Evaluation of Clinical Features and Renal Replacement Therapy in Children with Typical Hemolytic Uremic Syndrome

Tipik Hemolitik Üremik Sendromlu Çocuklarda Klinik Özelliklerin ve Renal Replasman Tedavisinin Değerlendirilmesi

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ABSTRACT

Objective: A subset of typical Hemolytic-uremic syndrome (HUS) patients requires initiation of renal replacement therapy (RRT) despite aggressive medical intervention. This study aims to evaluate the clinical and laboratory findings of patients diagnosed with typical HUS and efficacy and safety of peritoneal dialysis (PD) and hemodialysis (HD) were compared in managing these cases.

Material and Methods: Patients having a diagnosis of typical HUS were retrospectively determined, and assessment of the effects of RRT modalities on renal survival.

Results: The present study included 49 children with typical HUS, and the mean age was 2.99 ± 1.88 years. Neurological involvement was detected in 15 (30.6%) patients. The neutrophil/lymphocyte ratio (NLR) was significantly higher in the neurological involvement group (odds ratio (OR) 15.42, 95% CI (3.99-70.1), p = 0.005). In total, 43 (87.7%) patients received RRT and the median time from the first recorded symptom to RRT was six days (range 3-11). While throughout RRT, 10.2% of patients required mechanical ventilation. In this study, 26 (53.1%) patients were managed with PD, and 17 (34.6%) patients were managed with HD. During follow-up, 10.2% of all patients progressed to chronic kidney disease (CKD), proteinuria was detected in 61.1% and hypertension in 40.8%. The risk of CKD was significantly lower in the 3-month period in PD patients than in HD patients (odds ratio (OR) 7.69, 95% CI (0.77-76.07), p = 0.04).

Conclusion: We concluded that PD might be as effective and safer as HD concerning kidney recovery. Clinical features and inflammatory markers can predict neurological involvement in typical HUS cases.

Key Words: Children, Biomarkers, Renal replacement therapy, Typical Hemolytic uremic syndrome

ÖZ

Amaç: Tipik hemolitik üremik sendrom (HÜS) hastalarının bazılarında, agresif tıbbi müdahaleye rağmen renal replasman tedavisi (RRT) gerekebilir. Bu çalışmamız amacı, tipik HÜS tanı alan hastaların klinik ve laboratuvar bulgularının değerlendirilmesi, HÜS tanılı hastalarda periton diyalizi (PD) ile hemodiyalizin (HD) etkinlik ve güvenilirliğinin karşılaştırılmasıdır.

Conflict of Interest / Çıkar Çatışması: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / Etik Kurul Onayı: This study was conducted in accordance with the Helsinki Declaration Principles. Study Sami Ulus Obstetrics, Gynecology and Child Health and Diseases Clinical Research Ethics Committee approved (Number: E-21/03-119-04.03.2021).

Contribution of the Authors / Yazarların katkısı: GUNGOR T: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study. Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. Taking responsibility in logical interpretation and conclusion of the results. Taking responsibility in necessary literature review for the study. Taking responsibility in the writing of the whole or important parts of the study. Reviewing the article before submission scientifically besides spelling and grammar. KARAKAYA D: Constructing the hypothesis or idea of research and/or article. KARGIN ÇAKICI E: Planning methodology to reach the Conclusions. Taking responsibility in the writing of the whole or important parts of the study. YAZILITAS F: Organizing, supervising the course of progress and taking the responsibility of the research/study. Taking responsibility in the writing of the whole or important parts of the study. UYSAL YAZICI M: Organizing, supervising the course of progress and taking the responsibility of the research/study. Taking responsibility in necessary literature review for the study. CELİKKAYA E: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. AZAPAGASI E: Taking responsibility in necessary literature review for the study. BULBUL M: Constructing the hypothesis or idea of research and/or article, Taking responsibility in logical interpretation and conclusion of the results. Reviewing the article before submission scientifically besides spelling and grammar.

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INTRODUCTION

Hemolytic uremic syndrome (HUS) is one of the most common etiologies for acute kidney injury (AKI) and a critical cause of acquired chronic kidney disease (CKD) in children. Hemolytic uremic syndrome is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure that is generally classified into two main types: typical and atypical (aHUS). Hemolytic-uremic syndrome induced by Shiga-toxin-producing Escherichia coli (STEC) is the most common type of the disease and ordinarily has a good prognosis, but aHUS is rare that has a poor prognosis with a relapsing course. Extrarenal manifestations may be occurred in 25-30% of cases, including neurological, gastroenterological, cardiac and endocrine involvement (1-4).

