

Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: Prophylaxis and treatment controversies

Daniel KL Cheuk

Daniel KL Cheuk, Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China
Author contributions: Cheuk DKL solely contributed to this paper.

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Correspondence to: Daniel KL Cheuk, MD, FHKAM, Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong, China. cheukkl@hkucc.hku.hk

Telephone: +852-22553909 Fax: +852-22551523

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PhD, Professor, The Pelé Pequeno Príncipe Institute, Child and Adolescent Health Research, Av. Silva Jardim, 1632, Curitiba, 80250-200, Country, Brazil

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Abstract

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, is a major complication of hematopoietic stem cell transplantation and it carries a high mortality. Prophylaxis for hepatic VOD is commonly given to transplant recipients from the start of conditioning through the early weeks of transplant. However, high quality evidence from randomized controlled trials is scarce with small sample sizes and the trials yielded conflicting results. Although various treatment options for hepatic VOD are available, most have not undergone stringent evaluation with randomized controlled trial and therefore it remains uncertain which treatment offers real benefit. It remains controversial whether VOD prophylaxis should be given, which prophylactic therapy should be given, who should receive prophylaxis, and what treatment should be offered once VOD is established.

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INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) is a standard therapeutic modality for many different malignant and non-malignant diseases. However, complications from HSCT may result in severe morbidity and mortality. Major complications of HSCT include hepatic veno-occlusive disease (VOD), also known as hepatic sinusoidal obstruction syndrome. It is one of the major causes of non-relapse, transplant-related mortality. Hepatic VOD can occur after autologous or allogeneic HSCT, regardless of the underlying disease, stem cell source, or type of pre-transplant conditioning. The incidence of hepatic VOD after HSCT varies from 0 to 77%, depending on the risk of the patient cohort; and the median incidence is 13.3%^[1]. The mortality of severe VOD is high at average of 84%^[1]. Because of its high incidence and mortality, prophylaxis for hepatic VOD is widely practiced, using different regimens in different centers. However, whether prophylaxis alters the occurrence of VOD and which regimen is effective remains controversial. When hepatic VOD is established, specific therapy is usually given in addition to general supportive care, especially in moderate or severe cases. Different treatment strategies are tried with variable success, and no consensus regarding standard treatment is currently available. We therefore briefly review the existing evidence base for prophylaxis and treatment of hepatic VOD in this editorial and highlight the uncertainties and deficiencies in the evidence.

DIAGNOSIS OF HEPATIC VOD

Diagnosis of hepatic VOD is based on a constellation of symptoms and signs and serum bilirubin level. Hepatic VOD is clinically characterized by jaundice caused mainly by conjugated hyperbilirubinemia, tender hepatomegaly, fluid accumulation manifested as rapid weight gain and ascites. Most commonly used diagnostic criteria for VOD includes the Seattle criteria^[2], the modified Seattle criteria^[3], and the Baltimore criteria (also called Jones criteria)^[4]. Since different studies on prophylaxis and treatment of hepatic VOD might have used different criteria for diagnosis of VOD, comparisons of effectiveness of prophylaxis and treatment regimens across different studies may be difficult.

The severity of VOD is usually categorized into 3 grades: mild, moderate, or severe, depending on adverse effect from VOD, treatment required, duration of disease and mortality^[3]. While mild hepatic VOD may resolve without specific therapy, severe VOD carries a high mortality despite intensive therapeutic efforts. Because of variability and subjectivity in the definition of disease severity and the distribution of different severities within different cohorts of patients, comparisons of treatment results in different studies may be misleading.

PATHOGENESIS AND RISK FACTORS

The pathogenesis of hepatic VOD is incompletely understood. The clinical manifestations of hepatic VOD are thought to be caused by hepatic sinusoidal obstruction with or without occlusion of intrahepatic central venules, resulting from dysfunction of hepatic sinusoidal endothelial cells (SEC)^[5,6]. The cause of SEC dysfunction is multifactorial, and includes cytotoxic chemotherapy and radiotherapy, with concomitant glutathione and nitric oxide depletion, increased matrix metalloproteinases and vascular endothelial growth factor, and disturbances of inflammatory cytokines and coagulation and fibrinolytic system. Prophylaxis and treatment of VOD therefore generally aims at preventing or relieving possible thrombotic obstruction of hepatic sinusoids and venules, or trying to prevent or restore the function of SEC, replenish anti-oxidants, promote vasodilation, and counterbalance proinflammatory cytokines.

