ARTICLE ORIGINAL / ORIGINAL ARTICLE

EFFECTS OF PREOPERATIVE ENOXAPARIN ON BLEEDING AFTER CORONARY ARTERY BYPASS SURGERY

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Abi Ghanem M, Saliba E, Irani J, Darwish R, Kawkabani N, Yared T, Naim C, Abu Khalil B. Effects of preoperative enoxaparin on bleeding after coronary artery bypass surgery. J Med Liban 2015 ; 63 (4) :185-190.

ABSTRACT • Background : Low molecular weight heparins are replacing unfractionated heparin in practice prior to cardiac surgery. This study examines postoperative (post-op) bleeding indicators in patients who received enoxaparin and underwent elective isolated first time coronary artery bypass graft. **Methods** : A total of 125 consecutive patients who underwent this procedure between 2009 and 2011 at one tertiary center were reviewed and divided into three groups : Group A (n = 50) received the last dose of enoxaparin between 12 and 24 hours before surgery, Group B (n = 25) received the last dose before 24 hours and Group C (n = 50) did not receive enoxaparin. Perioperative bleeding indicators and transfusion rates were compared. **Results** : Preoperative patients' characteristics were comparable between the three groups. There were no perioperative deaths, return to the operating room for any reason, nor major bleeding. Post-op bleeding indicators were similar in the three groups. The average chest tube drainage at 24 hours post-op was 880 mL, 695 mL and 830 mL in Group A, B and C respectively ($p = 0.71$). Transfusion rates of red blood cells were not statistically different (Group A 56%, B 64% & C 62% ; $p = 0.747$). In multivariate analysis, female gender, older age, and preoperative clopidogrel intake (stopped 5 days prior to surgery) were associated with higher transfusion rates. **Conclusion** : In elective first time coronary artery bypass graft patients who had no aspirin or clopidogrel intake 5 days prior to surgery, the use of enoxaparin up to 12 hours prior to skin incision does not increase the risk of post-op bleeding.

Keywords : enoxaparin, coronary artery bypass, postoperative hemorrhage

Abi Ghanem M, Saliba E, Irani J, Darwish R, Kawkabani N, Yared T, Naim C, Abu Khalil B. Effets de l'énoxaparine reçue en préopératoire sur le saignement après chirurgie de pontage coronarien. J Med Liban 2015 ; 63 (4) : 185-190.

RÉSUMÉ • Contexte: Les héparines de bas poids moléculaire remplacent dans la pratique l'héparine non fractionnée avant la chirurgie cardiaque. Cette étude examine les indicateurs hémorragiques postopératoires chez les patients ayant reçu de l'énoxaparine et subi un pontage coronarien électif isolé pour la première fois. **Méthodes** : 125 patients consécutifs ayant subi cette procédure entre 2009 et 2011 dans un centre tertiaire ont été examinés et divisés en trois groupes: groupe A (n = 50) ont reçu la dernière dose d'énoxaparine entre 12 et 24 h avant la chirurgie, groupe B (n = 25) ont reçu la dernière dose avant 24 h, et le groupe C (n = 50) n'ont pas reçu d'énoxaparine. Les indicateurs de saignements peropératoires et les taux de transfusion ont été comparés. **Résultats** : Les caractéristiques des patients préopératoires étaient comparables entre les trois groupes. Pas de décès per opératoires et pas de retour au bloc opératoire pour hémorragie majeure ou autre raison quelconque. Les indicateurs de saignements postopératoires étaient similaires dans les trois groupes. Le drainage thoracique moyen à 24 heures postopératoires était de 880 ml, 695 ml et 830 ml dans les groupes A, B et C respectivement ($p = 0,71$). Les taux de transfusion de globules rouges n'étaient pas statistiquement différents (groupe A 56%, B 64% et C 62%, $p = 0,747$). Une analyse multivariée a montré que le sexe féminin, l'âge, et le clopidogrel en préopératoire (arrêté 5 jours avant la chirurgie) ont été associés à des taux plus élevés de transfusion. **Conclusion** : Chez les patients opérés d'un pontage coronarien électif pour la première fois et qui n'avaient pas pris d'aspirine ou de clopidogrel 5 jours avant la chirurgie, l'utilisation de l'énoxaparine jusqu'à 12 heures avant l'incision de la peau n'augmente pas le risque d'hémorragie postopératoire.

