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Perioperative beta-blocker and its effect on coronary artery bypass graft patients outcome after surgery

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Abstract

Background: Beta-adrenergic receptor blockers have been studied for minimizing the effects of catecholamines by blocking their activation of beta receptors. They are used to prevent or treat hypertensive crises, tachycardia, ischemic cardiomyopathy, and arrhythmias. Several studies have shown the efficacy of such drugs in decreasing postoperative morbidity and mortality.

Aim of the study: This study aimed to evaluate the benefit of perioperative beta-blocker therapy in improving the outcome of CABG surgery regarding intra- and postoperative arrhythmias and ventricular function.

Method: It was a prospective controlled nonrandomized study conducted on 50 patients undergoing elective CABG in Ain Shams University hospitals, in which the study group, who were the patients who were compliant on beta-blocker therapy, received 1 mg of propranolol before removal of aortic cross clamp and continued on beta-blocker therapy in the postoperative period, while the control group who were not on beta-blocker therapy received an equivalent volume of normal saline before removal of aortic cross clamp and received beta-blocker therapy in the postoperative period. Both groups were assessed regarding the heart rate, ventricular systolic function by transesophageal echo intraoperatively and transthoracic echo postoperatively, duration of ICU and hospital stay, and incidence of intra- and postoperative arrhythmias.

Results: Perioperative beta-blockers decreased the incidence of intra- and postoperative arrhythmias.

Conclusion: In the absence of contraindications, CABG patients should receive perioperative beta-blockers as they improve the systolic ventricular function, decrease the incidence of intra- and postoperative arrhythmias, and shorten the duration of hospital and ICU stay.

Keywords: Beta-blockers, Propranolol, Coronary artery bypass surgery

Background

Beta-adrenergic receptor blockers have been studied for minimizing the effects of catecholamines by blocking their activation of beta receptors. They are used to prevent or treat hypertensive crises, tachycardia, ischemic cardiomyopathy, and arrhythmias, mainly supraventricular arrhythmias. Several studies have shown the efficacy

of such drugs in decreasing postoperative morbidity and mortality (Bosco & Braz, 2001).

It is proved that beta-adrenergic antagonists (β -blockers) attenuate the extent of injury to myocardium during periods of ischemia and reperfusion. The negative inotropic and chronotropic effects of these drugs are thought to have beneficial effects to the ischemic myocardium by reducing myocardial oxygen consumption, decreasing sympathetic tone, reducing myocardial usage of substrates, and stabilizing cell membranes (Bessho & Chambers, 2001).

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Beta-blocker therapy in the perioperative period has the potential to reduce perioperative cardiovascular complications such as myocardial ischemia, stroke, and heart failure by neutralization of tachycardia and catecholamine-induced hypertension. The function of ventricles can be improved by early beta-blocker administration during cardiopulmonary bypass (CPB) (Sun et al., 2011).

Beta-blocker therapy should be maintained throughout the perioperative period to keep the desired drug effects and to prevent the risk of hyperactivity of the sympathetic nervous system with abrupt discontinuation of the drugs due to the upregulation of receptors (Stoelting et al., 2015).

Aim of the work

This study aimed to evaluate the benefit of perioperative beta-blocker therapy in improving the outcome of

CABG surgery regarding intra- and postoperative arrhythmias and ventricular function.

Methods

This study was a prospective controlled nonrandomized study conducted at Ain Shams University hospitals after obtaining approval of research ethical committee and informed consents from patients during from February 1, 2018 to December 31, 2018.

Study population

Sample size: based upon the difference in the auto-rebeat ratio of 33% in the study group compared to 86% in the study group of the previous study done by Sun et al. (2011), MedCalc® version 12.3.0.0 program “Ostend, Belgium” was used for calculations of sample size; 25 patients in each group would be enough to detect such difference with statistical calculator based on 95% confidence interval and power of the study 80% with α error

