Research Paper

Impact of Rivaroxaban on Coagulation Function, Inflammatory Factors and Endothelial Function in Coronary Heart Disease after Percutaneous Coronary Intervention

LI YE, JINGLIN CHENG* AND XUEXIANG LI

Department of Internal Medicine, The Second Hospital of Anhui Medical University, Hefei, Anhui Province 230601, China

To assess how rivaroxaban affects coagulation function, inflammatory factors and endothelial function in individuals who have received percutaneous coronary intervention for coronary heart disease sheds light on its physiological impact. From January 2019 to December 2021, a group of 184 individuals with coronary heart disease underwent percutaneous coronary intervention at the hospital. A random number table was utilized to allocate 92 patients into both the control group and the study group. While the control group received heparin treatment, the study group was subjected to rivaroxaban treatment. The differences in cardiac function, coagulation function, inflammatory factors, and endothelial function indicators between the two groups were compared. The occurrence of cardiovascular adverse events was examined during the 3 mo follow-up period, aiming to compare outcomes between the two groups. Following treatment, the study group showed significant improvements as opposed to the control group. The left ventricular end-diastolic diameter exhibited a significant decrease ($p<0.05$), while the left ventricular ejection fraction showed a significant increase ($p<0.05$). The study group also exhibited prolonged prothrombin time and decreased levels of fibrinogen and D-dimer ($p<0.05$). Additionally, levels of inflammatory markers such as interleukin-6, tumor necrosis factor-alpha, C-reactive protein, transforming growth factor beta 1, and pentraxin-3 significantly decreased in the study group ($p<0.05$), while levels of nitric oxide and flow-mediated dilation significantly increased ($p<0.05$). Relative to the control group, the study group showed significantly lower levels ($p<0.05$) of endothelin-1 and von Willebrand factor. Furthermore, the incidence of cardiovascular adverse events was significantly lower in the study group after treatment ($p<0.05$). Rivaroxaban treatment can improve cardiac function and coagulation function after percutaneous coronary intervention in coronary heart disease patients, alleviate inflammatory response and endothelial dysfunction, minimize the presence of major cardiovascular complications and improve the prognosis.

Key words: Percutaneous coronary intervention, coronary heart disease, rivaroxaban, coagulation function, inflammatory factors, endothelial function

With a global impact, Coronary Heart Disease (CHD) ranks as the primary cause of mortality and, in China, it holds the second position in terms of fatalities[1]. Epidemiological reports show an increasing incidence of CHD among young people in China[2]. Despite advancements in the treatment of CHD in recent years, the readmission rate and mortality rate among CHD patients remain high[3]. Percutaneous Coronary Intervention (PCI) is the primary choice for treating CHD in clinical practice. It quickly clears blocked coronary arteries, effectively improving myocardial blood flow, while offering the benefits of minimal surgical impact and prompt postoperative recuperation for patients[4]. However, during PCI, the clearance of arterial lumens may lead to the detachment of small embolic fragments to distal vessels, heightening the cardiovascular risk for patients and triggering inflammatory responses within diseased vessels, which detrimentally affects their prognosis and overall outcomes[5]. Rivaroxaban is a novel anticoagulant that directly inhibits the activity of thrombin and has ideal anticoagulant effects[6]. Evidence from studies

***Address for correspondence**
E-mail: cjl120429@163.com

suggests that the utilization of rivaroxaban can be advantageous for patients receiving PCI for acute coronary syndrome[7]. Nonetheless, there is a scarcity of clinical investigations concerning the effectiveness of rivaroxaban in individuals with CHD following PCI. This research seeks to analyze the effectiveness of rivaroxaban on coagulation function, inflammatory factors, and prognosis in CHD patients after PCI, with the aim of providing scientific evidence for the application of rivaroxaban in CHD patients.

MATERIALS AND METHODS

General information:

In this study, a cohort of 184 individuals with CHD who underwent PCI at the hospital from January 2019 to December 2021 was chosen as the participants.

Inclusion criteria: Met the relevant diagnostic criteria for CHD[8] and confirmed diagnosis through coronary angiography and all patients received PCI treatment.

