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Original Article

A prospective observational study on the effect of Erythropoiesis stimulating agents in chronic kidney disease Anemia patients

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ABSTRACT:Background and Objectives: Anemia is a frequent complication, and significant morbidity and mortality in patient with chronic kidney disease (CKD). Erythropoiesis Stimulating Agents (ESAs) have become the standard care for anemia therapy and reduces need for blood transfusions. The objective of the study was to evaluate the safety and effect of ESAs and to create the awareness among patients regarding the Erythropoiesis stimulating agents through patient information leaflets. **Methods**: The prospective observational study of 6-month duration was conducted in a tertiary care hospital. A total of 162 patients on ESAs were enrolled in the study. Patients were followed for continuously and the mean difference is assessed by monitoring the primary and secondary hematological parameters before and after ESAs administration. Patient information leaflet was given to the patients for education and awareness about ESAs. **Results**: Out of 162 patients, after the administration of ESAs mean value increase in hemoglobin level was found from base line 6.9g/dL to 11.6g/dL. Significant improvement was noted in CKD anemia patient indicating impact of patient counseling. **Conclusion**: It can be concluded that Erythropoiesis Stimulating Agents in treatment of anemia along with effective counseling from clinical pharmacist benefits CKD patients and improves the health outcomes.

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INTRODUCTION

Chronic Kidney Disease (CKD) is rising to be a vital chronic disease globally. One reason is rapidly increasing worldwide incidence of diabetes and hypertension. In India, >1 billion, the rising incidence of CKD is likely to pose major problems for healthcare. Indeed, it has been recently estimated >1,00, 000 new patients enter renal replacement programs annually in India[1].The National Kidney Foundation defines chronic kidney disease (CKD) as either kidney damage or a decreased glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m^2 for at least 3 months. Anemia in patients with CKD is multifactorial in origin, primarily associated with relative erythropoietin deficiency. The evidence now seems to suggest that hemoglobin target level between9-11g/dL, should be the aim for patients with CKD.Anemia is a very common clinical problem in patients with chronic kidney disease (CKD) and is associated with increased morbidity and mortality in CKD patients.

Erythropoietin is a growth factor in the kidney and it stimulates red blood cell production in the bone marrow. It is deficient in the majority of patients with advanced kidney disease thereby predisposing to anemia [2].Anemia can be determined by using simple blood tests that give values for a Hematocrit (Hct), Hemoglobin (Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), and Red Blood Cell (RBC) counts. Iron and folate parameters like Serum iron, Serum ferritin, Total Iron Binding Capacity (TIBC), and Transferrin saturation (TSAT). According to Kidney Disease Improvement Global Outcome (KDIGO) and Kidney Disease Outcome Quality Initiative - National Kidney Foundation (KDOQI-NKF) guideline recommends the diagnosis and treatment of anemia should be started in the initial state to avoid further severity of the disease. The guideline also recommends Erythropoietin Stimulating Agents (ESAs) as the first-line treatment among CKD anemia patients.

Patients with moderate to severe CKD may require frequent hemoglobin monitoring due to high risk of anemia among this population and more frequent monitoring is also required at least monthly once. Because anemia is associated with increased morbidity and transfusion risk in CKD patients, treatments such as intravenous (IV) iron and Erythropoiesis Stimulating Agents have been a fundamental aspect of CKD management for the past two decades.

In KDOQI guidelines, several drugs of choice have been given for the treatment of anemia in CKD patients followed by iron supplementation (IV or oral), ESAs and blood transfusion. Iron supplementation, particularly with intravenous iron, can enhance erythropoiesis and raise hemoglobin levels in CKD patients. It is also associated with improving the erythropoietic response to Erythropoiesis Stimulating Agents (ESAs) treatment. The selection of the preferred route of iron supplementation depends upon the severity of anemia, iron deficiency (baseline iron level), tolerance and adherence to oral iron administration, cost of the drug. Iron stores are typically assessed through the evaluation of two biomarkers; Serum ferritin and Transferrin saturation (TSAT).

