# Continuous Renal Replacement Therapy with Low Dose Systemic Heparin in Liver Transplant Recipients

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**Introduction.** Continuous renal replacement therapy (CRRT) is an effective dialysis method in critically ill patients. Citrate and heparin are commonly used as anticoagulants to prevent premature circuit clotting. The aim of this study was to evaluate the safety and efficacy of using low dose systemic heparin while on CRRT in liver transplant recipients.

**Methods.** We retrospectively evaluated and analyzed data from 29 liver transplant recipients undergoing CRRT in the postoperative course in this cross-sectional study. Numerous variables were recorded, such as coagulation parameters, duration of intensive care unit (ICU) stay, duration of dialysis, heparin dose, circuit life span, and anticoagulant complications.

**Results.** Out of 29 recipients, there were 16 (55%) female and 13 (45%) male. All participants underwent whole organ liver transplantation with a median age of 45 years. Overall, 98 successful dialysis sessions were recorded in this study with a mean circuit life span of 36 hours. Mean ± SD duration of CRRT for each recipient was 4.8 ± 3.1 days. The median total dose of heparin used for each recipient was 25,000 units , and the median dose of heparin per-day for each recipient was about 3,300 units. There were no episodes of anticoagulant-related bleeding complications. Thirteen (13.2%) episodes of premature circuit clotting occurred. We found a significant association between the first dose and total dose of heparin usage with first postoperative INR and PTT level ($P < .05$, $P < .05$, $P < .001$, and $P < .05$).

**Conclusion.** In liver transplant recipients, low dose heparin during CRRT for patency of circuit is well tolerated.

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## INTRODUCTION

Premature circuit clotting is a critical issue in clinical practice during dialysis. It is associated with higher resource utilization and cost and more blood loss.[1] Performing renal replacement therapy (RRT) increases survival among critically ill patients.[2-5] It has different modalities, including intermittent hemodialysis, continuous renal replacement therapy, peritoneal dialysis, and prolonged intermittent renal replacement therapy. Continuous renal replacement therapy(CRRT) is an effective method for RRT in critically ill and hemodynamically unstable patients.[3] To provide more effective continuous renal replacement therapy, avoiding clot formation is necessary. Heparin is the most common anticoagulant used for CRRT.[6] Anticoagulation prevents circuit clotting, but at the same time increases bleeding complication,

especially in liver transplant recipients.[7] Therefore, heparin utilization should be with caution and the probable risks and benefits in each patient should take into consideration.

Uchino *et al.* reported CRRT without the need for anticoagulation.[8] Tan *et al.* suggested minimal dosage of heparin in medically high-risk patients.[9] However, to the best of our knowledge, very few publications have addressed this issue with practical considerations in liver transplant recipients. It was hypothesized that to securely use of anticoagulation in liver transplant recipients, the dosage should be modulate according to primary post-op platelet count , INR and PTT levels.

## MATERIALS AND METHODS

### Participants

Any orthotopic liver transplantation (OLT) recipient who underwent CRRT in the postoperative course between March 2015 and May 2016 in Shahid Namazi hospital in Shiraz were enrolled in this study. Any participant on heparin therapy for other medical conditions, such as hepatic artery stenosis and high resistance index (RI), was excluded. Among 609 OLT patients in this period, 36 (5%) patients underwent CRRT for different etiologies after transplantation. Three patients (8%) were excluded due to receiving heparin as a therapeutic method for other medical conditions, two (6%) of them for high resistance hepatic artery flow on Doppler ultrasonography and one patient (3%) for portal vein thrombosis after endovenectomy (Figure 1). Four (11%) patients were excluded due to technical problems during CRRT, which represented human and machine errors. Finally, 29 (81%) OLT patients with deceased donors were studied. This cross-sectional study was approved in the institutional board review and ethics committee.

### Data Collection

Multiple variables were recorded, including age, gender, etiology of liver failure, coagulation parameters, duration of dialysis, intensive care unit (ICU) length of stay, tital heparin dose, circuit life span, and anticoagulant complications.

### Indications for CRRT

The decision to initiate CRRT was a collaborative task by the transplant surgery and anesthesiology teams. Patients with anuria or oliguria (< 500 mL/24 hours) were considered as candidates for CRRT.

