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The Effect of Acute Diarrhoea on Tacrolimus Trough Level Among Post Kidney Transplant Recipients at Ibn Sina Hospital - Khartoum, Sudan: A Cross-sectional Study

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ABSTRACT

Background: Diarrhoea is very common among post kidney transplant recipients which can lead to dehydration and an increase in tacrolimus (TAC) trough level. These will lead to intoxication and loss of graft function. TAC is heavily metabolized by CYP3A4 and CYP3A5 enzymes and p-glycoprotein efflux pumps located in the mature apical enterocytes of the small intestine, acute diarrhoea selectively breaches and disrupts this localized metabolic barrier, allowing a significantly higher fraction of unchanged drug to pass directly into the portal circulation, increasing systemic trough concentrations. **Objective:** To assess the effect of acute diarrhoea on tacrolimus trough level among post kidney transplant recipients. **Methods:** This is a descriptive, cross-sectional analytical hospital-based study, conducted at Ibn Sina Hospital during the period from April to June 2021. 100 post kidney transplant recipients were enrolled in the study. 50 of them had acute diarrhoea, the other 50 had no acute diarrhoea (taken as control). **Results:** Regarding the range of tacrolimus trough level, the findings revealed that it was above normal (target level) in 58%(n=29) with an absolute-mean of 33.3 ,SD 24.1 of those who had acute diarrhoea compared to18%(n=9) with an absolute- mean of 33.3 , SD 23.1 of the control group, which indicates significant association between elevated trough levels of tacrolimus and acute diarrhoea among post kidney transplant recipients ($P < 0.05$). A high level of serum creatinine was reported in 38%(n=19) with an absolute mean of 50.0 , SD16.9 of the one who had acute diarrhoea in comparison to 18%(n=9) with an absolute mean of 50.0 , SD 45.25 of the control group, indicates significant association between elevated levels of serum creatinine and acute diarrhoea among post kidney transplant recipients (P value < 0.05). **Conclusion:** The study showed a significant association between acute diarrhoea and increase tacrolimus trough level among post- kidney transplant recipients. Moreover, there was a significant association between elevated levels of serum creatinine and acute diarrhoea among post- kidney transplant recipient.

Keywords: Acute Diarrhoea, Tacrolimus trough level, Post Kidney Transplant recipient, Kidney Allograft Rejection, Sudan.

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INTRODUCTION

Kidney transplantation (KTx) is currently the best available treatment for end-stage renal disease. Tacrolimus (TAC), a calcineurin inhibitor (CNI), mycophenolate mofetil (MMF), and prednisolone form the immunosuppressive regimen most commonly used to prevent graft rejection. [1] Although currently used immunosuppressive protocols effectively prevent acute

and chronic rejection, several problems arise during TAC treatment due to its variable bio-availability (8–69%), large intra- and inter-individual pharmacokinetic variability, and interactions with food and drugs, which calls for dose individualization. Therefore, no fixed dosing scheme is recommended; instead, TAC doses are tailored individually according to the guidelines regarding TAC blood trough concentrations (TAC Cp trough) for certain periods following transplantation. TAC treatment poses a challenge, as both over and underestimation of its dose can lead to graft damage. [2]

Suboptimal TAC blood concentrations may result in acute or chronic graft rejection. On the other hand, overly high TAC concentrations may cause delayed graft function, thrombotic microangiopathy, deterioration of blood pressure control, diabetes, susceptibility to infections, and neurotoxicity. [3] One of side effects of TAC or cyclosporine treatment is CNI nephrotoxicity (CNIT). Acute CNIT, observed shortly after kidney transplant and potentially reversible, it is associated with vasoconstriction of the afferent arterioles, though the direct mechanism remains unclear. Chronic CNIT leads to irreversible interstitial fibrosis and tubular atrophy (IFTA), usually progressive and contributing to poor graft function. The underlying cause of TAC nephrotoxicity is yet to be discovered. Although nephrotoxicity is usually attributed to high TAC blood concentrations, it was suggested to be associated with the TAC metabolism rate instead, as it reportedly occurred in patients whose TAC blood concentrations fell within the therapeutic range. [4]

