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Editorial

Cell Therapy in Chronic Kidney Disease: Between Hope and Challenges

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Chronic kidney disease (CKD) continues to represent a major global health challenge, affecting hundreds of millions worldwide and contributing substantially to morbidity, mortality, and healthcare costs.[1] The number of CKD patients increases with rising prevalence due to aging populations and increasing rates of diabetes and hypertension. Despite advances in medical care, CKD is still incurable, and current therapies largely aim to slow progression rather than reverse damage. The disease is typically progressive, often culminating in end-stage kidney disease that necessitates dialysis or transplantation. While these interventions prolong life, they do not restore normal kidney function and carry significant limitations such as reduced quality of life, donor organ shortages, and high treatment costs. These constraints underscore the urgent need for novel therapeutic approaches capable of halting or reversing CKD progression.[2]

In recent years, cell-based therapies have emerged as promising candidates in regenerative nephrology.[2] Preclinical studies have shown that stem cells, particularly mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), possess potent immunomodulatory, anti-inflammatory, and anti-fibrotic properties that can create a renal microenvironment conducive to repair.[1,3] These properties have been linked to reduced renal fibrosis, enhanced tubular regeneration, and improved functional outcomes in experimental models of CKD.[2,3] Cell therapy for CKD is still in an investigational phase and has not yet become a standard treatment option. Clinical trials have shown promising safety profiles and some indications of benefit, such as reduced incidence of dialysis or death at one year with autologous CD34+ cell therapy in CKD patients. However, changes in kidney function parameters remain limited, and outcomes have been inconsistent across studies due to small sample sizes and short follow-up durations.

Early-phase clinical trials in humans have produced encouraging results, including improvements in estimated glomerular filtration rate (eGFR) and reductions in biomarkers of renal injury following MSC administration.[1,4] Nonetheless, significant barriers remain before these therapies can be widely implemented. Concerns include potential immune rejection, tumorigenic risk, high manufacturing costs, and a lack of standardized protocols to ensure consistent safety and efficacy.[4,5] In addition, ethical and regulatory frameworks require further refinement to address patient selection criteria, trial oversight, and equitable access.[2]

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From our perspective, cell therapy has the potential to redefine the management of CKD, provided that its development is guided by robust scientific evidence and validated through large, well-designed multicentre clinical trials.[4,5] Achieving this will require coordinated efforts from clinicians, researchers, biotechnological companies, and policymakers.[2]

Looking forward, the true value of cell therapy may lie not only in slowing disease progression but in restoring meaningful kidney function, shifting the paradigm from disease maintenance to genuine organ repair. Realizing this vision will demand sustained research funding, standardized methodologies, and a clear regulatory pathway to ensure these therapies are delivered safely, effectively, and equitably to the patients who need them most.[4] In summary, cell therapy in CKD is an emerging field with significant potential to transform treatment by going beyond symptom management toward organ regeneration and functional preservation. Continued research is needed to address technical and clinical challenges before widespread clinical application can be realized.

Declarations

Competing interest

The author declares no conflict of interest.

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Original Article

The Effect of Hemodialysis Adequacy on Inflammatory Status in Stage 5 Chronic Kidney Disease Patients (A Study at Dr. Adhyatma, MPH Regional Hospital, Semarang)

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a critical global health issue, particularly Stage 5 CKD, where kidney function is severely impaired. Hemodialysis, essential for managing such patients, aims to remove waste and excess fluids. Chronic inflammation, common among CKD5-HD patients, heightens cardiovascular risks and worsens quality of life. Hemodialysis adequacy, measured by the Kt/V ratio, plays a vital role in outcomes, yet its relationship with inflammatory markers, such as Hs-CRP, albumin, and TIBC, remains unclear.

Objective: This study aimed to evaluate the relationship between hemodialysis adequacy, as reflected by Kt/V values, and inflammatory markers such as C-reactive protein (CRP), albumin, and total iron binding capacity (TIBC) in CKD stage 5 patients undergoing hemodialysis, providing insights into optimizing dialysis protocols to mitigate inflammation.

Methods: A cross-sectional study of 45 CKD5-HD patients assessed Kt/V values and inflammatory markers (Hs-CRP, albumin, TIBC). Data were analyzed using Shapiro-Wilk, Independent t-tests, or Mann-Whitney U tests based on data distribution.

Results: The mean Kt/V value was 1.31 ± 0.21. Lower Kt/V values were significantly associated with elevated Hs-CRP levels ($p = 0.018$). No significant differences in Kt/V values were observed concerning albumin ($p = 0.546$) or TIBC ($p = 0.523$). Correlations between Hs-CRP and albumin or TIBC were non-significant ($p = 1.000$).

Conclusion: Adequate hemodialysis, reflected in optimal Kt/V values, is crucial for reducing systemic inflammation marked by Hs-CRP. Albumin and TIBC levels showed no significant association, underscoring the multifactorial nature of inflammation in CKD5 patients.

Keywords: Hs-CRP, Albumin, Kt/V, Adequacy, Hemodialysis, Inflammation.

Introduction

Chronic Kidney Disease (CKD) is a serious global health problem, especially Stage 5 CKD, which requires dialysis or kidney transplantation to survive. In 2021, more than 850 million people worldwide were affected by kidney disease, far exceeding the prevalence of diabetes, cancer, or HIV/AIDS.[1] In Indonesia, the 2018 Basic Health Research (Riskesdas) reported a CKD prevalence of 0.38% (3.8 cases per 1,000 population), with 60% requiring dialysis.[2] The 2020 Indonesian Kidney Registry identified hypertensive kidney disease as the leading cause of CKD requiring dialysis, followed by diabetic nephropathy and glomerulopathy. Chronic inflammation in patients undergoing

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hemodialysis (CKD5-HD) contributes significantly to increased morbidity, mortality, and decreased quality of life, often due to its association with cardiovascular disease.[3]

Hemodialysis is a life-saving treatment for patients with CKD-5, which aims to remove waste products and excess fluid from the blood when the kidneys can no longer perform these functions. In contrast, hemodialysis effectiveness is mostly the same as adequacy, differs among patients, and is essential to reduce complications.[4,5] The Kt/V ratio is usually used to measure hemodialysis adequacy, which shows the efficiency of the dialysis process in removing urea from the blood. Maximum Kt/V values are related to improved patient outcomes, whereas inadequate dialysis causes adverse effects, such as increased inflammation.[6–8]

Inflammation among CKD5-HD patients is frequently measured through biomarkers like high-sensitivity C-reactive protein (Hs-CRP), albumin, and Total Iron Binding Capacity (TIBC).[9–11] Hs-CRP is the standard marker used to measure this inflammation, which is thought to be caused by the chronic kidney disease itself, the type of dialysis filter, and the hemodialysis procedure. The primary reason Hs-CRP is used as a marker is because high levels are a strong predictor of poor outcomes. Multiple studies have confirmed that elevated Hs-CRP in CKD5-HD patients is linked to a higher risk of hospitalization, death from cardiovascular disease, and death from any cause.[12]

The Hs-CRP levels showed systemic inflammation related to a higher risk of cardiovascular events.[6,13,14] Atherosclerosis is recognized as an inflammatory disease, and this type of chronic inflammation is very common in patients on hemodialysis, affecting 30-65% of them. Albumin and TIBC are also employed to measure nutritional status and inflammation, where hypoalbuminemia commonly shows malnutrition and inflammatory states. The connection between inflammatory markers and hemodialysis adequacy indicates an active investigation area, with studies showing that inadequate dialysis could exacerbate inflammation.[13,15,16]

Despite the importance of hemodialysis adequacy, there is limited agreement about the optimal Kt/V threshold needed to control inflammation effectively in CKD5-HD patients. Previous studies have shown various results, including a strong correlation between low Kt/V values and developed inflammation and no significant association. This discrepancy underlines the need for further research to clarify the role of hemodialysis adequacy in managing inflammation in specific patients.

This study aims to explore the hemodialysis adequacy effect with Kt/V on the inflammatory status of CKD5-HD patients, especially Hs-CRP, albumin, and TIBC levels. The study, through analysis of the relationship among the variables, aims to show the optimizing dialysis adequacy to reduce chronic inflammation in the vulnerable patient population. To conclude, understanding the effects of hemodialysis adequacy on inflammation gains treatment protocols and better results for patients with CKD Stage 5. By emphasizing critical inflammatory indicators and their relationship to Kt/V values, the study supports continuous efforts to improve the care for patients with hemodialysis.

Methods

Design and participants

The study was conducted with a cross-sectional design, which is fit to analyze the relationships among variables at a single point in time. The target population consisted of patients diagnosed with Chronic Kidney Disease Stage 5 (CKD5) with routine hemodialysis (HD) treatment at Dr. Adhyatma MPH Hospital, Semarang. The 45 patients selected according to certain inclusion criteria, such as patients with hemodialysis for at least three months and who had stable clinical conditions, with acute infections, malignancies, or other conditions that could independently impact inflammatory markers, were excluded to ensure the result's validity. The intervention received by the

research subjects was hemodialysis sessions performed twice a week, with a duration of 4.5 hours per session, and using a high-flux dialyzer. No patients dropped out during the study. All patients undergo a complete dialysis session in HD.

Study Covariate

The cross-sectional design is used to analyze the relationship among variables at one point in time. The 45 patients with CKD on stage 5 with routine hemodialysis at Dr. Adhyatma MPH Hospital, Semarang. The inclusion criteria required patients with hemodialysis for at least three months with stable clinical conditions, with acute infections, malignancies, or conditions that might affect inflammatory markers, to be excluded, to maintain the validity of the results.

Data collected encompassed demographic information (age, sex, underlying causes of kidney disease, duration of hemodialysis, and type of vascular access) alongside key variables: hemodialysis adequacy (measured via Kt/V ratio) and inflammatory indicators (Hs-CRP, albumin, TIBC). Blood samples were obtained prior to scheduled dialysis sessions and analyzed with standardized methods. Kt/V values were calculated using Watson's formula, incorporating patient weight and dialysis duration to assess the adequacy of treatment.

Statistical analysis

Statistical analysis was performed to determine the relationship between hemodialysis adequacy and the inflammatory markers. The data was processed using SPSS 17.0 statistical analysis. The Shapiro-Wilk test was first used to assess the normality of the data distribution. Depending on the results, either the Independent t-test or the Mann-Whitney U test was employed to compare the Kt/V values between groups with different levels of inflammatory markers. A p-value of less than 0.05 was considered statistically significant. Additionally, correlation analyses were conducted to explore potential associations between Hs-CRP, albumin, and TIBC levels. These analyses aimed to identify whether variations in hemodialysis adequacy could be linked to changes in the patients' inflammatory status.

Results

Patient selection

1. Baseline Characteristics

The study involved 45 chronic hemodialysis patients, with a mean age of 50.51 ± 13.05 years, ranging from 20 to 78 years. The male participants constituted 55.6% (n=25), while females made up 44.4% (n=20). The average duration of hemodialysis was 3.74 ± 3.07 years, with a median of 2.5 years (0.67 to 11 years). The majority of patients had hypertension as the primary cause of their kidney disease (62.2%, n=28), followed by diabetes mellitus (22.2%, n=10), and a combination of hypertension and diabetes mellitus (15.6%, n=7). In terms of vascular access, 97.8% (n=44) of the patients used an arteriovenous (AV) shunt, while only 2.2% (n=1) used a double lumen catheter. The baseline characteristics can be seen in Table 1.

Table 1. Baseline Characteristics of The Patients

Characteristic	Value
Total Patients	45
Age (years)	50.51 ± 13.05
Age Range (years)	20 - 78
Gender	
- Male	25 (55.6%)
- Female	20 (44.4%)
Duration of Hemodialysis (years)	3.74 ± 3.07
Hemodialysis Duration Range (years)	0.67 - 11
Cause of Kidney Disease	
- Hypertension	28 (62.2%)
- Diabetes Mellitus	10 (22.2%)
- Hypertension & Diabetes Mellitus	7 (15.6%)
Vascular Access	
- AV Shunt	44 (97.8%)
- Double Lumen	1 (2.2%)

2. Inflammatory Parameters

The inflammatory status was assessed using Hs-CRP (high-sensitivity C-reactive protein), with 57.8% (n=26) of the patients classified as having high Hs-CRP levels, 24.4% (n=11) with moderate levels, and 17.8% (n=8) with low levels. Albumin levels were predominantly normal in 97.8% (n=44) of the patients, with only 2.2% (n=1) having elevated levels. For TIBC (Total Iron Binding Capacity), 71.1% (n=32) of the patients had normal levels, while 28.9% (n=13) had reduced levels. Inflammatory Parameters can be seen in Table 2.

Table 2. Inflammatory Parameters in the study patients

Inflammatory Parameter	**All Patients** (N=45)	**Patients with High Hs-CRP** (n=26)	**Patients with Low/Medium Hs-CRP** (n=19)	**p-value**
Hs-CRP Levels (n, %)				
High	26 (57.8%)	26 (100%)	0 (0%)	-
Medium	11 (24.4%)	0 (0%)	11 (57.9%)	
Low	8 (17.8%)	0 (0%)	8 (42.1%)	
Albumin Levels (n, %)				
High	1 (2.2%)	1 (3.8%)	0 (0%)	1.000
Normal	44 (97.8%)	25 (96.2%)	19 (100%)	
TIBC Levels (n, %)				
Low	13 (28.9%)	9 (34.6%)	4 (21.1%)	1.000
Normal	32 (71.1%)	17 (65.4%)	15 (78.9%)	

3. Hemodialysis Adequacy

Hemodialysis adequacy was measured using the Kt/V parameter, with a mean value of 1.31 ± 0.21, and a median of 1.29 (0.94 to 1.87). The study revealed significant differences in Kt/V values based on Hs-CRP levels, where patients with high Hs-CRP levels had lower Kt/V values (mean ± SD: 1.26 ± 0.18) compared to those with normal Hs-CRP levels (mean ± SD: 1.42 ± 0.24), with ap-value of 0.018, indicating a significant difference ($p < 0.05$). However, there were no significant differences in Kt/V values based on Albumin ($p = 0.546$) and TIBC ($p = 0.523$) levels. Additionally, correlation tests showed no significant relationship between Hs-CRP and Albumin ($p = 1.000$) or between Hs-CRP and TIBC ($p = 1.000$). Hemodialysis adequacy can be seen in Table 3.

Table 3. Correlation Tests

Parameter	Mean ± SD	Median (Range)	p-Value	Significance
Overall Kt/V	1.31 ± 0.21	1.29 (0.94 to 1.87)	-	-
Kt/V by Hs-CRP Levels			0.018	Significant difference ($p < 0.05$)
High Hs-CRP	1.26 ± 0.18	-	-	-
Normal Hs-CRP	1.42 ± 0.24	-	-	-
Kt/V by Albumin Levels	-	-	0.546	No significant difference ($p > 0.05$)
Kt/V by TIBC Levels	-	-	0.523	No significant difference ($p > 0.05$)
Correlation Tests	-	-	-	No significant relationship
Hs-CRP and Albumin	-	-	1.000	-
Hs-CRP and TIBC	-	-	1.000	-

Discussion

This study investigated the effect of hemodialysis adequacy, as measured by Kt/V, on inflammation in patients with Chronic Kidney Disease Stage 5 (CKD5) undergoing regular hemodialysis. The results revealed a significant association between Kt/V values and high-sensitivity C-reactive protein (Hs-CRP) levels, a marker of systemic inflammation. Patients with lower Kt/V values, indicating inadequate hemodialysis, were found to have optimum Hs-CRP levels. The suggestion is that inadequate dialysis could increase inflammation, which is a problem for cardiovascular complications and decreased quality of life in CKD5 patients.

