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CLIN APPL THROMB HEMOST 2014 20: 673 originally published online 10 June 2014
DOI: 10.1177/1076029614538490

The online version of this article can be found at:
http://cat.sagepub.com/content/20/7/673
Do Postliver Transplant Patients Need Thromboprophylactic Anticoagulation?

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Abstract

Postoperative thromboprophylactic anticoagulation against Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) is standard of care with current evidence-based guidelines. However, majority of liver transplant (LT) patients have thrombocytopenia and/or prolonged INR before surgery. Studies or guidelines regarding role of prophylactic anticoagulation after LT are lacking. There is a need to balance the risk of thrombosis with significant hemorrhage, implying those needing transfusion or return to OR due to bleeding. We conclude that after LT, anticoagulation is not required routinely for DVT/PE prophylaxis. Rather, it is indicated in specific circumstances, chiefly for prophylaxis of hepatic artery thrombosis or portal vein thrombosis in cases with use of grafts, pediatric cases, small size vessels, Budd Chiari syndrome, amongst others.

Keywords

anticoagulants, deep venous thrombosis, thrombosis prophylaxis, venous thromboembolism

Introduction

Prophylactic anticoagulation is practiced to prevent deep vein thrombosis (DVT) and pulmonary embolism (PE), a potentially life-threatening complication. The benefit of thromboprophylactic anticoagulation in postoperative general surgical patients has been established beyond doubt.¹ The practice is now standard of care.

Liver transplantation is considered to be a much bigger operation. Yet the role of routine prophylactic anticoagulation after liver transplant is not well established.² Here, we appraise the related literature and discuss the risk and benefit of using anticoagulation after liver transplant.

Thromboembolism in General Surgery

Deep Vein Thrombosis and PE After Major General Surgery With No Thromboprophylaxis

The incidence of DVT following general surgery is 25% (n = 4310, data from 54 trials, mostly undergoing gastrointestinal surgeries). Deep vein thrombosis following surgery in patients with malignant disease is 29% (n = 546, data from 16 trials). The incidence of PEs was 1.6% (n = 5091, data from 32 trials) and that of fatal PEs was 0.9% (n = 5547, data from 33 trials).

Most of these thrombotic incidents are asymptomatic to begin with, even those which are eventually fatal.³,⁴ Fatality from PEs is usually rapid, in about 30 minutes.⁵,⁶ Although the incidence of fatal PEs is about 0.9%, they are considered preventable. These reasons have contributed to thromboprophylactic anticoagulation becoming standard of care.

Risk of Bleeding With Pharmacologic Thromboprophylaxis in General Surgery

On the other hand, there are justified concerns over the risk of bleeding with anticoagulation. A 65% to 66% increase in the odds of bleeding was noted. Although the proportional increase in risk of bleeding appeared significant, a more modest absolute increase was reported between 2% and 10%.⁷ More recently, Kakkar et al reported a major bleeding rate of 3.6% to 4.8% in a large multicentric randomized trial of 3809 patients undergoing major abdominal surgery.⁸ Claggett et al concluded after reviewing several trials and meta-analyses that there was no significant increase in major bleeding.⁹ Although the incidence of wound hematomas was increased, they can be managed successfully and mortality does not increase.⁵,⁸ The incidence of heparin-induced thrombocytopenia was <3% and vascular thrombotic events attributable to it are uncommon.⁹

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Benefits of Thromboprophylaxis in General Surgery

Following the widespread use of prophylactic measures, there has been a significant reduction in the incidence of DVT to 7% to 8% from ~25% without prophylaxis (about 70% decrease in incidence, data from 70 trials). Similarly, the incidence of fatal PE was decreased by two-thirds, and hospital mortality was decreased by 25%. Use of heparin saves about 41 lives per 10,000 patients treated. Considering these observations, thromboprophylaxis has become a standard of care in general surgical practice today.

