Rivaroxaban: A New Hope for Anticoagulation in LDLT Recipients

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Abstract

Purpose:
Thromboembolic complications remain a significant concern in postoperative patients, particularly those who have undergone liver transplantation. Warfarin has been the standard oral anticoagulant. Direct oral anticoagulants (DOACs) have several advantages over warfarin, including rapid onset of action and standardized dose guidelines. However, their use in the liver transplant population remains poorly studied. We aimed to assess the safety of rivaroxaban in living donor liver transplantation (LDLT) recipients.

Methods:
This study was a single-center, retrospective descriptive analysis of LDLT recipients who received rivaroxaban between December 2020 and April 2022. A total of 27 recipients received rivaroxaban postoperatively. Liver function tests and immunosuppression levels were recorded before the initiation of rivaroxaban & then on post-therapy days 1, 7, 14, 28, 90, and 180.

Results:
Among the 27 recipients receiving rivaroxaban postoperatively, portal venous thrombosis was the most prevalent indication for anticoagulation (44.4%), followed by Budd-Chiari Syndrome (29.6%). Nine patients had a twofold increase in either ALT or AST values, two of whom were treated for biliary strictures and the others for rejection. Eighteen patients were given tacrolimus, and eight were on cyclosporine, with one patient switched from tacrolimus to cyclosporine due to insufficient therapeutic levels. There were no incidents of bleeding or re-thrombosis during the 180-day follow-up period.

Conclusion:
Rivaroxaban may be a safe and effective alternative in LDLT recipients with no significant adverse incidents. Further studies with larger sample sizes are needed to confirm these findings and determine this population's optimal dose and duration of rivaroxaban therapy.

INTRODUCTION
Thromboembolic complications are a growing concern among the postoperative population, especially patients undergoing solid organ transplantation [1]. Following liver transplantation, venous or arterial thrombus formation incidence ranges from 2–10%. It includes perioperative factors such as surgical clamping, ischemic reperfusion damage, and venous stasis due to immobilization of the patient [1, 2]. Warfarin has been the first-line oral anticoagulant in preventing thromboembolism for most patients, but it has several drawbacks. These include the need for close monitoring [3], the risk of drug-drug and drug-
food interactions [4], and the significant potential for adverse consequences such as bleeding [5]. There was no other alternative oral anticoagulant to warfarin in the United States until the introduction of dabigatran in 2010. Following the approval of this medicine by the Food and Drug Administration (FDA), three more oral anticoagulants, namely rivaroxaban, apixaban, and edoxaban, were subsequently evaluated and authorized.

Direct oral anticoagulants (DOACs) offer numerous benefits over warfarin, making them more appropriate for use. Along with their rapid onset of action, these medications have standardized dose guidelines and a broad therapeutic range, eliminating the need to be monitored frequently [6]. Furthermore, DOACs have been shown to have fewer documented drug-drug interactions than warfarin [7].

However, the use of DOACs in patients who undergo solid organ transplantation has not been thoroughly studied, with a scarcity of data supporting their use in this population [8]. The need for analysis is especially pertinent for patients who undergo liver transplants because it is not only the risk of thrombosis that needs to be addressed in these patients, but the risk of bleeding due to physiological changes in prothrombotic and antithrombotic factors needs to be accounted for [2]. Moreover, all DOACs are at least partially metabolized by cytochrome P450 (CYP450) enzymes, and the activity of this enzyme complex is typically modulated by calcineurin-inhibitors such as cyclosporine and tacrolimus, drugs used for immunosuppression following solid organ transplantation. As a result, their usage in the liver transplant population remains a topic of discussion [9, 10].

The main objective of this study was to analyze outcomes and incidence of any adverse effects in recipients of Living Donor Liver Transplantation (LDLT) who were administered rivaroxaban postoperatively for anticoagulation. By studying our variables and outcomes, we hoped to shed more light on the feasibility of using rivaroxaban as a first-line drug for future recipients after LDLT.

**METHODS**

The study was a single-center, Institutional Review Board (IRB) approved (IRB approval no. 0117) retrospective descriptive analysis of liver transplant recipients who received rivaroxaban between December 2020 and April 2022, irrespective of transplant date. This study was performed in line with the principles of the Declaration of Helsinki.

