

State-of-the-art - Coronary

**Idiopathic thrombocytopenic purpura and coronary artery disease:
comparison between coronary artery bypass grafting and
percutaneous coronary intervention**Antonio Russo*, Marina Cannizzo, Gabriele Ghetti, Elena Barbaresi, Elisa Filippini,
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Received 13 March 2011; received in revised form 20 April 2011; accepted 21 April 2011

Summary

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by a low platelet count and an increased risk of bleeding. At the same time, ITP patients present an increased risk of thrombosis and atherosclerosis related to the high presence of haemostatic factors and chronic steroid therapy. Although relatively rare, the association of ITP and coronary artery disease represents a complex therapeutic challenge. In particular, no recommendations exist regarding the best management approach. We reviewed the literature making a comparison between coronary artery bypass grafting and percutaneous coronary intervention.

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Keywords: Idiopathic thrombocytopenic purpura; Coagulation disorder; Coronary artery disease; Percutaneous coronary intervention; Coronary artery bypass grafting; Cardiopulmonary bypass

1. Introduction

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune syndrome involving antibody- and cell-mediated destruction of platelets and suppression of platelet production that may predispose to bleeding [1]. Patients with ITP present an increased risk for thrombosis and coronary artery disease (CAD) related to more adhesive platelets, direct endothelial damage due to antigenic mimicry [2], and the negative effect of steroid therapy [3].

The relatively low number of patients with ITP and CAD has limited the conduct of clinical trials to evaluate, between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG), the best revascularization strategy. Surgical interventions are associated with increased risk for bleeding in ITP patients compared to the general population. This is especially true for cardiac operations with cardiopulmonary bypass (CPB) because of the full heparinization and the destructive effects of CPB on all blood components, and particularly on platelets [4]. In addition, percutaneous procedures pose an obvious concern because stent implanting requires intensive antiplatelet therapy. There are no previous studies comparing PCI and CABG in patients with ITP and CAD. Therefore, we reviewed all the cases in the literature involving surgery and percutaneous revascularization in these patients.

2. Materials and methods

The review considered studies that focus on ITP patients undergoing myocardial revascularization performed by PCI or CABG. Candidate studies were identified by searching Google Scholar and PubMed. All searches covered the period November 1989 through July 2010. Key words used included 'ITP', 'coagulation disorder', 'CAD', 'PCI', 'CABG', and 'CPB'. We also perused the bibliographies of retrieved articles and relevant reviews to identify further relevant studies. From each study, we extracted patient characteristics including platelet counts, perioperative treatments, type of myocardial revascularization, and outcomes. We reviewed 35 reports of cardiac revascularization in ITP patients.

3. Results**3.1. CABG in patients with ITP**

To the best of our knowledge, 20 reports involving 32 patients affected by ITP who underwent CABG have been published (Table 1) [5–24]. The mean age of the patients was 63 ± 10 years, and most were male. Five patients were affected by stable angina, three patients by unstable angina, and four patients by acute myocardial infarction; data about CAD presentation were unreported. On admission, the range of platelet values was wide, from $8000/\mu\text{l}$ [6] to $>80,000/\mu\text{l}$ [17, 18].

Most of patients had multivessel CAD, and two or more grafts were completed in 23 patients. A single graft was

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Table 1. Cases including patients affected by idiopathic thrombocytopenic purpura who were undergoing coronary artery bypass grafting

Study	Patients		Platelet count on admission (/μl)	Treatment				Preoperative platelet count (/μl)	Procedure	Grafts number	Bleedings
	Age (years)	Sex		STER	IVIG	PC	SPLE				
Thompson et al. (1989) [5]	61	M	68,000			•		68,000	On-pump	3	Major
Koike et al. (1989) [6]	37	M	8000	•		•	•	n.a.	On-pump	3	No
Bowman (1990) [7]	53	F	65,000	•		•		65,000	On-pump	2	No
Terada et al. (1990) [8]	n.a.	n.a.	58,000		•	•		128,000	On-pump	n.a.	No
Jubelier (1992) [9]	n.a.	n.a.	n.a.	•		•		n.a.	On-pump	n.a.	Major
	n.a.	n.a.	n.a.			•		n.a.	On-pump	n.a.	
Sato et al. (1994) [10]	60	M	14,000		•	•	•	87,000	On-pump	n.a.	No
Briffa et al. (1994) [11]	69	M	63,000	•	•			64,000	On-pump	1	No
Hofmeister (1995) [12]	64	M	18,000	•	•	•		110,000	On-pump	3	No
Hayashi et al. (1996) [13]	76	F	53,000		•	•		199,000	On-pump	3	Minor
Mathew et al. (1997) [14]	72	M	40,000		•	•		57,000	On-pump	3	No
	72	F	49,000		•			168,000	On-pump	3	No
	69	M	65,000		•	•		87,000	On-pump	3	No
Onoe et al. (1999) [15]	57	M	26,000		•	•		26,000	On-pump	n.a.	No
Gaudino et al. (1999) [16]	72	M	19,300	•	•	•		46,000	On-pump	3	Major
Christiansen et al. (2000) [17]	Group 1 (5 patients) 65 ^a	M/F	54,000 ^a		•	•		112,000 ^a	On-pump	3.6 ^a (2-5)	No
	Group 2 (5 patients) 53 ^a	M	>80,000 ^a			•		>80,000 ^a	On-pump	2.8 ^a (2-4)	Major 1 patient
Koner et al. (2001) [18]	59	M	88,000	•	•	•		138,000	On-pump	4	No
Ohno et al. (2002) [19]	76	F	57,000		•	•		110,000	On-pump	1	No
Gotoh et al. (2002) [20]	77	M	50,000					50,000	MIDCAB	1	Minor
Inoue et al. (2004) [21]	60	F	42,000		•			187,000	Off-pump	3	No
Tani et al. (2007) [22]	n.a.	n.a.	n.a.	•	•	•	•	n.a.	Off-pump	n.a.	No
Fatimi et al. (2010) [23]	54	F	n.a.	•				135,000	On-pump	3	No
Rossi et al. (2010) [24]	47	M	55,000					55,000	On-pump	3	No

