

Clinical Case Study

Evaluation of the Effects of a Single Bolus of Erythropoietin on Reducing the Incidence of Atrial Fibrillation after Coronary Artery Bypass Graft Surgery; A Randomized, Double-Blind, Placebo-Control Study

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ABSTRACT

Introduction: Atrial Fibrillation is the most common arrhythmia developing after coronary artery bypass surgery. Many studies have been done to reduce the incidence of post CABG AF. In our recent study we used Indocid and showed that it can reduce the incidence of AF by reducing the inflammatory reactions. In this study we want to understand if we can reduce the incidence of post CABG AF with reducing the ischemia during the cross-clamp time in CABG by a single bolus of Erythropoietin.

Material and methods: 43 patients that were referred to Mazandaran Heart Center (Sari, Iran) for elective CABG between September 2010 and October 2011 were included in this study and randomly divided into two groups :Erythropoietin group and control group. Patients in Erythropoietin group were treated by common medical therapies and CABG plus 700 IU/kg Erythropoietin (PD Poietin, puyeshdaroo, Iran), intravenously infusion, exactly 5 min after termination of cross clamp: at the start of reperfusion and patients in control group were treated by common medical therapies and CABG surgery plus 10cc normal saline as placebo.

Results: There was no significant differences between two control and EPO group according to their age, sex ,involved vessels ,number of grafts, cross-clamp and pump time. There was statistically lower incidence of post CABG AF in EPO group.

Discussion: Showing that the incidence of post CABG AF has been reduced by decreasing the cross-clamp time and therefore the ischemia during surgery in our previous study, we planned this study to find that a single bolus of Erythropoietin used in CABG can reduce the incidence of post CABG AF by reducing the ischemia occurred by post perfusion injury.

Key-words: Erythropoietin, Atrial Fibrillations, Coronary Artery Bypass Graft surgery (CABG)

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Introduction:

Atrial fibrillation (AF) is the most frequent arrhythmic complication after coronary artery bypass grafting (CABG) that occurs in 10-65% of these patients, depending on patients profile, type of surgery, method of arrhythmia surveillance, and definition of arrhythmia^{1,2,3}.

Although it is usually a self-limiting arrhythmia, it has been associated with prolonged hospital stay, postoperative stroke, congestive heart failure and increased mortality, often resulting in limited quality of life³⁻⁵. Although several risk factors for postoperative AF have been elucidated, the mechanism by which AF develops is not completely understood⁴.

Anderson et al⁶ showed that C-reactive protein (CRP), an inflammatory marker, is associated with occurrence of AF. Gaudino et al⁷ demonstrated the interleukin-6 (IL6) gene polymorphism influences the occurrence of AF after CABG. It has been suggested that inflammation participates in the pathogenesis of postoperative AF in patients with CABG. We also had shown there was no significant difference in CRP levels between the groups, although CRP levels were higher in the AF group³. The IL6 level elevated after surgery and was higher in patients with postoperative AF. It remains unclear why CRP and IL6 levels are elevated in AF. The role of inflammation in the pathogenesis of AF has not been clearly defined. Histological changes, such as inflammatory infiltrates, myocyte necrosis, and fibrosis has been reported in the atrial biopsy specimens of patients with AF^{3,7}. Studies showed that administration of glucocorticoids, which significantly reduce plasma levels of IL6, could reduce the incidence of AF after on-pump CABG^{3,7}.

In our latest study we showed that prescription of Indocid peri-operatively will reduce the risk of AF after CABG⁹.

In our latest study there was %7 AF in our patients after CABG⁹. There was a significant reduction in incidence of AF in comparison to our previous study in control group (at our previous study the AF incidence was 20.4%)³. We concluded that the decreased cross-clamp and pump time by the same surgeon who had found more experience after 8-10 years of surgery as an independent surgeon most probably because of lowering ischemia during surgery was the prominent cause of decreasing the risk of postoperative AF in our latest study⁹. Therefore we decided to study the risk of AF after CABG in patients who had received a single bolus dose of Erythropoietin in CABG. Because in one of our previous studies we showed that the reperfusion ischemia will be reduced after a single bolus dose of Erythropoietin administration after de-clamping of Aorta^{8,10}.