All patients were examined retrospectively using an electronic medical record file review to obtain relevant basic biographical and laboratory parameters. The dose of rivaroxaban treatment was determined by the treating physician in conjunction with the multidisciplinary transplant team, which included a transplant pharmacist and cardiology and hematology consultants. The attending made decisions on perioperative anticoagulant treatment interruption in accordance with established guidelines. An experienced professional examined the suitability of anticoagulant dose in each individual, considering the renal and liver function and concurrent use of drugs. Postoperatively, a Doppler ultrasound was performed at the initial four visits and then subsequently to check for thrombosis only when deranged liver function tests (LFTs) were observed.
The primary endpoint for this analysis was the incidence of new clinically relevant significant side effects. Secondary endpoints assessed included new or progressive thrombosis confirmed with Doppler ultrasound. Patient data were collected retrospectively, using online medical record numbers to review pertinent data. The recorded data included the demographics of the patient, including their gender, age, details of any laboratory investigations performed on days 1, 7, 14, 28, 90, and 180 post-therapy, imaging studies, and follow-up notes with a particular focus on any adverse effects from the use of rivaroxaban.

The data were analyzed with the SPSS 27 statistical package (IBM Corp, NY). Data were presented as mean and standard deviation. The Chi-square or Fisher exact test tested differences between categorical variables. A p-value < 0.05 was considered significant.

RESULTS

Between December 2020 and April 2022, 27 recipients with indications for anticoagulation who had undergone LDLT received oral rivaroxaban following the standard eight days of heparin infusion. Nineteen (70.4%) were males. The mean age of the patients was 44 years, and the mean BMI was 24.7 kg/m². Of the 27 individuals, 9 (33.3%) were initially on warfarin (n = 5) or a combination of enoxaparin and warfarin (n = 4) before being switched to rivaroxaban (the median time to switch from these drugs to rivaroxaban was 175 days). The most common indications of transplant for this cohort included Hepatitis C (40.7%, n = 11) followed by Budd-Chiari Syndrome (29.6%, n = 8) (Table 1).
Table 1
Recipient characteristics.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>44.4 ± 15.6</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>19 (70.4%)</td>
</tr>
<tr>
<td>Females</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>24.7 ± 4.8</td>
</tr>
<tr>
<td>MELD score</td>
<td>17.4 ± 5.1</td>
</tr>
<tr>
<td>Indication for transplant</td>
<td>Frequency (Percentage)</td>
</tr>
<tr>
<td>Hepatitis C Virus</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Cryptogenic Cirrhosis</td>
<td>6 (22.2%)</td>
</tr>
<tr>
<td>Hepatitis B Virus</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Secondary Biliary Cirrhosis</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>Indication for Anticoagulation</td>
<td></td>
</tr>
<tr>
<td>Portal Venous Thrombosis</td>
<td>12 (44.4%)</td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Vascular reconstruction using conduit or vascular intervention</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>Duration of anticoagulant therapy</td>
<td></td>
</tr>
<tr>
<td>2 months</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>5 months</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>6 months</td>
<td>7 (25.9%)</td>
</tr>
<tr>
<td>7 months</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>8 months</td>
<td>1 (3.7%)</td>
</tr>
<tr>
<td>12 months</td>
<td>2 (7.4%)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>13 (48.1%)</td>
</tr>
</tbody>
</table>

Among the 27 patients, the most common indication for anticoagulation was portal venous thrombosis, accounting for 44.4% of cases, followed by Budd-Chiari Syndrome at 29.6% and vascular reconstruction using conduit or vascular interventions mandating anticoagulation therapy at 25.9%. The latter category
included a range of indications, such as postoperative MI angiography and stenting, aortic conduit using the great saphenous vein (GSV), an ilial conduit to the aorta with the right hepatic artery (RHA), an IVC filter for deep vein thrombosis (DVT), and an IVC replacement with Dacron graft. (Table 1).

