e-ISSN 2830 5442

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Volume 2 / No. 3

August 2023

www.apghn.com

Published by
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition

e-ISSN 2830 5442

Volume 2, No. 3, August 2023

APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

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e-ISSN 2830 5442

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APGHN

Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Original Article

Nutritional Status in Children with End-Stage Kidney Disease Undergoing Hemodialysis and Other Related Factors

Namira Metasyah[1], Eka Laksmi Hidayati[2]

[1]Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia

[2]Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Namira Metasyah
namira.metasyah@ui.ac.id

Published:
31st August 2023

DOI:
https://doi.org/10.58427/apghn.2.3.2023.13-24

Citation:
Metasyah N, Hidayati EL. Nutritional Status in Children with End-Stage Kidney Disease Undergoing Hemodialysis and Other Related Factors. *Arch Pediatr Gastr Hepatol Nutr.* 2023;2(3):13-24.

Abstract:

Background: Chronic kidney disease causes several changes in the body's function in metabolizing nutrients. This has led to the discovery of cases of malnutrition in chronic kidney disease patients, especially in ESRD patients undergoing hemodialysis. This certainly needs to be a concern because nutrition is very important for children's growth. Therefore, this study was conducted to find out the effect of hemodialysis and other influencing factors on the nutritional status of children.

Methods: The study was conducted with a cross- sectional design by taking secondary data in the form of disease stage, duration of disease, primary etiologic factors, and comorbidities from medical records. Data on the nutritional status of children was obtained by measuring weight and height, and upper arm circumference and then entered into the WHO Anthro application. Demographic data, such as the education level of the father & mother, family economic status, age, and gender were obtained by filling out the Case Report Form (CRF). Twenty respondents met the inclusion and exclusion criteria of this study.

Results: The average nutritional status assessment seen from the body mass index according to age showed results of -2 SD < x < 1 SD with good nutrition interpretation and x <-2 SD (short stature) in terms of height according to age. Based on bivariate analysis, there was no significant effect between duration of hemodialysis, frequency of hemodialysis, etiology, age, sex, and comorbidities ($p>0.05$) in children with chronic kidney failure who were undergoing hemodialysis on their nutritional status.

Conclusion: The nutritional status of CKD children undergoing hemodialysis was assessed based on body mass index and height according to age. The average results were good nutrition but with short stature. There was no effect of duration, frequency, etiology, age, gender, and comorbidities in children with chronic kidney failure undergoing hemodialysis on their nutritional status.

Keywords: end-stage kidney disease, hemodialysis, nutritional status, children

Introduction

End Stage Kidney Disease (ESKD) is defined as a permanent decline in kidney function to the point where the body cannot function normally. Globally, 33.7% of children with kidney failure require intensive care hospitalization, and the mortality rate among these cases is 13.8%. In Indonesia, data from 14 referral hospitals revealed a higher mortality rate of 23.6% for all pediatric patients with kidney failure.[1] At this stage of failure, the therapy of choice is either dialysis or kidney transplantation. The implementation of these procedures affects patients and families both physically and psychologically. Looking at the physical factors, patients will experience condition such as a loss of appetite due to disturbances in the digestive system.[2]

Previous studies have shown that patients with kidney failure undergoing extensive hemodialysis are prone to malnutrition particularly regarding their protein levels. Protein malnutrition increases the risk of hospitalization and mortality to the patient. Although not yet clear, hemodialysis procedure is considered as a significant contributing factor to the occurrence of malnutrition in kidney failure patients. Metabolic and hormonal disorders such as acidosis, inflammation, and resistance to the anabolic properties of insulin and growth hormone are all involved in the development of protein energy malnutrition (PEM) in patients undergoing dialysis.[3-5]

This issue becomes even more pertinent when considering child patients, for whom proper nutrition is a fundamental requirement for growth. A deficiency in essential nutrients, particularly protein, could lead to growth disorders and diminished ability for tissue formation. Such shortcomings in nutrition can not only affect the immediate well-being of these children but also have lasting impacts on their development.

The considerations outlined above underscore the need for this research. Through focusing on the relationship between hemodialysis and nutritional status, this study aims to shed light on a critical area that has substantial implications for patient care. By investigating these connections, this research hopes to contribute valuable insights to the existing body of knowledge, with the potential to guide future interventions and enhance the quality of life for those affected by terminal kidney failure.

