The Effect of Ramipril When Administered Early After Coronary Artery Bypass Grafting Surgery

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Access this article online

Quick Response Code:

Website: www.innovativepublication.com

DOI: 10.5958/2394-4994.2015.00026.8

INTRODUCTION

The use of angiotensin converting enzyme inhibitors (ACEI) after coronary artery bypass graft surgery (CABG) has been under debate for more than a decade. The various randomized controlled trials and retrospective studies have produced mixed results. However all the studies done so far focused on long term mortality and adverse cardiac events. A recent prospective study did conclude that continuation of ACEI therapy or de novo initiation of ACEI therapy, after CABG is associated with improved in hospital outcomes.[1] The early administration of ACEI (<7 days after CABG) has also been associated with adverse events with no improvement in clinical outcome upto 3 years after CABG (IMAGINE trial).[2] However, as has been documented for B blockers and statins, studies are yet to demonstrate a long term survival benefit for ACEI.[3,4] It has also been proven that compared to ACEI alone, a combination of ACEI and B blockers is more beneficial for patients who have suffered acute myocardial infarction.[3] Because of their survival benefit B blockers and statins are started early in the postoperative period (postoperative day 1) but clinicians are still wary to start ACEI early. So the ACEI are usually initiated on postoperative day 3 or 4, if started at all.

The angiotensin converting enzyme II has different effects on cardiac and vascular system. There is a rapid pressor response in form of direct vasoconstriction which may be mediated by increased sympathetic discharge, adrenal medullary catecholamine release and vascular responsiveness to noradrenaline. This effect is the first to recover in patients who stop their ACEI just prior to surgery. Likewise this effect should also be the first to be blunted at the initiation of ACEI therapy. Other effects of ACE II which are blunted by ACEI is a slow pressor response (mediated by sodium reabsorption and direct renal vasoconstriction) and growth factors mediated vascular and cardiac remodeling.

This study was designed to analyze the acute effects of ramipril on the hemodynamic parameters of patients who have undergone CABG with the aid of cardiopulmonary bypass when ramipril is initiated in the early postoperative period.

PATIENTS AND METHODS

This prospective observational study was conducted over a period of 6 months at cardiothoracic centre AIIMS. Inclusion Criteria: Adult patients with coronary artery disease destined to undergo Coronary Artery Bypass Grafting (CABG) surgery and taking ACEI for more than 3 months atleast. Exclusion Criteria: CAD with concomitant valvular heart disease, renal disease, Redo CABG, Off pump coronary artery bypass graft surgery, permanent pacemeker, history of angioedema with ACEI therapy, postoperative use of Intraaortic counterpulsation balloon pump and development of atrial fibrillation.

Preoperatively, as per institutional protocol, all the patients received their cardiac medications 2 hours prior to surgery except for angiotensin converting enzyme inhinbitors (ACEI) and angiotensin receptor blockers (ARB). Morphine suphate (0.1mg/kg) and promethazine (0.5mg/kg) was given, intramuscularly, as premedication 1 hour prior to surgery. In the operating room (OR), ECG, pulse oximetry, invasive arterial pressure monitoring and central venous pressure monitoring were obtained. Bispectral Index (BIS) monitor (Aspect Medical Systems, USA) was applied after the induction of anaesthesia and maintained between 40-60.

General anesthesia was induced with intravenous midazolam 2 mg, fentanyl 3-5 ugm/kg and thiopentone 3-5 mg/kg. Endotracheal intubation was facilitated by intravenously administered rocuronium bromide in a dose of 1 mg/kg. The lungs were mechanically ventilated with a tidal volume of

8ml kg^{-1} and a mixture of air and oxygen in the ratio of50:50 The ventilator parameters were adjusted to attain a PaCO2 of 35-40 mmHg. Maintenance of anaesthesia (BIS 40-60) was done using additional boluses of fentanyl and midazolam. Intravenous vecuronium bromide 0.1mg kg^{-1} was administered intermittently to maintain neuromuscular blockade.

All patients underwent hypothermic (32 deg C) cardiopulmonary bypass with the same standard protocol. At the time of rewarming, intravenous nitroglycerine and dopamine were started in doses of 0.5 and 5 µg kg^{-1} min^{-1}, respectively to enable separation from CPB. All patients will be rewarmed gradually to a nasopharyngeal temperature of 36 deg centigrade (as per the institutional protocol) and pacing was instituted if the heart rate was less than 80 beats per minute. After surgery all patients were transferred to the intensive care unit (ICU). They were weaned off mechanical ventilation as soon as they were normothermic, hemodynamically stable (with no major bleeding) and had achieved adequate level of consciousness.

