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RESEARCH ARTICLE

IMPACT OF AKI IN PATIENTS WITH CIRRHOTIC LIVER AND RECEIVED HCV TREATMENT

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ABSTRACT

Background and Aims: Egypt had controlled liver cirrhosis who received HCV vaccine in line to modulate its impact among nephrotic patients. Current clinical trial aim to investigate acute kidney injury (AKI) impact among liver cirrhosis individuals who received HCV treatment. ***Material and methods:*** A prospective, multi-center clinical trial, on 50 liver cirrhosis patients who eligible to receive HCV treatment. They equally divided into Group A 25 patient with eGFR >90 ml/min, Group B 25 patients with chronic kidney disease (CKD) stages II-TTT (eGFR <90, >30 mL/min). Fluctuations in serum creatinine, and eGFR evaluated while on-therapy, and by the end of the trail. ***Results:*** Both groups A and B revealed significant differences in reading of serum creatinine during and by the end of the study ($p < 0.005$). the impact of AKI was moredetermined with eGFR >90 ml/min in compare with who had eGFR <90 mi/min and >45 ml/min ($p < 0.005$). ***Conclusion:*** Impact of AKI were reported in their kidney functions especially patients with normal serum creatinine than among liver cirrhosis patients who revealed improvements by the end of the study.

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INTRODUCTION

An epidemiological published study by 2008 on Egyptian Demographic Health Survey involving huge hepatitis C virus (HCV) biomarkers had estimated an earlier HCV incidence among youth up to 14.7% (1). Thus, Egypt has an elevated HCV prevenance at the last decade globally (2). Nearby 25% of chronic HCV infected individuals had developed liver cirrhosis, plus its suspected complications involving hepatocellular carcinoma(3).HCV successful management has been addressed in sustained virologic response (SVR) that absent in detecting viral RNA levels in serum beyond six months of complete therapeutic interventions (4). Recent antiviral acting agents targeting HCV-encoded proteins including with replication. Those involving non-structural (NS) components i.e., RNA-dependent RNA polymerase (NSSB), protein NSSA 'a role in formation of replication complex' and NS3-NS4A serine protease also cofactor proteins (5). Fixed-dose combined currently available involving sofosbuvir-ledipesvir '400 mg/90 mg', ombitasvir-peritaprevir- ritonavir 'double pills 12.5-75-50 mg per each, respectively' in addition to dasabuvir '250 mg' sofosbuvir-daclatasvir '400 mg/ 60 mg', sofosburvir- simeprevir '400 mg/ 150 mg' also ribavirin(6).

In line with Kidney Disease Improving Global Outcomes guidelines, AKI is addressed as an increase in serum creatinine up to ≥0.3 mg/dL within 48 hours or elevated serum creatinine ≥1.5 times at baseline of the study around a week even urine volume around half ml/kg/ hour every six hours (6). No doubt, there is null clinical trial had documented definitive overall benefits on kidney management. up to date, available data had obtained an earlier therapy based on interferon or ribavirin protocols. As well, the extent to which heterogenicity of individuals features plus determining any additional manifestations e.g., cryoglobulinemia (6). By the last decade, a meta-analysis conducted on 11 clinical trials on more than one-hundred nephrotic patients had received interferon with/ or without ribavirin, it was a regression in proteinuria to a variable extent among who achieved end- to management viral response. A tiny patient` percentage had developed a relapse where viral clearance was un-sustained. Plus, no obvious alterations in serum creatinine with null posttreatment biopsy positive (7). Unique sofosbuvir was eliminated based on renal routine among late CKD stage patients or among who undergone haemodialysis, unless no clear recommendations. Elevated sofosburvir concentrations could be explained based on its pharmacological features, as it is a kidney excreted metabolic medicine among unaffected individuals GS 331007 (7).

An earlier clinical trial had ensured that progressive worsening clinical manifestation as ensured via worsened renal functioning tests among CKD individuals who received sofosbuvir protocol. Unless, it was stated among patients without any renal pathologies (8). The need of this study developed from the rarity of data in the published articles about the impact of AKI in liver cirrhosis patients, who received HCV treatment. Thus, the current study aimed to study the impacts of AKI in liver cirrhosis patients, who received HCV treatment.

MATERIALS AND METHODS

Study design: A prospective, randomly assigned, double-blind, controlled experiment was performed from July 2023 to March 2024 at the nephrology Unit of three Hospitals, Shebin El-Kom City, Menofyia, Egypt.

Participants: Twenty-five patients were enrolled based on specific inclusion criteria: they included aged 20 to 40 years who have HCV and liver cirrhosis.

