart failure NYHA(II)	6 (21.4%)	1 (5.9%)	4 (19%)	2 (9.5%)	6 (31.6%)
Diabetes mellitus	10 (35.7%)	5 (29.4%)	6 (28.6%)	3 (14.3%)	6 (31.6%)
Valvular heart disease	2 (7.1%)	3 (17.6%)	1 (4.8%)	2 (9.5%)	1 (5.3%)
Hyperthyroidism	3 (10.7%)	2 (11.8%)	1 (4.8%)	4 (19%)	2 (10.6%)
Asthma/COPD (mild)	5 (17.9%)	3 (17.6%)	4 (19%)	3 (14.3%)	4 (21.1%)
Other data					
Serum potassium (mmol/l)	4.2 ± 0.1	4.2 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.2 ± 0.1
Left atrium size (average) mm³	37.9 ± 1.3	36.8 ± 1.0	38.6 ± 1.1	38 ± 1.2	39.9 ± 1.2

			Concomitant treatment*		
ACE-inhibitors	18 (64.3%)	10 (58.8%)	14 (66.7%)	11(52.4%)	12 (63.2%)
Digoxin	5 (17.9%)	2 (11.8%)	2 (9.5%)	2 (9.5%)	3 (15.8%)
Beta blockers	5 (17.9%)	3 (17.6%)	3 (14.3%)	4 (19%)	4 (21.4%)
			ECG data and heart rate		
Heart Rate (BPM)	133.7 $\pm$ 5.3	138.2 $\pm$ 3.6	146.1 $\pm$ 4.1	135.0 $\pm$ 4.6	132.1 $\pm$ 5.8
QRS wave (msec.)	99.5 $\pm$ 5.3	102.9 $\pm$ 3.6	101.0 $\pm$ 4.1	101.6 $\pm$ 4.6	106.6 $\pm$ 5.8
QTc interval (msec.)	422.5 $\pm$ 17.3	406.1 $\pm$ 12.6	402.5 $\pm$ 18.9	421.0 $\pm$ 9.9	417.7 $\pm$ 16.0

Some patients have more than one concomitant disease or drug treatment ; BPM = beats per minute , msec.= milliseconds

Study end-points and Data measured

The primary end-point was conversion of atrial fibrillation to sinus rhythm within 8 hours and the secondary end point within 24 hours after start of the medications. If sinus rhythm was not restored after 24 hours; ECG data at 24th hour was depended. Time required to restore sinus rhythm; P, PR interval, QRS, QTc, (corrected QT interval; Bazett's correction) Heart Rate, percent of conversion; and other indices were measured.

Statistical analysis

Data analyzed by Microsoft Excel® 2010 software and Medcalc® V12.5 software 2011; which is specialized software for medical data analysis. The means and standard of errors were calculated for different variables, namely age, time before starting drug administration, left atrium size, serum potassium, ECG data ;which include P, PR, QRS, QT, QTc (corrected QT interval; Bazett's correction), and heart rate, in addition to time required to restore sinus rhythm, in all study groups that named above. The significance of differences in means, for above dat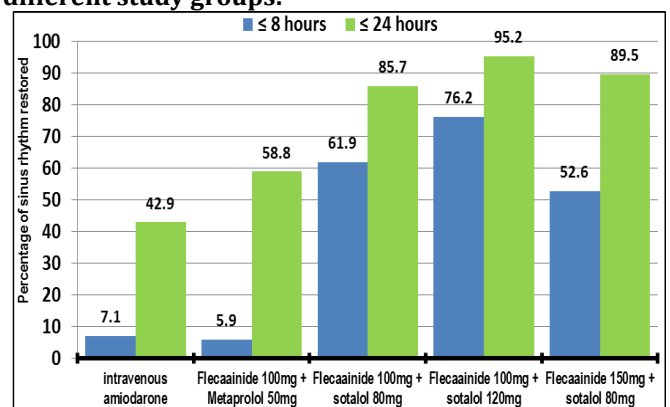a, was determined by using student *t*-test. Chi analysis of frequency was used to compare differences in rate of conversion to sinus rhythm, male/female, class of atrial fibrillation, ratio of concomitant diseases and drugs ratio and other ratios. Finally; P value<0.05 was considered as significant difference.

