EFFECTIVENESS AND SAFETY OF ENOXAPARIN AS ANTICOAGULANT IN PATIENTS UNDERGOING ELECTIVE PERCUTANEOUS CORONARY INTERVENTION FOR STABLE CORONARY ARTERY DISEASE: FIVE-YEARS EXPERIENCE OF A SINGLE CENTER

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ABSTRACT

Objective: To determine the effectiveness and safety of enoxaparin as anticoagulant in patients undergoing elective percutaneous coronary intervention for stable coronary artery disease.

Methodology: This study was conducted at the Department of Department of Cardiology, Hayat Abad Medical Complex, Peshawar, from March 2013 to December 2017. All patients who underwent elective percutaneous coronary intervention (PCI) for stable coronary artery disease were included in the study. We retrospectively analysed our data for short term outcome of efficacy and safety with use of enoxaparin as procedural anticoagulant. The dose of enoxaparin used was 0.75-1mg/kg. Sheath removal with manual compression haemostasis was performed 6 hours after the femoral route and within first hour after the radial procedure. Data were analysed by SPSS version 23.

Results: A total of 3190 elective PCIs with enoxaparin as anticoagulant were performed in the study period. Mean age of the patients was 57.48 ±6.9 years and 70% were males. Among the efficacy end points, major adverse cardiovascular events occurred in 1.4%. Mortality of any cause was 0.34% in the total patients studied. Urgent repeat revascularization for acute stent thrombosis was performed in 0.4% of patients. Acute MI and ischemic strokes occurred in 0.50% and 0.15% of patients respectively. Among the safety end points, major bleeding occurred in 0.37% of patients. Intracerebral bleeds and coronary perforations were 0.06% each. Minor bleeding that did not cause any significant morbidity were in 2.85% patients.

Conclusion: Enoxaparin in a weight based regimen can be used effectively and safely for percutaneous coronary interventions for stable coronary artery disease.

Key Words: Anticoagulants, Enoxaparin, Percutaneous coronary intervention, Coronary artery disease

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INTRODUCTION

Anticoagulation is mandatory during PCI both for elective and acute coronary syndrome patients. It is given to prevent the ischemic complication of putting foreign body (stents) inside the vessel lumen. Stent placement can disrupt the endothelium and predisposes the underlying tissue to stimulate the coagulation cascade. This may lead to acute stent thrombosis causing acute myocardial infarction, death and also long term complications. The ideal anticoagulant for PCI should have a rapid onset of action, effective in reducing ischemic complications with a dose-dependent and predictable effect and not associated with increased risk of bleeding. Additionally, it should have a wide therapeutic window and quick reversibility is possible with antidote or short half-life. However, all these properties are not possessed by any of the available anticoagulant drugs.

Currently, unfractionated heparin, low molecular weight heparin, bivalirudin and fondaparinox are used during PCI. The most widely used and studied anticoag-

ulant during PCI is unfractionated heparin and has got class 1 recommendation in most guidelines[1-3]. However, there are several limitations for the use of unfractionated heparin. These include heparin-associated thrombocytopenia, not binding to clot-bound thrombin and variable response in different individuals. Moreover, due to its unpredictable effect and need for close monitoring with activated clotting time, its use during PCI is limited[4,5].

The anticoagulant response of heparin is made non-linear because of the the complex kinetics of heparin clearance and every incremental dose results in disproportionately increased duration of effect. One study reported that after an intravenous bolus of 100 U/kg, the half-life of heparin increases to 60 minutes and with a bolus of 400 U/kg it further raised to 150 minutes[6]. The current European Society of Cardiology guidelines recommends heparin in a dose of 70–100 IU/kg for PCI of stable coronary artery disease[7]. With use of heparin, activated clotting time of 300 to 350 is associated with least bleeding as well as ischemic complications. Because of its dose dependant and person dependant variability, heparin requires frequent activated clotting time monitoring during the procedure. It is also associated with poor control on von Willebrand factor release, platelet activation leading to pro-thrombotic properties and the phenomenon of rebound thrombin generation upon discontinuation[8].

In 2012, several acute stent thromboses occurred in hours after PCI in our Cath. lab in a series of cases. The problem was traced to be related to heparin. Several manufactural versions of heparin are available here including original manufacturer and several generics. There is additional problem of storing it, at times for long time, in our tropical environment. Taking these considerations into account, we switched our procedures from then onward to enoxaparin. Enoxaparin is the only low molecular weight heparin with large volume of published evidence regarding its use in interventions for both stable ischemic heart disease and acute coronary syndrome[8,9]. It provides predictable anticoagulation effect and does not require frequent monitoring[10,11].