TAC metabolism is affected by several factors including age, sex, and body mass index (BMI). It is mainly controlled by cytochrome P450 enzymes: CYP3A4 and CYP3A5 and glycoprotein P. Patients with CYP3A5 * 1 are usually described as fast TAC metabolizers, while most slow metabolizers express CYP3A5 * 3, however, clinical application of this observation is limited by its unconfirmed influence on graft function in long-term observation and inaccessibility of routine genetic testing. [5]

Recently, the relationship between TAC metabolism and kidney graft function has been increasingly appreciated; therefore, a clinically feasible indicator of TAC metabolism would be of great clinical importance. Thölking et al showed that the TAC C/D ratio (TAC blood trough concentration normalized by TAC daily dose) as an indicator of TAC metabolism rate is associated with graft function after kidney transplant and kidney function after liver transplantation (LTx). [6]

Diarrhoea is very common among post kidney transplant recipients which can lead to dehydration and increase tacrolimus (TAC) trough level and these will lead to intoxication and loss of graft function.

TAC is heavily metabolized by CYP3A4 and CYP3A5 enzymes and p-glycoprotein efflux pumps located in the mature apical enterocytes of the small intestine, acute diarrhoea shedding selectively disrupts this localized metabolic barrier, which allows much higher fraction of unchanged drug to pass directly into the portal circulation, increasing systemic trough concentrations.

Diarrhoea is defined as an increase in the frequency of motions to three or more times per day (or passage of at least 200 g of stool per day) along with a decrease in consistency of stool (typically soft or liquid). “Acute diarrhoea” is defined as diarrhoea lasting up to 14 days. [7]

Diarrhoea is a frequent complication in post kidney transplant recipients. Although diarrhoea is often considered to be benign, severe episodes can cause dehydration with weight loss, high creatinine levels, and a fluctuation in serum immunosuppressive drug concentrations, resulting in a significant increase in mortality and morbidity and a poorer functional prognosis for the graft. [8]

There is a wide range of causes for diarrhoea in transplant recipients, but the most common causes are Clostridium difficile infection, cytomegalovirus and norovirus. Tacrolimus is an immunosuppressive drug whose main use is after organ transplant to reduce the activity of the patient's immune system and so the risk of organ rejection. Tacrolimus inhibits calcineurin, which is involved in the production of interleukin-2, a molecule that promotes the development and proliferation of T cells, as part of the body's learned (or adaptive) immune response. Biological half-life in healthy persons (43 hours on average) and in transplanted kidney 16 hours). [9]

Objectives

General objective

To assess the effect of acute diarrhoea on tacrolimus trough level among post kidney transplant recipients.

Specific objectives

To assess the association between high serum creatinine level and high tacrolimus trough level in post kidney transplant recipients who had acute diarrhoea.

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METHODOLOGY

Study design
This is a descriptive, cross sectional, analytical hospital-based study.

Study area
The study was conducted at Ibn Sina Hospital, a tertiary healthcare facility located in Khartoum State, Sudan. The hospital includes inpatient wards, an intensive care unit, and outpatient referral clinics, providing services to patients from Khartoum State as well as referred patients from other states.

Study period
The study was conducted in a period from April to July 2021.

Study population
The study population were Sudanese patient of post kidney transplantation attending outpatient transplant refer clinic and inpatient ward at Ibn Sina Hospital during the study period, 100 patients enrolled in the study as random sample,50 patients had acute diarrhoea and 50 patients had no diarrhoea as control group attended for tacrolimus trough level monitoring.

Inclusion criteria
- Patients of either sex.
- Age above 18 years.
- Patients of post kidney transplant.

Exclusion criteria
- Age less than 18 years.
- Patients do not fill the consent.
- Patients who already had developed graft rejection prior to diarrhea episode.

Sample size and sampling technique
Total coverage estimated 100 post kidney transplant participants.

Data collection tools and methods
Data was collected by researchers using direct Questionnaires, in addition to data gathered from record including the investigations done for the patients.

Method of measuring tacrolimus trough level
Whole blood trough concentrations (C0), typically drawn 12 hours after the last dose for immediate- release formulations. The Chemiluminescent Immunoassay (CLIA) principle was used for measuring tacrolimus trough level. *Manufacturer: COBUS*

Target therapeutic range of tacrolimus:
< 1month: 8 to12ng/ml (consensus guidelines) Nguyen et al, 2023.
1 to 3 months :6 to 9 ng/ml.
> 3 months (Maintenance): 4 to 8 ng/ml (Han et al ,2024)

Study Variable
Dependent variable
- Tacrolimus level.
- Renal function test.

