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Thrombosis prophylaxis in pediatric liver transplantation: A systematic review

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Abstract

AIM

To review current literature of thrombosis prophylaxis in pediatric liver transplantation (PLT) as thrombosis remains a critical complication.

METHODS

Studies were identified by electronic search of MEDLINE, EMBASE and Cochrane Library (CENTRAL) databases until March 2018. The search was supplemented by manually reviewing the references of included studies and the references of the main published systematic reviews on thrombosis and PLT. We excluded from this review case report, small case series, commentaries, conference abstracts, papers which describing less than 10 pediatric liver transplants/year and articles published before 1990. Two reviewers performed study selection independently, with disagreements solved through discussion and by the opinion of a third reviewer when necessary.

RESULTS

Nine retrospective studies were included in this review. The overall quality of studies was poor. A pooled analysis of results from studies was not possible due to the retrospective design and heterogeneity of included studies. We found an incidence of portal vein thrombosis (PVT) ranging from 2% to 10% in pediatric living donor

liver transplantation (LDLT) and from 4% to 33% in pediatric deceased donor liver transplantation (DDLT). Hepatic artery thrombosis (HAT) was observed mostly in mixed LDLT and DDLT pediatric population with an incidence ranging from 0% to 29%. In most of the studies Doppler ultrasonography was used as a first line diagnostic screening for thrombosis. Four different surgical techniques for portal vein anastomosis were reported with similar efficacy in terms of PVT reduction. Reduced size liver transplant was associated with a low risk of both PVT (incidence 4%) and HAT (incidence 0%, $P < 0.05$). Similarly, aortic arterial anastomosis without graft interposition and microsurgical hepatic arterial reconstruction were associated with a significant reduced HAT incidence (6% and 0%, respectively). According to our inclusion and exclusion criteria, we did not find eligible studies that evaluated pharmacological prevention of thrombosis.

CONCLUSION

Poor quality retrospective studies show the use of tailored surgical strategies might be useful to reduce HAT and PVT after PLT; prospective studies are urgently needed.

Key words: Pediatric liver transplantation; Prophylaxis; Hepatic artery thrombosis; Surgical technique; Portal vein thrombosis

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Core tip: Graft loss and patient death after pediatric liver transplantation (PLT) are most frequently caused by hepatic artery thrombosis and portal vein thrombosis. For this reason, the prevention of hepatic artery and vein thrombosis represents a primary interest for clinicians and researchers, considering the scarcity of hepatic allografts. In our systematic review, we found only nine poor quality retrospective studies showing that tailored surgical strategies might be useful to reduce thrombosis. We did not find eligible studies evaluating pharmacological prevention strategies. Prospective studies are urgently needed to standardize thrombosis prevention in PLT.

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INTRODUCTION

Vascular complications are relevant causes of poor outcome for patient and allograft after pediatric liver transplantation (PLT)^[1-5]. Among vascular complications of PLT hepatic artery thrombosis (HAT) and portal vein

thrombosis (PVT) are one of the most frequent^[1-7] and serious causes of graft loss and also patient death^[1,2,6-9]. In particular HAT is an extremely serious complication resulting in bile duct necrosis and often requiring retransplantation^[10,11]. Thrombosis of other intra-abdominal vessels, such as the hepatic vein and inferior vena cava occurs less frequently^[6,11,12]. In the first years of PLT the observed incidence of thrombosis was very high, up to 42%^[13-15]. In the last years, an improvement of perioperative care has significantly decreased the thrombosis incidence^[1-3]. More recently, an incidence rate of HAT ranging from 2% to 10% after liver transplantation in the pediatric population has been reported^[1,6,7,11]; likewise, the incidence rate of PVT ranged from 2% to 10%^[1,6,7,9].