Oral iron is convenient and inexpensive but its efficacy is limited by poor tolerance. Oral iron is prescribed approximately 200mg of elemental iron daily. IV iron may be provided as a single large dose or repeated small dose depending on the specific IV preparation used. The initial course of IV iron amounting to approximately 1000mg, this may be repeated if an initial dose is ineffective.

Treatment with ESAs should be offered to patients with CKD anemia when IV iron fails to respond or the patient is intolerable. Commonly used ESAs are Darbepoetin alpha (25 mcg / 40mcg weekly once) and Epoetin alpha (2000IU/ 4000IU weekly twice). The selection of agents depends on patient factors. ESAs are the best therapy for the patients by reducing enervating symptoms, improvingtheir quality of life and avoiding blood transfusion along with their associated complications such as infection, sensitization, and electrolyte imbalance.

The study was aimed to evaluate the effect and safety of Erythropoiesis stimulating agents in CKD anemia patients and patient counselling were done by clinical pharmacist to create awareness about ESAs.

MATERIALS AND METHODS

Study design:

A prospective observational study was conducted in 162 patients from the Nephrology Department at G Kuppuswamy Naidu Memorial Hospital, Coimbatore for duration of 6 months. The complete study was done after obtaining the permission granted by the Institutional Ethical Committee from the hospital.

Study criteria:

Inclusion criteria:

- Both male and female patients
- Both OP and IP patients
- Patients on age group above 18 years
- Patients with hemoglobin less than 9g/Dl

Exclusion criteria:

- Patients taking any bone marrow suppressants medication
- Patient with other diagnosed cause of anemia
- Patients with evidence of ongoing chronic blood loss
- Patients who are not taking Epoetin alpha and Darbepoetin from 1 month

Plan of work:

Using the study protocol, clinical information was recorded for all patients from each nephrology unit. Patients who had not given their consent were excluded from the study. The information was also collected on the use of Erythropoiesis stimulating agents. Blood pressure was recorded in the supine position. The comorbid conditions at the initiation of drug therapy were reviewed from medical records. The hematological parameter was recorded at the baseline and after the administration of the ESAs.The patient data collection form was used to collect information about the patient. During the study, the patient information leaflet was prepared for chronic kidney disease patients to follow.

Data collection:

Prescription and dialysis booklet of the outpatient and treatment chart of the inpatients were reviewed prospectively and patient demographic details, social habits, educational status and laboratory data which include pre hemoglobin, RBC, MCH, MCV, HCT, serum iron, TIBC and after follow up post values were also enrolled in the patient data collection form.

Statistical analysis:

Sample size was calculated in Rao software with a confidence level of 95%. Data were presented in number (%) or mean of

total value. Microsoft Word and Microsoft excel 2010 were used to make graphs and tables necessary for the analysis.

RESULTS

In the present study describes the outcomes of 162 patients suffering from CKD and anemia as the main complication, in which majority of the patients belong to age group of 61-80years were 79(48.76%), 41-60 years were 61(37.65%) followed by these13(8.02%) belongs to 20-40 age group (Table 1).

Table 1: Age wise distribution of patients with Chronic Kidney Disease (n=162)

Age Groups	Number of patients
20-40 (years)	13
41-60 (years)	61
61-80 (years)	79
Above 81(years)	9

The total sample in our study was 162 which is characterized by 114(70.37%) male and 48(29.62%) female, which concluded that males are under high risk of CKD as compared to female patients (Fig. 1).

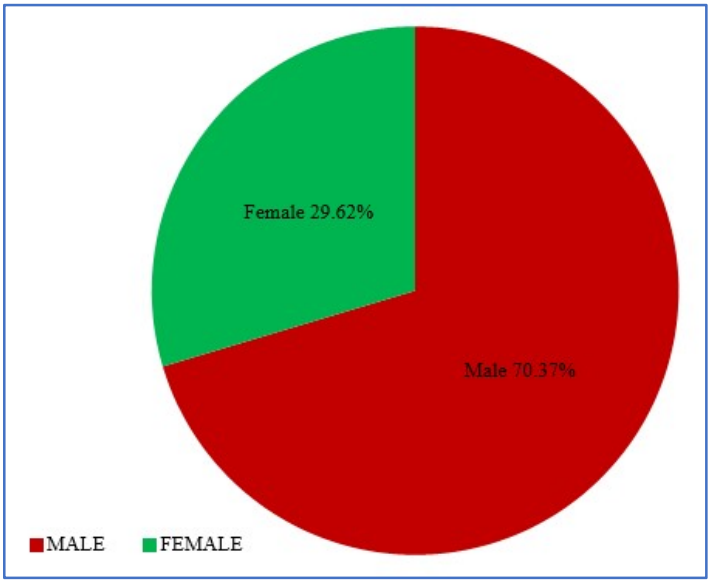

Figure 1: Gender wise distribution of patients with Chronic Kidney Disease (n=162)