Methods

This study is a cross-sectional study carried out at the pediatric hemodialysis unit at Cipto Mangunkusumo Hospital (CMH). The population is children with terminal kidney failure who underwent hemodialysis at CMH during the sample collection period, and who met specific inclusion and exclusion criteria.

Inclusion criteria were defined as children with terminal kidney failure between the ages of 0-18, who had been receiving hemodialysis for at least 3 months prior to the study. Exclusion criteria ruled out children who underwent a combination of peritoneal dialysis and hemodialysis, those who had kidney transplants, those with incomplete medical records, and those whose parents did not consent to participate in the study.

Research instruments included a research form (Case Report Form), World Health Organization (WHO) Anthropometry and WHO Antro-plus applications. Data collection involved gathering information from subjects who met the inclusion and exclusion criteria, including disease stage, disease duration, primary etiology factors, comorbidities from medical records, and the child's nutritional status obtained by measuring weight, height, and upper arm circumference, then inputting the data into the WHO anthropometry application. Demographic data such as parents' education levels, family economic status, age, and gender were collected through the Case Report Form (CRF).

Variables were identified as independent (duration and frequency of hemodialysis, age, gender, primary etiology factors, and comorbidities), dependent (nutritional status), and confounding (family economic status, parents' education levels). Socio-demographic data were analyzed descriptively, and normality tests were applied accordingly. Bivariate analysis was used to examine the correlations between nutritional status and hemodialysis duration, frequency, and age, as well as the relationship between nutritional status, primary etiology factors, and comorbidities. Additional tests were applied as needed, including ANOVA, Post-Hoc test, independent sample t-test, or Mann-Whitney test, depending on the normality of distribution. All analyses were performed using SPSS Statistics for Windows version 25.0 (Armonk, NY: IBM Corp), with the possibility of subsequent multivariate analysis.

Operational definitions for variables were clearly set, including the duration and number of hemodialysis treatments, age, gender, primary etiology factors, and specific comorbidities like hypertension, anemia, and bone mineral disorders. Other factors such as family economic status and parents' education levels were also defined. The nutritional status was assessed using anthropometric methods, including measurements of weight, height, and upper arm circumference, categorized into various scales and subcategories. The study aimed to create a comprehensive and scientifically valid framework for examining the complex relationships between these variables in the context of pediatric hemodialysis, with a focus on understanding nutritional status and its associated factors.

Results

A total of 20 patients are included in this study after screening for inclusion and exclusion criteria. The majority of subjects were male, comprising 55% of the sample. The mean age is 13.27 with a standard deviation of 3.68 years. The majority of the fathers (70%) and mothers (55%) had attained at least a high school education or its equivalent. Economically, most of the families (55%) are earning above the local minimum wage. Details of patients' sociodemographic characteristics are presented in **Table 1**.

Table 1. Sociodemographic characteristics of subjects

Variable	Frequency (%)
Age (years)	
Mean ± SD	13.27 ± 3.68
Gender	
Male	11 (55%)
Female	9 (45%)
Family economic status	
Below minimum wage	9 (45%)
Above minimum wage	11 (55%)
Father's education level	
Primary school or equivalent	1 (%)
Middle school or equivalent	3 (15%)
High School or equivalent	14 (70%)
University or higher	2 (10%)
Mothers' education level	
Primary school or equivalent	3 (15%)
Middle school or equivalent	2 (10%)
High school or equivalent	11 (55%)
University or higher	4 (20%)

SD: standard deviation

The medical records summary of the subjects can be seen in **Table 2**, with hemodialysis durations ranging from 2 to 4 hours and frequencies varying from 2 to 3 times per week, with a median of 4 hours and 2 times. An abnormal distribution was found using the Shapiro-Wilk test. The majority of patients suffered from chronic kidney disease, primarily caused by congenital anomalies of the kidney and urinary tract (CAKUT), and were found to have hypertension, anemia, and bone mineral disorders following hemodialysis.

The assessment of nutritional status revealed a normal distribution in the Shapiro-Wilk normality test conducted on variables such as weight for age (W/A), height for age (H/A), and body mass index for age (BMI/A) in z-scores, calculated using the WHO Anthro application for children under five years and WHO Anthroplus for children aged 5-18 years. Arm circumference measurements were not conducted, taking into consideration the absence of edema in patients, and the lack of weight-for-height variables due to only one respondent being under five years of age.