Treatment of STEC-HUS is primarily supportive care consisting of volume expansion, antihypertensive therapy, regulation of hematological problems and renal replacement therapy (RRT). Renal replacement therapy is required in 50%-70% of cases in the acute phase of typical HUS. General indications for acute RRT in the management of AKI are applied. Oligoanuria, clinical manifestations of uremia, hyperkalemia, severe metabolic acidosis, persistent and symptomatic hyponatremia unresponsive to conservative treatment, whereas these indications are nonspecific and the general consensus in our center is that RRT should be offered early (12-14).

The new Schwartz formula (K = 0.413) was used to calculate the estimated glomerular filtration rate (eGFR) (15). Proteinuria was defined when urinary protein creatinine ratio is above 0.2 mg/mg or 24-h protein excretion was >4 mg/m²/h in at least two consecutive evaluations (16). Hypertension was defined as a systolic blood pressure and/or diastolic blood pressure ≥ 95th percentile, according to age, gender, and height (17).

Neurological involvement was defined as encephalopathy, focal neurological deficit, and/or seizure activity (5,7). The groups with and without neurological involvement were compared concerning inflammatory markers. The neutrophil to lymphocyte ratios and platelet to lymphocyte ratio were calculated using the data obtained from the hemogram analyses. Systemic immune-inflammation index (SII) was calculated from the equation SII = Platelet x neutrophil count/lymphocyte count.

Dialytic management and therapeutic decisions in our children were individualized based on the patient’s age, specific clinical and hemodynamic status. RRT available in our center includes PD, intermittent hemodialysis (IHD), or continuous renal replacement therapies. Temporary vascular access was established (HD catheter insertion into the internal jugular,
The present study included 49 children with typical HUS, and the mean age was 2.99 ± 1.88 years. The male-to-female ratio was 1:1.2. At presentation, 43/49 (87.7%) children had diarrhea, of whom 24 (49%) patients had bloody diarrhea. At admission, 24 (49%) patients had oliguria, and 20 (40.8%) patients had anuria. Other main clinical manifestations included edema, vomiting, and dehydration (87.7%, 48.9%, 10.2%, respectively). At the presentation time, the mean serum creatinine level was 3.9 ± 1.93 mg/dL, and the mean eGFR was 20.37 ± 19.11 mL/min/1.73 m². C₄ complement was low in 12.2% of the patients, C₄ complement was low in 10.2%. All patients had high LDH levels. Thirty (61.2%) patients were hypertensive at admission or during hospitalization. Concomitant hematuria and proteinuria were detected in 23 (46.9%) of the patients (Table I).

Neurological involvement was detected in 15 (30.6%) patients. The most common presentation was seizures and encephalopathy for neurological involvement. Electroencephalogram and neuroimaging were performed in all these children during the acute illness for diagnosis. Patients with neurological involvement required significantly more mechanical ventilation (p = 0.01). The neutrophil/lymphocyte ratio (NLR) was significantly higher in the neurological involvement group [odds ratio (OR) 15.42, 95% CI (3.39-70.1), p = 0.005], whereas white blood cell count (WBC), neutrophil, platelet counts, platelet/lymphocyte ratio (PLR) and SII values were not significantly different between the groups. Lactate dehydrogenase concentration was no significant difference in the groups (p > 0.05) (Table II). Of the 15 children with neurological involvement, 14 (93.3%) achieved a complete neurological recovery.

In total, 43 (87.7%) patients received RRT. While throughout RRT, 10.2% of patients required mechanical ventilation. The median time from the first recorded symptom to RRT was six days. The survival probability was compared between the study arms using log-rank test. A value of p < 0.05 was accepted as being statistically significant.

### RESULTS

The present study included 49 children with typical HUS, and the mean age was 2.99 ± 1.88 years. The male-to-female ratio was 1:1.2. At presentation, 43/49 (87.7%) children had diarrhea, of whom 24 (49%) patients had bloody diarrhea. At admission, 24 (49%) patients had oliguria, and 20 (40.8%) patients had anuria. Other main clinical manifestations included edema, vomiting, and dehydration (87.7%, 48.9%, 10.2%, respectively). At the presentation time, the mean serum creatinine level was 3.9 ± 1.93 mg/dL, and the mean eGFR was 20.37 ± 19.11 mL/min/1.73 m². C₄ complement was low in 12.2% of the patients, C₄ complement was low in 10.2%. All patients had high LDH levels. Thirty (61.2%) patients were hypertensive at admission or during hospitalization. Concomitant hematuria and proteinuria were detected in 23 (46.9%) of the patients (Table I).