Seven patients (25.9%) were on therapy for six months, while two (7.4%) were on treatment for 5 and 12 months, respectively. One patient (3.7%) each was on therapy for 2, 7, and 8 months. Most patients (48.1%) were on anticoagulant therapy till the date of follow-up (Table 1). The average time frame for anticoagulant treatment was approximately 88 days.

At the time of initiation of rivaroxaban, baseline laboratory investigations were recorded, including total and indirect bilirubin, ALT, AST, INR, and serum creatinine. These laboratory investigations were subsequently repeated on postoperative days 7, 14, 28, 90, and 180. Most patients were found to have steady-state levels of ALT and AST throughout the follow-up period (Figs. 1a and 1b), as well as serum creatinine. Nine patients had a twofold increase in either ALT or AST values, two of whom were treated for biliary strictures and the others for rejection.

Regarding immunosuppressants, tacrolimus was the baseline immunosuppressant at the initiation of rivaroxaban in 18 patients, whereas cyclosporine was used in 8 patients when rivaroxaban was started. One patient was receiving a combination of tacrolimus and mycophenolate mofetil. There were no rapid changes in immunosuppression levels with routine blood tests, which showed steady-state levels for both drugs (Figs. 2a and 2b). However, one patient was changed from tacrolimus to cyclosporine after 14 days due to insufficient therapeutic levels of tacrolimus in routine blood investigations. We were, however, unable to determine why this happened as we did not monitor rivaroxaban levels.

Notably, the study observed no incidents of bleeding or re-thrombosis during the 180-day follow-up period. Additionally, no instances of uncontrolled International Normalized Ratio (INR) were detected.

**DISCUSSION**

Direct oral anticoagulants (DOACs) have become increasingly popular among physicians since the Food and Drug Administration's (FDA) approval. DOACs accounted for roughly half of all anticoagulant prescriptions in the United States in 2014 [11]. However, they have traditionally been administered and evaluated in clinical studies that excluded individuals with severe liver disease. Most investigations on such patients employing DOACs have been restricted to case reports or case series, much less for living donor liver transplants (LDLTs) [1, 12, 13]. Altered hepatic functionality after liver transplantation is a significant risk for anticoagulant usage because it might affect drug metabolism, increasing the body's exposure to anticoagulants. Portal hypertension, found in several patients with end-stage liver disease (ESLD), can diminish the first-pass metabolism of drugs excreted via the hepatic route, enhancing their bioavailability. Additionally, hypoalbuminemia can increase the free fraction of highly protein-bound drugs like rivaroxaban, potentiating its anticoagulant effects [14]. Rivaroxaban is primarily excreted by the biliary tract following oxidative metabolism. Its use has been limited in our study population due to higher biliary and vascular complication rates in split liver graft procedures compared to whole-liver
transplantations [15]. These potential risks should be considered when choosing an anticoagulant so as not to cause harmful effects secondary to hepatic dysfunction.

Based on our results of using rivaroxaban in 27 patients with an extended follow-up period of 180 days, we concluded that rivaroxaban is a safe and efficacious option for such patients. A review completed by Lee et al. found decreased rates of major bleeding (HR: 0.65; 95% CI: 0.57 to 0.73) and all-cause mortality (HR: 0.69; 95% CI: 0.63 to 0.76) among patients who were given DOACs when compared to warfarin [16]. In another single-center retrospective review of Santeusanio et al. on comparing DOACs with warfarin among two matched groups of liver transplant patients, the authors discovered a clinical significance in bleeding events in a matched cohort of patients on warfarin (p-value = 0.01). In addition, only 3 out of 27 patients in the DOAC group developed at least one clinically relevant bleeding event [17]. We did not elicit a single significant side effect from our patients for the study, including any bleeding events, re-thrombosis, or fluctuations in INR. Thus, our findings support the usage of rivaroxaban by demonstrating a considerable reduction in adverse effects with the added benefit of no monitoring necessary.

