Prothrombotic Disorders in a Cohort of 25 Patients Undergoing Transplantation: Investigation and Management Implications

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ABSTRACT

Background. Many patients referred for intestinal transplantation have a history of thrombosis. We undertook an analysis of transplanted patients to describe the history and frequency of thrombosis, clinical course, and management strategies used.

Results. Twenty-five patients underwent transplantation of intestine containing blocks between 2007 and 2012; 20 of 25 are still alive. Five of 25 patients were transplanted with history of portomesenteric thrombosis, 6 of 25 had experienced loss of venous access due to thrombosis, and 6 of 25 had history of mesenteric ischemia. Pretransplantation, 16 of 25 patients were anticoagulated. Thrombophilia screens identified 3 of 16 patients who were JAK2 positive, 1 of 25 who had antithrombin deficiency, and 1 of 25 who had a factor V Leiden heterozygote. Post-transplantation, of all 16 patients who were anticoagulated pretransplantation and continued postoperatively, 1 of 16 infarcted their small bowel graft and 4 of 16 developed a further venous thrombosis despite anticoagulation. Of the 9 without a previous history of thrombosis, 1 had a pulmonary embolus more than a decade after transplantation and another had an upper limb deep vein thrombosis associated with a line. Both were then anticoagulated. Seven of 25 are not anticoagulated, although they are administered antiplatelet prophylaxis. Postoperative bleeding complications of anticoagulation occurred in 3 patients. After a subarachnoid hemorrhage in 1 of those 3 patients, anticoagulation was stopped. The other 2 patients bled during ileal biopsy, and both remain on low molecular weight heparin treatment.

Conclusion. Those with identifiable thrombophilic tendency and a history of venous or arterial thrombosis are considered to be at high risk for recurrent thrombosis. Those without such a history could be considered low risk. Our practice is to anticoagulate all high-risk individuals before and after transplantation and offer antiplatelet prophylaxis to low-risk patients as the risk of anticoagulation probably outweighs the risk of thrombosis for them. Early input from hematologists is vital in the management of high-risk patients, particularly those who thrombose when anticoagulated.
Thrombophilic disorders are acquired or inherited defects in coagulation that lead to a predisposition towards arterial or venous thrombosis. The incidence of deep vein thrombosis in the population is approximately 1 per 1000 per year and of those with unprovoked deep vein thrombosis only approximately 50% have an identifiable thrombophilic disorder. The majority of patients with a thrombophilic tendency only develop a thrombosis in the presence of another risk factor [3]. The thrombophilia screen refers to a panel of tests that aims to identify a genetic cause for an increased risk of thrombotic events and includes factor V Leiden deficiency, prothrombin gene mutation, antiphosphlipid syndrome, and protein S and C deficiency.

A large proportion of patients referred for transplantation in our unit have had at least one episode of thrombosis. Some patients have had recurrent problems or have an identifiable disorder. Thrombophilia screening forms part of our assessment of patients referred for transplantation.

The purpose of this study is to describe the frequency of preoperative thrombotic disorder, the clinical course of patients, and to discuss our approach and management strategy at Addenbrookes Hospital, Cambridge, United Kingdom.

**METHODOLOGY**

Our study included patients undergoing transplantation of intestine containing grafts in Cambridge between 2007 and 2012. One living patient who was transplanted in 1998 and is followed up by our unit was also included. The medical records and electronic database of patients who have undergone transplantation were used to obtain information relating to the history of thrombotic episodes, management of this situation, and clinical course.

**RESULTS**

Table 1 shows the demographics of the cohort. Twenty-five patients (7 females and 18 males) underwent transplantation during the study period. Twenty of 25 are alive. The average age of the cohort is 43 years (range, 22 to 66 years). Seventeen of 25 (70%) had a history of thrombosis. This included 6 of 25 who had a diagnosis of mesenteric infarction and 3 with a history of portal vein thrombosis (PVT) associated with cirrhosis. Loss of venous access was an indication for transplantation in 12 of 25.

Pretransplantation, 16 of 25 patients were anticoagulated. The thrombophilia screen in those 16 patients identified 5 with a characterizable thrombophilic disorder: 3 were Jak 2-positive, 1 patient had antithrombin deficiency, and 1 was heterozygous for factor V Leiden. Pretransplantation thrombotic history included 5 patients with portomesenteric vein thrombosis, 1 with previous pulmonary embolus, 6 with loss of venous access due to thrombosis, and 6 with mesenteric ischemia. During the assessment process, only one new diagnosis of thrombophilia was made (Jak 2).

Figure 1 shows the clinical course of transplanted patients. Post-transplantation, 16 patients continued to be anticoagulated. One of 16 patients infarcted their small bowel graft, and 5 of 16 had a further episode of thrombosis including thrombosis in a vessel containing a line, non-occlusive thrombus in the aortic conduit, and partial portal vein thrombus.

Of the whole cohort, only 9 patients had no pretransplantation history of thrombosis; and of these, 1 patient had a pulmonary embolus more than 10 years after transplantation and 1 an upper limb DVT associated with a line after transplantation. These patients were subsequently anticoagulated. Only 7 of our cohorts remain not anticoagulated.

Of the 18 patients formally anticoagulated, bleeding complications occurred in 3. One patient had a subarachnoid hemorrhage and 2 patients bled after the ileal biopsy resulting in hemodynamic compromise. One of these patients had a platelet function disorder (storage pool disorder) associated with their Jak 2/myeloproliferative disorder.
Anticoagulation was stopped in the patient who had subarachnoid hemorrhage and after recovery was started on an antiplatelet agent. The 2 who bled at biopsy remain anticoagulated.

In our unit, it is standard practice to anticoagulate using warfarin or low molecular weight heparin. Of those patients with recurrence of clot whilst adequately anticoagulated most were started on fondaparinux as an alternative anticoagulant based on the advice of our haematologists. One patient was given aspirin as an additional agent to their low molecular weight heparin.

DISCUSSION

Patients referred for intestinal transplantation frequently have a history of either mesenteric infarction and/or a history of recurrent thrombosis related to presence of an indwelling catheter. Although the presence of the CVC or high tip position may predispose to thrombosis, it would seem that certain individuals on PN are at particularly increased risk of recurrent thrombosis. The majority (>70%) of patients on home PN do not have significant problems with thrombosis [1].

In our unit, based on this experience, we consider that any patient referred with a history of thrombosis or mesenteric infarction, regardless of result of the thrombophilia screen, is at high risk. We have recently started testing for Jak 2 status as a routine in patients referred with PVT and have identified two new cases yet to undergo transplantation (and therefore not included in this study). It is our practice to anticoagulate high-risk individuals pre- and postoperatively unless there is a specific contraindication (eg, large varices yet to be banded). A low-risk patient is one who has no previous history of thrombosis. These individuals are started on antiplatelet prophylaxis when discharged from the hospital and low molecular weight heparin prophylaxis is used during the transplantation admission process.

CONCLUSION

Approximately 70% of our patients have a history of thrombosis before transplantation and 20% have an identifiable thrombophilic disorder. Approximately 30% of those patients with history of thrombosis who are anticoagulated have a further thrombosis while anticoagulated. Bleeding complications do occur but infrequently. We adopt high-/low-risk stratification in the management of our patients. The involvement of hematologists in the investigation and management of patients particularly those who thrombose whilst anticoagulated is essential.

REFERENCES