INTRODUCTION

Unfractionated heparin (UFH) plays a major role as antithrombotic agent in the treatment of acute coronary syndrome (ACS) [1-3]. However, its use is associated with an unpredictable anticoagulant effect requiring frequent blood testing to adjust the dose, a tendency to rebound and a risk of thrombocytopenia. Thus, low molecular weight heparins (LMWH), particularly enoxaparin, became more popular, replacing UFH in many indications and many centers around the world. In fact, enoxaparin has a higher bioavailability, is easily administered, and has more predictable dose-response characteristics with no required laboratory monitoring. Furthermore, enoxaparin has been shown to be more effective than UFH in preventing coronary events in patient with ACS [4-6].

LMWHs duration of activity is longer than that of UFH and only partially neutralized by protamine sulfate [6-7], with a potential risk of increased bleeding when used around the time of a coronary artery bypass graft (CABG) surgery.

In this paper, we describe our experience with the use of enoxaparin prior to CABG, and its effect on bleeding

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in the postoperative (post-op) phase in general and according to its stopping time preoperatively.

MATERIAL AND METHODS

We retrospectively reviewed consecutive patients who underwent elective first time CABG at our tertiary center between 2009 and 2011. The study was approved by the Institutional Review Board (IRB) at the University of Balamand.

We included all first time isolated CABG patients and excluded those who had hematologic diseases, elevated creatinine (Cr) levels (Cr > 1.2), those on heparin and those who were on anti-platelet therapy in the last five preoperative (pre-op) days. Patients with elevated creatinine were excluded since, according to the manufacturer, enoxaparin associated risk of bleeding is increased with the degree of renal impairment.

We divided eligible patients into three groups: Group A received enoxaparin until 12 to 24 hours before surgery, Group B received the last dose of enoxaparin more than 24 hours before surgery and Group C consisted of patients who did not receive enoxaparin at all (control). The dose of enoxaparin given was 1 mg/kg twice a day. The enoxaparin used in our center was Lovenox® (Sanofi-Aventis, Canada).

We collected the following data on all eligible patients: baseline hematologic characteristics, creatinine level, duration of enoxaparin treatment, time between the last enoxaparin dose and surgery and pre-op use of oral anti-platelets agents (aspirin, clopidogrel). Data regarding the CABG procedure, that was undertaken by the same senior surgical team, included the duration of cardiopulmonary bypass (CPB), number of grafts, activated clotting time (ACT) and the volume of blood and blood products transfused during the operation. Hematologic and transfusion data collected included perioperative hematocrit (Hct) measurement as well as the quantity of packed red blood cells (PRBC), fresh frozen plasma (FFP) and platelets administered intraoperatively and during the first 72 hours after surgery.

All CABG procedures were performed by the same surgical team, including the general anesthesia, radial artery cannulation, median sternotomy, central cannulation, non-pulsatile CPB with moderate systemic hypothermia (32-33°C) and antegrade and retrograde cold blood cardioplegia. All patients received tranexamic acid 10 mg/kg at induction of the general anesthesia and then 250 mg on CPB. Anticoagulation was established by a standard dose of UFH (4 mg/kg) via the central line. Additional UFH was given in order to maintain an ACT greater than 480 sec. After the discontinuation of bypass support, UFH was reversed by administration of 1 mg protamine per 100 U of UFH to achieve an ACT of 130-140 sec. The cardiopulmonary bypass prime was 1.55 L: 0.5 L of sodium bicarbonate 1.4%, 0.5 L of Haes sterile 6% (Fresenius Kabi, India), 0.5 L of Ringer (Taj pharmaceuticals, India) and 0.05 L of albumin 20%.