Interestingly, the study shows no difference in significance in Kt/V values when stratified using other inflammation markers, including Albumin and Total Iron Binding Capacity (TIBC), that are related to nutritional status and iron metabolism, and the lack of significant connection with Kt/V indicates the levels might be affected by factors other than dialysis adequacy. It highlights the complexity of the inflammatory process in CKD5 patients.

Furthermore, the significant association between Hs-CRP, albumin, and TIBC further highlights the multifaceted nature of inflammation in CKD5 patients. While Kt/V is an essential factor in managing inflammation, from Hs-CRP levels, which may be another factor in engaging the broader inflammatory status in the patients. The findings highlight the comprehensive approach to managing inflammation, which involves addressing other factors to elevated Hs-CRP levels.

In this study, we selected CRP, albumin, and TIBC as inflammatory markers based on their clinical relevance and accessibility in routine practice. CRP was chosen as a representative acute-phase reactant that rises in response to systemic inflammation and has been widely used in previous studies evaluating inflammation in hemodialysis patients. Albumin and TIBC, although not acute-phase reactants, were included as negative inflammatory markers reflecting chronic inflammation and nutritional status, which are also frequently altered in chronic kidney disease and dialysis populations. The finding that CRP, but not albumin or TIBC,

was associated with dialysis adequacy may reflect the difference in sensitivity and temporal dynamics of these markers. While CRP levels can rapidly respond to changes in inflammatory status and may be influenced by dialysis clearance, albumin and TIBC are more stable and may be affected by other non-inflammatory factors such as liver function or malnutrition. We acknowledge that CRP levels can be affected by dialysis modality, particularly with convection-based therapies; however, all patients in our study underwent conventional hemodialysis, thereby minimizing this confounder.

To conclude, the study emphasizes the importance of achieving adequate hemodialysis with Kt/V to manage systemic inflammation in patients with CKD5. However, the study also focuses on gaps in how dialysis adequacy connects with other markers of inflammation like Albumin and TIBC. Future studies should investigate these connections more deeply and likely identify further mechanisms that can be focused on to enhance the treatment outcomes. Therefore, it may be possible to develop more effective and targeted treatment protocols, ultimately gaining the patients' quality of life with hemodialysis.

Conclusion

This study shows that hemodialysis adequacy using Kt/V significantly affects inflammation in patients with CKD5 with hemodialysis, particularly as indicated by Hs-CRP levels. Patients with inadequate dialysis showed lower Kt/V values, with higher levels of systemic inflammation. However, no significant association was found between Kt/V and other inflammation markers, such as albumin and TIBC. The findings suggest that to optimize dialysis adequacy, it is essential to manage inflammation in CKD5 patients; other factors and markers must be considered in treatment strategies. Further studies are needed to explore the associations and improve care and outcomes for CKD5 patients.

Limitations of the Study

However, several limitations to this study should be acknowledged. First, the cross-sectional design limits the capacity to establish causality between hemodialysis adequacy and inflammation. The data provides a snapshot of the relationship at a single point in time, so it is difficult to determine the changes in Kt/V over time that may differentially impact inflammatory markers. Moreover, the modest sample of the study is 45 patients, which may limit the relevance of the result to the general CKD5 patient population. There are other possible influencing factors, including comorbid conditions or variations in dialysis protocols, that were not fully completely considered in the analysis.

Declarations

Ethics approval and consent to participate

This study adhered to the guidelines for clinical research and received approval from the Ethics Committee of the dr. Adhyatma Hospital, under reference number: 088/KEPK.EC/IX/2023.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: DW. Design: DW. Control/supervision: DLP, L. Data collection/ processing: DW. Analysis/interpretation: DW, DLP. Literature review: DW, DLP, L, AN, AA, SC. Writing the article: DW, DLP, L, AN, AA, SC. Critical review: DW, DLP, L, AN, AA, SC. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Profile of Catheter-Related Infections in Hemodialysis Patients with Double Lumen Catheters at Dr. Reksodiwiryo Hospital, Padang

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ABSTRACT

Background: Hemodialysis (HD) is the primary therapy for patients with advanced-stage chronic kidney disease (CKD). Although effective, the use of double lumen catheters (CDL) as vascular access in HD carries a high risk of infection.
Objective: This study aims to identify the infection profile in CKD patients using CDL during hemodialysis at Dr. Reksodiwiryo Hospital in Padang.
Methods: This study employs a retrospective descriptive design involving 60 hemodialysis patients from May to July 2024. The variables analyzed include age, gender, etiology, clinical manifestations, catheter location, catheter duration, and hematological parameters (leukocytes), with catheter-related infections (CRI) as the main dependent variable.
Results: The results show that the majority of patients were under 60 years old (51.7%), and more than half (56.7%) used CDL for less than 8 weeks. CDL infections most frequently occurred in the right jugular vein access (90.0%) with fever and chills as the primary symptoms (53.3%).
Conclusion: Using CDL for less than 8 weeks is linked to a high infection rate, with fever and chills as common symptoms. Recommendations include strict aseptic techniques during catheter insertion, prophylactic antibiotics for high leukocyte levels, and early planning for arteriovenous fistula (AVF) to minimize complications from long-term catheter use.
Keywords: Chronic Kidney Disease, Hemodialysis, Catheter Infection.

Introduction

HD is the most commonly used method of kidney replacement therapy for patients with CKD.[1,2] CKD has become a significant public health issue, with the number of cases increasing each year. At the terminal stage of the disease, hemodialysis is necessary to replace kidney function for patient survival.[3] Globally, it is estimated that around 843.6 million people are affected by CKD.[4] Recent data indicate that from 1990 to 2016, the global incidence and prevalence of CKD increased by 89% and 87%, particularly in countries with medium and low socio-demographic indices.[4] Over the past three decades, deaths from CKD are estimated to have doubled, making it the 11th leading cause of death in 2016, up from the 18th position in 1990.[4] The prevalence of hemodialysis reaches up to 89%. In Indonesia, data from the Indonesian Renal Registry indicate a significant rise in both new and ongoing HD cases in 2018, with new cases increasing from 30,831 in 2017 to 66,433 in 2018, and active cases growing from 77,892 to 132,142.[1,2] Effective hemodialysis depends on access to large blood vessels, which is often achieved through central venous catheterization using a double lumen catheter.[5]

However, using CDL carries a risk of infections, which can lead to higher mortality and

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morbidity rates.[6] Infections such as bloodstream infections, exit-site infections, and tunnel infections are common complications that can reduce the effectiveness of therapy and lead to increased healthcare costs.[7] Infection is the second most common cause of death among dialysis patients, and the rate of hospitalizations due to infections among hemodialysis patients has risen by 34% between 1993 and 2014 in the US.[8] Older patients, especially those over 60, are at a higher risk for catheter-related infections.[9] According to the Indonesian Kidney Registry, hypertension is the leading cause of death among dialysis patients, with many patients with CDL infections also suffering from comorbidities such as hypertension and diabetes.[10] Clinical signs of catheter-related infections include inflammation, fever, and elevated white blood cell counts.[11] The risk of catheter-related bloodstream infections (CLABSI) increases with the duration of catheter use, particularly after 20 days.[12] Most CDL placements (86.5%) in the right internal jugular vein risk infection, requiring proper care and monitoring.[13] This study identifies infections in CKD patients with CDL undergoing hemodialysis.

Methods

Design and participants

This study used a retrospective design and involved 60 patients with chronic kidney disease (CKD) undergoing hemodialysis with double lumen catheters (CDL) at Dr. Reksodiwiryo Hospital, Padang, during the period of May to July 2024. Included in the study were patients who used CDL as vascular access for hemodialysis and had complete medical records, including clinical and laboratory data. Patients who did not use CDL, had incomplete data, or were experiencing other active infections unrelated to the catheter were excluded from the study. The sample size was determined using a total sampling method, in which all patients who met the inclusion criteria during the study period were included. This approach is appropriate for retrospective studies with limited populations, as it allows for optimal use of available data and ensures that the findings are representative of the CDL patient population at the hospital.

Study Covariate

Operational definitions include: age (<60 or ≥60 years), gender (male/female), CKD etiology (hypertension, diabetes, or both), clinical manifestations (fever, chills, hyperemia, purulent secretion, etc.), catheter location (right femoral, right jugular, left jugular vein), duration of hemodialysis and catheter use (<8 or ≥8 weeks), leukocyte count (<5000, 5000-10000, >10000 cells/mm^3), and CDL infection (diagnosed via clinical symptoms and lab results).

Statistical analysis

Data were analyzed using SPSS 22.0 for Macintosh. Descriptive statistics included frequencies, percentages, means, and medians. Normality testing was performed on numerical data, with means reported for normally distributed data and medians for non-normal distributions. Cross-tabulation was used to examine relationships between categorical variables. Comparative analysis involved chi-square and other statistical tests to assess variable associations.

Results

Patient selection

In this section, the characteristics of the respondents are described, including age, gender, etiology, clinical manifestations, duration of HD, duration of CDL use, CDL access location, and leukocytes. To facilitate understanding, the results of the descriptive analysis will be explained as follows.

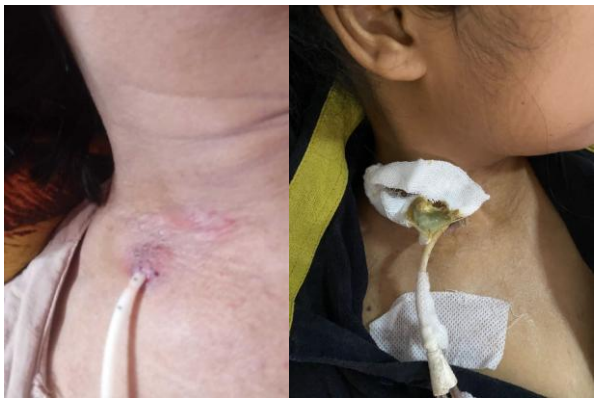
This study involved 60 respondents who were deemed eligible and met the criteria established by the researchers for inclusion. Based on Table 1, the characteristics of the respondents in this study are outlined. In terms of age, the majority of respondents in this study were under 60 years old, with 31 respondents (51.7%), while the remaining 29 respondents (48.3%) were 60 years old or older. Regarding gender, it was found that the majority of respondents in this study, 31 respondents

(51.7%), were female, while the remaining 29 respondents (48.3%) were male. Based on etiology, it can be observed that the majority of respondents, 49 people (81.7%), experienced hypertension or high blood pressure, followed by 6 people (10.0%) who had diabetes mellitus (DM), and the remaining 5 people (8.3%) who had both hypertension and diabetes mellitus. Regarding clinical manifestations in this study, it was found that the majority of respondents, 32 people (53.3%), experienced symptoms of fever with chills, while 11 people (18.3%) did not experience any clinical manifestations. A total of 8 people (13.3%) experienced symptoms of fever/chills, hyperemia, and purulent secretion, 6 people (10.0%) experienced symptoms of fever/chills and purulent secretion, and the remaining 3 people (5.0%) experienced clinical manifestations of fever/chills and hyperemia. Based on the duration of HD in this study, it was found that the majority of respondents, 55 people (91.7%), had undergone HD for 8 weeks or more, while the remaining 5 people (8.3%) had undergone HD for less than 8 weeks. Most respondents (56.7%) used CDL for less than 8 weeks, while 43.3% used it for 8 weeks or more. Regarding CDL access location, 90.0% had access in the right jugular vein, 6.7% in the left jugular vein, and 3.3% in the right femoral vein. (Figure 1) In terms of leukocyte levels, 51.7% had levels between 5000-10000, 25.0% above 10000, and 23.3% below 5000.

Table 1. Characteristics of hemodialysis patients using Double Lumen Catheter (CDL)

Respondent Characteristics	Frequency	Percentage
Age		
a. < 60 years	31	51.7%
b. > = 60 years	29	48.3%
Gender		
a. Male	29	48.3%
b. Female	31	51.7%
Etiology		
a. DM	6	10.0%
b. Hypertension	49	81.7%
c. Hypertension+ DM	5	8.3%
Clinical Manifestations		
a. Fever with chills	32	53.3%
b. Fever / Chills, Hyperemia, Purulent Secretion	8	13.3%
c. Fever/ Chills, Hyperemia	3	5.0%
d. Fever/ Chills, Purulent Secretion	6	10.0%
e. None	11	18.3%
Duration of HD		
a. < 8 weeks	5	8.3%
b. > = 8 weeks	55	91.7%
Duration of CDL		
a. < 8 weeks	34	56.7%
b. > = 8 weeks	26	43.3%
Location of CDL		
a. Vena Femoralis Dextra	2	3.3%
b. Vena Jugularis Dextra	54	90.0%
c. Vena Jugularis Sinistra	4	6.7%

Leukocyte			
a.	< 5000	14	23.3%
b.	5000 - 10000	31	51.7%
c.	> 10000	15	25.0%



(a) **(b)**

Figure 1. Patients with infected CDL (Central Double Lumen Catheter)

Discussion

This study involved 60 hemodialysis patients at Dr. Reksodiwiryo Hospital in Padang, with the majority (51.7%) being under 60 years old. This aligns with Gupta et al. (2016), who also found that the average age of patients with CDL-related infections was under 60 years.[14] The theory states that elderly patients have reduced immune function and a higher risk of CKD-related comorbidities like hypertension and diabetes, increasing their risk of complications. In terms of gender, most respondents were female (51.7%).[15] Weldetensae et al. (2023) did not specify whether gender directly influences the risk of catheter-related bloodstream infections in hemodialysis patients.[11] The majority of respondents (81.7%) had hypertension, which was also found to be the primary cause of catheter-related infections in the study by Hajji et al. (2022), where 86% of hemodialysis patients with catheter infections had hypertension.[16] Hypertension is common among CKD patients and is a major cause of end-stage renal disease (ESRD), with 26.4% of patients having hypertension as the cause of their CKD.[17] Hypertension can worsen the progression of CKD and increase the risk of complications, including infections. Patients with uncontrolled hypertension are at higher risk of cardiovascular complications and infections, which can further deteriorate their kidney condition.[18] Meanwhile, only 10% of respondents had diabetes mellitus. Theoretically, elderly patients with comorbid diabetes mellitus are at higher risk of infection due to decreased organ function and a compromised immune system.[19]

In this study, most respondents (53.3%) exhibited symptoms of fever with chills. Iqbal et al. (2021) found that fever and chills occurred in 100% of patients with CDL infections, highlighting these symptoms as key indicators of serious systemic infections.[20] Fever and chills are the body's response to systemic infections, triggered by pyrogens released by either bacteria or the body itself in reaction to pathogens in the bloodstream.[21] In CDL infections, bacteria from the skin or catheter can enter the bloodstream, leading to a systemic immune response.[12] The frequent occurrence of fever and chills suggests they may be early indicators of severe systemic infections, highlighting the need for early detection and treatment to prevent serious complications like sepsis and reduce mortality.[22] In this study, most respondents (91.7%) had

undergone hemodialysis for 8 weeks or more. However, hemodialysis duration does not directly affect the risk of catheter-related bloodstream infections in CVC patients.[23]