The patients were classified based upon their comorbidity and we found that all patients who were in the study had hypertension (100%) while 20.98% patients had diabetes mellitus alone and 46.29% of patients were suffering from both diabetes mellitus and hypertension followed by this Coronary artery disease was present in 17.90% and 10.49% patients were suffering from congestive cardiac failure (Fig.2).

Anemia is the most commonly experiencing complication among CKD patients. Out of 162 total populations, all were suffering from anemia either mild or severe, 16.66% patients were present with pulmonary edema along with anemia and other commonly experiencing complications were metabolic acidosis (4.9%), hyperkalemia (5.55%), hyperphosphatemia (5.55%) and hypernatremia (1.23%) (Fig 3).

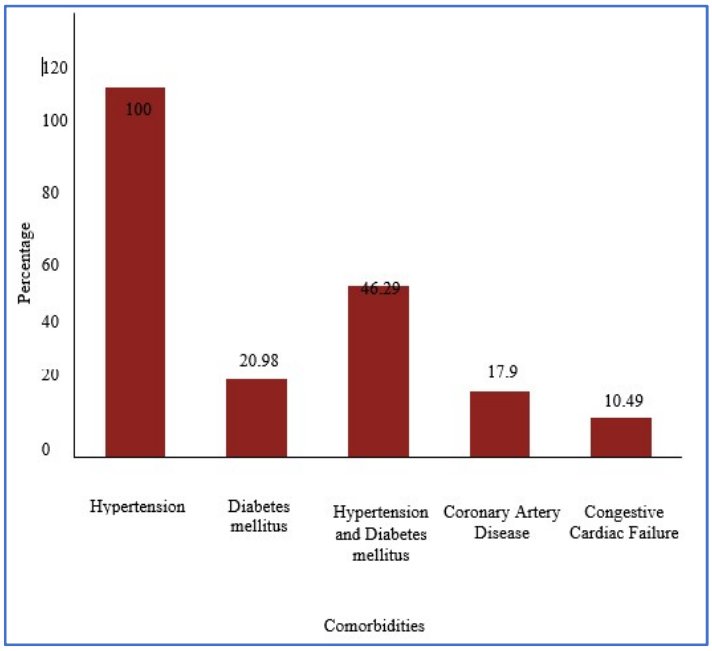

Figure 2: Distribution of comorbidities in patients with Chronic Kidney Disease (n=162)

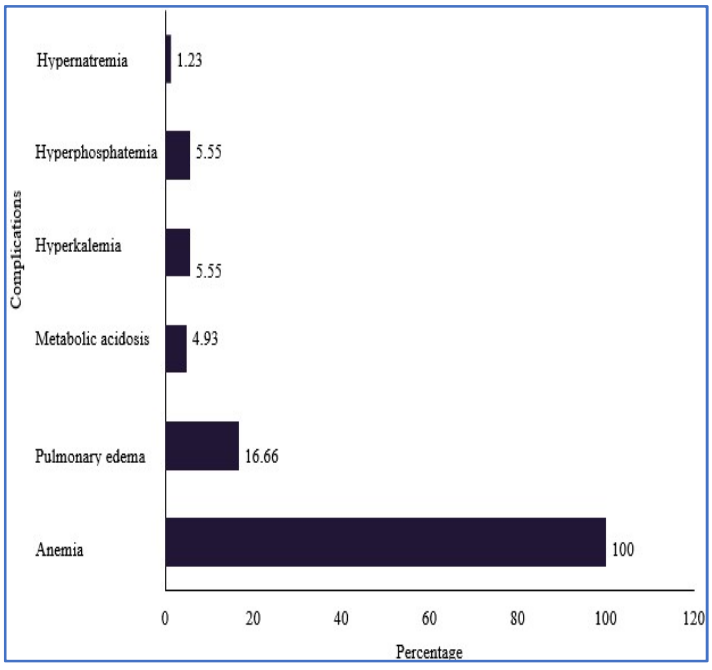

Figure 3: Distribution of complications in patients with Chronic Kidney Disease (n=162)