Exclusion criteria: Severe liver or kidney dysfunction; coagulation dysfunction; hematological disorders and use of antiplatelet drugs within the past month and severe cerebrovascular disease or malignant tumors. Through the utilization of a random number table, the patient population was bifurcated into a control and a study group equally (92 in each). There were no notable dissimilarities in general information between groups ($p>0.05$), thereby ensuring their comparability as shown in Table 1.

Methods:

After admission, both groups of patients underwent routine examinations and received PCI treatment. Before the procedure, all patients in both groups received routine treatments including aspirin and clopidogrel. In the control group, patients received heparin (Jiangsu Wanbang Biopharmaceutical Group Co., Ltd., specification of 2 ml:125 000 U, Chinese drug approval number was I32020612) in addition to the routine treatment. The initial dose of heparin was administered intravenously at 5000-10 000 U, followed by a dose of 100 U/kg every 4 h. In the study group, in addition to the routine treatment, patients were also given bivalirudin (Jiangsu Haosen Pharmaceutical Co., Ltd., specification of 0.25 g/vial, Chinese drug approval number was H20140057). Intravenous administration of bivalirudin was performed at a dosage of 0.75 mg/kg during the procedure, along with a subsequent continuous infusion (1.75 mg/kg/h) until the surgery concluded. Subsequently, a continuous intravenous infusion (0.25 mg/kg/h) was maintained for 4 h, with the activated coagulation time rechecked. If necessary, a maintenance dose of 0.3 mg/kg was administered intravenously. Both groups received routine postoperative treatment.

Observation indicators:

After treatment, the levels of cardiac function, coagulation function, inflammatory factors, and vascular endothelial function were compared between the two groups.

Cardiac function: Assessment was conducted through echocardiography, which included the detection of Left Ventricular Ejection Fraction (LVEF) and Left Ventricular End-Diastolic Diameter (LVEDD).

Coagulation function: Serum samples were obtained from fasting peripheral blood collected from both groups of patients, and Enzyme-Linked Immunosorbent Assay (ELISA) was employed to measure Fibrinogen (FIB), Prothrombin Time (PT) and D-Dimer (D-D) levels.

Inflammatory factors: Serum was obtained by collecting fasting peripheral blood samples from both patient groups. Interleukin-6 (IL-6), Tumor Necrosis Factor-Alpha (TNF-α), Transforming Growth Factor-Beta 1 (TGF-β1), and N-Pentamerin (PTX3) levels were measured using ELISA, while immunoturbidimetric assay was employed to measure serum C-Reactive Protein (CRP) levels.

Vascular endothelial function: Plasma was obtained by collecting fasting peripheral blood samples from both patient groups. ELISA was used to measure levels of Endothelin-1 (ET-1), Nitric Oxide (NO) and vascular von Willebrand Factor (vWF). Doppler ultrasound was utilized to assess Flow-Mediated Dilation (FMD) of the brachial artery, a measure of vascular dilation function.

Major adverse cardiovascular events: A 3 mo follow-up was conducted to observe and record the presence of major cardiovascular complications in

TABLE 1: GENERAL INFORMATION

Group	n	Gender		Age	Lesion Location				Disease Type	
		Male	Female		Left Anterior Descending	Right Coronary	Left Main	Left Circumflex	Acute Myocardial Infarction	Unstable Angina
Control	92	49	43	61.47±8.63	42	29	12	9	45	47
Study	92	52	40	61.02±8.59	45	21	16	10	43	49
χ^2/t		0.198		0.354	2.008				0.087	
p		0.657		0.723	0.571				0.768	

both groups of patients.

Statistical methods:

Statistical Package for the Social Sciences (SPSS) version 25.0 was utilized for the statistical analysis of the data. Intergroup comparisons for continuous data were performed using independent t-tests, while within-group analysis involved conducting paired t-tests. The results are presented as mean±standard deviation. To compare inter groups for categorical data; either a Chi-square (χ^2) test or Fisher's exact probability test was opted, with the results reported as percentages (%). The threshold for statistical significance was set at a $p<0.05$.

RESULTS AND DISCUSSION

The absence of a significant difference in LVEDD and LVEF between groups was observed prior to treatment ($p>0.05$). Subsequent to treatment, LVEDD showed a significant decrease, while LVEF displayed a significant increase in each group ($p<0.05$). Additionally, the study group exhibited a significantly lower LVEDD in comparison to the control group, and a notable elevation in LVEF was also observed ($p<0.05$) as shown in Table 2.