Many different risk factors of VOD have been described, and they can be classified into patient factors, disease factors, and treatment factors (Table 1). Since many risk factors for hepatic VOD are not modifiable, prophylactic therapy is commonly administered to selected high-risk transplant recipients to prevent its occurrence. Some centers routinely give VOD prophylaxis to all transplant patients. However, the benefits and risks of VOD prophylaxis in different situations are not entirely clear.

VOD PROPHYLAXIS

Prophylactic medications that have been used for hepatic VOD with some success include heparin^[7-10], low

Table 1 Risk factors of hepatic veno-occlusive disease

Risk factors	Ref.
Patient factors	
Younger age in children	[75-77]
Older age in adults	[78]
Poor performance status	[13,79,80]
Glutathione S-transferase M1 null genotype	[81]
Hemochromatosis C282Y allele	[82]
Pre-existing hepatic dysfunction	[2-4,79]
Hypoalbuminemia	[83]
Hyperbilirubinemia	[83]
High serum ferritin	[84]
Positive CMV serology	[85]
Elevated plasma transforming growth factor β level	[86]
Hepatitis B or C infection	[7,87-90]
History of pancreatitis	[85]
Disease factors	
Thalassemia major	[76]
Advanced malignancy	[83,91]
Acute leukemia	[89]
Neuroblastoma	[75,77]
Delayed platelet engraftment	[75,76]
Presence of acute graft- <i>vs</i> -host disease	[83]
Treatment factors	
Interval between diagnosis and transplantation greater than 13 mo	[83]
Allogeneic HSCT	[75,79]
Unrelated donor HSCT	[3,13,85,91]
Mismatched donor	[3,83]
Second or subsequent transplants	[7,84]
Prior use of gemtuzumab ozogamicin	[92]
Prior use of norethisterone	[93]
Prior abdominal irradiation	[3,7,77,79]
Use of total parenteral nutrition within 30 d before HSCT	[85]
High dose cytoreductive therapy	[79]
Conditioning regimen containing busulfan with or without cyclophosphamide	[3,75,76,84,85]
Conditioning regimen containing fludarabine	[85]
Conditioning regimen containing melphalan	[94,95]
Total body irradiation	[83,84]
Graft- <i>vs</i> -host disease prophylaxis with cyclosporin with or without methotrexate	[80,83,85]
Use of sirolimus	[96]
Use of tranexamic acid	[97]
Platelet transfusion containing ABO-incompatible plasma	[95]

HSCT: Hematopoietic stem cell transplantation.

molecular weight heparin^[11-13], danaparoid^[14], ursodeoxycholic acid^[15,16], prostaglandin E1^[10,17,18], glutamine^[19], defibrotide^[20-25], and fresh frozen plasma (FFP)^[7]. Some of these have also been tried in combination^[7,13]. Prophylaxis is generally given continuously from the commencement of conditioning till neutrophil engraftment or 1-3 mo after HSCT, during which hepatic VOD is most likely to develop. Some centers administer VOD prophylaxis to all patients who are undergoing HSCT while others only give prophylaxis to high risk patients, but the criteria for "high risk" is variable. High level evidence from randomized controlled trials supporting VOD prophylaxis is limited, and is only available for ursodeoxycholic acid, heparin, enoxaparin, glutamine, and FFP. They are briefly summarized below.

Table 2 Randomized controlled trials of ursodeoxycholic acid for hepatic veno-occlusive disease