RESULTS AND DISCUSSION

Effect of treatment on conversion rate and time after 8 hours from staring treatment

Flecainide - sotalol treated groups showed significantly higher conversion rate (at p<0.05) as compared with intravenous amiodarone and flecainide - metaprolol group. Where conversion rate was [13/21 (61.9%); 95% CI= 38.4% - 81.9%] for flecainide 100 mg plus sotalol 80mg, [16/21 (76.2%); 95% CI= 52.8% - 91.8%] for flecainide 100 mg plus sotalol 120mg, and [10/19 (52.6%); 95% CI=28.8% - 75.5%] for flecainide 150 mg plus sotalol 80mg, versus [2/28 (7.1%); 95% CI=0.86% - 23.45%] for intravenous amiodarone and [1/17 (5.9%); 95% CI= 0.15% - 28.7%] for flecainide 100mg plus metaprolol 50mg. (Table **2**)

Table 2. Shows number, percentage of patients restored sinus rhythm within 8 and 24 hours and average time required to restore sinus rhythm from starting treatment in different study groups.

Study groups	Conversion rate at ≤8 hours	Conversion rate at ≤24 hours	Average conversion time (hours)
Intravenous Amiodarone group N=28	**2 (7.1%)** 95% CI= 0.15% - 28.7%	**12 (42.9%)** 95% CI=24.5% - 62.91%	**16.8 $\pm$ 1.8**
Flecainide 100mg + metaprolol 50mg group N=17	**1 (5.9%)** 95% CI=0.86% - 23.45%	**10 (58.8%)** 95% CI= 32.9% - 81.5%	**14.2 $\pm$ 1.2**
Flecainide 100mg + Sotalol 80mg group N=21	**13 (61.9%)**ab 95% CI= 38.4% - 81.9%	**18 (85.7%)**a 95% CI= 63.6% - 96.9%	**8.4 $\pm$ 0.6**ab
Flecainide 100mg + Sotalol 120mg group N=21	**16 (76.2%)**ab 95% CI= 52.8% - 91.8%	**20 (95.2%)**ab 95% CI= 76.1% - 99.8%	**6.8 $\pm$ 0.4** abc
Flecainide 150mg + Sotalol 80mg group N=19	**10 (52.6%)**ab 95% CI=28.8% - 75.5%	**17 (89.5%)**ab 95% CI=66.9% - 98.7%	**8.0 $\pm$ 0.4**abd

a = significant at P<0.05 as compared with values of intravenous amiodarone group; **b** = significant at P<0.05 as compared with values of Flecainide 100mg + Metaprolol 50mg group; **c** = significant at P<0.05 as compared with values of Flecainide 100mg + Sotalol 80mg group; **d** = significant at P<0.05 as compared with values of Flecainide 100mg + Sotalol 120mg group; **CI** = confidence interval

Effect of treatment on conversion rate and time after 24 hours from staring treatment

There were increments in conversion rate; Flecainide 100mg - sotalol 120mg and flecainide 150mg - sotalol 80mg groups had significantly higher conversion rate (at p<0.05) as compared with intravenous amiodarone and flecainide 100mg - metaprolol 50mg groups. While flecainide 100mg - sotalol 80mg group showed only significant higher conversion rate (at p<0.05) as compared with intravenous amiodarone group. Where conversion rate was [18/21 (85.7%); 95% CI= 63.6% - 96.9%] for flecainide 100 mg plus sotalol 80mg, [20/21 (95.2%); 95% CI= 76.1% - 99.8%] for flecainide 100 mg plus sotalol 120mg, [17/19 (89.5%); 95% CI=66.9% - 98.7%] for flecainide 150 mg plus sotalol 80mg, versus [12/28 (42.9%); 95% CI=24.5% - 62.91%] for intravenous amiodarone and [10/17 (58.8%); 95% CI= 32.9% - 81.5%] for flecainide 100mg plus metaprolol 50mg. There were no significant differences (at p<0.05) between flecainide - sotalol groups in rate of conversion to sinus rhythm at 8 and 24 hours after treatment. (Figure **1**)

Figure 1. Percentage of patients restored sinus rhythm within ≤8 hours and ≤ 24 hours; after treatment in different study groups.