Prior to treatment, no notable disparities were detected in PT, FIB and D-D levels between the two cohorts ($p>0.05$). Following treatment, a significant prolongation in PT was observed ($p<0.05$), alongside significant decrease in FIB and D-D levels ($p<0.05$) within both groups. Moreover, the study group displayed a statistically significant elevation in PT levels relative to the control group ($p<0.05$), while the levels of FIB and D-D were significantly decreased in the study group ($p<0.05$) as shown in Table 3.

Prior to treatment, no significant variation in IL-6, TNF-α, TGF-β1 and CRP levels between the two cohorts was observed ($p>0.05$). Following treatment, substantial decreases in CRP, IL-6, TGF-β1 and TNF-α levels ($p<0.05$) were witnessed among both groups. Furthermore, the study group exhibited significantly lower levels of CRP, IL-6, TGF-β1 and TNF-α compared to the control group ($p<0.05$) as shown in Table 4.

Analysis revealed no significant variations in the levels of NO, ET-1, vWF and FMD between the groups prior to treatment ($p>0.05$). Following treatment, a notable improvement in NO and FMD levels ($p<0.05$) was observed, accompanied by significant decreases in ET-1 and vWF levels ($p<0.05$) within both cohorts. Furthermore, the study group presented significant enhancements in NO and FMD levels when compared to the control group ($p<0.05$), while concurrently displaying significant reductions in ET-1 and vWF levels

TABLE 2: COMPARISON OF CARDIAC FUNCTION ($\bar{x}$±s)

Group	Time	LVEDD (mm)	LVEF (%)
Control (n=92)	Before	57.03±4.59	39.24±3.36
	After	52.46±3.91[a]	45.18±4.69[a]
Study (n=92)	Before	57.11±4.62	39.33±3.41
	After	48.27±3.76[ab]	49.52±4.83[ab]

Note: [a]$p<0.05$, compared to pre-treatment and [b]$p<0.05$, compared to the control group

TABLE 3: COMPARISON OF COAGULATION FUNCTION (x̄±s)

Group	Time	PT (s)	FIB (g/l)	D-D (mg/l)
Control (n=92)	Before	9.61±1.14	4.78±0.92	1.85±0.48
	After	13.15±1.39[a]	4.06±0.76[a]	0.93±0.30[a]
Study (n=92)	Before	9.67±1.18	4.75±0.93	1.82±0.51
	After	16.40±1.47[ab]	3.62±0.68[ab]	0.49±0.16[ab]

Note: [a]p<0.05, compared to pre-treatment and [b]p<0.05, compared to the control group

TABLE 4: COMPARISON OF INFLAMMATORY FACTORS (x̄±s)

Group	Time	IL-6 (pg/ml)	TNF-α (pg/ml)	CRP (mg/l)	TGF-ß1 (pg/ml)	PTX3 (ng/ml)
Control (n=92)	Before	87.41±13.08	169.62±28.51	21.05±4.24	63.17±10.35	8.52±2.33
	After	64.79±10.83[a]	125.46±16.97[a]	6.82±1.59[a]	45.29±8.62[a]	5.17±1.43[a]
Study (n=92)	Before	87.23±13.16	170.39±29.05	20.97±4.22	63.02±10.18	8.23±1.96
	After	39.36±7.14[ab]	82.91±12.28[ab]	4.23±0.81[ab]	33.85±6.47[ab]	3.60±0.78[ab]

Note: [a]p<0.05, compared to pre-treatment and [b]p<0.05, compared to the control group

TABLE 5: COMPARISON OF ENDOTHELIAL FUNCTION (x̄±s)

Group	Time	NO (μmol/l)	ET-1 (ng/l)	vWF (%)	FMD (%)
Control (n=92)	Before	51.86±8.34	107.24±16.18	192.58±24.71	6.17±0.55
	After	64.01±9.59[a]	79.38±11.72[a]	140.15±20.37[a]	7.99±0.62[a]
Study (n=92)	Before	51.92±8.33	107.03±16.25	194.06±24.68	6.13±0.54
	After	70.79±10.06[ab]	62.85±9.14[ab]	107.42±16.43[ab]	8.48±0.69[ab]

Note: [a]p<0.05, compared to pre-treatment and [b]p<0.05, compared to the control group

relative to the control group (p<0.05) as shown in Table 5.