Independent variable
- Demographic data.
- Disease duration.

Data analysis:
Data was analysed through software (SPSS) data analysis tool, version 25, graphic chart and tables designed by the use of Microsoft office excel 2010, descriptive statistic and frequency count was done on the data and the result was reported in tables and figures, the test of significance was used if P-value of < 0.05.

Ethical consideration:
- Ethical clearance obtained from the Research Ethics Committee of the Educational Development Centre (EDC) of the Sudan Medical Specialization Board (SMSB).
- Approval was obtained from the Khartoum State Ministry of Health's Research Department. Approval was obtained from the medical directors of the hospitals, the clinic registrars, and the supervising doctors at the clinics.
- The Research purpose and objectives were explained to the Participants in clear, simple language.
- Voluntarily written informal consent was obtained from all participants.
- Participant had the right to be free from harm.
- Confidentiality preserved through coding.
- The participant had the right to benefit from the researcher's expertise.
- The researcher fills out the data collection sheet without interrupting the health service provided.

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RESULTS

The study included 100 post kidney transplant recipients (50 patients had acute diarrhea and 50 patients had no diarrhea (taken as a control group). Males were 74%(n=74) and females were 26%(n=26). **(Figure 1)**

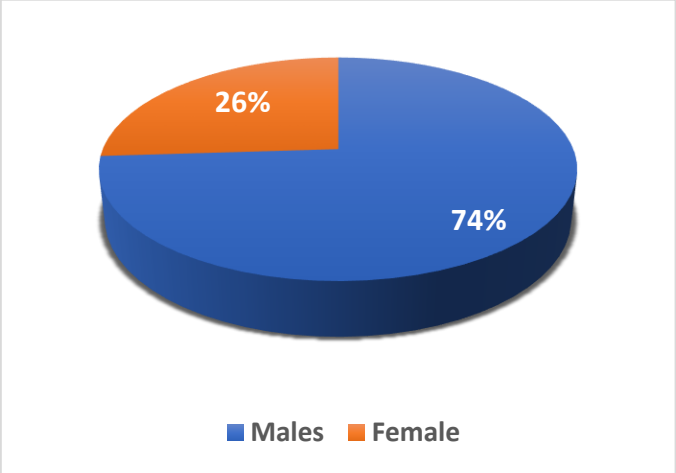

Figure 1 Distribution of the post kidney transplant recipients according to

Patients aged 36 – 44 years were 26%(n=26), between 54 – 65 years 24%(n=24), between 45 – 53 years 16%(n=16) between 18 – 26 years 16%(n=16), between 27 – 35 years 15%(n=15). **(Figure 2)**

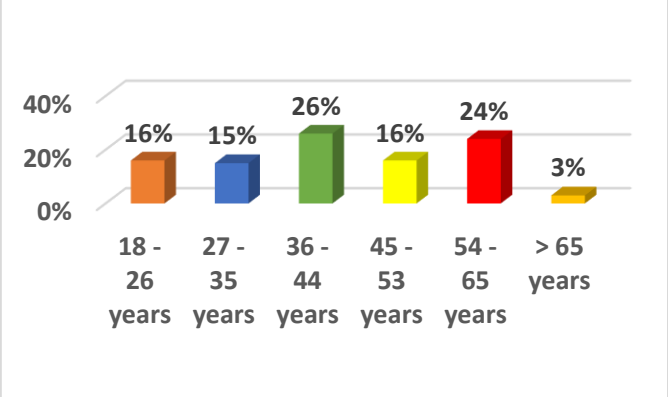

Figure 2 Distribution of the post kidney transplant recipients according to age.

