Study the Effect of Erythropoietin Therapy on LVH in Patients with ESRD on Hemodialysis

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Abstract

Background and Objective: The cardiac risk associated with renal disease in individuals undergoing regular hemodialysis (HD) is a primary contributor to their heightened cardiac morbidity and mortality. Mortality is often linked to the presence and progression of left ventricular hypertrophy (LVH). Anemia commonly accompanies chronic kidney disease (CKD). This study aimed to assess the impact of anemia treatment using erythropoietin on cardiac morphology and function in anemic patients with LVH who are on regular HD.

Patients and Methods: A cross-sectional evaluation was performed on 50 patients with end-stage renal disease (ESRD) on regular HD therapy; all were administered the same erythropoietin dosage. Cardiac assessments, including echocardiographic measurements such as left ventricular end-diastolic diameter (LVEDD), interventricular septal diameter (IVSD), posterior wall diameter (PWD), and left ventricular mass (LVM), were utilized to appraise the extent of LVH.

Results: The average age of participants was 55.90 ± 5.95 years, with 37 (74%) males. Diabetes mellitus and glomerulonephritis were the predominant causes of CKD (24% and 20%, respectively). Post-erythropoietin treatment showed a notable elevation in hemoglobin levels, red blood cell count, and hematocrit values. Additionally, significant enhancements were observed in cardiac parameters, including LVEDD, IVSD, PWD, and LVM.

Conclusion: Cardiac evaluation in patients with ESRD, particularly those with anemia, is imperative. Erythropoietin treatment has demonstrated substantial benefits not only in elevating hemoglobin levels but also in improving cardiac parameters.

Keywords: erythropoietin, end-stage renal disease, hemodialysis, left ventricular hypertrophy.

Introduction

The heightened recognition of the prevalence of cardiovascular disease (CVD) among individuals undergoing dialysis has prompted nephrologists and medical researchers to investigate contributing factors and conditions that affect these patients before they commence dialysis treatment. The overlap of risk factors for both kidney disease and cardiovascular disease could explain why CVD is so common among the dialysis demographic (1).

Nonetheless, there are specific risk elements for CVD that uniquely impact

those with chronic kidney disease (CKD), such as anemia, hyperparathyroidism, dysregulation of mineral metabolism, and acidosis. Studies have repeatedly shown a correlation between anemia, reduced hemoglobin levels, and kidney disease across various populations (2, 3).

The condition of left ventricular hypertrophy (LVH) is independently associated with increased mortality and cardiovascular insults, affecting not just the dialysis community but the broader population as well. Emerging research suggests that LVH and the enlargement of the left ventricle (LV) are prevalent among kidney disease patients even before they begin dialysis. The causes for LVH in these patients include both traditional risk factors like hypertension and non-traditional ones, such as anemia (4, 5).

The introduction of recombinant human erythropoietin (hrEpo) has sparked a deeper investigation into how chronic anemia influences the development of CVD. Evidence supports the theory that anemia can lead to cardiac volume overload and, when combined with factors like overhydration, high fistula flow, and hypertension-induced pressure overload, it can significantly contribute to the development of cardiac hypertrophy (6, 7).

Subsequent follow-up studies have indicated that the partial amelioration of anemia through recombinant Epo therapy can enhance cardiac oxygen delivery and reduce some pathological alterations in the left ventricle's structure. Despite these benefits, the impact of reducing left ventricular volume has been more prominent than the changes in wall thickness (8, 9).

The objective of the present study was to analyze the impact of anemia on LVHin patients with end-stage renal disease (ESRD) undergoing regular hemodialysis (HD). Furthermore, this work aimed to assess how anemia treatment with erythropoietin can improve the morphological and functional characteristics of the hearts of anemic patients with LVH who are on regular HD treatment.

2. Patients and Methods

2.1 Study setting and designs

A cross-sectional investigation was conducted in the Internal Medicine Department at Al Mabara Hospital in Assiut City.

2.2 Participants

This study included a cohort of 50 individuals diagnosed with ESRD who were receiving consistent HD treatments, had LVH, were anemic, and had not started erythropoietin therapy.

2.3 Inclusion and Exclusion Criteria

The study included participants confirmed to have ESRD through clinical, laboratory assessments and abdominal ultrasound who were on a regular HD regimen (3 sessions per week, 4 hours each for 6 months (the study duration)) and had anemia with mean hemoglobin 7, with an age range of 18 to 65 years.

