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*Original Article*

# Effect of Heparin Dosage on Adequacy of Haemodialysis

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## ABSTRACT

Background: Adequate anticoagulation is essential for maintaining extracorporeal circuit patency during haemodialysis and preventing subclinical clotting that may reduce dialyzer efficiency and solute clearance. Empiric weight-based heparin regimens are widely used but may not account for inter-patient variability in anticoagulation requirements. Objective: To evaluate the effect of individualized heparin dosing guided by pharmacokinetic modelling and activated clotting time monitoring on haemodialysis adequacy compared with empiric dosing. Methods: This prospective observational study was conducted in the Nephrology Department of Pak Emirates Military Hospital from 1st March to 31st August 2023. Twenty-eight clinically stable maintenance haemodialysis patients receiving thrice-weekly dialysis were enrolled. Baseline dialysis was performed using empiric heparin regimens, followed by an intervention phase using individualized dosing. Outcomes included heparin dose, effective clearance, pre-dialysis urea, time-averaged concentration of urea, hematocrit, and normalized protein catabolic rate. Results: Mean heparin dose increased from 2175.3 ± 345.8 IU to 4461.7 ± 782.5 IU. Effective clearance improved from 209.2 ± 33.5 to 238.3 ± 34.7 mL/min, pre-dialysis urea decreased from 83.7 ± 16.4 to 74.4 ± 15.0 mg/dL, and time-averaged concentration of urea declined from 50.2 ± 22.5 to 39.3 ± 21.7 mg/dL, with all comparisons showing statistical significance. Hematocrit remained unchanged and no bleeding complications were reported. Conclusion: Individualized heparin dosing improved dialysis adequacy and solute control without compromising short-term safety, supporting monitoring-based anticoagulation as a practical alternative to empiric regimens. Keywords: haemodialysis, heparin, anticoagulation, dialysis adequacy, activated clotting time, urea kinetics

## INTRODUCTION

Chronic kidney disease (CKD) represents a significant and escalating global health burden, affecting approximately 10% of the population and progressing to end-stage renal disease (ESRD) in a substantial proportion of patients requiring renal replacement therapy (1). Haemodialysis (HD) remains the most widely utilized modality worldwide, supporting over 3.9 million patients as of 2024, with a disproportionately increasing burden observed in low- and middle-income regions such as South Asia due to rising prevalence of diabetes, hypertension, and cardiovascular disease (1,2). Despite advancements in dialysis technology, achieving optimal dialysis adequacy continues to be a major clinical challenge, directly influencing patient morbidity, mortality, and quality of life.

Dialysis adequacy is conventionally assessed using urea kinetic modeling parameters, including single-pool Kt/V and time-averaged concentration of urea (TACurea), which collectively reflect solute clearance and metabolic control (2). However, adequacy is multifactorial, influenced by dialyzer characteristics, blood and dialysate flow rates, ultrafiltration parameters, and critically, the efficiency of anticoagulation during extracorporeal circulation (3). Among these, anticoagulation with unfractionated heparin plays a pivotal role in maintaining circuit patency by preventing thrombus formation within the dialyzer and

tubing, thereby preserving effective membrane surface area and ensuring uninterrupted solute exchange (4,5).

The administration of heparin in haemodialysis requires a delicate balance. Suboptimal dosing predisposes to circuit clotting, fiber bundle obstruction, and reduced dialyzer efficiency, ultimately compromising solute clearance and increasing TACurea levels (6,7). Conversely, excessive anticoagulation elevates the risk of bleeding complications, particularly in patients with comorbid conditions or concurrent antithrombotic therapy (8). Despite this critical importance, current clinical practice in many dialysis units relies on empiric, weight-based heparin regimens that fail to account for inter-individual variability arising from factors such as vascular access type, comorbid disease burden, dialyzer geometry, and intrinsic coagulation status (8,9).

Emerging evidence suggests that pharmacokinetically guided and monitoring-based anticoagulation strategies, particularly those utilizing activated clotting time (ACT), may optimize heparin dosing by tailoring therapy to individual patient needs while minimizing complications (9). However, existing literature remains limited in quantifying the direct impact of individualized heparinization on dialysis adequacy metrics such as effective clearance and TACurea in real-world clinical settings, especially within resource-constrained environments where dialyzer reuse and cost considerations further complicate treatment optimization.

Given these gaps, there is a need for prospective evaluation of the relationship between heparin dosing strategies and dialysis adequacy outcomes. Understanding this relationship is essential for refining anticoagulation protocols, improving solute clearance, and enhancing overall treatment efficiency without increasing adverse events. Therefore, this study aims to assess the effect of pharmacokinetically guided, ACT-monitored individualized heparin dosing compared with empiric regimens on haemodialysis adequacy, with specific focus on solute clearance, TACurea, and treatment safety outcomes.