In this study, the majority of respondents (56.7%) used CDL catheters for less than 8 weeks. Iqbal et al. (2021) reported that 68.4% of patients who used catheters for more than 14 days developed infections. Although the duration of CDL use may influence the risk of infection, this study did not find a significant association between using CDL for more than two weeks and the incidence of infection. Several studies suggest that using non-tunneled CDL for less than one week and replacing it regularly may reduce the risk of infection.[20] Non-tunneled catheters are commonly used as temporary access due to their ease of insertion, but they carry a higher risk of infection because they lack a subcutaneous cuff that serves as a barrier to bacterial colonization. In contrast, tunneled catheters are designed for long-term use and have a lower infection rate due to the cuff, which helps prevent the migration of microorganisms from the skin into the catheter lumen.[23] The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines do not specify an exact time limit for CDL use, but emphasize the importance of regular monitoring and prompt removal once an arteriovenous fistula (AVF) matures or other permanent vascular access options become available.[23]

In clinical practice, CDL usage may range from several weeks to years, depending on the availability and quality of vascular access and the facility's ability to manage complications. Therefore, routine evaluation of catheter condition and implementation of infection prevention standards such as aseptic technique, proper dressing care, and minimizing catheter manipulation are essential to reducing the incidence of CDL-related infections.[12] According to CDC guidelines, several proven methods to prevent infection include daily skin cleansing with chlorhexidine, routine disinfection of the catheter hub (access site), the use of antimicrobial-coated catheters, and replacing sutures with sutureless securement devices. If these procedures are implemented consistently, the risk of infection can be significantly reduced, even when the catheter is used for a relatively short period.[24]

In this study, the majority of respondents (90.0%) had CDL catheters inserted in the right jugular vein, while only 3.3% had them placed in the right femoral vein. This finding aligns with the report by Dahlan et al. (2023), which stated that approximately 86.5% of CDL placements were performed in the right internal jugular vein. Although this site is anatomically considered safer and associated with a lower risk of infection compared to other sites, particularly the femoral vein, infections can still occur.[13] Several studies support this site preference in clinical practice. Meta-analyses have shown that femoral catheters carry a significantly higher risk of catheter-related bloodstream infections (CRBSI), especially when used for less than one week, up to three times higher than catheters placed in the jugular vein. A study in Pakistan involving 400 patients also reported a higher incidence of CRBSI at femoral sites (14%) compared to jugular sites (6.5%).[25] These findings reinforce that placement of CDL in the right internal jugular vein, as shown in this study, is consistent with evidence-based practice aimed at minimizing infection risk.

However, the occurrence of infections even at lower-risk sites indicates that catheter location alone does not guarantee safety. Insertion technique, hygiene, wound care, and regular monitoring remain critical components in preventing catheter-related infectious complications.[12] Based on leukocyte levels, it was found that the majority of respondents in this study, 31 people (51.7%), had leukocyte levels ranging from 5,000 to 10,000. In the study by Weldetensae et al. (2022), more than half (60.6%) of the participants had leukocyte levels below 10,000 cells/mm3.[11] High leukocyte levels are usually considered a sign of the body's immune response to infection. However, in the context of the mentioned study, high leukocyte levels (more than 10,000 cells/mm3) do not necessarily indicate an increased risk of catheter infection, but can be used as one of the clinical parameters to aid in diagnosis and monitoring.[11] To reduce

the risk of catheter infection based on leukocyte levels, regular blood tests should be performed to monitor leukocyte levels. High leukocyte levels may indicate an ongoing infection or potential risk of infection.[12]

Conclusion

The study found that using a double lumen catheter for less than 8 weeks is associated with a high infection rate, with over half of the patients experiencing infections. The most commonly reported clinical symptoms were fever and chills, indicating the body's response to the infection. Therefore, close monitoring of patients using CDL is crucial to detect and prevent further complications. Catheter insertion should be done using strict aseptic techniques to prevent contamination. Prophylactic antibiotics may be beneficial, especially for patients with high leukocyte counts or a history of infections. Families should be educated about signs of infection, such as fever and redness at the catheter site. Early planning for an arteriovenous fistula (AVF) is recommended to minimize risks from prolonged catheter use.

Limitations of the Study

Limitations include an observational design, a single-center sample, a short observation period, and the lack of evaluation of infection impact on quality of life.

Declarations

Ethics approval and consent to participate

This study adhered to the guidelines for the Declaration of Helsinki and received approval from the Ethics Committee of the Dr. Reksodiwiryo Hospital, Padang, Indonesia, under reference number B/251/VII/2024.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: MPP, AV, EV, HH. Design: MPP, AV, EV, HH. Control/ supervision: MPP, AV, EV, HH. Data collection/ processing: MPP, AV, EV, HH. Analysis/interpretation: MPP, AV, EV, HH. Literature review: MPP, AV, EV, HH. Writing the article: MPP, AV, EV, HH. Critical review: MPP, AV, EV, HH. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Effect of Tacrolimus Once Daily XR on Variance of Blood Tacrolimus Concentrations in Comparison with Twice Daily Tacrolimus in Kidney Transplant Recipients

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ABSTRACT

Background: Variability of tacrolimus concentration in the plasma of recipients is associated with nephrotoxicity, acute rejection, and affects graft survival.
Objective: To test the hypothesis that the coefficient variation of plasma tacrolimus in new tacrolimus XR (extended-release) once daily is lower than conventional twice daily.
Methods: The study was conducted in two phases. Phase 1, a comparative observational analysis with a single-group crossover, comparing periods of divided-dose treatment with crossover to prolonged-dose treatment. Phase 2, a cross-sectional design, is used to correlate IVP and serum creatinine variation.
Results: A total of 19 kidney post-transplant recipients were included. There was a significant difference in blood tacrolimus CoV between XR tacrolimus and divided dose therapy (22.22±7.39% vs 44.32±15.54%, p<0.001). A significant linear correlation was observed between blood tacrolimus CoV and serum creatinine CoV in all patients (r=0.74; r^2= 0.54; b=1.15; p<0.001). Subgroup analysis revealed a significant correlation between blood tacrolimus CoV in divided dose tacrolimus therapy subgroup (r=0.58; r^2= 0.33; p=0.02) but not in the XR group (r=0.06; r^2= 0.004; p=0.84). Multivariate ANCOVA showed serum CoV was associated with CoV of blood tacrolimus (B=0.72; r^2= 0.255; p=0.01). Furthermore, XR tacrolimus was associated with lower serum creatinine CoV (B= -20.7; r^2=0.20; p=0.02).
Conclusion: XR tacrolimus therapy produces significantly lower variance of blood tacrolimus concentrations in kidney transplant recipients. This variance is associated with serum creatinine variance, especially in divided-dose tacrolimus therapy. Serum creatinine variance is linked to variances in blood tacrolimus levels, and XR tacrolimus therapy is associated with lower serum creatinine variance.
Keywords: Tacrolimus Extended Release, Variance of Blood Tacrolimus, Variance of Serum Creatinine, Kidney Transplant Recipients.

Introduction

Kidney transplantation is one of the replacement therapies for kidney failure. It has several advantages over other replacement therapies, including a better quality of life and independence from regular dialysis treatment.[1] The goal of immunosuppressive therapy is to maintain graft survival by preventing allograft rejection while reducing the risks of drug nephrotoxicity and infection. After transplantation, immunosuppressive management, including dosing and monitoring, particularly in tacrolimus regimens, plays a central role in increasing organ survival, maintaining long-term organ function, and preventing rejection and allograft loss. Most of the transplantation centers use triple immune-suppressive agents during induction, maintenance, and reversal when rejection occurs.[2] The use of mycophenolate mofetil (MMF), tacrolimus (Tac), and sirolimus

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combination has become increasingly common in recent years.[3]

Tacrolimus belongs to the immunophilin calcineurin inhibitor class, which strongly inhibits the activation of T lymphocytes. The intracellular transduction pathway of T cells is inhibited by binding of tacrolimus and FK506-binding proteins (FKBP), forming a tacrolimus-FKBP complex. This complex molecule is a strong inhibitor of the transcription gene of T cells that produces interleukin (IL)-2, other growth factor cytokines, TNF-α, and protooncogenes. It also suppresses the expression of IL-2 and IL-7 receptors. Tacrolimus also has inhibitory properties on mixed lymphocyte reaction, cytotoxic T cell generation, and T cell-dependent B cell activation. Tacrolimus has no inhibitory activity on T cell proliferation due to its lack of effect on T cell activation by IL-2, antigen presentation, mononuclear phagocytic function, and natural killer cell activity.[4]

The variability of tacrolimus concentrations in the plasma of recipients is associated with nephrotoxicity, a side effect of tacrolimus, and affects graft survival and patient prognosis. This variability has also been linked to acute rejection and long-term prognosis of transplant recipients.[5] Histopathologic features of this nephrotoxicity of tacrolimus are supported by histopathologic findings of interstitial fibrosis, tubular injury, and arteriolopathy. Some cytokines may mediate these processes, such as growth factor TGF-β.[6,7] An extended-release of tacrolimus is an alternative preparation to the older divided-dose tacrolimus for immunosuppressive treatment of kidney transplant recipients. Some reports have shown that divided-dose tacrolimus is associated with a higher risk of acute rejection compared to prolonged-release tacrolimus.[8]

This study aims to test the hypothesis that the coefficient of variation (CoV) of plasma tacrolimus in new extended-release (XR) tacrolimus is significantly lower than that in conventional twice-daily immunosuppressive regimens among kidney transplantation recipients. In addition, this study also aims to determine the correlation between plasma CoV of tacrolimus and CoV serum creatinine concentrations in those patients.

Methods

Design and participants

The study design is divided into Phase 1, a comparative observational analysis with a single-group pre- and post-test design, comparing the CoV of tacrolimus between the period of divided dose treatment (first period) and the period of crossover to XR (second period) of tacrolimus treatment. A phase 2, cross-sectional design is used to correlate the CoV of tacrolimus and the CoV of serum creatinine.

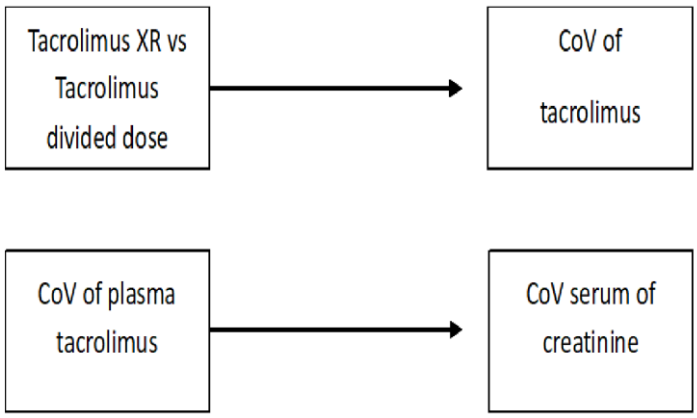

Figure 1. Diagram of study design

This study was conducted at the Transplant Outpatient Clinic, Prof. dr. I.G.N.G. Ngoerah Central General Hospital, Bali, Indonesia, from March 2019 to August 2021. Study variables are divided into:

Phase 1 study:

- Dependent variable was the CoV of tacrolimus
- Independent variable was intervention: tacrolimus XR vs tacrolimus divided dose (twice daily tacrolimus)

Phase 2 study:

- Dependent variable CoV of serum creatinine.
- Independent variable was the CoV of plasma tacrolimus

Controlled variables were: age, gender, body mass index, ischemic time.

CoV of tacrolimus plasma concentrations is the standard deviation divided by the mean of plasma tacrolimus concentrations, and expressed as a percentage value (%). The formula can be expressed as: CoV = SD/Mean × 100%. Tacrolimus concentrations were measured from blood samples taken 12 hours after the first dose, just before the following scheduled doses of the day. Concentrations were examined by Chemiluminescent Microparticle Immunoassay (CMIA) assay and expressed in units of ng/L. The CoV will be categorized into a quartile range (percentile 25). Serum creatinine concentrations were examined using the Cobas Integra 401 method and expressed in mg/dL.

All kidney post-transplant recipients were evaluated for tacrolimus treatment, blood tacrolimus, and serum creatinine concentrations. Data from patients who visited the transplant polyclinic were openly evaluated regarding both the study drugs and the data from the Hospital Information Management System's medical records. We have re-evaluated the data of some patients who received a divided dose and found that CoV was high. Information about these results was notified to the Hospital Department of Pharmacy and the Hospital Director. After the evaluation, it was decided that Astellas would supply Tacrolimus Extended Release to curb the potential long-term harmful effects of kidney grafts caused by the use of divided-dose tacrolimus immunosuppressive treatment.

Tacrolimus immunosuppressive treatment is divided into two periods. The first period was considered a time when divided dose (conventional) tacrolimus was used for immunosuppressive treatment. The second period is a period during which tacrolimus XR was replaced and used for immunosuppressive treatment. All patients underwent regular visits for clinical evaluation, including dose adjustments of tacrolimus treatment, blood tacrolimus concentration measurements, and serum creatinine examinations. All clinical data, including gender, age, body weight, and height, as well as ischemic times, were extracted. Additionally, lab data on plasma tacrolimus and serum creatinine concentrations were collected and analyzed. The CoV plasma tacrolimus and CoV creatinine concentrations during the first and the second period are calculated and compared.

Statistical analysis

Descriptive analysis to describe patient characteristics such as age, gender, of the donors and recipients, body weight and height, co-treatment (antihypertensives, immune-suppressive combination), and information of transplantation operation (ischemic times). CoV of tacrolimus and quartile distribution will be analyzed and expressed as mean and percentage. The Shapiro-Wilk test is used to analyze the normalcy of numeric data.

An independent t-test is used to compare the coefficient of variance of tacrolimus and quartile distribution between the tacrolimus XR group during the first and second periods. Pearson's correlation and linear regression analysis between the CoV of tacrolimus and the CoV of serum creatinine will be done when appropriate. Significance level (alpha) is set on p-value < 0,05. Data precision is set at a 95% confidence interval. The ethical committee of the Medical Faculty of Udayana University has approved this study.

Results

During the study, 15 patients were treated with a divided dose, n=15, and patients were treated with an extended-release dose, n=15 (Figure 2). Table 1 presents the characteristics of patients included in the study.