F, Female; IVIG, intravenous immunoglobulin; M, male; MIDCAB, minimally invasive direct coronary artery bypass; n.a., not available; PC, platelet concentrate; SPLE, splenectomy; STER, steroids. ^aData are shown as the mean.

made in three cases: in one patient with early re-stenosis after PCI, in one patient during reoperative CABG, and in one patient in whom multivessel grafting was infeasible because of hypoplasia and a diffuse lesion of the circumflex and right coronary arteries. Except for two patients, perioperative support treatment was always administered. Nine patients were treated with steroids (STER) and 19 with intravenous immunoglobulins (IVIGs). Platelet transfusion was completed in nearly every case. Prophylactic or combined splenectomy (SPLE) was performed in three patients [6, 10, 12]. At the time of operation, 20 patients had a platelet count >80,000/μl, and eight had a count of <80,000/μl, including two cases with a count <50,000/μl. Off-pump CABG was performed in only two cases [21, 22].

The CABG procedure was successfully completed in all the patients. Four cases of major and two cases of minor bleeding were reported, with a rate of significant bleeding of 12.5%. A platelet count <80,000/μl was reported in two out of four instances of major bleeding, and in one case the platelet count was not available. Among the instances of major bleeding, it was in one case necessary to carry out surgical re-exploration for bleeding from the anatomical bed of the mammary artery [5], and in one case a pericardial effusion required drainage [9]. The rate of surgical re-exploration was around 3%. The need for blood transfusion and antiplatelet therapy at discharge was not reported.

3.2. PCI in patients with ITP

From 1999 to January 2010, 15 cases of patients affected by ITP who underwent PCI were reported (Table 2) [25-39].

The mean age of the patients was 62±16 years; six patients were female, and nine patients were male. In six patients, CAD presentation was ST elevation myocardial infarction (STEMI), five patients were affected by non-STEMI or unstable angina, and four patients presented with stable angina.

PCI was performed with extremely different platelet counts, ranging from 3000/μl [26] to 170,000/μl [30]. Generally, a bare metal stent (BMS) was implanted during PCI. Drug-eluting stent (DES) implantation was reported for two patients [33, 35], Angioplasty without stent implantation was completed in two cases [29, 34], but in one case it led to rapid in-stent re-stenosis needing stent implantation [29]. Glycoprotein (GP) IIb/IIIa inhibitors were not used. Nine patients (60%) received steroid therapy, both before and after the procedure, to increase their platelet count. IVIGs were administered in seven cases (46%), and platelet transfusions were completed in three cases (20%). One instance of major bleeding [25] and two of minor bleeding [30, 34] were reported. Age, sex, platelet count, type of stent, and perioperative treatment were not associated with an increased risk of bleeding. No predictors of bleeding were reported by the authors.

