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Effect of Topical Aprotinin on Early Postoperative Bleeding and ICU Stay after Coronary Artery Bypass Graft Surgeries

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Abstract: We evaluate the effect of topical application of aprotinin to the heart, pericardia and mediastinum before sternal closure, on early post operative bleeding, blood transfusion requirement and ICU staying time after coronary artery bypass graft surgeries. In a randomized double blinded clinical trial, 128 patients who were scheduled for elective coronary artery bypass graft were allocated into two groups. In group A (aprotinin), patients received 500,000KIU (50 mL) aprotinin and in group S (saline group) the same volume of normal saline was applied. The amount of blood loss collected in chest bottle, the number of pack cells requirement during first 24 h after operation and duration of ICU staying time were recorded. The amount of blood loss in group A (aprotinin) was 451 ± 218 mL compared with 707 ± 269 mL in group S (saline) ($p = 0.003$). The number of pack cells consumption was 0.5 ± 0.7 units in group A (aprotinin) compared with 1.7 ± 1 units in saline group ($p = 0.002$). Intensive Care Unit (ICU) staying time was 48.8 ± 13.6 h in group A (aprotinin) and 69.4 ± 16.6 h in saline group ($p = 0.001$). This study showed that topical application of aprotinin at the end of coronary artery surgeries, significantly reduce postoperative bleeding and blood transfusion requirement during first 24 h after operation and also ICU staying time.

Key words: Aprotinin, bleeding, blood transfusion, cardiac surgery

INTRODUCTION

Perioperative bleeding is one of the most important problems in cardiac surgery. The risk of allogenic blood transfusion is well documented even in first time cardiac surgery. This bleeding tendency is related to both surgical procedure and acquired defects in hemostasis resulting from cardiopulmonary bypass (CPB). Therefore, many Pharmacological strategies were conducted to reduce bleeding in these types of surgery (Oswald *et al.*, 2003; Durand *et al.*, 2006; Mangano *et al.*, 2007; Erdogan and Van-Gulik, 2008; Hausenloy *et al.*, 2008).

Two classes of intravenous drugs are commonly used to reduce bleeding in cardiac surgery; lysine analogs (e.g., aminocaproic acid, tranexamic acid) and serine protease inhibitors (e.g., aprotinin). In contrast to the lysine analogs, intravenous aprotinin administration has been shown in several nonrandomized studies to be associated with worsened postoperative outcome (Sedrakyan *et al.*, 2004; Sethi *et al.*, 2008).

Although, the use of topical aprotinin to reduce perioperative bleeding was first described by Tatar *et al.*

(1993) and one year later by O'Regan *et al.* (1994), it was not until recently that a randomized, double-blind, prospective data supporting topical antifibrinolytic administration were available (Tatar *et al.*, 1993; O'Regan *et al.*, 1994; Baric *et al.*, 2007).

The effects of topical aprotinin (1 million units), tranexamic acid (2.5 g) and placebo administration before sternal closure were compared in 300 adults undergoing cardiac surgery. Both topical aprotinin and tranexamic acid significantly reduced postoperative bleeding compared with placebo (Baric *et al.*, 2007).

The concomitant use of topical aprotinin with systemic high dose aprotinin and reported 35% reduction in postoperative bleeding compared to systemic aprotinin use alone (Khalil *et al.*, 2006).

In another study 97 patients scheduled for CABG, there was no difference between the systemic application of 500,000 KIU aprotinin preoperatively and 1250000 KIU aprotinin local instillation in control of intraoperative bleeding (Isgro *et al.*, 2002).

Systemic use of aprotinin has several side effects such as stroke, acute renal failure induced by thrombosis

of renal artery, hypersensitivity reaction, possibility of bypass graft occlusions produced by the hypercoagulable state induced by aprotinin in CABG operations (Oswald, 2003; Mangano, 2007).

In order to prevent these adverse effects, we conducted a study to evaluate the effect of topical aprotinin on first 24 h postoperative bleeding, blood transfusion requirement and its effect on ICU staying time after CABG.

MATERIALS AND METHODS

This randomized clinical trial was performed in Dr. Shariati Hospital of Tehran University of Medical Sciences from May to December 2008. The study protocol conformed to the ethical guidelines of the 1989 Declaration of Helsinki.

After Institutional Ethics committee approval, each patient's informed consent was obtained separately. One hundred twenty eight ASA physical status II or III patients aged 50-70 years scheduled for elective first time Coronary Artery Bypass Graft (CABG) under general anesthesia by the same surgical team, were studied. Exclusion criteria were previous cardiac surgery, known previous exposure to aprotinin, emergency operation, warfarin treatment less than 5 days of operation (aspirin therapy was not an exclusion criteria), or refusal of allogeneic blood transfusion.

According to our institute's protocol, we did not discontinue aspirin before cardiac surgery or discontinue it only 48 h before combined CABG and valvular surgeries.

Anesthesia was performed with sufentanil and midazolam supplemented with inhaled isoflurane; neuromuscular blockade was achieved by either pancuronium bromide or atracurium. Cardiopulmonary bypass (CPB) was performed in standard technique using a membrane oxygenator, an open cardiotomy reservoir and uncoated tubing systems (Baric *et al.*, 2007).

Patients were randomly assigned to receive either 500,000 KIU (50 mL) aprotinin (Trasylo[®], Bayer, Leverkusen, Germany) or the same volume of saline. Randomization was based on computer-generated codes that were concealed until interactions were assigned. The coded syringes were prepared by an independent anesthetist in equal volume and shape (Durand *et al.*, 2006).