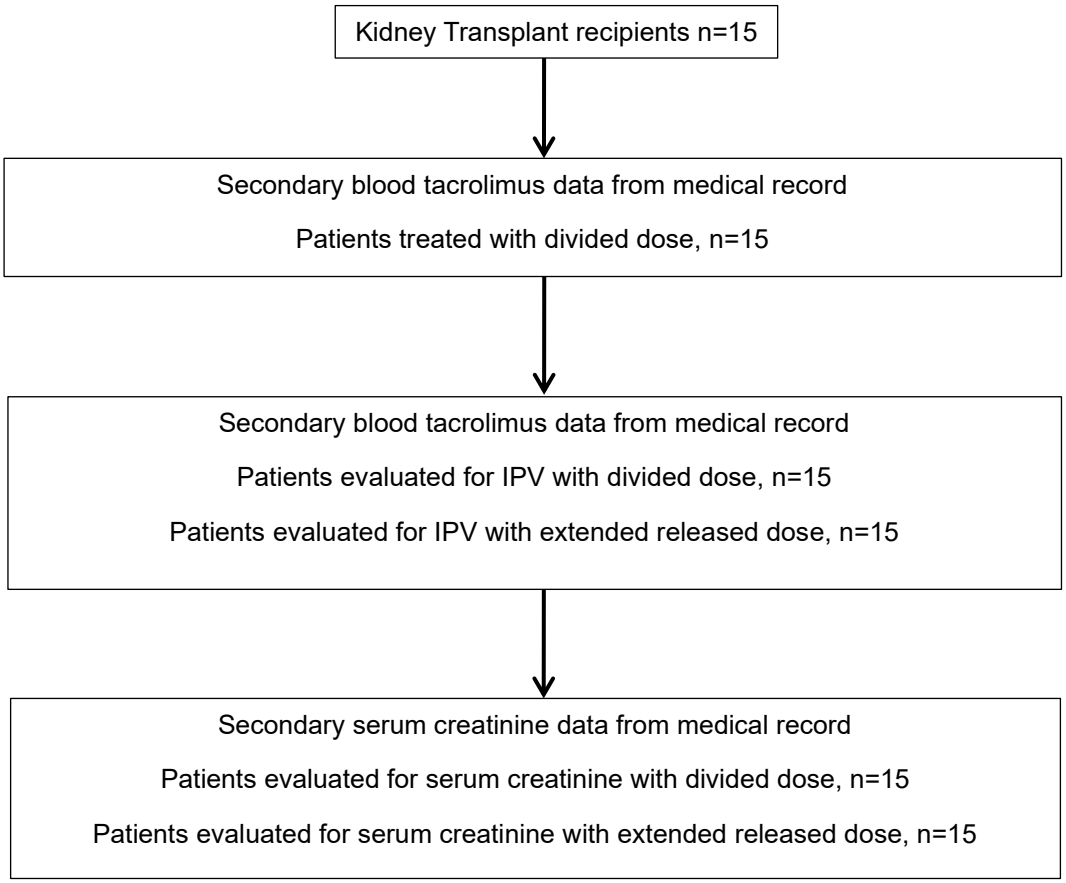

Figure 2. Flow diagram of the study

Table 1. Characteristics of patients included in baseline (n=15)

Variables	mean±SD	n (%)
Age (years)	31±8	
Gender		
Males		13 (87)
Females		2 (13)
Body weight (kg)	61±11	
Body height (cm)	167±6	
Body mass index (kg/m2)	21.7±2.8	
Albumin (g/dL)	3,84±0,53	
Blood sugar (mg/dL)	99,47±33,78	
ALP (U/L)	32,30±33,66	
ALT (U/L)	61,97±88,40	

There was a significant difference between blood tacrolimus CoV of patients with tacrolimus XR and divided dose tacrolimus therapy (22.22± 7.39% vs 44.32±15.54%, $p<0.001$). There was a half lower of blood tacrolimus CoV in patients with tacrolimus XR than divided dose tacrolimus therapy. In general, the median CoV of tacrolimus was 29.79% with

an interquartile range between 20.51% and 45.80%. If this CoV is divided between groups, the median tacrolimus CoV value was 21.02% with an interquartile range between 17.96% and 27.73% in patients with tacrolimus XR, and the median value was 45.65% with an interquartile range of 32.51% to 48.39% in divided dose tacrolimus. This data showed that the median tacrolimus coefficient of variance value was more than twice as high in patients receiving extended-release compared to those receiving divided doses (Figure 3).

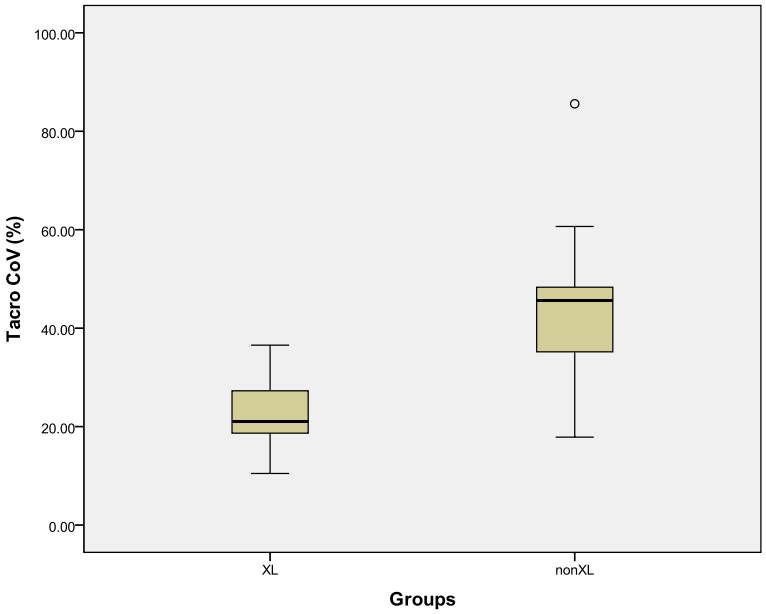

Figure 3. Diagram box plot of the mean of blood tacrolimus CoV (coefficient of variation) between XR (extended-release) and divided dose tacrolimus treatment

If we divide association between treatment with tacrolimus XR and divided dose tacrolimus and quartile (25 percentile) of blood tacrolimus CoV, it was showed that there was significant association between treatment with groups of tacrolimus XR or divided dose and quartile (25 percentile) of blood tacrolimus CoV (p=0.001), where, 6 (85.6%) vs 1 (14.3%) of patients with tacrolimus XR and divided dose tacrolimus were in quartile 1 and none vs 7 (100%) of patients with tacrolimus XR to divided dose tacrolimus treatment (Table 2).

Table 2. Quartile Coefficient of variance of Tacrolimus in Extended Release (XR) and Divided Dose Tacrolimus Therapy

		Group of tacrolimus therapy		
		XR	Divided dose	Total
CoV	1st quartile	6	1	7
	2nd quartile	7	1	8
	3rd quartile	2	6	8
	4th quartile	0	7	7
Total		15	15	30

X2=17.1; df=3; p=0.001

Figures 4,5, and 6 show that there was a significant linear correlation between blood tacrolimus CoV and serum creatinine CoV in all patients (r=0.74; r^2= 0.54; b=1.15; p<0.001). However, if this association was analyzed in a subgroup of therapy, there was only a significant linear correlation between blood tacrolimus CoV in the subgroup with divided dose tacrolimus therapy (r=0.58; r^2= 0.33; p=0.02) and none in patients with tacrolimus XR therapy (r=0.06; r^2= 0.004; p=0.84).

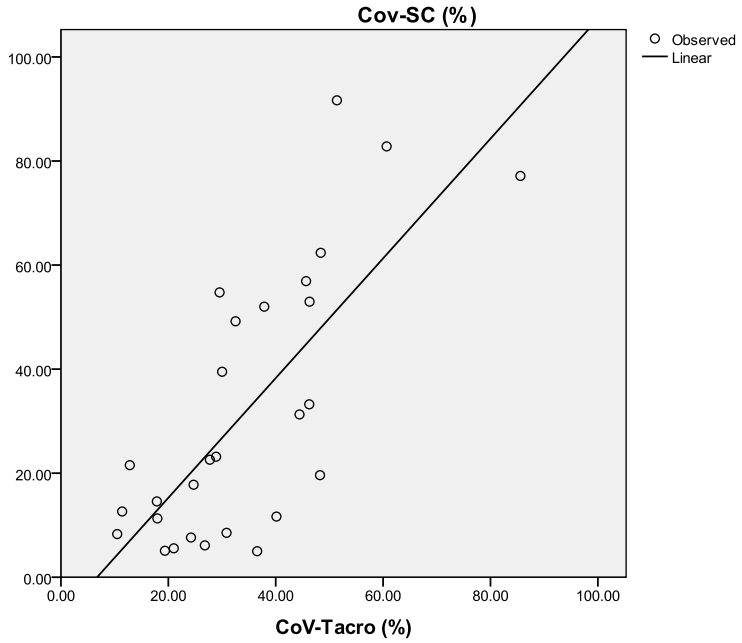

Figure 4. Scatter diagram and linear association between blood tacrolimus covariance and serum creatinine covariance in all patients (r=0.74; r^2= 0.54; b=1.15; p<0.001)

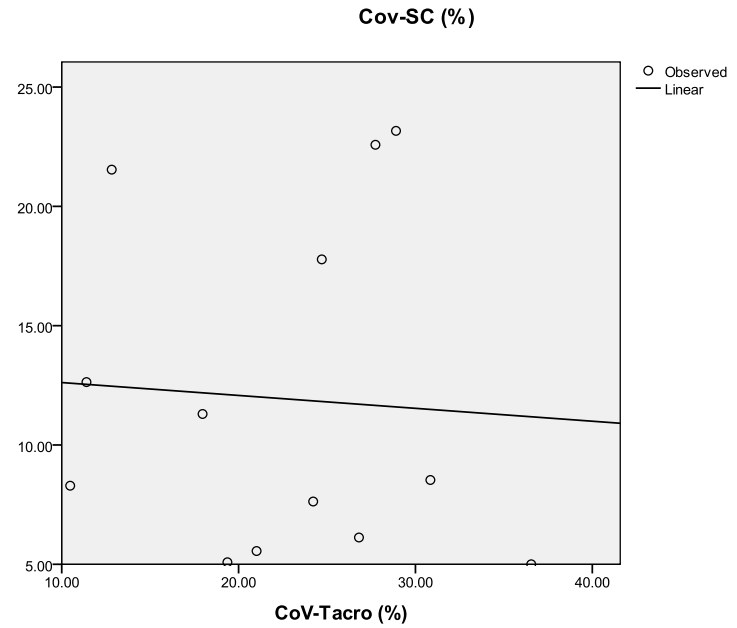

Figure 5. Scatter diagram and linear association between blood tacrolimus coefficient of variance and serum creatinine covariance in extended-release patients (r=0.06; r2 = 0.004; p=0.84)

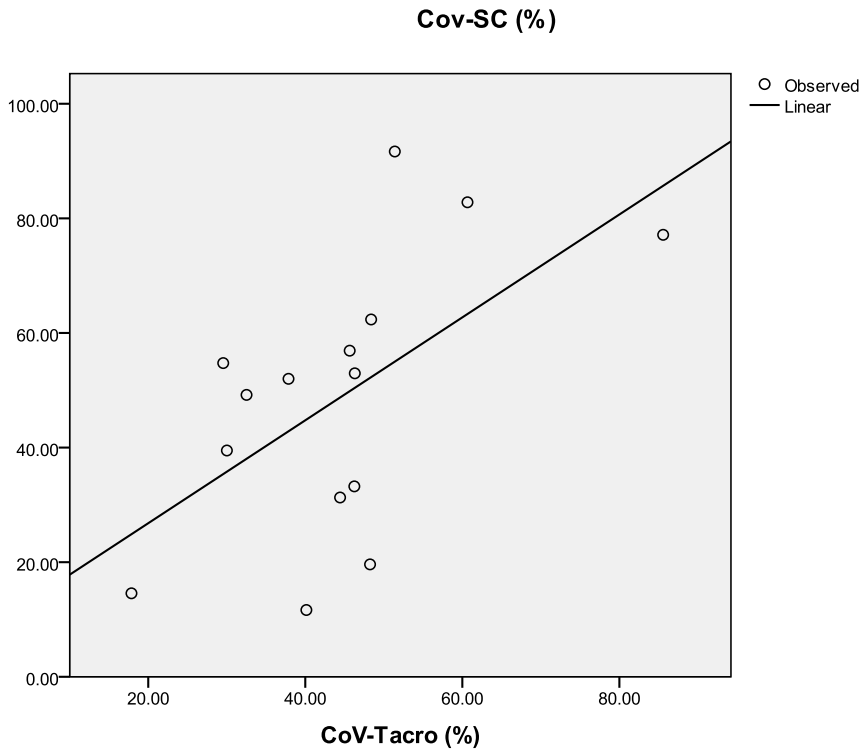

Figure 6. Scatter diagram and linear association between blood tacrolimus coefficient of variance and serum creatinine coefficient of variance in divided dose patients (r=0.58; r^2= 0.33; p=0.02)

Discussion

Variability of tacrolimus concentrations in plasma of the recipient, namely intra-patient variability (IPV), is frequent during tacrolimus therapy and is measured by its CoV.[9] Nephrotoxicity is one of the main side effects of tacrolimus, which may affect graft survival and patient prognosis. Histopathologic features of this nephrotoxicity include interstitial fibrosis, tubular injury, and arteriolopathy, which may be mediated by several cytokines, such as the growth factor TGF-β.[5] The renin-angiotensin system may also contribute significantly to the pathogenesis of tacrolimus nephrotoxicity.[7] This IVP is strongly associated with acute rejection and long-term prognosis of transplant recipients.[6] This study showed that there is a linear correlation between blood tacrolimus CoV and serum creatinine CoV in all patients. The present findings suggest that an unstable concentration of tacrolimus may produce nephrotoxicity, as indicated by variability in serum creatinine concentration. When tacrolimus target levels are less than 5 ng/mL, the impact of this IVP on acute rejection will become obvious.[10] On the other hand, high IVP may produce an increased risk of over-immunosuppression, when tacrolimus concentration exceeds the target of treatment, which results in nephrotoxicity and risk of infection. On the contrary, those with under-immunosuppression due to fewer treatment targets may cause allograft rejection.[4,11] The delay of blood test for tacrolimus concentration and adjusting the doses may result in a high degree of variability and increased risk of nephrotoxicity and rejection. During the Phase 1 period of the study, using a divided dose of tacrolimus treatment, the variance of blood tacrolimus is high (mean value 45%). The introduction of tacrolimus XR therapy in Phase 2 results in a lower half of its covariance coefficient. The decrease in variance of blood tacrolimus with extended release may be able to lower the risk of rejection and/or drug toxicity.

This study showed that, firstly, the CoV in blood tacrolimus is a half lower in patients with

extended-release (XR) tacrolimus than those with divided-dose tacrolimus therapy. The second finding is that the association between CoV of blood tacrolimus and CoV of serum creatinine is significant in the subgroup receiving divided-dose tacrolimus therapy, but not in patients receiving extended-release therapy. These findings may support the concept that slow-release tacrolimus therapy can stabilize blood concentration and blunt the variation of tacrolimus. Each unit of tacrolimus CoV increases 0.7 serum creatinine CoV. In addition to tacrolimus CoV, the use of tacrolimus XR blunts the variation of serum creatinine.

The common method to evaluate the effectiveness of immunosuppression and patient compliance with tacrolimus treatment is to monitor its plasma concentrations and calculate the IVP. The IVP is influenced by genetic factors, the interaction of tacrolimus with food and other drugs in the gut, and can be used to assess patients' compliance with the treatment.[12] We may not be able to explain whether high variation in the phase study is caused by genetic variation in our patients or lack of close monitoring and prompt adjustment of tacrolimus doses.