Exclusion criteria encompassed patients with inherent structural cardiac conditions (such as congenital, valvular, or ischemic heart diseases), those undergoing antihypertensive therapy, AKI, Blood transfusion, acute coronary syndrome, and individuals younger than 18 years.

2.4 Study Techniques

Participants underwent detailed interviews to document demographic information, dialysis duration, and potential causes of renal disease. A comprehensive clinical assessment was conducted, looking for anemia symptoms such as pallor, and increased heart rate, gallop, murmurs, as well as cardiac assessment for LVH and heart failure signs, including a displaced cardiac apex and basal lung crackles, the dose of erythropoietin (rhEpo) being administered at the initial consultation was also recorded (subcutaneous rhEpo therapy, at a dose 4000 International Unit /W and it is fixed-dose to all patients)

2.5 Laboratory Tests

A full blood count (CBC) was performed using the Phoenix system, Cutoff Hb level 8. This was carried out at the beginning of the study as a baseline measurement and then again after six months of rhEpo therapy.

2.6 Echocardiographic

Evaluation Echocardiography was performed on all subjects, ensuring consistency using the same operator and equipment to minimize variability. This test assessed parameters such as ejection fraction (EF), left ventricular end-diastolic diameter (LVEDD), interventricular septal diameter (IVSD), posterior wall diameter (PWD), and left ventricular mass (LV mass), with the latter normalized for body surface area. Echocardiograms were conducted before the initiation of rhEpo treatment and after six months of therapy.

2.7 Statistical Analysis

Data were compiled and analyzed using the SPSS software (Statistical Package for the Social Sciences, version 20, IBM, Armonk, New York). Quantitative data were presented as means ± standard deviation or medians (range), and qualitative data as frequencies (percentages). The paired t-test was used to compare continuous variables (CBC parameters, LVEDD, IVSD, PWD, LV mass, LV index, and ejection fraction) for the patient group pre- and post-rhEpo treatment. A p-value of less than 0.05 was considered indicative of statistical significance.

2.8 Ethical Considerations: IRB No.: 04-2023-200426

Approval from the Ethics of Scientific Research Committee, Faculty of Medicine, and Assiut University was obtained. Verbal and written consents were obtained from all the caregivers of the infants.

3. Results

3.1 Demographic Characteristics of the Participants (Table 1):

The average age was 55.90 ± 5.95 years, with males comprising 74% (37 patients) and females 26% (13 patients) of the study population. The group's mean body mass index (BMI) was 27.79 ± 2.69 kg/m^2. Among the participants, 24% (12 patients) had a diagnosis of diabetes mellitus.

Table 1: Demographic Characteristics of Participants Variables | Total (N=50)

Variables	**N= 50**
Age (years)	55.90 ± 5.95
Sex Male	 37 (74%)

Female	13 (26%)
Body mass index (kg/m^2)	27.79 ± 2.69

Note: Data are presented as mean ± SD and frequency (percentage).

3.2 Characteristics of Renal Disease (Table 2):

The duration of renal disease ranged from 5 to 18 years, with a median duration of 9 years. The most commonly identified causes of renal disease were diabetes mellitus, glomerulonephritis, and idiopathic causes, each accounting for 24% and 20%, respectively.

Table 2: Characteristics of Renal Disease Variables | Total (N=50)

Variables	N= 50
Duration of the disease (years)	9 (5- 18)
Etiology of renal disease (Frequency [Percentage])	
Diabetes mellitus	12 (24%)
Glomerulonephritis	10 (20%)
Idiopathic	10 (20%)
Obstructive uropathy	8 (16%)
Polycystic kidney	5 (10%)
Pyelonephritis	3 (6%)
Congenital anomaly	2 (4%)

Note: Data are presented as median (range) and frequency (percentage).

3.3 Complete Blood Count Changes with Erythropoietin Treatment (Table 3, Figure 1):

Table 3 demonstrates the hematological changes post erythropoietin administration. There was a notable enhancement in red blood cell count (from 3.47 ± 1.11 to 5.21 ± 4.04; P=0.03), hemoglobin levels (from 8.24 ± 0.88 g/dl to 11.01 ± 1.55 g/dl; P < 0.001), and hematocrit values (from 21.68 ± 2.01% to 33.92 ± 2.55%; P < 0.001). Meanwhile, platelet and white blood cell count changes were insignificant.

