CASE REPORT – OPEN ACCESS

International Journal of Surgery Case Reports 28 (2016) 251–254

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Fondaparinux for intra and perioperative anticoagulation in patients with heparin-induced thrombocytopenia candidates for peripheral vascular surgery: Report of 4 cases

Giulio Illuminati (MD)[a,*], Francesco G. Calio' (MD)[b], Giulia Pizzardi (MD)[a], Chiara Amatucci (MD)[a], Federica Masci (MD)[a], Piergaspare Palumbo (MD)[a]

[a] The Department of Surgical Sciences, The University of Rome "La Sapienza", Rome, Italy
[b] The Department of Vascular Surgery, Sant'Anna Hospital, Catanzaro, Italy

ARTICLE INFO

Article history:
Received 13 July 2016
Received in revised form 5 October 2016
Accepted 5 October 2016
Available online 8 October 2016

Keywords:
Heparin induced thrombocytopenia
Vascular surgery
Fondaparinux

ABSTRACT

INTRODUCTION: Intra and perioperative anticoagulation in patients with heparin induced thrombocytopenia (HIT), candidates for peripheral vascular surgery remains a challenge, as the best alternative to heparin has not yet been established. We evaluated the off-label use of fondaparinux in four patients with HIT, undergoing peripheral vascular surgery procedures.
PRESENTATION OF CASES: Four patients of whom 3 men of a mean age of 66 years, with proven heparin induced thrombocytopenia (HIT) underwent two axillo-femoral bypasses, one femoro-popliteal bypass and one resection of a splenic artery aneurysm under fondaparinux. No intra or perioperative bleeding or thrombosis of new onset was observed.
DISCUSSION: In the absence of a valid alternative to heparin for intra and perioperative anticoagulation in HIT, several other anticoagulants can be used in an off-label setting. However, no general consensus exist on which should be the one of choice. In this small series fondaparinux appeared to be both safe and effective.
CONCLUSIONS: These preliminary results seem to justify the off-label use of fondaparinux for intra and perioperative anticoagulation in patients with HIT, candidates for peripheral vascular surgery interventions.

1. Introduction

The first cases of heparin-induced thrombocytopenia (HIT) associated with arterial and venous thrombosis were reported in 1958 [1]. Since then several other observations confirmed the role of heparin in occasionally inducing thrombocytopenia, arterial and/or venous thrombosis due to a grayish clot for which the term "white clot" syndrome was also used [2]. Patients with HIT form immunoglobulin G and/or immunoglobulin M antibodies against a complex of platelet factor 4 (PF 4) and heparin [3]. This thrombocytopenia with white clot formation is also triggered by calciparin and low-molecular weight heparins, which, as well as sodium heparin, are strongly contraindicated in this condition. Heparins can be fairly easily replaced by other anticoagulants in the current medical settings requiring anticoagulation, in case of heparin induced thrombocytopenia [4]. On the other hand, replacing heparin for intraoperative anticoagulation in vascular surgery is not as simple, since sodium heparin bears the unique advantages of immediate efficacy, possibility of direct graft and runoff vessels irrigation, and immediate action reversal with protamine. No other anticoagulant has all these same properties and, given the rarity of this syndrome, the optimal alternative to heparin for intraoperative anticoagulation has not yet been established [5]. For this purpose, argatroban and hirudin have been successfully used in isolated patients undergoing peripheral vascular surgery and cardiopulmonary bypass [6,7]. Danaparoid and lepirudin have also been used in the setting of vascular surgery patients with alternate success [4]. Nonetheless, intra and perioperative anticoagulation in patients with known heparin induced thrombocytopenia, candidates for vascular surgery, remains a challenge. Fondaparinux has been used off-label in patients with HIT, despite a few reported, suspect fondaparinux-induced HIT cases, and the consequent debate on this off-label indication [8]. According to the SCARE criteria [9], we report four consecutive patients with HIT, managed at an Academic Hospital and one affiliated surgical center, undergoing peripheral vascular surgery under fondaparinux for intra and perioperative anticoagulation, in order to evaluate its off-label use in this special setting.

* Corresponding author at: Via Vincenzo Bellini 14, 00198 Rome, Italy.
E-mail address: giulio.illuminati@uniroma1.it (G. Illuminati).

http://dx.doi.org/10.1016/j.ijscr.2016.10.013

2. Presentation of cases

Four consecutive patients, of whom 3 men of a mean age of 66 years (range 52–74 years), with a known HIT, underwent 4 elective vascular surgery operations under fondaparinux. The study and the use of fondaparinux was approved by the institutional advisory board and the patients gave informed consent for both anticoagulant and surgical treatment. All the operations were performed by the senior surgeons (GI, FGC). The essential clinical data of the patients are resumed on Table 1.