A prolonged-release tacrolimus may be an alternative preparation to a divided dose for immunosuppressive treatment of the recipients after kidney transplantation. Peak plasma concentrations and the time interval are expressed as the area under the curve (AUC) and over the dosage time interval (AUCT). The under the curve (AUC) over the dosage time interval (AUCT) is reported to be a good marker of systemic exposure of tacrolimus and has a strong association with clinical efficacy outcomes. Due to the lower tacrolimus time interval, divided-dose tacrolimus is associated with a higher risk of acute rejection than prolonged-release tacrolimus. Intestinal absorption of prolonged-release tacrolimus is slower than immediate-release, divided-dose tacrolimus, resulting in a longer time interval than immediate-release.[8]

Intestinal absorption of tacrolimus depends on the presence of food in the gut lumen, bile acids, and intestinal motility.[5] In blood circulation, tacrolimus strongly binds to erythrocytes and plasma proteins. Tacrolimus is broadly distributed across various tissues, including the lungs, heart, brain, spleen, kidneys, pancreas, muscles, and liver. It passes through the placental barrier, resulting in a concentration that is approximately one-third of the plasma concentrations in the umbilical cord. Tacrolimus is also detected in low concentrations in breast milk.[13] Tacrolimus is metabolized mainly in the liver and to a lesser extent in the intestinal mucosa. CYP3A4 isoenzymes mediate its metabolism. Its major metabolite is 13-O-dimethyl-tacrolimus. Inhibitors of CYP3A4 can increase tacrolimus blood concentrations, while CYP3A4 inductors can reduce its concentrations.[14] Interaction between tacrolimus and affecting factors may occur at the level of absorption, distribution, metabolism, and excretion.[12] Variability of blood concentrations depends on gastrointestinal motility, primarily due to phase 1 metabolism. Individual variation of blood concentration also depends on the variability of absorption and bioavailability. Fatty food, magnesium oxide, aluminum oxide, and sodium bicarbonate in the gastrointestinal lumen can reduce its absorption. Finally, variability of intestinal absorption is affected by genetic polymorphism of CYP3A or P-glycoprotein.[2,15]

Conclusion

Extended-release tacrolimus therapy produces significantly lower variance of blood tacrolimus concentrations in kidney transplant recipients. The variance in blood tacrolimus concentrations is associated with the variance in serum creatinine, especially in divided-dose tacrolimus therapy.

Limitations of the Study

This study is subject to some limitations, most notably the small sample size, which may result in a lack of statistical power. A single-group pre- and post-test design, which inherently carries over the effect of the first treatment to the second treatment, cannot be ruled out. Larger sample sizes are needed for more generalized and robust

conclusions. This study was a retrospective analysis taken from hospital medical records; therefore, several drawbacks arose from the study design, retrospective evaluation, and controlled variables, which may have confounded the conclusions.

Declarations

Ethics approval and consent to participate

This study adhered to the guidelines for clinical research and received approval from the Ethics Committee of the Prof. dr. I.G.N.G. Ngoerah Central General Hospital Denpasar under reference number : 1366/UN14.2.2.VII.14/LP/2019.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: IGRW. Design: IGRW. Control/supervision: IGRW. Data collection/ processing: IMRP, SAW. Analysis/ interpretation: IGRW. Literature review: IGRW, IMRP. Writing the article: IGRW. Critical review: IGRW. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Original Article

Microbiological Profile of Peritoneal Dialysis-Related Peritonitis at Dr. Hasan Sadikin Hospital, Bandung

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ABSTRACT

Background: Peritonitis is a frequent complication in patients undergoing peritoneal dialysis. To provide appropriate therapy, identification of the pathogen that causes peritonitis is required.

Objective: This study aims to understand the microbiological profile of CAPD peritonitis in hospitalized patients at Dr. Hasan Sadikin Hospital, Bandung.

Methods: This was a descriptive retrospective study using secondary data of peritonitis patients undergoing CAPD in 2020-2023. A total sampling technique was used, where all cases that met the inclusion criteria were included. The criteria were patients aged ≥ 18 years with CAPD peritonitis, having complete medical record data, and CAPD fluid culture results. In addition, the data were analyzed using SPSS software.

Results: A total of 67 peritonitis patients undergoing CAPD were included, with 36 (53.7%) having monomicrobial infections. In addition, 7.5% had polymicrobial infection and 38% had culture-negative. Gram-negative bacteria were the most common microbe found in 18 cases, and most patients recovered from peritonitis (86.6%), followed by catheter removal (9%), and death (4.5%). Gram-negative predominance contrasts with Ozdemir et al.'s findings, possibly due to regional antibiotic practices.

Conclusion: Empirical antibiotic treatment and culture results helped in providing effective management. Adhering to ISPD guidelines and improving sampling techniques could improve microbiological diagnosis and patient outcomes.

Keywords: CAPD, Microbiological Profile, Peritonitis.

Introduction

In end-stage kidney disease, kidney replacement therapy, such as hemodialysis, peritoneal dialysis, or transplantation, is required. The number of patients receiving kidney replacement therapy exceeds 2.5 million and is projected to double to 5.4 million by 2030.[1] Peritoneal dialysis is an effective and commonly used modality. The main and serious complication of peritoneal dialysis is peritonitis, which necessitates hospitalization and hemodialysis, with a variable mortality rate ranging from 2 to 25%.[2] Continues Ambulatory Peritoneal Dialysis (CAPD)-related peritonitis was defined, based on ISPD criteria, as at least two of the following criteria are present: (1) abdominal pain and/or cloudy dialysis effluent, (2) effluent WBC >100/μL with >50% PMN after ≥2 hours dwell, and (3) positive effluent culture. The microbiological profile in this study encompasses the identity of causative organisms in CAPD-associated peritonitis, as determined by culture of peritoneal effluent.

Several factors have been reported to be associated with the incidence of CAPD peritonitis, but remain inconsistent, including age, gender, body mass index (BMI), race, and

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comorbidities, such as diabetes mellitus. Other factors include hypoalbuminemia, hypokalemia, vitamin D supplementation, and a history of previous infection. Understanding the risk factors, microbiological profile, and antibiotic resistance patterns is crucial for the management of peritonitis.[3,4]

The most common microbes causing peritonitis in patients undergoing PD are gram-positive pathogens. However, *Pseudomonas aeruginosa* and fungi are associated with prolonged infection and worse outcomes.[4] The early diagnosis and rapid initiation of therapy are essential to prevent poor outcomes. To provide appropriate therapy, it is important to identify the microorganism causing the complication.[5] This study aims to (1) characterize the microbiological profile of CAPD peritonitis, and (2) evaluate clinical outcomes. Therefore, this study aims to determine the characteristics of patients with peritoneal dialysis-related peritonitis, identify risk factors, and analyze the microbiological profile causing infection. The clinical outcomes of patients after treatment, including the success rate of therapy and the mortality rate, were also assessed. By understanding the microbiological profile, this study can be an important reference in the initial management, selection of appropriate antibiotics, and improvement of the quality of care. In addition, it can contribute to reducing the mortality rate of peritoneal dialysis-related peritonitis.

Methods

Design and participants

Secondary data were obtained from medical records, and data collection was carried out from July to August 2024, hence, this was a descriptive retrospective study. The population in this study was all patients who underwent *Continuous Ambulatory Peritoneal Dialysis* (CAPD), experienced peritonitis, and were hospitalized at Dr. Hasan Sadikin Central Hospital, Bandung, during the period 2020-2023. The study sample used a total sampling technique, in which all cases that met the inclusion criteria were included in the study. Inclusion criteria included patients older than 18 years, confirmed according to the criteria for diagnosis of CAPD peritonitis, having complete medical record data, and CAPD fluid culture results. As exclusion criteria, incomplete medical records were excluded from the analysis, and the total sample was 67 subjects. This study had received approval from the Hasan Sadikin Hospital Bandung Study Ethics Committee under reference number DP.04.03/D.XIV.6.5/302/2024.

Study Covariate

In this study, CAPD-associated peritonitis was diagnosed based on ISPD-recommended criteria.[6] Data on baseline characteristics and laboratory characteristics were extracted from medical records. Baseline characteristics included age, gender, education, CAPD duration, etiology of CKD, comorbid, BMI, and Peritoneal Equilibration Test (PET). In addition, laboratory characteristics included culture results, hemoglobin, albumin, random blood glucose, urea, and creatinine.

Microbiological procedures

Effluent was obtained in cases of suspected peritonitis (cloudy dialysate and/or abdominal pain). Using aseptic technique, 5–50 mL of dialysate was drained into a sterile container. Effluent cultures were inoculated into aerobic BACTEC bottles. Laboratory analysis included Gram staining, cell count, and standard culture, with additional fungal, mycobacterial, or molecular studies performed when indicated.

Statistical analysis

Data analysis was performed descriptively using IBM SPSS Statistics. Descriptive analysis aimed to describe the characteristics of CAPD peritonitis patients, including frequency distribution, mean, and proportions of the studied variables. The analysis results were presented in table form to facilitate the interpretation and understanding of the microbiological profile of peritonitis in CAPD.

Results

In A total of 67 cases of peritonitis in CAPD patients were included in the study. The mean age was 44 years (23 - 70 years), with 43 male patients (64.2%) and 24 female patients (35.8%). Based on education level, most patients had senior high school education with 34 patients (50.7%), followed by bachelor's 30 patients (44.8%), diploma 2 patients (3%), and junior high school 1 patient (1.5%). Furthermore, the mean duration of CAPD used until peritonitis occurred was 29 months (± 23.625). The etiology of CKD was mostly caused by hypertensive nephrosclerosis in 27 patients (40.3%), followed by diabetic kidney disease in 20 patients (29.9%), glomerulonephritis in 16 patients (23.9%), and other causes in 4 patients (6%). The most common comorbidity was hypertension, which was present in all patients (100%). Diabetes mellitus found in 21 patients (31.3%), coronary artery disease in 1 patient (1.5%), heart failure in 16 patients (23.9%), hepatitis C in 19 patients (28.4%), hepatitis B in 7 patients (10.4%), gout in 13 patients (19.4%), stroke in 2 patients (3%), HIV in 1 patient (1.5%), and tuberculosis in 2 patients (3%). Based on BMI, 44 patients (65.7%) had normal body weight, followed by overweight 14 patients (20.9%), obese 5 patients (7.5%), and underweight 4 patients (6%). Peritoneal Equilibration Test (PET) results showed 21 patients (31.5%) were low average transporters, 19 (28.4%) were high average transporters, and 8 (11.9%) were high transporters. There were no patients in the low transporter category.

Table 1. Demographic Characteristics

Variables	N = 67
Age (years)	44.81 years (23-70)
Gender	
Male	43 (64.2%)
Female	24 (35.8%)
Education	
Junior high school	1 (1.5%)
Senior high school	34 (50.7%)
Diploma	2 (3%)
Bachelor	30 (44.8%)
CAPD duration (month)	29.776 months (23.625)
Etiology of CKD	
Hypertension	27 (40.3%)
Diabetes Mellitus	20 (29.9%)
Glomerulonephritis	16 (23.9%)
More	4 (6%)
Comorbid	
Hypertension	67 (100%)
Diabetes Mellitus	21 (31.3%)
Coronary Artery Disease	1 (1.5%)
Heart Failure	16 (23.9%)
Stroke	2 (3%)
Uric Acid	13 (19.4)
Hepatitis B	7 (10.4%)
Hepatitis C	19 (28.4%)
HIV	1 (1.5%)
Tuberculosis	2 (3%)
BMI	
Underweight	4 (6%)
Normal	44 (65.7%)
Overweight	14 (20.9%)
Obesity	5 (7.5%)

Variables	N = 67
Peritoneal Equilibration Test (PET)	
Low transporter	0 (0%)
Low average transporter	21 (31.3%)
High average transporter	19 (28.4%)
High transporter	8 (11.9%)
Not yet PET	19 (28.4%)
Dialysis Center	
Hasan Sadikin Hospital	44 (66.7%)
Other	23 (34.3%)

Patients participating in this study showed laboratory results with varying mean values and ranges of values. The mean hemoglobin was 9.003 g/dL (± 8.372), with values ranging from 5.10 to 13.6 g/dL. Mean albumin was 2.417 g/dL (± 0.726), with a range of values between 0.79 and 4.09 g/dL. Random blood glucose had an average of 115.746 mg/dL (± 52.357), with values ranging from 72 to 470 mg/dL. The patients' urea average level was 89.531 mg/dL (± 38.893), with a range of 33.4 to 248 mg/dL. The average creatinine level was 10.295 mg/dL (±3.314), with a range of values between 4.77 to 22.98 mg/dL. These values reflected the clinical condition of the patients at the time of sampling and provided an overview of their health status in terms of kidney function, nutritional status, and glucose control (Table 2).

Table 2. Laboratory Characteristics

Laboratory	Mean ± SD
Hemoglobin (g/dL)	9.003 ± 8.372
Albumin (g/dL)	2.417 ± 0.726
Random Blood Glucose (mg/dL)	115.746 ± 52.357
Ureum (mg/dL)	89.531 ± 38.893
Creatinine (mg/dL)	10.295 ± 3.314

The microbiological profile of peritoneal dialysis-related peritonitis in this study population was listed in Table 3. There were 36 (53.7%) patients with monomicrobial infection, which were mostly caused by gram-negative bacterial infection in 18 cases, followed by gram-positive in 15 cases, tuberculosis infection in 2 cases, and fungal infection in 1 case. There were 5 cases (7.5%) of polymicrobial infections, which were multiple gram-positive organisms found in 3 patients (*Staphylococcus aureus – Staphylococcus hominis, Staphylococcus epidermidis – Staphylococcus haemolyticus, Streptococcus mitis – Streptococcus gordonii*), and mixed gram-negative-positive organisms found in 2 patients (*Staphylococcus haemolyticus – Klebsiella pneumoniae, Pseudomonas aeruginosa – Acinetobacter baumanii – Enterococcus faecium*). In this study, there were 26 (38,8%) culture-negative cases, and based on outcomes (Table 4), there were 58 patients (86.6%) who recovered from peritonitis, 6 patients (9%) had catheter removal, and 3 patients (4.5%) died.

Table 3. Microbiological Profile

Pathogens	N = 67 (%)
Gram Positive	**15 (22.3%)**
Staphylococcus Aureus	3
Staphylococcus Epidermidis	2
Staphylococcus Haemolyticus	4

Staphylococcus Hominis	1
Staphylococcus Warneri	1
Enterococcus Faecalis	4
Gram Negative	**18 (26.9%)**
Pseudomonas Aeruginosa	11
Pseudomonas Fluorescens	1
Pseudomonas Putida	1
Escherichia Coli	3
Klebsiella Pneumoniae	1
Enterobacter aerogenes	1
Other	**3 (4.5%)**
Candida Tropicalis	1
Mycobacterium Tuberculosis	2
Polymicrobial	**5 (7.5%)**
Negative culture	**26 (38.8%)**

Table 4. Outcome

Outcome	**N = 67**
Recovery from peritonitis	58 (86.6%)
Catheter removal	6 (9%)
Died	3 (4.5%)

Discussion

This study investigated the microbiological profile in patients with peritonitis undergoing CAPD, which was the most common complication in this patients.[6] Gram-negative bacteria were the most common pathogen found in culture examinations, presented in 18 (26.9%) cases, followed by gram-positive bacteria in 15 (22.3%) cases, and other pathogens in 3 (4.5%) cases which included 1 fungal peritonitis and 2 tuberculosis peritonitis. Gram-negative predominance (26.9%) aligns with Solin et al.'s Indonesian cohort (29.4%) but contrasts with Ozdemir's Turkish data (32.1% Gram-positive). Regional variations in antibiotic prophylaxis may explain this disparity.[7,8]

In this study, the most common gram-negative bacteria were *Pseudomonas* sp, as many as 11 cases (61.1%) out of a total of 18 gram-negative cases. Özdemir's study showed that the most common gram-negative bacteria found were *Acinetobacter* sp. and *Pseudomonas* sp.[8] The most common gram-positive bacteria found in this study were coagulase-negative *Staphylococcus,* as many as 8 cases (53.4%) out of 15 gram-positive cases. This result was similar to Solin et al and Hu et al.[7,9] In addition, *Pseudomonas* was the most common pathogen found in 11 (16.4%) cases out of 67 culture examinations.