Thromboembolic Phenomena After Liver Transplantation

There is a lack of data regarding incidence of venous thromboembolic (VTE) phenomena in liver disease and following orthotopic liver transplantation (OLT).

Hemorrhagic Complications After Liver Transplantation

With end-stage liver disease, majority of patients have prolonged international normalized ratio (INR) and thrombocytopenia. Transplanted livers may have delayed primary function, and coagulation does not improve immediately after transplantation. Hemorrhagic complications and the consequent transfusion and/or reoperations entail significant morbidity and mortality. The incidence of major bleeding necessitating transfusion and/or reoperation was reported as 8.4% by Liang et al and 27% by Hendriks et al, both of whom did not use postoperative prophylactic anticoagulation and 15% by Kaneko et al who used it. In the series of Liang et al, the in-hospital mortality of patients with hemorrhage was 41% (9 of 22) and over mortality from hemorrhage was 3.4%. Four patients died of infection and 5 of multiorgan failure. Of note, the risk of bleeding following liver transplantation is intrinsically even without anticoagulation.

Thromboembolism After OLT

Intraoperative thromboembolic phenomena. Although intraoperative thromboembolic phenomena were uncommon (estimated 1%-1.5%), associated mortality was high. In an extensive systematic review (74 cases), Warnaar et al noted very high mortality (68% overall) in cases of intraoperative PE, including intracardiac thrombosis. Similar figures (50%) are echoed by Ellenberger et al.

Notable risk factors were venovenous bypass, use of antifibrinolytic agents, use of pulmonary artery catheters, octreotide, and hepatitis B immunoglobulin among others. Interestingly, in this series, PE along with intracardiac thrombus had lower mortality (50%) than PE alone (91%; \( P < .001 \)). Treatment included thrombectomy and thrombolysis in addition to conventional measures like hemodynamic support with use of fluids and inotropes; however, the outcome was not encouraging (intraoperative mortality 82%). However, causes of intraoperative thromboembolism are more often from venovenous bypass circuit where clots could be formed from a low flow system. With more experience and less often utilization of bypass systems such incidences are lower. Certainly, adding anticoagulation in an already coagulopathic in a major surgical procedure is not without risk. Furthermore, some of the PE incidences may be from air embolism, where air is being trapped in inferior vena cava in between the clamps during the anastomosis which is propagated to right atrium on release of clamp. Such incidences are not amenable to prophylactic anticoagulation.

Postoperative thromboembolic phenomena. Ishitani et al in their retrospective study involving 299 patients and 342 liver transplants reported an incidence of 2.7% for DVT, diagnosed a mean of 70 days (range 13-210 days) after the transplant. The incidence of PE was 1%. Pulmonary embolism was diagnosed a mean of 128 days (range 41-317 days) after transplant. One case of PE was immediately fatal (0.3%). Venovenous bypass and bicaval anastomosis were used in all patients. Intermittent pneumatic compression devices were used in all patients following OLT till ambulatory.

Cherian et al reported a 0.37% (8 cases) incidence of PE following OLT in a single-center review of 3000 OLTs over 25 years. The median time of presentation following transplantation was 24 days (range 0-50 days). Two cases, both intraoperative PE, died. However, there were no deaths in the cases of PE presenting after the transplant. In this retrospective study spanning 25 years, the authors could not conclusively ascertain that all patients received anticoagulation or mechanical prophylaxis uniformly.

Specific Needs of Anticoagulation After Liver Transplant

Rather than VTE, 2 other entities specific to OLT may have significant consequences, namely, hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT).