In this context, the prevention of HAT and PVT remains very important for PLT outcome and it should be a matter of primary interest for clinicians and researchers, considering the ongoing scarcity of hepatic allografts^[1,2,11,12,16-18]. In clinical practice, there is not a standardized approach for thrombosis prevention in PLT. Different surgical techniques and pharmacological prophylaxis have been purposed in several studies^[1,5,6,12,14,19-27]. Therefore, we performed a systematic review of current literature about surgical and pharmacological prophylaxis for prevention of thrombosis after PLT to evaluate the current evidence available.

MATERIALS AND METHODS

Search strategy

The publications were selected through an electronic search of the MEDLINE and EMBASE and Cochrane Library (CENTRAL) databases up to March 2018. The search strategy used the following Medical Subject Headings (MeSH) and Emtree terms and text words: ("liver transplantation"/exp OR "liver transplantation") AND ("thromboembolism"/exp OR "thromboembolism" OR "ischemia"/exp OR "ischemia" OR "vascular disease"/exp OR "vascular disease") AND ("prophylaxis"/exp OR "prophylaxis" OR "prevention"/exp OR "prevention") AND ([newborn]/lim OR [infant]/lim OR [child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim). In addition the references of the selected studies and two systematic reviews on thrombosis and PLT^[11,17] were screened to identify further relevant studies.

Two reviewers (Giulia Maria Ruggeri and Giovanna Colombo) performed an independent study selection, solving any disagreements through discussion and the opinion of a third reviewer (Mirco Nacoti). They obtained study characteristics like year of publication, design, study centre, patients' characteristics like number, mean age and gender, treatments and number of arterial and venous thrombotic complications.

The following criteria were needed in order to be considered potentially eligible for this systematic review: (1) phase III randomized clinical trials or cohorts including case series with more than 10 patients undergoing

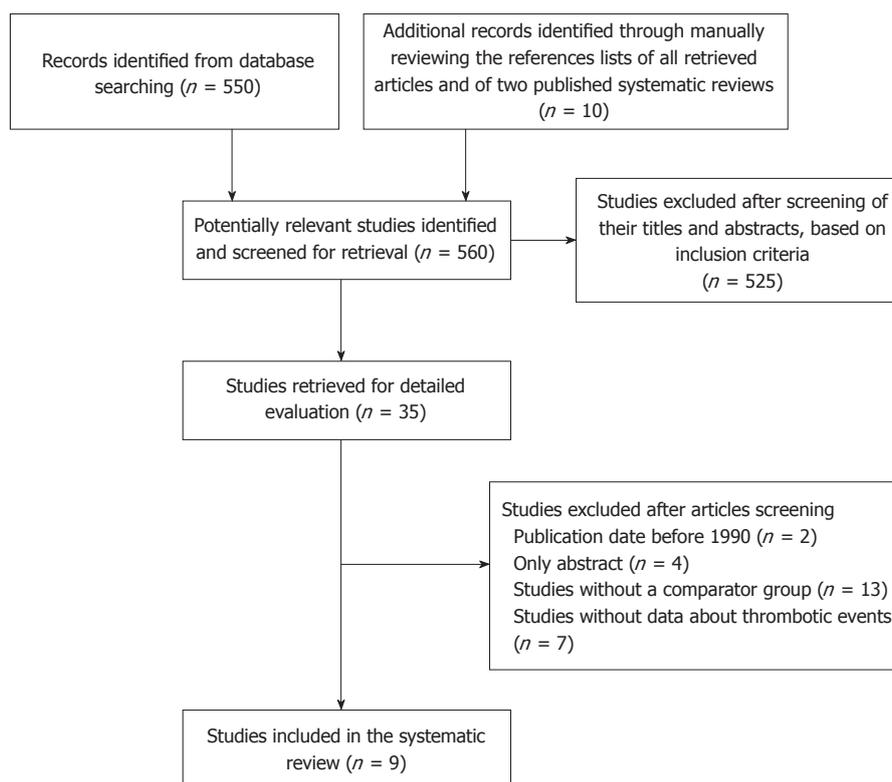


Figure 1 Flow-chart of study selection process.

elective PLT (age ranged from 0 to 18 years); and (2) reporting arterial and venous thrombosis as primary or secondary events in all different groups according to the used prophylaxis strategy. If data from a study were reported in several publications, data from the most recent paper were used. Studies describing less than 10 PLT/year were excluded as significant high mortality is associated with low volume center^[28,29]. Articles published before 1990 were also excluded because new developments in perioperative PLT have dramatically improved the survival^[1-3].

