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Case report

Low-molecular-weight heparin followed by rivaroxaban for acute occlusive portomesenteric vein thrombosis in a cirrhotic patient treated with multiple endoscopic variceal procedures

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ABSTRACT

Acute portomesenteric vein thrombosis is potentially lethal. In the present paper, a cirrhotic patient with a previous history of esophageal variceal bleeding presented with acute occlusive portomesenteric vein thrombosis, but achieved complete recanalization by low-molecular-weight heparin followed by rivaroxaban. Notably, no bleeding episode occurred during anticoagulation therapy. This case supported early initiation of anticoagulation in such patients.

1. Introduction

Portal vein thrombosis (PVT) is commonly encountered and associated with an increased risk of mortality in cirrhotic patients [1,2]. There are various classifications of PVT (i.e., degree, stage, and extension) [3]. Cirrhotic patients with PVT are often asymptomatic, but patients with acute PVT extended to mesenteric vein may present with sudden onset of abdominal pain that is out of proportion to abdominal signs, and should even need surgical intervention [4]. Early diagnosis of PVT is warranted and contrast-enhanced computed tomography (CT) is preferred to determine the location and extension of thrombus [5]. Current guidelines and consensus recommend that anticoagulation therapy should be considered in candidates to liver transplantation or cirrhotic patients, if PVT is extended to superior mesenteric vein [5,6]. However, a critical issue about balancing the recanalization of PVT and potential bleeding complication after anticoagulation therapy has been raised.

In this paper, we reported that a cirrhotic patient with previous esophageal variceal bleeding who was diagnosed with acute occlusive portomesenteric vein thrombosis achieved complete recanalization by timely anticoagulation therapy. Notably, no bleeding episodes occurred during anticoagulation therapy.

2. Case presentation

On October 10, 2017, a 53-year-old male with a 6-year history of alcoholic liver cirrhosis was admitted to our department due to persistent left-upper abdominal pain for 2 days. In 2015, he was diagnosed with moderate esophageal varices. In April 2016, he underwent esophageal variceal ligation and gastroesophageal variceal adhesive injection. In July 2016 and November 2016, he underwent endoscopic surveillance showing mild esophageal varices, and did not undergo endoscopic treatment. He did not adhere to the use of non-selective beta-blockers (NSBBs). On July 31, 2017, he underwent contrast-enhanced CT scans showing patent portal vein and superior mesenteric vein (Fig. 1A). On physical examinations, his abdomen was soft without tenderness, rebound, or muscular tension. On laboratory tests, white blood cell (WBC) was 7.6×10^9/L (reference range: $3.5–9.5 \times 10^9$/L), hemoglobin (Hb) was 86 g/L (reference range: 130–175 g/L), platelet count (PLT) was 150×10^9/L (reference range: $125–350 \times 10^9$/L), total bilirubin (TBIL) was 23.2 μmol/L (reference range: 5.1–22.2 μmol/L), direct bilirubin

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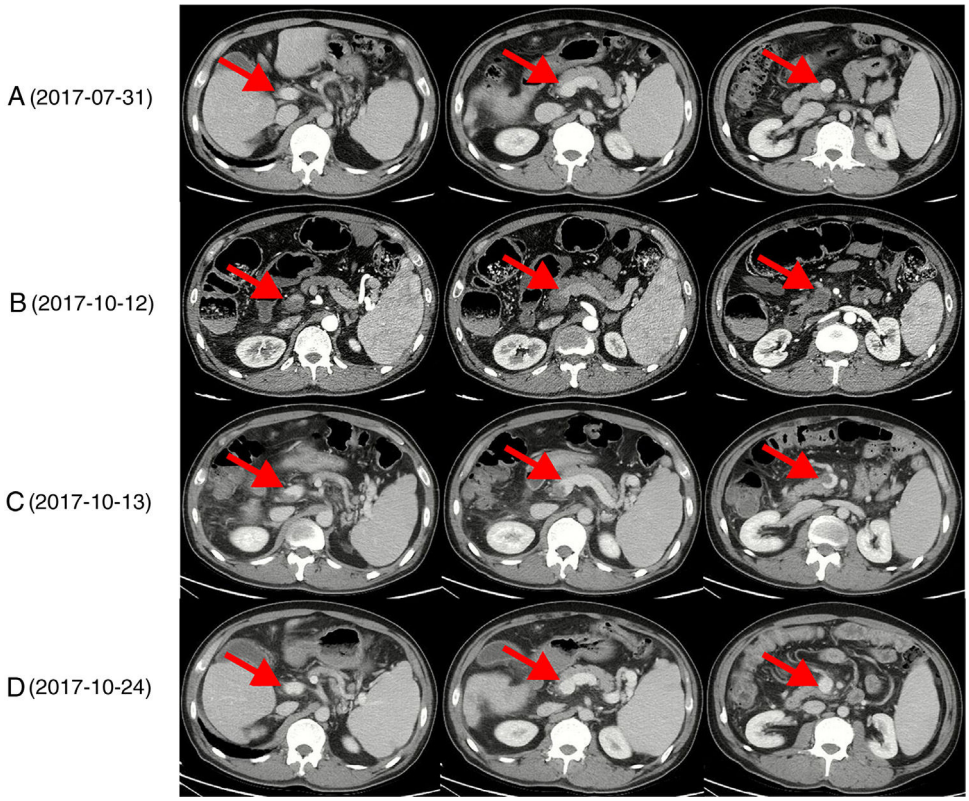