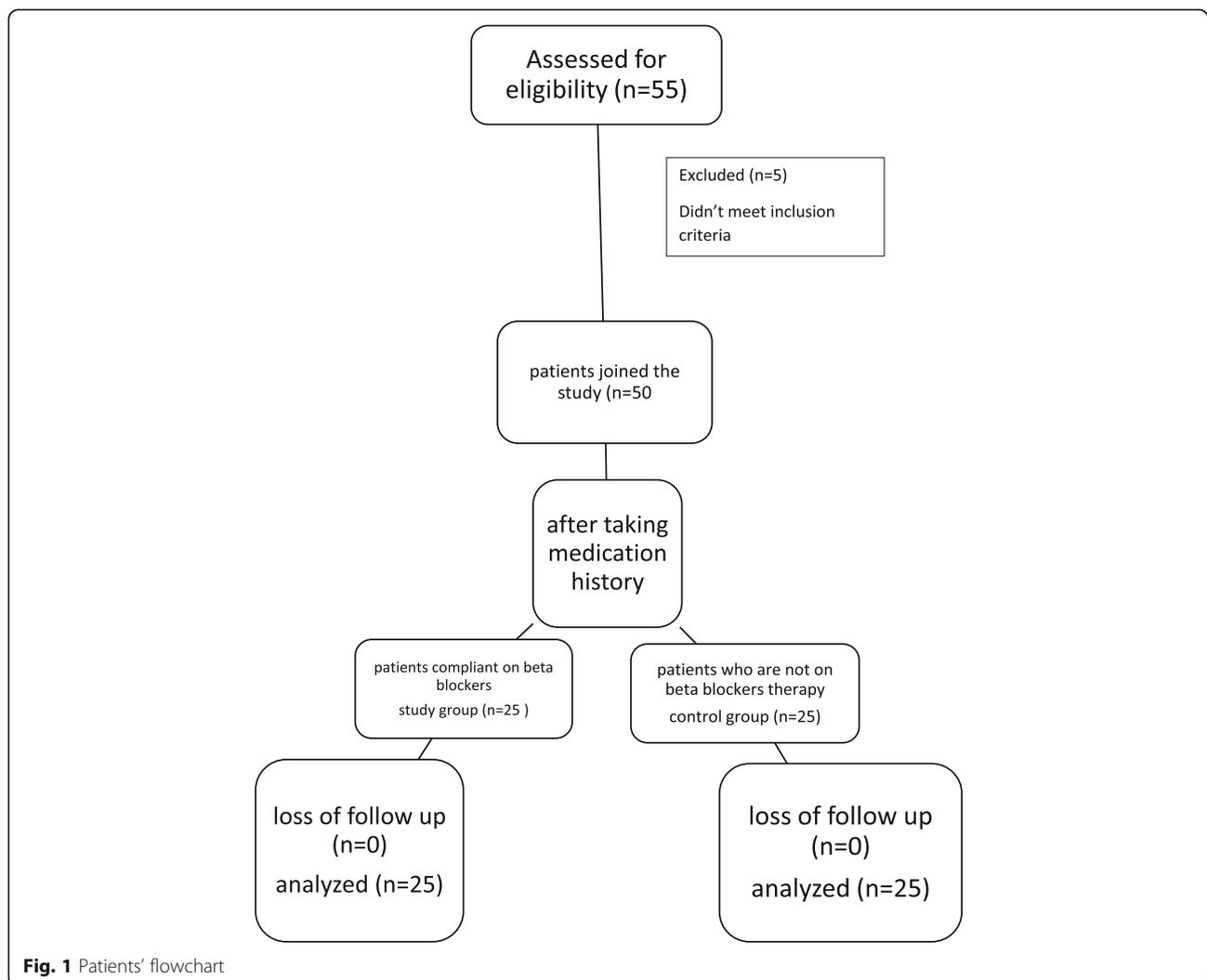


Fig. 1 Patients' flowchart

5%. Fifty patients joined the study; after taking medication history, those who were compliant on oral beta-blocker till night of the operation were identified as the study group, and who were not on preoperative beta-blocker therapy were identified as the control group (Fig. 1).

Inclusion criteria: patient of both sexes between the age of 40 and 70 years undergoing elective CABG surgery

Exclusion criteria:

1. Patient refusal
2. Poor ventricular function with ejection fraction below 40%
3. Asthmatic patients
4. Combined surgeries (CABG+ valves)
5. Emergency surgeries
6. Pre-existing arrhythmia
7. Patients with heart block
8. Off-pump CABG

Study procedure

All patients received alprazolam 0.5 tablet on the night before surgery.

In preparatory room, pulse oximeter and 5 lead electrocardiogram were attached, and under the effect of local anesthetic, intra-arterial catheter 20 G for invasive blood pressure monitoring (basal arterial blood gases (ABG) was withdrawn on room air), wide bore intravenous cannula 16 G, and central venous catheter triple lumen were placed in situ.

