Annals of Medical Case Reports

ISSN: 2689-5927

Case Report

Off-Label Use of Bivalirudin on a Patient with Ventricular Septal Defect after Myocardial Infarction: A Case Report

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Abstract

Background: Bivalirudin is a direct thrombin inhibitor that is increasingly used for percutaneous coronary intervention and patients with Heparin Induced Thrombocytopenia (HIT). Nevertheless, the off-label use of bivalirudin is not rare, especially in patients undergoing mechanical circulatory support. Here, we are trying to analysis of the use of bivalirudin anticoagulant therapy on a patient with Post-Infarction Ventricular Septal Defects (PIVSD) to provide an insight into the off-label use of bivalirudin.

Case presentation: A 67-year-old male patient diagnosed with PIVSD received a continuous infusion of bivalirudin as the primary anticoagulant. Though the patient never received heparin during hospitalization nor had a prior diagnosis of HIT, thrombocytopenia occurred.

Conclusion: Off-label use of bivalirudin may cause thrombocytopenia, but there were no major bleeding and thromboembolic events. Perioperative anticoagulation property of bivalirudin after myocardial infarction is satisfactory, but the mechanism of continuously pumping the low-dose of the drug is unsafe and uncertain.

Keywords: Bivalirudin; Anticoagulation; Off-label drug use; PIVSD; Thrombocytopenia

Abbreviations

HIT: Heparin Induced Thrombocytopenia; PIVSD: Post-Infarction Ventricular Septal Defects; TCC: Transcatheter Closure; OLDU: Off-Label Drug Use; LAD: Left Anterior Descending Branch; PTCA: Percutaneous Transluminal Coronary Angioplasty; IABP: Intra Aortic Balloon Pump; ACT: Activated Clotting Time; PLT: Platelets; APTT: Activated Partial Thromboplastin Time; INR: International Normalized Rate; VAD: Ventricular Assist Device

Introduction

Ventricular septal defect is a rare but critical complication after acute myocardial infarction. Current treatments include conserved medical interventions based on mechanical assisted circulation, surgical thoracotomy repair and Transcatheter Closure (TCC) [1]. However, irrespective of intervention, coagulation system and thrombin activity, hypercoagulation of blood is always activated in patients with PIVSD [2]. Moreover, circulation assisting devices, cardiopulmonary bypass and interventional operation can further activate the internal/exogenous coagulation system [3]. Hence, incidences of thrombosis are high in myocardial infarction perioperative cases. Therefore anticoagulation drugs should be used reasonably to guarantee efficiency and safety these therapeutic agents.

Heparin is still the most effective, reliable and widely used first-line anticoagulant in clinical practice [4]. However, it has certain limitations, such as inconsistent inhibition of thrombin across individuals; it needs frequent laboratory monitoring and puts patients at risk of developing HIT [5]. Bivalirudin is a thrombin-inhibiting oligopeptide that reversibly binds and inhibit both free and bound thrombin. It is safer than heparin, mainly due to the occurrence of fewer bleeding events and almost no HIT [6]. Currently in cardiology, bivalirudin is widely being used in patients at risk of bleeding and HIT. There is also increasing application of bivalirudin in cardiac surgery and paediatrics.

In clinical practice, the complexity of various diseases associated with coagulation and accompanying anticoagulation strategies coupled with limitations of understanding new direct thrombin inhibitors has resulted in empirical and habitual use of drugs beyond the approved guidelines. Bivalirudin is one drug without antagonistic properties. It also does not have standard anticoagulation monitoring method. This has increased the risk of off-label use of the drug. In recent years, there is rising concern on Off-Label Drug Use (OLDU), yet, most countries or territorial regions lack relevant laws that govern this practice. This case study explores dynamics surrounding such practice, with an emphasis on bivalirudin.

Case Presentation

A 67-year-old male patient was admitted at Shenzhen Hospital of

Citation: Ming Y, Qian C, Qiang L. Off-Label Use of Bivalirudin on a Patient with Ventricular Septal Defect after Myocardial Infarction: A Case Report. Ann Med Case Rep. 2021;3(1):1024.

Publisher Name: Medtext Publications LLC

Manuscript compiled: Apr 09th, 2021

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Fu wai, Chinese Academy of Medical Sciences on March 1, 2019, with two days of chest and back discomfort and half a day of fatigue. He was also in shock at admission. On physical examination, his health condition was as follows; P: 118 beats/min, BP: 85/43 mmHg and a 4/6 systolic rough murmurs accompanied by tremor on the left border of the sternum. The patient had also a long-term history of smoking (20 cigarettes/day × 40 years). Emergency coronary angiography revealed an occlusion of the Left Anterior Descending branch (LAD). Laboratory tests revealed the following; TnT 2.67 ng/ml, TnI 22.20 ng/ml; NT-proBNP: 9630 pg/mL. ECG: Q waves in leads II, III, avF, V1-V4 and ST-segment elevation in leads V1-V6. Echocardiography on its part revealed a ventricular septum defect near the apical segment whereas a left-to-right shunt signal was seen in the ventricular septum.