Table 3: Blood Count Changes Pre- and Post-Erythropoietin Treatment

Variables	**Before**	**After**	***P-value***
Red blood cells (x 10^9/l)	3.47 ± 1.11	5.21 ± 4.04	**0.03**
Hemoglobin (g/dl)	8.24 ± 0.88	11.01 ± 1.55	< **0.001**
Hematocrit value (%)	21.68 ± 2.01	33.92 ± 2.55	< **0.001**

Note: Data are presented as mean ± SD. A P-value <0.05 is considered significant.

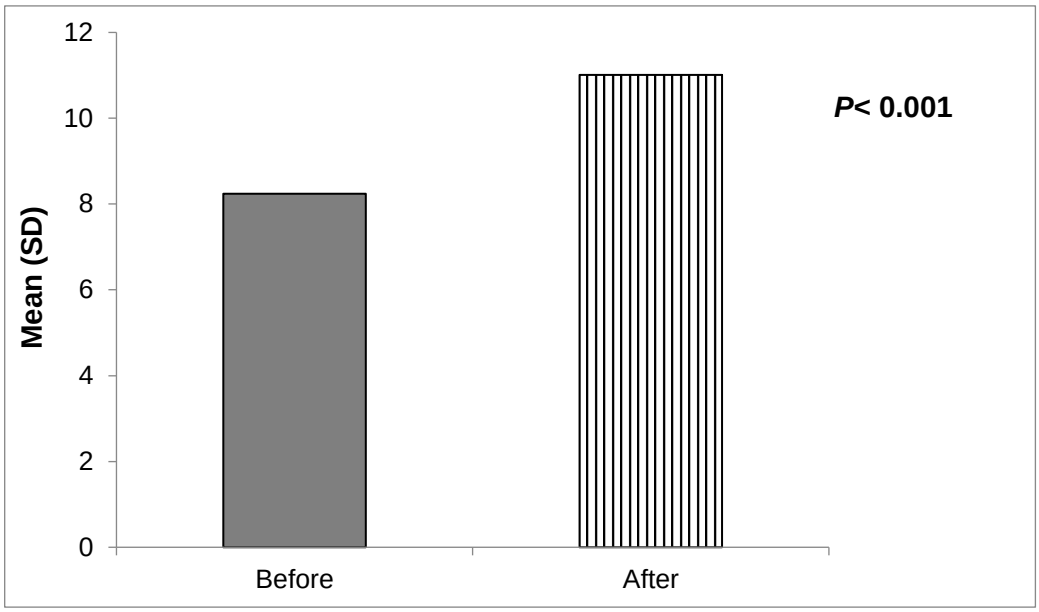

Figure 1: Hemoglobin level before and after erythropoietin use in the current study.

3.4 Echocardiographic Measurements (Table 4, Figures 2-6):

The echocardiographic assessment revealed a significant reduction in the LVEDD and IVSD after erythropoietin treatment, with percentage reductions of 1.12% and 2.36%, respectively. Other measurements, such as left ventricular mass and index, showed significant reductions, while the ejection fraction exhibited a significant increase.

Table 4: Echocardiographic Measurements Pre- and Post-Erythropoietin Treatment

Variables	**Before**	**After**	**% of change**	***P-value***
LVEDD (mm)	52.81 ± 3.36	52.22 ± 3.19	- 1.12	< **0.001**
IVSD (mm)	12.31 ± 1.31	12.02 ± 1.23	- 2.36	< **0.001**
PWD (mm)	12.37 ± 1.28	12.09 ± 1.28	- 2.26	< **0.001**
Left ventricular mass	269.62 ± 61.55	252.10 ± 61.60	- 6.5	**<0.001**
Left ventricular index	137.50 ± 29.85	130.68 ± 27.89	- 4.96	< **0.001**
Ejection fraction (%)	59.12 ± 5.18	61.96 ± 5.22	4.8	< **0.001**

Data was expressed in the form of mean (SD). *P-value* was significant if < 0.05. **LVEDD,** left ventricular end-diastolic diameter; **IVSD,** interventricular septal end diastole; **PWD;** posterior wall end diastole.