## MATERIALS AND METHODS

This prospective observational study was conducted in the Nephrology Department of Pak Emirates Military Hospital, Rawalpindi, Pakistan, over a six-month period from 1st March to 31st August 2023, following approval from the institutional ethical review committee. The study was designed to evaluate the impact of individualized heparin dosing, guided by pharmacokinetic modeling and activated clotting time (ACT) monitoring, on haemodialysis adequacy compared with conventional empiric regimens. The observational design was selected to reflect real-world clinical practice while allowing within-subject comparison between baseline and intervention phases.

A total of 28 patients undergoing maintenance haemodialysis were enrolled using a consecutive sampling approach. Eligible participants included clinically stable adult patients receiving thrice-weekly haemodialysis for at least one year. Patients with active bleeding disorders, recent use of anticoagulants other than heparin, or residual renal function were excluded to minimize confounding influences on coagulation dynamics and solute clearance. All participants provided informed consent prior to inclusion in the study.

Haemodialysis sessions were standardized across all participants to reduce procedural variability. Treatments were performed using Fresenius haemodialysis machines with high-flux polysulfone dialyzers and bicarbonate-based dialysate. Blood flow rates were maintained between 300 and 350 mL/min, while dialysate flow was fixed at 500 mL/min. Ultrafiltration targets were individualized based on clinical assessment but remained consistent for each patient across both study phases. Each patient was dialyzed using the same machine model, dialyzer type, and treatment duration throughout the study period to ensure internal consistency.

The study was conducted in two sequential phases within the same cohort. During the baseline phase, patients continued their routine empiric heparin regimen, typically consisting of a weight-based bolus dose (25–35 IU/kg) followed by maintenance infusion. In the intervention phase, heparin dosing was individualized using a pharmacokinetic model incorporating initial bolus dose, infusion rate, and estimated heparin clearance, with dose adjustments guided by serial ACT measurements. Target ACT values were maintained at approximately twice the baseline level, consistent with contemporary anticoagulation monitoring strategies. ACT was measured at 5 and 45 minutes following heparin administration to guide real-time dose modification, ensuring adequate anticoagulation while minimizing bleeding risk.

Biochemical and dialysis adequacy parameters were assessed at baseline and after implementation of individualized dosing. Blood urea nitrogen (BUN) levels were measured pre- and post-dialysis at monthly intervals. Urea kinetic modeling was applied to calculate single-pool Kt/V using the Daugirdas formula, while time-averaged concentration of urea (TACurea) was derived to reflect cumulative solute exposure. Effective dialyzer clearance (K) was calculated based on kinetic modeling, and total blood compartment volume was monitored to assess dialyzer performance. Nutritional status was evaluated using normalized protein catabolic rate (nPCR), and hematocrit levels were measured to monitor hematologic stability and detect potential bleeding complications.

All variables were operationally defined prior to analysis, with dialysis adequacy primarily assessed through changes in TACurea and effective clearance. Potential confounders, including patient weight, dialysis duration, and treatment parameters, were controlled through protocol standardization across both phases. The within-subject study design further minimized inter-individual variability.

Statistical analysis was performed using appropriate software, with continuous variables expressed as mean ± standard deviation. Paired comparisons between baseline and intervention phases were conducted using two-tailed Student's t-test for dependent samples. Pearson correlation analysis was applied to assess the relationship between heparin dose and TACurea. Regression analysis was conducted to identify predictors of improved dialysis clearance. A p-value of less than 0.05 was considered statistically significant. No missing data were observed during the study period, and all analyses were conducted on complete datasets.

Ethical approval was obtained prior to study initiation, and the study adhered to principles of patient confidentiality, data integrity, and reproducibility. Standardized protocols for data collection, dialysis delivery, and laboratory measurements were maintained throughout the study to ensure methodological rigor and allow reproducibility in similar clinical settings.

## RESULTS

A total of 28 maintenance haemodialysis patients were included in the final analysis. The cohort had a mean age of 47.4 ± 13.2 years, with an observed range of 25 to 80 years, and a mean body weight of 78.6 ± 17.6 kg, ranging from 50.0 to 117.6 kg. All enrolled participants completed both study phases and were included in the paired comparison of empiric versus individualized heparin dosing.