Also all flecainide - sotalol treated groups showed significantly shorter conversion time (at p<0.05) as compare with intravenous amiodarone and flecainide - metaprolol groups. Flecainide 100mg - sotalol 120mg group showed significantly shortest conversion time (at

p<0.05) as compared with other study groups. Where conversion times were (8.4 ± 0.6 hours) for flecainide 100mg plus sotalol 80mg, (6.8 ± 0.4 hours) for flecainide 100mg plus sotalol 120mg and (8.0 ± 0.4 hours) for flecainide 150mg plus sotalol 80mg, versus (16.8 ± 1.8 hours) for intravenous amiodarone and (14.2 ± 1.2 hours) for flecainide 100mg-metaprolol 50mg. (Figure **2**)

Figure 2. Average time (hours) required for restoring sinus rhythm after treatment; in different study groups.
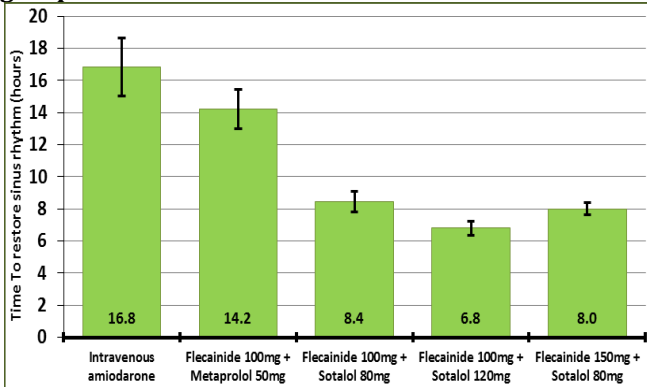
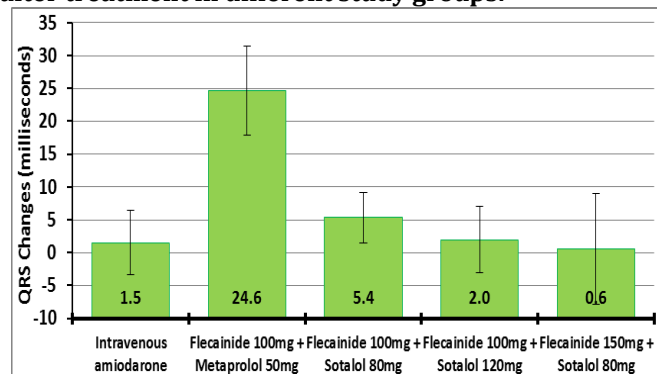**Effect of treatment type on heart rate and ECG Data**
Effect of treatment type on QRS wave prolongation: Flecainide - sotalol groups and intravenous amiodarone group were not differ significantly (at p<0.05) in QRS

wave prolongation; but these groups differ significantly (at p<0.05) from flecainide 100mg - metaprolol 50mg group which showed higher magnitude of prolongation; Flecainide –sotalol treated groups are also insignificantly different (at p<0.05) from each other in their effect on QRS duration. Where the magnitudes of QRS elongation were (5.4 ± 3.8 milliseconds) for flecainide 100mg plus sotalol 80mg, (2.0 ± 5.0 milliseconds) for flecainide 100mg plus sotalol 120mg, and (0.6 ± 8.4 milliseconds) for flecainide 150mg plus sotalol 80mg, versus (1.5 ± 4.9 milliseconds) for intravenous amiodarone and (24.6 ± 6.7 milliseconds) for flecainide 100mg plus metaprolol 50mg. (Table **3**, Figure **3**)

Effect of treatment type on QTc intervals: Flecainide - sotalol treated groups were not significantly different in magnitude of QTc prolongation (at p<0.05) and they are not significantly differ (at p<0.05) from flecainide 100mg - metaprolol 50mg and intravenous amiodarone groups. Where the magnitudes of QTc prolongation were (55.7 ± 17.5 milliseconds) for flecainide 100mg plus sotalol 80mg, (48.4 ± 11.6 milliseconds) for flecainide 100mg plus sotalol 120mg, and (26.2 ± 23.4 milliseconds) for flecainide 150mg plus sotalol 80mg, versus (21.8 ± 16.1 milliseconds) for intravenous amiodarone and (56.0 ± 26.4 milliseconds) for flecainide 100mg plus metaprolol 50mg. (Table **3** figure **4**)

Table 3. Shows effects of treatment type on average declining in heart rate and changes in ECG data including QRS, QTc, PR interval and P wave durations. Data are expressed as mean ± Standard error.