After extubation, inotropes and vasodilators were tapered slowly. Once the inotropes have been stopped for atleast 2-3 hours patients were administered oral B blockers and statins. Tab Ramipril 5 mg was started, once a day, at least 24 hours after B blockers and, in cases of severe hypertension 6 hours after B blockers. All observations were made under the same standard settings. The following parameters were recorded at the described time intervals: Heart rate (HR), Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP). ICON monitor (Osypka Medical, germany) was used to measure other parameters like, Systemic vascular resistance index (SVRI), Cardiac index (CI), Left ventricular ejection time (LVET), Stoke volume variation (SVV) and Thoracic Fluid Content (TFC). Time intervals: T1: Before starting ACEI but after starting B blockers (at least 6 hours); T2: 24 hours after starting ACEI and T3: 48hours after starting ACEI.

STATISTICAL ANALYSIS

Demographic, preoperative and post-operative data was expressed as mean ± standard deviation or proportion. The hemodynamic variables were expressed as mean ± SD and were compared using repeated measures analysis of variance (ANOVA) where a p value of < 0.05 was taken as significant.

RESULTS

Table 1 shows the demographic and pre-operative data of the patients. Thirty two patients were enrolled in this study. There was no statistically significant difference in heart rate, diastolic blood pressure, mean arterial pressure, left ventricular ejection time and stroke volume variation at all the three time intervals. Twenty four hours after initiation of ramipril systolic blood pressure (SBP) decreased but this was not statistically significant. Thereafter a significant increase in SBP occurred at 48 hours (128.00 ± 14.93 vs 119.50 ± 23.03 mm Hg) after the intiation of ramipril. The SVRI was comparable to baseline at 24 hours after ramipril but decreased significantly 48 hours later (1979.60 ± 484.49 vs 2219.38 ± 463.17). Both cardiac index and TFC decreased marginally at T2 time point in comparison to baseline. However, compared to T2 time point both the variables increased significantly at T3 interval (3.23 ± 0.46 vs 3.01± 0.35 l/min and 25.75 ± 9.28 vs 22.75 ± 3.77 Ω^{-1}, respectively).

Table 3 shows the postoperative variables. Four patients developed atrial fibrillation and 2 patients required IABP support. One patient developed renal injury (as per RIFLE criteria) in the postoperative period and one more was reintubated.

Table 1: Demographic Data

S No	Variable	Values
1	Age (y)	55.22 ± 8.61
2	Weight (kg)	62.77 ± 6.82
3	Gender (Male/ Female)	29/3
4	Body Surface Area (m2)	1.66 ± 0.21
5	Diabetics (n)	9/32
6	Smokers(n)	6/32
7	Hypertensives (n)	28/32
8	Patients on Nitrates (n)	28/32
9	Patients on B blockers(n)	25/32
10	Ejection Fraction(%)	50.55 ±11.63
11	Cardiopulmonary Bypass time(min)	81.00 ± 19.10

12	Aortic cross clamp time (min)	42.88 ±12.18

Table 2: Comparison of different hemodynamic variables as measured by ICON monitor at three different time intervals

Variable	T1 (before ACEI)	T2 (24 H after ACEI)	T3 (48 h after ACEI)
HR (/min)	92.87± 18.23	93.50 ± 18.10	95.62 ± 15.13
SBP (mm Hg)	126.37 ± 24.48	119.50 ± 23.03	128.00 ± 14.93*
DBP (mm Hg)	69.62 ± 11.2	69.5 ± 9. 9	72.62 ± 7.48
MAP (mm Hg)	89.00 ± 13.72	85.87 ± 13.84	90.87 ± 7.37
SVRI (dyn.s.cm^{-5}/m^2)	2215.40±636.3	2219.38 ± 463.17	1979.60 ± 484.49*
CI (l/min/m^2)	3.21 ± 0.79	3.01± 0.35	3.23 ± 0.46*
LVET (msec)	267.38 ± 35.14	256.13 ± 37.62	254.25 ± 32.03
SVV (%)	14.62 ± 6.39	14.50 ± 2.39	14.50 ± 4.24
TFC (kΩ $^{-1}$)	23.25 ±3.88	22.75 ± 3.77	25.75 ± 9.28*