Patients were excluded if they had: co-infection with hepatitis B virus, patients with advanced liver disease, portal vein thrombosis or hepatocellular carcinoma, with clinically significant illness i.e., psychiatric or cardiac diseases or any other medical disorder that may interfere with subject treatment and/or adherence to protocol, who developed drop in haemoglobin level, patients with eGFR less than or equal to 30 ml/min/1.73 m^2, with sight or hearing impairments, neurological, psychiatric, or cognitive disorders, or exhibited uncooperative behavior.

Sample size calculation: A sample size of 76 patients was estimated utilizing G*POWER statistical software (version 3.1.9.4; Franz Faul, Universität Kiel, Germany) to achieve adequate statistical power. The sample size estimation was dependent on renal function tests data from a previous study by Aref et al. (918), which reported a significant incidence of acute kidney injury among HCV population who received direct acting antivirals. Accordingly, the required sample size was determined to be 25 subjects per group. The calculations were based on a two-sided 5% significance level, an effect size of 0.7, and a power of 85%.

Randomization: Every participant was provided with information regarding the characteristics, objectives, and benefits of the research, as well as their right to withdraw or decline participation at any point. After signing the consent forms, demographic data were obtained. An independent researcher then employed computer-generated random cards enclosed in sealed and opaque envelopes to assign the 50 participants randomly and equally to either Group A or B. The envelopes were sealed and sequentially numbered to ensure the concealed allocation and participants were unaware of their group allocation.

Group A: 25 patients with eGFR>90 ml/min/1.73m^2.

Group B: 25 patients with CKD with eGFR >30 mL/min stage IIa, b based on estimated CKD-EPI equation.

GFR = 141 X min (Scr/κ, 1)α X max (Scr/κ, 1)-1.209 X 0.993Age X 1.018 (if female) X 1.159. Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

Outcomes measures: Laboratory investigations that include CBC, liver function and renal function tests, PT, PTT and INR and abdominal ultrasound measurements were taken both before and after the 8-week intervention.

Statistical analysis: An unpaired t-test was utilized to compare subject characteristics across groups. The quantitative data were presented as mean, standard deviation (SD) and range values. Independent t- test was used for comparing quantitative variables (eGFR, and Creatinine) readings between group A and B and p-value ≤ 0.05 was considered significant. Qualitative data were presented as number and percentage. Fisher exact test was done for comparing qualitative variables (AKI) between group A and B and p-value ≤ 0.05 was considered significant. Repeated measure ANOVA test was used for comparing quantitative variables (eGFR, and Creatinine) readings overtime, and different readings overtime between groups A & B and p-value ≤ 0.05 was considered, utilizing SPSS version 25 for Windows (IBM SPSS, Chicago, IL, USA). There were no withdrawals from this study, and all individuals terminated the treatment program.

RESULTS

Participant characteristics: Table 2 shows the 50 participantswith HCV and liver cirrhosis, where their baseline laboratory tests results ($p > 0.05$). The mean differs represented age of participants` mean with non-significant differs between groups in their baseline outcome measures. Although, mean difference readings of serum creatinine in group A and B on their therapy along months and posttreatment by the end of the study. (Figure 1-2).

There weresignificant differences between groups regarding impact of AKI, that was higher impact of AKI in Group A than in Group B all over the study duration, unless these differences represented non-significant statistical differences($p < 0.05$) (Tables 2).

DISCUSSION

The study's main findings revealed that AKI impact after usage of antiviral treatment in form of daclatasvir/sofosbuvir/ribavirin combination that was effective in who were in stage I-II, III CKD by 96%. There were AKI events during and by the end of therapy particularly in who with normal baseline serum creatinine. Unless, clinically it was not significant. Patients with CKD stage II and III experienced improvement in their kidney functions during and by the end of therapy. The main purpose of HCV eradication is to prevent progression of cirrhosis, liver-related complication, and HCC development.

Tab. 1. Comparing the characteristics of participants between both groups

	Group A	Group B	Independent t-test	p-value
	Mean ± SD	Mean ± SD		
Age (years)	52.5 ± 6.5	53.5 ± 5.15	-3.629	0.002*
Hb (g/dL)	14.6 ± 1.7	14.5 ± 1.7	0.032	0.974
PLT (10^3/uL)	200.8 ± 45.2	201.6 ± 41.1	-0.078	0.937
AST (IU/L)	51.7± 5.8	48.2 ± 4.3	0.577	0.565
ALT (IU/L)	55.8± 3.1	42.8 ± 7.9	1.676	0.097
Total Bil (mg/dL)	0.8± 0.04	0.8 ± 0.03	-0.772	0.445
Albumin (g/dL)	4.3 ± 0.5	4.6 ± 0.4	-1.968	0.056
INR	1.1 ± 0.1	1.1 ± 0.02	-0.574	0.571
Baseline serum creatinine (mg/dL)	0.9 ± 0.2	1.2 ± 0.3	-9.342	0.003*
Baseline eCFR	112.3 ± 14.7	72.6 ± 11.9	11.746	0.002*

SD, standard deviation; MD, mean difference; p-value, probability value.

