Estimation of Serum Sodium, Potassium and Calcium Levels as Prognostic Markers in Cirrhosis of Liver: A Study Protocol

Abstract:

Background: Cirrhosis of the liver is final stage of chronic liver disease (1), which can lead to complications associated with portal hypertension and liver failure. In a much remunerated state, the cirrhotic patient maintains close association to traditional solution and acid–base standing, however this delicate balance may be discontinuous by malady progression, infection, dietary indiscretion/deprivation, or medicine intervention. Many mineral metabolism disorders are represented in relation with hepatic diseases. This study aims to estimate the levels of Sodium, Potassium and Calcium in Cirrhosis of Liver and correlate them with severity of cirrhosis and in-hospital morbidity and mortality.

Material and Methods: This cross-sectional study is planned to be carried out in Medicine department, AVBRH, Wardha. Total 50 patients with liver diseases will be enrolled. The lab. investigations will include different parameters of liver function tests along with assessment of sodium, potassium and calcium level. Child-Pugh, end-stage liver disease scores model will be determined using required formulas. All such patients' in-hospital death records will be collected. Data will be collected and analyzed. The mean and standard deviations of the measurements per cluster will be used for applied analysis (SPSS twenty-two.00 for windows; SPSS INC, Chicago, USA). For every assessment purpose, data will be statistically analyzed using factorial ANOVA. Distinction between 2 groups determined using student t-test similarly as chi sq. test ($p < .05$).

Expected Results: We expect significant correlation between the level of Na, K and Calcium with in-hospital morbidity and mortality in patients of cirrhosis.

Conclusion: Serum levels of calcium, potassium and sodium should be integrated into model for predicting in-hospital mortality in patients of cirrhosis. Considering that prognostic accuracy of elements may well be comparatively modest, any studies ought to confirm clinical quality of liquid body substance sodium, potassium, and Ca concentrations.

Keywords: Liver, Cirrhosis, Sodium, Potassium, Calcium, Mortality, Deaths, Prognostic Marker.

UNDER PEER REVIEW

Introduction:

Cirrhosis of the liver is final stage of chronic liver disease (1), which can lead to complications associated with portal hypertension and liver failure. In a much remunerated state, the cirrhotic patient maintains close association to traditional solution and acid–base standing, however this delicate balance may be discontinuous by malady progression, infection, dietary indiscretion/deprivation, or medicine intervention. It's clinically necessary to predict first mortality in patients of liver cirrhosis. The data is useful for alerting doctors, patients and families of patients who are at high risk of early death. This has mentioned in varied studies (2),

The main focus of few studies has been on the role balancing in predicting the various results in liver cirrhosis.

Many mineral metabolism disorders are associated with hepatic diseases, however, their etiology, complication is nevertheless to be known. Several components play necessary roles within living body such as elements of metalloproteins, metalloenzymes further as catalyst cofactors (3). Because the synthesis of these compounds occurs primarily in the liver, studies of minerals in liver diseases have been of considerable interest. Causes associated with liver disorders, metabolism of minerals are also unknown. Since hepatic pathology and cirrhosis of the liver cause deterioration of liver tissue, modifications within the levels of necessary minerals could play a vital part in the pathological process of hepatic fibrosis (4).

Sodium play major role with progression of disease in patients with cirrhosis of the liver. Impaired water and sodium excretion have been involved in Pathological Mechanism of pathology growth (4-6). Symptoms in patients with hepatic cirrhosis may be normal (7-9). Potassium may also be altered in liver pathology mainly by ion and its metabolism. Persistent symptom findings in liver diseases (10) are usually assigned to total potassium insufficiency in body. In hepatic fibrosis and related diseases, disruptions in calcium metabolism are identified.

Sodium and Potassium are the most important extra-cellular and intra-cellular cations in living cells. They transport across the plasma membranes through a vigorous, energy expenditure method. In all animal cells, the plasma membrane enzyme, sodium potassium ATPase, decides the characteristic low intracellular sodium as well as high concentrations of potassium and the resulting transmembrane electrochemical gradients as ions. No other ones excluding the more closely related membrane-bound ATPases, enzymes that get detected in extra mitochondrial membranes which directly transform metabolic energy into necessary work. Solute movement against gradient of concentration. ATP is taken during hydrolysis, which involves the distribution of three sodium ions to the extracellular fluid on the inner side of the membrane, in-exchange for two potassium ions (like in the nerve impulse). It's generally accepted that resulting electrochemical sodium ion gradient provides driving force of a variety of solutes for bile and certain amino acids found in secondary active, sodium-coupled transport. Unequal stoichiornetry reports on the characteristic negative intracellular potential, combined with diffusion of potassium out of cell.