Study groups	QRS elongation (milliseconds)	QTc elongation (milliseconds)	Heart rate declining (beats/minute)	P Wave Duration (Milliseconds)	PR interval (Milliseconds)
Intravenous Amiodarone group N=28	1.5 ± 4.9	21.8 ± 16.1	37.8 ± 7.2	122.1 ± 7.0	164.1 ± 9.0
Flecainide 100mg + metaprolol 50mg group N=17	24.6 ± 6.7[a]	56.0 ± 26.4	35.8 ± 5.1	120.3 ± 4.3	179.7 ± 4.1
Flecainide 100mg + Sotalol 80mg group N=21	5.4 ± 3.8[b]	55.7 ± 17.5	56.5 ± 7.2[b]	124.6 ± 6.8	151.4 ± 6.9[b]
Flecainide 100mg + Sotalol 120mg group N=21	2.0 ± 5.0[b]	48.4 ± 11.6	57.3 ± 4.7[ab]	111.9 ± 0.7	153.4 ± 1.6[b]
Flecainide 150mg + Sotalol 80mg group N=19	0.6 ± 8.4[b]	26.2 ± 23.4	43.5 ± 6.4[b]	115.9 ± 2.3	150.8 ± 3.7[b]

a = significant at P<0.05 as compared with values of intravenous amiodarone group; **b** = significant at P<0.05 as compared with values of Flecainide 100mg + Metaprolol 50mg group

Figure 3. Average Changes in QRS wave durations; after treatment in different study groups.


Effect of treatment type on the Heart rates: Flecainide-sotalol treated groups showed significant greater slowing in heart rate (at p<0.05) as compared with flecainide 100mg plus metaprolol 50mg group. In addition to that; flecainide 100mg plus sotalol 120mg showed significantly slowing in heart rate (at p<0.05) as compared with intravenous amiodarone group. Where heart rate declining were (56.5 ± 7.2 bpm) for flecainide 100mg plus sotalol 80mg, (57.3 ± 4.7 bpm) for flecainide 100 mg plus sotalol 120mg, and (43.5 ± 6.4 bpm) for flecainide 150mg plus sotalol 80mg, versus (37.8 ± 7.2 bpm) for intravenous

**Figure 4. Average Changes in QTc intervals; after treatment in different study groups.**
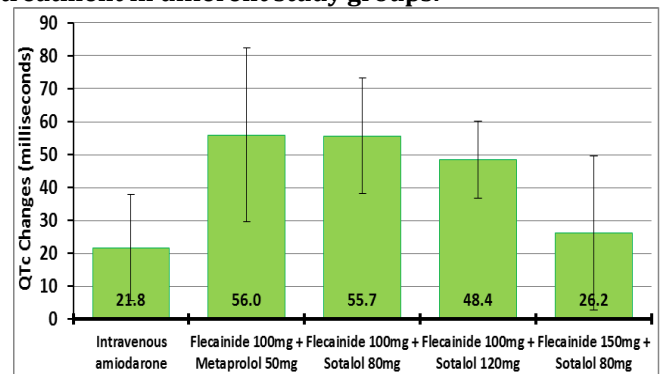
amiodarone and (35.8 ± 5.1 bpm) for flecainide 100mg plus metaprolol 50mg. (Table **3**, figure **5**)
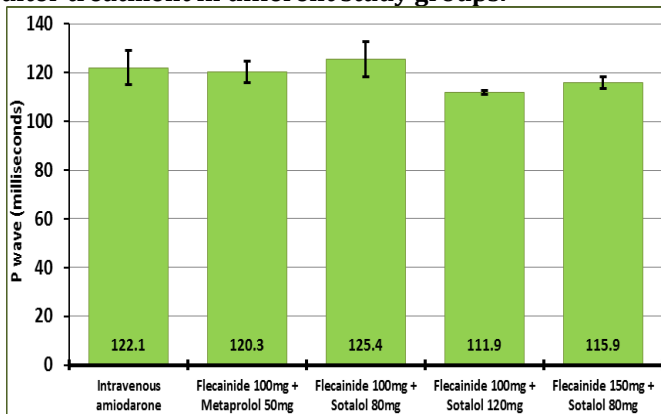
Effect of treatment type on P waves: Table **3** showed that; all study groups were not significantly different (at p<0.05) in P wave duration after sinus rhythm was restored. Where P wave durations were (124.6 ± 6.8 milliseconds) for flecainide 100mg plus sotalol 80mg, (111.9 ± 0.7 milliseconds) for flecainide 100mg plus sotalol 120mg, and (115.9 ± 2.3 milliseconds) for flecainide 150mg plus sotalol 80mg, versus (122.1 ± 7.0 milliseconds) for intravenous amiodarone and (120.3 ±