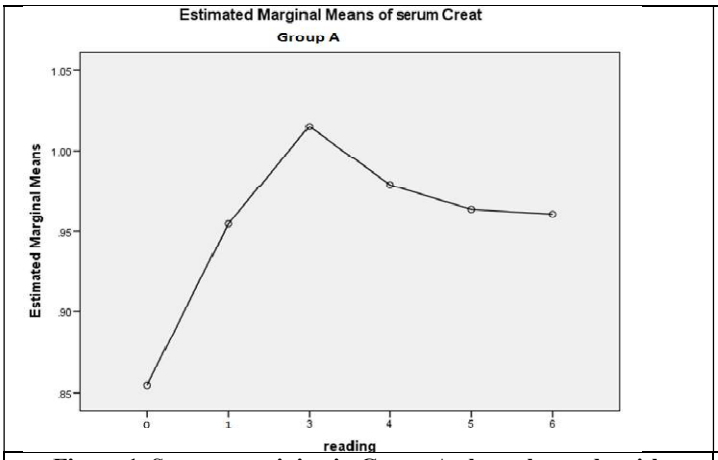

Figure 1. Serum creatinine in Group A along the study with improvement without reaching the baseline

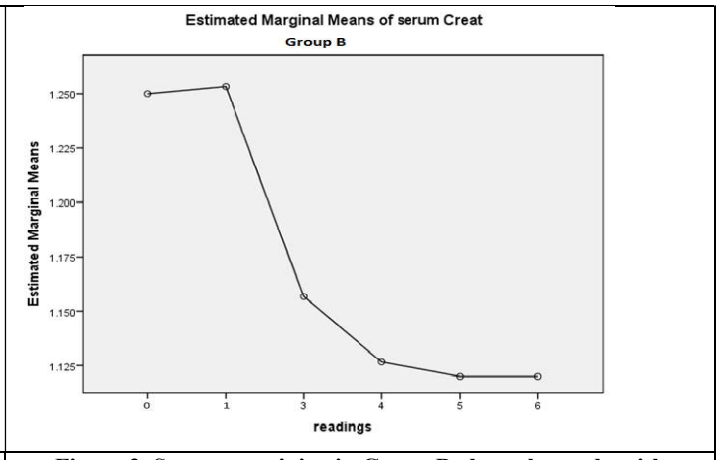

Figure 2. Serum creatinine in Group B along the study with significant improvement reaching a plateau by the end of the study

Tab. 2. AKI in study population

		Group A		Group B		p-value
		No	%	No	%	
Baseline		25	100%	25	100%	0.002*
After 1st month	No AKI	16	64%	24	96%	0.974
	AKI	9	36%	1	4%	
After 3rd month	No AKI	18	78%	24	96%	0.937
	AKI	7	28%	1	4%	
After 4th month	No AKI	20	80%	24	96%	0.565
	AKI	5	20%	2	4%	
After 5th month	No AKI	21	84%	24	96%	0.097
	AKI	4	16%	1	4%	
After 6th month	No AKI	22	88%	24	96%	0.003*
	AKI	3	12%	1	4%	

*Fisher exact test was used.

In addition to these main reasons to treat HCV infection in patients with CKD who are potential candidates of kidney transplantation, there is an additional reason is to prevent HCV specific complications associated with kidney transplantation. Despite these hepatic and extrahepatic benefits of eradicating HCV in CKD patients, traditionally accepted interferon-based therapy in CKD patients has been unsatisfactory due to its suboptimal effects, depending on comorbid conditions and the extent of renal impairment. Therefore, eradicating HCV in CKD patients has been challenging. However, the emergence of direct-acting antivirals has changed the treatment trend of patients with chronic hepatitis C infection, and the decision to treat HCV in CKD patients has also been less challenging (10). As reviewed in the literature, to the best of our knowledge, this may be the prime study to investigateof acute kidney injury (AKI) among liver cirrhosis individuals who received HCV treatment (11).

