Original Article

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Creatinine Clearance by Timed Urine Collection for Measurement of Glomerular Filtration Rate in Liver Cirrhosis: A Feasible Method

Jose Devasia[1], Neelakandan Ramya[2], K Jeyapalan[3], Sethu Prabhu Shankar[3]

[1]Assistant Professor, Department of General Medicine, Aarupadai Veedu Medical College & Hospital, Puducherry, India, [2]Associate Professor, Department of General Medicine, Aarupadai Veedu Medical College & Hospital, Puducherry, India, [3]Professor, Department of General Medicine, Aarupadai Veedu Medical College & Hospital, Puducherry, India

Abstract

Background: Renal dysfunction is one of the common and major complications in liver cirrhosis with poor prognosis.

Aim: To study the role of` serum creatinine and creatinine clearance in assessing renal function in patients with liver cirrhosis and to study the advantages of measuring the creatinine clearance by timed urine collection over creatinine clearance measured by Cockcroft-Gault formula.

Materials and Methods: All adult patients of both sexes diagnosed to have liver cirrhosis were included in the study. Liver function test, renal function tests, 24-h urine volume, and urine creatinine were done. Creatinine clearance was calculated using the formula urine creatinine/serum creatinine multiplied by 24-h urine volume and also by the Cockcroft-Gault formula. Comparison between serum creatinine and creatinine clearance calculated by these two methods were done.

Results: Of the 43 patients included in the study, 35 were male while remaining 8 were female. Mean blood urea and serum creatinine were 22.42 mg/dl and 1.01 mg/dl. 10 patients had a creatinine clearance of <30 ml/min based on timed urine collection. Measurement of creatinine clearance using the Cockcroft-Gault formula showed significantly higher values when compared to that measured using timed urine collection. Ascites was present in 38 out of the 43 patients. Kidney size and corticomedullary differentiation were normal in all patients.

Conclusion: Creatinine clearance should be done routinely in advanced liver disease to assess renal reserve. Creatinine clearance by timed urine collection has a strong predictive value when compared to creatinine clearance done using by Cockcroft-Gault formula.

Key words: Cockcroft-Gault formula, Glomerular filtration rate, Liver cirrhosis, Timed urine creatinine clearance

INTRODUCTION

Renal dysfunction is one of the common and major complication in liver cirrhosis with poor prognosis.[1,2] Assessment of renal function is important to monitor the progression of renal disease in liver cirrhosis.[1] Most widely used standard methods to assess renal function like blood urea nitrogen, serum creatinine are likely to give erroneous impressions in liver cirrhosis.[3] Accurate measurement of glomerular filtration rate requires use of a validated filtration marker, such as iothalamate, iohexol, or inulin.[2] Inulin clearance is the gold standard for measurement of glomerular filtration rate.[4-6] However, the applicability of these markers is restricted by its cost and feasibility and is rarely used in clinical practice.[4] Here, we have studied the advantages of using a more practically feasible marker of glomerular filtration rate, the creatinine clearance to assess the renal function in routine clinical practice.

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MATERIALS AND METHODS

In Present, Study was carried out in Aarupadaai Veedu Medical College and Hospital, Pondicherry, India during

Corresponding Author: Jose Devasia, Department of General Medicine, Aarupadai Veedu Medical College & Hospital, Kirumampakkam, Puducherry - 607 403, India. Phone: +91-7598225986, 9894835015. E-mail: dr.josedevasia87@yahoo.com

the period of October 2012 to September 2015. All adult patients of both sexes diagnosed to have liver cirrhosis were included in the study. As glomerular filtration rate decreases with age,[6,7] patients of age more than 60 years were excluded from the study. Patients with chronic kidney disease, primary renal disease, diabetes mellitus, systemic hypertension, serum creatinine >1.5, hepatic encephalopathy, recent gastrointestinal bleed were also excluded from the study. Laboratory investigations liver function test, renal function tests, serological tests for hepatitis virus B and C, 24-h urine volume, and urine creatinine was done. Ultrasonogram of the abdomen was done to identify the liver size, echotexture, portal vein diameter, splenomegaly, presence of ascites and kidney size, echotexture. Evidence of liver cirrhosis was defined by a compatible clinical profile[8,9] along with altered liver function tests, reversal of albumin-globulin ratio, shrunken liver with altered echotexture in ultrasonogram. Creatinine clearance calculation was done by two methods, one by timed urine collection[10] using the formula urine creatinine/serum creatinine multiplied by 24-h urine volume (UCr/PCr) × V. This was divided by 1440 to get the value in ml/min. The patients were sub-grouped into three based on their creatinine clearance using (U×V)/P. Group I having values more than 60 ml/min, Group II 30-60 ml/min and Group III <30 ml/min. Creatinine clearance was also calculated using the Cockcroft and Gault formula[10] (140−age)×weight/(serum creatinine×72). For female patients this value to be multiplied by 0.85. Comparison between serum creatinine and creatinine clearance calculated by these two methods were done.