### CRRT Modality

The CRRT was performed by B/Braun (Medizintechnologie GmbH, Germany) platform. The hemofiltration solution was B/Braun Avitum AG (Germany). Also, we used heparin from Caspian Tamin Company (Rasht- Iran). Continuous venovenous hemofiltration (CVVH) was used as dialysis mode in all cases.

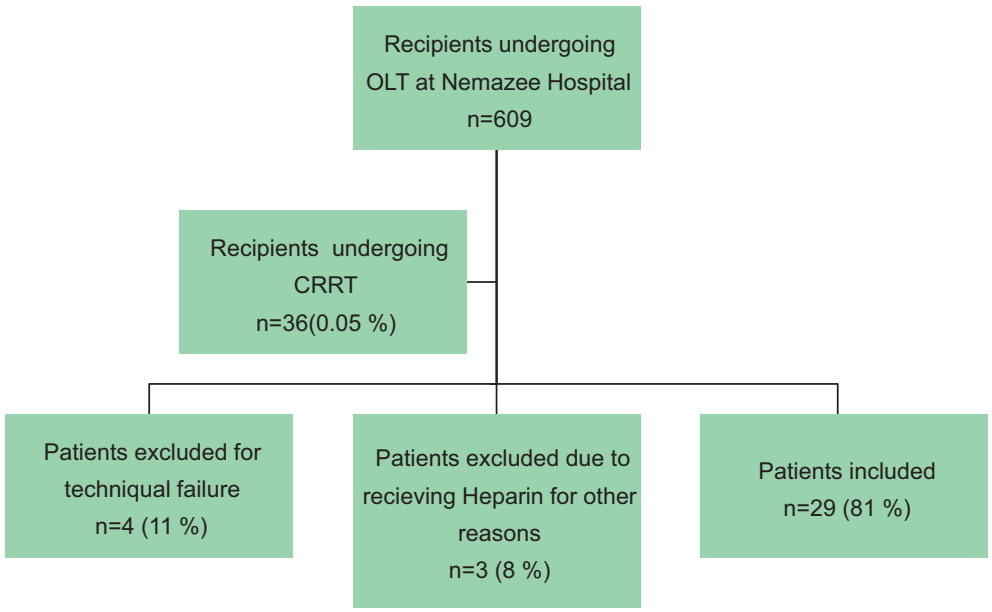


**Figure 1.** Flow Chart of the Study (Abbreviations: CRRT, continuous renal replacement therapy; OLT, orthotopic liver transplantation)

### Vascular Access

Vascular access in all cases was a 12-Fr, double lumen, and non-tunneled temporary dialysis catheter via internal jugular vein which was inserted in the operating room under direct ultrasonography guidance.

### Heparin Dosage

The CRRT setting was confirmed by the attending nephrologist and anesthesiologist. Following local protocols, depending on the first INR after the operation, heparin use was considered. For INR > 3, no anticoagulant was used in priming and maintenance. The total amount of heparin used was calculated at the end of the process.

### Statistical Method

According to the small sample size of our study (n < 30) and the absence of normality assumption, the degrees of correlation between variables were estimated by Spearman's rank correlation coefficient. All statistical analysis was performed with SPSS version 21.

## RESULTS

Among 29 enrolled patients, 14 (45%) were male. The median and IQR of participants' age were 45 and 20 years with the youngest patient 16 years old and the oldest 65. Recipients stayed in ICU at least for 2 days, and the longest stay was 25 days with median and IQR of 8 and 5 days, respectively.

Examining the etiology of patients' primary liver disease (Figure 2) indicated that autoimmune hepatitis with 21% (n = 6) was the most common cause among the participating patients. Cryptogenic with 17% (n = 5) and HBV with 14% (n = 4) were the next etiological factors among patients.

Table 1 shows different reasons for performing CRRT in the postoperative course of 29 liver transplant recipients. Accordingly, acute kidney injury (AKI) was the most common indication for CRRT.

The mean time for CRRT was about 5 ± 4 days, ranging from 1 to 17 Days. There were overall 98 successful dialysis sessions recorded in this study with mean circuit life span of 36 hours.

