Original Article

Bleeding in patients Undergoing Percutaneous Coronary Intervention (PCI)

Wajih-ur-Rehman[1], Shahid Hameed[2], Tahir Naveed[3]

ABSTRACT

Objectives: To study the frequency of bleeding and associated risk factors among patients undergoing Percutaneous Coronary Intervention (PCI).

Methodology: This cross-sectional study was conducted on 500 consecutive patients, who underwent PCI at Punjab Institute of Cardiology, Lahore. Bleeding was defined according to REPLACE – 2 criteria.

Results: There were 82 females (16.4%) and 418 males (83.6%); mean age 53.4 (± 9.6 years). Bleeding complications occurred in 6.2% (n=31) of patients; major bleed 0.8% (n= 4) and minor bleed 5.6% (n= 27). One patient with major bleed (retroperitoneal) died in hospital. The frequency of bleeding complications was 8.5% among females and 5.7% among males (P=0.24). Radial route was used in majority (88.6%). The risk factors found to be significantly associated with the development of post-PCI bleeding were diabetes (OR: 6.4; P < 0.0001), hypertension (OR: 13.2; P < 0.0001), smoking (OR:8.31; P<0.0001) and BMI > 40 (OR: 6.8; P < 0.002), use of streptokinase (OR: 3.1; P < 0.0005), femoral approach (OR:4.2; P < 0.02), anaemia (OR: 44.8; P < 0.0001) and ACT ≥ 350 (OR: 3.73; P < 0.0005). In our study, female gender, procedure time ≥60 minutes, use of Glycoproteins IIb/IIIa inhibitors (GPI), and patient's age ≥50 years did not show significant association with post PCI bleeding.

Conclusion: Major bleeding complications during Percutaneous Coronary Intervention (PCI) though occur rarely, are an important cause of patient morbidity and mortality.

KEY WORDS: Percutaneous Coronary Intervention (PCI), Bleeding, Risk factors, Site.

Pak J Med Sci October - December 2011 Vol. 27 No. 5 958-962

How to cite this article:

Wajih-ur-Rehman, Hameed S, Naveed T. Bleeding in patients undergoing Percutaneous Coronary Intervention (PCI). Pak J Med Sci 2011;27(5):958-962

INTRODUCTION

Bleeding is the most common non-cardiac complication after percutaneous coronary intervention (PCI).[1] The use of newer anti-platelets, glycoprotein IIb/IIIa inhibitors (GPI) and anti-coagulants after PCI has markedly reduced the ischemic complications, though at risk of increased bleeding.[2-4] Bleeding complications after coronary intervention are associated with prolonged hospitalization, increased hospital costs, patient dissatisfaction, morbidity, early and late mortality.[4-7]

Major bleeding has been strongly associated with increased rates of myocardial infarction (MI), stroke and repeat revascularization procedures after PCI.[1,8] The reported incidence of bleeding episodes after PCI varies between 1.4% to 12.8%.[9,10] It is generally non-access site and multiple site bleeding which leads to adverse outcome, and GIT bleed is the commonest.[1,7,8,11] More than 5% of patients who undergo PCI require blood transfusions. Contrary

1. Wajih-ur-Rehman, FCPS, Senior Registrar,
2. Shahid Hameed, MRCP, Associate Professor,
3. Tahir Naveed, FCPS, Senior Registrar,

1-3: Department of Cardiology, Punjab Institute of Cardiology, Lahore, Pakistan. *

Correspondence:

Dr. Wajih-ur-Rehman, FCPS,
House No. 44/1, Street 1, Sector B,
Phase 5, DHA, Lahore.
E-mail: wajihurrehman@hotmail.com

