DIGOXIN AS A RESCUE DRUG IN INTRA AORTIC BALLOON PUMP AND INOTROPE DEPENDENT PATIENTS

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Background: In absence of cardiac transplant program in our country, when patients with poor left ventricular (LV) functions undergo coronary revascularisation surgery, they are on one or more inotropic supports with intra aortic balloon pump (IABP) at the time of weaning off from cardiopulmonary bypass (CPB). Post-operatively, due to the poor LV function, many of these patients become dependent on inotropic supports and IABP and eventually have a poor outcome. We used digoxin in these patients as a rescue drug, where more than one attempts to wean them off IABP and inotropic support had failed. Objective of the study was to evaluate the efficacy of digoxin as a rescue drug in intra-aortic balloon pump (IABP) and inotropic support-dependent, post-CABG patients in terms of improvement in their left ventricular ejection fraction (LVEF), serum lactate and mixed venous oxygen saturation. **Methods:** It is a descriptive case series conducted at Department of Cardiac Anesthesia & Intensive Care, Armed Forces Institute of Cardiology and National Institute of Heart Diseases, Rawalpindi, Pakistan, from 1 Nov 2002 to 31 Dec 2007. Thirty post-coronary re-vascularisation patients who were inotrope and IABP dependant and could not be weaned off from supports were given a trial of digoxin to see any improvement in the cardiac functions. Mixed venous oxygen saturation (SvO_2), serum lactate levels and left ventricular ejection fraction (LVEF) in the bed side echo were monitored at pre-digoxin stage and then at three intervals: at serum digoxin level of up to 0.5 ηg/ml; then up to 1.0 ηg/ml and then up to 1.5 ηg/ml. Paired sample *t*-test was applied and 2-tailed significance was calculated. **Results:** Significant improvement was seen in the mean SvO_2, serum lactate levels and LVEF when patient's serum digoxin level were around 1.5 ηg/dL. Clinically, 20 out of 30 patients (66.67%) improved with digoxin administration and were ultimately weaned off from IABP and inotropic supports. There was no significant correlation between patient's improvement and presence of diabetes mellitus or hypertension. However, pre-operative IABP placement had a significant correlation as 6 out of 8 patients (75%) were successfully weaned off at digoxin levels around 1.5 ηg/mL. **Conclusion:** Improvement in significant number of patients suggests that digoxin can be used as a rescue drug in IABP and inotropic support dependent patients after CABG surgery especially in countries where heart transplant program does not exist. However, more clinical trials with larger sample size are recommended for further evaluation.

Keywords: Digoxin, CABG, IABP-dependent, Inotrope-dependent

INTRODUCTION

Despite improvements in the surgical techniques, interventional cardiology and medical therapies, the management of patients with coronary artery disease (CAD) and very low ejection fraction (EF) remains a challenge. Current treatment options for this group of patients include intensive medical therapy, surgical re-vascularisation, ventricular remodeling, and heart transplantation.

Patient with ischemic heart disease usually report very late to the hospital in Pakistan and quite a big population suffers from ischemic cardiomyopathy with poor left ventricular (LV) functions. Heart transplantation offers excellent results with a 65.6% 5-year survival rate in the countries where it is available.[1] In the absence of cardiac transplant program in our country, when such patients come to the cardiac centers for coronary re-vascularisation surgeries, the anaesthesiologist is left with two options: either refuse surgery for fear of complications, or operate and let the patient suffer with prolonged hospital stay and poor outcome. CABG in this group is associated with higher postoperative morbidity and mortality compared with patients with normal LV function.[2–4] These patients usually require more than one inotropic support with intra aortic balloon pump (IABP) on weaning off from cardiopulmonary bypass (CPB) and some of them become dependent on inotropic supports and IABP. This leads to morbidity associated with a longer ICU stay and a possible fatal outcome.

Though always under debate, digoxin has been used to treat congestive heart failure for last couple of centuries. It acts as an oral inotrope in congestive cardiac failure and as anti-dysrhythmic drug by increasing the intracellular calcium for myocardial contraction and increasing the parasympathetic activity. Its use both as an inotrope and anti-arrhythmic has been advocated but its role

in the treatment of heart failure has remained controversial and studied in clinical trials over the years.

