

Role of Plasmapheresis in Renal Transplantation

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Cite this paper as: Enas Abdelbaset Labib, Abdelkader Ahmed Hashim, Abd El Rhman Abdelhamid Elsayed, Walid Ahmed Bichari, (2025) Role of Plasmapheresis in Renal Transplantation. *Journal of Neonatal Surgery*, 14 (8s), 653-659.

ABSTRACT

Focal segmental glomerulosclerosis (FSGS) is a progressive kidney disease that frequently leads to end-stage renal disease (ESRD) and is a major cause of nephrotic syndrome. In patients undergoing renal transplantation, the recurrence of primary FSGS poses a significant challenge, as it can lead to graft dysfunction and loss. The pathogenesis of recurrent FSGS is not completely understood, but it is believed that circulating permeability factors contribute to podocyte injury, leading to glomerular damage and proteinuria. Plasmapheresis, also known as therapeutic plasma exchange (TPE), has emerged as a key strategy for both the prevention and treatment of recurrent FSGS. By removing these circulating factors, plasmapheresis aims to reduce proteinuria and preserve graft function. However, the efficacy of plasmapheresis is highly variable, and many patients require adjunctive therapies to achieve remission. This review explores the pathophysiology of recurrent FSGS, associated risk factors, and the role of plasmapheresis in disease management. Despite its promise, challenges remain, including the need for standardized treatment protocols and better predictors of response. Future research should focus on refining patient selection, optimizing treatment strategies, and exploring novel therapeutic approaches to improve outcomes in renal transplant recipients with recurrent FSGS.

Keywords: Focal segmental glomerulosclerosis, renal transplantation, plasmapheresis, proteinuria, nephrotic syndrome, podocyte injury, graft survival, therapeutic plasma exchange.

1. INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a histopathological pattern of kidney injury that can arise from various etiologies, including genetic mutations, infections, toxins, and hyperfiltration injury. However, primary FSGS, characterized by an idiopathic cause, is particularly aggressive and often leads to end-stage renal disease (ESRD). Among patients requiring renal transplantation, FSGS remains a leading cause of graft loss due to its high recurrence rate, which poses a significant challenge to long-term transplant success (1).

The recurrence of FSGS in the renal allograft is primarily linked to the presence of circulating permeability factors that induce podocyte injury and disrupt the integrity of the glomerular filtration barrier. This results in early-onset nephrotic-range proteinuria, which, if left untreated, can rapidly progress to graft failure. Identifying effective strategies to prevent and manage recurrent FSGS is crucial for improving transplantation outcomes (2).

Plasmapheresis has emerged as a key therapeutic intervention for recurrent FSGS, based on the hypothesis that removing circulating permeability factors can mitigate podocyte damage and reduce proteinuria. Since its first reported success in the 1980s, plasmapheresis has been widely used in transplant recipients with FSGS recurrence. Despite its potential benefits, the response to plasmapheresis varies among patients, and there is no universal consensus on the optimal frequency, duration, or timing of treatment. Additionally, plasmapheresis is often used in conjunction with immunosuppressive therapies, such as rituximab or calcineurin inhibitors, to enhance its effectiveness (3).

This review aims to study the role of plasmapheresis in prophylaxis and treatment of primary focal segmental glomerulosclerosis in patients undergoing renal transplantation, the directions of plasmapheresis in managing this complex disease.

2. PATHOPHYSIOLOGY OF RECURRENT FSGS

Recurrent focal segmental glomerulosclerosis (FSGS) after renal transplantation is a complex phenomenon with multiple underlying mechanisms. Unlike secondary forms of FSGS, which are associated with known etiologies such as infections, toxins, or hyperfiltration, primary FSGS is believed to be mediated by systemic factors that cause direct podocyte injury. Recurrence of FSGS post-transplant suggests that these factors persist even after the native kidneys are removed, indicating an underlying circulating pathogenic mechanism (1).

➤ Role of Circulating Permeability Factors

One of the most widely accepted theories explaining recurrent FSGS is the presence of circulating permeability factors that directly damage podocytes, leading to proteinuria and glomerulosclerosis. These factors are believed to alter the integrity of the glomerular filtration barrier by affecting the cytoskeleton and adhesion properties of podocytes. Several candidate permeability factors have been proposed, including: (4).

- **Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR):** Elevated levels of suPAR have been detected in patients with recurrent FSGS. It is thought to activate integrins on podocytes, leading to cytoskeletal disruption and increased glomerular permeability.
- **Cardiotrophin-like Cytokine Factor 1 (CLCF1):** This factor has been implicated in inducing podocyte dysfunction, although its exact role remains under investigation.
- **Anti-CD40 Autoantibodies:** Some studies suggest that immune-mediated mechanisms involving anti-CD40 antibodies contribute to podocyte injury in recurrent FSGS.
- **Other Unidentified Plasma Factors:** Some patients with recurrent FSGS demonstrate rapid improvement following plasmapheresis, supporting the hypothesis that unidentified circulating factors play a role in disease pathogenesis.