After 3 mo, the study group exhibited a significant decline in major cardiovascular adverse events, with an incidence rate of 18.00 %, in contrast to the control group's incidence rate of 4.00 % (p<0.05) as shown in Table 6.

CHD refers to a medical condition characterized by inadequate blood supply to the heart muscle caused by the buildup of plaque in the coronary arteries, leading to complications related to the heart. Its clinical manifestations include chest tightness, chest pain, palpitations and fatigue. If not promptly treated, it may directly affect the patient's life safety[9]. PCI, as a commonly used clinical revascularization procedure, is a primary approach used in the management of CHD. This method can quickly restore blood flow, improve myocardial perfusion, effectively relieve local coronary artery ischemia, and has many advantages such as minimal trauma and rapid postoperative recovery[10]. However, PCI can still cause endothelial damage, platelet aggregation, thrombus formation, and the release of various inflammatory factors. This further impairs the endothelial function of the diseased vessels and affects the patient's cardiac function and prognosis[11]. Therefore, exploring effective treatment methods for CHD patients after PCI is of paramount importance.

Aspirin, clopidogrel and other drugs are currently the most commonly used adjunctive anticoagulant medications after PCI, but both drugs have a relatively high incidence of adverse reactions[12,13]. Bivalirudin, a synthetic specific thrombin inhibitor, consists of 20 amino acids with an average molecular weight of approximately 2000 kDa. It has a rapid onset of action, a short half-life, and can inactivate both fibrin-bound and free thrombin, showing significant anticoagulant effects[14]. As a novel thrombin inhibitor, bivalirudin has been shown to have transient and reversible anticoagulant effects in PCI treatment. Compared to traditional anticoagulant drugs, it has significant advantages in reducing adverse reactions related to intraoperative bleeding[15]. When treating acute ST-segment elevation myocardial infarction, the utilization of bivalirudin during PCI can lead to a substantial decrease in overall bleeding incidents

and a decrease in the occurrence of cardiovascular complications[16]. In the study group, the results indicate significant decreases in LVEDD, FIB and D-dimer levels in comparison to the control group. Conversely, the PT time was significantly prolonged and the LVEF was significantly elevated when compared to the control group. This indicates that bivalirudin can improve both cardiac function and coagulation function in patients. These results align with earlier reports[17,18]. To further explore the therapeutic effects of bivalirudin on CHD patients after PCI, this study further analyzed its impact on inflammatory factors, endothelial function, and major cardiovascular adverse events. The aim is to provide reference for the clinical application of bivalirudin in CHD patients.

Inflammatory factors are important contributors to thrombosis formation and the development of atherosclerosis, which may lead to aggravated focal inflammation after PCI due to their release. Such alterations in the coronary artery vascular wall could potentially contribute to an elevated risk of cardiovascular adverse events[19]. IL-6 and TNF-α can promote thrombosis formation and atherosclerosis and are closely associated with acute myocardial infarction[20]. CRP, an acute-phase protein synthesized by the liver, can partially provide insights into the extent of coronary artery disease severity[21]. TGF-β1 can activate vascular smooth muscle cell proliferation, increase intimal hyperplasia and further promote atherosclerosis[22]. PTX3 is a cytokine that serves a crucial function in innate immunity and induces immune effects such as phagocytosis during inflammatory states. It is associated with cardiovascular calcification and atherosclerosis[23]. Comparisons between the control and study groups in this study reveal that the use of bivalirudin significantly lowers IL-6, TNF-α, CRP and TGF-β1 levels in CHD patients following PCI, suggesting its efficacy in curbing the inflammatory response. This may be attributed to bivalirudin ability to directly inhibit thrombin activity. Bivalirudin can exert direct anticoagulant effects and also inhibit platelet aggregation, thereby increasing coronary artery blood flow and reducing inflammation. The initiation and progression of CHD, which is primarily driven by atherosclerosis, heavily relies on the development of endothelial dysfunction[24]. NO and ET-1 are important indicators reflecting endothelial cell function. NO is mainly secreted by vascular endothelial cells, and when the endothelial cell function of the coronary artery is impaired, NO levels decrease significantly, while ET-1 levels increase significantly, further exacerbating endothelial cell dysfunction and worsening CHD[25]. vWF is a biomarker of endothelial dysfunction and its levels can reflect the degree of endothelial injury. FMD is a biomarker reflecting endothelial cell relaxation function, and it promotes NO secretion and subsequent smooth muscle cell relaxation in response to physical stimulation, thereby improving endothelial function[26]. This study's findings indicate that patients receiving bivalirudin treatment after PCI for CHD exhibited notable improvements in endothelial function, as evidenced by significantly elevated levels of NO and FMD, and significantly reduced levels of ET-1 and vWF. These results suggest that bivalirudin effectively ameliorates endothelial injury. Moreover, the 3 mo follow-up period in this study revealed a marked decrease in the overall presence of cardiovascular adverse events in the study group, highlighting the favorable impact of bivalirudin on patient prognosis. These results indicate that bivalirudin significantly improves patient outcomes and diminishes the occurrence of cardiovascular adverse events. However, the size of samples was limited, and the follow-up duration was relatively short. Further expansion