In the recent past, a neurohormonal effect of digoxin has been demonstrated as it reduced the plasma nor-epinephrine levels and it has been successfully used, in lower dosage, for treatment of moderate congestive heart failure. In this series of cases, we used digoxin in patients with severe LV dysfunction after CABG surgery where more than one attempts to wean them off IABP and inotropic support had failed. At higher normal serum levels of digoxin, patients' clinical improvement and success in weaning off from IABP was noted.

MATERIAL AND METHODS

This case series was done at the Post-cardiac Surgical Intensive Care Unit of the Armed Forces Institute of Cardiology/National Institute of Heart Diseases, Rawalpindi, Pakistan from 1 December 2002 to 31 December 2007. We followed thirty patients of age group 40–75 years who had undergone coronary re-vascularisation and were on inotrope and IABP supports postoperatively. These patients were on IABP support 1:1 with two or more inotropes and, due to poor left ventricular (LV) functions, at least 2 attempts of weaning off from supports had failed. Patients having combined valvular and coronary arteries bypass grafting (CABG) surgeries; patients undergoing emergency CABG; patients with left ventricular aneurysm and patients with ischemic ventricular sepal defect (VSD) were not included in the study.

All of these patients were received in the postoperative ICU after CABG. IABP had been placed either preoperatively or intra-operatively at the time of separation from the cardiopulmonary bypass (CPB). Routine postoperative monitoring of cardiac rate, rhythm and ST segment changes; invasive and noninvasive blood pressure; central venous pressures (CVP) and cardiac output were done. Two attempts were made, at least 48 hours apart, to wean the patient off from IABP by decreasing the IABP to 1:2 ratio, and when these attempts failed, the patient was declared as 'dependant' on inotropic supports. Pulmonary artery catheter was passed and left ventricular functions were monitored with mixed venous oxygen saturation (SvO_2), serum lactate levels and left ventricular ejection fraction (LVEF) on a bedside trans-thoracic echocardiography.

After ensuring normalised serum cardiac enzymes, baseline levels of SvO_2, serum lactate and LVEF were recorded. Each of the selected patients was loaded with intravenous digoxin, 12 μg/kg as the first dose, followed by a dose of 6 μg/kg at 6 and 12 hours intervals. Daily maintenance dose of 125–250 μg was ensured. Serum digoxin level were measured 6 hours after first dose and then daily. Reduced maintenance doses were used in the elderly and renal impaired patients and with drugs increasing digoxin concentration like amiodarone, verapamil. Serum potassium levels were monitored 4 hourly and renal function tests were done daily. Twice daily a 12-lead ECG was done and the ECG was monitored closely on cardiac monitor 24 hours a day and arrhythmias, if any, were recorded. The adverse symptoms of digoxin toxicity like nausea, vomiting, headache, confusion and visual symptoms were also noted.

SvO_2 less than 75%, serum lactate more than 20 mg/dl, and LVEF less than 30% were considered as indicators of low cardiac output state (LCOS). These variables were recorded at three intervals: at serum digoxin level up to 0.5 ηg/ml, then up to 1.0 ηg/ml and then up to 1.5 ηg/ml. The pre-digoxin levels of SvO_2 and serum lactate were then compared with the readings of these intervals using SPSS-10.0. Paired sample *t*-test was applied and 2-tailed significance was calculated. Correlation of patient's improvement (outcome in regards weaning off from inotropic supports and IABP) was also found out with the pre-operative LV function state, hypertension and diabetes mellitus, and placement of preoperative IABP. The correlation was analysed using Chi-square test. Incidence of dysrrhythmias and other complications was also noted.

RESULTS

Results were available for 30 patients (26 male and 4 female). Mean age of the patients was 58.42 years (±7.86). Sixteen patients (53.3%) were diabetic, while twelve (40%) were hypertensive. Nine patients (30%) had preoperative left ventricular ejection fraction (LVEF) less than 30% and eight out of these had elective IABP placement preoperatively.