Hepatic Sodium Potassium +-ATPase is subject to a gear spread for each acute and semi-permanent control. The effects of Glucagon and insulin on the transport function of sodium potassium-ATPase within freshly secluded rat hepatocytes were examined by measuring successful absorption of 86 Rb++ by ouvain sensitivity. Each Glucagon and insulin acutely stimulate Rb+ uptake, while amiloride (a particular sodium influx matter) abolishes insulin stimulation by selection. Insulin could also promote the flow of Sodium, which could successively increase the activity of the pump, while glucagon could also act directly on the catalyst while not moving the input of sodium. In primary cultures of adult rat hepatocytes, it is indicated that hepatic sodium potassium-ATPase ion pumping activity can be jointly detected by modulating the entry of sodium elements coupled to the uptake of matter. There were similar effects with monensin, an ionophore sodium ingredient, and cold exposure together.

Alanine absorption does not only end up with an increased entry of sodium through coupled transport system, instead jointly induces increase in porosity, effluence of potassium. Increased potassium effluence in combination with increased ion pumping of sodium potassium-ATPase-mediated ion pumping could also counteract the influence of short-term changes within sodium-coupled transport processes on gradient of sodium chemistry, negativity of living things. In particle transport, minute-to-minute physiological state mechanisms may also be important for each of these responses to preserve the sodium gradient in chemical science during different solvent movement needs.

On hepatic Na+ K + -ATPase, various cholestatic and choleretic agents have major regulatory effects. Estradiol, in humans and other beings, reduces the movement of the catalyst, the fluidity of the membrane lipid in combination with an increase in free and esterified sterol concentration inside the cell wall once administered for several days. By administering the non-ionic detergent Triton WR-1339, all of those anomalies can be reversed. Therefore, Na+ K+ -ATPase, like most alternative membrane-associated enzymes, is susceptible to alterations in its lipid environment.

The cell wall has a pivot role in the entire physiological state of calcium product cells. Disproportionately reduced cytosolic concentration of the free calcium ends up in passive entry of external calcium along calcium's ionic gradient, further counteracted before active displacement and sequestration between compartments of living stuff. Two distinct pathways for effluence of calcium are described. In many epithelial systems, energy-dependent calcium extrusion has been uncontested, and glycolysis and oxidative phosphorylation inhibitors result in increased intracellular calcium concentration within the perfused rat liver. More recently, in rat liver plasma membranes that resort to intracellular Ca2+ extrusion, Ca2+-activated Mg2+-dependent ATPase has been seen in rat liver plasma membranes. The hepatocyte enzyme relies on a well-defined endogenous membrane protein activator than calmodulin, unlike the erythrocyte ATPases and the sarcolemma plasma membrane. Moreover, calcium antagonists, including verapamil, may inhibit enzyme activity, leading to speculation that hepatic damage sometimes found with these compounds may be mediated by this enzyme.

Metabolism of mineral in dimethyl nitrosamine-induced hepatic fibrosis was studied by Joseph Saint George et al (11) in 2006. Negative relationships of liver function have been determined. Blood serum mineral levels and tests, except for albumin. Calcium, Mg, potassium and sodium factor concentrations within blood serum were bated until liver damage was caused. As DMN was administered, calcium content of liver accumulated. No shift in liver sodium content occurred. However, the content of Mg and Potassium within the hepatic tissue was greatly decreased. The investigators inferred that hepatic fibrosis caused by DMN plays a binding role in the modification of essential components. One of the more relevant factors of deficiency of mineral metabolism within hepatic fibrosis may also be the reduced levels of albumin and the associated ascites.

Although the function of minerals in liver diseases can be obtained with relevant intelligent information, the connection between mineral modification and the production of hepatic fibrosis is not obvious. Moreover, little to no study on shifts in the minerals inside the cirrhotic

UNDER PEER REVIEW

liver are found. Therefore, an assessment of the sum of sodium, potassium and calcium in liver cirrhosis was performed in the current report.