*Table 1. Baseline Characteristics of the Study Population (n = 28)*

| Variable | Value |
|---|---|
| Sample size, n | 28 |
| Age, years (mean ± SD) | 47.4 ± 13.2 |
| Age range, years | 25–80 |
| Body weight, kg (mean ± SD) | 78.6 ± 17.6 |
| Body weight range, kg | 50.0–117.6 |

Following pharmacokinetically guided heparin modeling, the mean heparin dose increased from 2175.3 ± 345.8 IU to 4461.7 ± 782.5 IU, corresponding to an absolute rise of 2286.4 IU and a relative increase of 106.2%. This dose intensification was accompanied by a statistically significant improvement in effective dialyzer clearance, which increased from 209.2 ± 33.5 mL/min to 238.3 ± 34.7 mL/min, yielding a mean

gain of 29.1 mL/min or 13.9%. These findings indicate that individualized anticoagulation was associated with better extracorporeal circuit performance and more efficient dialysis delivery.

Pre-dialysis urea declined from 83.7 ± 16.4 mg/dL to 74.4 ± 15.0 mg/dL after intervention, representing an absolute reduction of 9.3 mg/dL and an 11.2% decrease. Similarly, TACurea fell from 50.2 ± 22.5 mg/dL to 39.3 ± 21.7 mg/dL, corresponding to a reduction of 10.9 mg/dL and a 21.7% improvement. The larger proportional reduction in TACurea compared with single pre-dialysis urea suggests that individualized heparinization improved not only session-level clearance but also cumulative inter-dialytic solute control.

Hematocrit remained unchanged at 28.4 ± 3.9% before and after intervention, indicating hematologic stability and supporting the absence of overt bleeding complications during the monitored dosing phase. Nutritional adequacy, assessed by normalized protein catabolic rate, remained essentially stable at 0.9 ± 0.3 g/kg/day in both phases, although the manuscript reports a small calculated percentage increase of 2.2% with statistical significance. This pattern suggests that while optimized heparinization materially improved dialysis adequacy parameters, its short-term influence on nutritional indices was minimal.

*Table 2. Comparison of Hemodialysis Parameters Before and After Individualized Heparin Modeling*

| Variable | Pre-intervention (mean ± SD) | Post-intervention (mean ± SD) | Mean Difference | % Change | p-value |
|---|---|---|---|---|---|
| Heparin dose, IU | 2175.3 ± 345.8 | 4461.7 ± 782.5 | +2286.4 | +106.2% | <0.05 |
| Effective clearance, mL/min | 209.2 ± 33.5 | 238.3 ± 34.7 | +29.1 | +13.9% | <0.05 |
| Pre-dialysis urea, mg/dL | 83.7 ± 16.4 | 74.4 ± 15.0 | -9.3 | -11.2% | <0.05 |
| TACurea, mg/dL | 50.2 ± 22.5 | 39.3 ± 21.7 | -10.9 | -21.7% | <0.05 |
| Hematocrit, % | 28.4 ± 3.9 | 28.4 ± 3.9 | 0.0 | 0.0% | NS |
| nPCR, g/kg/day | 0.9 ± 0.3 | 0.9 ± 0.3 | ~0.0 | +2.2% | <0.05* |

*NS = not significant. The manuscript reports statistical significance for nPCR despite no visible rounded change in mean values; this should be retained carefully and interpreted as statistically significant but clinically negligible based on the presented aggregates.

Taken together, the tabulated findings show a coherent pattern in which higher individualized heparin exposure was associated with better dialysis adequacy without detectable compromise in safety markers. The most pronounced benefit was observed in TACurea, which decreased by 21.7%, followed by the 13.9% rise in effective clearance and the 11.2% decline in pre-dialysis urea. In contrast, hematocrit showed no measurable change, supporting the manuscript's statement that no bleeding complications were observed. Overall, these data support the interpretation that monitoring-guided heparin optimization improved dialyzer patency and solute removal while maintaining short-term hematologic safety.

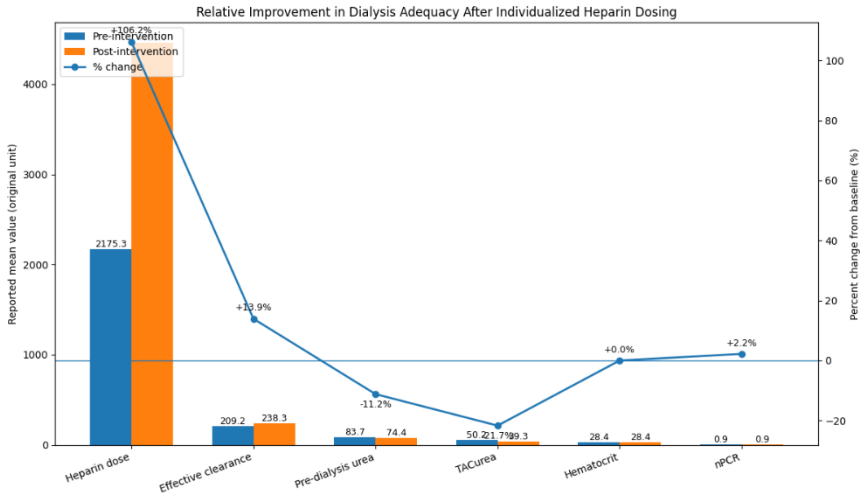


*Figure 1 Relative Improvement in Dialysis Adequacy After Individualized Heparin Dosing*