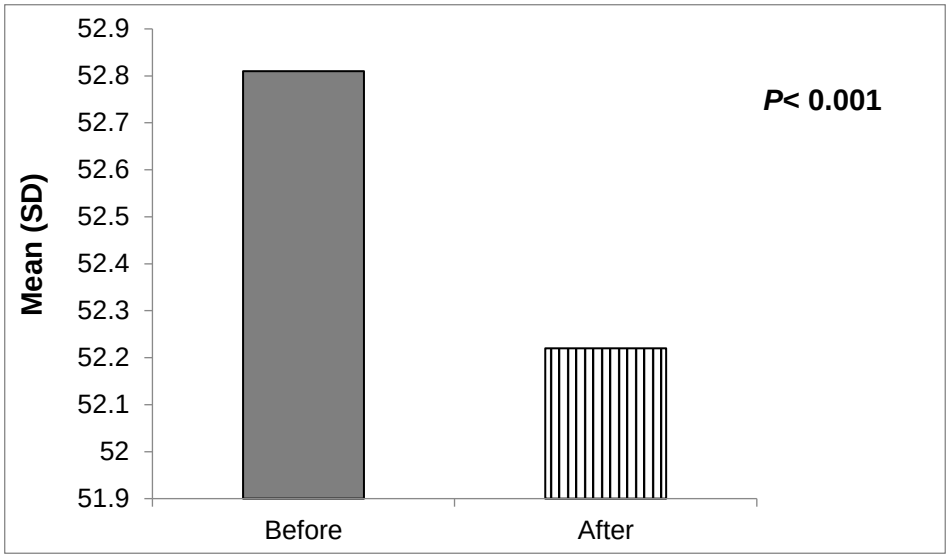

Figure 2: LVEDD before and after erythropoietin use in the current study.

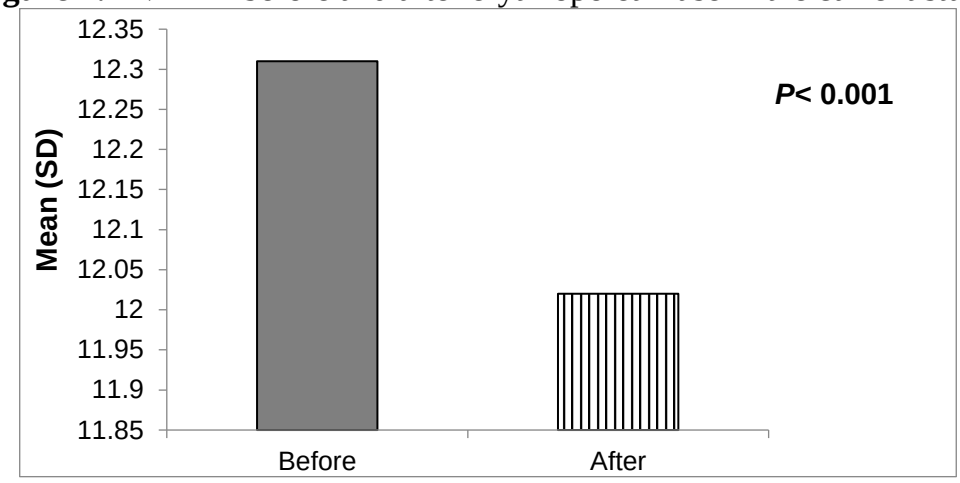

Figure 3: IVED before and after erythropoietin use in the current study.