**Table 1.** The reasons for Performing CRRT in Postoperative Course Liver Transplant Recipients (n = 29)

| Etiology | n (%) |
|---|---|
| CKD | 2 (7) |
| HRS | 3 (10) |
| Primary Hyperoxaluria 1 | 1 (3) |
| PDF | 7 (24) |
| PNF | 7 (24) |
| AKI | 9 (31) |

Abbreviations: CRRT, continuous renal replacement therapy; HRS, hepatorenal syndrome; PDF, primary graft dysfunction; AKI, acute kidney injury; CKD, chronic kidney disease.

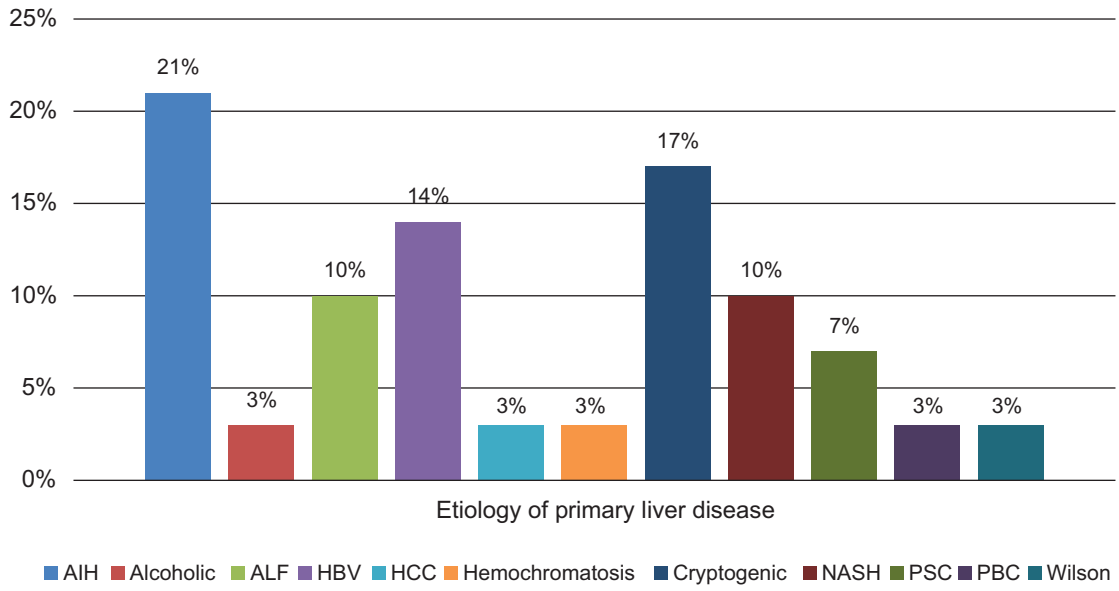


**Figure 2.** The Etiology of Primary Liver Disease in 29 Liver Transplant Recipients Undergoing CRRT in Their Postoperative Course (Abbreviations: AIH, Autoimmune hepatitis; ALF, acute liver failure; HCC, hepatocellular carcinoma; NASH, non-alcoholic steohepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis)

There were no episodes of anticoagulant-related bleeding complications. Thirteen (13.2%) episodes of premature circuit clotting occurred. The median and IQR dosage of total heparin used were calculated based on the nursing report, which were 25,000 and 35,000 units, ranging from 0 to 160,000 units. The median and IQR dose for heparin used per day for every recipient was 3,300 and 4,700 units respectively. Table 2 describes the distribution of heparin usage for recipients.

Table 3 shows the mean of the first post-op INR, platelet count, and PTT, which were 4.5, 70,000/mL, and 75seconds; respectively. In addition to the Spearman correlation, we found a significant correlation between the first and total heparin dose and the first post-op value of INR and PTT ($P < .05$, $P < .05$, $P < .001$, $P < .05$).

Figure 3 illustrates correlation between mean first post-op INR and total dose of heparin used per day. In-hospital mortality was 47%, and all other recipients survived for six months after discharge.