Patients from Khartoum state were 60%(n=60) and 40%(n=40) from outside Khartoum State. **(Figure 3)**

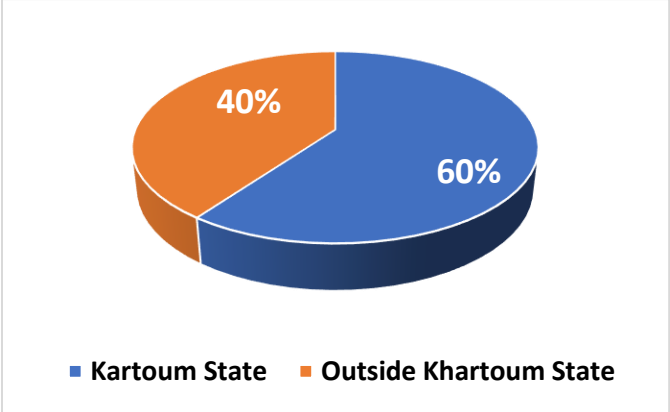

Figure 3 Distribution of the post kidney transplant recipients according to Residence.

Secondary school level of education reported in 43%(n=43) of the patients, primary school 27%(n=27), university graduate 13%(n=13), postgraduate 11% (n=11) and 6%(n=6) of the patients were illiterates. **(Figure 4)**

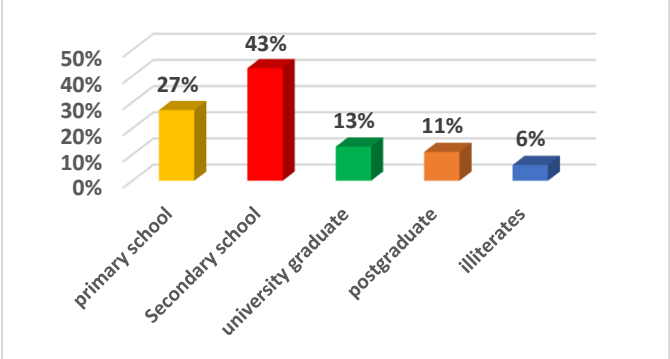

Figure 4 Distribution of the post kidney transplant recipients according to

The majority of the patients 78%(n=78%) were nonsmokers, 16%(n=16) were ex- smokers and 6%(n=6) current smokers. **(Figure 5)**

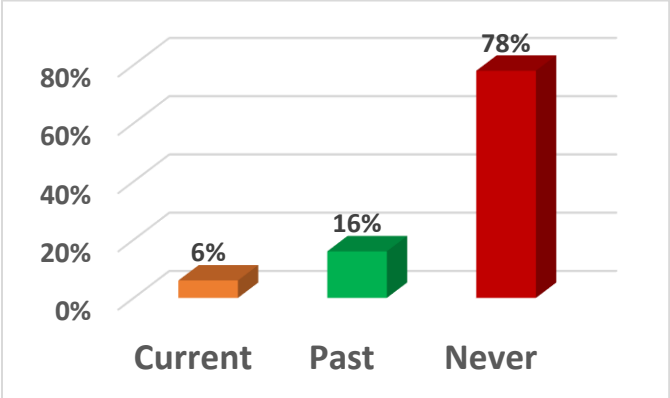

Figure 5 Distribution of the post kidney transplant recipients according to

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Kidney recipients who had acute diarrhoea were 50%(n=50) and the other half had no acute diarrhoea. Regarding the range of tacrolimus trough level, the findings revealed that it was above normal (target level) in 58%(n=29) with absolute-mean 33.3 , SD 24.1 of the one who had acute diarrhoea compared to18%(n=9) with absolute- mean 33.3 , SD 23.1 of the control group, which indicates significant association between elevated trough levels of tacrolimus and acute diarrhoea among post kidney transplant patients (P < 0.05). **(Table 1)**

Table 1 Distribution of the post kidney transplant recipients according to clinical presentations.

Clinical presentation	N	%
No diarrhea	50	50.0
Mild 2 - 3 motions 24 hrs	15	15.0
Moderate 4 - 10 motions 24 hrs	30	30.0
Severe > 10 motions 24 hrs	5	5.0

High level of serum creatinine was reported in 38% (n=19) with absolute mean 50.0, SD16.9 of the one who had acute diarrhoea in comparison to 18%(n=9) with absolute mean 50.0 SD 45.25 of the control group, indicates significant association between elevated levels of serum creatinine and acute diarrhoea among post kidney transplant recipients (P value < 0.05). **(Table 2)**

Table 2 Distribution of the post kidney transplant recipients according to have acute diarrhea in relation to duration of transplant.