Risk of bias assessment

Although the evaluation of quality for observational studies is controversial^[30], Giulia Maria Ruggeri and Giovanna Colombo assessed the risk of bias using the following items for cohort studies: Type of study (prospective or retrospective); selection of the patients (consecutive or not); thrombosis as pre-specified outcome; quality of measurements (studies in which thrombotic events were measured in an objective way were considered higher quality than studies without these characteristics). A scoring system was put in place to identify the following two quality categories: Studies at low-risk of bias (4 points) and studies at high-risk of bias (≤ 3 points).

RESULTS

Results of the search strategy

The study process is presented in Figure 1. A total of

560 publications (550 retrieved with the electronic search strategy and 10 by manually reviewing the reference lists of all retrieved articles) were identified. After reading their titles and abstracts 525 were excluded, according to inclusion and exclusion criteria. The remaining 35 publications were analyzed in full for detailed evaluation. Twenty-six papers were eliminated for the following reasons: Publication date before 1990 ($n = 2$), only abstract ($n = 4$), studies without a comparator group ($n = 13$) and studies ($n = 7$) which did not contain explicit data about pediatric thrombotic events.

Nine manuscripts^[31-39], which included a total of 1034 PLT in 991 subjects, were included in this systematic review (Table 1). None of the all included studies were at high risk of bias according to pre-defined requirements (Table 2). In particular, no study were prospective, only 7 studies reported thrombosis as a pre-defined outcome, and 8 studies detailed how the diagnosis of thrombosis had been made. The poor quality and the heterogeneity of included studies did not allow us to perform a pooled analysis of results.

Incidence of the artery and PVT

Table 1 shows detailed incidence of artery and PVT as reported in the included studies. Most studies reported a total incidence (early and late) of thrombosis. The incidence of PVT varies from 2% to 10% in pediatric living donor liver transplantation (LDLT)^[37,39] and from 33% in pediatric LDLT to 4% in pediatric deceased donor liver transplantation (DDLTL) with reduced graft^[33]. HAT is presented mostly in mixed LDLT and DDLTL pedia-