TABLE 6: COMPARISON OF MAJOR CARDIOVASCULAR ADVERSE EVENTS

Group	n	Recurrent angina	Myocardial infarction	Arrhythmia	Cardiac death	Total events (%)
Control	92	8	3	5	0	16 (17.39)
Study	92	2	0	2	0	4 (4.35)
χ^2						8.078
p						0.004

of the sample size and extension of the follow-up period are needed to observe long-term effects and provide more supportive evidence.

In summary, the use of bivalirudin treatment can improve post-PCI cardiac function and coagulation function in CHD patients, alleviate inflammatory response and endothelial dysfunction, reduce the presence of cardiovascular complications, and improve patient prognosis. It is worth considering and applying as a valuable reference.

Conflict of interests:

The authors declared no conflict of interests.

REFERENCES

1. Li X, Da Z, Ren X, Qiao Y, Xie P, Sun X, *et al.* Trends and distribution of coronary heart disease mortality rate in Hexi Corridor, Gansu, China from 2006 to 2015. Rev Cardiovasc Med 2021;22(3):1003-8.
2. Liu S, Li Y, Zeng X, Wang H, Yin P, Wang L, *et al.* Burden of cardiovascular diseases in China, 1990-2016: Findings from the 2016 global burden of disease study. JAMA Cardiol 2019;4(4):342-52.
3. Lai M, Li J, Chen L. Analysis of all-cause mortality, readmission rate and its influencing factors in patients with coronary heart disease after PCI. J Pract Med 2020;36(6):801-7.
4. Zhou Y, Hong L, Shao L. Effects of Sakubatan sodium combined with spontaneous breathing exercise on cardiac function and vascular endothelial function in elderly patients with coronary heart disease undergoing PCI. Chin J Gerontol 2021;41(11):2250-3.
5. Geng B, Wang S, Miao H. Effect of Huoxue Huayu Yangxin Tongluo formula on angina pectoris and inflammatory factors in patients with angina pectoris after PCI. Chin J Hosp Pharm 2020;40(22):2341-4.
6. Laine M, Lemesle G, Dabry T, Panagides V, Peyrol M, Paganelli F, *et al.* Bivalirudin during percutaneous coronary intervention in acute coronary syndromes. Exp Opin Pharmacother 2019;20(3):295-304.
7. Wang W, Wang H, Li Z. Effect of bivalirudin on endothelial injury and inflammatory response in patients with acute coronary syndrome after intervention. Anhui Med J 2017;38(8):1016-9.
8. Chinese Medical Association Cardiology Branch, Editorial Board of Chinese Journal of Cardiovascular Diseases. Guidelines for diagnosis and treatment of coronary heart disease (2007 ed). Chin J Cardiovasc Dis 2007;35(3):195-206.
9. Zheng YY, Wu TT, Yang Y, Hou XG, Gao Y, Chen Y, *et al.* Personalized antiplatelet therapy guided by a novel detection of platelet aggregation function in stable coronary artery disease patients undergoing percutaneous coronary intervention: A randomized controlled clinical trial. Eur Heart J Cardiovasc Pharmacother 2020;6(4):211-21.
10. Li J, Qiu H, Yan L, Guo T, Wang Y, Li Y, *et al.* Efficacy and safety of ticagrelor and clopidogrel in East Asian patients with coronary artery disease undergoing percutaneous coronary intervention. Curr Med Res Opin 2020;36(11):1739-45.
11. Sun Y, Song Y. Clinical effect of Guhong injection on recurrent angina pectoris after PCI and its effect on inflammatory factors and vascular endothelial function in patients with coronary heart disease. Liaoning J Tradit Chin Med 2020;547(9):66-8.
12. Koo BK, Kang J, Park KW, Rhee TM, Yang HM, Won KB, *et al.* Aspirin *vs.* clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): An investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;397(10293):2487-96.