In post-op, we collected the chest tube output for the first 24 and 48 hours in addition to the amount of blood products administration in the first 72 hours. All chest tubes were removed systematically on day 2 post-op. Patients were given PRBC to keep their Hct level above 25%. FFP was given for fibrinogen levels below 100 or for an international normalized ratio (INR) more than 1.7. Platelets were given for platelet count below 50000. Post-op hematologic characteristics were also recorded.

Statistical Analysis

At first, we used means, medians and standard deviations (SD) to describe our quantitative data, and proportions to describe our qualitative data. We used traditional statistical tests to compare between variables, Student *t*-test, ANOVA for normally distributed variables and Mann-Whitney and Kruskall-Wallis tests when appropriate. We used chi-square test to compare qualitative data, and Fisher exact test when appropriate. We ran a logistic regression model to analyze the factors associated with the outcome variable 'need for PRBC transfusion', and we included in the model all the variables that were associated to this outcome in the bivariate analysis, in addition to the variable 'group belonging'. Model calibration was assessed using Hosmer-Lemeshow test. The c-statistic was calculated as a measure of discrimination. All *p*-values below 0.05 were considered statistically significant. We used SPSS v16.0 and MedCalc v 12.3 for statistical analysis.

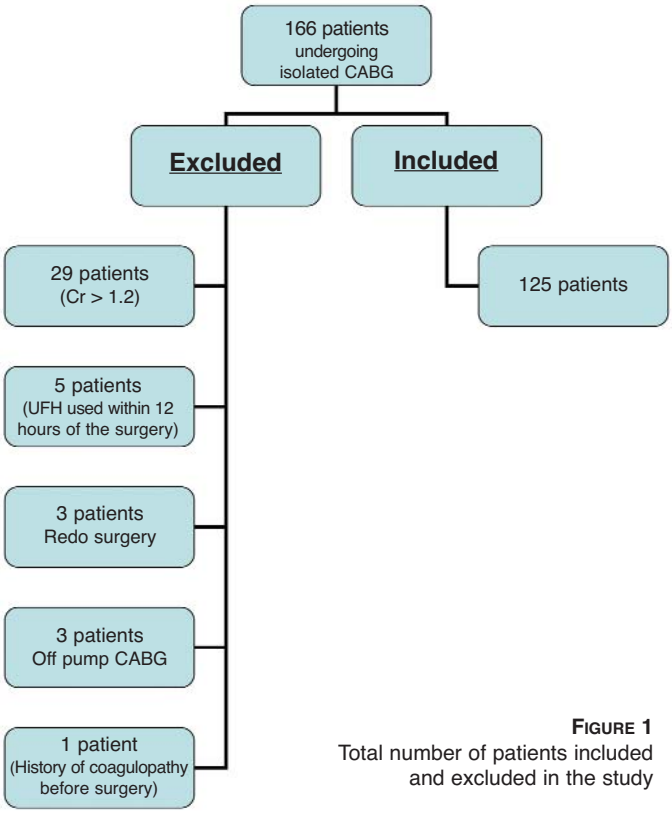

FIGURE 1
Total number of patients included and excluded in the study

RESULTS

Among 166 patients who had the procedure between June 2009 and October 2011, 125 met our selection criteria (Figure 1).

We analyzed the data on all 125 patients. Collected patients' demographics (such as age, sex, etc.) were identical and equally distributed between the three groups (Table I). The average age of the studied sample was 65.8 years. Most of our patients were male (80%). Base-line hematocrit, platelets count, creatinine levels, and diabetic status were comparable between the different groups. The prothrombin time (PT) and partial thromboplastin time (PTT) were similar, as well as the average bypass time. The pre-op ACT was slightly more elevated in the Group A compared to Group B (mean 146 *vs*. 139, $p = 0.010$ post-hoc analysis).

Seventy-five patients (60%) received one or more unit of PRBC during the observed period. Only 17 patients (13.6%) needed FFP, and 10 patients (8%) needed platelet transfusion. In order to estimate the severity of bleeding, we analyzed the "need for PRBC transfusion" as an outcome variable. In the three groups, the need for PRBC transfusion was 56% in Group A (28 patients), 64% in Group B (16 patients) and 62% in Group C (31 patients) ($p = 0.747$; Table II).

