ROLE OF ASCORBIC ACID & STATIN IN REDUCTION OF THE INCIDENCE OF THE ATRIAL FIBRILLATION IN PATIENTS UNDER B-BLOCKER AND UNDERGOING CORONARY ARTERY BYPASS GRAFT OPERATION IN EARLY POST-OPERATIVE PERIOD

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Abstract
Atrial fibrillation (AF) is the most common sustained arrhythmia that is associated with significant morbidity and mortality. Current available treatments remain ineffective for symptom management and secondary prevention and are often associated with serious side effects. While electrophysiological remodelling has been identified as a significant initiating stage, the mechanisms underlying AF pathogenesis are poorly understood. Growing research recently has implicated oxidative stress and inflammation in AF pathogenesis. In order to support the use of antioxidant vitamins C and anti-inflammatory statin combined with B-blocker in the prevention of AF post CABG, we searched the literature for proof. Antioxidant vitamin C has shown a role in AF prevention post CABG through its reactive-oxygen-species-(ROS-) scavenging impact.

Methodology: A prospective controlled randomized study will include three hundred patients aged from 40 to 65 years of both sexes. They will be divided into three groups of patients:

**Group I:** A hundred (CABG) patients commenced on only B-blocker for at least one week pre-operatively.

**Group II:** A hundred (CABG) patients commenced on B-blocker & ascorbic acid for at least one week pre-operatively.

**Group III:** A hundred (CABG) patients commenced on B-blocker & statin for at least one week pre-operatively.

Results: 24 patients out of 100 patients in the 1st group experienced atrial fibrillation, compared with 6 out of 100 in the 2nd group, and 7 out of 100 patients in the 3rd group experienced atrial fibrillation.

Conclusion: combination of B-blocker with ascorbic acid & statin is better than B-blocker alone in reduction of atrial fibrillation after CABG in early post operative period.

Introduction: With the exception of sinus tachycardia, the most common arrhythmia that accompanies coronary artery bypass grafting (CABG) (1) is atrial fibrillation. Depending on the precise meaning used, the recorded occurrence of atrial fibrillation after CABG varies widely. The way in which patients undergo postoperative monitoring and the profile of patients undergoing CABG (2). In studies involving 300 or more patients, the frequency of post-CABG atrial fibrillation ranges from 10% to 30% (3)....
fibrillation ranged between 17 and 40 percent (3). A higher frequency of postoperative atrial fibrillation is seen in patients undergoing combined CABG and valve surgery than in patients undergoing CABG alone (4).

In most cases, 80% of patients return to sinus rhythm within 1 to 3 days after initiation of digoxin or β-blocker therapy (1), but patients who experience postoperative atrial fibrillation have substantially higher monthly mortality rates (5). In most cases, atrial fibrillation after CABG is self-limited. The clear prophylactic efficacy of β-adrenergic blockers has been demonstrated in several randomised trials, and all patients without contraindications should receive β-blockers before and after cardiac surgery (4). β-blockers alone, however, are not adequate. Post-CABG atrial fibrillation prevention and antiarrhythmic medication administration can be ineffective and even dangerous, likely due to pro-arrhythmic and other side effects (6).

The function of inflammation and oxidative stress in electrical remodelling is currently being studied. Therapeutic interventions targeting inflammation and oxidative stress may have beneficial effects on atrial electrical remodelling (7). Ascorbate can minimise electrical remodelling and the occurrence of postoperative atrial remodelling may be reduced. Because of fibrillation (8).

Aim of the work:
The goal of this research was to assess the effectiveness of β-blocker, statin, and ascorbic acid combination therapy in achieving further reduction of post-CABG atrial fibrillation compared to β-blocker therapy alone in the early post-operative period.

Patients and Methods:-
study design:
1. A prospective controlled randomized study includes (three hundred patients aged from 40 to 65 of both sexes).
2. They will be divided into three groups of patients:
3. The first group: A hundred (CABG) patients will commence on B-blocker only (bisoprolol...5mg-once-per-day) for at least one week pre-operatively.
4. The second group: A hundred (CABG) patients will commence on B-blocker (bisoprolol...5mg-once-per-day) & ascorbic acid (2 gram-daily) for at least one week pre-operatively.
5. The third group: A hundred (CABG) patients commence on B-blocker (bisoprolol...5mg-once-per-day) & statin (ator...40mg-once-per-day) for at least one week pre-operatively.
6. Patient will be followed up for atrial fibrillation after (CABG) for the short term (one week post-operative).
7. The research will concentrate on evaluating the role of ascorbic acid & statin in reducing the incidence of atrial fibrillation in patients undergoing B-blocker and short-term coronary artery bypass graft surgery.
8. Study made from January, 2019 to August, 2020, at National Heart Institute.