Enoxaparin is given by intravenous injections during primary PCI for its rapid onset of anticoagulation effect. For elective PCI, it has been used both by intravenous and subcutaneous routes. Only one multinational company manufactured enoxaparin is available in our country. It is available in prefilled syringes in multiple strengths and cold chain is well maintained. Evidence of it safety and efficacy is available[8,9]. Although data of enoxaparin safety and efficacy in comparison to heparin is available in interventions for stable coronary artery disease, it is still not used routinely as sole anticoagulant for PCI. Most centres in Pakistan and internationally still use heparin. Local evidence for the use of enoxaparin as anticoagulant in elective PCI is not available. Therefore, we decided to determine the effectiveness and safety of enoxaparin as alternative to heparin in elective PCI for stable coronary artery disease by analysing our five-years data. Intra-arterial use of enoxaparin was also looked for its safety.

METHODOLOGY

This study was conducted at the Department of Cardiology, Hayat Abad Medical Complex, Peshawar, from March 2013 to December 2017. All patients of any age and either gender who underwent elective PCI for stable coronary artery disease were included in the study. We retrospectively analysed our data for short term outcome of efficacy and safety with use of enoxaparin as procedural anticoagulant. The dose of enoxaparin used was 0.75-1mg/kg. Patients having weight less than 80 kg received 60 mg of enoxaparin and those having weight more than 80 kg received 80 mg of enoxaparin. Additional 20 mg enoxaparin was given to those having body weight of more than 110 kg.

As we have no primary PCI program, those patients who underwent PCI electively for failed thrombolysis or those patients who were having ongoing ischemia despite ST resolution with thrombolysis were also included. Occasional patients of acute coronary syndrome other than ST elevation myocardial infarction, who underwent PCI more than 24 hours after hospitalization were also included in the study. Exclusion criteria were all those patients who needed PCI and were on oral anticoagulants; patients who came for diagnostic coronary angiography and underwent PCI in emergency for critical lesions or as bailout procedure who became symptomatic during the procedure; and post CABG patients who underwent elective PCI for venous graft. Sheath removal with manual compression haemostasis was performed 6 hours after the femoral route and within first hour after the radial procedure. We also used enoxaparin intra-arterially in the arterial sheath of both femoral and radial arteries or through the guiding catheter in the aorta but never intra-coronary. This intra-arterial use of enoxaparin for PCI has never been reported elsewhere.

The primary efficacy outcome included ischemic events occurring in hospital (short term) or within 7 days. Major adverse cardiovascular event was defined as occurrence of myocardial infarction, urgent revascularization of target vessel or lesion, stroke or death. Myocardial infarction was defined as acute MI after the PCI procedure who were thrombolysed or otherwise treated and ECG findings were suggestive of occlusion of the vessel being stented and did not undergo cardiac catheterization. Safety endpoints included the bleeding complications of PCI and were defined as given in Ta-

ble 1. Descriptive statistics (frequency, percentages and mean ±SD) were used accordingly. Data were analysed by SPSS version 23.

RESULTS

AA total of 3190 elective PCIs with enoxaparin as anticoagulant were performed in the study period. Mean age of the patients was 57.48 ±6.9 years and 70% were males. However, there was an increasing trend of female patients progressively each year (Figure 1). Hypertensive patients were 22.8% of the total number. Female diabetic patients (30.43%) were more than males (28.67%). Diabetes and hypertension both were present in 11.7% of all the patients. More female patients (14.87%) were both hypertensive and diabetic compared to 10.31% of male patients (Table 2).

Among the efficacy end points, major adverse cardiovascular events occurred in 1.4% of patients. Mortality of any cause was 0.34% in the total patients studied. Urgent repeat revascularization for acute stent thrombosis was performed in 0.4% of patients. Other details are shown in Table 3.

Among the safety end points, major bleeding occurred in 12 (0.37%) of patients. Groin haematomas that caused mortality or drop in haemoglobin concentration and required three or more blood transfusions were included in major bleeds and occurred in 8 (0.25%) of patients. Minor bleeding that did not cause any significant morbidity were in 91 (2.85%) patients. Access site haematomas that responded to manual compression were found in 1.72% patients. Other details are shown in Table 4.