The 38.8% culture-negative rate, higher than International Society for Peritoneal Diagnosis (ISPD)'s recommended <15%, likely reflects non-compliance with effluent sampling guidelines (e.g., delayed processing, delayed sample delivery). Similar rates in Solin et al. (34.3%) suggest systemic challenges in resource-limited settings. Future interventions should prioritize bedside inoculation and rapid transport to mitigate false negatives.[7] Meanwhile, Abaraham et al showed a higher result of culture-negative cases with 64.7% of cases.[5] All 3 results did not meet the criteria recommended by the ISPD guidelines.[6] These guidelines recommend that sample collection should be performed at the bedside by inoculating 5-10 mL of effluent into two blood culture bottles (aerobic and anaerobic). Specimens must be delivered to the laboratory within 6 hours of collection. When immediate delivery is not possible, specimens should be maintained at 37°C.[6]

The difference in negative culture results among the 3 studies could be due to a different sampling process or examination methods that did not follow ISPD recommendations. In this study, the sample collection and delivery process were non-ISPD-compliant sampling, which caused the inoculation process not to be conducted directly bedside, resulting in a time gap between sample collection and effluent fluid inoculation into *BACTEC* culture bottles, and varied sample delivery times.

The examination of effluent fluid was limited to one sample due to the unavailability of anaerobic culture examinations and cost-control limitations in patient care. These factors likely contributed to the higher percentage of negative cultures compared to ISPD standards. This resulted in peritonitis, which could be caused by prior antibiotic exposure, non-ISPD-compliant sample collection, or the use of substandard techniques and culture media.[6]

Our data suggest, 58 patients (86.6%) showed improvement from peritonitis, these observations align with Abraham et al, where the total cases showing improvement were 95.5%.[5] The high rate of improvement could be related to the adequate management, empirical antibiotic use, and supported by culture results and antibiotic resistance testing.

Catheter removal was performed in 6 (9%) cases, and patients were transferred to hemodialysis. This study showed better outcomes compared to Abraham et al, with 19.3%, and Phui et al, with 26.6% of catheter removal cases.[5,10] In this study, indications for catheter removal were peritonitis caused by tuberculosis infection, fungal peritonitis, and recurrent peritonitis. Culture results included *Candida Tropicalis* in 1 patient, *Mycobacterium Tuberculosis* in 2 patients, and *Pseudomonas aeruginosa* in 3 patients. These results were similar to the study by Phui et al., where the majority of catheter removal cases were due to *Pseudomonas* infections. Peritonitis caused by *Pseudomonas, tuberculosis,* or *fungi* was associated with prolonged infections, antibiotic resistance, catheter removal, and poor outcomes.[4,10]

Our data demonstrate the risk factors and demographics of CAPD-associated peritonitis in our patient population. All patients had hypertension (100%), and 31.3% had diabetes mellitus. These observations align with findings from an Indian study reporting that diabetes increased Gram-negative infection risk (OR 2.3).[11] The mean CAPD duration was 29 months, consistent with ISPD guidelines indicating that long-term CAPD (>2 years) elevates biofilm-related infection risk.[6]

Our data suggest mortality rate (4.5%) was lower than North China (14.7%) but similar to Sarawak, Malaysia (5.1%),[10] possibly due to comorbidities, our cohort had fewer diabetics (31.3% vs. 45% in Hu et al.).[9] High Pseudomonas resistance in China vs. our isolates' susceptibility to empiric ceftazidime. The microorganisms causing peritonitis in the deceased patients included *Escherichia Coli*, *Enterococcus Faecalis,* and one case with no microorganisms found. The comorbidities in the patients included pneumonia, diarrhea, chronic hepatitis B, and diabetes mellitus. In this study, peritonitis was not the main cause of death, but all 3 patients were admitted with pneumonia, and respiratory failure was the cause of death.

Conclusion

Gram-negative bacteria, notably Pseudomonas, dominated CAPD peritonitis in our cohort. Despite suboptimal culture yields, adherence to ISPD sampling guidelines and targeted antibiotic therapy improved outcomes (86.6% cure rate). Improved sampling techniques and examination methods following ISPD recommendations could reduce negative culture rates and enhance the management of peritonitis in CAPD patients. Future studies should prospectively evaluate resistance patterns.

Limitations of the Study

This study has several limitations. First, its retrospective design may introduce selection bias, as only patients with complete medical records and culture results were included.

Second, the high culture-negative rate likely reflects non-ISPD-compliant sampling techniques (e.g., lack of bedside inoculation, delayed sample delivery), unavailability of anaerobic culture examinations, and cost-control limitations in patient care.

Declarations

Ethics approval and consent to participate

This study has received approval from The Hasan Sadikin Hospital Bandung Research Ethics Committee under reference number DP.04.03/D.XIV.6.5/302/2024.

Competing interests

There are no conflicts of interest in writing this article.

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Author's Contribution

Idea/concept: DA. Design: DA. Control/supervision: LS, RA. Data collection/ processing: DA. Analysis/interpretation: DA, LS, RA. Literature review: -. Writing the article: DA. Critical review: -. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Review Article

Automated Peritoneal Dialysis Versus Continuous Ambulatory Peritoneal Dialysis for People with Kidney Failure: A Review

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ABSTRACT

Background: Peritoneal dialysis is a well-established renal replacement therapy for patients with end-stage kidney disease, offering two primary modalities: Automated Peritoneal Dialysis (APD) and Continuous Ambulatory Peritoneal Dialysis (CAPD). Both methods provide effective solute and fluid removal, cost-effectiveness, accessibility, and impact on patient lifestyle that vary significantly, particularly in resource-limited settings such as Indonesia.
Objective: This review compares APD and CAPD in terms of efficacy, convenience, cost-effectiveness, and accessibility, with a focus on their implications for patient care in Indonesia.
Methods: A systematic review of relevant literature was conducted to evaluate the benefits and limitations of both dialysis modalities. Factors such as treatment outcomes, cost, infection risk, insurance coverage, and availability were analyzed to determine the most suitable option for different patient populations.
Results: APD offers greater convenience, improved quality of life, and a lower risk of peritonitis due to fewer disconnections. However, its higher cost, dependency on electricity, and limited insurance coverage reduce its accessibility. Conversely, CAPD is more cost-effective, widely available, and covered by BPJS Kesehatan, making it the preferred option for many patients. Despite its affordability, CAPD requires greater patient commitment, increases peritonitis risk, and may interfere with daily activities.
Conclusions: Both APD and CAPD are effective dialysis options, but CAPD remains the more accessible and cost-effective choice in Indonesia. APD may benefit select populations if economic and infrastructural challenges are addressed. Expanding insurance coverage, reducing equipment costs, and improving infrastructure are crucial to increasing APD accessibility and optimizing dialysis care in Indonesia.
Keywords: Peritoneal Dialysis, Automated Peritoneal Dialysis, Continuous Ambulatory Peritoneal Dialysis, Chronic Kidney Disease Stage V, Quality of Life.

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Introduction

Those with stage V or terminal chronic kidney disease—defined by a glomerular filtration rate less than 15 mL/min/1.73 m^2—need therapeutic intervention to replace renal function. Either kidney transplantation or one of the current dialysis modalities—hemodialysis (HD) or peritoneal dialysis (PD)—may be part of this treatment.[1] By eliminating solutes and water, both modalities of dialysis help to restore electrolyte balance and correct acidosis, therefore facilitating renal replacement. Whereas HD depends on blood flow via an extracorporeal circuit through vascular access, PD uses the peritoneal membrane as the dialysis interface to allow the exchange of water and solutes between the peritoneal capillaries' blood and the dialysate that is injected into the peritoneal cavity via a catheter. The patient or carer is trained by qualified nursing staff to use hygienic methods to attach the transparent, flexible plastic bags containing the dialysis solution to the catheter at home or in another appropriate location (like their place of employment).[2] Compared to HD, PD has the major benefit of portability because the patient or carer administers the therapy, allowing for more freedom to travel and greater autonomy from nursing and medical staff.[3]

Globally, Automated peritoneal dialysis (APD) acceptance varies depending on a number of factors, including patient preferences, health-care infrastructure, and economic considerations. The use of APD has grown in industrialized nations as a result of technological developments and a move toward home-based therapy.[4] However, APD adoption is still low in many poor countries, including Indonesia. Widespread healthcare is hampered by issues including exorbitant prices, a shortage of qualified healthcare workers, and restricted equipment availability. PD use in Indonesia has decreased, falling from 6.6% in 2014 to 1.6% in 2018.[5] To date, there has been little progress in the government's and the Indonesian Nephrologist Organization's (PERNEFRI) efforts to promote Parkinson's disease. APD is a viable choice for PD optimization in Indonesia due to its ease of use and possible advantages. However, a number of obstacles prevent its widespread use.[5]

The many forms of APD include tidal PD (TPD), nocturnal intermittent PD (NIPD), intermittent PD (IPD), and continuous cyclical PD (CCPD). A minimum of three to five exchanges must be made each day by the patient or caregiver in CAPD.[6,7] A renewed interest in APD has been sparked by the many problems with CAPD, such as decreased patient motivation over long periods of time, procedural errors, and recurrent peritonitis.[8,9] For all patients judged suitable for PD, APD has been proposed as a substitute for CAPD. APD is recommended by the Renal Association (UK) and the European Best Practice Guidelines for peritoneal dialysis for patients with high peritoneal transporter status, especially those who need to avoid excessive volumes.[10] Research suggests that CAPD may be less expensive than HD.

Due to a number of issues, such as exorbitant prices, a small market, and a lack of knowledge, APD is currently not widely accessible in Indonesia. Numerous actions could be taken to increase accessibility. To increase availability, medical device manufacturers must be encouraged to enter the Indonesian market with APD equipment and supplies.[11] In addition, lowering the financial burden on patients through the implementation of subsidies or the expansion of insurance coverage would make APD a more attractive alternative. In order to ensure appropriate implementation and patient support, it is also crucial to establish training programs for healthcare workers to expand their expertise with APD. Additionally, patients and their families can better comprehend APD as a treatment option by increasing public awareness through educational programs. Finally, to make it easier to distribute APD equipment throughout Indonesia's various and geographically difficult regions, infra-structure and logistics must be improved.[8] Patients in Indonesia may find APD to be a more affordable and accessible renal replacement treatment if these important concerns are addressed. The effectiveness of Continuous Ambulatory Peritoneal Dialysis (CAPD) and

Automated Peritoneal Dialysis (APD) was evaluated in this review.

Methods

The databases chosen for this study were PubMed and Google Scholar, utilizing the terms peritoneal dialysis, automated peritoneal dialysis, and continuous ambulatory peritoneal dialysis, chronic kidney disease stage V, quality of life. The criteria for inclusion were: (a) evaluate the effectiveness of Continuous Ambulatory Peritoneal Dialysis (CAPD) and Automated Peritoneal Dialysis (APD) in patients with stage V CKD; (b) publish between 2018 and 2024; (c) have papers written in English or Bahasa Indonesia; and (d) be human studies. (a) discussing various types of dialysis methods; (b) texts that were not published in English or Bahasa Indonesia; and (c) animal studies were the exclusion criteria. The search strategy will use a combination of MeSH terms and keywords, such as ("automated peritoneal dialysis" OR "APD") AND ("continuous ambulatory peritoneal dialysis" OR "CAPD") AND ("kidney failure" OR "end-stage renal disease" OR "ESRD") AND ("outcomes" OR "mortality" OR "survival" OR "peritonitis" OR "quality of life" OR "cost-effectiveness"). Authors selected a collection of papers and analyzed databases. After duplicate papers were eliminated, a preliminary screening was carried out by looking at the publications' titles and abstracts. The materials were filtered based on the preset inclusion and exclusion criteria after a comprehensive screening that involved reading the entire text. The author was consulted for adjudication when the writers' opinions were inconsistent throughout the screening process.

Result and Discussion

Ninety-two records advanced to full-text evaluation after 87 records were eliminated at the initial screening stage due to title and abstract screening. Of these, 22 studies were left for additional assessment after 70 records were eliminated for lacking sufficient data. Five papers that satisfied all inclusion criteria were included in the systematic review after 17 studies that merely included study protocols were eliminated during the final screening stage.

Risk of Bias Assessment

The risk of bias assessment for the five included cohort studies, evaluated using the Newcastle-Ottawa Scale (NOS), showed generally low to moderate risk across domains. In the selection domain, three studies scored three out of a maximum of four stars, two studies have a maximum score indicating stronger methodological rigor in selecting study participants. For comparability, all studies consistently received two stars, reflecting adequate control for potential confounders. The Exposure domain revealed more variation: two studies scored two out of three stars, while three studies obtained maximum stars, suggesting stronger methodological rigor in exposure ascertainment. Overall, the NOS results indicate that all studies were of reasonable quality.

Table 1. Risk of bias across the studies

Author, year	Selection	Comparability	Exposure	Overall
Yang *et al.*, 2018 (9)	***	**	***	
Wang *et al.*, 2020 (6)	***	**	**	
Lin *et al.*, 2020 (12)	****	**	***	
Li *et al.*, 2018 (13)	****	**	***	
Zhong *et al.*, 2020 (15)	***	**	**	

Adequacy in Peritoneal Dialysis

According to the International Society of Peritoneal Dialysis (ISPD) Guidelines, the effectiveness of peritoneal dialysis should be evaluated not only with numbers but also through a comprehensive clinical assessment. This includes looking at hemoglobin levels, response to erythropoiesis-stimulating agents, calcium and phosphorus metabolism, blood pressure control, nutritional status and appetite, volume status with adequate ultrafiltration to prevent overload, and the patient's overall quality of life.[12]

For patients who still have residual renal function, the National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF KDOQI) recommends that the total Kt/V (from both peritoneal clearance and residual renal clearance) should be at least 1.7 per week, measured at the end of the first month on PD and then every four months thereafter.[10] To preserve remaining kidney function, steps should be taken such as prescribing angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers for hypertensive patients, and avoiding nephrotoxic substances like iodinated contrast media, aminoglycosides, and nonsteroidal anti-inflammatory drugs.[13]

In patients without residual renal function, the minimum recommended PD dose is a weekly peritoneal Kt/V of at least 1.7. This should also be checked at one month and then every four months.[14] For those who fall short of this target, the clearance of small molecules can be improved by increasing exchange frequency and/or infusion volume. In APD, strategies like adding a daytime "wet" dwell or performing an extra daytime exchange can help improve adequacy.[15] Medium molecule clearance, on the other hand, depends more on the length of time the dialysate remains in the peritoneal cavity.