All patients received sedation in form of midazolam (0.03–0.05 mg/kg IV) and were transferred to operating room where general anesthesia was induced with thiopentone 3–5 mg/kg (titrated dose), fentanyl 5–10 µg/kg (titrated dose), rocuronium 1 mg/kg followed by endotracheal intubation confirmed by capnography and equality was checked by auscultation of four lung zones and epigastrium.

Intraoperative monitoring included pulse oximeter, invasive arterial blood pressure, capnography, 5-lead ECG showing the two waves simultaneously of lead II and lead V, temperature probe (nasopharyngeal), transesophageal echocardiography (TEE), and urinary catheter was also placed in situ for urine output monitoring.

Patients were then maintained on oxygen 60%, isoflurane and muscle relaxant infusion rocuronium at rate of 0.01 mg/kg/min and during bypass is done by propofol 0.1 mg/kg/min and rocuronium infusion 0.01 mg/kg/min.

During cardiopulmonary bypass (CPB), all myocardial preservation protocols were followed, cold cardioplegia was used, and temperature was maintained between 30 and 32 °C.

The study group received 1 mg of propranolol prior to removal of aortic clamp and resumed oral beta-blocker the day next to the operation, while the control group received equal volume of isotonic saline before removal of the aortic clamp.

Patients were assessed regarding the following:

- Primary outcome measured: incidence of intra- and postoperative arrhythmias ventricular fibrillation (VF) and atrial fibrillation (AF)
- Secondary outcome measured:
- Vital data (mean arterial blood pressure and pulse) at times:
 - T0 before induction
 - T1 just after induction
 - T2 before going on CPB
 - T3 after weaning from CPB
 - T4 immediately after transfer to ICU
- Ventricular functions pre-bypass and post-bypass using the TEE (global systolic function EF by M mode, regional wall motion abnormalities (RWMA), postoperative by transthoracic echocardiography (TTE) using global systolic function EF by M mode, regional wall motion abnormalities on day of surgery and the following day).
- Duration of mechanical ventilation
- Postoperative need of inotropes and assistive mechanical devices
- The need for pacemaker
- Length of ICU stay
- Length of hospital stay

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, IL, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-sample *t* test of significance was used when comparing between two means.
- Chi-square (χ^2) test of significance was used in order to compare proportions between qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p* value was considered significant as the following:
- Probability (*p* value)
 - *p* value < 0.05 was considered significant.
 - *p* value < 0.001 was considered as highly significant.
 - *p* value > 0.05 was considered insignificant.

Table 1 Demographic data

Demographic data	Control group (n = 25)	Study group (n = 25)	t/ χ^2 #	p value
Age (years)				
Range	40–70	40–70	0.679	0.503
Mean \pm SD	58.76 \pm 8.23	57.20 \pm 8.01		
Sex				
Male	16 (64.0%)	15 (60.0%)	0.087	0.768
Female	9 (36.0%)	10 (40.0%)		
Time of operation (h)				
Range	5–7	5–7	0.639	0.526
Mean \pm SD	6.40 \pm 0.90	6.24 \pm 0.87		

Results

The study was performed on 55 patients undergoing elective CABG, 5 patients were excluded as they met the exclusion criteria of the study. The remaining 50 patients were allocated to the groups of the study. The patients included in the study were nearly of the same age group ranging from 40 to 70 years, 60% were males due to higher incidence of IHD in males (Table 1).

The study group showed significantly lower heart rate both intra- and postoperatively as the beta-blockers. The results show a significant difference between the two groups regarding automatic re-beat and regaining the sinus rhythm as the initial reperfusion rhythm; it was higher in the study group as 72% of the study group, compared to the control group which was 48%, regained the sinus rhythm spontaneously after the removal of the cross clamp, while the control group needed electric and pharmacological cardioversion in about 52%, increasing the time needed to wean from CPB in the control group more than the study group. The postoperative arrhythmias were mainly AF, with much higher rate in the control group about 40% compared to the study group which was only 20%.

There was no significant difference regarding the need for inotropic drugs between the two groups, neither in the number of patients needed nor in the rate of their infusion, as the propranolol in this dose minimally affect the blood pressure. Mechanically assistive devices and pacemaker were not used in any of the patients included in the study.