Figure 1: Number of patients for PCI during study period

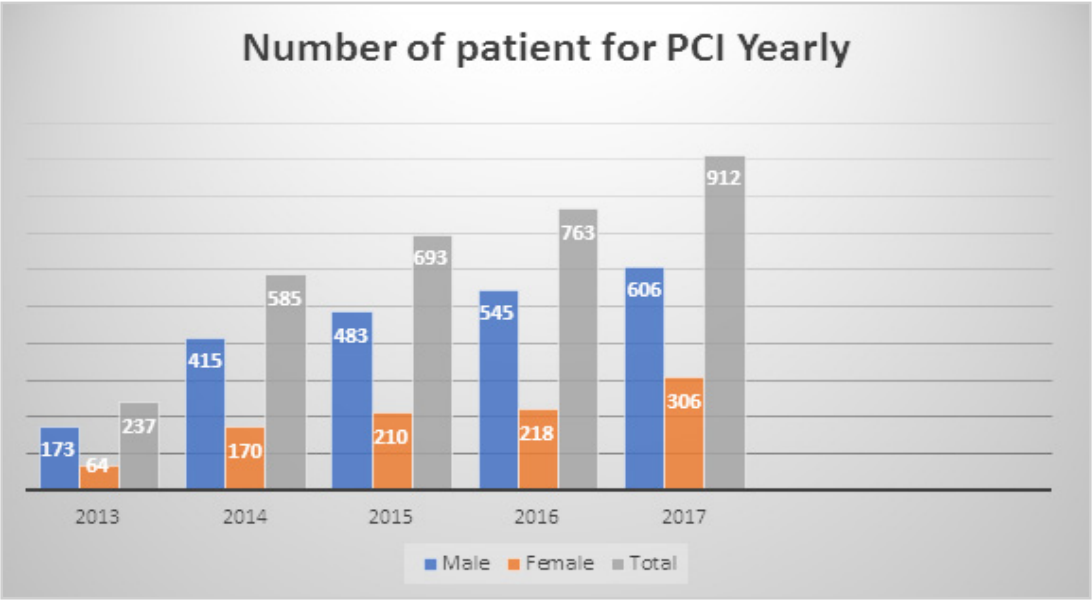

Table 1: Bleeding complications of PCI

Type	Examples
Major Bleeding	Fatal bleeding Bleeding requiring transfusion Bleeding requiring surgical intervention Retroperitoneal bleed Intra-cerebral bleed
Minor Bleeding	Access site hematoma not requiring transfusion or surgical intervention Gross hematuria Epistaxis Sub-conjunctival hemmorrhage

Table 2: Baseline demographic and clinical characteristic of patients

Variables	Male	Female	Total
Mean Age (years)	58.69 ± 7.55	55.84 ± 6.24	57.48 ± 6.9
Weight (Kg)	83.46 ± 9.6	74.32 ± 8.4	79.63 ± 8.7
Hypertension	519 (23.4%)	214 (22.1%)	727 (22.8%)
Diabetes	637 (28.67%)	294 (30.43%)	931 (29.2%)
Diabetes and Hypertension	229 (10.31%)	144 (14.87%)	373 (11.7%)

Table 3: Primary efficacy end points in PCI patients with enoxaparin (n=3190)

Events	Frequency	Percentage
Major Adverse Cardiovascular Events	45	1.4%
Death of any Cause	11	0.34%
Urgent repeat Revascularization	13	0.41%
Myocardial infarction (Not Revascularized)	16	0.50%
Ischemic Stroke	5	0.15%

Table 4: Safety end points in PCI patients with enoxaparin (n=3190)

Complications	Frequency	Percentage
Major Bleeding	12	0.37%
Haematoma	8	0.25%
Intracerebral Bleeding	2	0.06%
Coronary Perforation	2	0.06%
Minor Bleeding	91	2.85%
Access site Haematoma	55	1.72%
Haematuria	16	0.5%
Conjunctival Haemorrhage	07	0.21%
Epistaxis	13	0.4%
Death	1	0.03%

DISCUSSION

Unfractionated heparin is recommended by all guidelines as anticoagulant in percutaneous coronary intervention but has got its own limitations. It has been replaced recently in guidelines by bivalirudin but that is very expensive and not available in our part of the world. The safety and superiority of enoxaparin over unfractionated heparin has been shown in a large randomized controlled trial[12]. In ATOLL trial of primary PCI, enoxaparin was found to be superior to unfractionated heparin in decreasing ischemic events as well as mortality[13]. Enoxaparin has got pharmacological and practical advantages of its use that simplify patient management[14].