Fig. 1. Computed tomography images in this patient. Panel A: Contrast-enhanced computed tomography performed on July 31, 2017 demonstrated patent main portal vein and superior mesenteric vein (red arrow). Panel B: Computed tomography angiography performed on October 12, 2017 demonstrated complete occlusive main portal vein and superior mesenteric vein (red arrow). Panel C: Contrast-enhanced computed tomography performed on October 13, 2017 demonstrated partially recanalized main portal vein and superior mesenteric vein (red arrow). Panel D: Contrast-enhanced computed tomography performed on October 24, 2017 demonstrated completely recanalized main portal vein and superior mesenteric vein (red arrow).

(DBIL) was 11.6 μmol/L (reference range: 0–8.6 μmol/L), alanine aminotransferase (ALT) was 20.42 U/L (reference range: 9–50 U/L), aspartate aminotransaminase (AST) was 21.26 U/L (reference range: 15–40 U/L), albumin (ALB) was 42.7 g/L (reference range: 40–55 g/L), blood urea nitrogen (BUN) was 3.93 mmol/L (reference range: 2.9–8.2 mmol/L), creatinine (Cr) was 80.8 μmol/L (44–133 μmol/L), prothrombin time (PT) was 14.3 s (reference range: 11.5–14.5 s), international normalized ratio (INR) was 1.09, D-dimer was 2.51 mg/L (reference range: 0.01–0.55 mg/L), antithrombin III (ATIII) was 89% (reference range: 80–120%), and homocysteine (HCY) was 11.98 μmol/L (reference range: 0–15 μmol/L). His Child–Pugh score was 6 and model for end-stage liver disease (MELD) score was 7.69. He was symptomatically treated with esomeprazole and nutritional support.

At 1 o'clock on October 11, 2017, his abdominal pain aggravated. Abdominal X-ray showed that his bowel was extended with air accumulation (Fig. 2A).

On October 12, 2017, abdominal pain was further aggravated than before, and abdominal tenderness became apparent. Abdominal X-ray showed that his bowel was extended with multiple air-fluid levels (Fig. 2B). CT angiography showed PVT and superior mesenteric vein thrombosis (SMVT) (Fig. 1B). Since then, low-molecular-weight heparin (LMWH) was given subcutaneously with a dose of 4250 IU per day.

On October 13, 2017, abdominal pain mildly alleviated. Abdominal X-ray showed that his bowel was slightly extended without air-fluid level (Fig. 2C). Contrast-enhanced CT showed partial recanalization of PVT and SMVT (Fig. 1C). LMWH was continued with a dose of 4250 IU twice a day.

On October 17, 2017, abdominal pain significantly alleviated. Abdominal X-ray showed that his bowel was not extended (Fig. 2D).

On October 24, 2017, abdominal pain disappeared. Contrast-enhanced CT showed complete recanalization of PVT and partial recanalization of SMVT (Fig. 1D). Dosage of LMWH was modified from 4250 IU twice a day to 4250 IU per day.