There was a significant difference in the length of ICU and hospital stay 2.18 ± 1.16 and 7.62 ± 2.32 days respectively in the study group compared to 3.05 ± 1.14 and 9.16 ± 2.28 days in the control group; this difference

is mainly to manage the increased incidence of postoperative arrhythmias which was higher in the control group.

Table 2 shows statistically significant difference between groups regarding CPB time (min).

Table 3 shows no statistically significant difference between groups regarding mean arterial blood pressure (mmHg).

Table 4 shows a significant lower heart rate of study group compared to control group regarding heart rate (beat/min).

Table 5 shows a significantly higher EF, shorter duration of hospital and ICU stay, and lower incidence of intra- and postoperative arrhythmias in the study group compared to control group.

Discussion

The 50 patients included in the study were nearly of the same age group ranging from 40 to 70 years, 60% were males due to higher incidence of IHD in males.

The results show a significant difference between the two groups regarding automatic re-beat and regaining the sinus rhythm as the initial reperfusion rhythm; it was higher in the study group as 72% of the study group, compared to the control group which was 48%, regained the sinus rhythm spontaneously after the removal of the cross clamp, while the control group needed electric and pharmacological cardioversion in about 52%, increasing the time needed to wean from CPB in the control group more than the study group. These results go with the results of the study done by Sun et al. (2011)3 which showed 86% automatic re-beat in patients given beta-blockers during CPB except they used esmolol infusion instead of single-dose propranolol, and also with the results published by Ahuja et al. (2016) where 90% of

Table 2 CPB and aortic cross-clamp time

CPB time (min)	126.48 \pm 24.03	108.12 \pm 20.54	2.904	0.006*
Aortic cross-clamp time (min)	56.14 \pm 11.05	53.04 \pm 10.08	1.036	0.305

t independent sample t test, # χ^2 chi-square test, p value > 0.05 NS

*p value < 0.05 S

Table 3 MAP (mmHg)

MAP (mmHg)	Control group (n = 25)	Study group (n = 25)	t test	p value
T0	87.96 ± 7.04	84.92 ± 6.79	1.554	0.127
T1	78.86 ± 6.31	76.84 ± 6.15	1.618	0.118
T2	76.84 ± 6.15	73.80 ± 5.90	1.684	0.110
T3	70.77 ± 5.66	74.81 ± 5.99	1.549	0.124
T4	69.76 ± 5.58	73.80 ± 5.90	1.425	0.140

t independent sample t test, p value > 0.05 NS

patients receiving beta-blockers intraoperative regained auto-re-beat after removal of the cross clamp.

There was a significant improvement in ventricular function and regional wall motion abnormality among the study group detected by both the TEE intraoperatively and the TTE postoperatively, so the β -blockers are supposed to decrease the extent of myocardial injury during ischemia and reperfusion. It also protects the myocardium from the surge of the catecholamines produced during the period of the aortic cross clamp during CPB. The negative inotropic and chronotropic effects of these drugs are thought to reduce myocardial oxygen consumption, decrease sympathetic tone, and stabilize cell membranes, thereby exerting a beneficial effect on ischemic myocardium; these results go with the results published by Cork et al. (1995).

The postoperative arrhythmias were mainly AF, with much higher rate in the control group about 40% compared to the study group which was only 20%. AF is a well-known complication of cardiac surgery increasing the length of hospital stay and is associated with a greater risk of postoperative congestive heart failure, cerebrovascular stroke, and mortality as published by Peretto et al. (2014).

While betablockers are used routinely nowadays, in the past, they were not frequently administered in the perioperative period for patients undergoing CABG, for fear of that they would affect the myocardial contractility increasing the harm than benefit. In fact, in the 1980's CABG operations were to be postponed if patients had been given preoperative beta-blockers, due to the belief

they would lead to increased risk of surgical mortality, until the first study against this beliefs. Chen et al. (2000) reported that beta-blocker therapy was safe and effective for CABG patients, improving the 1-year rate of survival of MI patients undergoing CABG surgery.

Ferguson et al. (2002) published the same results after observational study using the database of Society of Thoracic Surgeons evaluating the outcomes of more than 600,000 CABG patients who had their surgery done between 1996 and 1999. Based on these results, preoperative beta-blocker became the standard of care for patients undergoing CABG.