**Table 2.** Total Doses of Heparin Per Day (n = 29)

| Heparin Dose | n (%) |
|---|---|
| No Heparin | 6 (21) |
| 1 to 5000 | 15 (52) |
| 5001 to 10000 | 7 (24) |
| >10000 | 1 (3) |

## DISCUSSION

Premature circuit clotting is a major concern in CRRT. It increases cost, work effort, and morbidity.[1] Continuous renal replacement therapy demands an extracorporeal blood circuit without clotting. There are multiple tasks to be performed to increase circuit life span, including non-coagulant and coagulant measures. To reduce flow stasis, there should be well-functioning vascular access. Characteristics of catheters, including diameter, length, material, heparin coating, position, and insertion technique, all can influence the possibility of clotting.[1] Trained nursing staff with enough experience could reduce the rate of premature clotting. The modality of dialysis, CRRT machine characteristics, and filtration fraction can also influence this issue.

**Table 3.** Correlation Between Heparin Doses and Coagulation Parameters

| | Value* | First Heparin Dose | | Total Heparin Dose | |
|---|---|---|---|---|---|
| | | Correlation | *P* | Correlation | *P* |
| First Post-op INR | 4.50 ± 2.90 | -0.561 | < .05 | -0.624 | < .0001 |
| First Post-op Plt | 70,000 ± 58,000 | 0.103 | < .05 | 0.568 | > .05 |
| First Post-op PTT | 73.0 ± 32.0 | -0.530 | < .05 | -0.440 | < .05 |