Hepatic Artery Thrombosis

The incidence of HAT was reported as 4.2% by Jain et al in their long-term follow-up study of OLT following OLT in 1000 patients. Similar figures (HAT incidence of 4.4%) were quoted by Bekker et al in their systematic review of 71 studies. After 13 years of follow-up, overall 43.2% (72.7% children and 32.9% adults) were alive. Overall retransplantation rate was 53.1% (61.9% in children and 50% in adults). Both authors found significantly higher incidence of HAT and retransplantation in children than adults. However, survival was superior in children. Nikeghbalian et al reported early (within 2 weeks) HAT rate of 4.3% (11 of 256).
In a more recent study (n = 1379 adults, 188 pediatric), incidence of HAT was significantly (P < .001) higher with the use of aortohepatic conduits (4.1% vs 0.7% in adults) with an adjusted hazard ratio for graft loss of 1.38 with the use of conduits. The differences were not observed in children. The authors concluded that the use of aortohepatic conduits should be reserved to avoid the higher incidence of HAT.24

In a study (n = 914) by Warner et al, HAT was noted in 4.7%. Prominent risk factors scrutinized by univariate and multivariate analyses included graft number, abnormal donor arterial anatomy, bench arterial reconstruction, aortic conduit use, multiple anastomoses, reperfusion time (interval between portal vein reperfusion and restoration of arterial flow), and the number of units of blood transfused. In the background of their findings, the authors recommended prospective evaluation of the use of strict surveillance using arterial Doppler and selective anticoagulation.25

Due to the high incidence of mortality and/or graft loss in HAT transplant, regulatory authorities in most countries allow relisting and retransplantation on a priority basis. Obviously, such an event is better prevented and may justify judicious use of anticoagulants in high-risk cases like pediatric transplants, live donor cases, small caliber or diseased vessels, use of arterial grafts, and systemic hypercoagulable states like Budd-Chiari syndrome.

**Portal Vein Thrombosis**

You et al reported 9 cases of post-OLT PVT of the 402 (incidence of 2.2%). In all, 1 needed a retransplantation and 6 of the 9 died, a mortality of 67%.26,27 Khalaf et al in their study of 224 OLTs (155 donor who died and 69 living donor) reported an incidence of PVT of 2.6% (4 of 155) in the donor recipients who died with 75% (3 of 4) mortality.28 Among living donor recipients, a 2.9% (2 of 69) incidence of PVT was noted and both died. In both the groups, vascular complications were associated with poor graft and patient survival, particularly in the living donor recipients and pediatric cases. In their series, Khalaf et al did not use routine prophylactic systemic anticoagulation. It was selectively employed in cases with high risk of PVT: diseased portal vein intima in recipient or graft, a technically complex or difficult anastomosis, damaged or tiny vessels, recipient PVT, jump venous grafts, and hypercoagulable states like Budd-Chiari syndrome.

Important risk factors for PVT after OLT were preoperative PVT, pediatric cases, pathological changes in portal vein, abnormal blood stream dynamics, systemic hypercoagulable states, and improper surgical technique.26,29,30 In PVT, no special status is granted for relisting a patient, hence prevention is of utmost importance and underlines the role of anticoagulants in this population.

**Postoperative Thromboembolic Phenomena in Pediatric Liver Transplant**

Ooi et al reported incidence of DVT following pediatric OLT as 8%. Intra-abdominal thrombotic events including HAT, PVT, hepatic vein, and inferior venacaval thrombosis occurred at a rate of 8%.31 Another series of 76 OLTs in children, mostly infants and toddlers, reported incidence of HAT as 11.8% and PVT as 2.6%.32 In their series (n = 64) of OLT in infants below 6 kgs, Shiroyzu et al reported PVT of 14% and HAT of 7.7%.33 Broniszczak et al reported HAT of 5.6% and PVT of 11.2% in 71 live-related living donor transplants in children 6 months to 10 years of age.34

In most reported pediatric series, most of whom receive living donor or split liver cadaveric donors, the incidence of HAT and PVT is usually higher than in adults. Thus, this group represents a special risk.