Trial reference	Essell <i>et al</i> ^[26] 1998	Ohashi <i>et al</i> ^[27] 2000	Ruutu <i>et al</i> ^[28] 2002	Park <i>et al</i> ^[29] 2002
Blinding	Double-blind	Non-blind	Non-blind	Non-blind
Type of transplants	Allogeneic	Allogeneic or autologous	Allogeneic	Allogeneic or autologous
Donor	Related	Variable	Variable	NA
Stem cell source	Bone marrow	NA	Variable	NA
Conditioning	Busulfan and cyclophosphamide or busulfan alone	Variable	Variable	Variable
No. of patients (treatment <i>vs</i> control)	35 <i>vs</i> 32	71 <i>vs</i> 65	124 <i>vs</i> 120	82 <i>vs</i> 83
Treatment regimen	Ursodeoxycholic acid 300 mg BD (< 90 kg) or 300/600 mg BD (> 90 kg), given before conditioning till Day+80	Ursodeoxycholic acid 600 mg daily, given from Day-21 till Day+80	Ursodeoxycholic acid 6 mg/kg per day BD, given 1 d before conditioning till Day+90	Ursodeoxycholic acid 300 mg BD, heparin 5 units/kg per hour, given 12-24 h before conditioning till Day+30
Control	Placebo	No drug	No drug	Heparin alone
Age of patients (yr, treatment <i>vs</i> control)	Mean 38 (22-56) <i>vs</i> 37 (21-56)	Mean 34.5 <i>vs</i> 35.7	Median 38 (5-59) <i>vs</i> 40 (1-58)	Median 39 <i>vs</i> 38
VOD criteria	Seattle	Seattle	Baltimore, Seattle	Modified Seattle
Frequency of VOD (treatment <i>vs</i> control)	14.3% <i>vs</i> 40.6%	2.8% <i>vs</i> 18.5%	Baltimore 2.4% <i>vs</i> 4.2%; Seattle 11.3% <i>vs</i> 11.7%	15.9% <i>vs</i> 19.3%
Mortality at Day+100 (treatment <i>vs</i> control)	22.9% <i>vs</i> 40.6%	NA	NA	11.0% <i>vs</i> 10.8%

NA: Data not available; VOD: Veno-occlusive disease.

Ursodeoxycholic acid

There were 4 randomized controlled trials evaluating ursodeoxycholic acid for prophylaxis of hepatic VOD in HSCT recipients. Their characteristics and results are summarized in Table 2. The first randomized controlled trial was the only double-blind, placebo-controlled trial^[26]. Five of 35 patients (14.3%) who received ursodeoxycholic acid compared with 13 of 32 patients (40.6%) who received placebo developed hepatic VOD, which was significantly different (RR 0.35, 95% CI: 0.14-0.88, $P = 0.02$). Survival at Day+100 appeared higher in the ursodeoxycholic acid group, but the difference was not statistically significant (77% *vs* 59%, $P = 0.15$). The second randomized controlled trial compared ursodeoxycholic acid with no ursodeoxycholic acid^[27]. Two of 71 patients (2.8%) in the ursodeoxycholic acid group and 12 of 65 patients (18.5%) in the control group developed hepatic VOD, which was significantly different (RR 0.15, 95% CI: 0.04-0.66, $P = 0.01$). None of the patients in both groups died with hepatic VOD. The overall mortality was similar in both groups (21.1% *vs* 24.6%, RR 0.86, 95% CI: 0.46-1.59, $P = 0.63$). The third randomized controlled trial again compared ursodeoxycholic acid with no ursodeoxycholic acid^[28]. Three of 124 patients (2.4%) in the ursodeoxycholic acid group compared with 5 of 120 patients (4.2%) in the control group developed hepatic VOD according to the Baltimore criteria, which was not significantly different (RR 0.58, 95% CI: 0.14-2.38, $P = 0.45$). If the Seattle criteria for VOD diagnosis were used, 14 patients in each group developed hepatic VOD, again not significantly different between the 2 groups (RR 0.97, 95% CI: 0.48-1.94, $P = 0.93$). Hyperbilirubinemia occurred in 18 and 31 patients in the 2 groups respectively, which was significantly less frequent in patients who received ursodeoxycholic acid (RR 0.56, 95% CI: 0.33-0.95,

$P = 0.03$). There were 2 deaths related to hepatic VOD in the control group but none in the treatment group, but the difference was not statistically significant (RR 0.19, 95% CI: 0.01-3.99, $P = 0.29$). The fourth trial compared ursodeoxycholic acid plus heparin with heparin alone^[29]. Thirteen of 82 patients (15.9%) in the combined treatment group compared with 16 of 83 patients (19.3%) in the heparin alone group developed hepatic VOD, which was not significantly different (RR 0.82, 95% CI: 0.42-1.60, $P = 0.56$). There was also no significant difference in the frequency of severe VOD (2.4% *vs* 6.0%, RR 0.40, 95% CI: 0.08-2.03, $P = 0.27$). Survival at Day+100 was also similar between the 2 groups (89.0% *vs* 89.2%).