Seven patients (46%) were discharged on double antiplatelet therapy of acetylsalicylic acid (ASA) and clopidogrel (Clop), and two patients only on aspirin or ticlopidine. Two patients did not receive any antiplatelet agent at discharge because of severe platelet reduction. In four reports, antiplatelet therapy at discharge was not specified. Many authors used the radial artery because of evidence of a lower risk of bleeding, guaranteed by an easy site for

Table 2. Cases of patients affected by idiopathic thrombocytopenic purpura undergoing percutaneous coronary intervention

Study	Patients		CAD	PLT count (/μl)	Vessel treated	Stent type	Vascular access	Bleeding	Treatment			Discharge therapy
	Sex	Age (years)							STER	IVIG	PC	
Fuchi et al. (1999) [25]	F	72	NSTEMI	59,000 n.a.	One One	n.a. n.a.	Femoral Femoral	Major No	• •	•	•	n.a.
Caputo et al. (2000) [26]	M	62	Stable angina	3000	One	BMS	Radial	No	•			ASA + Clop
Segal et al. (2001) [27]	M	n.a.	STEMI	40,000	More than one	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Kikuchi et al. (2002) [28]	F	68	STEMI	22,000	One	BMS	Femoral	No				Ticlopidine
Stouffer et al. (2004) [29] (twice)	M	77	Stable angina NSTEMI	64,000 78,000	One One	No BMS	n.a. n.a.	No No				ASA
Mendez et al. (2004) [30]	M	72	NSTEMI	17,000	Two	BMS	Radial	Minor	•			ASA + Clop
Marques et al. (2005) [31]	M	54	Unstable angina	15,000	Two	BMS	Brachial	No	•	•	•	n.a.
Kim et al. (2006) [32]	F	47	STEMI	21,000	One	BMS	Femoral	No		•		ASA + Clop
Fong et al. (2006) [33]	F	71	NSTEMI	119,000	One	DES	Radial	No	•	•		ASA + Clop
Park et al. (2007) [34] (three times)	F	61	Stable angina	4000 34,000 20,000	No Two Two (re- stenosis)	No BMS No	Femoral Femoral Femoral	Minor No No	• • •	• • •		No
Moretti et al. (2008) [35] (twice)	M	66	Unstable angina	110,000 200,000	Two Two	BMS DES	n.a. Femoral	No No	• •	•		ASA + Clop ASA + Clop
Garcia et al. (2008) [36]	M	37	STEMI	39,000	One	BMS	Femoral	No				ASA + Clop
Can et al. (2009) [37]	M	76	Stable angina	100,000	One	BMS	n.a.	No				n.a.
Neskovic et al. (2010) [38]	M	80	STEMI	5000	One	BMS	Femoral	No	•			ASA + Clop
Yildiz et al. (2010) [39]	F	23	STEMI	35,000	One	BMS	Femoral	No	•			ASA + Clop

ASA, acetylsalicylic acid; BMS, bare metal stent; CAD, coronary artery disease; Clop, clopidogrel; DES, drug-eluting stent; IVIG, intravenous immunoglobulin; n.a., not available; NSTEMI, non-ST elevation myocardial infarction; PC, platelet concentrate; PLT count, platelet count; STEMI, ST elevation myocardial infarction; STER, steroids.

hemostatic compression, early ambulation, and patient comfort. Transfemoral access was performed with good results as well even though major bleeding occurred in one case [25].

4. Discussion

The present study represents, to the best of our knowledge, the largest report of patients affected by ITP and CAD undergoing CABG or PCI. ITP is an autoimmune disorder characterized by a low platelet count and bleeding. At the same time, patients with ITP show an increased thrombotic and atherosclerotic risk, related to larger and more adhesive platelets, direct endothelial damage, and the negative effects of chronic steroid therapy. The combination of ITP and CAD is not unusual, and it poses serious management problems in which a good balance between the prevention of thrombosis and hemorrhagic risk must be achieved. Target platelet counts during major and minor surgery are considered by consensus guidelines to be $\geq 80,000/\mu\text{l}$ and $\geq 50,000/\mu\text{l}$, respectively [40]. Both the revascularization strategies CABG and PCI were successfully carried out in the ITP population, with a moderate increase in bleeding risk compared to the general population. The wide use of perioperative support treatment, increasing the number of platelets, probably minimized the complication rate, which overall appeared less than expected.

The pathogenic mechanism of thrombocytopenia in ITP was classically interpreted as increased platelet destruction mediated by autoantibodies. However, today it is well-known that more complex mechanisms are involved, including impaired platelet production and T-cell-mediated effects. Recently, it has been suggested that there is an increased thrombotic risk in patients with ITP compared to the general population and to patients with acquired

thrombocytopenia [2, 3, 41]. In patients with ITP, thrombocytopenia itself is not protective, and cases of acute coronary syndrome have been reported [42]. This implies that some factors other than platelet number are involved. Patients may be predisposed to coronary thrombosis because their platelets are larger and more adhesive to the vascular surface [43, 44]. Evidence of the involvement of platelet microparticles in the activation of inflammation, the coagulation cascade, and vascular dysfunction has been reported [41, 45]. Some authors suggest an antigenic mimicry between platelets and endothelial cells that may cause endothelial damage [2]. Finally, steroid treatment of ITP may be related to an increased risk of CAD and thrombosis [3].