**Role of Anticoagulation After Liver Transplant**

We note the lower incidence of VTE, especially fatal PEs following OLT. Also of note is the high incidence of hemorrhagic complications and its consequent morbidity and mortality even without anticoagulation. Therefore, pharmacologic thromboprophylaxis after OLT may not be used routinely to prevent DVT and PE. Rather in special high-risk situations, to prevent HAT and PVT, anticoagulation may be used judiciously. Even in the latter cases, it is generally not started until posttransplant INR is below 1.5 to 2 and platelet count is above 25 000 to 50 000.

Using the definitions used by Ooi et al,31 McLin et al reviewed their series of 110 pediatric transplants. Using a unique protocol of thromboprophylactic heparin and FFP to supply antithrombin III for the heparin to act, they achieved HAT rates of 1.9%. Sanchez et al noting higher incidence of HAT in pediatric OLT recipients with malignancies recommended prospective evaluation of prophylactic anticoagulation regimens.36

Shay noted that aspirin (325 mg postoperatively daily) prophylaxis immediately after transplant resulted in a significantly lower incidence of early HAT leading to graft loss (0% in ASA group, n = 165% vs 3.6% in the non-ASA group, n = 304, P < .05, total study population = 439 all adults). Although the incidence of PVT was lower (0.6% in ASA group vs 2% in the non-ASA group) and that of early HAT not leading to graft loss was also lower (1.8% in ASA group vs 3.9% in the non-ASA group), the results were not statistically significant. In this series, the differences in significant surgical bleeding (in this study defined as needing >2 U packed red cells) or bowel perforation between the ASA and the non-ASA groups were not statistically significant.37

Similarly, Vivarelli et al reported significantly lower incidence of late HAT with use of aspirin prophylaxis post-OLT (0.4%, 1 of 236 on ASA vs 2.2% 13 of 592 no ASA, P = .049).38 The above-selected representative examples illustrate our premise that thromboprophylactic anticoagulation in selected high-risk OLT scenarios may be considered carefully.

**Discussion**

The central question is “What is different about liver transplant recipients compared to other general surgical patients?”
To begin with, the transplant recipient is coagulopathic before the surgery. As the liver disease advances with decreased hepatic synthesis of coagulation factors, patients develop a rise in INR. The associated portal hypertension, hypersplenism, and decrease in hepatogenetic thrombopoietic agents lead to thrombocytopenia. This results in a hypocoagulable state with a bleeding tendency. After OLT, the coagulation may not normalize immediately.\textsuperscript{12,13} The new liver may take some time before it starts producing adequate coagulation factors. The thrombocytopenia persists for about 2 weeks.

Orthotopic liver transplantation is a very demanding operation. Major bleeding and reoperation have been reported to be as high as 27\%.\textsuperscript{15} Mortality in patients who bleed is reported to be up to 41\%.\textsuperscript{14} In contrast to the reported incidence of VTE after general surgery (DVT \textasciitilde 25\% without any prophylaxis and \textasciitilde 7\%-8\% with prophylaxis, PE \textasciitilde 1.6\%, and fatal PE \textasciitilde 0.9\% both without prophylaxis), its incidence following OLT is significantly lower. Also, there is a delayed presentation of VTE following OLT (mean of 70 days for DVT and 128 days for PE), whereas in general surgery, the week or so is the most common time for presentation of VTE.

Anticoagulation may potentially delay the performance of critical procedures like biopsy, endoscopy, insertion of lines, and so on, as reversal of anticoagulation is needed. As the initial post-OLT period is very crucial, during this delay other new complications may appear or the existing complications may progress and even treatable ones become untreatable.

Possibly for these reasons, prophylactic anticoagulant therapy is not a routine practice following OLT, although mechanical means like elastic stockings, intermittent pneumatic compression, and early ambulation are routinely employed. The Centers for Medicare and Medicaid Services, a federal agency in the United States regulating government-sponsored health insurance, does not reimburse or reduce reimbursement agency in the United States regulating government-sponsored health insurance, does not reimburse or reduce reimbursement for the prevention of deep venous thromboembolism. Am J Gastroenterol. 2006;101(7):1524-1528; quiz 1680.