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### Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics for Windows v.22.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to determine the normality of the distribution of the study variables. Parametric variables were shown as mean ± SD, and nonparametric variables were shown as median (range). Categorical variables were presented as numbers and percentages. The student’s t-test was used to compare parametric variables and the Mann-Whitney U test was used to compare nonparametric variables. The χ² test or Fisher’s exact test was used to compare categorical variables. Kaplan-Meier survival analysis was performed and the renal survival probability was compared between the study arms using log-rank test. A value of p < 0.05 was accepted as being statistically significant.

### Table I: Baseline characteristics of children with typical HUS.

| Characteristic                          | Value |
|----------------------------------------|-------|
| Female gender, *                       | 27 (55.1) |
| Patient age, years, †                  | 2.99±1.88 |
| Mechanical ventilation, *              | 5 (10.2) |
| Anuria, *                              | 20 (40.8) |
| Baseline hemoglobin (g/dl), †          | 8.02±1.7 |
| Baseline platelet count (x10³/L), †    | 63.81±39.19 |
| Baseline white blood count (x10⁴/L), † | 14.56±7.65 |
| Baseline lactate dehydrogenase (U/L), †| 2322.2±712.64 |
| Baseline serum BUN (mg/dl), †          | 85.27±38.76 |
| Baseline serum creatinine (mg/dl), †    | 3.9±1.93 |
| Baseline eGFR (ml/min/1.73 m²), †      | 20.37±19.11 |
| Baseline serum sodium (mEq/L), †       | 131.14±4.13 |
| Baseline serum potassium (mEq/L), †    | 4.94±1.08 |
| Baseline blood pH, †                   | 7.32±0.05 |
| Baseline HCO₃-, †                      | 15.76±3.33 |
| Dialysis indication, *                 | 43 (87.7) |
| Oliguria-anuria                         | 36 (83.7) |
| Electrolyte imbalances                 | 5 (11.6) |
| Others                                 | 2 (4.7) |
| Time to start of RRT (days), median, (range) | 6 (3-11) |
| Renal insufficiency, *                 | 5 (10.2) |
| Hypertension in survivors, *           | 2 (4.1) |
| Proteinuria in survivors, *            | 3 (6.1) |

* n(%), † mean ± SD
days (range 3-11). Twenty-six (53.1%) patients were managed with PD, and 17 (34.6%) patients were managed with HD. Continuous venovenous hemodialysis (CVVHD) was started at admission in six patients who were septic and hemodynamically unstable and then continued with IHD. The internal jugular vein is the most common vascular access site for extracorporeal dialysis in 76.4% of the centers, followed by the femoral vein (23.5%). Peritoneal access was established by placement of a double-cuff tunneled Tenckhoff catheter inserted. The characteristics of the two cohorts were not different, except that children selected for PD were significantly younger than those recruited for IHD (p = 0.01). The main indications for dialysis were oliguria and anuria in both groups.

The median number of IHD sessions was seven (range 3-35); the mean session duration was 137.70 ± 16.37 min. The post/pre-BUN ratio was 0.58 in the first IHD session. Bicarbonate, potassium, and sodium dialysate concentrations were adjusted according to individual requirements. The fluid extraction requirement was specified as 10-15 ml/kg/h per dialysis session, and the weight loss did not exceed 5% of the patient’s body weight. The mean blood flow rate was 5.71 ± 1.16 ml/kg/min, and the mean dialysate flow rate was 500 ml/min. Low-molecular-weight heparin (LMWH) was used for anticoagulation in 59.1% of IHD sessions. The median duration of PD was four (range 10-25) days. The mean holding volume was 676.92 ± 89.70 ml/m2. PD solution containing 1.36, 2.27, and 3.86% glucose was used in 76.92%, 26.92% and 3.84% of children, respectively.

Although blood volume was monitored during IHD sessions, three patients (17.6%) had transient hypotensive episodes, and two patients (11.7%) had transient hypertensive episodes during or within one hour of IHD sessions. In contrast, there were no transient hypertensive or hypotensive episodes with PD. Catheter occlusion (11.7%) was the most common complication during IHD; resolved with catheter replacement, catheter infection was detected in 5.88% of the patients. Peritonitis occurred in four patients with PD (15.3%) and the PD effluent turned sterile in all cases with intraperitoneal antibiotic therapy. Catheter leak and migration were the main mechanical complications in PD, resolved by catheter repositioning and reducing the volume of dialysate per cycle. Mechanical complications occurred with similar frequency in both treatment modalities (PD 11.5% vs. IHD 11.7%).