In this retrospective analysis, we looked into the safety and efficacy of our five-years data and compared it with already reported international efficacy and safety of enoxaparin in elective PCI. The overall mortality of 0.34% that occurred in our patients is almost the same reported internationally in this group of patients with enoxaparin[12]. The acute stent thromboses causing myocardial infarction and/or urgent repeat revascularization are due to decreased efficacy of anticoagulant used.

The ischemic complications, such as strokes, occurred in 0.15% of our patients. These complications although similar to those reported in other trials, may be due to prolonged radial procedures or disruption of atheromatous plaques in the aorta during the procedure using femoral approach. Ischemic cerebrovascular accidents occurring with decreased frequency were due to the better efficacy profile of enoxaparin.

Peri-procedural bleeding is the most common non-cardiac complication of PCI and is associated with increased health care cost of and risk of early mortal-

ity[15]. Intravenous enoxaparin was compared with unfractionated heparin in the STEEPLE study which was a large randomized clinical trial of patients who underwent elective PCI. Femoral approach was used as access route in that trial. Target levels of anticoagulation was achieved significantly more often with enoxaparin as compared to unfractionated heparin (79 vs 20%) respectively with p value <0.001)[16]. Similarly, decreased frequency (6.5%) of major or minor bleeding was reported in the enoxaparin group. Our bleeding complications were less because we used both radial and femoral access routes.

In a meta-analysis of 23 trials comparing efficacy and safety of enoxaparin with heparin in PCI in the overall population, relative risk of mortality was reduced by 34% with enoxaparin compared to heparin (p <0.001) transforming into absolute risk reduction in mortality of 1.66%[8]. In this meta-analysis, the safety outcomes of bleeding were reduced by 20% with enoxaparin. The intravenous use of enoxaparin was found to be superior to subcutaneous use regarding bleeding complications. Moreover, the hemorrhagic access site complications of about 2% are less compared to that reported in a large trial of 6.5% with enoxaparin and 8.5% with heparin because only femoral access route was utilized. The bleeding risk can be minimized if bleeding avoidance strategies are adopted. These may include radial artery access, arterial closure devices and using bivalirudin as anticoagulant[16].

Two of our patients had intra-cerebral bleed. The patients survived, did not lose consciousness and CT scan brain showed hematoma to be of small size. Intra-cerebral bleeds occur probably more with heparin than enoxaparin. Pre-procedure bleeding risk calculation and use of smaller doses of enoxaparin or heparin can reduce this dreadful complication. The hematuria of 0.5% that occurred in our population are slightly more than reported elsewhere[12]. Majority occurred in patients who were catheterized post procedure and were traumatic hematuria in nature. None required dual antiplatelet cessation, transfusion or surgical intervention. Proper pre-procedure evaluation identifying high risk group and reducing the dose of anticoagulation can reduce this complication. Radial procedure will lead to early mobilization and decrease the need for catheterization. Pre-procedural surgical assessment and performance of any elective surgery before PCI can reduce hematuria in the elderly patients. Most of these elderly patients need urological procedure before elective intervention for stable ischemic heart disease.

There was increasing trend of CAD in female and young population in this study as predicted by INTERHEART study and reported by us in our previous study[17,18].

LIMITATIONS

This was a single center retrospective analysis of relatively small sample having no parallel group. But we assumed that superiority of enoxaparin has already been shown. Furthermore, this was an overall analysis and not looked into special consideration of risk groups predisposed for particular complication. As the operators were different and the procedures were not standardized for the trial, therefore, the operator variability and length of procedure might have affected the outcome and reliability of the study. Large multi-center prospective trials are needed to establish these facts.

CONCLUSION

Enoxaparin in a dose of 0.75 to 1 mg/kg body weight can be used effectively and safely in all elective percutaneous coronary interventions for stable coronary artery disease. Moreover, intra-arterial injection of enoxaparin for PCI was found effective and safe in our patients.

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CONTRIBUTORS

MAK conceived the idea, planned the study, and drafted the manuscript. MAR, IK, RJ and MH helped acquisition of data, did literature search and statistical analysis. ZAA critically revised the manuscript and supervised the study. All authors contributed significantly to the submitted manuscript.