The results of the H/A z-scores showed a majority of values below -2 standard deviations (SD). Interpreted, this means that most patients fall into the category of stunted or severely stunted. Meanwhile, the BMI/A z-scores generally ranged from -2 SD to -1 SD, indicating good nutritional status.

Table 2. Summary of medical records finding

Variable	Frequency (%)
Duration of hemodialysis (hours)	
Median (Min – Max)	4 (2-4)
Frequency of hemodialysis (times)	
Median (Min – Max)	2 (2-3)
Primary etiology	
CAKUT	8 (40%)
SRNS	7 (35%)
Chronic glomerulonephritis	3 (15%)
Others	2 (10%)
Hypertension	13 (65%)
Anemia	18 (90%)
Bone mineral abnormality	10 (50%)
Nutritional status	
Weight / age (Mean ± SD)	-2.33 ± 1.41
Height / age (Mean ± SD)	-3.11 ± 1.48
BMI / age (Mean ± SD)	-1.21 ± 1.60

CAKUT: congenital anomalies of the kidney and urinary tract, SNRS: steroid-resistant nephrotic syndrome. BMI: body mass index. SD: standard deviation

Relationship between nutritional status and gender, income, and comorbidity

An independent-sample t-test was conducted with two categories: gender, family income, and three types of comorbidities, including anemia, hypertension, and bone mineral disorders. From this test, no meaningful relationships were found between groups with nutritional status indicators such as H/A and BMI/A. The relationship between groups with W/A and W/H could not be identified due to the age of 19 out of 20 respondents being over 5 years old. The summarized results of the analysis are presented in **Table 3**.

Table 3. Relationship between nutritional status and gender, income, and comorbidity

	Height / Age			BMI / Age		
	Levene's Test	Mean difference	p - value	Levene's Test	Mean Diference	p- value
Gender						
Male	0.42	0.56	0.42	0.34	0.11	0.88
female						
Income						
Below minimum wage	0.99	1.13	0.09	0.27	1.15	0.11
Above minimum wage						
Hypertension						
Yes	0.82	-0.13	0.86	0.75	-1.19	0.11
No						
Anemia						
Yes	0.03	-0.43	0.88	0.67	1.42	0.24
No						
Bone mineral abnormality	0.79	0.59	0.39	0.65	0.31	0.68
Yes						
No						

Relationship between nutritional status and age, duration of hemodialysis, and frequency of hemodialysis

A normality test was performed on all numeric dependent and independent variables, including age, the duration and frequency of hemodialysis, weight-for-age (W/A), height-for-age (H/A), weight-for-height (WH/A), and BMI-for-age (BMI/A). The Spearman correlation was determined to be the suitable test for evaluating the relationship between the duration and frequency of hemodialysis, while the Pearson correlation was used for the age variable. The results, as summarized in **Table 4**, indicate that there is no significant correlation between the nutritional status and the age, duration, or frequency of hemodialysis.

Table 4. Statistical analysis between nutritional status and several factors

	W/A	H/A	BMI/A
Age	r = 0.174 pp = 0.826 n = 4	r = -0.179 pp = 0.451 n = 20	r = -0.241 pp = 0.306 n = 20
Duration of hemodialysis	r = 0.632 ps = 0.368 n = 4	r = 0.135 ps = 0.571 n = 20	r = -0.105 ps = 0.658 n = 20
Frequency of hemodialysis	r = N/A ps = N/A n = N/A	r = -0.338 ps = 0.145 n = 20	r = -0.338 ps = 0.145 n = 20

r: Correlation, ps : Spearman p-value, pp: Pearson p-value. N/A: not available

Relationship between nutritional status and etiology and parent's education level

A one-way ANOVA test was conducted to determine if there were differences among the groups, the results of which are detailed in **Table 5**. No significant relationships were found among the three variables. Consequently, due to these findings, a post-hoc test was not performed.