Overall, there was significant improvement in the mean SvO_2 and serum lactate levels and mild improvement in the mean LVEF at digoxin levels ~1.5 ηg/ml (Table-1). Clinically, 20 out of 30 patients (66.67%) improved with digoxin administration and were ultimately weaned off from IABP and inotropic supports. There was no significant correlation between patient's improvement and his/her preoperative status of diabetes mellitus or hypertension. However, out of the eight patients who had poor LVEF and had been placed on IABP preoperatively, 6 (75%) were successfully weaned off at digoxin levels ~1.5 ηg/ml.

Table-1: Mean SvO_2, serum lactate and LVEF at different serum digoxin levels

	Mean	SD
Mixed Venous Oxygen Saturation (SvO_2) Levels		
Pre-digoxin SvO_2	61.74	7.28
SvO_2 at digoxin up to 0.5 ηg/ml	70.74	7.20
SvO_2 at digoxin up to 1.0 ηg/ml	70.71	7.13
SvO_2 at digoxin up to 1.5 ηg/ml	74.27	10.08
Serum Lactate Levels		
Pre-digoxin lactate (mg/dl)	46.36	43.06
Lactate at digoxin up to 0.5 ηg/ml	27.26	20.56
Lactate at digoxin up to 1.0 ηg/ml	29.12	25.25
Lactate at digoxin up to 1.5 ηg/ml	13.77	3.06
Left Ventricular Ejection Fraction (LVEF)		
Pre-digoxin LVEF	28.17	3.82
LVEF at digoxin up to 0.5 ηg/ml	28.67	3.92
LVEF at digoxin up to 1.0 ηg/ml	30.17	4.25
LVEF at digoxin up to 1.5 ηg/ml	31.5	4.95

DISCUSSION

Depressed myocardial function is common after cardiopulmonary bypass (CPB) and cardioplegic arrest.[5] It has been described in patients with normal and decreased preoperative ejection fractions.[6] Advanced age, diabetes, hypertension, longer cross-clamp and cardiopulmonary bypass times, severity of angina and functional classes (class III–IV of NYHA and CCS) are the determinants of poor outcome after CABG Surgery.[4] Surgery in patients with low EF has been reported to be superior to medical therapy by several authors. Alderman et al[7] showed that patients with an EF≤35% who were treated with medical management had a 43% 5-year survival rate compared with a 63% 5-year survival in the surgically treated patients. Unfortunately, low EF has been shown to be an independent predictor of higher operative mortality.[7,8] Peri-operative mortality has been shown to be 9 to 11%.[9, 10] Similarly, in a large review from the New York State database, the early mortality of patients with EF≤20% has been found to be >4 times higher than patients with EF>40% (4.6% versus 1.0%).[11]

Inotropic drugs are frequently administered to improve post-bypass ventricular dysfunction but these inotropic drugs increase the myocardial oxygen demand by increasing heart rate and may precipitate arrhythmias. Intra-aortic balloon pump (IABP) helps to maintain the balance of the myocardial oxygen supply and demand; and, improvement of cardiac output (CO), ejection fraction (EF), an increase of coronary perfusion pressure, systemic perfusion and a decrease of heart rate, pulmonary capillary wedge pressure and systemic vascular resistance also occurs.[12–14]

Congestive cardiac failure is syndrome of anatomic functional and biologic alterations that interact together in complex manner. Over period of time it has been recognized that is associated with low cardiac output and excessive peripheral vasoconstriction thus the neurohormonal model evolved[15]. According to this, heart failure progress as a result of over expression of biologically active molecules that exert toxic effects on heart and circulation.[16,17]

With its recent use in non-cardiac surgeries[18], the main use of intra-aortic balloon pump (IABP) remains in unstable angina, cardiogenic shock[19] and refractory ventricular failure. It has been used as a bridge to cardiac revascularization procedures (CABG)[20] as well as post-operatively when there is inability of patients to be weaned off from cardiopulmonary bypass[21]. Although IABP placement in patients with poor LVEF has given better outcome of patients with low mortality as compared to similar patients not having IABP[22,23], there have been retrospective cohort studies showing higher mortality ratios in such patients with IABP.[24,25] Such patients with poor left ventricular functions are already on two or more inotropes postoperatively and many of them become IABP-dependent being difficult to wean off IABP.