Heparin

There were 2 open-label randomized controlled trials evaluating heparin for hepatic VOD prophylaxis. The first trial comparing low dose heparin infusion (1 mg/kg per day from Day 0 till discharge) with no heparin for VOD prophylaxis in autologous bone marrow transplant recipients showed no significant difference in the incidence of hepatic VOD between the 2 groups^[9]. Four of the 52 patients (7.7%) in the heparin group developed hepatic VOD and 1 of the 46 patients (2.2%) in the control group had hepatic VOD (RR 3.54, 95% CI: 0.41-30.53, $P = 0.25$). However, patients with increased risk to develop VOD were excluded from randomization and it was not clear what constituted "increased risk". In contrast, the second trial comparing low dose heparin infusion (100 units/kg per day from Day-8 to Day+30) with no heparin in both allogeneic and autologous HSCT recipients showed a significantly lower incidence of VOD in the heparin group^[30]. Only 2 of 81 patients (2.5%) in the treatment group developed hepatic VOD, which was significantly less frequent compared to the control group,

in which VOD occurred in 11 of 80 patients (13.7%) (RR 0.18, 95% CI: 0.04-0.78, $P = 0.02$). Two patients in the heparin group and 7 patients in the control group died with VOD, which was not significantly different (RR 0.28, 95% CI: 0.06-1.32, $P = 0.11$). On subgroup analysis, none of the 39 patients (0%) who received heparin after allogeneic transplant developed hepatic VOD, but 7 of the 38 allogeneic transplant recipients (18.4%) who did not receive heparin had hepatic VOD, giving a relative risk of 0.07 favoring the heparin group (95% CI: 0.00-1.10), with borderline statistical significance ($P = 0.06$). For autologous or syngeneic transplants, the difference between the 2 groups was not significant, as 2 of 42 patients (4.8%) in the heparin group and 4 of 42 patients (9.5%) in the control group developed hepatic VOD (RR 0.50, 95% CI: 0.10-2.58, $P = 0.1$).

Low molecular weight heparin

There was one double-blind randomized controlled trial assessing the efficacy of enoxaparin for prevention of hepatic VOD in allogeneic and autologous bone marrow transplant recipients above 15 years of age^[31]. Sixty-one patients were randomized to receive enoxaparin 40 mg daily by subcutaneous injection from 1 d before conditioning till Day+40 (28 patients) or placebo (33 patients). The incidence of hepatic VOD was not reported in this study. However, it was found that 23 patients (82.1%) in the enoxaparin group and 28 patients (84.8%) in the control group had hyperbilirubinemia (RR 0.97, 95% CI: 0.77-1.21, $P = 0.78$); 17 patients (60.7%) in the enoxaparin group and 27 patients (81.8%) in the control group had hepatomegaly (RR 0.74, 95% CI: 0.53-1.04, $P = 0.08$); 6 patients (21.4%) in the enoxaparin group and 13 patients (39.4%) in the control group had right upper quadrant abdominal pain (RR 0.54, 95% CI: 0.24-1.24, $P = 0.15$); 20 patients (71.4%) in the enoxaparin group and 21 patients (63.6%) in the control group had weight gain (RR 1.12, 95% CI: 0.79-1.59, $P = 0.52$); and 2 patients (7.1%) in the enoxaparin group and 2 patients (6.1%) in the control group had ascites (RR 0.59, 95% CI: 0.12-2.98, $P = 0.52$). None of these outcomes were significantly different between the 2 groups. However, the duration of hyperbilirubinemia and hepatomegaly appeared shorter in the enoxaparin group compared to the control group (mean 7.4 d *vs* 15.3 d, $P = 0.008$; and mean 2.4 d *vs* 5.5 d, $P = 0.03$, respectively). All patients in this study survived.

Glutamine

There was one double-blind randomized controlled trial that compared glutamine with isonitrogenous amino acid mixture for protection of hepatic function in allogeneic or autologous bone marrow transplant recipients^[19]. Eighteen patients received daily infusion of 50 g glutamine and 16 patients received daily infusion of isonitrogenous amino acid mixture. Treatment was given from the start of conditioning till discharge from the transplant unit. No hepatic VOD was observed in both groups of patients. One patient in the control group died from sep-

sis and acute graft-*vs*-host disease, while all patients in the glutamine group survived. There was no significant difference between the 2 groups in overall mortality (RR 0.3, 95% CI: 0.01-6.84, $P = 0.45$). Of note is that 4 patients in each group withdrew from treatment, among whom one was due to abdominal discomfort.