The integrated visualization demonstrates that individualized heparin dosing was associated with a marked 106.2% increase in mean heparin exposure, from 2175.3 IU to 4461.7 IU, accompanied by clinically favorable shifts in dialysis adequacy parameters. Effective clearance increased by 13.9%, rising from 209.2 to 238.3 mL/min, while pre-dialysis urea declined by 11.2%, from 83.7 to 74.4 mg/dL. The most pronounced adequacy gain was observed in TACurea, which decreased by 21.7%, from 50.2 to 39.3 mg/dL, indicating substantially improved cumulative solute control. In contrast, hematocrit remained unchanged at 28.4%, supporting short-term hematologic safety, and nPCR showed only a minimal 2.2% increase, remaining at 0.9 g/kg/day on rounded reporting. Collectively, the pattern indicates that the increase in anticoagulation intensity was accompanied by meaningful improvement in solute clearance and uremic burden without evidence of measurable hematologic compromise in the reported aggregates.

## DISCUSSION

The present study demonstrated that individualized heparin dosing guided by pharmacokinetic modelling and activated clotting time monitoring significantly improved haemodialysis adequacy compared with empiric weight-based anticoagulation. The intervention was associated with a 106.2% increase in mean heparin dose, a 13.9% increase in effective clearance, an 11.2% reduction in pre-dialysis urea, and a 21.7% reduction in TACurea, while hematocrit remained unchanged and no bleeding complications were observed. These findings support the concept that anticoagulation adequacy is not merely a technical adjunct to dialysis delivery but an essential determinant of extracorporeal circuit efficiency and overall solute control. In routine haemodialysis, inadequate anticoagulation may permit subclinical clot formation within the dialyzer and tubing, reducing functional membrane surface area and impairing solute transfer even in the absence of complete circuit failure. The observed improvement in clearance after individualized heparinization therefore appears biologically plausible and clinically meaningful, particularly because it was accompanied by lower cumulative urea burden rather than only isolated session-level changes.

The reduction in TACurea is especially important because this parameter reflects time-averaged solute exposure between dialysis sessions and thus captures the broader metabolic adequacy of treatment more comprehensively than a single pre-dialysis biochemical value. In the present study, TACurea decreased from 50.2 ± 22.5 mg/dL to 39.3 ± 21.7 mg/dL, representing a relative improvement of 21.7%, which exceeded the proportional fall observed in pre-dialysis urea alone. This pattern suggests that tailored anticoagulation improved sustained solute control rather than simply producing a modest biochemical shift during isolated treatments. Contemporary mechanistic evidence supports this interpretation. Reduced dialyzer blood compartment volume and circuit thrombogenicity have been associated with excessive clot formation during haemodialysis, leading to compromised membrane performance and reduced clearance efficiency (10). By minimizing these effects, individualized heparinization likely preserved dialyzer patency and facilitated more complete delivery of prescribed dialysis dose.

Another notable finding was the maintenance of hematologic safety despite substantial escalation in anticoagulation intensity. Hematocrit remained stable at 28.4 ± 3.9% across both phases, and no bleeding events were reported, indicating that monitoring-based dose adjustment can permit higher effective heparin exposure without measurable short-term hemorrhagic compromise. This is clinically relevant because the reluctance to intensify heparin dosing in dialysis practice often stems from concern regarding bleeding complications, particularly in fragile patients with multiple comorbidities. Recent clinical work evaluating anticoagulation strategies in haemodialysis has similarly emphasized that individualized protocols guided by circuit performance and bedside coagulation monitoring can optimize dialysis delivery while maintaining safety margins in patients at variable bleeding risk (11,12). Reviews of anticoagulation management have also underscored that bleeding risk should not be inferred solely from dose magnitude but rather from the interaction between patient-specific susceptibility, vascular access characteristics, and monitoring strategy (13).