*mean ± SD

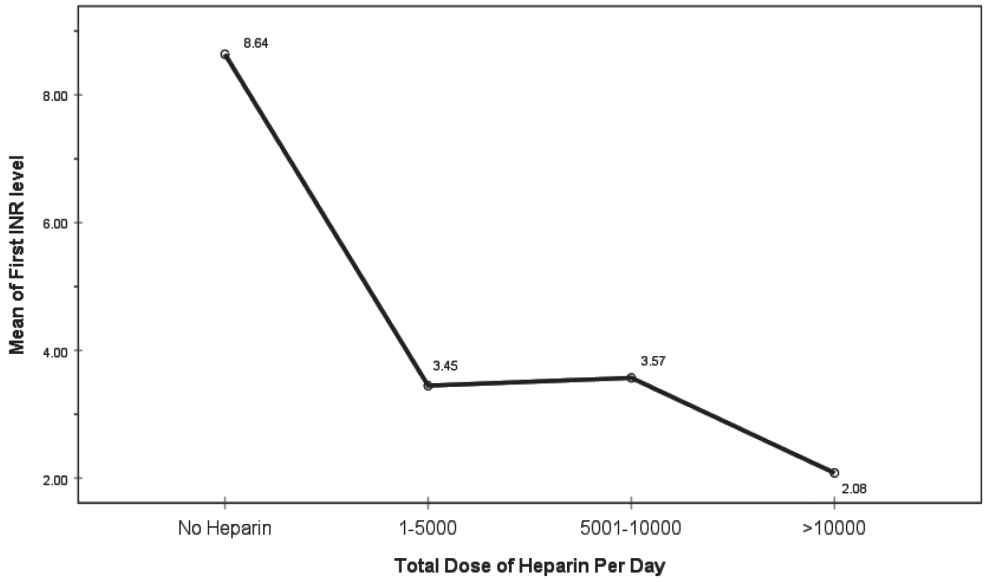


**Figure 3.** Correlation Between Mean of First INR and Total Heparin Dose/d

Anticoagulant is used to optimize circuit function in CRRT and to prevent or delay clotting by giving sufficient time for blood to return to circulation without obstruction in the circuit.[7,10] There are multiple anticoagulation methods. Unfractionated heparin, regional unfractionated heparin-protamine, low molecular weight heparin, heparinoids such as Danaparoid, thrombin antagonists, regional citrate, platelet-inhibiting agents, and prostacyclin[11] are alternatives in clinical practice.[7] Unfractionated heparin (UFH) acts by potentiating antithrombin Ш action by blocking factor ***X***a, and thrombin to prevent or delay circuit clotting. The advantages of UFH included its availability, cost, staff expertise and familiarity, reversibility with protamine sulfate, and being monitorable. However, the disadvantages are bleeding complications, resistance, and the probability of heparin-induced thrombocytopenia. Administration of heparin requires specific knowledge and monitoring. Therefore, it should be used with caution and with careful assessment of the likely risks and benefits in a transplant recipient. The usual starting dose of heparin is 2000 to 5000 IU (30 IU/kg) as a bolus, followed by 5 to 10 IU/kg/h. It is monitored by aPTT which should be maintained between 50 to 80 seconds or 1.5 to 2.5 times normal. It is continued by adding heparin to the circuit on an hourly basis or increasing the dose depending on the circuit status. If an obstruction occurs in the circuit, the heparin dose would be increased. Regional citrate anticoagulation (RCA) is another option for CRRT. Citrate is a chelator for ionized calcium, critical for coagulation and platelet aggregation.[12] It has less bleeding complication in comparison with systemic anticoagulation with the usual dosage.[13] The efficacy and safety of RCA in liver transplant recipients have been investigated in several studies.[14,15] Although citrate metabolism is impaired in liver cirrhosis, liver failure is not a contraindication for citrate usage in severely impaired hepatic function, but citrate monitoring is mandatory.[10]

Numerous studies have revealed CRRT as an essential and applicable measure for renal dysfunction in liver transplantation during surgery.[16,17] Also, it has been shown that CRRT improves the outcome in this population.[2,4,5] In postoperation period, liver transplant recipients have coagulopathy, thrombocytopenia, and hypertension. This emphasizes the need for a safer method during operation and afterward.

Uchino *et al.* conducted CRRT without the need for anticoagulants.[8] They found a correlation between the number of PLTs and the need for anticoagulants, and no significant difference in mean circuit patency life was observed. Tan *et al.* showed acceptable circuit life span after performing CVVH in high bleeding risk patients without the need for anticoagulants.[9] They did not find any correlation between INR, aPTT, PLT count, and circuit life span. There is no definite consensus on the anticoagulant dosage, either starting or maintenance. Therefore, the total heparin dosage is mostly higher than 30,000 units per day. Adding heparin to the priming solution provides some benefits. Pre-dilution preparation, using priming dose of heparin to the circuit and ongoing review chart of coagulation profile all promote a longer circuit life span. Hence, not all patients require heparin.

The heparin dose requirement was different between patinets based on the PLT count, INR, and PTT level, as it was in our study. Our study also indicates that the higher the INR, the less heparin was used, which was also true for PTT level. We did not find any statistically meaningful cut-off point for INR, PTT, or PLT in which no anticoagulation was needed above or below it, but clinically, INR above 3, PLT under 100,000/μL, and PTT 2.5 times longer than normal range needs less or no anticoagulant for CRRT. Our attention was mostly focused on the dosage of anticoagulant. Considering the given data, almost three forth of our patients received less than 5,000 units of heparin. Mean heparin dosage was 6,000 IU per session. Since the pre-dilution dose of heparin was only 5,000 units, most patients did not receive any anticoagulant during CRRT. Considering the mean circuit life span of 36 hours and circuit failure rate of about 13% without any episode of bleeding complication, it is practical to use less anticoagulants while on CRRT in this population.

High INR levels, especially in early post liver transplant are common. As the grafted liver starts to function, INR decreases. In our study, total heparin used was directly related to coagulation status of the recipient. The less heparin used, the less bleeding complications and side effects were observed. We had few surgical related bleeding complications.

However, this study had multiple limitations. It was a single center and retrospective study.

Another limition was that there are many factors other than anticoagulation dose which could affect coagulation during CRRT; including blood flow rate, replacement fluid volume, site of adding replacement fluid (pre-dilution or post dilution), mode of CRRT (hemofiltration versus hemodialysis) and the ultrafiltration volume, which we didn't consider in this study.

In summary, when using CRRT after OLT, the anticoagulant dose , needed to prevent premature circuit clotting could be either minimal or nearly zero, which has the advantage of less postoperative bleeding complication. In our experience, the higher the post-op PLT counts, the higher anticoagulant dosages were needed and the opposite was true for post-op INR and PTT levels.

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