Renal function returned to normal in 24.4% of the patients after two weeks, in 67.3% of the patients at the end of the first month. The rate of patients with complete kidney recovery after two weeks, in 67.3% of the patients at the end of the first month. The rate of patients with complete kidney recovery (eGFR> 90 ml/min/1.73 m²) was 89.7% in the third month. Except for patients who developed CKD, the need for dialysis continued for a median of 9 days (range 3-35), and renal failure continued for a median of 22 days (range 7-84). During the follow-up, hypertension was detected in 4.08% and proteinuria was present in 6.1% of all patients. Albeit the follow-up of the patients is still carried on in our department, there was one patient (2.04%) with ESRD, and four patients (8.16%) were assessed as stage 2 or stage 3 CKD.

In the HD group, the renal function returned to normal in 23.5% of the patients after two weeks and in 58.8% of the patients after first month. In the PD group, the renal function returned to normal in 15.3% of the patients after two weeks and in 65.3% of the patients after the first month. When two groups were compared, no significant difference was found between normalization of renal function at the end of two weeks and first month (p = 0.3, p = 0.4, respectively). The mean biochemical indices of renal function were better in patients who received PD at three months than those who received HD (p = 0.04). The choice of RRT modality (PD vs. HD) significantly affected CKD

| Table II: Clinical characteristics and laboratory parameters of patients with and without neurological involvement. |
|---------------------------------|---------------------------------|---------------------------------|
|                                | Patients with Neurological     | Patients without Neurological    | p          |
|                                | involvement (n = 15)            | involvement (n = 34)             |            |
| Sex (F/M)                       | 8/7                            | 19/15                           | 0.800      |
| Age, mean, years                | 4.08±2.68                      | 2.51±1.16                       | 0.006      |
| WBC, mean x 10³/L               | 14.31±7.71                     | 14.67±7.74                      | 0.800      |
| ANC, mean x 10⁹/L               | 10.22±6.65                     | 8.26±5.59                       | 0.200      |
| Platelet, mean x 10⁹/L          | 60.46±30.57                    | 65.29±42.78                     | 0.600      |
| NLR                             | 4.81±4.62                      | 2.09±1.83                       | 0.005      |
| PLR                             | 28.01±22.94                    | 19.83±26.34                     | 0.300      |
| SII, mean x 10⁹/L               | 199.44±161.18                  | 124.26±113.60                   | 0.060      |
| CRP, mean, mg/L                 | 37.9±35.23                     | 27.92±23.85                     | 0.200      |
| LDH, mean, U/L                  | 2398.87±578.46                 | 2288.38±770                     | 0.600      |
| Creatinine, mean, mg/dl         | 3.97±1.32                      | 3.87±2.16                       | 0.800      |
| eGFR, mean, ml/min/1.73 m²      | 14.48±8.7                      | 22.97±21.82                     | 0.100      |

WBC: white blood cell count, ANC: absolute neutrophil count, NLR: neutrophil/lymphocyte ratio, PLR: platelet/lymphocyte ratio, SII: Systemic immune-inflammation index, CRP: C-reactive protein, LDH: lactate dehydrogenase, eGFR: estimated glomerular filtration rate
Table III: Comparison of clinical and laboratory characteristics of patients received hemodialysis and peritoneal dialysis.

|                          | Peritoneal dialysis (n=26) | Hemodialysis (n=17) | p    |
|--------------------------|-----------------------------|---------------------|------|
| Female gender,*          | 18 (69.2)                   | 9 (52.9)            | 0.200|
| Patient age, years, mean ± SD | 2.45 ± 1.04               | 4.05 ± 2.62         | **0.008**|
| Mechanical ventilation,* | 1 (3.8)                     | 4 (23.5)            | **0.040**|
| Anuria,*                 | 11 (42.3)                   | 9 (52.9)            | 0.300|
| Time to start of RRT (days), median, (range) | 6.5 (4-11)            | 6 (3-11)            | 0.500|
| Serum creatinine (mg/dl), median, (range) | 4.13 ± 2.09           | 4.44 ± 1.2          | 0.500|
| eGFR (ml/min/1.73 m2), median, (range) | 17.93 ± 16.29          | 11.58 ± 16.29       | 0.100|
| Hemoglobin (g/dl), mean ± SD | 7.5 ± 1.33                | 8.35 ± 2.01         | 0.100|
| Platelet count (x10^9/L), mean ± SD | 68.8 ± 46.21             | 55.82 ± 30.17       | 0.300|
| Lactate dehydrogenase (U/L), mean ± SD | 2350.88 ± 540.96      | 2547.06 ± 775.11    | 0.300|
| Renal insufficiency,*    | 1 (3.8)                     | 4 (23.5)            | **0.040**|
| Hypertension,*           | 1 (3.8)                     | 1 (5.8)             | 0.700|
| Proteinuria,*            | 1 (3.8)                     | 2 (11.7)            | 0.300|

RRT: renal replacement therapy, eGFR: estimated glomerular filtration rate, * n (%)  
risk at the end of the three months (odds ratio (OR) 7.69, 95% CI (0.77-76.07), p = 0.04) (Figure 1). The need for mechanical ventilation was significantly higher in the CKD group (p = 0.04) (Table III).