Most recently, Wang et al. (2018) performed a meta-analysis of 6 observational studies with over 1 million patients to evaluate the effects of beta-blocker therapy before CABG surgery. Wang reported that perioperative mortality or complication rates were not significantly reduced by beta-blocker therapy. This recent study has increased uncertainty if preoperative beta-blocker therapy can affect perioperative outcomes. Perhaps the outcomes from surgical coronary revascularization have improved to the point where there is no additional benefit from preoperative beta-blocker therapy that meets the threshold of statistical significance.

Conclusion

For patients undergoing CABG, our study has suggested that perioperative beta-blocker therapy is beneficial, improving LV functions, decreasing ICU and hospital stay, and decreasing rate of intraoperative and postoperative arrhythmias. In the absence of contraindications, nearly

Table 4 Heart rate (beat/min)

Heart rate (beat/min)	Control group (n = 25)	Study group (n = 25)	t test	p value
T0	72.79 ± 5.82	64.70 ± 5.18	4.192	< 0.001**
T1	70.77 ± 5.66	56.62 ± 4.53	9.752	< 0.001**
T2	76.84 ± 6.15	61.67 ± 4.93	8.281	< 0.001**
T3	92.00 ± 7.36	72.79 ± 5.82	10.237	< 0.001**
T4	95.03 ± 7.60	75.83 ± 6.07	7.300	< 0.001**

t independent sample t test,

**p value < 0.001 HS

Table 5 Ventricular functions (EF), duration of mechanical ventilation (h), postoperative need of inotropes, auto-re-beat ratio, length of ICU stay (days), length of hospital stay (days), postoperative AF

Ventricular functions (EF%)	Control group (n = 25)	Study group (n = 25)	t test	p value
Intraoperative by TEE	53.42 ± 5.70	58.46 ± 4.92	3.347	0.002*
Postoperative by TTE	52.47 ± 3.42	57.51 ± 4.56	4.421	< 0.001**
Length of mechanical ventilation (h)	Control group (n = 25)	Study group (n = 25)	t test	p value
Mean ± SD	12.16 ± 3.50	10.83 ± 2.92	1.291	0.078
Post-operative need of inotropes	Control group (n = 25)	Study group (n = 25)	χ^2	p value
Needed	23 (92%)	20 (80%)	0.664	0.415
Not needed	2 (8%)	5 (20%)		
Auto-re-beat ratio	Control group (n = 25)	Study group (n = 25)	χ^2	p value
Auto-re-beat	12 (48%)	18 (72%)	6.083	0.048*
The rest	13 (52%)	7 (28%)		
Length of ICU stay (days)	Control group (n = 25)	Study group (n = 25)	t test	p value
Mean ± SD	3.05 ± 1.14	2.18 ± 1.16	2.675	0.011*
Length of hospital stay (days)	Control group (n = 25)	Study group (n = 25)	t test	p value
Mean ± SD	9.16 ± 2.28	7.62 ± 2.32	2.367	0.022*
Postoperative AF	Control group (n = 25)	Study group (n = 25)	χ^2	p value
Yes	10 (40%)	5 (20.0%)	3.481	0.027*
No	15 (60%)	20 (80.0%)		

t independent sample t test, χ^2 chi-square test

p value > 0.05 NS

*p value < 0.05 S

**p value < 0.001 HS

all CABG patients are candidates for perioperative beta-blocker therapy. However, further study is necessary to confirm its perioperative benefits, including the conduct of a definitive large randomized clinical trial of CABG patients, with adequate statistical power, focusing on the incidence of AF and other postoperative clinical endpoints.

Abbreviations

ABG: Arterial blood gases; AF: Atrial fibrillation; CABG: Coronary artery bypass graft; CPB: Cardiopulmonary bypass; EF: Ejection fraction; ICU: Intensive care unit; LV: Left ventricle; RWMA: Regional wall motion abnormality; TEE: Transesophageal echocardiography; TTE: Transthoracic echocardiography; VF: Ventricular fibrillation

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Authors' contributions

ME designed the study, revised literature, followed up the patients, and critically reviewed the manuscript; WR designed the study, analyzed the data, and wrote and critically revised the manuscript; OS revised literature, followed up the patients, collected the data, performed the analysis, and wrote the manuscript; MT revised literature, followed up the patients, collected the data, performed the analysis, and wrote the manuscript. All authors approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Approval of research ethical committee of Faculty of Medicine, Ain-Shams University was obtained (code number: FMASU M D 32/2018) and informed consent was obtained from patients or their first degree relatives.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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