Historically, CABG was the first revascularization strategy described in these patients. CABG was generally preferred to PCI because of better results with all kinds of lesion and for an easier management of antiplatelet therapy after the procedure. Despite the low platelet count, CABG was successfully carried out with a moderate increase in bleeding risk compared to CABG in the general population. The risk of significant bleeding was higher in the ITP population, 12.5%, compared to 5.4% in the general population [46]. The need for re-exploration for significant bleeding, 3%, was no different from that of the general population undergoing CABG, at 2.2% [47].

Perioperative treatments allow the complication rate to be reduced by increasing the platelet count: 63% of patients had more than $80,000/\mu\text{l}$ and 81% more than $50,000/\mu\text{l}$ platelets at the time of operation. Among the preoperative therapies, SPLE was the first option temporally [6]. Preoperative steroid treatment was associated with good results [12, 18, 21], especially in elective procedures. The effectiveness of IVIG has been demonstrated in patients refrac-

tory to steroid treatment [11, 18], and some authors suggest preoperative IVIG as a treatment of choice [14, 19], particularly when a rapid increase in platelet count is necessary. Platelet transfusions were largely administered. Associations between IVIG and platelet transfusion and myocardial ischemia or infarction have been reported; therefore, caution should be taken when administering such therapies. Rotational thromboelastometry as a point-of-care test of the coagulation status should reduce the frequency of transfusion of blood products [24]. An off-pump CABG technique, minimizing problems related to extracorporeal circulation, may be a safer strategy, especially if combined with preoperative IVIG [21]. Given the minimal bleeding rate, extending the conduit use to include the internal mammary arteries appears appropriate [14]. Details of antiplatelet therapy after CABG and long-term hemorrhagic and thrombotic complications were rarely available in the reports reviewed.

PCI has been successfully performed in patients with ITP despite the extremely different platelet counts, ranging from 3000/ μl [26] to 170,000/ μl [30], and major bleeding was the exception. The rate of major bleeding was 6%, higher than reported in the general population, at around 1–2%. Generally, bare metal stents were implanted during PCI, also if DES implantation was reported in two patients. Perioperative ITP treatment certainly minimized the complication rate in the PCI population as well. The first-line option was STER [25, 29, 31], but if a rapid platelet count elevation were required, IVIG supplementation [32, 38, 39] could be administered. Great attention must be paid when administering such therapies because of the increased risk of myocardial infarction. The use of platelet transfusion should be carefully considered in patients who have undergone recent coronary artery stent implantation because cases of acute thrombosis have been reported [48]. The administration of GP IIb/IIIa inhibitors is discouraged due to the high bleeding risk [30, 31]. Regarding vascular access, the radial artery should be preferred as a result of evidence of a lower bleeding risk, guaranteed by an easy approach to hemostatic compression, early ambulation, and patient comfort [26, 30, 33].

A total of 46% of patients were discharged on double antiplatelet therapy of ASA and Clop, 13% of patients received aspirin or ticlopidine, and 13% of patients did not start any antiplatelet therapy cause severe platelet reduction. Both revascularization techniques require long-term antiplatelet therapy, but in the presence of thrombocytopenia this is a matter of debate, and there are no widely accepted protocols. The risks and benefits of antiplatelet therapy should be critically weighed in order to achieve optimal outcomes and minimize bleeding sequelae in patients who have ITP. As mentioned above, instead of a lower platelet count, such patients have a prothrombotic status.

Aspirin is one of the most cost-effective therapies available for the prevention and treatment of platelet-mediated vascular occlusive disorders. The major indication for aspirin after CABG is to reduce the incidence of vein graft occlusion, but recently it has shown a lower incidence of postoperative myocardial infarction, congestive heart failure, and death compared to patients who did not receive it [49]. A long-lasting result for a percutaneous procedure

is linked to stent implantation, which requires aggressive antiplatelet therapy. A careful choice of antiplatelet therapy must be made. Individualized dose combinations of aspirin and Clop have been used in each case depending on platelet count, bleeding risk assessment, and stent type. Moreover, the association of Clop and aspirin has not been tested in all cases and generally only for short time after PCI, but no instances of major bleeding occurred. On the other hand, aspirin can be safely continued after CABG and PCI unless clinical bleeding occurs, or until the platelet count falls to 10,000–20,000/ μl [50]. Hematologic therapy that supports the platelet number allows a safer antiplatelet administration.

Finally, the association of ITP and CAD produces an fascinating management problem in which a good balance between the prevention of thrombosis and the hemorrhagic risk must be achieved. In general, both myocardial revascularization techniques seem to be safe and feasible, having a good early outcome and a low complication rate, especially if perioperative treatment is associated with an increase in the number of platelets, even if this leads to an increased risk of myocardial infarction and stent thrombosis. The choice between a surgical and a percutaneous procedure should take into account the coronary anatomy, platelet count, urgency, and associated diseases. Long-term antiplatelet therapy seems a safe option until the platelet number decreases to below 20,000/ μl or signs of bleeding appear.

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