* Received for Publication: August 29, 2011
* Revision Received: September 9, 2011
* Revision Accepted: September 29, 2011

to common belief, transfusions increase mortality.[10] Factors contributing to the occurrence of bleeding after PCI include, advanced age,[1,2,6] female gender,[1,2,6,12] anemia,[4,8,13] renal insufficiency,[1,2,4] body mass index,[4,12] increased activated clotting time (ACT),[14] diabetes mellitus,[6,8,13] hypertension,[1,2,6] smoking,[8] hypercholesterolemia,[2] and peripheral vascular disease,[1] an admission diagnosis of ST-elevation myocardial infarction,[1,2] cardiogenic shock,[1,13,15] emergency procedure,[1,15] duration of intervention,[2] femoral artery access,[2] larger sheath diameter,[15] and the use of intra -aortic balloon pump. (IABP) are other contributory factors.[4,10]

Radial artery access,[5,16,17] vascular closure devices,[4,5] weight adjusted heparin,[14,18] and the direct thrombin inhibitor (bivalirudin) have reduced the number of bleeding episodes after PCI.[3,5,7,15]

The objectives of our study were to assess the occurrence of bleeding in patients undergoing PCI and to identify factors contributing to the development of bleeding in our setup.

METHODOLOGY

This was a cross sectional study of 500 consecutive patients undergoing PCI at Punjab Institute of Cardiology between December 2009 and April 2010. These were Acute Coronary Syndromes (ACS) as well as stable angina cases. Patients with previous history of systemic bleeding or bleeding diathesis and patients with elevated urea and creatinine were excluded. Bleeding was defined according to the Randomized Evaluation in the PCI Linking Angiomax to Reduced Clinical Events (REPLACE – 2) criteria.

Major bleeding was defined as either any intracranial, intraocular, retroperitoneal, or clinically-overt bleeding with a drop of hemoglobin of 3 g/dl, or any drop of hemoglobin of 4 g/dl, or the transfusion of two or more units of packed red blood cells. Minor bleeding was defined as clinically-overt bleeding not meeting the above criteria. Written informed consent was taken from all patients and study was approved by the ethical review committee of the institution. Demographic, clinical, periprocedural and laboratory data were collected. The in-hospital bleeding events, the site of bleeding, patient's hemodynamic status, drop in hemoglobin levels, number of blood transfusions, the length of stay and outcome were also recorded.

All patients were loaded with Aspirin 300mg and Clopidogrel 600mg, at least two hours prior to PCI. Six French (6F) arterial sheath was used in all patients. Per-procedure intravenous bolus (50-100 units/kg) of unfractionated heparin (UFH) was administered to achieve an activated clotting time (ACT) of 200-250 seconds (with GPI) and ACT of 300-350 seconds (without GPI).

Arterial access route (radial or femoral), use of bare metal or drug eluting stents and the use of GPI (eptifibatide/ abciximab/tirofiban) were at the discretion of the operating physician. Arterial sheath removal was with post procedure ACT <180 seconds. Hemostasis was secured by manual compression at the access site in all patients. Routinely patients were observed for 24 hrs in the hospital. In case of bleeding they were hospitalized longer, and post-discharge they were advised to report for any bleeding problem.

Statistical calculations were performed using SPSS version 17. Data were expressed as mean (±SD) or percentage as appropriate. Categorical variables were compared using Chi-square test and continuous variables by using Student *t*-test. A *p*-value ≤ 0.05 was considered as statistically significant.

RESULTS

There were 82 females (16.4%) and 418 males (83.6%). Their ages ranged from 26 to 79 years with a mean age of 53.4 ± 9.6 years. The mean Body Mass Index (BMI) was 28.7 ± 5.1 Kg/m^2. Radial route was followed in 443 (88.6%) patients, while 57 (11.4%) patients were approached through the femoral route.

Thirty one patients (6.2%) developed bleeding complications after PCI; major bleed in four cases (0.8%) and minor bleed in 27 cases (5.6%). The frequency of bleeding complications was 8.5% among females and 5.7% among males (P=0.24). Four patients required blood transfusion (0.8%). Distribution of various bleeding sites is shown in Table-I. Vascular access site bleeding occurred in 14 out of 31 patients (45.2%) and was more frequent in femoral access patients (17.2%, OR 4.2, P < 0.02).

The cases were divided into two groups: bleeders and non-bleeders; and their association with

Table-I: Sites of Bleeding.