FFP

One open-label randomized controlled trial compared FFP infusion with no FFP for prophylaxis of hepatic VOD in allogeneic HSCT recipients^[32]. The patients were stratified into children and adults for randomization. Patients allocated to the FFP group (23 patients) received twice weekly FFP infusions from the start of conditioning till Day+28 after HSCT and patients in the control group (20 patients) did not receive FFP. Hepatic VOD occurred in none of the patients (0%) in the FFP group and 3 adult patients (15%) in the control group. The difference was not statistically significant (RR 0.13, 95% CI: 0.01-2.28, $P = 0.16$). Mortality was not reported in this trial.

VOD TREATMENT

Fluid restriction, diuretics, and avoidance of hepatotoxic medications are essential supportive care for patients who developed hepatic VOD. Specific therapeutic options on top of these include tissue plasminogen activator^[33-44], heparin^[36], thrombomodulin^[45], antithrombin III^[46-49], protein C^[50], prostaglandin E1^[51], glutamine^[52,53], acetylcysteine^[54], methylprednisolone^[55], and defibrotide^[56-63]. Some of the above have also been tried in combination^[36,51,64-66]. Treatment is usually given until hepatic VOD resolves or the treatment is considered ineffective. In some cases, charcoal hemofiltration^[67], transjugular intrahepatic portosystemic shunt^[68-71] or liver transplantation is performed as last resort^[72,73]. However, little high level evidence on the treatment of hepatic VOD exists and only one randomized controlled trial is available which evaluated 2 different doses of defibrotide for treatment of hepatic VOD.

This multicenter open-label randomized controlled trial compared defibrotide at 25 mg/kg per day (arm A, 76 patients) with 40 mg/kg per day (arm B, 75 patients), both divided into 4 daily doses, given for at least 2 wk or until complete response^[74]. Both pediatric and adult patients with either autologous or allogeneic HSCT were included. This trial found no significant difference in complete response rate between arms A and B (49% *vs* 43%), survival at Day+100 (44% *vs* 39%), or treatment-related adverse events (7% *vs* 10%).

SUMMARY OF EVIDENCE

High level evidence from randomized controlled trials supporting prophylaxis for hepatic VOD is scarce. Most trials were not double-blind and therefore susceptible to performance and assessment biases. The sample sizes

were also small, limiting generalizability of results and the statistical power to make definitive conclusion. Ursodeoxycholic acid might reduce the incidence of hepatic VOD but trial results were conflicting. It is also uncertain which sub-group of patients is more likely to benefit. Nevertheless, all trials failed to show any survival benefit in those who received ursodeoxycholic acid. Trial results on low dose heparin infusion for VOD prophylaxis were also conflicting, with 1 trial showing reduction of VOD with heparin while the other trial showing no difference between the treatment and the control groups. It seemed that heparin was more likely to benefit allogeneic transplant recipients as compared to autologous transplant recipients but there was insufficient statistical power to draw a more definitive conclusion. Similar to trials on ursodeoxycholic acid, both trials on heparin prophylaxis failed to show survival benefit. Trials on enoxaparin, glutamine and FFP all failed to demonstrate efficacy on reduction of VOD or overall mortality when given prophylactically.

High level evidence on treatment options for hepatic VOD is even less. Only one randomized controlled trial was available. However, this trial just demonstrated that different doses of defibrotide resulted in similar response rate and survival, without informing us whether defibrotide itself was really effective or not. We are also uncertain to what extents treatment benefits patients with different severities of VOD.

CONCLUSION

High quality clinical evidence on prophylaxis and treatment of hepatic VOD in hematopoietic stem cell transplant recipients is scarce. Although anecdotal reports and some clinical trials suggested certain strategies may be effective for preventing and treating hepatic VOD, it remains controversial whether any of these is indeed effective. It is also unclear who should receive prophylaxis and which treatment is most likely to offer the best risk-benefit ratio. Large, double-blind, randomized controlled trials evaluating prophylactic and treatment options for hepatic VOD is therefore urgently needed.

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