On November 6, 2017, the patient was discharged without complaints. Notably, after discharge, rivaroxaban was given orally with a dose of 10 mg per day regularly.

On January 28, 2018, the patient was re-admitted to our department without haematemesis or melena while rivaroxaban was continued. Laboratory tests revealed that Hb was 104 g/L, TBIL was 11.4 μmol/L, DBIL was 5.0 μmol/L, ALT was 15.78 U/L, AST was 20.40 U/L, ALB was 46.8 g/L, BUN was 5.89 mmol/L, Cr was 72.26 μmol/L, PT was 16.1 s, INR was 1.3, and D-dimer was 0.26 mg/L. Considering the potential risk of bleeding, the patient denied endoscopic surveillance.

On February 23, 2019, a telephone follow-up showed that he did not have any complaints, and no hematemesis or melena occurred during taken rivaroxaban. He has stopped taking rivaroxaban for 3 months for endoscopic examination and potentially necessary variceal therapy.

3. Discussion

The present case has several features. First, the patient presented with occlusive portomesenteric vein thrombosis. Second, anticoagulation therapy of LMWH followed by rivaroxaban achieved complete recanalization that could be free of surgical

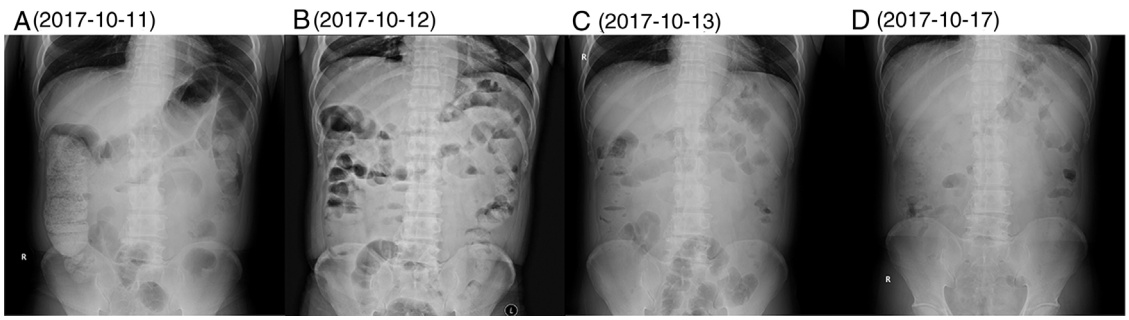

Fig. 2. Abdominal X-ray images in this patient. Panel A: Abdominal X-ray performed on October 11, 2017 demonstrated that his bowel was extended with gas accumulation. Panel B: Abdominal X-ray performed on October 12, 2017 demonstrated that his bowel was extended with multiple air-fluid levels. Panel C: Abdominal X-ray performed on October 13, 2017 demonstrated that his bowel was slightly extended without air-fluid level. Panel D: Abdominal X-ray performed on October 17, 2017 demonstrated that his bowel was not extended.

intervention. Third, despite this patient had esophageal varices, anticoagulation was safe without any bleeding episode.

3.1. Risk factors associated with portal vein thrombosis

Inherited and acquired coagulation disorders, portal venous endothelial injury, and decreased portal vein velocity are the potential risk factors for the development of PVT in cirrhotic patients. As for our patient, the reason for the development of PVT is uncertain. First, we couldn't confirm whether this patient had an inherent coagulation disorder due to the absence of genetic tests. However, two risk factors of coagulation disorders for the development of PVT could be obtained during this hospitalization: ATIII level was 89% and HCY level was 11.98 μmol/L. Both of them were in the normal range. Since not all coagulation function were tested, whether the patient had an inherent or acquired coagulation disorder was uncertain. In fact, previous meta-analysis found that the inherent coagulation disorder, such as factor V gene and prothrombin II gene mutation, was associated with portal vein thrombosis in liver cirrhosis [7]. However, our previous study also suggested that factor V gene and prothrombin II gene mutation were rare in Chinese patients with portal vein thrombosis or Budd-Chiari syndrome [8,9]. Second, the patient didn't have any history of abdominal surgery or trauma before this admission, but he had a history of endoscopic therapy, which might lead to portal venous endothelial injury. Third, portal vein velocity was not detected by color Doppler ultrasound during this admission. Additionally, NSBBs might decrease portal vein velocity and increase the risk of PVT [10]. However, this patient did not adhere to the use of NSBBs.