RESULTS

Of the 43 patients included in the study, 35 were male and 8 were female. Age of the patients ranged from 22 to 58 years (Table 1). The mean age was 42.14 years. The liver disease was associated with alcoholism in 21 patients, hepatitis B virus in 6 patients, Wilson's disease in one and autoimmune hepatitis in one patient. In the remaining 14 patients, etiology could not be ascertained. A number of patients with creatinine clearance <30 ml/min based on timed urine collection was 10 (Table 2). Mean blood urea level was 22.42 mg/dl. The serum creatinine was 0.90 mg/dl Group I patients (Table 3) and the mean serum creatinine level was 1.01 mg/dl. The 24-h urine volume in Group III patients was 690 ml, and the mean 24-h urine volume was 1317.44 ml. Measurement of creatinine clearance using the Cockcroft-Gault formula showed significantly higher values when compared to that measured using timed urine collection (Table 4). Mean serum albumin was 3.37 mg/dl (Table 5). The mean bilirubin was 1.64 mg/dl (Table 6). Ultrasound abdomen showed shrunken liver with altered echotexture and splenomegaly in all the patients. Ascites was present in 38 out of the 43 patients. Kidney size and corticomedullary differentiation were normal in all patients.

Table 1: Age and number of patients

Age group (years)	Number of patients
<30	2
30-39	9
40-49	24
50-60	8

Table 2: Number of patients and creatinine clearance by timed urine collection

Group	Creatinine clearance (ml/min)	Number of patients
Group I	>60	14
Group II	30-60	19
Group III	<30	10

Table 3: Renal parameters across three groups

Renal parameter	Group I	Group II	Group III
Blood urea (mg/dl)	22.43	22.42	22.4
Serum creatinine (mg/dl)	0.90	1	1.2
24-h urine volume (ml)	2010.71	1136.84	690
Creatinine clearance (UxV/P) ml/min	85.33	43.41	18.55
Creatinine clearance (CG formula) ml/min	85.02	63.87	44.90

Table 4: Comparison of creatinine clearance by two methods

Creatinine clearance (ml/min)	By (U×V)/P (%)	By Cockcroft Gault formula (%)
<20	6 (13.95)	0 (0)
20-40	12 (27.90)	4 (9.30)
40-60	11 (25.58)	11 (25.58)
60-80	5 (11.63)	17 (39.54)
>80	9 (20.93)	11 (25.58)

Table 5: Serum albumin and renal function

Serum albumin (mg/dl)	Group I	Group II	Group III
>3.5	8	2	0
3.2-3.5	4	14	3
<3.2	2	3	7

Table 6: Serum bilirubin and renal function

Serum bilirubin (mg/dl)	Group I	Group II	Group III
<1.2	2	2	3
1.2-2	8	12	4
>2	4	5	3