After admission, Percutaneous Transluminal Coronary Angioplasty (PTCA) was performed in the LAD assisted with an Intra Aortic Balloon Pump (IABP). The TIMI blood flow was found to be at grade III. A single intraoperative bivalirudin anticoagulation injection (0.75 mg/kg) was first administered, and then maintained at 1.75 $mg.kg^{-1}.h^{-1}$ till the end of the operation (Figure 1A). The intraoperative dose was given in the early postoperative period (<4 h), and followed by a low-dose continuous micro-pumping until selective surgical thoracotomy repair was performed (0.025 $mg.kg^{-1}.h^{-1}$). Activated Clotting Time (ACT) (Figure 1B), Platelets (PLT) (Figure 1C), Activated Partial Thromboplastin Time (APTT) (Figure 1D) and International Normalized Rate (INR) (Figure 1E) were monitored.

Initially, the patient deteriorated during hospitalization. He had worse ventricular septal defect, complicated pulmonary infection and pulmonary hypertension. The more risky thoracotomy was therefore replaced with transcatheter closure. The operation was performed successfully, and even improved the cardiac function. The intravenous pumping of bivalirudin was stopped one day after TCC. The IABP was also removed.

The patient never received heparin treatment during the hospitalization period. Except for minor gum and corneal bleeding, we did not observe any thromboembolic complication. The bleeding disappeared after reducing or stopping bivalirudin infusion but then thrombocytopenia occurred. Because the patient was not exposed to heparin and the blood platelet antibody was negative, the thrombocytopenia was considered to be associated with bivalirudin. Although bivalirudin was implicated, thrombocytopenia is a common complication for IABP implantation; therefore it is difficult to be definitive.

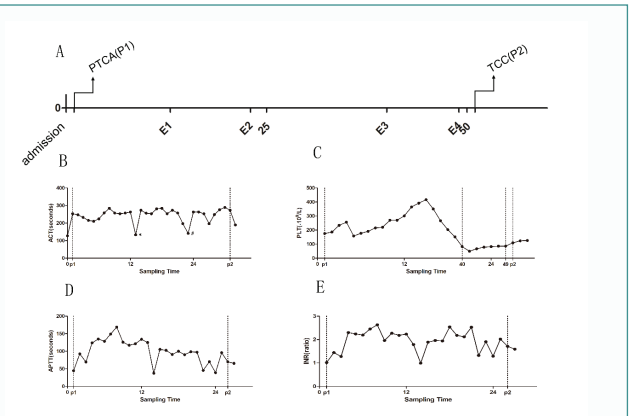

Figure 1: A) Timeline: PTCA (P1): Receive the first intervention on the day of admission; TCC (P2): Transcatheter interventional closure treatment on the 51st day after admission; E1: Day 13 of hospitalization; E2: Day 23 of hospitalization; E3: Day 40 of hospitalization; E4: Day 49 of hospitalization. B) ACT: measuring activated clotting time, Gum bleeding and conjunctival bleeding occurred at E1 and E1, respectively, and the bleeding symptoms disappeared after reducing the dosage of bivalirudin. C) PLT: platelets: severely thrombocytopenia occurred between E3 and E4, without special intervention, and gradually returned to normal after P2. D) APTT: Activated Partial Thromboplastin Time. E) INR: International Normalized Rate.

Discussion

Bivalirudin is recommended for percutaneous coronary intervention especially in individuals a risk of bleeding during the pre-operative period and also individuals at risk of developing HIT [3]. In this case study, bleeding and thrombocytopenia may not be fully attributed to bivalirudin because the condition may arise in patients who completely depend on IABP during the pre-operative period of myocardial infarction. Long-term use of IABP has indeed been shown to increase the risk of developing thrombocytopenia [8], however the side effects for using heparin in similar condition may be more severe. Additionally, the use of a bivalirudin-based anticoagulation strategy during the implantation of Ventricular Assist Device (VAD) overcomes many limitations of heparin [9]. Pharmacologically, it is more advantageous to use bivalirudin for anticoagulation than heparin.

For bivalirudin, intravenous pumping should be continued for a period of time, but generally for not more than 20 hours after an intravenous injection, regardless of the risk of bleeding or thrombocytopenia [3]. In our case, bivalirudin was administered for several weeks, against the recommended use. There are individual reports on continuous pumping of low bivalirudin dose during cardiopulmonary bypass, but the treatment time lasted for up to 12 days [9]. There is need for further research on the combined benefits of concentration-dependent pharmacokinetic characteristics and the anticoagulation effect on long term, low dose use of bivalirudin pumped intravenously.