*****pvalue < 0.05 - significant

Table 3: Postoperative variables

	Variable	Value
1	Mediastinal Chest tube drainage (ml)	450.36 ± 263.12
2	Packed Red Blood cells (ml)	558.90 ± 324.33
3	Fresh Frozen Plasma (ml)	385.71 ± 301.1
4	Platelet concentrates (ml)	51.78 ± 54.30
5	Reexploration (n)	2/32
6	Duration of mechanical ventilation (h)	14.89 ± 16.31
7	Duration of ICU stay (h)	45.0 ± 25.01

*ICU – intensive care unit

DISCUSSION

In the recent past, a significant amount of literature has surfaced regarding the use of ACEI, with some very large studies,[1-8] emphasizing on the incidence of adverse cardiac events, non-fatal complications and mortality benefits. Only a few studies like IMAGINE trial and that of Drenger et al, for example, specifically laid emphasis on initiation of ACEI in the early postoperative period. The IMAGINE trial concluded that early initiation of ACEI was not beneficial in low risk patients. An exactly opposite conclusion was drawn by APRES study[5] that ramipril benefits non high-risk patients after revascularization surgery. This short study was designed to discover the changes, if any, in the hemodynamic parameters of patients when ACEI were started in the early postoperative period.

In our study 24 h after initiation of ramipril insignificant changes occurred in the cardiac index, SVRI and systolic blood pressure. Forty eight hours after initiation of ACEI the SBP achieved its baseline values, with a significant increase in CI and decrease in SVR. In patients with normal or slightly impaired left ventricular contractility ACEI use decreases afterload and improves cardiac index as observed in our study. But ACEI use has been proven to increase cardiac output in dilated cardiomyopathy also where the left ventricular contractility may not increase in response to decrease afterload. The increase in cardiac output in dilated cardiomyopathy is attributed to improved myocyte contractile function and B adrenergic responsiveness explained by normalization of B adrenergic receptor function and enhanced myocardial collagen support. [9]

The systolic blood pressure depends on the volume and velocity of LV ejection, peripheral arteriolar resistance, distensibility of arterial wall, viscosity of blood and end diastolic volume in the arterial system. The decrease in SVR caused by the blockade of ACE II is because of obtunded rapid response of direct vasoconstriction. The SBP, therefore, is maintained by increase in cardiac output in patients who have adequate reserves whereas patients with left ventricular dysfunction do not tolerate ACEI well.[10] Angiotensin converting enzyme inhibitors are also known to improve systemic endothelial function after surgical revascularization, as measured by brachial artery flow mediated dilatation.[11]

An increase in TFC was also observed in our study. Thoracic fluid content (TFC) is composed of intravascular, intra-alveolar and interstitial fluid within the thorax. The TFC in our study increased 48 hours after the initiation of ACEI and not at 24 hours. Since the cardiac index increased at time interval T3 it is possible that the increase in blood flow in the pulmonary vasculature may have contributed to this effect. Also, ACEI do not decrease TFC like diuretics.[12] The decrease in body fluid content is a slow process dependent on renin-angiotensin-aldosterone axis. The initial effect is of vasodilatation which may require higher central venous volume to maintain the same systemic blood pressure. It would have been prudent to observe the when does TFC actually begin to decrease.

In our study the ACEI were withheld in the preoperative period as a standard practice. Many studies did study the effect of continuation of ACEI in the perioperative period and reported varying incidences of hypotension after induction of anaesthesia.[13,14] When morning dose of ACEI was omitted there was no disproportionate decrease in the systemic blood pressure. Also, prophylactic use of vasopressin was found useful in abating the decrease in SVR after induction of anaesthesia when morning dose of ACEI was admnistered.[15] Therefore it is quite conceivable that a single dose of ACEI does not cause significant changes in hemodynamic parameters and it takes about 48 hours for the ACEI to make a visible effect in terms of hemodynamic monitoring.

CONCLUSION

A single dose of oral ramipril has no significant effect on hemodynamics and it takes 24-48 hours after the initiation of ramipril to show visible effect on cardiac index and systemic vascular resistance.

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