3.2. Factors associated with portal vein recanalization

Predictive factors associated with portal vein recanalization varied among studies. The already established predictors, which included the time interval between diagnosis of PVT and anticoagulation <14 days [11] or <6 months [12,13], a lower platelet count [14], a lower Child–Pugh score [15], degree of superior mesenteric vein occlusion <50% [16], absence of previous portal hypertension related bleeding [12], and a lower spleen thickness at baseline [13], were associated with higher rates of partial and complete portal vein recanalization. Based on the above-mentioned findings, our case has two features associated with a higher probability of portal vein recanalization, including early initiation of anticoagulation therapy and a low Child–Pugh score.

3.3. Efficacy of anticoagulation

Even a spontaneous recanalization of PVT may occur without any anticoagulation therapy; however, this phenomenon seems to be limited to patients with mild or moderate PVT [17]. As for our patient, it seems to be more likely that the fast recanalization of PVT might be due to the effect of anticoagulation therapy. There are the two following points for explaining this consideration. First, the patient had complete occlusive portomesenteric thrombosis suggesting a severe PVT. Second, the patient had intestinal ischemia which also indicated that he had an acute and severe PVT and anticoagulation therapy was urgently needed. Indeed, current guidelines and consensus suggest that cirrhotic patients with PVT and extension to superior mesenteric vein could receive anticoagulants [5,6]. Evidence also supports the efficacy of anticoagulation therapy in achieving complete portal vein recanalization [18,19]. Our previous meta-analysis reported that the total rate of portal vein recanalization was 66.6% and the rate of complete portal vein recanalization was 41.5% in cirrhotic patients under anticoagulation therapy [18]. Also, an updated meta-analysis reported similar results [19]. Recently, a large single-center study included 182 cirrhotic patients with PVT and found that the rate of complete portal vein recanalization was consistent with that reported by the two meta-analyses; importantly, anticoagulation therapy was strongly associated with longer survival [20]. Therefore, anticoagulation therapy may be recommended in cirrhotic patients with PVT. Certainly, randomized trials are needed to assess the effect of anticoagulants on survival in cirrhotic patients with PVT.

3.4. Type of anticoagulants

Both traditional anticoagulants and direct-acting oral anticoagulants (DOAC) have been attempted in cirrhotic patients with PVT. Advantages and disadvantages of several major anticoagulants are summarized (Table 1). Until now, there is no clear-cut recommendation regarding which type of anticoagulants works better than others. First, recanalization and bleeding complications seemed to be similar between LWMN and vitamin K antagonist [14]. By comparison, rivaroxaban appeared to be superior to warfarin in achieving complete recanalization and improving survival [21]. Secondly, DOAC and traditional anticoagulants displayed similar safety in terms of total bleeding episodes in cirrhotic patients [22,23]. However, a lower major bleeding rate of 4% was reported in DOAC group compared with 28% in traditional anticoagulants [23]. Also, a systematic review found a lower major bleeding risk of 4–15% in DOAC groups compared with 7–28% in traditional anticoagulants groups [24]. Hence, according to the above-mentioned findings, DOAC might be more effective and safe than traditional anticoagulants. Our patient received LMWH during hospitalization which was switched to rivaroxaban after discharge.

Table 1
Characteristics of several major anticoagulants.

Type of anticoagulants	Targets	Laboratory monitoring	Advantages	Disadvantages
Traditional anticoagulants				
Unfractionated heparin	IIa, Xa	APTT	Fast-acting; Protamine reversal; No need to adjust dose according to renal function.	Low bioavailability; HIT; Risk of bleeding; Require monitoring.
LWMH	IIa, Xa	Not required	Protamine partially reversal; Less bleeding episodes than unfractionated heparin.	HIT; Injection-site tissue necrosis.
Warfarin	II, VII, IX, X	INR	Cheap; Longtime-acting.	Require monitoring; Drug-drug and drug-food interactions.
Direct-acting oral anticoagulants				
Rivaroxaban	Xa	Not required	High bioavailability; Fast-acting.	No antagonist.
Dabigatran	Thrombin inhibitor	dTT, ECT, APTT	Fast-acting.	Low bioavailability.