Aim and Objectives

Aim: To determine the levels of Sodium, Potassium and Calcium in Cirrhosis of Liver.

Objectives:

1. To correlate the levels of Sodium, Potassium and Calcium with in-hospital morbidity and mortality in patients of cirrhosis.
2. To correlate the levels of Sodium, Potassium and Calcium with the Severity of Disease.

Material and Methods

Setting: Study will be conducted at the Department of medicine, at AVBRH, a tertiary care teaching hospital placed within geographic region of Wardha District. Study is done when approved via institute moral committee (applied for).

Patients: We'll prospectively register all consecutive patients > eighteen years aged despite gender or ethnicity at AVBRH, Sawangi. Written consent is obtained from all participants.

Study design: Cross sectional study.

Inclusion criteria: All patients over eighteen years aged, diagnosed with liver disease at Medicine Department at AVBRH, Sawangi WHO have given written consent are enclosed within the study.

Exclusion criteria: Patients with heart failure, chronic kidney disease and on medicine like SSRIs, TCA, MAO inhibitors, cytotoxic medicine etc., will be excluded from the study.

Methods: Elaborated history and examination of the patients are undertaken. Baseline information like age, sex, etiology for liver disease, ascites, hepatic encephalopathy and routine laboratory information are collected. Grade of ascites, hepatic encephalopathy is setup as per relevant criteria (12,13). Laboratory information primarily can embody alkaline phosphatase, red cell count, alanine aminotransferase, creatinine, platelet count, indirect bilirubin, albumin, blood urea nitrogen, direct bilirubin, total bilirubin, gamma-glutamyl transpeptidase, INR (international normalized ratio), prothrombin time, white cell count, aspartate aminotransferase, APTT (activated partial thromboplastin time), hemoglobin, Na, K, Ca. The reference value of body fluid sodium, K and Ca are 135-145 mmol/L, 3.5-4.5 milimoles per litre and 2-2.5 milimoles per litre severally. Child-Pugh, end-stage liver disease scores model will be determined using required formulas (14). The patients will be treated consequently. In-hospital death and explanation for death are recorded.

Sample size:

UNDER PEER REVIEW

Sample in descriptive terminology may be cluster of persons, objects or items that are taken for analysis from wider population. Survey should be demographic representative to confirm that findings of sample study are generalized to population as whole.

Sample size:

n = [Z alpha /2 sq. X P (1-P)] /d sq.

Where, Z alpha /2 is that level of great importance at five-hitter =1.96

P= Prevalence of cirrhosis=1.28%

So, sample size is 19 patients, but considering the attrition and drop outs, sample size will be increased to fifty patients.

Statistical analysis:

Data therefore collected was tabulated in excel sheet, below the steerage of statistician. The mean and standard deviations of the measurements per cluster were used for applied analysis (SPSS twenty-two.00 for windows; SPSS INC, Chicago, USA). For every assessment purpose, data was statistically analyzed using factorial ANOVA. Distinction between 2 groups determined using student t-test similarly as chi sq. test and also level of significance was set at p < zero.05.

Expected Results:

The study aims to correlate the degree of Na, K and Calcium with in-hospital morbidity and mortality in patients of cirrhosis and to correlate the degree of Sodium, K and Ca with the Severity of malady. We have a tendency to expect from our results that higher blood serum sodium, potassium, and Ca concentrations are going to be completely related to enlarged in-hospital mortality in patient of cirrhosis.

Discussion:

Many studies have confirmed that symptom is considerably related to poor prognosis in patients of cirrhosis. Angeli et al., 997 patients suffering from liver disease and pathology from twenty-eight centres in Europe, North and South America, Asia, were prospectively identified between March 2003 and August 2003. Blood serum potassium had the greatest association with mortality in an extremely Swedish multicenter study (15-16). Nested case-control research by Principal Yin et al. Unquestionable correlational statistics of serum blood Calcium component level with liver disease risk. Genovesi et al. jointly discovered that low levels of plasma metallic elements were substantially associated with longer QTc periods, which could possibly cause fatal complications (17). Many studies reflected on cirrhosis of liver(18-20). Bawankule et. al. reported on Clinical profile of patients with hepatic encephalopathy in cirrhosis of liver(21-31). This research too aims to correlate the degree of Na, K and Ca element with in-hospital morbidity and mortality in patients of cirrhosis. Also, to correlate the degree of Na, Potassium and Calcium element with the Severity of disease.