While these factors are strong candidates, no single biomarker has been definitively proven to be responsible for all cases of recurrent FSGS. The heterogeneity of the disease suggests that multiple factors may be involved, either alone or in combination, leading to variability in clinical presentation and response to therapy (5).

➤ Podocyte Injury and Glomerular Barrier Dysfunction

Podocytes are highly specialized epithelial cells that form the outer layer of the glomerular filtration barrier. They maintain structural integrity through their complex interdigitating foot processes, which are connected by slit diaphragms composed of proteins such as nephrin and podocin. When podocytes are injured or lost, the filtration barrier becomes compromised, leading to increased permeability and proteinuria (2).

In recurrent FSGS, permeability factors alter the podocyte cytoskeleton, causing effacement of foot processes. This disruption weakens the slit diaphragm and results in the leakage of proteins into the urine. Podocyte detachment may also occur, leading to progressive glomerular scarring and loss of renal function (6).

Additionally, the degree of podocyte injury correlates with disease severity. Some patients with early-stage recurrence exhibit mild foot process effacement and respond well to plasmapheresis, whereas others with more extensive podocyte loss may develop irreversible glomerular damage, leading to graft failure (7).

➤ Role of Immune Dysregulation

Although FSGS is not classically considered an autoimmune disease, increasing evidence suggests that immune dysregulation may contribute to disease recurrence. Certain immune system abnormalities, such as dysregulated T-cell and B-cell responses, have been implicated in recurrent FSGS. Some patients respond to immunosuppressive therapies, such as rituximab (a monoclonal antibody targeting B cells), suggesting an immune-mediated component in some cases of recurrence (8).

Furthermore, a history of prior graft loss due to recurrent FSGS is a strong predictor of recurrence in subsequent transplants. This suggests that the immune system may develop a form of "memory" for disease recurrence, possibly through sustained production of pathogenic factors (8).

3. HEMODYNAMIC AND MECHANICAL STRESS ON THE TRANSPLANTED KIDNEY

In addition to circulating factors and immune mechanisms, hemodynamic and mechanical stressors may contribute to recurrent FSGS. The newly transplanted kidney is often subjected to altered hemodynamic forces, which may exacerbate glomerular injury in susceptible individuals. Factors such as ischemia-reperfusion injury, post-transplant hypertension, and hyperfiltration of remaining nephrons can further stress the glomeruli, making them more vulnerable to damage from circulating permeability factors (9).

Hyperfiltration is particularly relevant in patients with a single transplanted kidney, as the reduced nephron mass must compensate for the body's filtration needs. This increased workload may accelerate podocyte injury and glomerulosclerosis, worsening disease progression (9).

"The Impact of Restrictive Versus Conservative Intraoperative Fluid Strategies upon the Renal Outcome in Colorectal Surgeries. A Randomized Controlled Trial" investigates the effects of two different intraoperative fluid management strategies on postoperative renal outcomes in patients undergoing elective colorectal surgery. The study was conducted by Khaled Abdelbaky Abdelrahman and colleagues at Assiut University Hospitals in Egypt (10).

1. **Objective:** The study aimed to compare the impact of restrictive (6 mL/kg/h of lactated Ringer's solution) versus conservative (12 mL/kg/h of lactated Ringer's solution) intraoperative fluid strategies on postoperative renal complications, hemodynamics, and hospital stay.
2. **Methods:** A double-blinded, randomized controlled trial was conducted with 60 adult patients (ASA grade II-III) undergoing elective colorectal surgery. Patients were divided into two groups: restrictive (Group R) and conservative (Group C) fluid management. Renal outcomes were assessed using serum Neutrophil Gelatinase-associated Lipocalin (NGAL) levels, KDIGO criteria for acute kidney injury (AKI), serum urea, creatinine, and intraoperative hypovolemia events.
3. **Results:**
 - Serum NGAL levels increased in a few patients in both groups, but the difference was not statistically significant.
 - The restrictive fluid group (Group R) had a significantly higher incidence of postoperative AKI according to KDIGO criteria compared to the conservative group (Group C).
 - Intraoperative urine output was significantly lower in the restrictive group.
 - No significant differences were found in serum urea, creatinine, intraoperative hypovolemic episodes, blood transfusion rates, or hemodynamic events between the two groups.
 - Postoperative complications and hospital stay were similar in both groups.
4. **Conclusion:** The study found no significant difference in early postoperative serum NGAL levels and other systemic complications between restrictive and conservative fluid strategies. However, the restrictive fluid strategy was associated with a higher incidence of postoperative AKI.
5. **Limitations:** The sample size may have been insufficient to detect significant differences in NGAL levels and other complications. Additionally, the study did not follow up on patients after hospital discharge, potentially missing late complications.
6. **Financial Support:** The research did not receive any specific grant and was supported solely by departmental resources.