Digoxin has been used to treat congestive heart failure for more than 200 years[26] but its role in patients with congestive heart failure and sinus rhythm has always remained debatable. Mackenzie and Christan two eminent clinicians and co-editor of Oxford medicine debated this issue in 1922. Mackenzie only advocated use of Digoxin in heart failure with associated atrial arrhythmias. Christen argued digoxin effective irrespective of irregular pulse. In 1938 Gold and Caltell first showed a direct inotropic effect of digoxin on cardiac muscle.[27] The role of digitalis in the treatment of heart failure has continued to be controversial and has been studied in clinical trials over the years. Over the past decade, Digoxin has received renewed attention because of recognition of its neurohormonal effect, and the successful use of its lower dosage and its role was recently addressed by the Digitalis Investigation Group (DIG) in a large multi-centre trial in the United States and Canada.[28]

In 1993, two famous trials were conducted, the prospective randomised study of ventricular failure and efficacy of Digoxin (PROVED[29]) and randomized assessment of digoxin on inhibitors of angiotensin converting enzyme (RADIANCE[30]). Studies examined the effects of withdrawal of digoxin in patient with stable, mild to moderate heart failure and LV systolic dysfunction EF <35%. Digoxin prevented clinical deterioration and hospitalisation, and improved exercise tolerance and LV function in patient, but no survival benefits were seen. Neurohormonal effect of digoxin was first demonstrated in small study in 1987 showed Digoxin reduced plasma norepinephrine level.[31,32]

The cost effectiveness and safety of digoxin therapy in heart failure patients with low doses have been identified. A double-blind placebo-controlled study by van Veldhuisen has shown digoxin to significantly increase the exercise time after 6 months.[33] Unlike other agents with positive inotropic properties, digoxin does not increase all-cause mortality and has a substantial benefit in reducing heart failure hospitalisations. Consensus guidelines have recently been published by the Heart Failure Society of America and the American College of Cardiology/American Heart Association and in the treatment recommendations, it has been highlighted that digoxin toxicity is less common with serum levels <1.2 ηg/ml.[34] Serum levels of <1.0 ηg/ml in the geriatric patients have been shown to be associated shorter hospitalisation and low mortality.[35] Hoppe *et al* stress on low therapeutic levels of digoxin to reduce its toxicity.[36] In an analysis of both men and women receiving digoxin for systolic heart failure, Rathore *et al* found that those with digoxin concentrations of 0.5 to 0.8 ηg/mL (0.6–1.0 nmol/L) had a 6.3% lower all-cause mortality and a 5.9% lower hospitalisation rate compared with patients receiving placebo. Patients with serum concentrations greater than 1.2 ηg/mL (1.5 ηmol/L) had an 11.8% higher mortality and also higher rates of hospitalisation and digoxin toxicity than those treated with placebo.[37] Digoxin levels are used to assist in the evaluation of toxicity, not the efficacy of the drug.[38] Secondly, the studies support its efficacy in patients with only mild heart failure.[39,40]

We tried to evaluate the efficacy of digoxin in its higher therapeutic doses as a desperate measure to wean off from IABP and inotropic support the patients with severe ventricular dysfunction after CABG surgery. The target serum level of digoxin up to 1.5 ηg/ml were achieved in these inotropic support and IABP-dependent patients and it was kept below 2.0 ηg/ml and we had no incidence of any toxic effect of digoxin in any patient. We were able to wean off 20 out of 30 patients from IABP using digoxin, with significant improvements in their serum lactate levels and SvO_2 and some improvement in the LVEF. Six out of 8 patients with elective preoperative IABP insertion were successfully weaned off with digoxin therapy and this is similar to the findings of Kapadia *et al* where elective insertion of IABP showed better outcome pattern compared to emergency situations.[26] Although, no such trial has been done in the past, the results of our study strongly indicate digoxin's role in this particular scenario.

CONCLUSION

A high proportion of patients with improvement suggests digoxin to be a rescue drug in IABP and inotropic support dependent patients after CABG surgery. However, more clinical trials with larger sample size are recommended for further evaluation.

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