Table 2 represents the mean value of primary and secondary hematological parameters along with iron and folate parameters. It was observed that laboratory tests such as hemoglobin, MCV, MCH, MCHC, Hematocrit and RBC were carried out monthly once. When the hemoglobin level of patients was valuated it was found that mean hemoglobin value increases every month when compared to previous month. In this study it was observed that

serum ferritin, serum iron and Transferrin Saturation (TSAT) values had shown an increase in their mean values. In the second test when compared with values in first test, Total Iron Binding Capacity (TIBC) showed significant decrease in mean values.

Table 2: Laboratory data

PRIMARY AND SECONDARY HEMATOLOGICAL PARAMETERS			
	BASELINE VALUE	1st FOLLOW UP	2nd FOLLOW UP
Hemoglobin	6.94 g/dL	8.36g/dL	11.6g/Dl
MCV	76.63fL	80.48fL	85.73fL
MCH	26.2pg	27.95pg	30.94pg
MCHC	27.94g/dL	30.88g/dL	33.17g/dL
Hematocrit	27.76 %	30.34 %	35.74 %
RBC	$2.13x10^{12}$/L	$3.08x10^{12}$/L	$3.67x10^{12}$/L
IRON AND FOLATE PARAMETERS			
Serum iron	48.73mcg/dL	58.63mcg/dL	69.98mcg/dL
Serum ferritin	106.83ng/mL	118.95ng/mL	130.89ng/mL
TIBC	287.51mcg/dL	271.37mcg/dL	257.73mcg/dL
Transferrin saturation	17.82%	26.35%	31.22%

In this study, drug was administered at a dose of Epoetin alpha 4000IU and Darbepoetin 40mcg until the target reached. Hemoglobin of patients with ESAs were increase to 11.6g/dL from the baseline 6.94g/dL. TIBC were decreases to 257.73mcg/dL from the baseline287.51mcg/dL and Transferrin saturation were increases to 31.22% from the baseline 17.82%.

The present study also classified the patients based on the ESAs given for anemia. It was found that 75 patients were given withEpoetin alpha and 87patients was on Darbepoetin. The drug related events of ESAs in CKD anemia patients, out of 75 Epoetin alpha cases 3 patients experienced sudden raise in blood pressure after Epoetin alpha administration. Out of 87 patients administered with Darbepoetin, 2 of them experienced dizziness and advised to take rest after drug administration and 1 patient was found to experience headache (Fig 4).

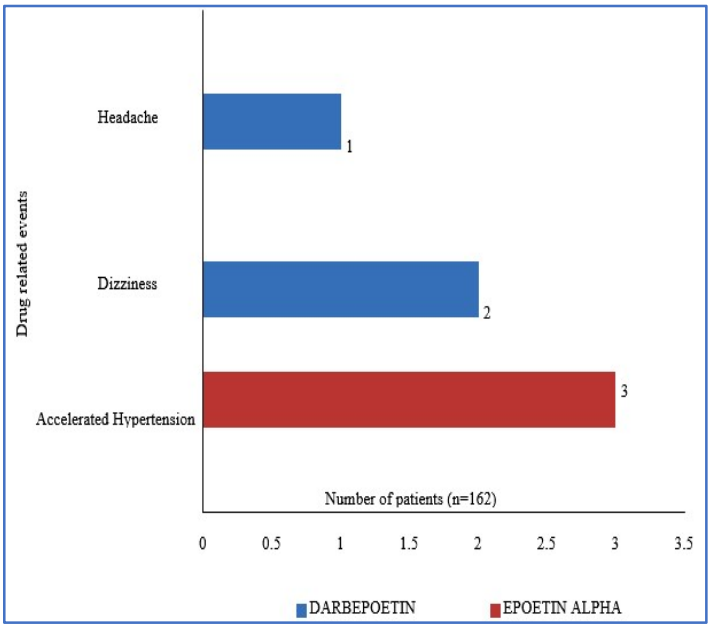

Figure 4: Drug related events of Erythropoiesis Stimulating Agents (n=162)

Patients were counselled by providing patient information leaflet. The information regarding patient disease, lifestyle and their management on each follow up by clinical pharmacist.