4.3 milliseconds) for flecainide 100mg plus metaprolol 50mg. (Figure **6**)

Figure 5. Average declining in hearts rate in beats per minute; after treatment in different study groups.
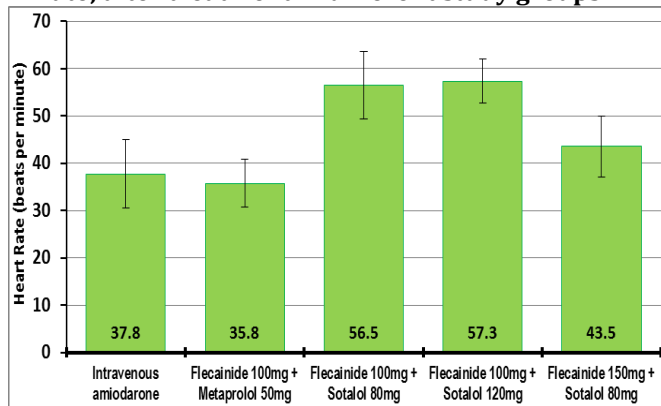

Figure 6. Average P wave durations in milliseconds after treatment in different study groups.

Effect of treatment type on PR intervals: Flecainide-sotalol treated groups showed only significant shorter (at p<0.05) PR intervals as compared with flecainide 100mg plus metaprolol 50mg group. Where PR intervals were (151.4 $\pm$ 6.9 milliseconds) for flecainide 100mg plus sotalol 80mg, (153.4 $\pm$ 1.6 milliseconds) for flecainide 100mg plus sotalol 120mg, and (150.8 $\pm$ 3.7 milliseconds) for flecainide 150mg plus sotalol 80mg, versus (164.1 $\pm$ 9.0 milliseconds) for intravenous amiodarone and (179.7 $\pm$ 4.1 milliseconds) for flecainide 100mg plus metaprolol 50mg. (Figure **7**)

Figure 7. Average PR interval durations in milliseconds, after treatment, in different study groups
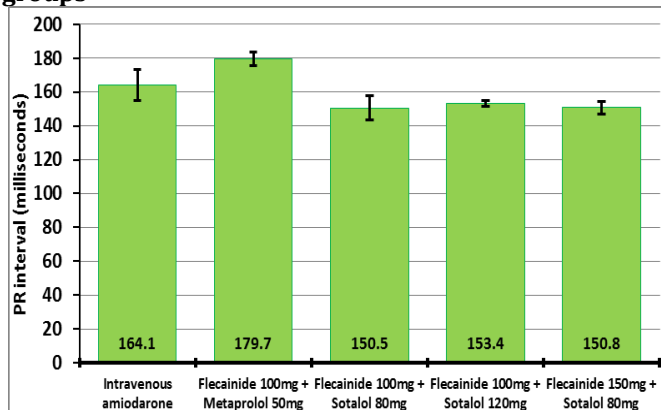
Discussion

Amiodarone is well known and widely used as intravenous infusion to control symptomatic atrial fibrillation. It has low conversion rate, even at higher doses, and conversion to sinus rhythm, if it happened, may occur late, mostly more than 12 hours.[10] Also, amiodarone has not been consistently more efficacious than placebo in converting paroxysmal atrial fibrillation to normal sinus rhythm[11]; and reported conversion rate in this study is in agreement with published converting rate from 35% to 84% within 24 hours.[12] Flecainide characterized by high conversion rate, approximately 90%, when used in large intravenous dose[13] and vary (40 -90%), when maximum oral dose was used.[14,15] Metaprolol a beta blocker is effective in maintaining sinus rhythm and controlling the ventricular rate during atrial fibrillation. It was not effective for restoring sinus rhythm in paroxysmal atrial fibrillation.[16]