Summary:

The study concludes that while restrictive intraoperative fluid management does not significantly affect early postoperative serum NGAL levels or other systemic complications, it is associated with a higher risk of postoperative acute kidney injury compared to a conservative fluid strategy. The findings suggest caution in adopting restrictive fluid strategies in colorectal surgeries, particularly concerning renal outcomes (10).

"Role of Renal Resistive Index in Early Detection of Diabetic Nephropathy in Type II Diabetic Patients," investigated the use of the Renal Resistive Index (RI) as a diagnostic tool for early detection of diabetic nephropathy (DN) in patients with Type 2 Diabetes Mellitus (T2DM). The study was conducted by Nihal O. Youssif Ali and colleagues at South Valley University in Egypt (11).

1. **Objective:** The study aimed to assess the diagnostic value of the Renal Resistive Index (RI) in the early detection of diabetic nephropathy (DN) in T2DM patients.
2. **Methods:**
 - A cross-sectional study was conducted on 82 T2DM patients and 18 healthy controls.
 - Patients were divided into three groups:
 - Group 1: T2DM without DN (normoalbuminuric, ACR <30 mg/g).
 - Group 2: T2DM with DN (hyper-albuminuric, ACR >30 mg/g).
 - Group 3: Healthy controls.

- Participants underwent clinical examination, gray-scale renal ultrasound, Doppler evaluation of renal RI, and laboratory tests for glycemic control and renal function.

3. **Results:**

- T2DM patients with DN were significantly older, had higher BMI, longer disease duration, and poorer glycemic control compared to T2DM without DN and healthy controls.
- T2DM with DN had significantly higher renal RI values (0.71 ± 0.015) compared to T2DM without DN (0.639 ± 0.017) and healthy controls (0.56 ± 0.02).
- Renal RI showed a positive correlation with albuminuria and disease duration.
- The RI cutoff value of >0.68 had an AUC of 1.0, with 100% sensitivity, specificity, PPV, and NPV for discriminating T2DM with DN from T2DM without DN.

4. **Conclusion:**

- Poor glycemic control and obesity negatively impact renal function in T2DM patients.
- Renal RI > 0.68 is a valuable tool for early detection of diabetic nephropathy, providing a non-invasive method to assess renal hemodynamic changes.

5. **Limitations:**

- The study did not address long-term outcomes or the impact of interventions on renal RI.
- The sample size was relatively small, and the study was conducted at a single center.

6. **Financial Support:** The research did not receive any specific grant and was supported by departmental resources.

Summary:

The study concludes that the Renal Resistive Index (RI) is a highly effective, non-invasive tool for the early detection of diabetic nephropathy in T2DM patients. A cutoff value of RI > 0.68 can accurately discriminate between T2DM patients with and without DN, highlighting its potential clinical utility in managing diabetic kidney disease (11)

Age-related Histological Changes in the Renal Telocytes in Male Albino Rats

1. **Objective:** The study aimed to evaluate age-related changes in telocytes (TCs) in the renal tissue of male albino rats across different age groups (3 weeks, 3 months, and 1 year) (12).
2. **Key Findings:**
 - Telocytes (TCs) were identified in the renal interstitium using H&E staining, CD34 immunohistochemistry, and transmission electron microscopy (TEM).
 - Age-related decline in TCs:
 - The number of TCs significantly decreased with age, with the lowest count observed in the 1-year-old group (Group III).
 - Group I (3 weeks): 5.05 ± 1.20 TCs per high-power field (hpf).
 - Group II (3 months): 3.0 ± 0.93 TCs per hpf.
 - Group III (1 year): 1.83 ± 0.81 TCs per hpf.
 - Degenerative changes in TCs:
 - In the 1-year-old group, TCs showed shrinkage, disintegration, and fragmentation of their telopodes (Tps).
 - The number of telopodes (Tps) emerging from each TC also decreased significantly in the older age group.
 - Morphometric Analysis:
 - TCs cell body length decreased significantly in older age groups.
 - TCs nucleus diameter increased in the 1-year-old group, suggesting age-related nuclear changes.
 - Telopodes (Tps) length showed a non-significant decrease with age, but fragmentation was observed in the oldest group.
 - Histological Changes:

- In the 1-year-old group, renal tubules showed vacuolation, degeneration, and congestion of blood vessels, indicative of age-related renal degeneration.
- Ultrastructural Changes:
 - TEM revealed disintegrated TCs and fragmented Tps in the 1-year-old group, along with increased intracellular and extracellular vesicles and caveolae.
- Functional Implications:
 - The reduction in TCs with aging may contribute to the decreased regenerative capacity of renal tissue in older rats.
 - TCs are believed to play roles in tissue repair, regeneration, and intercellular signaling, and their decline may exacerbate age-related renal dysfunction.