Although no thromboembolic events occurred in the entire process, previous studies found that using bivalirudin does not reduces the risk of bleeding and it may also increase the risk of ischemic events within 30 days after interventional therapy [10]. Because the continuous intravenous pumping of bivalirudin is performed alongside adequate antiplatelet therapy and efficient cardiac rehabilitation training, which ultimately favors the prognosis of myocardial infarction, the eventual outcomes cannot be fully attributed to the unconventional continuous intravenous pumping of bivalirudin.

For individuals at risk of HIT, 0.75 mg/kg of bivalirudin is injected once, intravenously. Thereafter, 1.75 $mg.kg^{-1}.h^{-1}$ of the same drug is maintained until 3 to 4 hours after surgery. If necessary after the 4 hours, a small dose of 0.2 $mg.kg^{-1}.h^{-1}$ can be maintained for up to 20 h after surgery [3]. For patients at high risk of bleeding, 0.75 mg/k of bivalirudin is administered intravenously, and then maintained at 1.75$mg.kg^{-1}.h^{-1}$ for 3 to 4 hours after surgery [10].

Because bivalirudin does not accumulate in the body, coupled with a half-life of only 25minutes, it can be administered at unconventionally low doses. The side effects of bivalirudin are concentration-dependent, therefore there should be a balance between a dose effective for anti thrombosis and one that reduces the risk of bleeding.

Compared with heparin, bivalirudin results to lower incidence of thrombocytopenia. Indeed a study by BRIGHT revealed that

the incidence of thrombocytopenia in patients under (bivalirudin) was only 0.1% [11]. In general, the probability of developing thrombocytopenia when using bivalirudin is low, but here, thrombocytopenia occurred without exposure to heparin and or pre-existing platelet antibodies. Thrombocytopenia is nonetheless a common complication associated with prolonged use of IABP [8,12], therefore clinical risks associated with using unconventionally lower doses of bivalirudin should be further investigated.

Conclusion

Delayed-type hypersensitivity based on the subcutaneous injection of heparin, cross-reaction between different types of heparin and induction of HIT limits the use of heparin for anticoagulation therapy. Therefore alternative methods are needed during cardiac surgery, extracorporeal circulation, and paediatrics among other related complications. The off-label use of bivalirudin in individuals at high risk of bleeding (such as PIVSD, described in this article) and HIT (such as VAD, IABP implantation, etc.) should be further investigated.

Currently, the main disadvantages of bivalirudin are lack of known antidote. Off-label use of bivalirudin is likely to increase incidences of bleeding. Additionally, continuous intravenous pumping at a low dose may increase the occurrence of thromboembolic events. When treating these complications, possible adverse reactions caused by OLDU were kept in check. At the same time, possible consequences of OLDU such as safety of patients and the increased risk of medical disputes undertaken by physicians were also kept into account. Therefore, it is safe to use bivalirudin for PIVSD treatment process.

OLDU is both a local and global challenge in clinical medicine. In some complicated clinical situations, drugs cannot be used in accordance with recommended guidelines, particularly in rare and extreme cases, where there are no medical based evidence to inform the appropriate use of the drugs. Such is the case with bleeding and thrombosis mentioned above. Therefore in complex anticoagulation attempts, OLDU may be discretionally used. Even so, clinical health care professionals should always evaluate safety concerns of OLDU. These aside, use of therapeutic agents is always evolving, with new ways of using drugs being explored. The current clinical trials, including use of bivalirudin in cardiac surgery and pediatric anticoagulation have vindicated this view. At the same time, there should be timely clinical intervention on OLDU. This can not only help avert occupational risks but also ensure safety and effective use of the drugs.

Declarations

Ethics approval and consent to participate

Ethics approval for the study was given by Fu Wai Hospital Shenzhen Hospital (ChiCTR2100042809).

Consent for publication

The report was approved by the ethics review committee of our institution (Fu Wai Hospital Shenzhen Hospital, Guangdong) and consent was obtained from the patient and his family for their personal or clinical details along with any identifying images to be published in this study.

Availability of data and materials

All available information is contained within the present manuscript.

Competing interests

The authors declare that they have no competing interests.

Funding

The work was supported partly by the Shenzhen Science and Technology Research and Development Fund (NO JCY20180302173849459).

Authors' Contributions

YM, CQ and LQ were involved in compilation of data and major contributors writing the manuscript. CQ performed the follow up. LQ performed the myocardial perfusion imaging. All authors have read and approved the submitted manuscript.

Acknowledgments

We are grateful for the contribution and support of the family members.

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