DISCUSSION

Of the total 43 patients included in the present study with liver cirrhosis, male (81%) patients were more common that female (19%) patients. Most common age group (Table 1) of presentation with liver cirrhosis in the present study was 40-49 years with 24 (56%) patients. Alcoholism was the commonest cause of liver disease in the present study with 21 (49%) patients, followed by hepatitis B in 6 (14%) patients. In our study, there was no significant variation in blood urea levels (Table 3) in all the three groups, suggesting that estimation of blood urea will not be of much use in determining renal impairment. Blood urea nitrogen levels may also vary in the absence of glomerular filtration rate changes as blood urea levels may be lower than expected in patients with liver disease because of reduced hepatic synthesis, and it may also increase because of gastrointestinal hemorrhage or catabolic states.[11] Hence, its use to assess renal dysfunction is very limited. It was noted that in 10 patients with normal serum creatinine levels below 1.2 mg/dl, the creatinine clearance was less than 30 ml/min (Table 2) of, suggesting that moderate to severe renal dysfunction may be masked by seemingly normal creatinine levels.[13] This is possibly due to the fact that the hepatic production of creatinine is impaired in cirrhosis[13,14] and the presence of malnutrition, increased tubular secretion in cirrhosis further reduce the serum creatinine level and decrease the accuracy of serum creatinine in assessing the renal function in cirrhosis liver.[1] Patients with cirrhosis and serum creatinine above 1.5 mg/dl have a glomerular filtration rate below 30 ml/min.[9] Hence, patients with creatinine levels >1.5 mg/dl were excluded from our study. The present study showed that serum creatinine alone in patients with the advanced liver disease is of limited value for identification of renal dysfunction. This is in agreement with the findings in a study by MacAulay *et al.*[12] Another prospective study of a large number of cirrhotic patients by Papadakis and Arieff[13] also indicated that the glomerular filtration rate can be very low, even when the serum creatinine is <1.0 mg/dl. In our study, patients with greater degrees of renal impairment were found to have lesser urine output, thus suggesting that eliciting history of oliguria in a cirrhotic patient with normal serum creatinine level should call for a high index of suspicion of renal dysfunction. Serum albumin (Table 5) was found to have a direct correlation with renal function,[15] patients with higher creatinine clearance level were seen to have higher serum albumin levels. Serum bilirubin (Table 6) did not show any direct correlation with renal function.[19] Except for the five patients belonging to Group I with creatinine clearance >60 ml/min, all other (88%) patients had ascites, though their serum creatinine was normal thus suggesting that presence of ascites may be one of the first changes of worsening renal function.[19] The present study showed that patients with alcoholic liver disease[5] were predisposed to develop renal impairment when compared with liver disease of other etiologies. Only 20% of alcoholic patients had a creatinine clearance of >60 ml/min as compared to 50% of cirrhotic patients due to hepatitis B. Present study, also showed calculating creatinine clearance by Cockcroft-Gault formula (Table 4) overestimates renal function. This is probably due to discrepancies in weight due to fluid retention which is one of the consequences of renal impairment in cirrhotics. As weight is one of the variables in the numerator of the formula, an increase in weight due to edema or ascites will give a spuriously high creatinine clearance. The study by MacAulay *et al.* also supports this finding.[12] This overestimation of renal function was highest in patients with lower glomerular filtration rate, which was observed in present Study also. Inulin clearance[2] along with other more accurate methods like radioisotopes 99mTc-DTPA, 169Yb-DTPA, or 125I-iothalamate to estimate glomerular filtration rate is not feasible in routine clinical practice because of the complexity, cost, and limited availability.[4-6] MacAulay *et al.*[12] observed that among the creatinine-based glomerular filtration rate formulas, the MDRD formula developed by the modification of diet in renal disease (MDRD) study group is the best formula for detection of moderate renal dysfunction among those with cirrhosis. Francoz *et al.*,[16] in their study have observed that MDRD which does not take into account the body weight seems to be less inaccurate than Cockcroft in cirrhotic patient. However, they also observed that the accuracy of MDRD, even if slightly superior to that of Cockcroft, remains limited. Eren and Kantarci[2] in their study have observed that all these equations have been validated in patients with end-stage renal disease[17] and in renal transplant recipients,[18] but they have not been validated in either the cirrhotic or the post-liver transplant population. As MDRD formula requires web-based calculations, it will be impractical to rely on it as a parameter of assessing renal function in a resource limited setup. However, the above-mentioned studies did not include any formulas requiring urine collection. Measured creatinine clearance from timed urine collections is a relatively inexpensive, accessible method used in clinical practice. In present Study measurement of creatinine clearance using Cockcroft Gault formula showed significantly higher values, suggesting overestimation in measurement of glomerular filtration rate. Five out of the 28 patients (18%) with creatinine clearance >60 ml/min by Cockcroft-Gault formula were found to have creatinine clearance values <40 ml/min, when calculated by timed urine collection. *P* value calculated was found to be <0.0001, which is statistically significant. Present Study showed that creatinine clearance from timed urine collections provides a better estimate of a renal reserve than serum creatinine or predicted creatinine

clearance by Cockcroft-Gault formula. A systematic review and meta-analysis of patients with cirrhosis by Proulx *et al.*[9] showed that creatinine clearance measured by timed urine collections is a preferable method in clinical practice, as it is more reliable than serum creatinine or creatinine clearance calculated by Cockcroft-Gault formula. Proulx *et al.*[9] also suggested that creatinine clearance was an aid in determining true glomerular filtration rate when inulin clearance was not available or feasible and may be a useful clinical test in the evaluation of renal insufficiency in cirrhotic patients with normal serum creatinine values.

CONCLUSIONS

Creatinine clearance should be done routinely in all patients with liver cirrhosis to assess renal function, as blood urea and serum creatinine are not reliable markers of renal dysfunction in liver cirrhosis. Creatinine clearance measurement by timed urine collection is a more practically feasible and cost effective method, and it has a strong predictive value when compared to calculating creatinine clearance by Cockcroft-Gault formula in the measurement of glomerular filtration rate to assess the renal function in patients with liver cirrhosis.

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