Materials and Methods:

43 patients that were referred to Mazandaran Heart Center (Sari, Iran) for elective CABG between September 2010 and October 2011 randomly divided into two groups. Patients in erythropoietin group were treated by common medical therapies and CABG plus 700 IU/kg erythropoietin (PD Poietin, puyeshdaroo, Iran), intravenously infusion, exactly 5 min after termination of cross clamp: at the start of reperfusion and patients in control group were treated by common medical therapies and CABG surgery

plus 10cc normal saline as placebo. We monitored all the patients for 5 days after CABG. Daily 12 leads ECG was taken each morning in these five days.

It was a randomized, double-blind, clinical trial study which has been approved by Mazandaran University of Medical Sciences research vice chancellor and its Ethical committee (code: 88-97).

Inclusion Criteria:

All patients who have been candidate for CABG upon Angiographic evidences were included in this study.

Exclusion Criteria:

All patients with a history of recent MI in previous 3 months, history of major surgery, EF lower than %30, and chronic renal failure with creatinin level more than 2.5, receiving SK or EPO in previous six months before CABG were excluded from this study.

Statistical analysis:

We examined the data by *t-test* and *paired t-test*. The data distributions were checked with *Kolmogorov-Smirnov* test.

We also used *Mann-Whitney* test and also χ^2 test. The results were considered statistically significant when the variability level was < 0.05 . We used *SPSS* software (version 16) to statistical analysis.

Results:

The mean age of 21 patients who were in Control group was 62.57 ± 8.6 yr. vs. 59.73 ± 7.73 yr. in 22 patients who were in EPO group, and there was no meaningful difference between them ($P=1.878$).

The number of stenosed vessels in control group was (2.27 ± 0.787) vs. (2.29 ± 0.784) in EPO group therefore there was no significant difference between two groups ($P=0.863$).

In control group there was 14 smokers vs. 13 in control group ($P=0.4$), in EPO group 8 were diabetic vs. 10 in control group ($P=0.9$), BMI was 25.82 ± 1.83 kg/m² in EPO group vs. 24.36 ± 2.12 kg/m² in control group ($P=0.9$). EF in EPO group was 46.36 ± 8.04 vs. 45.90 ± 8.41 in control group ($P=0.178$), The number of grafted vessels was 3.14 ± 0.88 in EPO Group vs. 3.38 ± 0.74 in control group ($P=0.33$), Pump time was 78.21 ± 18.8 min in EPO group vs. 79.76 ± 12.25 min in control group ($P=0.6$), and Cross-clamp time was 50.95 ± 10.85 min in EPO group vs. 53.86 ± 9.13 min in control group ($P=0.08$).

There was 2 patients(9%) in control group who developed Atrial Fibrillation(AF) rhythm in 5 days after CABG, but we have no patients(0.0%) showing Atrial Fibrillation(AF) in EPO group in 5 days after CABG($P=0.01$).

Only those patients were considered as developing AF which the duration of AF was more than one hour continuously.

Discussion:

Atrial Fibrillation is the most common arrhythmia that happens after CABG, it's incidence in different studies was between 10% to 65%, usually it is a self-limiting complication but can lengthen hospital stay for the patients and causes morbidity^{1, 2, 3}.

In our first study the incidence of AF was 20.4% but in our latest study in which we assessed the influence of Indocid on AF occurrence the incidence of AF in control group was 7% which was significantly lower than our previous study($P=0.001$)⁹. The most important difference between two studies was the experience of the same surgeon after 8 yrs. working and it lead to a very shorter pump time and cross-clamp time in the newest study⁹, therefore we suggested that ischemia during cross-clamping and pump time may be an important cause of postoperative AF. Thus we planned this study in which by reducing the ischemia during surgery by using a single bolus dose of Erythropoietin 5 minutes after de-clamping of Aorta⁸ also we can reduce the incidence of post CABG Atrial Fibrillation.

We showed that post CABG Atrial Fibrillation was significantly lower (0.0%) in the EPO group in comparison with control group (9%).

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