Table 1 Summary of findings of the nine included studies

Reference	Country	Population (n)	Study design	Method used for diagnosis and follow-up duration	Intervention	Outcome	Main results
Sabra <i>et al</i> ^[37]	Japan	113 pediatric LDLT	Retrospective	Doppler US twice daily till 1 st week. If any PV complications were found, specific tests such as angiography were performed 1 yr of follow-up	PV reconstruction with VG (31 pts) PV reconstruction with EEA (82 pts)	Preoperative recipient factors PVT incidence Pt survival Graft survival	Global incidence PVT (2.6%) in the first 3 mo after OLT 1 PVT in 31 VGs vs 2 PVT in 82 without VGs No significant difference for PVT, Pt survival, Graft survival In the two groups
Julka <i>et al</i> ^[38]	Taiwan	87 pediatric LDLT	Retrospective	Routine doppler US post LT; CT angiography for HAT confirmation 5 yr of follow-up	HA reconstruction with two arterial stumps. 2 HA stumps with 2 HA reconstruction = 20 pts 2 HA stumps with 1 HA reconstruction = 22 pts 1 HA stump with 1 HA reconstruction = 45 pts	HAT incidence BC incidence	Overall HAT incidence 6.9% The incidence of HA thrombosis and biliary complications was similar in the three groups
Saad <i>et al</i> ^[39]	Japan	110 LDLT in pediatric pts	Retrospective LDLT	Doppler US, performed routinely before, during and after surgery Follow-up not defined	Different types of portal vein reconstructions Type 1: End- to- end anastomosis = 36 pts Type 2: Branch patch anastomosis = 27 pts Type 3: Anastomosis to the confluence (superior mesenteric vein-splenic vein) = 16 pts Type 4: Vein graft = 32 pts Chosen according to the surgical evaluation	C TC SC Survival rate	Type 1: 1 SC / 36 pts Type 2: 2 TC / 27 pts Type 3: 0 / 16 pts Type 4: 1 TC / 32 pts Overall survival rate 86%
Shackleton <i>et al</i> ^[31]	California	194 pediatric OLT for biliary atresia (mixed LDLT and DDLT)	Retrospective	Clinical suspect confirmed by angiography and/or surgical exploration. 3 yr of follow-up	Gr 1: Conventional artery reconstruction (n = 166) Gr 2: MHR (n = 28)	Risk factors for HAT Impact of MHR on incidence of HAT, need of re-OLT, patient and graft survival	Impact of MHR HAT incidence: Gr 1 32/166 (19%) vs Gr 2 0/28 (0%), P = 0.006 Re-OLT: Gr 1 31/166 (19%) vs Gr 2 1/28 (4%), P = 0.05 1 yr actuarial survival: Gr 1 81% vs Gr 2 100%, P = 0.02 (univariate analysis) BUT P = 0.076 in step wise Cox regression for patient survival
López <i>et al</i> ^[32]	Spain	104 OLT in 82 pediatric pts (mixed LDLT and DDLT)	Retrospective	Doppler US routinely and selective arteriography for confirmation. 3 yr of follow-up	Arterial revascularization technique: Gr 1 (n = 48) AhG Gr 2 (n = 56) EEA Chosen according to the surgical evaluation	HAT incidence Survival rate	HAT incidence Gr 1. (AhG): 6.25% Gr 2. (EEA): 8.92% (P not significant) Graft Survival rate (1 yr) 61.5% (AhG) vs 60% (EEA) (P < 0.05) Graft survival rate (5 yr): 77.5% (AhG) vs 75.1% (EEA) (P < 0.05)
Millis <i>et al</i> ^[33]	Illinois	66 pediatric LDLT and 48 pediatric cadaveric RLT	Retrospective	Doppler US every day for the first 3 d and at 1, 3, 6, 12, 18, and 24 mo after transplantation + angiography for confirmation 5 yr of follow-up	Portal anastomosis with venous graft conduit in LDLT Gr 1 (n = 18): Native reconstructed vein Gr 2 (n = 37): Cryopreserved iliac vein; Gr 3 (n = 11):	Incidence of PVC Graft survival Patient survival	Incidence PVC LDLT 33/66 (50%) vs RLT 4/48 (8%) P < 0.0001 Early PVT LDLT Gr 1: 6 (33%) ^a LDLT Gr 2: 3 (8%) LDLT Gr 3: 1 (9%) RLT: 2 (4%)