Patients:
The patients with ischemic heart diseases who need surgical intervention in the form of CABG surgery will be the candidates for the study.

Inclusion criteria:
1. The patients who will participate in the study will sign a form of an informed written consent.
2. Elective cases of CABG.
3. Patients with ejection fraction above 30%.
4. Patients with one to four grafts.
5. Sinus isolated ischemic heart disease without other cardiac disease (rheumatic, congenital, etc ….)
6. With or without non significant ischemic mitral regurgitation which doesn't necessitate mitral valve surgery.

Exclusion criteria:
1. CABG associated with significant ischemic mitral regurgitation which necessitates mitral valve surgery.
2. Patients who underwent CABG before.
3. Emergency cases of CABG.
4. Patients with ejection fraction less than 30%.
5. Patients have contraindications to B-blocker or ascorbic acid or statin.
6. Ischemic heart disease with other cardiac disease (rheumatic, congenital, etc ….).

Steps of surgery:
1. Preoperative preparation and anesthesia.
2. Full median sternotomy & Harvesting left internal mammary artery (LIMA) & saphenous vein graft (SVG).
3. Aorto-caval cannulation, then starting cardiopulmonary bypass.
4. Cross clamping of ascending aorta & administrating cardioplegia (anti-grade warm cardioplegia).
5. Applying the distal & proximal anastomosis.
6. Finally, weaning from cardiopulmonary bypass & applying drains and closure in layers after hemostasis.
7. In off pump surgery, usage of heart stabilizer (octopus-Medtronic) without need to cross clamp or cardioplegia. Also usage of sialastic with or without intra coronary shunts.

Post-operatively:
1. Routine ICU admission and ventilation.
2. Using inotropic agents when indicated.
3. Prophylactic antibiotics for 5 days.
4. Drains removed when drainage stops.

End point:
1. Side effects of B-blocker for example (Heart block, bradycardia, and bronchial asthma).
2. Hypersensitivity symptoms and gastritis caused by ascorbic acid & statin.

Judgment criteria:
The main judgment criteria will be:
1. Vital signs (blood pressure, temperature, pulse, urine output, & oxygen saturation).
2. ECG first day, 48 hours, and end of the first week.
3. Echocardiography.

Intraoperative assessment:
1. Number and sites of anastomosis.
2. The need for inotropic drugs after revascularization.
3. The need for intra aortic balloon pump.
4. Cardiac bypass time.
5. Aortic cross clamp time.

Results:-
Table (1):- Descriptive table.

| Items                              | Control group | Vitamin C Group | Statin Group | Tests |
|------------------------------------|---------------|-----------------|--------------|-------|
|                                    | Group I       | Group II        | Group III    |       |
| N                                  | %             | N               | %            |       |
| Gender                             | Female        | 44              | 44.0         | 44    | 44.0    | 0.245 | 0.885 |
|                                   | Male          | 56              | 56.0         | 59    | 59.0    | 56    | 56.0    |
| Mean age                           | 55.67±5.3     | 53.86±5.3       | 51.96±4.7    |       |
| Hypertension                       | 43            | 43.0            | 47            | 47.0  | 45      | 45.0  | 0.323 | 0.851 |
| Diabetes mellitus                  | 58            | 58.0            | 61            | 61.0  | 58      | 58.0  | 0.102 | 0.950 |
| Smoking                            | 57            | 57.0            | 58            | 58.0  | 54      | 54.0  | 0.352 | 0.838 |
| Family history of CAD              | 39            | 39.0            | 35            | 35.0  | 45      | 45.0  | 2.117 | 0.347 |
| Non significant ischemic mitral regurgitation | 15 | 15.0            | 13            | 13.0  | 14      | 14.0  | 0.143 | 0.931 |
| Inotrop during first 24 hr after surgery | 71 | 71.0            | 57            | 57.0  | 70      | 70.0  | 5.437 | 0.066 |
| Ventilation time > 24 hr           | 4             | 4.0             | 5             | 5.0   | 1       | 1.0   | 2.690 | 0.261 |
| off pump                           | 6             | 6.0             | 5             | 5.0   | 7       | 7.0   | 0.355 | 0.838 |
| AF                                 | 24            | 24.0            | 6             | 6.0   | 7       | 7.0   | 18.929 | <0.001* |
| Mean LV ejection fraction %        | 53.3±4.9      | 54.7±5.4        | 54.1±5.9     | 0.085 | 0.925 |
| Mean diameter of left atrium (cm)  | 3.8±0.9       | 3.6±0.2         | 3.6±0.2      | 0.890 | 0.412 |
| Mean LV end-systolic diameter (cm) | 3.8±0.3      | 4.5±0.9         | 3.8±0.2      | 1.776 | 0.171 |
| Mean LV end-diastolic diameter(cm) | 5.4±0.5      | 5.6±0.6         | 5.6±0.7      | 0.089 | 0.915 |
| Mean NO. of grafted vessels        | 2.7±0.6       | 2.8±0.5         | 2.7±0.6      | 0.683 | 0.506 |
Graph 1: As shown in graph 1: there is a high significant statistical difference among 3 groups as regard the occurrence of atrial fibrillation as P value is <0.001. AF is much lower in groups II & III than group I. Moreover, it is lower in group II than both groups I & III.