Time of transplantation	Group			
	Control (no diarrhoea)		Cases (had diarrhea)	
	N	%	N	%
0 - 14 days	0	0.0	1	2.0
3 - 6 weeks	4	8.0	1	2.0
2 - 3 months	3	6.0	3	6.0
3 - 6 months	2	4.0	2	4.0
After 6 months	41	82.0	43	86.0
Total	50	100.0	50	100.0

P value = 0.069 (> 0.05 not significant)

High level of serum creatinine was reported in 38% (n=19) with absolute mean 50.0, SD16.9 of the one who had acute diarrhoea in comparison to 18%(n=9) with absolute mean 50.0 SD 45.25 of the control group, indicates significant association between elevated levels of serum creatinine and acute diarrhoea among post kidney transplant recipients (P value < 0.05). **(Table 3)**

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Table 3 Distribution of the post kidney transplant recipients according to have acute diarrhea in relation to level of serum creatinine.

Creatinine	Group			
	Control (no diarrhoea)		Cases (had diarrhoea)	
	N	%	N	%
Normal	41	62.0	31	62.0
High (> 1.3mg/dl)	9	38.0	19	38.0
Total	50	100.0	50	100.0
Mean		50		50
SD		16.96		16.96

DISCUSSION

The study included 100 post kidney transplant recipients, with main objective to assess the effect of acute diarrhoea on tacrolimus trough level among post kidney transplant recipients at Ibn Sina Hospital during the period from April to July 2021).

Patients who had diarrhoea were 50 patients and the other half had no diarrhoea. Regarding the range of tacrolimus trough level, the findings revealed that it was above normal in 58%(n=29) of the one who had acute diarrhoea compared to 18%(n=9) of the control group, which indicates significant association between elevated trough levels of tacrolimus and acute diarrhoea among post kidney transplant recipients ($P < 0.05$) ,Similar to Hochleitner, et al measured the tacrolimus trough levels of four male and two female recipients of solid organs before, during, and after gastroenteritis. The average age of these six patients was 31 (1-60) years. Four patients had received a kidney transplant, one patient had undergone simultaneous kidney-pancreas transplantation, and another patient had received a liver transplant. Rotavirus was identified in the faeces specimen of a 1-year-old child that had undergone liver transplantation. All patients showed an elevated tacrolimus trough level (peak 20-60 ng/ml) after onset of gastroenteritis. Under symptomatic therapy and adequate adjustment of tacrolimus dose, the gastroenteritis stopped and tacrolimus levels returned to the therapeutic range. We recommend that FK506 levels be carefully monitored during diarrhoea in order to prevent intoxication. [53] van Boekel et al assessed the degree of unnoticed tacrolimus overexposure in renal transplant patients with mild diarrhoea while on treatment with tacrolimus and MMF. The C0 did not differ between patients with mild diarrhoea and controls (mean [95% confidence interval], 9.6 µg/L [8.6-10.9 µg/L] and 8.3 µg/L [6.9-9.9 µg/L]). In addition, there was no significant difference in the 12-hr area under the curve between patients with mild diarrhoea and controls (185.6 µg·h/L [153.6-224.2 µg·h/L] vs. 170.5 µg·h/L [137.2-221.8 µg·h/L]). As a result, the ratio between the 12-hr area under the curve and C0 was similar in both groups (19.2 [17.5-21.1] vs. 20.6 [19.0-22.4]).

The intraindividual variability in tacrolimus exposure was limited and not affected by the presence of mild diarrhoea. [54] Davies, et al reported that Gastrointestinal (GI) adverse events are common following renal transplantation and all immunosuppressive regimens have been associated with such events. Mycophenolate mofetil (MMF) or enteric-coated mycophenolate sodium (EC-MPS) are potential components of immunosuppression regimens, and are associated with the most successful outcomes in kidney transplantation. The effects of MMF and EC-MPS are likely mediated via the active metabolite mycophenolic acid (MPA). The GI events caused by both MMF and EC-MPS may, in part, be related to MPA, independent of the formulation or route of administration. MPA may produce GI events either through direct action or through the action of its metabolites. However, many other factors may cause GI events observed following renal transplantation. These include the surgery itself and concurrent diseases such as diabetes, and bacterial, viral, fungal and parasitical infections. Additionally, numerous concomitants non immunosuppressive