This study was conducted on 50 male patients, treatment-naive. Only one CKD II patient continued treatment for six months. We detected that the AKI impact in patients with eGFR > 90 ml/min per 1.73 m^2 in comparison with those with eGFR < 90 ml/min per 1.73 m^2 also> 45 ml/min per 1.73 m^2, where after 1st, 3rd,4th,5th and 6th months of start of treatment, 36%, 28%, 20 %, 16% and 12% respectively for Group A, who developed AKI in patients with eGFR > 90 ml/min in comparison with 4% in those with eGFR < 90 ml/min but of no statistical significance. Group A revealed 9 patients with baseline eGFR > 90 ml/min developed AKI where 2 of them recovered at 3rd month by end of treatment while 3 patients with baseline eGFR 76 ml/min developed AKI. In contrast to the study by Shin et al. (12), the first real world study, which evaluated efficacy and safety of diverse sofosbuvir-containing regimen in CKD stage 3 patients and confirmed the current guideline that sofosbuvir-based regimen can be used in

patients with mild to moderate renal impairment (eGFR ≥30 mL/min/1.73m^2). The SVR rate at 12 weeks after end of the therapy was 85.7%. Although greater than 30% decrease of eGFR was seen in 4 out of 28 patients and renal function was subsequently improved to normal in all 4 patients (12). In comparison with the study of Saxena et al. (13) which studied the outcomes of sofosbuvir-based regimens on patients with baseline eGFR ≤ 45 mL/min/1.73 m^2 in comparison with those with eGFR > 45 mL/min/1.73 m^2, our study compared the effect between patients with eGFR > 90 mL/min/1.73 m^2 to those with eGFR < 90 mL/min/1.73 m^2 and > 45 mL/min/1.73 m^2 on mainly kidney functions (13). Saxena et al. (13) reported the outcomes of sofosbuvir-based therapy on patients with renal dysfunction by using the HCV-TARGET database, which is a multicenter, real-world cohort. Of the 1789 enrolled patients, 73 had eGFR of less than 45 mL/min/1.73 m^2 (18 patients with eGFR ≤ 30 mL/min/1.73 m^2 and 5 patients on dialysis). These patients were compared to 1716 patients with eGFR > 45 mL/min/1.73 m^2. The included treatment regimen was sofosbuvir/simeprevir at 40%, sofosbuvir/ RBV at 30%, sofosbuvir/PEG-INF/RBV at 18% and sofosbuvir/ simeprevir/RBV at 11%. All patients with eGFR ≤ 45 mL/min/1.73 m^2 were treated with sofosbuvir 400 mg once a day. Patients with baseline eGFR ≤ 45 mL/min/1.73 m^2 had a significantly higher rate of cirrhosis (73%) as compared to the control group (24%). SVR12 was achieved in 53 of the 64 (83%) patients with eGFR < 45 mL/min/1.73 m^2. This was comparable with patients with eGFR > 45 mL/min/1.73 m^2. In addition, 15 of the 17 (88%) patients with eGFR ≤ 30mL/min/1.73 m^2 and all 5 patients on HD at baseline achieved SVR12. However, in the safety analysis, the patients with eGFR ≤ 45 mL/min/1.73 m^2 had experienced significantly higher rates of anemia (31%), worsening of the renal function (10%), and any serious AEs (18%). The authors concluded that patients with renal impairment need close expert monitoring (13). In our study, there was a significant difference between different readings of serum creatinine in both groups on therapy and on follow up during the next 3 months after the end of therapy. We noticed a rise in serum creatinine in (group A) during 3 months of therapy with slight improvement during follow up after end of therapy without reaching the baseline. While in group B there was a slight increase in serum creatinine after 1st month of start of therapy then there was a significant improvement after 3rd and 4th months of start of therapy to come to a plateau by the end of 6th month (Tables 2 & 3). Estimated marginal means of s. creatinine were illustrated in figures (1 & 2).

Strengths and limitations: This study has several limitations. First, the limited number of treated patients in this series limits the power. Also, only one type of regimen was studied as that was the available at the time of our study. Our finding that eGFR improvement was associated with sustained virologic response in patients with reduced eGFR at baseline, although statistically significant, had wide confidence intervals and will need to be validated in larger cohorts of patients with CKD. Assessments of proteinuria were not available before and after therapy as proteinuria also defines CKD. Further studies are needed to measure the effect of direct-acting antiviral therapy on proteinuria. Future studies are needed to determine predictors of kidney recovery with HCV eradication and confirm the long-term effects of HCV eradication on kidney function.

CONCLUSION

This study suggests that impact of AKI was reported in their kidney functions especially patients with normal serum creatinine than among liver cirrhosis patients who revealed improvements by the end of the study. This could be due to higher drug exposure to antiviral medications eliminated by the kidney or decreased effect of viremia on kidneys after treatment. Larger studies will be needed to determine if eradication of HCV therapy slows or prevents progression to end stages in patients with CKD and HCV.

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