Table (2): Intensive care unit stay.

| Groups                  | Mean intensive care unit stay (day) | ANOVA |
|-------------------------|-------------------------------------|-------|
|                         | Range                              | Mean  | ±    | SD  | f   | P-value |
| Group I                 | 2 - 5                              | 2.640 | ±   | 1.059 | 12.835 | <0.001* |
| Group II                | 2 - 5                              | 2.150 | ±   | 0.520 |       |        |
| Group III               | 2 - 5                              | 2.180 | ±   | 0.609 |       |        |

Tukey's test

|                  | Group I & Group II | Group I & Group III | Group II & Group III |
|------------------|--------------------|--------------------|----------------------|
|                  | <0.001*            | <0.001*            | 0.959                |

Table (2): As shown in table 2: There is a high significant statistical difference among 3 groups as regard the intensive care unit stay as P value is <0.001. As intensive care unit stay is much lower in groups II & III than group I. More over, it is lower in group II than both groups I & III.

Table (3): Group I (Qualitative data).

| Group I Control | No | Yes | Total | X²  | P-value |
|-----------------|----|-----|-------|-----|---------|
| Sex             |    |     |       |     |         |
| Female          | 38 | 50.0| 6     | 25.0| 44      | 44.0 | 4.627 | 0.031* |
| Male            | 38 | 50.0| 18    | 75.0| 56      | 56.0 |       |        |
| Hypertension    |    |     |       |     |         |
| No              | 47 | 61.8| 10    | 41.7| 57      | 57.0 | 3.029 | 0.082 |
| Yes             | 29 | 38.2| 14    | 58.3| 43      | 43.0 |       |        |
| Diabetes mellitus|   |     |       |     |         |
| No              | 32 | 42.1| 10    | 41.7| 42      | 42.0 | 0.001 | 0.970 |
| Yes             | 44 | 57.9| 14    | 58.3| 58      | 58.0 |       |        |
| Smoking         |    |     |       |     |         |
| No              | 37 | 48.7| 6     | 25.0| 43      | 43.0 | 4.174 | 0.041* |
| Yes             | 39 | 51.3| 18    | 75.0| 57      | 57.0 |       |        |
| Family history of CAD |    |     |       |     |         |
| No              | 49 | 64.5| 12    | 50.0| 61      | 61.0 | 1.606 | 0.205 |
| Yes             | 27 | 35.5| 12    | 50.0| 39      | 39.0 |       |        |
| Non significant ischemic mitral regurgitation | No | 72 | 94.7 | 13 | 54.2 | 85 | 85.0 | 23.547 | <0.001* |
Table (3):
As shown in table 3:
1. With regard to the frequency of AF in gender, there is a substantial statistical difference between Group I. P value = 0.031 as it occurs more in males than in females.
2. There is a significant statistical difference among group I as regard the occurrence of AF in smokers. As it happens more in smoker patient P value = 0.041
3. There is a high significant statistical difference among group I as regard the occurrence of AF in patient with non significant ischemic mitral regurgitation. As it is more frequent with non significant ischemic mitral regurgitation P value = <0.001.
4. There is a high significant statistical difference among group I as regard need of inotropic support during 1st 24 hours after surgery. As inotropic support needed more with AF patient P value = <0.001.
5. There is a high significant statistical difference among group I as regard the need of ventilation more than 24 hours. AF patient needed to be ventilated more than patient without AF P value=<0.001.