2.1. Patient # 1

A 74-year-old diabetic patient, 81 kg of body weight, was admitted for the treatment of a critical lower limb ischemia associated with severe and extended aorto-ilio-femoral stenoses. At preoperative coronary angiography, a critical stenosis of the right coronary artery was detected and treated with percutaneous intervention (PCI) consisting of stenting with a drug-eluting stent. Intravenous sodium heparin was administered during the procedure. Standard blood tests the morning following PCI showed a platelet count drop to 22×1000/dl. HIT was suspected and was confirmed by ELISA test. The patient received dual antiplatelet therapy (100 mg of oral aspirin + 75 mk oral clopidogrel/day) and subcutaneous fondaparinux 2.5 mg every 12 h. This treatment was continued till the evening before operation, resumed the same evening of the operation and continued until discharge from the hospital. Operation was scheduled 5 days after PCI, when platelet count was 73×1000/dl. Peripheral arterial revascularization consisted of an axillo-biprofunda femoris bypass via a 8 mm polytetrafluoroethylene (PTFE) bypass (W.L. Gore and Associates, Flagstaff, Ariz). For flushing and tunneling, the graft was filled with saline solution. No significant bleeding or arterial thrombosis of new onsed occurred intraoperatively. Postoperative course was uneventful and the patient was discharged home on postoperative day 6. Upon discharge fondaparinux administration was stopped, whereas the dual antiplatelet treatment was maintained.

2.2. Patient # 2

A 52-year-old woman, 59 kg of body weight, current smoker with a history of coronary artery disease (CAD), assuming warfarin for atrial fibrillation, was admitted for the treatment of a 4.2 cm diameter aneurysm of the splenic artery. Two days before admission warfarin was stopped and replaced with 6000 IU of subcutaneous enoxaparin twice a day. At preoperative coronary angiography a tight stenosis of the circumflex branch of left coronary artery was detected and treated by PCI and implantation of a drug-eluting stent. Intravenous sodium heparin was administered during the procedure. A drop of platelet count to 37×1000/dl was observed at standard blood test the day after PCI and with a diagnosis of suspect HIT, subsequently confirmed at ELISA test, dual antiplatelet treatment was continued and enoxaparin was replaced with 2.5 mg of subcunaeous fondaparinux every 24 h. She was scheduled to undergo open resection of the aneurysm, due to its aberrant origin from the superior mesenteric artery, as occurred in a previously reported case [10], 8 days after PCI, with a platelet count of 88×1000/dl. Fondaparinux and dual antiplatelet treatment were continued till the day before operation and resumed the evening of operation itself. Intra and postoperative course was uneventful and the patient was discharged home on postoperative day 7, under dual antiplatelet therapy and fondaparinux. This latter was replaced by warfarin two weeks after.

2.3. Patient # 3

A 69-year-old diabetic man, 73 kg of body weight, was admitted for the treatment of a critical ischemia of the left lower limb and received heparin administration for the treatment of arterial disease. Two days after heparin administration his platelet count dropped to 46×1000/dl, in the absence of any symptom of thrombosis of new onset. HIT was suspected and subsequently confirmed at ELISA test. He was then administered 100 mg oral aspirin and 2.5 mg of fondaparinux subcutaneously twice a day. He was scheduled for below-knee, femoropopliteal bypass with a reversed saphenous vein graft, when platelet count reached 98000/dl 6 days after, with aspirin and fondaparinux continued till the evening of the operation and resumed the same evening of operation itself. Tunnelling and flushing of the graft was performed by filling it with simple saline solution. Intra and postoperative course was uneventful and the patient was discharged home on postoperative day 9, under dual antiplatelet treatment. Fondaparinux was stopped upon discharge from the hospital.

2.4. Patient # 4

A 72-year-old man, 74 kg of body weight, with a history of CAD, was admitted for the treatment of a popliteal artery aneurysm. At preoperative coronary angiography a significant stenosis of the right coronary artery was detected and treated by PCI, with deployment of two drug-eluting stents. Heparin was administered during the procedure and platelet count the day after PCI dropped to 42×1000/dl, without any apparent symptom of arterial or venous thrombosis. The patient was kept under dual antiplatelet treatment, and scheduled for aneurysm resection 5 days later, when platelet count was 110×1000/dl. Dual antiplatelet treatment was continued till the evening before operation and resumed the same night of operation itself. The morning of operation he was administered 2.5 mg of fondaparinux subcutaneously and subsequently underwent aneurysm resection/reversed saphenous vein grafting. Fondaparinux was resumed six hours after the end of operation and continued twice a day (2.5 mg/12 h), together with dual antiplatelet treatment unitl discharge from the hospital, on post-operative day 7, after an uneventful course.