Conclusion:

UNDER PEER REVIEW

Serum levels of calcium, potassium and sodium should be integrated into model for predicting in-hospital mortality in patients of cirrhosis. Considering that prognostic accuracy of elements may well be comparatively modest, any studies ought to confirm clinical quality of liquid body substance sodium, potassium, and Ca concentrations.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

References:

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014; 383: 1749-61.
2. D'Amico G, De Franchis R, Cooperative Study G. Upper digestive bleeding in cirrhosis. Post-therapeutic outcome and prognostic indicators. Hepatology 2003; 38: 599-612.
3. McDowell LE. Minerals in animal and human nutrition. 2nd ed. Amsterdam: Elsevier Science; 2003. p. 1–630.
4. Rosner MH, Gupta R, Ellison D, Okusa MD. Management of cirrhotic ascites: physiological basis of diuretic action. Eur J Intern Med 2006;17:8–19.
5. Sandhu BS, Sanyal AJ. Management of ascites in cirrhosis. Clin Liver Dis 2005;9:715–32.
6. Arroyo V, Badalamenti S, Gines P. Pathogenesis of ascites in cirrhosis. Minerva Med 1987;78:645–50.
7. Castello L, Pirisi M, Sainaghi PP, Bartoli E. Hyponatremia in liver cirrhosis: pathophysiological principles of management. Dig Liver Dis 2005;37:73–81.
8. Castello L, Pirisi M, Sainaghi PP, Bartoli E. Quantitative treatment of the hyponatremia of cirrhosis. Dig Liver Dis 2005;37:176–80.
9. Borroni G, Maggi A, Sangiovanni A, Cazzaniga M, Salerno F. Clinical relevance of hyponatraemia for the hospital outcome of cirrhotic patients. Dig Liver Dis 2000;32:605–10.
10. Weiner ID, Wingo CS. Hypokalemia—Consequences, causes, and correction. J Am Soc Nephrol 1997;8:1179–88.
11. Ning Z, Qi X, Hou F, et al. Serum sodium, potassium, calcium, and chlorine for predicting the in-hospital mortality in cirrhotic patients with acute upper gastrointestinal bleeding: a retrospective observational study. Int J Clin Exp Med. 2016;9(5):8264-71.
12. George J. Mineral metabolism in dimethylnitrosamine-induced hepatic fibrosis. Clinical biochemistry. 2006;39(10):984-91.
13. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716-21.