Type / Site	*No. (n=31)*	*Percent*
Bruises (Arm, Shoulder, Back)	4	12.9
Epistaxis	1	3.2
G.I. Bleed	2	6.5
Gums	8	25.8
Haematoma (Arm)	7	22.6
Haematoma (Thigh)	7	22.6
Retroperitoneal	2	6.4

known risk factors for post-PCI bleeding was studied (Table-II). The risk factors found to be significantly associated with the development of post-PCI bleeding were diabetes (OR: 6.4; P < 0.0001), hypertension (OR: 13.2; P.< 0.0001), smoking (OR: 8.31; P<0.0001) and BMI > 40 (OR: 6.8; P < 0.002). Use of Streptokinase within 24 hours preceding PCI was also associated with increased frequency of post-PCI bleeding (OR: 3.1; P < 0.0005) and so was femoral approach (OR 4.2; P <0.02), post procedure ACT ≥ 350 (OR: 3.73; P < 0.0005) and anemia (OR: 44.8; P < 0.0001). Post - PCI bleeding occurred in 58.3% anemics and 3.1% non-anemics. In our study, female gender (P = 0.28), the procedure time >60 minutes (P=0.17), use of GPI (P=0.86) and patient's age > 50 years (P = 0.74) did not show significant association with post PCI bleeding. Mortality was 3.2% (1/31) for bleeders. Thirteen bleeders (41.9%) stayed in hospital for one day, five (16.12%) stayed for two days while 13 (41.9%) bleeders had to stay for more than two days.

DISCUSSION

In this observational study post-PCI bleeding occurred in a small number (6.2%) and major bleeding was rare (in 0.8%). The bleeding rates have varied widely according to variation in definitions, access site difference, types of patients and adjunct pharmacotherapy used.[2,3,5,12,17,19] There is also temporal trend over the years in reduction of bleeding.[5]

We chose to define and compare bleeding complications using the REPLACE-2 trial definitions,[3] as this trial used a sensitive definition of bleeding and reported the lowest rates of bleeding in the context of modern PCI.[12] Major bleeding reported in REPLACE-2 trial was 3.2%.[3] National Cardiovascular Data Registry (NCDR) reported bleeding complications of 2.4%.[1] Major bleeding complications occurred in 6.5% and 5.4% in two studies using the STEEPLE definition.[6,11] Kinnard et al used the TIMI bleeding definition and noted major bleeding in 5.4% and minor bleeding in 12.7% of their patients.[10] Pooled data from the PURSUIT and PARAGON B trials (15,454 patients) found that the rate of severe bleeding by using the GUSTO criteria was 1.2% and by using the TIMI criteria, the major bleeding was found to be 8.2% in the same patient population.[9] There had been efforts to reach at consensus on a universal definition of bleeding, This was finally defined as Bleeding Academic Research Consortium (BARC), with six grades ranging from grade 0 (no bleeding) to grade 6 (fatal bleeding).[19]

Major bleeding in our study was much less as compared to the above cited studies. The main reason was that radial route was followed in 88.6% of our patients. This route is preferred for coronary intervention at our centre due to smaller risk of local complications, early ambulation, patients' preference and convenience. RIVAL trial (radial vs femoral access) showed reduction in access site bleeding by 64% and major vascular complication rate of 1.4%.[17] The radial approach has not been universally adopted as yet. Based on data from the National Cardiovascular Device Registry, only 4.2% of PCI cases in the United States are performed via radial access.[20]

Majority of our patients were younger (mean age 53.4±9.6 years) and men. As previously published, this is the spectrum of population presenting to our unit.[21] Patients with renal insufficiency and history

Table-II: Association of various Risk Factors with post-PCI bleeding.