3. Discussion

The results of this study seem to show that the off-label use of fondaparinux for intra and perioperative anticoagulation, in patients with HIT, candidates for peripheral vascular surgery is both safe and effective. The management of patients with HIT remains challenging and an optimal, alternative anticoagulation has not been established yet [5]. This is especially true in patients candidates for cardiac and vascular surgery [11]. As an alternative, argatroban [6], hirudin [7], lepirudin [12] have been used, with alternate results, as bleeding requiring reoperation or allogenic transfusions have also been observed [6,13]. Off-label use of fondaparinux in case of suspected HIT has already been reported [14]. In this case series we studied a further off-label use of fondaparinux, which is intra and perioperative anticoagulation in peripheral vascular surgery. The preliminary results seem to be encouraging, as two axillo-bifemoral, one femoro-popliteal and one splenic artery aneurysm resection could be safely performed without either thromboembolic or bleeding episodes. In the present study fondaparinux could be administered subcutaneously through the intra and perioperative period, at regular, standard doses, without requiring either intraoperative infusion or monitoring of the coagulation. Tunnelling of the grafts, which is usually performed under tension and previous filling of the graft with heparinized

Table 1
Essential clinical data of the patients' series. HIT, Heparin Induced Thrombocytopenia; CAD, Coronary Artery Disease; ASA, aspirin; GSV Greater Saphenous Vein.

Pt ♯	Sex	Age (years)	Body weight (Kg)	Comorbidities	Arterial disease	HIT-Triggering circumstance	Fondaparinux Dosage	Associated antiplatelet dosage	Intervention
1	M	74	81	Diabetes, CAD	Critical limb ischemia	Coronary angiography and stenting	5 mg/24 h	ASA + Clopidogrel	Axillo-bifemoral bypass
2	F	52	59	CAD, atrial fibrillation	Splenic artery aneurysm	Coronary angiography and stenting	2,5 mg/24 h	ASA + Clopidogrel	Aneurysm resection
3	M	69	73	Diabetes, CAD	Critical limb ischemia	Heparin administration for ischemia	5 mg/24 h	ASA	Below-knee femoro-popliteal by pass (reversed GSV)
4	M	72	74	CAD	Popliteal artery aneurysm	Coronary angiography and stenting	5 mg/24 h	ASA + Clopidogrel	Resection/Reversed GSV grafting

solution, could be successfully performed after filling with simple saline. This is a fairly crucial point as tunneling of the graft under tension is especially important for infragenicular bypasses performed for critical ischemia or diabetic foot, in order to avoid kinking or twisting of the graft, which would cause graft thrombosis [15]. Simple saline was also used for irrigation of the graft and run-off vessels. Simplicity of use and reliability of fondaparinux was apparent in all the reported cases. Nonetheless, as suspect, fondaparinux-induced HIT cases have been reported [8,14,16–19], its systematic use in patients with HIT, candidates for peripheral vascular interventions should still be done with caution. Beside the limitations of any small patients' cohort, this study has the disadvantage of dealing with axillo-femoral and femoro-popliteal bypasses or splenic artery aneurysm resection, thus not testing fondaparinux in the setting of aortic surgery, which is expected to be associated with a higher bleeding risk than the former operations. Although aortic and digestive arteries surgery under dual antiplatelet treatment has been reported [20,21], large experience with the combination of dual antiplatelet treatment and fondaparinux in this setting is lacking. Apart such limitations, the results of this study support the off-label use of fondaparinux for peripheral vascular surgery in patients with HIT. Hopefully further studies based on larger number of patients will confirm and validate these preliminary results.

4. Conclusion

The present report adds to the existing literature the information that fondaparinux seems safe and effective, for intra and perioperative anticoagulation, in patients with HIT, candidates for peripheral vascular surgery. It may deserve consideration for standard use in this special clinical setting.

Conflicts of interests

No conflict of interests to be disclosed.

Funding

No sources of funding.

Ethical approval

Ethical approval was given by the Institutional Ethics Committee.

Consent

Written informed consent was obtained from the patients for publication of this case reports. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Study concept and design: G.I., F.C., P.P.
Data collection: G.P., C.A., F.M.
Analysis and interpretation: G.I., F.C., G.P., P.P.
Writing the paper: G.I.
Critical revision of the article: G.I., F.C., G.P., C.A., F.M., P.P.
Final approval of the article: G.I., F.C., G.P., C.A., F.M., P.P.