Abbreviations: LWMH, low-molecular-weight heparin; APTT, activated partial thromboplastin time; INR, International normalized ratio; HIT, heparin-induced thrombocytopenia; dTT, diluted thrombin time; ECT, ecarin clotting time.

Table 2
Bleeding complications and deaths in cirrhotic patients with PVT under anticoagulation therapy.

First author (year)	Included patients	No. Pts. treated with anticoagulants	Anticoagulation therapy	Bleeding complications in anticoagulation therapy group	Deaths in anticoagulation therapy group
Artaza (2018)	LC with PVT	32	Enoxaparin and VKA	Cerebral hemorrhage ($n = 1$).	Liver failure ($n = 4$); SBP ($n = 2$); Gastric neoplasia ($n = 1$); Acute pancreatitis ($n = 1$); Multiorgan failure of unknown origin ($n = 1$).
Bergère (2018)	LC with PVT	40	LWMN and VKA	Anemia ($n = 2$); Epistaxis ($n = 1$); Haematuria ($n = 1$); Metrorrhagia ($n = 1$); Subdural hematoma ($n = 1$); Bleeding after paracentesis ($n = 1$); Hematoma after skin-surgery ($n = 1$).	Liver failure ($n = 6$); Sepsis ($n = 3$); Hypoxic cardiac arrest ($n = 1$); Breast cancer ($n = 1$); Mesenteric ischemia ($n = 1$).
Pettinari (2018)	LC with PVT	81	LWMN, VKA and fondaparinux	Following trauma or accidental falls ($n = 4$).	None.
Fujiyama (2017)	LC with PVT	90	Danaparoid sodium	None.	NA.
La Mura (2017)	LC with PVT	63	VKA	Upper-GI-bleeding ($n = 5$); Cerebral hemorrhage ($n = 1$); Traumatic hematoma ($n = 1$); Hematuria ($n = 1$); Epistaxis ($n = 8$); Anemia of uncertain etiology ($n = 1$); Micro-hematoma ($n = 2$); Lower GI-bleeding ($n = 2$).	Unreported causes ($n = 2$).
Cui (2015)	LC with PVT	65	Enoxaparin	Injection-site hemorrhage ($n = 3$); Epistaxis ($n = 5$); Haematuria ($n = 2$).	Multiorgan failure after sepsis ($n = 1$).
Chung (2014)	LC with non-malignant PVT	14	Warfarin	None.	Septic shock ($n = 1$); Chemoembolization-induced renal failure ($n = 1$).
Werner (2013)	LC with PVT	28	Warfarin	Vaginal bleeding ($n = 1$).	NA.
Delgado (2012)	LC with PVT	55	LWMN and VKA	Lower GI bleeding ($n = 1$); Oral bleeding after dental extraction ($n = 1$); Obscure GI bleeding ($n = 1$); Vaginal bleeding ($n = 1$); Surgical wound hemorrhage ($n = 1$).	None.
Senzolo (2012)	LC with non-malignant PVT	33	NA	Epistaxis ($n = 1$); Haematuria ($n = 1$); Cerebral haemorrage ($n = 1$).	Sepsis ($n = 1$); Multiorgan failure ($n = 1$).
Amitrano (2010)	LC with PVT	39	LWMN	None.	Lymphoma ($n = 1$); Cardiac infarction ($n = 1$); Liver decompensation ($n = 2$).

Abbreviations: LC, liver cirrhosis; PVT, portal vein thrombosis; LWMN, low-molecular-weight heparin; GI, gastro-intestinal; VKA, vitamin K antagonist; NA, not available.

3.5. Dose of anticoagulants

Recommendation regarding the dose of anticoagulants in cirrhotic patients with PVT was obscure [5,6]. To date, only a study by Cui et al. compared 1.5 mg/kg per day and 1 mg/kg twice a day of enoxaparin in cirrhotic patients with PVT. They found a similar rate of complete and partial recanalization between the two groups, but a higher rate of bleeding (23.5% versus 6.4%) in the group with 1.5 mg/kg per day of enoxaparin [15].