DISCUSSION

The present study describes the outcomes of 162 patients suffering from CKD anemia. Initially, 167 patients were enrolled but out of the 5 were excluded from the study, 1 patient went for renal transplant, 1 patient was referred to the distant dialysis unit and 3 patients were not willing to participate in the study. In our study, patients between ages of 61-80 years constituted the higher number followed by 41-60 years and 20-40 years, which was found to be correlated to the study conducted by Tonelli M *et al*.,[3]. It shows that the elderly was at high risk of suffering from CKD. The overall study was conducted with 162 patients as the total population out of which 29.62% presents with female and 70.30% was male, which parallel the finding of Goldberg I *et al*., [4]. This shows that males are under high risk of CKD as compared to female patients.

A detailed scenario of the patients with co-morbidities was discussed that is diabetes mellitus, hypertension, hypertension with diabetes mellitus, Coronary Artery Disease and Congestive Cardiac Failure. A close association between the age and co-morbidities were found, that is the chances of occurring Diabetes Mellitus and Hypertension were more in geriatric population and the patient having a history of diabetes mellitus and hypertension are at high risk of CKD, which in contrast to the study conducted by van der Meer V *et al*., [5]. This shows that more than one-quarter of patients with diabetes and one-fifth of the patients with hypertension have CKD.

Progression of CKD is associated with several serious complications, including Cardiovascular disease,

Hyperlipidemia, Anemia and Metabolic bone disease among this Iron Deficiency Anemia is the most common complication of CKD. In a study conducted by Thomas R *et al*., [6], the decreased erythropoietin synthesis is the most important and specific etiology causing CKD-associated anemia, which is similar to our study.

The complication of CKD in 162 patients are analyzed, out of 162 patients all were suffering from anemia either mild or severe, 16.66% of patients were present with pulmonary edema along with anemia and other commonly experiencing complications were metabolic acidosis, hyperkalemia, hyperphosphatemia, and hypernatremia. McClellan W *et al*., [7] has stated in his study that anemia is the common complication of CKD and is strongly associated with cardiovascular risk and renal complications, resulting in increased hospitalization and mortality rate.

Primary parameters include Hemoglobin (Hgb) values and iron profile (Total Iron Binding Capacity (TIBC), Transferrin saturation, serum ferritin, and serum iron values). Secondary parameters were red blood cell indices (RBC, Hct, MCH, MCV, and MCHC). The iron requirement was calculated based on the TIBC and Hgb levels. TIBC value is inversely proportional to the iron level.

In our study, the mean value of primary and secondary hematological parameters along with iron and folate parameters were calculated. It was observed that laboratory tests such as Hemoglobin, MCV, MCH, MCHC, Hematocrit, and RBC were carried out monthly once. It was found that the mean primary and secondary hematological parameters value increases every month when compared to the previous month. During our study, it was observed that serum ferritin, serum iron, and Transferrin saturation values had shown an increase in their mean values from the baseline. In the second follow up when compared with baseline value, TIBC showed a significant decrease in their mean value.

The present study also classified the patients based on the ESAs given for anemia. It was found that 75 patients were given with Epoetin alpha and 87patients were on Darbepoetin. Followed by these 5 patients had irregular hospital visits and their hemoglobin was below 6g/dL due to lack of knowledge about drugs. Patients were counseled and blood transfusion had been done followed by ESAs administration.

Hemoglobin of patients with ESAs was increase to 11.6g/dL from the baseline 6.94g/dL. In the study, Agarwal SK pointed out that after receiving ESAs, the majority of the patients achieved a clinically relevant increase in Hgb levels ≥ 13g/dL at any time during the study [8]. Significant p-value was obtained in the statistical analysis. In the study population, the serum ferritin declined about 105 ng/ml from baseline but after the administration of ESAs, improvement in ferritin level was observed p value=0.048. Similarly, a mean increase of approximately 1.3 mcg/dL was observed in serum iron concentration from the baseline value.