Guarantor

Giulio Illuminati, first and corresponding author, takes full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

References

[1] R.E. Weisman, R.W. Tobin, Arterial embolism occurring during systemic heparin therapy, Arch. Surg. 76 (1958) 219–227.
[2] G.R. Rhodes, R.H. Dixon, D. Silver, Heparin induced thrombpcytopenia: with thrombotic and hemorrhagc manifestations, Surg. Gynecol. Obstet. 136 (1973) 409–416.
[3] M.R. Jackson, C. Krishnamurti, C.A. Aylesworth, B.M. Alving, Diagnosis of heparin-induced thrombocytopenia in the vascular surgery patient, Surgery 121 (1997) 419–424.
[4] T.E. Warkentin, M. Pai, R.J. Cook, Intraoperative anticoagulation and limb amputations in patients with immune heparin-induced thrombocytopenia who require vascular surgery, J. Thromb. Haemost. 10 (2011) 148–162.
[5] Y. Tokuda, M. Masahiko, S. Takaaki, et al., Vascular surgery using argatroban in a patient with a history of heparin-induced thrombocytopenia, Circ. J. 67 (2003) 889–890.
[6] F. Follis, G. Filippone, G. Montalbano, et al., Argatroban as a substitute of heparin during cardiopulmonary bypass: a safe alternative, Interact. Cardiovasc. Thorac. Surg. 10 (2010) 592–596.
[7] C.S. Carr, A. Rayner, J. Ponte, J.B. Desai, Off-pump coronary artery bypass grafting in a heparin-induced thrombocytopenia type II using hirudin, Ann. Thorac. Surg. 79 (2005) 696–698.
[8] T.E. Warkentin, B.T. Maurer, R.H. Aster, Heparin-induced thrombocytopenia associated with fondaparinux, N. Engl. J. Med. 356 (2007) 2653–2655.
[9] R.A. Agha, A.J. Fowler, A. Saetta, I. Barai, S. Rajmohan, D.P. Orgill, for the SCARE Group, The SCARE statement: consensus-based surgical case report guidelines, Int. J. Surg. (2016) (in press).
[10] G. Illuminati, G. LaMuraglia, G. Nigri, F. Vietri, Surgical repair of an aberrant splenic artery aneurysm: report of a case, Ann. Vasc. Surg. 21 (2007) 216–218.
[11] T.E. Warkentin, Heparin-induced thrombocytopenia and vascular surgery, Acta Chir. Belg. 104 (2004) 257–356.
[12] Y. Sun, P.E. Greilich, S.I. Wilson, M.R. Jackson, C.W. Whitten, The use of lepirudin for anticoagulation in patients with heparin-induced

thrombocytopenia during major vascular surgery, Anesth. Analg. 92 (2001) 344–346.
[13] A.C. Shah, M. Genoni, U. Niederhäuser, M. Malogne, M. Turina, R-hirudin (lepirudin, refludan) as an alternative anticoagulant in heparin-induced thrombocytopenia during cardiopulmonary bypass connection, Schweiz. Med. Wochenschr. 130 (2000) 896–899.
[14] M. Schindewolf, J. Steindl, J. Beyer-Westendorf, et al., Frequent off-label use of fondaparinux in patients with suspected acute heparin-induced thrombocytopenia (HIT) – findings from the GerHIT multi-center registry study, Thromb. Res. 134 (2014) 29–35.
[15] J.-B. Ricco, L. Thanh Phong, F. Schneider, et al., The diabetic foot: a review, J. Cardiovasc. Surg. 54 (2013) 755–762.
[16] M. Salem, S. Elrefai, M.A. Shrit, T.E. Warkentin, Fondaparinux thromboprophylaxis-associated heparin-induced thrombocytopenia syndrome complicated by arterial thrombotic stroke, J. Thromb. Haemost. 104 (2010) 1071–1072.
[17] T.E. Warkentin, A.K. Chakraborty, J.A. Sheppard, D.K. Griffin, The serological profile of fondaparinux-associated heparin-induced thrombocytopenia syndrome, J. Thromb. Haemost. 108 (2012) 394–396.
[18] T.E. Warkentin, W. Lim, Can heparin-induced thrombocytopenia be associated with fondaparinux use? Reply to a rebuttal, J. Thromb. Haemost. 6 (2008) 1243–1246.
[19] I. Elalamy, B. Tribout, Can heparin-induced thrombocytopenia be associated with fondaparinux use? A rebuttal, J. Thromb. Haemost. 6 (2008) 1242–1243 (author reply 1243–1246).
[20] G. Illuminati, A. D'Urso, G. Ceccanei, F. Calio', F. Vietri, Surgical treatment of pararenal aortic aneurysms in the elderly, J. Cardiovasc. Surg. 48 (2007) 705–710.
[21] G. Illuminati, F.G. Calio', A. D'Urso, V. Papaspyropoulos, P. Mancini, G. Ceccanei, The surgical treatment of chronic intestinal ischemia: results of a recent series, Acta Chir. Belg. 104 (2004) 175–183.