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agents, including antibiotics hypoglycaemic and proton-pump inhibitors, can be associated with GI events. In a recent trial in renal transplant patients with severe diarrhoea, approximately 50% of patients achieved resolution of diarrhoea through methods other than altering their immunosuppressive regimens. Indeed, altering of the immunosuppressive regimen may lead to the risk of acute rejection. [55]

High level of serum creatinine was reported in 19(38%) of the cases in contrast to 9(18%) of the control group, indicates significant association between elevated levels of serum creatinine and acute diarrhoea among post kidney transplant patients (P value < 0.05). Similar to Wang, et al described the relationship between kidney allograft function and diarrhoea, and to determine how diarrhoea is influenced by various immunosuppressive regimens at a single centre in Taiwan. They collected 62 patients for analyses, including 16 with infectious diarrhoea and 46 with non-infectious diarrhoea. At 3rd year post transplantation, patients with infectious diarrhoea demonstrated a significantly lower cumulative renal function rate (56.3% vs. 84.7%, p<0.05). No significant differences were found between recipients receiving different immunosuppressive regimens in terms of renal function. However, recipients receiving mammalian target of rapamycin (mTOR) inhibitor and mycophenolate mofetil (MMF) tended to show a slower rate for deterioration of renal function. [56] Lee et al investigated the relationship between the gut microbiota and tacrolimus dosing requirements in this pilot study of adult kidney transplant recipients.

They characterized bacterial composition in the faecal specimens by deep sequencing of the PCR amplified 16S rRNA V4-V5 region and we investigated the hypothesis that gut microbial composition is associated with tacrolimus dosing requirements. Initial tacrolimus dosing was similar in the Dose Escalation Group and in the Stable Group (4.2±1.1 mg/day vs. 3.8±0.8 mg/day, respectively, P=0.61, two-way between-group ANOVA using contrasts) but became higher in the Dose Escalation Group than in the Dose Stable Group by the end of the first transplantation month (9.6±2.4 mg/day vs. 3.3±1.5 mg/day, respectively, P<0.001). Our systematic characterization of the gut microbial composition identified that faecal Faecalibacterium prausnitzii abundance in the first week of transplantation was 11.8% in the Dose Escalation Group and 0.8% in the Dose Stable Group (P=0.002, Wilcoxon Rank Sum test, P<0.05 after Benjamini-Hochberg correction for multiple hypotheses). Faecal Faecalibacterium prausnitzii abundance in the first week of transplantation was positively correlated with future tacrolimus dosing at 1 month (R=0.57, P=0.01) and had a coefficient ± standard error of 1.0±0.6 (P=0.08) after multivariable linear regression. [57] Nowicka et al analysed the relationship between the early post-KTx TAC C/D ratio (blood trough concentration normalized by total daily dose) and kidney graft function in a 2-year follow-up. Patients were divided based on the TAC C/D ratio at 6 months after KTx of 1.47 ng/mL * 1 mg. Fast metabolizers (C/D ratio <1.47 ng/mL * 1 mg) presented with significantly worse graft function throughout the whole study period (p < 0.05 at each timepoint) and were significantly less likely to develop good graft function (estimated glomerular filtration rate ≥45 mL/min/1.73 m2) than slow metabolizers. [59]

CONCLUSION

There is significant association between elevated tacrolimus trough level and acute diarrhea among post kidney transplant recipients, moreover, there was significant association between elevated levels of serum creatinine and acute diarrhea among post kidney transplant recipients.

RECOMMENDATIONS

Management of acute diarrhea in post kidney transplant recipients should not be delayed, because it may lead to significant rise in tacrolimus trough level, with it is consequence effect on graft survival.

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Competing Interests:

The authors declare no competing interests.

Author's Contributions:

Conception/design: Both authors.
Provision of study material/patients, Data Collection and/or assembly of data: Ahmed Elnour Ali Omer.
Data analysis and interpretation: Both authors.
Manuscript writing: MYH
Final Approval of manuscript: Both authors.
Data Availability Statement: The data underlying this article will be shared upon request to the corresponding author.

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