TABLE I PATIENTS' CHARACTERISTICS

Variables	Total	Enoxaparin stopped 12 to 24h pre-op	Enoxaparin stopped > 24h pre-op	No Enoxaparin	*p*-value
Number (%)	125	50 (40)	25 (20)	50 (40)	
Age (SD)	65.8 (9)	65 (9)	68 (8)	66 (9)	*0.425*
Sex					
Male (%)	100 (80)	40 (80)	18 (72)	42 (84)	*0.472*
Female (%)	25 (20)	10 (20)	7 (28)	8 (16)	
Hematocrit pre-op (SD)	41.7 (4.5)	42.14 (4)	42.7 (6)	40.7 (4)	*0.132*
Platelet pre-op [x 1000] (SD)	238 (63)	233 (60)	242 (51)	241 (73)	*0.785*
Creatinine pre-op [mg/dl] (SD)	0.92 (0.23)	0.90 (0.15)	0.89 (0.24)	0.96 (0.28)	*0.362*
With diabetes (%)	49 (39)	24 (48)	6 (24)	19 (38)	*0.130*
Had Enoxaparin pre-op (%)	75 (60)	50 (100)	25 (100)	0	
Duration, mean [days] (SD)	3.1 (2.6)	2.4 (2)	4.5 (3)		*< 0.001*
Duration, median [days]	2.0	1.0	5.0	N/A	
Dose, mean [mg] (SD)	54 (14)	53 (16)	58 (9)		*0.128*
Dose, median [mg]	60	60	60		
Last dose, mean [hrs] (SD)	23.8 (10)	17.9 (3)	35.6 (10)	N/A	*< 0.001*
Last dose, median [days]	20.0	18.0	36.0		
Had Aspirin pre-op (%)	66 (53)	32 (64)	17 (68)	17 (34)	*0.003*
Last dose, mean [days] (SD)	5.9 (2.5)	6.3 (2.5)	5.5 (2.5)	5.5 (2.5)	*0.549*
Last dose, median [days]	6.5	7.0	5.0	6.0	
Had clopidogrel pre-op (%)	26 (21)	12 (24)	7 (28)	7 (14)	*0.286*
Last dose, mean [days] (SD)	5.3 (2.3)	5.2 (1.7)	5.4 (2.1)	5.1 (3.3)	*0.927*
Last dose, median [days]	5.5	5.0	6.0	6.0	
Activating clotting time					
Pre-op, mean (SD)	144 (14)	146 (14.6)	139 (12)	145 (14)	*0.046*
Mean on CPB, mean (SD)	580 (122)	575 (154)	543 (74)	604 (99)	*0.017*
Last on CPB, mean (SD)	571 (132)	570 (160)	544 (87)	586 (120)	*0.328*
Post CPB, mean (SD)	144 (15)	145 (15)	142 (17)	143 (13)	*0.394*
Prothrombin time					
Pre-op, mean (SD)	12 (0.9)	12 (0.8)	12 (0.8)	12 (1)	*0.250*
Post-op, mean (SD)	15 (1.5)	15.6 (1.4)	15.4 (1.7)	15.5 (1.4)	*0.567*
Partial thromboplastin time					
Pre-op, mean (SD)	34 (5.7)	33 (4)	33 (5)	34 (7)	*0.775*
Post-op, mean (SD)	43 (7.4)	43 (5)	44 (7)	43 (9)	*0.390*
Bypass time [min], mean (SD)	66 (18)	63 (16)	71 (18)	67 (19)	*0.273*
Total heparin intra-op	419 (91)	429 (91)	393 (106)	422 (83)	*0.258*

Mann-Whitney U Test* ***KrusKal-Wallis Test* **SD: standard deviation **CPB**: cardio-pulmonary bypass

There were no significant differences in PRBC transfusion nor in chest tube drainage post-op among the three groups (Table II), (Figure 2).