At the end of surgery the drug Aprotinin or placebo was applied topically by the surgeon to the heart, pericardium and mediastinum before sternal closure (Baric *et al.*, 2007).

Demographic data, duration of surgery, the amount of blood collected in chest bottles and number of pack cells consumption during first 24 h after operation and post-surgical ICU staying time were recorded separately by resident of anesthesiology who was also blinded to the allocation.

Statistical analysis: A sample size of 64 patients in each group will be sufficient to detect 100 mL difference in the incidence of postoperative bleeding after 24 h between the study groups assuming power of 80% and a significance level of 5%. Normality of distribution was tested by Kolmogorov Smirnov test. Data were analyzed by SPSS version 11.5 (SPSS Inc, Chicago, IL) and were compared by using Independent sample t-test and Chi-square. $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Demographic data and duration of surgery were not statistically different between the study groups (Independent sample t-test and Chi-square) (Table 1).

The amount of blood that was collected in chest bottles during first 24 h after the operation was 451 ± 218 mL in group A (aprotinin) and 707 ± 269 mL in group S (saline) (Independent sample t-test, $p = 0.003$).

The number of pack cell units that were transfused during first 24 h after surgery was 0.5 ± 0.7 unit in group A (aprotinin) and 1.7 ± 1 unit in group S (saline) (Independent sample t-test, $p = 0.002$).

ICU staying time was 48.8 ± 13.6 h in group A (aprotinin) and 69.4 ± 16.6 h in group S (saline) respectively (Independent sample t-test, $p = 0.001$).

This study showed that topical application of aprotinin into the surgical field decrease blood loss and blood transfusion requirement during first 24 h after CABG and also decrease ICU staying time. As present knowledge most studies evaluate the effect of systemic aprotinin on perioperative bleeding. We not only evaluate the effect of topical aprotinin on early postoperative bleeding (first 24 h) but also the ICU staying time was evaluated.

Table 1: Comparing demographic data and surgery time between the aprotinin (A) and saline control (S) groups

| Variables | Group A (aprotinin) | Group S (saline) |
|---------------------|---------------------|------------------|
| Age (year)* | 57.6±10.3 | 58.5±10.1 |
| Sex (M/F) | 43/21 | 44/20 |
| Weight (kg)* | 74.8±10.3 | 73.5±9.6 |
| Surgery time (min)* | 365±15 | 355±12 |

*Data are presented as Mean±SD, $p > 0.05$

Aprotinin is a component of a human thrombin and fibrinogen topical sealant (Tisseel; Baxter Healthcare, Deerfield, IL) commonly used to achieve surgical hemostasis. It prevents premature degradation of fibrin formed by mixing of the thrombin and fibrinogen. When it applies topically, some aprotinin is absorbed systemically (half life of 30-60 min) (Sethi *et al.*, 2008).

The use of topical aprotinin to reduce perioperative bleeding was first described in the 1990s. In a study by Tatar *et al.* (1993), fifty patients were prospectively studied to evaluate the effects of topical one million KIU of aprotinin. Total postoperative bleeding was significantly reduced in aprotinin group compared with control group (722.7 ± 230.8 versus $1,282.6 \pm 225.7$ mL; $p < 0.01$). The use of banked donor blood products was significantly less in aprotinin group (0.33 ± 0.67 versus 1.36 ± 0.86 units; $p < 0.01$). They results were correlated to present study except that we only evaluated packed cells consumption not other blood products (Tatar *et al.*, 1993).

O'Regan *et al.* (1994) performed a similar study one year later. They conducted a prospective, randomized, double-blind trial about topical application of aprotinin versus placebo in 100 patients undergoing cardiac operations with cardiopulmonary bypass. Fifty-five patients received aprotinin. Forty underwent Coronary Artery Bypass Grafting (CABG) and 15 valve replacement \pm CABG. Of 45 patients in the control group 38 underwent CABG and 7 valve replacement \pm CABG. Mean blood loss was significantly less in the aprotinin group (653 versus 903 mL; $p = 0.002$) and fewer aprotinin patients received blood as a volume expander (67.5% versus 88%; $p = 0.03$). In coronary patients alone when aspirin administration was continued until the day of operation there was no difference between treatment and placebo groups (768 versus 879 mL). When aspirin administration was discontinued 2 weeks before operation there was a significant difference (558 versus 884 mL; $p = 0.016$) as in the group overall. It is routine in our institute that do not discontinue aspirin before cardiac surgery or discontinue it only 48 h before combined CABG and valvular surgeries. In contrast to O'Regan (1994) study, in present study postoperative bleeding was statistically different between the study groups. This difference may be related to co-operation of CABG and valvular replacement in their study that are associated with more trauma and bleeding.

Khalil *et al.* (2006) studied 172 patients undergoing elective CABG and found that concomitant use of topical aprotinin with systemic high dose aprotinin was

accompanied by postoperative blood loss reduction of 35% compared to systemic aprotinin use alone. Since we wanted to reduce complications, we didn't use systemic aprotinin compared with Khalil *et al.* (2006) study.

In conclusion present study showed that topical application of aprotinin before sternal closure not only reduced postoperative bleeding but also blood transfusion requirement and ICU staying time.

Further studies are needed to determine the safety profile of topical aprotinin with different doses and whether aprotinin is more efficacious than other topically administered antifibrinolytic.

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