The negative association described between heparin dose and TACurea further strengthens the interpretation of a dose-dependent anticoagulation effect on dialysis adequacy. Although the exact correlation coefficient was not reported in the manuscript, the observed pattern indicates that patients receiving greater heparin dose adjustment experienced larger reductions in cumulative urea burden. This aligns with recent observations that thrombotic and clotting-related events remain common among haemodialysis patients despite standard anticoagulation approaches, implying that conventional empiric regimens may frequently underperform in preventing clinically silent circuit thrombosis (14). In practical terms, the findings suggest that routine dialysis units may underestimate the adequacy cost of subtherapeutic heparinization, particularly when overt clotting is absent but dialyzer efficiency is progressively reduced.

The effect of individualized anticoagulation on nutritional adequacy appeared limited. Although nPCR showed a nominal increase of 2.2% and was reported as statistically significant, the rounded mean value remained 0.9 ± 0.3 g/kg/day before and after intervention, indicating that the magnitude of change was clinically negligible. This suggests that while improved anticoagulation may enhance solute kinetics, it is unlikely to exert a major short-term influence on nutritional status in isolation. Hemocoagulation and extracorporeal circuit optimization may affect metabolic parameters indirectly, but broader nutritional outcomes are shaped by dietary intake, inflammation, catabolic state, residual illness burden, and dialysis vintage (15,16). Therefore, the principal benefit of individualized heparin dosing in this study lies in treatment efficiency and solute clearance rather than meaningful alteration of short-term protein catabolism.

The findings also highlight the limitations of fixed empiric heparin regimens in maintenance haemodialysis. Considerable inter-individual variability exists in anticoagulation requirement, influenced by body weight, vascular access type, comorbid cardiovascular disease, inflammatory status, and dialyzer-related thrombogenicity. Contemporary nephrology literature increasingly supports individualized anticoagulation decision-making in patients with kidney failure, especially where thrombotic and bleeding risks coexist and cannot be accurately managed through uniform protocols (17). The present study extends that rationale by showing that individualization is not only theoretically desirable but also operationally feasible in a real-world clinical unit and associated with measurable improvement in dialysis adequacy outcomes.

From a broader clinical perspective, optimizing anticoagulation may have implications beyond circuit patency alone. Persistent under-anticoagulation may contribute to repeated microthrombotic burden, inefficient treatments, avoidable blood loss from clotted circuits, and increased resource use, particularly in settings where dialyzer reuse and treatment cost remain relevant concerns. At the same time, excessive anticoagulation may expose patients to bleeding complications. Recent critical reviews in end-stage renal disease have emphasized the need to strike a precise balance between thrombotic protection and hemorrhagic safety in anticoagulation management (18). The present findings suggest that ACT-guided pharmacokinetic dosing may provide such a balance by allowing dose escalation where needed without compromising short-term hematologic stability.

Several limitations should be acknowledged when interpreting these results. The study was conducted at a single center with a relatively small sample of 28 patients, which may limit generalizability to other dialysis populations and practice settings. The observational within-subject design strengthens internal comparison but cannot entirely eliminate residual confounding. In addition, detailed regression outputs, confidence intervals, and subgroup analyses were not reported, limiting the precision with which treatment effect heterogeneity can be assessed. The study also focused on short-term adequacy and safety markers; therefore, long-term clinical outcomes such as hospitalization, access thrombosis, cardiovascular events, and mortality remain unknown. Nevertheless, the consistency of improvement across multiple adequacy parameters, together with the absence of bleeding complications, provides a

strong signal that individualized heparinization may represent a clinically valuable refinement of routine dialysis practice.

Overall, this study provides evidence that monitoring-based individualized heparin dosing can substantially improve haemodialysis adequacy by enhancing effective clearance and reducing cumulative solute burden without observable short-term safety trade-offs. These findings support movement away from rigid empiric anticoagulation strategies toward more responsive, patient-specific protocols that account for variability in circuit thrombogenicity and coagulation response. Larger multicenter studies with longer follow-up and more comprehensive statistical reporting are needed to confirm these results and determine whether improved adequacy through optimized anticoagulation translates into better long-term patient outcomes.

## CONCLUSION

Individualized heparin dosing guided by pharmacokinetic modelling and activated clotting time monitoring significantly improved haemodialysis adequacy in this study, as evidenced by higher effective clearance and lower pre-dialysis urea and TACurea levels, while maintaining stable hematocrit and showing no bleeding complications. These findings indicate that tailored anticoagulation is more effective than empiric weight-based heparinization for preserving extracorporeal circuit patency and optimizing solute removal. Incorporation of monitoring-based heparin adjustment into routine maintenance haemodialysis practice may therefore enhance treatment efficiency and metabolic control without compromising short-term safety.

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