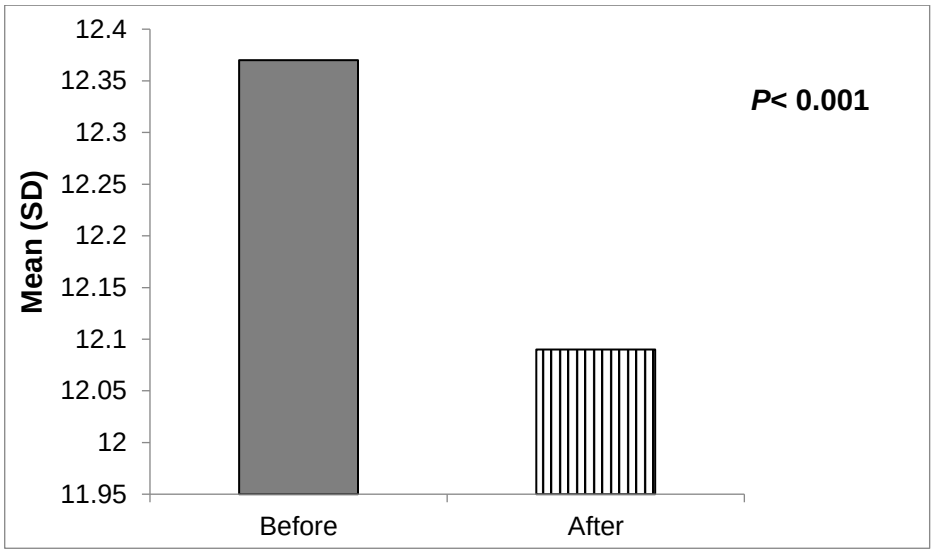

Figure 4: PWD before and after erythropoietin use in the current study.

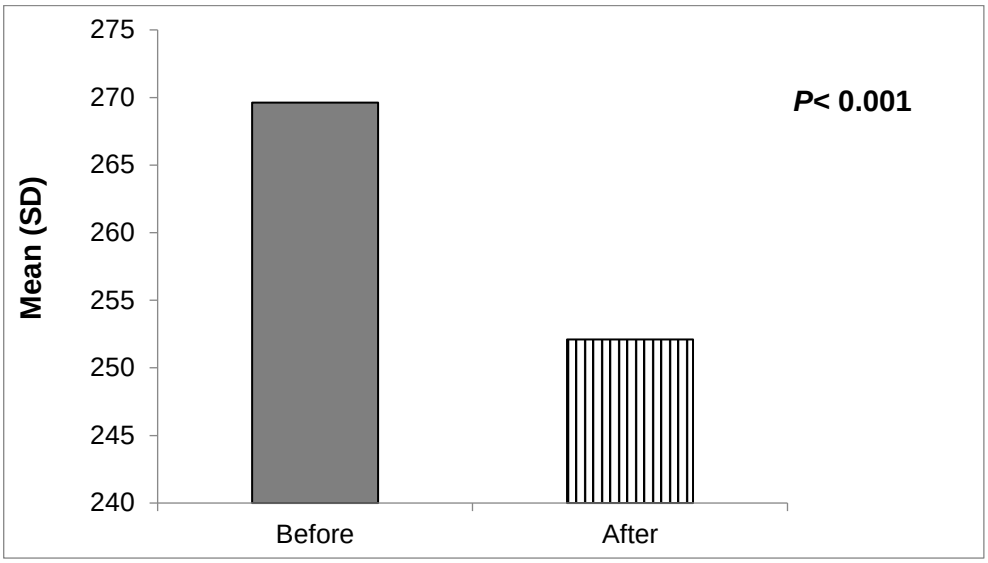

Figure 5: Left ventricular mass before and after erythropoietin use in the current study.