Table 5. One-way ANOVA test results

	W/A		H/A		BMI/A	
	F	p	F	p	F	p
Etiology	0.09	0.91	0.61	0.62	0.65	0.59
Father's education level	N/A	N/A	0.80	0.51	0.60	0.62
Mother's education level	1.63	0.48	0.79	0.51	1.42	0.27

N/A: not available

Discussion

Based on the data obtained from medical records, almost all respondents underwent hemodialysis for 4 hours in each session, with the number of visits being twice a week. This is in accordance with the dialysis procedure by Perhimpunan Nefrologi Indonesia (PERNEFRI) and the Ministry of Health, stating that hemodialysis is usually carried out 2-3 times a week for a duration of 4-5 hours.[6] However, in practice, a frequency of twice a week is sufficient for adequate hemodialysis and also makes patients more comfortable. Another factor is insurance funds, which only cover the implementation of HD twice a week, making this HD pattern common in Indonesia.[6]

According to the research results, the average patient had good nutrition as assessed by body mass index by age. However, when viewed from height by age, eight out of twenty respondents were stunted, and eight out of twenty were severely stunted. Only four out of twenty patients who underwent hemodialysis had a height appropriate for their age. Referring to the Chronic Kidney Disease in Children journal by Pardede SO, in advanced stages, CKD patients tend to have short stature, with 47% of dialysis patients having a value of <-2 SD.[7, 8] This is related to nutritional intake and metabolism where hemodialysis patients often experience a lack of nutritional intake, repeated vomiting, catabolism processes, and loss of fluids and electrolytes.[7, 8] Looking at body mass index by age, the majority of respondents had a normal body mass. There were only two patients with wasted and 3 with severely wasted nutritional status. Even so, this nutritional index must be carefully considered by doctors, nurses, and parents, as nutrition can affect the prognosis of the child's illness. According to research by Zhang et al., poor nutrition impacts longer hospitalization durations, increased mortality rates, and a decrease in the patient's quality of life.[9]

Comorbidities often occur in patients undergoing hemodialysis. This is proven by almost all respondents suffering from anemia and hypertension. According to Ikatan Dokter Anak Indonesia (IDAI), children with end-stage CKD have lower levels of erythropoietin in the body than normal due to kidney failure. Not only in the final stage, but patients with early-stage CKD are also prone to anemia, increasing its prevalence to 93.3% in stages four and five.[7] This is due to a significant decrease in hemoglobin level with a decrease of glomerular filtration rate by 0.3 g/dL for every 5 mL/minute/1.73 m2 when the rate is below 43 mL/minute/1.73 m2.7 Therefore, National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommends periodic hemoglobin examination if the value is below the fifth percentile by age and sex.[7]

In addition to erythropoietin and iron deficiency, anemia in CKD patients can also be caused by infection, hemolysis, loss of vitamin B12 and folic acid, and chronic blood loss. The occurrence of anemia causes fatigue and weakness in patients, leading to a decrease in the quality of life. Moreover, severe anemia can burden the heart, leading to the risk of heart failure and ischemic heart disease.[8, 10]

Another comorbidity that may occur in hemodialysis patients is hypertension. This is in line with the journal by Pardede SO, et al., which states that there are at least 80% of hypertension cases in patients with end-stage CKD.[7, 11, 12] The occurrence of hypertension is caused by increased activity in the renin-angiotensin-aldosterone system, increased water and salt levels, and endothelial dysfunction. [7, 11, 12] The importance of lowering blood pressure is related to reducing the risk and progression of cardiovascular diseases. [7, 11, 12]

Based on this research, there was no relationship found between the frequency of hemodialysis and nutritional status ($p>0.05$). Sahathevan S, et al.'s research mentions that increasing the frequency of HD with decreased duration per session can improve quality of life by reducing systolic blood pressure and supporting better fluid removal management.[13] However, other research shows that there is more weight gain and BMI increase in children who undergo HD four times a week compared to six times a week.[14] This suggests that the relationship between hemodialysis frequency and nutritional status might be more complex and could depend on various factors such as the individual patient's condition, the quality of the hemodialysis, and other underlying health issues.