3.6. Safety of anticoagulants

Studies regarding the safety of anticoagulants in cirrhotic patients with PVT are summarized (Table 2). Among the 11 studies reporting bleeding episodes under anticoagulation therapy [11–15,20,25–29], 3 studies reported no bleeding episode [13,26,28], and 8 studies reported that the rate of bleeding episode ranged from 3% to 33.3% [11,12,14,15,20,25,27,29] and bleeding episodes included gastrointestinal hemorrhage, injection-site

hemorrhage, epistaxis, haematuria, cerebral hemorrhage, and traumatic hematoma, etc. Ten studies also reported deaths under anticoagulation therapy [11–16,20,25,27,28]. Among them, 3 studies reported no death in anticoagulation groups [11,16,20], and 7 studies reported that the rate of death ranged from 1.5% to 30% in anticoagulation groups [12–15,20,25,28]. A majority of deaths were attributed to liver failure, followed by sepsis, multiorgan failure, and hepatic decompensation. No fatal bleeding complication related to anticoagulation therapy was reported in cirrhotic patients with PVT.

In conclusion, early diagnosis and initiation of anticoagulation therapy are critical for cirrhotic patients with acute portomesenteric vein thrombosis. Certainly, a close attention should be paid to the adverse effect of anticoagulation therapy, such as hemorrhage.

Abbreviations

PVT	portal vein thrombosis
CT	computed tomography
NSBBs	non-selective beta-blockers
WBC	white blood cell
Hb	hemoglobin
PLT	platelet count
TBIL	total bilirubin
ALT	alanine aminotransferase
AST	aspartate aminotransaminase
ALB	albumin
BUN	blood urea nitrogen
Cr	creatinine
PT	prothrombin time
INR	international normalized ratio
ATIII	antithrombin III
HCY	homocysteine
MELD	model for end-stage liver disease
SMVT	superior mesenteric vein thrombosis
LMWH	low-molecular-weight heparin
DOAC	direct-acting oral anticoagulants

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Conflict of interest

None.