Another important factor influencing solute clearance is the peritoneal transport status, determined through the peritoneal equilibrium test (PET). Traditionally, the PET involves instilling 2 L of 2.5% glucose dialysate (D) into the peritoneal cavity, then collecting dialysate samples at 0, 2, and 4 hours after infusion.[16] A plasma sample (P) is drawn at the 2-hour mark. Based on the creatinine D/P ratio at the second and fourth hours, the glucose D/D_0 ratio, and the total dialysate volume drained after four hours, patients are categorized into four transporter types.[17]

Preparation for PET differs slightly between CAPD and APD patients. For CAPD, the PET is usually performed after the overnight dwell has been drained, ensuring the peritoneal cavity is empty before instilling the 2 L test solution. For APD, the test is best scheduled after

a night of cycling, with the machine disconnected and the abdomen drained prior to the PET fill. In some cases, a short equilibration dwell may be used before the test to simulate CAPD conditions.[16]

Regarding transport characteristics: High transporters quickly reach a dialysis-to-plasma equilibrium for urea and creatinine, but they also absorb glucose rapidly, causing the osmotic gradient to disappear sooner. They tend to benefit from shorter dwell times.[18] Low transporters equilibrate more slowly, retain the osmotic gradient longer, and often require longer dwell times with larger fill volumes to optimize clearance.[19]

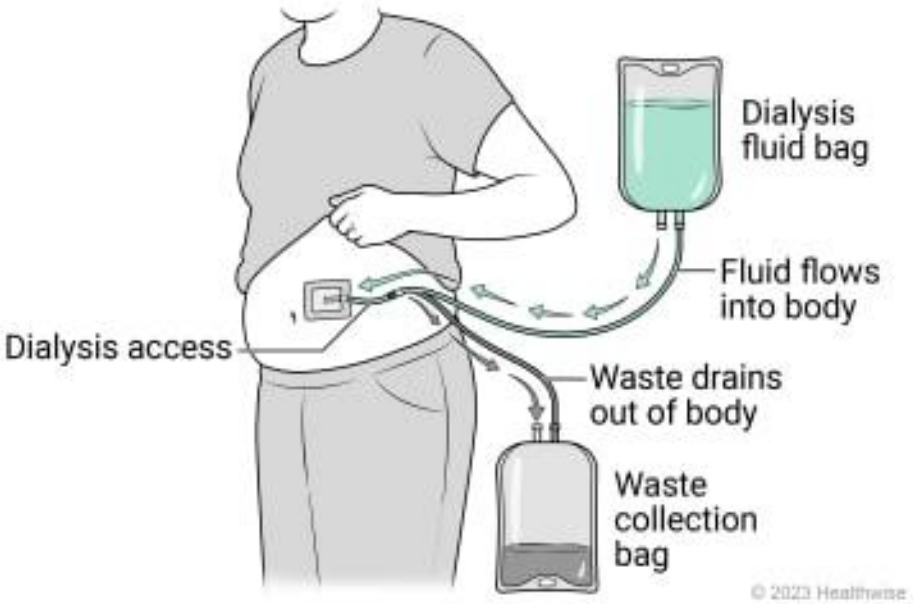

Figure 2. Scheme of Continuous Peritoneal Dialysis

Comparison of Clinical Outcomes and Patient Selection Criteria Between APD and CAPD

Critical clinical outcomes, such as mortality, peritonitis risk, switching to alternative dialysis modalities, hernias, PD fluid leaks, PD catheter removal, and hospital admissions, were not significantly different between APD and CAPD, according to the prior study. The two PD techniques' dialysis adequacy metrics were similar.[20]

There is ongoing debate over the relative effects of APD and CAPD on peritonitis rates; some research favor APD, while others support CAPD, and a small number of studies find similar rates of peritonitis in both conditions. There were no notable variations in the number of patients who developed peritonitis during the research period, according to our meta-analysis.[21] An analysis of a large group of patients (> 30,000) who started peritoneal dialysis over a three-year period showed that patients on automated peritoneal dialysis had significantly better dialysis technique and patient outcomes during the first year of dialysis.[6] Even after adjusting for age and diabetes status, there were still significant differences in patient and technique survival, even though patients on APD were younger than those on CAPD. Unlike this study, our evidence—derived from RCTs—did not show that APD and CAPD were superior in terms of patient or technique survival.[22] According to the CANUSA study and other studies, patients with CAPD who have high or rapid peritoneal membrane solute transport characteristics have higher mortality rates. There is currently no proof that APD leads to higher survival rates, even if it may offer these patients better small solute clearances than CAPD.[23] Although APD has the potential to provide better small solute clearances than CAPD, our meta-analysis found no differences in dialysis adequacy. This is not

surprising because previous studies have shown that the differences between the two modalities for creatinine clearances are, at most, negligible in real-world situations.[24]

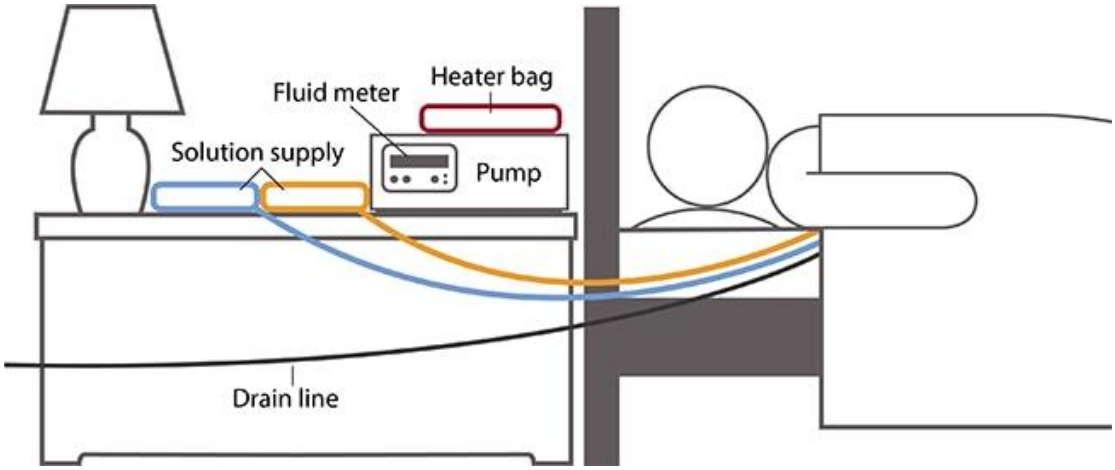

Figure 3. Scheme of Automated Peritoneal Dialysis

The selection between Automated Peritoneal Dialysis (APD) and Continuous Ambulatory Peritoneal Dialysis (CAPD) depends on various factors, including patient characteristics, clinical parameters, and lifestyle considerations.[23] Since APD is done overnight using a cycler, enabling patients to continue their regular activities uninterrupted, it is typically better suited for younger, more energetic people. Because the shorter dwell periods reduce glucose absorption and peritoneal membrane damage, it is especially advantageous for patients with high or high-average peritoneal transport characteristics. Additionally, because APD includes fewer connections throughout the day, which lowers the chance of infection, it may be beneficial for people who are more susceptible to peritonitis.[3] Because APD can be used in conjunction with daytime exchanges to maximize fluid balance, patients with intact residual renal function may also benefit from it. Furthermore, because APD does not require multiple manual exchanges during the day, it is a good choice for people who have trouble moving about or who have trouble sleeping.[4]

On the other hand, because CAPD does not require a machine and may be simpler to administer, it is frequently chosen for older patients or those with cognitive difficulties. Since the extended dwell durations enhance solute clearance, it is especially advantageous for people with low or low-average peritoneal transport characteristics. Because CAPD does not rely on automated technology, it is also more accessible to patients who have limited access to electricity or APD supplies.[1] Additionally, CAPD might be a more sensible choice for patients who would rather use a less complicated, machine-free dialysis technique. Because CAPD requires no additional equipment and fewer specialized consumables than APD, it is frequently more cost-effective in environments with limited resources.

Complications: CAPD vs. APD

1. Pericatheter leak

The break-in time is the amount of time that passes between inserting a catheter and starting peritoneal dialysis (PD). Break-in, a preventive measure used to avoid mechanical and infectious problems, is recommended for patients starting elective peritoneal dialysis for a period of two weeks.[25] It is better to administer the medication while supine and with a lower infusion volume for an unanticipated onset of Parkinson's disease. Peritoneal dialysis may be temporarily stopped or the dialysis schedule changed to intermittent overnight dialysis in the event of pericatheter peritoneal fluid leakage. The catheter needs to be replaced if the leak

continues.[26] CAPD shows a tendency for more frequent leaks. In one study, 25% (18 out of 72) of patients on CAPD experienced pericatheter leaks, while none of the APD-only patients did (though the difference was not statistically significant).[27]

2. Drainage failure (Catheter dysfunction)

There are two types of drainage failure: either the catheter does not infuse or drain, which is caused by folds and intramural blockage, or it infuses without draining, which is usually linked to intestinal constipation, tip migration, or omental sequestration.[28] There's limited direct comparison data between CAPD and APD on catheter dysfunction. One study focusing on unplanned dialysis starts (APD vs. CAPD) found no difference in catheter malposition or similar mechanical complications between groups.[29]

3. Hernias

Because of increased intra-abdominal pressure, 10% to 25% of peritoneal dialysis patients may develop hernias, which usually require surgery. The volume infused, recent surgery, obesity, and polycystic kidney disease are examples of potential risk factors.[30] If the patient has residual renal function, corrective surgery can be performed without stopping treatment. As a result, peritoneal dialysis can be started again with a lower infusion volume one or two days after surgery.[31] CAPD is more prone to hernias than APD, likely due to higher daytime intra-abdominal pressure. A 2022 study reported 0.08 hernias per patient-year in CAPD patients versus just 0.01 in APD-only patients (though not statistically significant).[27] Another cohort noted that 63% of established PD patients on CAPD developed hernias versus 47% on APD.[32]

4. Hydrothorax

A rare side effect of dialysate migrating into the pleural cavity through lymphatic channels or a congenital diaphragmatic abnormality is hydrothorax. Pleural fluid analysis, which shows increased glucose and decreased protein contents, is used to make the diagnosis; technetium scintigraphy and contrast-enhanced CT of the peritoneal cavity may also be used.[33] The course of treatment entails stopping dialysis for two to six weeks and putting intra-abdominal pressure-lowering techniques into practice, such as switching from CAPD to nocturnal APD with a dry peritoneal cavity during the day. Pleurodesis, surgery, and maybe technique transfer may be necessary if there is no improvement.[29] Dialysate leakage into the chest (hydrothorax) is recognized as a mechanical complication in PD that can affect either modality. However, there's no clear data differentiating CAPD and APD rates.

5. Edema and ultrafiltration failure

In dialysis patients, hypervolemia is a risk factor for cardiovascular disease and death on its own. It is associated with inflammation, dietary alterations, and ventricular hypertrophy.[23] Excessive sodium and fluid intake, decreased residual renal function, noncompliance with dialysis protocols, excessive dialysate absorption during prolonged exchanges, inadequate use of hypertonic solutions, mechanical problems (e.g., malfunctioning catheters and leaks), discrepancies between dialysis prescriptions and patient peritoneal equilibration tests, and ultrafiltration failure are among the causes of hypervolemia in peritoneal dialysis.[24] In a single-center study of CAPD patients, ultrafiltration failure (UFF) occurred in 15.5%, with incisional or exit site leaks (such as edema) reported in 4.4% of patients.[34] Comparative APD data on these issues is infrequent.

6. Weight gain, hypertriglyceridemia and hyperglycemia

Dialysate glucose absorption can result in calorie excess, which can cause hyperglycemia, hypertriglyceridemia, and weight gain.[24] To lessen the need for hypertonic bags, the treatment consists of a low-calorie diet, increased physical activity, and restricted water intake. An alternate therapeutic option for hypertriglyceridemia is the administration of dose fibrates that are regulated based on renal function. Insulin and/or oral hypoglycemic medications may need to be modified in response to hyperglycemia. If improvement is not obtained, consider changing the dialysis method. All PD patients—regardless of modality—absorb glucose, increasing the risk for weight gain, elevated triglycerides, and

hyperglycemia. While no directly comparative rate data between CAPD and APD exists, such metabolic concerns are well-recognized complications of chronic PD.[25]

7. Encapsulating peritoneal sclerosis

In patients receiving long-term peritoneal dialysis, encapsulating peritoneal sclerosis is a rare complication that is associated with substantial morbidity and mortality. It usually arises from intestinal blockage and malnourishment.[26] There are no well-defined diagnostic criteria; instead, the diagnosis is based on morphological and functional features, such as intestinal blockage and peritoneal fibrosis encapsulation features. Anemia and hypo-albuminemia are common, as are anorexia, nausea, vomiting, and weight loss. Hemo-peritoneum and recurrent sterile peritonitis are two symptoms of encapsulating peritoneal sclerosis. Encapsulating peritoneal sclerosis is a rare but serious long-term complication of PD affecting around 2.5% of patients. There's no evidence indicating a difference in EPS rates between CAPD and APD.[35]

Although laparotomy is the only way to provide a definitive diagnosis, it is usually avoided due to the high dangers involved. Diverse intestine loop diameters, dilated and adherent loops, septate ascites, calcification, and thickening of the intestinal wall and peritoneal membrane are all visible on computed CT scans. Peritoneal dialysis should be stopped in addition to giving nutritional supplements, which are frequently parenteral. Although immune-suppression, tamoxifen, and corticosteroids have been identified as possible treatments, their effectiveness is yet unknown. Another therapeutic approach that might be considered is surgery.[28]

Cost-Effectiveness

Healthcare infrastructure, insurance coverage, patient accessibility, and financial limitations all affect how cost-effective APD and CAPD are in Indonesia. Because of its cheaper initial costs, less reliance on specialist equipment, and low electricity use, CAPD is typically the more economical choice in Indonesia. Many patients, especially those from lower socio-economic backgrounds, choose CAPD because it is readily accessible and funded by Indonesia's national health insurance program (BPJS Kesehatan). Because CAPD can be done at home instead of requiring frequent hospital trips, transportation and facility-related costs are further decreased.[5]

However, because APD requires an automated cycler, which is costly and not readily available in all parts of Indonesia, its starting expenses are greater. Treatment costs are further increased by the requirement for a steady supply of energy and specialist supplies including APD tubing and particular dialysate compositions. Furthermore, APD is now only partially covered by BPJS Kesehatan, which limits its accessibility for a significant section of the population. Even though APD may have benefits like better treatment adherence, lower risk of peritonitis, and an enhanced quality of life, these must be balanced against the much higher cost, especially for patients in rural areas with less developed healthcare systems.[11]

CAPD patients usually perform three to four exchanges daily, each involving about 2 liters of dialysate, so the total daily volume typically ranges from 6 to 10 liters. The volume per exchange may vary based on patient size, with smaller adults or children often using 1.5 liters per exchange, while regular-sized adults use 2 liters, and in some cases, up to 3 liters if tolerated comfortably.[36] In comparison APD commonly done overnight with a cycler, often involves around five cycles per night, each with approximately 2 liters of dialysate. This adds up to about 9 to 10 liters used during the night. If daytime exchanges are added, total daily volume can go even higher.[36]

A study conducted at Dr. Hasan Sadikin General Hospital between 2014 and 2017 showed that, in comparison to HD, CAPD decreased costs by about IDR 23,227,857 per patient. During this time, the CAPD program generated IDR 1,661,972,000 in total savings. According to these results, CAPD might lessen the financial strain on Indonesia's National Health Insurance

program. Although there is little precise evidence on APD's cost-effectiveness in Indonesia, its advantages—such as the opportunity for remote monitoring and a decrease in manual labor—might make it a good choice in the future.[5]