Risk Factor	*Bleeders (31)*	*Non-Bleeders (469)*	*Odds Ratio*	*95% CI*	*Significance of Difference*
Diabetes mellitus	74.2 %	30.9%	6.4	2.8 – 14.7	P < 0.0001
Hypertension	87.1%	33.7%	13.2	4.5 – 38.5	P < 0.0001
Smoking	77.4%	29.6%	8.31	13.5 – 19.7	P < 0.0001
ACT ≥ 350	58.1%	27.9 %	3.73	1.78 – 7.83	P < 0.0005
Female Gender	22.6%	16.0 %	1.63	0.7 – 3.9	P = 0.28
BMI > 40	12.9 %	2.1%	6.8	2.0 – 23.1	P < 0.002
Femoral Approach	17.2%	4.9%	4.2	1.9 – 9.4	P < 0.02
Use of SK within 24 hours preceding PCI	48.4%	11.7%	3.1	1.2 – 7.9	P < 0.0005
Anaemia*	58.5%	3.1%	44.8	19.9 – 100.9	P < 0.0001
Age ≥ 50 years	22.6%	15.4%	1.61	0.67 – 3.87	P = 0.25
Procedure Time (≥ 60 minutes)	12.9%	8.13%	2.17	0.71 – 6.6	P = 0.17
Use ofGlycoprotein IIb/IIIa	93.5%	89.3%	0.95	0.57-1.61	P = 0.86

*Anaemia was defined as Hb ≤ 13 in males and ≤ 12 in female.[24]

of bleeding diathesis were excluded from our study. Due to frequent use of the trans-femoral route and enrollment of high risk patients the studies from West have shown much higher bleeding rates.

Vascular access site bleeding was noted in 14 out of 31 bleeders (45.2%). Seven out of 443 patients who underwent PCI through radial route (1.5%) had forearm hematoma, while seven out of 57 patients (12.3%) with femoral access had groin hematoma. In terms of bleeding complications at radial and femoral access sites, our results are comparable with the work done in Pakistan. Two studies from a tertiary care cardiac centre in Karachi have reported forearm hematoma in 0.37% and groin hematoma in 6.7% of their patients.[16,22]

Our PCI population comprised mainly of overweight and obese patients. (Mean BMI 28.7±5.1). Vascular access hematomas were more frequent in these patients. Females had higher frequency of vascular access hematoma. (57.14% vs 45.83%). Our findings are consistent with the previous studies which reported female gender and higher BMI as independent predictors of higher major and minor bleeding complications including local hematomas.[12,18]

Two of our patients (0.4%) with femoral access developed retroperitoneal hematoma. There was one mortality; 60 yrs old female, diabetic, hypertensive with STEMI (thrombolysed) Her BMI was 28.9 and had groin hematoma in addition to retroperitoneal hematoma. She had multivessel PCI with procedure time of 70 minutes. She had double bolus Eptifibatide and infusion. Her ACT at the end of procedure was 290. She expired within 24 hrs of the procedure.

BMC 2 Registry reported retroperitoneal hematoma in 482 out of 112,340 patients (0.4%), with significantly higher in-hospital mortality. The risk factors identified in the BMC 2 Registry were female gender, BSA <1.8 cm^2, emergency procedure, history of COPD, cardiogenic shock, pre-procedural I/V heparin, pre-procedural GP IIb/IIIa, adoption of sheath size ≥ 8-F and use of vascular closure devices. Use of bivalirudin was associated with lower risk.[15]

Two of our patients (0.4%) with major gastrointestinal bleeding (one male and one female) were older than 65 years and had history of diabetes and hypertension, and had baseline anemia. In two previous studies gastrointestinal bleeding was reported in 21% and 3.5% of patients which was associated with longer ICU stay and higher in-hospital and overall mortality rate.[11,13] Independent predictors of gastrointestinal bleeding are older age, diabetes, smoking and baseline anemia.[8]

The significantly higher bleeding in our patients with history of diabetes mellitus, hypertension and smoking was consistent with international data.[2,6,8,13] Baseline anemia is an independent predictor of major bleeding.[4,8] Our anemic patients also had a significantly higher frequency of bleeding.
In our study, ACT ≥350 seconds was associated with significantly higher bleeding. Brener and colleagues reported that there was a linear increase in risk of bleeding as ACT approached 365 seconds (P=0.01), which leveled off beyond that value.[14] Increasing unfractionated heparin weight–indexed dose was independently associated with higher bleeding rates.[14]