References

[1] Cool J, Rosenblatt R. Portal vein thrombosis prevalence and associated mortality in cirrhosis in a nationally representative inpatient cohort. J Gastroenterol Hepatol 2019;34:1088–92.
[2] Qi X, Bai M, Yang Z, Yuan S, Zhang C, Han G, et al. Occlusive portal vein thrombosis as a new marker of decompensated cirrhosis. Med Hypotheses 2011;76:522–6.
[3] Qi X, Han G, Fan D. Management of portal vein thrombosis in liver cirrhosis. Nat Rev Gastroenterol Hepatol 2014;11:435–46.
[4] Singal AK, Kamath PS, Tefferi A. Mesenteric venous thrombosis. Mayo Clin Proc 2013;88:285–94.
[5] EASL Clinical Practice Guidelines: vascular diseases of the liver. *J Hepatol* 2016;64:179–202.
[6] de Franchis R. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743–52.
[7] Qi X, Ren W, De Stefano V, Fan D. Associations of coagulation factor V Leiden and prothrombin G20210A mutations with Budd-Chiari syndrome and portal vein thrombosis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2014;12:1801–12, e7.
[8] Qi X, Wu F, Fan D, Han G. Prevalence of thrombotic risk factors in Chinese Budd-Chiari syndrome patients: results of a prospective validation study. Eur J Gastroenterol Hepatol 2014;26:576–7.
[9] Qi X, Wu F, He C, Fan D, Han G. Thrombotic risk factors in Chinese nonmalignant and noncirrhotic patients with portal vein thrombosis: an observational study with a systematic review of the literature. Eur J Gastroenterol Hepatol 2015;27:77–83.
[10] Xu X, Guo X, De Stefano V, Silva-Junior G, Goyal H, Bai Z, et al. Nonselective beta-blockers and development of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis. Hepatol Int 2019;13(4):468–81.
[11] Delgado MG, Seijo S, Yepes I, Achecar L, Catalina MV, Garcia-Criado A, et al. Efficacy and safety of anticoagulation on patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2012;10:776–83.
[12] Senzolo MT, Rossetto MS, Burra V, Cillo P, Boccagni UP, Gasparini D, et al. Prospective evaluation of anticoagulation and transjugular intrahepatic portosystemic shunt for the management of portal vein thrombosis in cirrhosis. Liver Int 2012;32:919–27.
[13] Chung JW, Kim GH, Lee JH, Ok KS, Jang ES, Jeong SH, et al. Safety, efficacy, and response predictors of anticoagulation for the treatment of nonmalignant portal-vein thrombosis in patients with cirrhosis: a propensity score matching analysis. Clin Mol Hepatol 2014;20:384–91.
[14] Bergere M, Erard-Poinsot D, Boillot O, Valette PJ, Guillaud O, Chambon-Augoyard C, et al. Portal vein thrombosis and liver cirrhosis: long-term anticoagulation is effective and safe. Clin Res Hepatol Gastroenterol 2019;43(4):395–402.
[15] Cui SB, Shu RH, Yan SP, Wu H, Chen Y, Wang L, et al. Efficacy and safety of anticoagulation therapy with different doses of enoxaparin for portal vein thrombosis in cirrhotic patients with hepatitis B. Eur J Gastroenterol Hepatol 2015;27:914–9.
[16] Chen H, Liu L, Qi X, He C, Wu F, Fan D, et al. Efficacy and safety of anticoagulation in more advanced portal vein thrombosis in patients with liver cirrhosis. Eur J Gastroenterol Hepatol 2016;28:82–9.
[17] Qi X, Guo X, Yoshida EM, Mendez-Sanchez N, De Stefano V, Tacke F, et al. Transient portal vein thrombosis in liver cirrhosis. BMC Med 2018;16:83.
[18] Qi X, De Stefano V, Li H, Dai J, Guo X, Fan D. Anticoagulation for the treatment of portal vein thrombosis in liver cirrhosis: a systematic review and meta-analysis of observational studies. Eur J Intern Med 2015;26:23–9.
[19] Loffredo L, Pastori D, Farcomeni A, Violi F. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: A systematic review and meta-analysis. Gastroenterology 2017;153:480–7, e1.
[20] Pettinari I, Vukotic R, Stefanescu H, Pecorelli A, Morelli M, Grigoras C, et al. Clinical impact and safety of anticoagulants for portal vein thrombosis in cirrhosis. Am J Gastroenterol 2018;114:258–66.
[21] Hanafy AS, Abd-Elsalam S, Dawoud MM. Randomized controlled trial of rivaroxaban versus warfarin in the management of acute non-neoplastic portal vein thrombosis. Vascul Pharmacol 2019;113:86–91.
[22] Intagliata NM, Henry ZH, Maitland H, Shah NL, Argo CK, Northup PG, et al. Direct oral anticoagulants in cirrhosis patients pose similar risks of bleeding when compared to traditional anticoagulation. Dig Dis Sci 2016;61:1721–7.
[23] Hum J, Shatzel JJ, Jou JH, Deloughery TG. The efficacy and safety of direct oral anticoagulants vs traditional anticoagulants in cirrhosis. Eur J Haematol 2017;98:393–7.
[24] Hoolwerf EW, Kraaijpoel N, Buller HR, van Es N. Direct oral anticoagulants in patients with liver cirrhosis: a systematic review. Thromb Res 2018;170:102–8.
[25] La Mura V, Braham S, Tosetti G, Branchi F, Bitto N, Moia M, et al. Harmful and beneficial effects of anticoagulants in patients with cirrhosis and portal vein thrombosis. Clin Gastroenterol Hepatol 2018;16:1146–52, e4.
[26] Fujiyama S, Saitoh S, Kawamura Y, Sezaki H, Hosaka T, Akuta N, et al. Portal vein thrombosis in liver cirrhosis: incidence, management, and outcome. BMC Gastroenterol 2017;17:112.
[27] Artaza T, Lopes M, Romero M, Gomez AZ, de la Cruz G, Sanchez JJ, et al. Efficacy and safety of anticoagulation in non-malignant portal vein thrombosis in patients with liver cirrhosis. Gastroenterol Hepatol 2018;41:611–7.
[28] Amitrano L, Guardascione MA, Menchise A, Martino R, Scaglione M, Giovine S, et al. Safety and efficacy of anticoagulation therapy with low molecular weight heparin for portal vein thrombosis in patients with liver cirrhosis. J Clin Gastroenterol 2010;44:448–51.
[29] Werner KT, Sando S, Carey EJ, Vargas HE, Byrne TJ, Douglas DD, et al. Portal vein thrombosis in patients with end stage liver disease awaiting liver transplantation: outcome of anticoagulation. Dig Dis Sci 2013;58:1776–80.