					Cryopreserved femoral vein		^a <i>P</i> < 0.005 <i>vs</i> RLT Late PVC LDLT Gr 1: 3 (16%) LDLT Gr 2: 19 (51%) ^a LDLT Gr 3: 1 (9%) RLT: 2 (4%) ^a <i>P</i> < 0.005 <i>vs</i> RLT; <i>P</i> < 0.02 <i>vs</i> Gr 1 and Gr 3 Graft survival PVC: 61% No PVC: 67%, <i>P</i> = NS Patient survival: PVC: 67% No PVC: 71%, <i>P</i> = NS HAT: Gr 1:0 (0%)/Gr 2:5 (29%) (<i>P</i> < 0.05) The incidence of biliary complications, bleeding (requiring surgical exploration) and chronic rejection were similar between the groups Overall HAT incidence: 14/143 (10%) HAT incidence between the 2 groups: Gr 1: 6/50 (12%) <i>vs</i> Gr 2: 8/93 (9%), <i>P</i> not significant; Gr 1 EEA 5/31 (16%) <i>vs</i> Gr 1 AhG 1/19 (5%); <i>P</i> not significant Gr 2 EEA 4/60 (6%) <i>vs</i> Gr 2 AhG 4/32 (12%) <i>P</i> not significant HAT incidence in 25% whole liver transplant <i>vs</i> 23% in LDLT <i>vs</i> 15% RLT (<i>P</i> = 0.06) Aortic anastomosis (supraceliac and infrarenal) reduces incidence of HAT (6% <i>vs</i> 24%, <i>P</i> = 0.02)
Jurim <i>et al</i> ^[34]	California	35 pediatric OLT Emergency transplants only (type of donor not specified)	Retrospective	Not reported. Follow-up not defined	Gr 1: RLT = 7 pts Gr 2: Whole graft = 18 pts	HAT incidence Incidence of other complications: Biliary; bleeding; chronic rejection	
Yandza <i>et al</i> ^[35]	France	143 DDLT in 122 pediatric pts	Retrospective	Doppler US daily the first 15 d, twice/wk until discharge Follow-up not defined	Gr 1 (<i>n</i> = 41 pts, <i>n</i> = 50 grafts) children < 10 kg Gr 2 (<i>n</i> = 81 pts, <i>n</i> = 93 grafts) children > 10 kg Surgical technique: EEA <i>vs</i> AhG	Effect of the site of liver graft arterial inflow on HAT incidence according to the recipient weight	
Stevens <i>et al</i> ^[36]	Chicago	134 OLT in 100 pediatric pts < 2 yr : mixed LDLT and DDLT	Retrospective	Doppler US, frequency not defined Follow-up	60 standard whole liver <i>vs</i> 74 RLT (13 LDLT) Surgical technique: Arterial inflow with 83 hepatic artery <i>vs</i> 32 celiac artery <i>vs</i> 5 supraceliac aorta <i>vs</i> 27 infrarenal aorta <i>vs</i> 7 unusual reconstruction	Effect of the graft type and site of arterial inflow on the incidence of HAT	

BA: Biliary atresia; BW: Body weight; CTA: CT angiography; Gr: Group; GRWR: Graft-to-recipient weight ratio; HAG: Hepatic artery graft; LT: Liver transplantation; OLT: Orthotopic liver transplantation; Pt: Patient; RLT: Reduced size liver transplantation; re-OLT: Re-transplantation; SC: Stenotic complication; TC: Thrombosis complication; US: Ultrasonography; LDLT: Living donor liver transplantation; PV: Portal vein; VG: Vein graft; EEA: End-to-end anastomosis; PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis; HA: Hepatic artery; BC: Biliary complications; C: Complications; MHR: Microsurgical hepatic arterial reconstruction; AhG: Aortohepatic interposition graft; PVC: Portal vein complications; DDLT: Deceased donor liver transplantation.

tric population; incidence of HAT varies from 0% to 29%^[31,32,34-36,38].

Screening protocol for thrombosis detection

Most of the studies used Doppler ultrasonography (US) as a first line diagnostic screening for thrombosis^[32,33,35-39]; frequency and duration of the screening is quite variable. Confirmation of the thrombosis detected by a second level diagnostic test, such as computer CT angiography, surgery or other methods is rarely specified^[31-33,37,38].

Intraoperative surgical prophylaxis

Table 1 summarizes the main results of the studies

analyzed. In LDLT there are four different modalities to perform portal vein anastomosis: (1) standard reconstruction with end to end anastomosis^[37,39]; (2) reconstruction with anastomosis to the bifurcation of the recipient left and right vein^[39]; (3) reconstruction with anastomosis to the confluence of the recipient mesenteric vein^[39]; and (4) reconstruction with an interposition of vein graft^[33,37,39]. The overall results of different techniques were similar. The choice of the type of reconstruction depended on the size (length and diameter) and quality of the portal vein and size mismatch between donor and recipient portal vein^[33,37,39]. Millis *et al*^[33] showed a low PVT incidence with reduced size liver transplant (RLT) [4%