4. CONCLUSION

- TCs decrease in number and undergo degenerative changes with aging, which may be associated with the reduced regenerative capacity of renal tissue in older individuals.
- The study provides evidence that TCs play a role in maintaining renal tissue homeostasis and that their decline with age may contribute to age-related renal degeneration (12).

"The Impact of Restrictive Versus Conservative Intraoperative Fluid Strategies upon the Renal Outcome in Colorectal Surgeries. A Randomized Controlled Trial" by Abdelrahman et al. (2023), investigates the effects of two intraoperative fluid management strategies—restrictive and conservative—on renal outcomes in patients undergoing elective colorectal surgery. The study was conducted at Assiut University Hospitals and involved 60 adult patients with ASA grade II-III (13).

Key Points:

1. **Objective:** The study aimed to compare the impact of restrictive (6 mL/kg/h of lactated ringer) versus conservative (12 mL/kg/h of lactated ringer) fluid strategies on postoperative renal complications, hemodynamics, and hospital stay.
2. **Methods:**
 - A double-blind, randomized controlled trial was conducted.
 - Patients were divided into two groups: restrictive (Group R) and conservative (Group C) fluid management.
 - Renal outcomes were assessed using serum Neutrophil Gelatinase-associated Lipocalin (NGAL), KDIGO criteria, serum urea, and creatinine levels.
 - Intraoperative hypovolemia events and fluid responsiveness were monitored using the Pleth Variability Index (PVI) (13).
3. **Results:**
 - **NGAL Levels:** No significant difference was found between the two groups in terms of NGAL levels, though a few patients in both groups showed elevated NGAL (>149 ng/ml).
 - **KDIGO Criteria:** The restrictive fluid group (Group R) had a significantly higher incidence of acute kidney injury (AKI) compared to the conservative group (Group C).
 - **Urine Output:** Intraoperative urine output was significantly lower in the restrictive group.
 - **Fluid Balance:** The restrictive group had a higher postoperative fluid balance on the 1st and 2nd postoperative days.
 - **Hypovolemia:** Three patients in the restrictive group experienced hypovolemic episodes, but the difference was not statistically significant.
 - **Hospital Stay and Complications:** No significant differences were observed in hospital stay or non-renal complications between the two groups (13).
4. **Conclusion:**
 - The study found no significant difference in early postoperative serum NGAL levels between restrictive and conservative fluid strategies.
 - However, the restrictive fluid strategy was associated with a higher incidence of postoperative AKI

according to KDIGO criteria.

- The authors suggest that restrictive fluid management may not be beneficial in preventing renal complications in colorectal surgeries.

5. Limitations:

- The sample size may have been insufficient to detect significant differences in NGAL levels and other complications.
- The study did not follow up on patients after hospital discharge, potentially missing late complications (13).

6. Financial Support: The study was supported solely by departmental resources, with no external funding (13).

Key Takeaways:

- Restrictive fluid management may increase the risk of postoperative AKI in colorectal surgery patients.
- Conservative fluid management did not show significant adverse effects and may be safer in terms of renal outcomes.
- The study highlights the importance of careful fluid management during major surgeries to prevent renal complications (13).

This paper contributes to the ongoing debate on optimal intraoperative fluid management strategies, particularly in colorectal surgeries, and suggests that a conservative approach may be more favorable for renal outcomes (13).

A Comparative Analysis of Outcomes: Percutaneous Nephrolithotomy vs. Extracorporeal Shock Wave Lithotripsy in Patients with Renal Insufficiency

This study aimed to shed light on the effectiveness of two prominent treatments for kidney stones—Percutaneous Nephrolithotomy (PCNL) and Extracorporeal Shock Wave Lithotripsy (ESWL)—specifically in patients facing the challenge of renal insufficiency. By examining their outcomes, we emphasize the importance of informed decision-making in clinical practice, ultimately striving to improve patient care and health results in this vulnerable population (14).

- **PNL** was found to be more effective as a single-session treatment with a higher stone-free rate compared to SWL, which often required multiple sessions.
- Both procedures were safe for patients with renal insufficiency, with **PNL** showing better preservation of kidney function.
- **SWL** was associated with a higher rate of complications, particularly hematuria and obstruction, likely due to the shock waves' impact on renal parenchyma.
- **PNL** is a safe and effective treatment for renal stones in patients with renal insufficiency, offering a high stone-free rate and minimal impact on kidney function.
- **SWL** is also safe but may require multiple sessions and is associated with a higher rate of complications.
- **PNL** is preferred for its single-session efficacy, while **SWL** may be considered for patients who cannot undergo PNL (14).

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