The following factors were significantly associated with receiving more PRBC: being a female, older age and having taken clopidogrel in pre-op independently of what group they belong to (Table III). Eighty-eight percent of female patients needed a transfusion versus 53% of male patients ($p = 0.001$). The mean age of patients receiving PRBC transfusion was 68 years compared to a mean of 62 years in those who did not receive any PRBC transfusion ($p < 0.001$). Of those patients who were on clopidogrel in pre-op (26 patients - stopped 5 days pre-op on average), 85% needed a PRBC transfusion compared to 53% of those who never had clopidogrel ($p = 0.004$).

After performing a logistic regression analysis, including in the model the following variables: sex, age, aspirin receipt in pre-op, clopidogrel in pre-op, pre-op Hct and UFH in per-op (Table IV), the factors 'age', 'sex' and 'prior use of clopidogrel' remained statistically associated with the outcome 'need for PRBC'.

When examining drains' output of the first 24 hours post-op, the following factors were found to be associated with a higher output: number of bypasses (more than two grafts) and being a male (Table V).

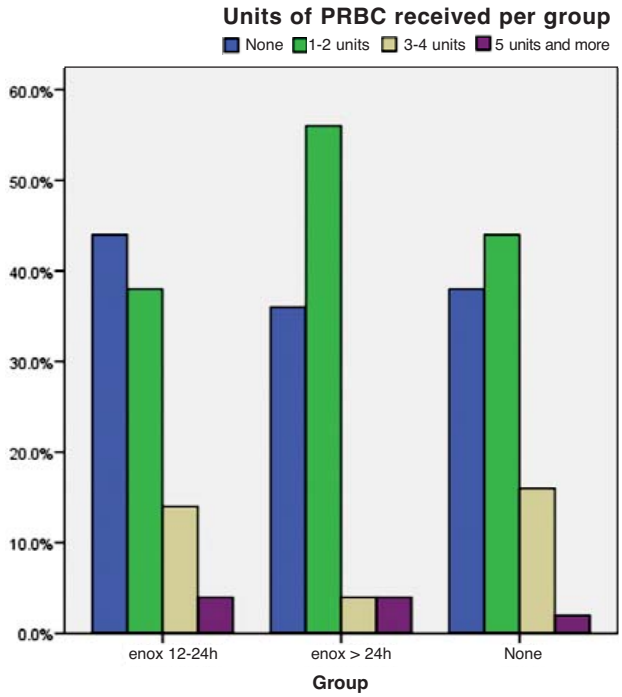

Figure 2. Amount of PRBC transfused per group

DISCUSSION

Anticoagulation has been considered to be the cornerstone of the management of ACS [1]. Since the 1970's, UFH was shown to benefit patients with acute myocardial infarction by exerting an activity against factor Xa and thrombin [1-2].

New formulation of LMWH, which have a greater activity against Xa, have been used in treating ACS [6]. In contrast to UFH, these molecules produce more predictable anticoagulation response, have a better bioavailability and do not require laboratory monitoring [6]. enoxaparin, which is a LMWH, has shown to be superior to UFH in the treatment of ACS, however its long duration of activity and its partial neutralization by protamine have raised concerns regarding bleeding complications in patients undergoing CABG treated by LMWH prior to surgery [6-7].

According to the latest guidelines concerning perioperative management of antithrombotic therapy published by the American College of Chest Physicians (ACCP) in 2012 [8], it is suggested continuing aspirin around the time of surgery in patients requiring CABG instead of stopping it 7 to 10 days before, and administering the last dose of LMWH 24 hours before surgery instead of 12 hours before. Those recommendations are grade 2C which means very weak recommendations with low-quality evidence; that's why those recommendations remain a sug-

TABLE II

SELECTED INDICATORS RELATED to BLOOD LOSS in the THREE GROUPS

Variables	Enoxaparin stopped 12 to 24h pre-op	Enoxaparin stopped > 24h pre-op	No Enoxaparin	*p*-value
Patients' number (%)	50 (40)	25 (20)	50 (40)	
Need for any PRBC transfusion [number (%)]	28 (56)	16 (64)	31 (62)	*0.747*
Total PRBC received [Units]	1.16/1	1.2/1	1.36/1	*0.619**
Need for any FFP transfusion [number (%)]	6 (12)	4 (16)	7 (14)	**
Total FFP received [Units]	0.4/0	0.64/0	0.46/0	*0.852**
Need for any platelets [number (%)]	4 (8)	0	6 (12)	**
Total platelets received [Units]	0.66/0	0	1/0	*0.197**
Bleeding in drain, 1st 24 hours [mL]	880/635	695/660	830/665	*0.710**
Total Bleeding in drains, 48 hours [mL]	1087/775	853/780	1006/835	*0.566**