Table 2 Risk of bias and quality of the studies

Reference	Study design	Consecutive enrolment	Thrombosis as pre-defined outcome	Methods use to the diagnosis of thrombosis
Shackleton <i>et al</i> ^[31]	Retrospective	Yes	Yes, HAT	Clinical grounds and angiography and/or surgical exploration for confirmation
López <i>et al</i> ^[32]	Retrospective	Yes	No	Doppler US and angiography for confirmation, post mortem second confirmation
Millis <i>et al</i> ^[33]	Retrospective	Yes	Yes, PVT	Doppler US and angiography for confirmation
Jurim <i>et al</i> ^[34]	Retrospective	Yes	Yes, HAT	Not reported
Yandza <i>et al</i> ^[35]	Retrospective	Yes	Yes, HAT	Doppler US
Stevens <i>et al</i> ^[36]	Retrospective	Yes	Yes, HAT	Doppler US
Sabra <i>et al</i> ^[37]	Retrospective	Yes	Yes, PVT	Doppler US
Julka <i>et al</i> ^[38]	Retrospective	Yes	No	Doppler US and angiography for confirmation
Saad <i>et al</i> ^[39]	Retrospective	Yes	Yes, PVT	Doppler US

PVT: Portal vein thrombosis; HAT: Hepatic artery thrombosis; US: Ultrasonography.

vs 33% with whole liver transplant (WLT) and native reconstructed vein, $P < 0.005$]; RLT was developed in attempt to resolve the mismatch size liver between donor and recipient and was applied to split liver transplantation and LDLT.

Three different surgical procedures seemed to reduce HAT incidence: RLT with cadaveric left lobe [incidence 0% vs 29% with WLT, $P < 0.05$ ^[34]]; aortic arterial anastomosis without graft interposition [incidence 6% vs 24% in celiac-hepatic artery anastomosis, $P = 0.02$ ^[36]] and microsurgical hepatic arterial reconstruction (MHR) [incidence 0% vs conventional artery reconstruction, $P = 0.006$ ^[31]].

López *et al*^[32] and Yandza *et al*^[35] did not find significant HAT difference between end-to-end anastomosis and aortohepatic interposition graft; Julka *et al*^[38] showed that single hepatic artery reconstruction did not increase the HAT incidence in pediatric LDLT having dual hepatic arterial stump in the liver graft.

Post-operative pharmacological prophylaxis

No studies on pharmacological prophylaxis compared clinical outcomes according to different treatments used^[1,9,11-13,17,22-24,27].

DISCUSSION

Vascular thrombotic complications were a serious life-threatening complication in the first year of PLT with an incidence up to 42% associated with mortality up to 50%^[13-15]. Although factors causing thrombotic complications are not fully understood^[15], a global improvement of perioperative care has significantly decreased the thrombosis incidence in the last 20 years^[1-3,6,7,9,11]. Several retrospective studies without control group tried to identify factors for thrombosis; among them should be mentioned medical factors, such as administration of fresh frozen plasma, elevated hematocrit, protein C deficiency^[1,14,40,41] and surgical factors, such as cold ischemia time, technique of anastomosis, small vessel diameter, the use of aortic grafts, donor arterial anatomy and reconstruction^[1,7,14,31,36], but without any definitive

conclusions.

Accordingly, the aim of this systematic review was to identify evidence based methods both surgical and pharmacological for the prevention of thrombosis after PLT. In this systematic review, we found no prospective studies and only 9 retrospective studies with a control group referred to surgical prevention.