**DISCUSSION**

A subset of typical HUS patients requires initiation of RRT despite aggressive medical intervention. Based on data from observational studies and comparative clinical studies, there is no consensus on the best dialysis technique and optimal dialysis dose in HUS (8-10). In this study, we analyzed the efficacy and safety of PD and HD were compared in managing typical pediatric HUS. The CKD rate was significantly higher in the HD group than in the PD group (p = 0.04). In addition, we determined the utility of inflammation markers in predicting neurological involvement, which is one of the most severe complications of typical HUS. The neutrophil/lymphocyte ratio (NLR) was significantly higher in the neurological involvement group [odds ratio (OR) 15.42, 95% CI (3.39-70.1), p = 0.005].

The present study evaluated the clinical and laboratory findings of patients diagnosed with typical HUS. In the literature, the male-to-female ratio was 1.7-1.4, and the median age was 17 months (range 10-108) of typical HUS. The most common complaints of the cases were diarrhea (30-60%) and bloody diarrhea (25-40%). Anuria development rate was 40-80% (19,20). Hypertension was found in 40-50% and proteinuria in 50% of the cases. Proteinuria persisted for a long time in 50% of cases. Hypertension, irritability and seizure are the most common findings. In studies conducted so far, markers to predict neurological involvement in patients have not been determined; some clinical scorings have been used. Rapid treatment of neurological involvement in typical HUS provides recovery without sequelae (25,26).
our study, neurological involvement was detected in 15 (30.6%) patients. Patients with neurological involvement required significantly more mechanical ventilation \((p = 0.01)\). The neutrophil/lymphocyte ratio (NLR) was significantly higher in the neurological involvement group \([\text{odds ratio (OR)} 15.42, 95\% \text{ CI (3.39-70.1)}, p = 0.005]\), whereas WBC, neutrophil, platelet counts, PLR and SII values were not significantly different between the groups. Of the 15 children with neurological involvement, 14 (93.3%) achieved a complete neurological recovery.

PD is frequently used in treating typical pediatric HUS and remains the method of choice in infants and young children for whom vascular access is a limiting factor. In addition to avoiding central venous puncture and anticoagulation, technical simplicity, relatively low cost, and low risk of treatment-related fluid-electrolyte imbalances in hemodynamically unstable patients are considered significant advantages of PD. On the other hand, the availability of significant technological advances in IHD and CVVHD in children is decreasing the use of PD for children who need RRT \((1.8, 19, 20)\). When HD and PD groups were compared, no significant difference was found between normalazation of renal function at the end of two weeks and the first month \((p = 0.3, p = 0.4\), respectively). The mean biochemical indices of renal function were better in patients who received PD at three months than those who received HD \((p = 0.04)\). The choice of RRT modality (PD vs. HD) significantly affected CKD risk at the end of the three months \([\text{odds ratio (OR)} 7.69, 95\% \text{ CI (0.77-76.07)}, p = 0.04]\). This finding may be because, in more severe and hemodynamically unstable patients, continuous RRT was started and then continued with hemodialysis.

In studies comparing HD and PD, transient hypotensive and hypertensive episodes were higher and mechanical complications were similar who received HD \((12, 13)\). The findings showed that three patients \((17.6\%)\) had transient hypotensive episodes, and two patients \((11.7\%)\) had transient hypertensive episodes during or within an hour of IHD sessions. In contrast, there were no transient hypertensive or hypotensive episodes with PD. Mechanical complications occurred with similar frequency in both treatment modalities \((PD 11.5\% \text{ vs. IHD 11.7\%})\).

Our study had some limitations. The present study reflected single-center data, the number of patients was limited, and it was designed as a retrospective study. However, our study will contribute to the literature, given that this is one of the few studies evaluating the effects of RRT modalities on renal survival and determining the utility of inflammation markers in predicting neurological involvement.

In conclusion, this study represents a valuable contribution to the modest existing evidence supporting the use of PD in children with typical HUS who need RRT. We evaluated the mean biochemical indices of renal function that were better in patients who received PD at three months than those who received HD. Hence, we concluded that PD might be as effective and safer as HD concerning kidney recovery. The use of clinical features and inflammatory markers to predict neurological involvement in typical HUS cases can be developed in further studies.

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