The combination of oral flecainide 100mg-metaprolol 50mg, the surprise is, the conversion rate of this combination was not differ significantly (at p<0.05) from intravenous amiodarone at 8 hours and after 24hours from starting treatment (which consider somewhat as low); in the face of the use of flecainide, which reported to have higher conversion rate for termination of paroxysmal atrial fibrillation.[15] It seems to be this conversion rate is related to dose where most published study reported conversion rate reach to 75% - 95% within 8 hours[15,17], and probably same at 24 hours, after using large oral doses 200-300mg.[18] But this study finding was in agreement with finding of Nakazato Y et al 1997, who reported conversion rate of (52%) after single daily dose of 200mg oral flecainide.[19]

Sotalol, like amiodarone, has class III antiarrhythmic activity with beta-blocker effect.[2] These class III agents, increase action potential duration and refractoriness in atrial tissue without affecting conduction. Sotalol was significantly less effective for termination of atrial fibrillation of recent onset (< 48 hours) to sinus rhythm. Conversion rates for sotalol in all studies combined ranged from 8-49%. Published studies do not support the drug for conversion of atrial fibrillation to sinus rhythm.[20] Both sotalol and flecainide have fast onset of action after oral administration; approximately within 3 hours.[21-23]

The combinations of flecainide and sotalol in this study showed additive or synergistic effect to restore sinus rhythm, producing significant higher conversion rate (at p<0.05) as compared with intravenous amiodarone and oral flecainide - metaprolol combination within 8 hours. After 24 the picture is same.

Except combination of flecainide 100mg - sotalol 80mg show no significant difference in conversion rate (at p<0.05) as compared with flecainide - metaprolol combination, possible explanation is that, flecainide - sotalol produced additive effect by combined of class IC effect of flecainide with both Class III and beta-blocking activity, of sotalol, this pharmacological effect of sotalol vary according to dose and plasma concentration. At low concentration, the predominant pharmacological effect is beta-blockade; while class III effect required higher plasma concentration, which achieved rapidly after oral administration.[24] Where; reported Tmax, "time required to reach maximum plasma concentration" for sotalol is occurred within 3 hours after oral administration, that why additive effect was pronounced within first 8 hours after treatment. After that plasma concentration will be declined ($t_{0.5}$ =15 hours) due to excretion process resulting in declining its class III effect and predominate beta blocker effect.[25] So that there is no significant differences (at p<0.05) in conversion rate were found between flecainide 100mg - sotalol 80 mg and flecainide 100mg-metaprolol 50mg, after 24 hours from starting treatment. Increasing dose of sotalol to 120mg in combination with

100mg flecainide made significant elevation (at $p<0.05$) of conversion rate as compared with flecainide - metaprolol, and amiodarone at 8 and 24 hours after treatment, Increasing dose of sotalol probably led to increase in class III effect[26]; and probably maintain additive effects of class IC of flecainide, with class III and Beta blocker effects of sotalol after 8 and 24 hours after treatment.

Flecainide antiarrhythmic action is dose related. Flecainide, in addition to its inhibitory effect on excitatory sodium channels (class IC effect), it has potent potassium channel blocking effect, (partial class III effect)[27,28]

At smaller concentrations (half maximal inhibitory concentration, flecainide blocks the cardiac fast inward Na+ current (INa) (Class IC effect) and the rapid component of the delayed rectifier K+ current (IKr). (partial Class III effect).[29] At higher concentrations, flecainide also inhibits the late Na+ current and other cardiac K+ channels. (Significant Class III effect).[30] Therefore, using flecainide dose of 150mg will increase these effects; resulting in prolongation in atrial effective refractiveness and slowed ectopic firing. This action is enhanced by predominant beta blocker effect of sotalol 80mg, which probably predominant after 24 hours from starting treatment, thus; the additive effects of Class Ic, III, and beta blocker effect will be maintained.[31] Since Flecainide action may persist due to longer half-life that reach to 27 hours.[32] Which may explain significant higher conversion rate (at $p<0.05$) by combination of flecainide 150mg plus 80 mg sotalol as compared with flecainide 100mg plus metaprolol 50mg and intravenous amiodarone.

Generally use of flecainide and sotalol as combination produce favorable additive effect by increasing conversion rate better than amiodarone or flecainide - metaprolol combination. Significantly shorter time required for conversion (at $p<0.05$) by the treatment with flecainide - sotalol combinations is in agreement with above explanations.