Table (4):- Group I (Quantitative data).

| Group I | AF | Yes | Total |
|---------|----|-----|-------|
|         | Mean ± SD | Mean ± SD | t   | P-value |
| Age     | 53.474 ± 4.968 | 51.292 ± 5.321 | -0.657 | 0.513 |
| Mean LV ejection fraction % | 52.632 ± 4.424 | 47.250 ± 3.915 | 5.333 | <0.001* |
| Mean diameter of left atrium (cm) | 3.562 ± 0.186 | 4.700 ± 0.819 | -1.721 | 0.088 |
| Mean LV end-systolic diameter (cm) | 3.846 ± 0.317 | 3.846 ± 0.296 | 0.003 | 0.998 |
| Mean LV end-diastolic diameter(cm) | 5.535 ± 0.528 | 5.613 ± 0.523 | -2.108 | 0.038* |
| Mean aortic cross-clamp time(min) | 54.139 ± 6.647 | 59.217 ± 9.180 | -2.894 | 0.005* |
| Mean pump perfusion time (min) | 91.931 ± 8.088 | 101.217 ± 13.003 | -4.088 | <0.001* |
| mean intensive care unit stay (day) | 2.079 ± 0.271 | 4.417 ± 0.504 | -29.325 | <0.001* |

Table (4):-As shown in table 4 regarding group I:
1. There is a high significant statistical difference among group I as regard the occurrence of AF & it's relation to mean LV ejection fraction. As it happens more in lower LV ejection fraction P value = <0.001.
2. There is a significant statistical difference among group I as regard the occurrence of AF & it's relation to mean LV end-diastolic diameter. As it happens more in larger LV end-diastolic diameter patient P value = 0.038.
3. There is a significant statistical difference among group I as regard the occurrence of AF & it's relation to Mean aortic cross-clamp time. As it is more frequent with longer aortic cross-clamp time P value = 0.005.

Table (5):- Group II (Qualitative data).

| Group II | Vitamin C | AF(n=6) |
|----------|-----------|---------|
|          | Yes | Total | Chi-square |
|          | N % | N % | X² | P-value |
| Sex      |     |      |    |        |
| Female   | 38  | 40.4 | 3  | 50.0 | 41 | 41.0 | 0.214 | 0.644 |
| Male     | 56  | 59.6 | 3  | 50.0 | 59 | 59.0 |        |        |
| Hypertension | No | 51 | 54.3 | 2 | 33.3 | 53 | 53.0 | 0.991 | 0.319 |
There is a significant statistical difference among group II as regard the occurrence of AF & its relation to non significant ischemic mitral regurgitation. As it is more frequent with non significant ischemic mitral regurgitation P value = <0.001.

There is a significant statistical difference among group II as regard need of inotropic support during 1st 24 hours after surgery. As inotropic support needed more with AF patient P value = 0.028.

There is a significant statistical difference among group II as regard the occurrence of AF & it's relation to mean intensive care unit stay. As intensive care unit stay is longer with AF patient P value = <0.001.

### Table (6): Group II (Quantitative data).

| Group II | AF | No | Yes | T-test | P-value |
|----------|----|----|-----|--------|---------|
|          |    | Mean ± SD | Mean ± SD | t | |
| Age      |    | 51.628 ± 5.014 | 52.500 ± 8.019 | -1.765 | 0.081 |
| Mean LV ejection fraction % |    | 54.872 ± 5.206 | 50.412 ± 6.615 | 2.003 | 0.047* |
| Mean diameter of left atrium (cm) |    | 3.565 ± 0.211 | 3.633 ± 0.121 | -0.783 | 0.436 |
| Mean LV end-systolic diameter (cm) |    | 4.525 ± 0.014 | 3.867 ± 0.137 | 0.320 | 0.750 |
| Mean LV end-diastolic diameter(cm) |    | 5.576 ± 0.752 | 5.583 ± 0.560 | -0.004 | 0.997 |
| Mean aortic cross-clamp time(min) |    | 53.197 ± 4.758 | 49.200 ± 4.109 | 2.008 | 0.046* |
| Mean pump perfusion time (min) |    | 88.270 ± 6.625 | 93.970 ± 7.222 | 2.034 | 0.044* |
| Mean intensive care unit stay (day) |    | 2.032 ± 0.177 | 4.000 ± 0.632 | -20.893 | <0.001* |