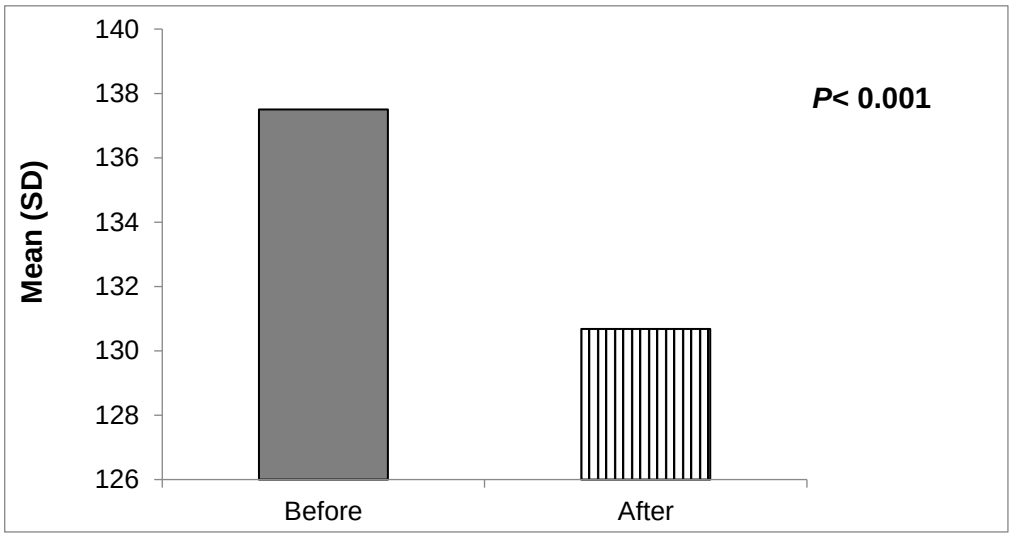

Figure 6: Left ventricular index before and after erythropoietin use in the current study.

4. Discussion

Understanding the multifactorial relationship between CKD, anemia, and cardiovascular morbidity is essential for improving patient outcomes. The occurrence of anemia in CKD is a well-documented phenomenon, and its prevalence increases as kidney function deteriorates (10, 11).

This study aimed to examine the effects of anemia correction with erythropoietin on the heart, particularly on patients with ESRD undergoing HD. We specifically investigated whether erythropoietin could reverse cardiac

remodeling and improve cardiac function in this patient population.

Our study group consisted of 50 patients, aged between 50 and 60, undergoing routine hemodialysis. The sample size reflects a typical clinical setting and allows for a focused exploration of the impact of anemia treatment on cardiac structure and function. At baseline, the prevalence of anemia among our study participants was high, mirroring the findings of the National Health and Nutrition Examination Survey, which has documented an inverse relationship between renal function and hemoglobin levels, with anemia prevalence increasing significantly when the glomerular filtration rate falls below 60 mL/min/1.73 m^2 (12).

The administration of rhEpo for six months led to a clinically significant increase in hemoglobin levels and red blood cell count. The rise in average hemoglobin levels from 8.24±0.88 g/dl to 11.01±1.55 g/dL is notable. It falls within the therapeutic target range for hemoglobin in HD patients, as supported by the studies of Abdu et al. and Al-Shohaib et al. This finding reaffirms the efficacy of rhEpo in managing anemia in the HD patients (13, 14). Efficacy and tolerability to correct anemia and to maintain hemoglobin within the target range of 11–12 g/dL in 80% of patients with ESKD on maintenance HD was previously achieved (15).

Alongside improved hemoglobin levels, we also observed favorable changes in cardiac structure. There was a significant decrease in the left ventricular end-diastolic dimension (LVEDD), with a reduction of 1.12%. This change, though modest, was in the same direction as the changes reported by Omczak-Watras et al., who observed improvements in cardiac parameters after anemia correction in CKD patients (16).

Furthermore, the left ventricular mass index (LVMI) showed a meaningful reduction of 4.96%, indicating a potential reversal of cardiac hypertrophy. This aligns with the findings of Hampl H and Ayus JC, who documented a decrease in LVMI with anemia treatment in HD patients (17, 18). It is worth noting, however, that these results stand in contrast to the studies by Foley RN and Roger SD, where no such correlation was established (19, 20).

Significant reductions in the interventricular septal dimension (IVSD) and posterior wall dimension (PWD) - 2.36% and - 2.26 %, respectively, were also observed after rhEpo treatment. These structural changes suggest that erythropoietin therapy may help ameliorate LVH, as supported by the study by Ayman M. (21).

In terms of cardiac function, there was a notable improvement in ejection fraction (EF), which increased by 4.8% after rhEpo administration. This finding is encouraging, as it points to improved cardiac performance. However, this observation does contrast with Wizemann V et al., who did not find significant EF changes following anemia correction with rhEPO (22).

5. Limitations of the Study

Our study is limited by its small sample size and short follow-up duration. Larger studies with a longer duration are needed to confirm these findings and to understand the long-term impact of anemia treatment on cardiac health. Furthermore, future studies should also consider the potential for adverse events associated with erythropoietin therapy, particularly when

hemoglobin levels are above the recommended upper limits.

6. Conclusion

This study suggests anemia treatment with rhEpo can favor cardiac structure and function in patients with HD. While the results are promising, they should be interpreted cautiously due to the study's limitations. Further research in this area is imperative to establish robust clinical guidelines for managing anemia in CKD, aiming to improve cardiovascular outcomes and patient quality of life.

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