PCI within 24 hours of thrombolysis with streptokinase was significantly associated with bleeding events. The NORDISTEMI study reported severe GUSTO bleeding (intracranial hemorrhage) in 1.9% of their patients within 12 hours of thrombolysis.[23] The National Cardiovascular Data Registry has reported more bleeding in patients with rescue PCI.[1] Studies have shown relationship of peri-procedural bleeding with advanced age,[1,2,6] longer procedure time,[2] female gender[1,2,6,12] and the use of Glycoprotein IIb/IIIa inhibitors.[2-4,10,15] In our study, the comparison of bleeders with non-bleeders showed that female gender, age > 50 years, procedure time > 60 minutes and the use of GP IIb/IIIa inhibitors were associated with more frequent post PCI bleeding, but the results could not achieve statistical significance.

In our study only four patients (0.8%) required blood transfusion. Data from Kinnard et al demonstrated that blood was transfused in 5.4% of post PCI patients. The in-hospital mortality for those who experienced major bleeding and received a blood transfusion was 10.6% as compared to just 5.1% for those with a major bleed without blood transfusion. The number of units transfused was linked to 1-year mortality per unit transfused.[10]

The limitations of our study were that it was non-randomized. The difference in the number of males and females was large and so was the number of radial and femoral access cases which caused difficulty in comparison of the two groups. Patients with advanced age were very few, due to which bleeding complications in this age group could not be properly studied. Patients with renal impairment were excluded and patients were observed only for in-hospital stay thus long term follow up was not done.

CONCLUSION

Major bleeding complications during PCI though occur rarely, are an important cause of patient morbidity and mortality. The frequency of bleeding in our study is less than that reported by studies from other countries. Improvement in procedural techniques and pharmacological strategies have played and important role universally in reduction of bleeding.

ACKNOWLEDGEMENT

The authors acknowledge the contribution of Dr. N. Rehan for his kind assistance in data analysis and compilation of results.