### Table (7): Group III (Qualitative data).

| AF(n=7) | Group III Statin | Chi-square | Total | Yes | No | P-value |
|---------|------------------|------------|-------|-----|----|---------|
|         |                  | X^2 | % | N | % | N | N |
| 0.394   | 0.727            | 44.0 | 44 | 28.6 | 2 | 45.2 | 42 | Female | Sex |
| 56.0    | 56               | 71.4 | 5  | 54.8 | 51 | Male |    |
Discussion:
Coronary artery bypass graft surgery (CABG) is an successful treatment for ischemic heart disease, but the incidence of atrial fibrillation following CABG is known to be one of the main problems associated with unpleasant effects and mortality.
Clinical studies have consistently shown that the combination of ascorbic acid and statins with b-blocker is better than b-blocker alone in reducing post-coronary artery bypass surgery risk and improving post-operative performance.

Our data shows that, when higher doses of statin combined with beta blockers atrial fibrillation incidence will be reduced postoperatively. Previously, Kourliouros et al had also found that higher dose statins were associated with greater reduction in postoperative AF (9).

Other studies have shown that when compared with on-pump surgery, the use of off-pump surgery did not substantially affect CRP and fibrinogen levels or the WBC count postoperatively (10).

Carnes and colleagues demonstrated a shortening of the atrial effective refractory period (ERP) with rapid atrial pacing. Treatment with ascorbate attenuated the pacing-induced atrial ERP shortening following 24 to 48 hours of pacing. This is in keeping with the established link between ERP changes and early development of AF (11).

Shiroshita-Takeshita et al. compared the effect of vitamin C and E on atrial remodeling to that of simvastatin. Dogs were fitted with internal atrial pacing and were subjected to 1 week of atrial tachypacing (12).

Regarding the predictors of postoperative atrial Fibrillation, we examined age, hypertension, left ventricular ejection fraction, family history, history of smoking, history of diabetes mellitus gender, and left atrial diameter as risk factors of postoperative AF.

We also analyzed the relationship between postoperative AF and number of grafts, duration of aortic cross-clamping, duration of cardiopulmonary bypass, operation performed (beating heart vs. not beating heart ), mild ischemic mitral regurgitation, Inotrop during first 24 hr after surgery & ventilation time more than 24 hours.

The most notable difference between the previous studies and the present investigation was that our study compared the effect of combination of both statin & ascorbic acid with b-blocker in three different groups, whereas, other studies compared the effect of combination of only ascorbic acid or statin respectively with b-blocker in 2 groups.

Another notable difference between the current and past study cohorts was that most of previous studies didn't exclude valvular operations, enlargement of left atrium, and other risk factor of atrial fibrillation which were excluded in our study to avoid any bias in the result of our study.

Our data shows that There is a high significant statistical difference among three groups as regard the occurrence of atrial fibrillation as P value is <0.001.

As AF is much lower in second group which is commenced on vitamin C plus b.blocker & third group which is commenced on statin plus b.blocker than first group which is commenced on b.blocker alone. Moreover, it is lower second group than first & third group

These findings are close to those of Eslami et al, which showed that oral ascorbic acid is more efficient than beta-blockers alone in preventing atrial fibrillation after coronary artery bypass grafting when combined with beta-blockers (13).

Also similar to those of Mithani et al. which showed that among cardiac surgery patients treated with postoperative beta blockers & Statin treatment the incidence of postoperative AF is reduced (14).

There is a strong substantial statistical difference between both groups regarding the frequency of AF in patients with mild ischaemic mitral regurgitation, as it is more normal with non-significant ischaemic mitral regurgitation P value = < 0.001. Another noteworthy difference between the present and past cohorts of the study was.

Current data suggest that off-pump surgery does not reduce incidence of postoperative AF as compared with on-pump surgery, this agree with the results in other studies, which is similar to Eslami et al (13).

In contrast, these results do not coincide with Buffiolo et al (15)
Also, we found a high significant relationship between AF patients & need for ventilation more than 24 hours in all groups. As AF patient needed to be ventilated more than patient without AF P value =<0.001. This result met with Banach et al (16)

**Conclusion:**
Postoperative Atrial Fibrillation is considered one of the most serious complications after CABG.

Our study showed that postoperative Atrial Fibrillation was less frequent in patients who treated with b.blocker combined with vitamin C & Statin than patients who treated with b.blocker alone (P value =<0.001). So, vitamin C & Statin in combination with Beta Blockers is more effective than Beta-Blockers alone in the prevention of atrial fibrillation after coronary artery bypass grafting in early post operative period.

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