APD may still be more affordable for some Indonesian populations in spite of the increased expenses, especially for working-age patients who want flexibility to keep their jobs, which would lower indirect economic losses. Additionally, by possibly lowering hospitalization rates and CAPD-related consequences such infections and peritoneal membrane failure, APD may help reduce long-term healthcare expenses. However, governmental changes, increased insurance coverage, subsidies, and domestic manufacturing of dialysis equipment are required to lower prices and increase accessibility in order for APD to become more feasible in Indonesia.[11]

Table 2. Difference between Automated Peritoneal Dialysis (APD) and Continuous Ambulatory Peritoneal Dialysis (CAPD)

Aspect	Automated Peritoneal Dialysis (APD)	Continuous Ambulatory Peritoneal Dialysis (CAPD)
Definition	Uses an automated cycler to perform dialysis at night while the patient sleeps.	Manual dialysis performed during the day without a machine.
Schedule	Performed mostly at night (8–10 hours) with possible daytime exchanges.	Requires 3–5 manual exchanges per day, each lasting about 30–40 minutes.
Indications	Suitable for active individuals, working patients, and those with high peritoneal transport rates.	Preferred for elderly, cognitively impaired patients, or those with low peritoneal transport rates.
Convenience	More convenient for patients with a busy lifestyle; no interruptions during the day.	Requires adherence to a strict schedule, which may interfere with daily activities.
Equipment	Requires an automated cycler, tubing, and electricity.	No machine required; performed manually using gravity-based exchanges.
Risk of Infection	Lower risk due to fewer disconnections per day.	Higher risk due to multiple daily connections, increasing peritonitis risk.
Cost	Higher initial and maintenance costs due to the need for a cycler and specialized supplies.	More cost-effective, with fewer equipment requirements and lower electricity consumption.
Insurance Coverage (Indonesia)	Limited coverage under BPJS Kesehatan, making it less accessible.	Widely covered by BPJS Kesehatan, making it the more affordable option.
Electricity Dependency	Requires a stable electricity supply, which may not be available in all regions.	Does not require electricity, making it more suitable for remote or rural areas.
Impact on Work/Lifestyle	Allows patients to work or attend school without daytime interruptions.	Requires frequent breaks for dialysis exchanges, which may interfere with work or daily activities.
Complications	Lower risk of peritonitis, but possible issues with catheter function and machine dependence.	Higher risk of infections and peritoneal membrane failure due to more frequent exchanges.
Availability in Indonesia	Limited availability due to high costs and lack of widespread insurance support.	More accessible and widely used due to affordability and government support.

Conclusion

End-stage kidney disease can be effectively managed with both Automated Peritoneal Dialysis (APD) and Continuous Ambulatory Peritoneal Dialysis (CAPD), each of which has unique benefits and drawbacks. APD is the best option for people who are active or have high peritoneal transport rates because it provides increased convenience, a better quality of life, and a decreased risk of infection. Accessibility is severely hampered by its greater expenses, reliance on electricity, and restricted insurance coverage in Indonesia. On the other hand, many patients choose CAPD since it is

more affordable, accessible, and fully covered by BPJS Kesehatan, particularly in settings with low resources.

Individual patient needs, peritoneal membrane properties, lifestyle circumstances, and budgetary considerations should all be taken into account when choosing between APD and CAPD. APD offers more flexibility, but in order to make it more affordable and accessible in Indonesia, regulatory changes, increased insurance assistance, and better infrastructure are needed. Ultimately, the best dialysis results and quality of life for people with renal failure depend on a customized, patient-centered approach.

Declarations

Competing interests

The authors declare no conflict of interest.

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Case Report

Successful Management of Thyroid Storm with Continuous Renal Replacement Therapy without Plasma Exchange

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ABSTRACT

Thyroid storm is a life-threatening endocrine emergency that needs urgent management. Conventional therapies, however, may not always yield a satisfactory outcome. Hereby, we report a case of refractory thyroid storm with hemodynamic and cardiac instability that showed significant improvement following continuous renal replacement therapy (CRRT) instead of therapeutic apheresis. A 46-year-old woman presented with severe thyrotoxicosis and pneumonia. On admission, she was alert and hemodynamically stable. Examination revealed irregular tachycardia, persistent fever, exophthalmos, diffuse goiter, and bilateral pulmonary rales. Laboratory tests showed primary thyrotoxicosis, leukocytosis, and elevated procalcitonin consistent with sepsis. The Burch-Wartofsky score was 65, confirming thyroid storm. Despite optimal medical therapy, she deteriorated with loss of consciousness and unstable supraventricular tachycardia. Given the poor response, continuous venovenous hemofiltration (CVVH) was initiated for 33 hours, resulting in clinical improvement with reduction in free thyroxine (fT4), hemodynamic stabilization, and recovery of consciousness. While therapeutic plasma exchange (TPE) is the recommended adjunctive therapy for refractory thyroid storm per the ASFA 2016 guidelines, it is often unavailable in many centers, particularly in low-resource settings. CRRT may serve as an alternative, offering hemodynamic stabilization through mechanisms not yet fully understood. CRRT may be considered a safe and effective alternative treatment for thyroid storm in patients who are refractory to standard medical therapy, and particularly for those presenting with hemodynamic instability.

Keywords: Medical-treatment Refractory Thyroid Storm, Continuous Renal Replacement Therapy, Hemodynamic Instability.

Introduction

Thyroid storm is a critical and potentially fatal endocrine emergency. Several precipitating factors can trigger this condition in patients with underlying hyperthyroidism, including infections, myocardial infarction, stroke, heart failure, non-thyroid surgery, poor adherence to antithyroid medications, and pregnancy or labor. The first-line treatment typically involves high-dose antithyroid drugs in combination with glucocorticoids. These conventional therapies aim to suppress thyroid hormone synthesis and release, as well as mitigate the peripheral effects of excessive hormone levels.

However, in some cases, patients may not respond adequately to standard treatment, resulting in prolonged thyrotoxicosis and an increased risk of cardiovascular complications. According to the 2016 American Thyroid

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Association (ATA) guidelines, therapeutic plasma exchange (TPE) may be considered for patients who fail to respond to conventional therapies. Continuous renal replacement therapy (CRRT), though less commonly reported, may offer benefits by facilitating the clearance of medium-to-large molecules. This case report aims to describe the successful use of CRRT as an alternative to therapeutic plasma exchange in a patient with thyroid storm and hemodynamic instability refractory to standard therapy.

Case Illustration

A 46-year-old woman presented to the emergency department with a one-week history of fever and productive cough. Her medical history included uncontrolled hypertension. She also reported non-radiating chest pain, palpitations, reduced appetite, and a 15 kg weight loss over two months. Symptoms of chronic hyperthyroidism—frequent bowel movements, hair thinning, tremors, heat intolerance, and anxiety—had recently worsened.

On admission, she was alert. Vital signs were: blood pressure 150/90 mmHg, irregular pulse 150 beats/min, respiratory rate 26 breaths/min, and temperature 38 °C. Examination revealed bilateral pulmonary rales, exophthalmos, and diffuse thyroid enlargement (Fig. 1A, 1C).

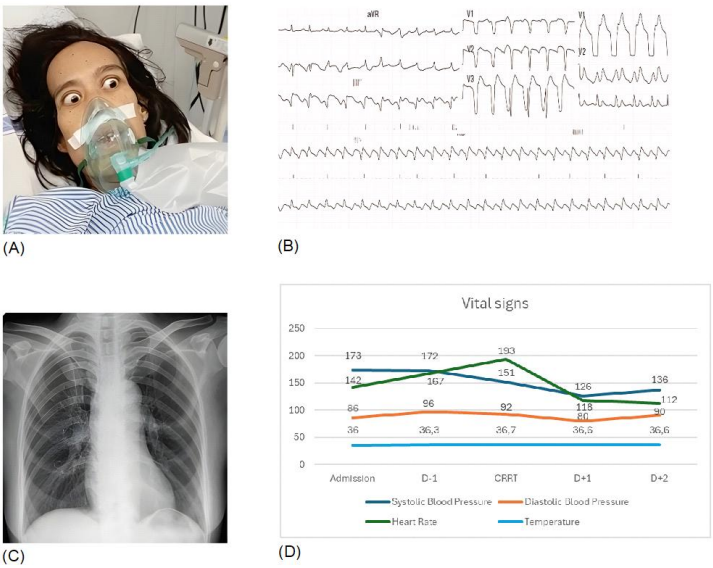

Figure 1. Clinical findings during hospitalization. (A) Exophthalmos, (B) Supraventricular tachycardia on electrocardiogram, (C) Bilateral pulmonary infiltrates, and (D) Trends of vital signs before and after CRRT

Laboratory results before and after continuous renal replacement therapy (CRRT) are shown in Table 1. The Burch-Wartofsky Point Scale (BWPS) score was 65, consistent with thyroid storm. Contributing factors included fever, tachycardia, atrial fibrillation, and signs of heart failure. On the following day, her condition worsened. Electrocardiography showed progression from atrial fibrillation to supraventricular tachycardia (Fig. 1B). Elevated cardiac troponin I confirmed non–ST elevation myocardial infarction (NSTEMI).

Table 1. Initial and Serial Laboratory Parameters before and after CRRT

Parameters	Before CRRT	After CRRT	Reference Value
Hemoglobin (g/dL)	9.9	8.7	11.5 – 15.5
White Blood Cell [WBC] (/uL)	14,400	12,700	5,000 – 10,000
Platelet count (/uL)	310,000	133,000	150,000 – 440,000
Procalcitonin (ng/dL)	2.25	< 0.07	<0.5: Normal 0.5 – <2: Systemic sepsis 2 – <10: Severe sepsis >=10 ng/mL: Septic shock
Cardiac Troponin I (ng/mL)	5.82	0.07	≤ 0.02
Ureum (g/dL)	27.9	N/A	16,5 – 48,5
Creatinine (g/dL)	0.61	N/A	0,50 – 0,95
Serum TSH	0.01	0.01	0.27 – 4.20
Serum free T4	>7.77	0.76	0.92 – 1.68

She received intravenous digoxin, hydrocortisone (300 mg/day), propylthiouracil (250 mg every six hours), propranolol (40 mg every six hours), and broad-spectrum antibiotics. Lugol's iodine was not available. Despite therapy, she developed hypotension refractory to vasopressors and inotropes, progressing to shock, decreased consciousness, and respiratory distress.

Continuous venovenous hemofiltration (CVVH) was initiated with a blood flow rate of 150–180 mL/min, post-dilution replacement fluid 1.5 L/hour, pre-dilution 500 mL/hour, and unfractionated heparin 600 U/hour. The session lasted 33 hours. Antithyroid drugs were continued without dose adjustment.

The patient demonstrated gradual clinical improvement. Heart rate decreased, mean arterial pressure (MAP) was sustained with reduced vasopressor support, and serum thyroid hormone levels declined notably by the third day of CVVH (Fig. 1D and Fig. 2). She was discharged on day 14 with a maintenance regimen of propylthiouracil 300 mg three times daily, propranolol 40 mg twice daily, and anticoagulation therapy for baseline atrial fibrillation.

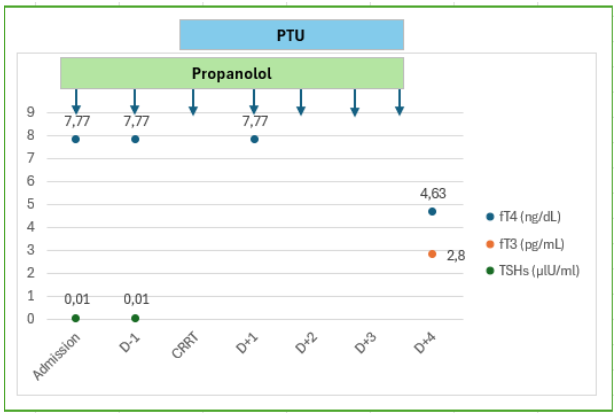

Figure 1. Trends of thyroid hormones before and after CRRT
fT4: free Thyroxine, fT3: free Triiodothyronine, TSHs: sensitive Thyroid Stimulating Hormone, WBC: White Blood Count, PCT: procalcitonin

Discussion

Thyroid storm carries a high mortality rate, ranging from 10% to 75%.[1] In severe cases that do not respond to conventional therapies, alternative treatments such as plasmapheresis and therapeutic plasma exchange (TPE) are often considered. These interventions are capable of removing both free and protein-bound thyroid hormones, as well as circulating autoantibodies.[2]

According to the 2016 American Thyroid Association (ATA) guidelines, TPE may be considered in patients with thyroid storm refractory to standard therapy or when conventional treatments are contraindicated.[3] Similarly, the 2019 American Society for Apheresis (ASFA) guidelines classify TPE as a second-line (Category II) therapy in thyroid storm management, especially when standard treatments are ineffective.[4,5] Despite these recommendations, the availability of TPE is very limited in many healthcare systems, particularly in resource-limited countries.

In the present case, we successfully utilized continuous renal replacement therapy (CRRT) alone, specifically continuous venovenous hemofiltration (CVVH), to manage a patient with thyroid storm complicated by shock, sepsis, and non–ST elevation myocardial infarction (NSTEMI) who failed to respond adequately to conventional therapy. While TPE is frequently employed in conjunction with CRRT,[6–8] This case highlights the potential utility of CRRT as a stand-alone modality in critical circumstances where TPE is unavailable.

A prior report has also described clinical improvement following CRRT without TPE in a similar setting.[8] Notable benefits included rapid reduction in body temperature, deceleration of heart rate, and improved blood pressure. The mechanisms by which CRRT contributes to such stabilization remain incompletely understood, but several plausible pathways have been proposed:

1. **Thermal modulation**: The use of large volumes of room-temperature dialysate and replacement fluids can induce mild hypothermia, attenuating the hypermetabolic state of thyrotoxicosis.
2. **Hormone-binding capacity**: Infusion of albumin and plasma components during CRRT may increase the binding of free thyroid hormones, thereby reducing the biologically active fraction.
3. **Cytokine clearance**: CRRT has been shown to facilitate the removal of pro-inflammatory cytokines and other mediators, which may mitigate the systemic inflammatory response and contribute to hemodynamic improvement in critically ill patients.[8]

Unlike intermittent hemodialysis, CRRT provides continuous solute and fluid removal over 24 hours, making it more tolerable for patients with unstable hemodynamics. Although TPE is highly effective—removing up to 80% of circulating T_3 and T_4—its effects are transient, typically lasting only 24–48 hours, and may be associated with rebound thyrotoxicosis if not accompanied by antithyroid medication.[4,9] Thus, ongoing pharmacologic therapy remains essential regardless of extracorporeal modality.

Limitations of this report include the description of a single case, absence of direct measurements of hormone-binding or cytokine clearance during CRRT, and lack of a head-to-head comparison with TPE. Nevertheless, this case adds to the growing body of evidence suggesting that CRRT may provide meaningful clinical benefit in thyroid storm, particularly in resource-limited settings where TPE is not readily accessible.

Conclusion

Early recognition and aggressive management of thyroid storm are essential to reduce its high mortality. While the 2016 ATA and 2019 ASFA guidelines recommend TPE as a second-line therapy in refractory cases, access remains limited in many healthcare settings. This case highlights that CRRT, particularly in patients with shock, sepsis, and hemodynamic instability,

may provide meaningful clinical benefit even in the absence of TPE. Despite the limitations of a single case report, our findings support consideration of CRRT as a feasible therapeutic option for critically ill patients with thyroid storm when TPE is unavailable.

Declarations

Competing interests

The authors declare no conflict of interest.

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