Numerical variables are listed as: Mean/Median *Kruskal-Wallis test **Statistical test not performed because of small number
PRBC: packed red blood cells **FFP**: fresh frozen plasma

TABLE III

ASSOCIATION BETWEEN SELECTED VARIABLES & NEED for PACKED RED BLOOD CELLS TRANSFUSION

Variables	Need for PRBC transfusion		*p*-value
	Yes	No	
Sex			
Male	53 (53%)	47 (47%)	*0.001*
Female	22 (88%)	3 (12%)	
Age	68/68	62/61	*< 0.001*
Clopidogrel intake in pre-op			
Yes	22 (85%)	4 (15%)	*0.004*
No	53 (53%)	46 (47%)	
Last dose Clopidogrel [days]	5.1/5	6.2/7	*0.316*
Taking Enoxaparin in pre-op			
Yes	44 (59%)	31 (41%)	*0.709*
No	31 (62%)	19 (38%)	
Taking Aspirin in pre-op			
Yes	44 (67%)	22 (33%)	*0.108*
No	31 (52%)	28 (48%)	
Platelets baseline [*1000]	234/236	243/236	*0.504*
ACT pre-op	146/143	143/141	*0.276*
ACT mean CPB	586/584	572/546	*0.161*
PT pre-op	12/12	12/12	*0.797*
PT post-op	16/15	15/15	*0.569*
PTT pre-op	33/33	34/32	*0.506*
PTT post-op	44/43	42/40	*0.065*
Hematocrit pre-op	40/41	42/43	*< 0.001*
Bypass time [min]	68/67	65/65	*0.637*
Total heparin use intra-op	1.0/0.0	0.16/0.0	*0.054*

Quantitative variables expressed as: Mean/Median
Chi-square used for qualitative variable; Mann-Whitney U test for quantitative variables.
ACT: activating clotting time **PT**: prothrombin time **PTT**: partial thromboplastin time

TABLE IV

ASSOCIATION BETWEEN SELECTED VARIABLES & "NEED FOR PACKED RED BLOOD CELLS"

Variables	OR (95% C.I.)	*p*-value
Groups	1.26 (0.7 – 2.1)	*0.384*
Sex	5.9 (1.4 – 25.0)	*0.016*
Age	1.1 (1.0 – 1.2)	*0.002*
Taking aspirin pre-op	1.8 (0.6 – 5.3)	*0.249*
Taking clopidogrel pre-op	4.4 (1.1 – 18.1)	*0.040*
Pre-op hematocrit	0.89 (0.80 – 1.00)	*0.053*
Heparin received in per-op	0.99 (0.99 – 1.00)	*0.288*

Variables included in this Logistic Model were: Group belonging, Sex, Age, Taking aspirin pre-op, Taking clopidogrel in pre-op, Pre-op hematocrit, and heparin received per-op (variables with $p < 0.10$ in the bivariate analysis)
(Model characteristics: Nagelkerke R^2 40%; Hosmer and Lemeshow Test p 0.427; c-statistic 0.837)

TABLE V

DRAIN OUTPUT DURING the FIRST 24 HOURS & ASSOCIATION with SELECTED VARIABLES

	Drain first 24 hours [mL] Mean/Median	*p*-value
Sex		
Male	909/745	*< 0.001*
Female	478/450	
Enoxaparin pre-op		
Yes	819/660	*0.972*
No	930/665	
Aspirin pre-op		
Yes	881/660	*0.163*
No	758/620	
Clopidogrel pre-op		
Yes	950/745	*0.122*
No	790/640	
Number of grafts*		
1-2	721/590	*0.033*
3	808/660	
4-5	1087/820	

Groups of 2 compared using Mann-Whitney U-Test
*Number of grafts correlated to drain during first 24 hours, Spearman 0.22 ($p = 0.015$)

gestion and other alternatives may be equally reasonable.