UNDER PEER REVIEW

14. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973; 60: 646-9.
15. Angeli P, Wong F, Watson H, Gines P, Investigators C. Hyponatremia in cirrhosis: Results of a patient population survey. Hepatology 2006; 44: 1535-42
16. Wallerstedt S, Simren M, Wahlin S, Loof L, Hultcrantz R, Sjoberg K, Gertzen HS, Prytz H, Almer S, Oden A. Moderate hyperkalemia in hospitalized patients with cirrhotic ascites indicates a poor prognosis. Scand J Gastroenterol 2013; 48: 358-65.
17. Genovesi S, Prata Pizzala DM, Pozzi M, Ratti L, Milanese M, Pieruzzi F, Vincenti A, Stella A, Mancia G, Stramba-Badiale M. QT interval prolongation and decreased heart rate variability in cirrhotic patients: relevance of hepatic venous pressure gradient and serum calcium. Clin Sci (Lond) 2009; 116: 851-9.
18. James, Spencer L, Chris D Castle, Zachary V Dingels, Jack T Fox, Erin B Hamilton, Zichen Liu, Nicholas L S Roberts, et al. "Estimating Global Injuries Morbidity and Mortality: Methods and Data Used in the Global Burden of Disease 2017 Study." Injury Prevention 26, no. Supp 1 (October 2020): i125–53. https://doi.org/10.1136/injuryprev-2019-043531.
19. James, Spencer L, Chris D Castle, Zachary V Dingels, Jack T Fox, Erin B Hamilton, Zichen Liu, Nicholas L S Roberts, et al. "Global Injury Morbidity and Mortality from 1990 to 2017: Results from the Global Burden of Disease Study 2017." Injury Prevention 26, no. Supp 1 (October 2020): i96–114. https://doi.org/10.1136/injuryprev-2019-043494.
20. Murray, Christopher J L, Cristiana Abbafati, Kaja M Abbas, Mohammad Abbasi, Mohsen Abbasi-Kangevari, Foad Abd-Allah, Mohammad Abdollahi, et al. "Five Insights from the Global Burden of Disease Study 2019." The Lancet 396, no. 10258 (October 2020): 1135–59. https://doi.org/10.1016/S0140-6736(20)31404-5.
21. Bawankule, S., S. Kumar, A. Gaidhane, M. Quazi, and A. Singh. "Clinical Profile of Patients with Hepatic Encephalopathy in Cirrhosis of Liver." Journal of Datta Meghe Institute of Medical Sciences University 14, no. 3 (2019): 130–36. https://doi.org/10.4103/jdmimsu.jdmimsu_88_18.
22. Kirnake, V., A. Arora, P. Sharma, M. Goyal, R. Chawlani, J. Toshniwal, and A. Kumar. "Non-Invasive Aspartate Aminotransferase to Platelet Ratio Index Correlates Well with Invasive Hepatic Venous Pressure Gradient in Cirrhosis." Indian Journal of Gastroenterology 37, no. 4 (2018): 335–41. https://doi.org/10.1007/s12664-018-0879-0.
23. Dangore-Khasbage, S., and R.R. Bhowate. "Evaluation of Risk of Liver Fibrosis in Areca Nut Habitual by Ultrasonography and Liver Enzyme Analysis-a Pragmatic Approach." International Journal of Clinical Dentistry 13, no. 2 (2020): 163–71.
24. Mohammad, S., A. Bhute, N. Acharya, and S. Acharya. "Moschcowitz Syndrome or Thrombotic Thrombocytopenic Purpura and Antiphospholipid Antibody Syndrome as a Rare Cause of Thrombocytopenia in Pregnancy Mimicking Hemolysis, Elevated Liver Enzymes, and Low Platelets Syndrome in a Patient with Bad Obstetric History: A Diagnostic Dilemma." Journal of SAFOG 12, no. 4 (2020): 250–53. https://doi.org/10.5005/jp-journals-10006-1791.

UNDER PEER REVIEW

25. Raja, K.K., A.H. Inamdar, S. Lahole, and P. Palsodkar. “Prevalence of Non-Alcoholic Fatty Liver Disease in Prediabetes and Diabetes.” International Journal of Pharmaceutical Research 11, no. 3 (2019): 1424–27. https://doi.org/10.31838/ijpr/2019.11.03.166.
26. James SL, Castle CD, Dingels ZV, Fox JT, Hamilton EB, Liu Z, Roberts NL, Sylte DO, Henry NJ, LeGrand KE, Abdelalim A. Global injury morbidity and mortality from 1990 to 2017: results from the Global Burden of Disease Study 2017. Injury Prevention. 2020 Oct 1;26(Supp 1):i96-114.
27. Kumar A, Chery L, Biswas C, Dubhashi N, Dutta P, Dua VK, Kacchap M, Kakati S, Khandeparkar A, Kour D, Mahajan SN. Malaria in South Asia: prevalence and control. Acta tropica. 2012 Mar 1;121(3):246-55.
28. Chole RH, Patil RN, Basak A, Palandurkar K, Bhowate R. Estimation of serum malondialdehyde in oral cancer and precancer and its association with healthy individuals, gender, alcohol, and tobacco abuse. Journal of cancer research and therapeutics. 2010 Oct 1;6(4):487.
29. Acharya S, Shukla S, Mahajan SN, Diwan SK. Acute dengue myositis with rhabdomyolysis and acute renal failure. Annals of Indian Academy of Neurology. 2010 Jul;13(3):221.
30. Pradhan S, Madke B, Kabra P, Singh AL. Anti-inflammatory and immunomodulatory effects of antibiotics and their use in dermatology. Indian journal of dermatology. 2016 Sep;61(5):469.
31. Gadbail AR, Chaudhary M, Patil S, Gawande M. Actual Proliferating Index and p53 protein expression as prognostic marker in odontogenic cysts. Oral Diseases. 2009 Oct;15(7):490-8.

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