Effects of treatment on ECG data: Flecainide widens the QRS complex. Significant widening in QRS[32-34] not only induced by intravenous loading dose of flecainide but even after acute administration of oral doses smaller than maximum loading dose.[35] These study findings are in agreement with finding of Boriani G et al; 1993 and Kingma JH et al 1992.

Sotalol may alter QRS duration in variable degrees, and it may reduce average QRS duration in some circumstances.[36] Thus; unlike to flecainide - metaprolol, addition of sotalol to flecainide; it resulted significantly less prolongation (at $p<0.05$) in QRS duration as compared with flecainide - metaprolol group; and this effect was not significantly different (at $p<0.05$) from intravenous amiodarone. This may be related to potential similarity in pharmacological spectrum of flecainide - sotalol combination and amiodarone.

QTc-interval prolongation may be related to selective blockade of the delayed rectifying potassium current (IKr), which related to pharmacological actions of sotalol[2,26] and flecainide[29] as prescribed early and a reverse rate dependence (related to sotalol).[26] But proarrhythmia potential is probably low with these agents that are able to block multiple ion channels, despite QT prolongation.[37]

Amiodarone[38], Sotalol[39,40] and metoprolol all have ability to reduce heart rate[41]. While flecainide has variable effect on heart rate, where bradycardia and tachycardia have been occasionally reported.[32] It is reported that sotalol slow down heart rate in magnitude greater than metoprolol.[41,42] That's why flecainide-sotalol combination shows significantly greater slowing in heart rate (at $p<0.05$) as compared with flecainide - metaprolol. This slowing in heart rate that induced by sotalol is dose depended; where in low doses (≤160mg). This action may be related to beta blocker effect of sotalol rather than Class III antiarrhythmic effect.[43] Therefore; increasing dose of sotalol to 120mg will result in significantly more slower heart rate which is observed in flecainide 100 - sotalol 120mg treated group. Where; heart rate was significantly slowest (at $p<0.05$) as compared with other groups include intravenous amiodarone group. Where; Sotalol reduce heart rate in greater magnitude than amiodarone when used in dose greater than 80mg.[44]

A prolonged signal averaged P wave duration and the presence of low-voltage atrial late potentials may be useful in identifying patients at risk for developing Paroxysmal atrial fibrillation[45,46], Indeed, P-wave-triggered signal-averaged ECG may have some prognostic value, as a P wave duration ≥145 milliseconds can be used as one of predictors of development of permanent atrial fibrillation.[47] So I think, probably high proportions of patients in all groups have low risk for development of new paroxysmal or permanent atrial fibrillation.

All the drugs used in the study; including amiodarone, Flecainide, metoprolol and sotalol causing AV nodal conduction delay and PR interval prolongation in variable degrees.[48] But; the prolongation induced by these drugs did not exceed normal range (120 to 200 milliseconds).[49,50]

The significant larger average PR interval reported by Flecainide 100-metoprolol 50mg may related to additive effect of metoprolol to Flecainide; which resulted in greater PR interval prolongation[32,51]; through more AV nodal conduction delay induced by this combination.[51,52] Although sotalol has beta adrenergic blocking effect; and Sotalol alone may prolong PR interval[53], but; the surprise is; its use as combination with flecainide, resulted in an effect not differ significantly (at $p<0.05$) from amiodarone induced AV nodal conduction depression or PR interval prolongation.[54] I think, the combination of flecainide and sotalol resulted in pharmacological action resemble; in certain degree, to that of amiodarone, which has multiple ion channels blocking activities; in addition to beta adrenergic blocking effect. Therefore; this combination showed no significant different (at $p<0.05$) from amiodarone on PR interval.[2]

CONCLUSION

Flecainide - sotalol oral combinations in doses lower than loading dose of individual drug; are highly efficient (high conversion rate) to restore sinus rhythm and do that more rapidly; which may reduce hospital stay and cost, although it is not measured in this study. Flecainide 100mg - sotalol 120mg oral combination showed highest conversion rate and shorter time for conversion. So; it could be considered better than other flecainide - sotalol combination tested in this study. These combinations have been found not significantly different from effect of intravenous amiodarone, at least on short term, on ECG data including P, PR, QRS, QTc and heart rate (flecainide 100mg - sotalol 120mg combination better than amiodarone in slowing heart rate).

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