In this study mean TIBC level decreases more significantly in response with an increasing iron level in ESAs patients. Kazancioglu R at his study of ESAs effectiveness in CKD anemia patients, suggested that the secondary efficacy parameters significantly increased from baseline in mean Hematocrit, MCH, MCV, MCHC, and RBC [9].All patients in our study received ESAs concurrently along with iron supplementation. The dose range for ESAs is Epoetin alpha4000IU and Darbepoetin 40mcg and individualized dosing was performed based on their hematological values.

NICE and KDIGOguidelines for anemia management in kidney disease recommended giving ESAs for CKD anemia patients.

Safety parameters were analyzed by examining drug interactions and adverse drug reactions. ESAs were well tolerated and no serious adverse drug reaction and major drug interaction were found. Out of 75 patients, 3 patients experienced a sudden rise in blood pressure after Epoetin alpha administration which is managed by antihypertensive agents and in some cases dose adjustment had been done from 4000IU to 2000IU. Out of 87 patients administered with Darbepoetin, 2 of them experienced dizziness and advised to take rest after drug administration and 1 patient was found to experience headache. Krapf R *et al*., [10] in his study stated that a sudden rise in blood pressure was commonly experiencing side effects of Epoetin alpha and Darbepoetin was associated with headache and dizziness. But the benefits of these drugs overweigh the drug-related risk of ESA agents.

Our study observed patients having hemoglobin level < 6.5g/dL were given blood transfusion followed by ESA agents, however patients with hemoglobin range between 6.5-10 g/dL were given with ESAs. The agents were selected based on the affordability of the patients and were regularly follow up until hemoglobin reaches 10g/dL and thereafter were maintained on oral iron tablets(200mg once daily). The present study reported that Darbepoetin alpha weekly once was more efficient in achieving target hemoglobin than those on weekly twice Epoetin alpha. The time taken for ESAs treatment to be effective will depend on individual factors, such as degree of anemia, stages of CKD and other comorbid conditions. The study conducted by Schmidt RJ *et al*., [11] also stated that monthly follow up was necessary to ensure the hemoglobin level does not overshoot the optimal range of 10-12g/dL.

Patient counselling was given based on disease, medication adherence, and lifestyle modification. In our counselling on medication adherence we counselled the patients on the following aspects;

- To learn the names and uses of medications prescribed for them.
- To take the diet and fluids as prescribed by the dieticians.
- To keep the blood sugar and blood pressure within the targeted range.
- To reduce the intake of salt and excessive protein (red meat).
- Not to stop or alternate the medications without doctor advice
- To inform the doctors about all prescription and non-prescription drugs being taken.

- To inform the doctor if experienced any unusual signs and symptoms.

The counselling could help in providing mental support and improving the self-esteem of the patients through patient information leaflets. In the comparison of pre-intervention and post-intervention, a significant difference in data had been observed. Clinical pharmacists are very good at helping patients to obtain therapeutic goals or outcomes by being vigilant about pharmacotherapy that is employed with CKD patients.

CONCLUSION

The use of ESAs such as Darbepoetin alpha and Epoetin alpha had shown significant improvement in the advanced stages of CKD. In light of the cost of anemia treatments and safety concerns of blood transfusion, the ESAs as anemia treatment strategy found to be effective in CKD patients.It is always a challenge to develop modules for integrating the caregiver community with adequate patient information and treatment for improved patient care but pharmacist play a crucial role in best patient care.

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ABBREVIATIONS

CKD: Chronic Kidney Disease; ESAs: Erythropoiesis Stimulating Agents; GFR: Glomerular Filtration Rate; KDIGO: Kidney Disease Improvement Global Outcome; KDOQI-NKF: Kidney Disease Outcome Quality Initiative - National Kidney Foundation; Hct:Hematocrit; Hgb: Hemoglobin; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean corpuscular Hemoglobin Concentration; TIBC: Total Iron Binding Capacity; TSAT: Transferrin saturation; NICE: National Institute for Health and Care Excellence.

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