RLT (with left lobe or segment of left lobe)^[34] direct aortic anastomosis and MHR^[31] seem the best surgical options for reducing thrombotic complications in PLT, but the impact of RLT and aortic anastomosis on HAT were not confirmed by Stevens^[36] and López-Yandza^[32,35] respectively. MHR is an arterial reconstruction performed with an operating microscope; it was introduced by the Kyoto group for the fine graft arteries (less than 2 mm in diameter) in LDLT^[42]. The amazing results of MHR (0 HAT in 28 PLT)^[31] need to be confirmed in a larger clinical trial. It is worth noting that one of the most extensive studies about incidence and risk factors for vascular complication in liver transplantation was excluded from this systematic review because it included a mixed adult and pediatric population, without an appropriate control group^[1].

Pharmacological prophylaxis is a relevant topic in PLT. Several studies^[1,9,11-13,17,22-24,26] reported their experience using different drugs, such as unfractionated heparin, low molecular weight heparin, vitamin K antagonist fresh frozen plasma, aspirin, dipyridamole, antithrombin concentrate, dextran 40, thrombin inhibitor, prostaglandin. Unfortunately, in these studies there was not a comparator group, necessary in order to achieve formal proof of efficacy and safety and according to the inclusion criteria of this systematic review. In this regard, for example, aspirin is one of the most extensive drugs used for HAT prevention^[11,14,17], but without formal evidence derived from prospective clinical trials.

The careful search of the literature and the inclusion of different types of studies are the main strengths of this review. Nevertheless, our study presents some weaknesses. First, the risk of thrombosis might have been underestimated because we assumed not all

authors systematically reported thrombotic events. Second, the description of methods for preventing vascular thromboses may be incomplete because only studies reporting the outcome were considered.

Although, HAT and PVT incidence has decreased in the last decades^[1-3,6,7,9,11], they remain one of the more frequent and serious complications causing a poor outcome after PLT^[1,2]. Furthermore, the old question "thrombosis after PLT - a medical or surgical event?"^[14] remains an unresolved issue. Concerning this, our systematic review of studies, in which different prophylaxis strategies were tested for the prevention of HAT and PVT failed to provide enough evidence for a definitive conclusion due to the poor quality of studies found^[31-39]. However, our analysis emphasizes the need of developing well-designed clinical studies in order to correctly determine PLT-associated thrombosis risk and to define an evidence-based antithrombotic prophylactic strategy. The recent "single ventricle trial"^[43] showed that randomized clinical trials are possible also in the pediatric surgery area.

ARTICLE HIGHLIGHTS

Research background

Hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT) commonly occur after pediatric liver transplantation (PLT) that may cause graft loss and patient death. Different surgical techniques and pharmacological prophylaxis have been purposed in several studies; nevertheless, there is not a standardized approach for thrombosis prevention in PLT.

Research motivation

Prevention of HAT and PVT remains very important for PLT outcome and it should be a matter of primary interest for clinicians and researchers, considering the ongoing scarcity of hepatic allografts.

Research objective

We performed a systematic review of current literature about surgical and pharmacological prophylaxis for prevention of thrombosis after PLT to evaluate the current evidence available.

Research methods

Studies were identified by electronic search of MEDLINE, EMBASE and Cochrane Library (CENTRAL) databases until March 2018. We excluded from this review case report, small case series, commentaries, conference abstracts, papers which describe less than 10 pediatric liver transplants/year and articles published before 1990. Two reviewers performed an independent study selection, solving any disagreements through discussion and the opinion of a third reviewer.

Research results

Nine retrospective studies were included in this review. They showed the use of tailored surgical strategies might be useful to reduce thrombosis. We did not find eligible studies evaluating pharmacological prevention strategies. The overall quality of studies was poor. A pooled analysis of results from studies was not possible due to the retrospective design and heterogeneity of included studies.

Research conclusions

This systematic review in which different prophylaxis strategies were tested for the prevention of HAT and PVT failed to provide enough evidence for a definitive conclusion due to the poor quality of studies found.

Research perspective

This systematic review showed there is no evidence based strategy for thrombosis prevention in PLT. Prospective studies are urgently needed. The recent "single ventricle trial" showed that randomized clinical trials are possible also in the pediatric surgery area.

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