REFERENCES

1. Mehta SK, Frutkin FA, Lindsey JB, House JA, Spertus JA, Rao SV, et al. Bleeding in patients undergoing percutaneous coronary intervention: the development of a clinical risk algorithm from the National Cardiovascular Data Registry. Circ Cardiovasc Intervent 2009;2:222-229.
2. Hochholzer W, Wiviott SD, Antman EM, Contant CF, Guo J, Giugliano RP. Predictors of bleeding and time dependence of association of bleeding with mortality. Insights From the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38). Circulation 2011;123:2681-268.
3. Lincoff AM, Bittl JA, Harrington RA, Feit F, Kleiman NS, Jackman JD, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 2003;289:853–863.
4. Nikolsky E, Mehran R, Dangas G, Fahy M, Na Y, Pocock SJ, et al. Development and validation of a prognostic risk score for major bleeding in patients undergoing percutaneous coronary intervention via the femoral approach. Eur Heart J 2007;28:1936–1945.
5. Dauerman HL, Rao SV, Resnic FS, Applegate RJ. Bleeding avoidance strategies consensus and controversy. J Am Coll Cardiol 2011;58(1):1-10.
6. Kim Y, Lee JY, Ahn JM, Song H, Kim WJ, Yun SC, et al. Impact of bleeding on subsequent early and late mortality after drug-eluting stent implantation. J Am Coll Cardiol Intv 2011;4:423-431.
7. Verheugt FW, Steinhubl SR, Hamon M, Darius H, Steg PG, Valgimigli M, et al. Incidence, prognostic impact, and influence of antithrombotic therapy on access and nonaccess site bleeding in percutaneous coronary intervention. JACC Cardiovasc Interv 2011;4(2):191-7.
8. Nikolsky E, Stone GW, Kirtane AJ, Dangas GD, Lansky AJ, McLaurin B, et al. Gastrointestinal bleeding in patients with acute coronary syndromes: Incidence, predictors, and clinical implications. Analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial. J Am Coll Cardiol 2009;54:1293-1302.
9. Rao SV, Grady K, Pieper KS, Granger CB, Newby LK, Mahaffey K, et al. A comparison of the clinical impact of bleeding measured by two different classifications among patients with acute coronary syndromes. J Am Coll Cardiol 2006;47:809–816.
10. Kinnaird TD, Stabile E, Mintz GS, Lee CW, Canos DA, Gevorkian N, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. Am J Cardiol 2003;92:930–935.
11. Cayla G, Silvain J, Barthelemy O, Connor OS, Payot L, Bellemain A, et al. Trans-radial approach for catheterisation in non-ST segment elevation acute coronary syndrome: an analysis of major bleeding complications in the ABOARD Study. Heart 2011;97:887-891.
12. Poludasu S, Cavusoglu E, Clark LT, Marmur JD. Impact of gender on in-hospital percutaneous coronary interventional outcomes in African-Americans. J Invasive Cardiol 2007;19(3):129-30.
13. Chua S, Liao C, Hung H, Cheng J, Chiu C, Chang C, et al. Gastrointestinal bleeding and outcomes after percutaneous coronary intervention for ST-Segment Elevation Myocardial Infarction. Am J Crit Care 2011;20(3):218-225.
14. Brener SJ, Moliterno DJ, Lincoff AM, Steinhubl SR, Wolski KE, Topol EJ. Relationship between activated clotting time and ischemic or hemorrhagic complications: analysis of 4 recent randomized clinical trials of percutaneous coronary intervention. Circulation 2004;110(8):994-998.
15. Trimarchi S, Smith DE, Share D, Jani SM, O'Donnell M, McNamara R, et al. Retroperitoneal hematoma after percutaneous coronary intervention: Prevalence, risk factors, management, outcomes, and predictors of mortality. A Report from the BMC2 (Blue Cross Blue Shield of Michigan Cardiovascular Consortium) Registry. J Am Coll Cardiol Intv 2010;3:845-850.
16. Khan M, Qadir F, Hanif B, Villani A, Ahmedins B. To determine the safety and success of transradial coronary angiography and angioplasty — A local experience. J Pak Med Assoc 2010;60(10):809-13.
17. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): A randomised, parallel group, multicentre trial. Lancet 2011;377(9775):1409-20.
18. Tizon-Marcos H, Bertrand OF, Rodes-Cabau J, Larose E, Gaudreault V, Bagur R, et al. Impact of female gender and transradial coronary stenting with maximal antiplatlet therapy on bleeding and ischemic outcomes. Am Heart J 2009;157(4):740-5.
19. Mehran R, Rao SV, Bhatt DL, Gibson CM, Caixeta A, Eikelboom J, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011; 123:2736-2747.
20. Rao SV, Ou FS, Wang TY, Roe MT, Brindis RG, Rumsfeld JS, et al. Trends in the prevalence and outcomes of radial and femoral approaches to percutaneous coronary intervention. A report from the National Cardiovascular Data Registry. J Am Coll Cardiol Intv 2008;1:379-386.
21. Hameed S, Tawwab S, Shahbaz A, Sami W, Sherwani M, Azhar M. Cardiac mortality trends in the emergency department of a tertiary care cardiac centre. Pak J Med Sci 2007;23:825-31.
22. Shaikh AH, Siddiqui MS, Hanif B, Malik F, Hasan K, Adhi F. Outcomes of primary Percutaneous Coronary Intervention (PCI) in a tertiary care cardiac centre. J Pak Med Assoc 2009;59:426-433.
23. Bohmer E, Hoffmann P, Abdelnoor M, Arnesen H, Sigrun H. Efficacy and safety of immediate angioplasty versus ischemia-guided management after thrombolysis in acute myocardial infarction in areas with very long transfer distances: Results of the NORDISTEMI (NORwegian study on District treatment of ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2010;55:102-110.
24. World Health Organization. Nutritional anaemias: report of WHO Scientific Group. Report No.: Technical Report Series No. 405. Geneva: World Health Organization; 1968.