Liver transplantation has been known to affect kidney function in more than 50% of recipients, especially during the first few months after surgery [18]. Renal dysfunction may be aggravated with immunosuppressants, such as cyclosporine or tacrolimus. These drugs exert nephrotoxic effects by constricting the afferent renal arteriole leading to decreased kidney perfusion [19]. Recent literature has reported that DOACs have some degree of renal elimination [20]. Although rivaroxaban, our choice of drug for this study, is contraindicated in patients with a glomerular filtration rate (GFR) of < 30ml/min, we only included patients with adequate pre-transplant renal function [21, 22]. Furthermore, rivaroxaban did not affect creatinine levels in our patients, proving its safety for use after a successful liver transplant procedure. In patients who require hemodialysis or have a GFR < 30ml/min, apixaban is the only DOAC safe for use [17].

One of the most substantial concerns of DOAC use, especially in post-transplant patients, is the possibility of drug-drug interactions. Rivaroxaban and apixaban usually undergo metabolism by the cytochrome P450 (CYP450) system [23]. Calcineurin inhibitors, which we typically administer in our patients for immunosuppression, have been known to act as substrates and exert inhibitor effects on the CYP450 enzymes [24]. Their use can dramatically reduce rivaroxaban excretion, thus putting the patient at risk for potential bleeding events. A study on the use of rivaroxaban for post-liver transplant patients found a significantly greater number of bleeding events in the cyclosporine and rivaroxaban combination group compared to the tacrolimus and rivaroxaban combination group (60% vs. 25%) [13]. While we reported zero major bleeding events in our patients, we also found no significant changes in the steady-state levels of cyclosporine and tacrolimus during follow-up visits.

When prescribing an anticoagulant for extended periods, it is imperative for the patient to regularly take the medication and report for timely follow-ups to ensure therapeutic levels are maintained. While transplant recipients are already on a plethora of different drugs for at least six months after the procedure, prescribing a once-daily anticoagulant can help the patient comply with the medication and
promote a better physician-patient relationship. The only available once-daily oral anticoagulant options include warfarin and rivaroxaban [25]. A study by Laliberté and colleagues discovered that a once-daily dosage schedule resulted in a 39% higher chance of adherence to the drug when contrasted with twice-daily dosing [26]. While warfarin requires regular INR levels and more time to reach therapeutic levels, rivaroxaban can be more likely to have greater compliance, as it does not need to be regularly monitored in the blood. It has also been shown to have a faster onset of action [27, 28].

While our study presented some helpful information on the benefits of rivaroxaban, there were some limitations to the study. Firstly, the study was a single-center, retrospective analysis, which may not be generalizable to other centers or populations. Secondly, the sample size of 27 patients was relatively small, which could limit the ability to detect significant outcomes with rivaroxaban use. There was a lack of a control group to compare the results of the rivaroxaban group, making it difficult to establish the efficacy and safety of rivaroxaban in this population. Despite these limitations, the study provided valuable preliminary information on using rivaroxaban in liver transplant patients, highlighting the need for further research.

CONCLUSION

In conclusion, this study evaluated the safety and efficacy of rivaroxaban as a first-line anticoagulant in LDLT recipients. The study showed that rivaroxaban is a feasible option for anticoagulation in LDLT recipients and has a low incidence of clinically significant adverse effects. Using rivaroxaban in this population eliminates the need for frequent monitoring, making it a convenient alternative to warfarin. The study provides valuable insight into the safety of using rivaroxaban in LDLT recipients, and further prospective randomized control studies with larger sample sizes are needed to confirm the findings. Nevertheless, the results of this study suggest that rivaroxaban may be a promising option for anticoagulation in LDLT recipients.

Declarations

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: None.

Ethics approval and consent to participate: The study was approved by the Institutional Review Board at Pakistan Kidney and Liver Institute & Research Center.

Availability of data and materials: Data can be provided upon reasonable request.

Acknowledgments: None

Authors’ Contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Abdullah Khalid and Bilal Ahmed Khan. The first draft of
the manuscript was written by Abdullah Khalid and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures
Figure 1

a. Trends in alanine aminotransferase (ALT) after initiating rivaroxaban.

b. Trends in aspartate aminotransferase (AST) after initiating rivaroxaban.
Figure 2

a. Trends in cyclosporine levels after initiating rivaroxaban.

b. Trends in tacrolimus levels after initiating rivaroxaban.