In order to elucidate this matter, many reports studied the incidence of bleeding complications in patients undergoing CABG treated prior to surgery by LMWH.

Some of these studies showed no significant risk of bleeding in those patients compared to subjects receiving UFH [9-10]. In fact, Renda *et al*. found that transfusional requirements of blood and plasma was similar in patients receiving either UFH or LMWH (stopped 12 hours prior to surgery) but their study had sample size limitation [9]. Medalion *et al*. found also that administration of enoxaparin more than 8 hours before surgery did not increase bleeding or products' transfusion rate [10].

However, these findings contrast with what Jones *et al*. found: a significant increase in incidence of re-exploration for post-op bleeding in a group of patient receiving enoxaparin [11]. Their study was done on a small size of patients who had some significant differences in the baseline characteristics between the two groups in relation to age, sex and type of surgery. It showed a lack of correlation between blood products usage and increased risk of surgical re-operation, and failed to describe any temporal relationship between the last dose of enoxaparin and post-op bleeding. The increased risk of bleeding and mediastinal re-exploration in a group treated by LMWH was also mentioned by two studies: a study by Myhre *et al*. [12] in 2004 and a study by McDonald *et al*. [13] in 2005. Kincaid *et al*. showed also that the preoperative use of enoxaparin less than 12 hours before CABG is associated with lower post-op hemoglobin values and higher rates of transfusion when compared to continuous use of UFH [14].

In our study, we showed that the use of enoxaparin in pre-CABG does not affect some bleeding parameters,

when stopped earlier than 12 hours prior to the surgery.

Enoxaparin is usually administered twice daily and since our patients had all elective surgery, we stopped enoxaparin at two different intervals prior to surgery. In one of the groups, enoxaparin was stopped 12 hours prior to surgery while in the other it was stopped 24 hours prior to surgery. We found that whether using enoxaparin and stopping it late (12-24 h prior) or early (24 h prior) did not affect bleeding parameters (tube drainage and transfusion rate) in comparison to the controls. Our series showed lower bleeding rates in general and that could be related to the use of tranexamic acid.

All patients who received enoxaparin did not have pre-op higher PT, PTT or ACT levels than the control group. There is no data in the literature about heparin resistance and pre-op use of enoxaparin.

The heparin use on bypass in this study was similar between all groups (p = 0.258; Table I). This implies absence of any heparin resistance, even though it is documented in the literature in around 26% of the cases [15]. Based on our findings, administering enoxaparin up to 12 hours prior to surgery appears safe.

The findings that the number of bypasses grafts and being a male increase chest tube drainage is interesting but not related to the use of enoxaparin (Table V).

On the other hand a multivariate analysis showed that female gender, age and administration of clopidogrel more than five days prior to surgery increase the need for transfusion. This also is not related to the use of enoxaparin, even though they are important findings and need to be affirmed in larger studies.

The fact that being of female gender was an indicator of increased need for transfusion with however lower absolute amounts of chest tube drainage is intriguing, but can be explained when looking to their smaller body surface area (BSA). In fact the female patients had a lower mean BSA (1.75) than male patients (1.91) and this may explain the higher transfusion rate in them even though they had lower chest tube drainage.

Our study has its own limitations; it is a one-center retrospective study, reflecting the practice of one group which might affect the generalizability of the findings. The sample size is relatively small and that might affect the ability to detect differences that really exist (type-2 error). Large multicenter studies would be required in order to shed more lights on this issue.

CONCLUSION

In elective first time CABG patients who had no aspirin or clopidogrel intake five days prior to surgery, the use of enoxaparin up to 12 hours prior to skin incision is safe and does not increase the risk of bleeding postoperatively or the transfusion rate.

However, the use of clopidogrel (more than five days prior to surgery), age and being a female may predict a higher transfusion rate.

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