13. Natsuaki M, Sonoda S, Yoshioka G, Hongo H, Kaneko T, Kashiyama K, *et al.* Antiplatelet therapy after percutaneous coronary intervention: Current status and future perspectives. Cardiovasc Interv Ther 2022;37(2):255-63.
14. Li J, Cheng L, Wang H. Comparison of safety and efficacy of bivalirudin and heparin during perioperative PCI. Chin J Cardiovasc Dis 2020;48(8):648-54.
15. Ren H, Huang L, Wang L. Anticoagulant effect of bivalirudin in patients with coronary heart disease complicated with end-stage renal disease undergoing percutaneous coronary intervention. Chin J Multiple Organ Dis Elderly 2021;20(6):444-8.
16. Sun X, Zhang S, Xing Xi. Safety of bivalirudin in emergency percutaneous coronary intervention in patients with metabolic syndrome with acute ST segment elevation myocardial infarction. J Pract Med 2019;35(9):1473-6.
17. Li Z, Tang L, Bai R. Comparison of anticoagulant effects of bivalirudin and heparin in patients with acute myocardial infarction after percutaneous coronary intervention. Chongqing Med 2022;51(4):569-73.
18. Ding S, Xu S, Chen X, Wu S. Effects of atorvastatin combined with bivalirudin on coagulation function, cardiac function and inflammatory factors of percutaneous coronary intervention in elderly patients with acute myocardial infarction. Ann Palliat Med 2020;9(4):1905-1.
19. Medina-Leyte DJ, Zepeda-García O, Domínguez-Pérez M, González-Garrido A, Villarreal-Molina T, Jacobo-Albavera L. Endothelial dysfunction, inflammation and coronary artery disease: Potential biomarkers and promising therapeutical approaches. Int J Mol Sci 2021;22(8):3850.
20. Yu F, Wu F, Zheng Y. Effect of Guanxinning tablet on myocardial perfusion and inflammatory reaction in patients with acute myocardial infarction after percutaneous coronary intervention. Chin J Mod Med 2021;31(10):60-4.
21. Tang X, Mao L, Chen J, Zhang T, Weng S, Guo X, *et al.* High-sensitivity CRP may be a marker of HDL dysfunction and remodeling in patients with acute coronary syndrome. Sci Rep 2021;11(1):11444.
22. Mohamed R, Dayati P, Mehr RN, Kamato D, Seif F, Babaahmadi-Rezaei H, *et al.* Transforming growth factor–β1 mediated CHST11 and CHSY1 mRNA expression is ROS dependent in vascular smooth muscle cells. J Cell Commun Signal 2019;13:225-33.
23. Liu B, Su H. Effect of long-term intensive treatment with atorvastatin on blood lipids and inflammatory indexes in patients with newly diagnosed coronary heart disease. Chongqing Med 2022;51(16):2755-61.

24. Oikonomou E, Siasos G, Tsigkou V, Bletsa E, Panoilia ME, Oikonomou IN, *et al.* Coronary artery disease and endothelial dysfunction: Novel diagnostic and therapeutic approaches. Curr Med Chem 2020;27(7):1052-80.
25. Li J, Guo Z. Effect of Tongxinluo capsule on vascular endothelial function and inflammatory factors in patients with coronary heart disease after percutaneous coronary intervention. Prop Chin Med 2019;41(5):1202-4.
26. Zhao F, Gao Y, Cai H. Effect of percutaneous acupoint electrical stimulation on vascular endothelial function and inflammatory factors after percutaneous coronary intervention. Acupunct Study Med 2021;46(8):684-9.

This article was originally published in a special issue, "Drug Development in Biomedical and Pharmaceutical Sciences" Indian J Pharm Sci 2023:85(5) Spl Issue "74-80"