The duration of hemodialysis was found to be a significant factor affecting nutritional status in children ($p<0.05$). The appropriate duration of hemodialysis sessions is crucial in ensuring the removal of toxins and maintaining the balance of electrolytes in the body.[15] Under-dialysis or shortening the session may lead to inadequate clearance of waste products, contributing to malnutrition and poor growth.[15] Conversely, over-dialysis or extending the session too long can cause excessive removal of nutrients, leading to malnutrition.[16] Therefore, individualized treatment plans considering the child's weight, age, and overall health are essential for optimal outcomes.[16, 17]

Children on hemodialysis often suffer from comorbidities like anemia and hypertension, which can be interrelated with their nutritional status. Malnourished children may have lower hemoglobin levels, contributing to anemia, while inadequate dietary intake may also affect blood pressure regulation.[18] Proper nutritional management is thus vital in controlling these comorbidities and improving the overall quality of life for these children.[19, 20]

Conclusion

The present study highlights the complexity of managing children undergoing hemodialysis in the CMH Kiara hemodialysis room. The findings underscore the importance of tailored hemodialysis frequency and duration, comprehensive nutritional assessment, and vigilant monitoring of comorbidities. Collaboration between healthcare providers, parents, and policymakers is required to optimize treatment protocols, consider insurance limitations, and ensure that children with end-stage CKD receive the best possible care.

Based on the findings of this research, several recommendations are made to enhance the treatment of children with chronic kidney disease (CKD). Individualized hemodialysis treatment plans should be created, taking into account each child's unique needs and condition.[21] This approach necessitates regular monitoring of nutritional status, anemia, and hypertension to detect and manage comorbidities early.[22] Furthermore, the importance of collaboration between nephrologists, dietitians, nurses, and parents cannot be overstated, as it is essential for creating and maintaining a comprehensive care plan.[23] Further study needed to be done by conducting a multi-center research at several hospitals in many cities in Indonesia thus the result will be more representative. Lastly, policymakers and insurance providers must also consider the unique challenges faced by children with CKD, ensuring that treatment plans are not limited solely due to financial constraints. By integrating these strategies, the quality of care for children suffering from CKD can be significantly improved.

These recommendations provide a pathway for improving the care of children undergoing hemodialysis and serve as a foundation for future research and policy development in this vital area of pediatric nephrology.

Conflict of Interest

None declared.

Funding Statement

There is no specific grant from any funding agency involved in this study.

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Esophagoduodenal Varices in Non-cirrhotic Portal Hypertension with Myelodysplastic Syndrome: A Case Report

Ina Rosalina[1], Reza Latumahina[1], Yudith Setiati Ermaya[1], Dwi Prasetyo[1]

[1]Gastrohepatology Division, Department of Child Health, Faculty of Medicine Padjadjaran University, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Corresponding author:
Ina Rosalina
inaspa@yahoo.com

Published:
31st August 2023

DOI:
https://doi.org/10.58427/apghn.2.3.2023.25-32

Citation:
Rosalina I, Latumahina R, Ermaya YS, Prasetyo D. Esophagoduodenal Varices in Non-cirrhotic Portal Hypertension with Myelodysplastic Syndrome: A Case Report. *Arch Pediatr Gastr Hepatol Nutr*. 2023;2(3):25-32.

Abstract:

Background: Esophagogastroduodenal varices are dilated submucosal of distal esophageal, gastric, and duodenal veins connecting the portal and systemic circulation. This case report aims to describe a unique case of a child with esophagoduodenal varices due to myelodysplastic syndrome.

Case: We reported a case of 3-year-old girl who came to Hasan Sadikin General Hospital on April 3 2022, complaining of black stools 1 time per day for two days before admission. She had previously been diagnosed with esophagogastroduodenal varices since 2019. On initial examination, the patient was fully conscious and appeared pale. The patient's clinical condition improved after adequate treatment of blood transfusion, octreotide, omeprazole and propanolol. However, patient later developed pancytopenia and underwent bone marrow puncture examination which revealed a myelodysplastic syndrome.

Discussion: Myelodysplastic syndrome is a condition where ineffective hematopoiesis occurs and can lead to blood malignancy, especially acute myeloblastic leukemia. In this patient, she presented with unequivocal hypertensive gastroesophageal varices, splenomegaly, absence of fibrosis and thrombocytosis supporting subsequent diagnosis of idiopathic non cirrhosis portal hypertension. On the other hand, non-cirrhotic portal hypertension can also be caused by myelodysplastic syndrome as described in this case report.

Conclusion: Myeloproliferative malignancies can be a cause of idiopathic non cirrhosis portal hypertension. Pancytopenia often occurs in patients with portal hypertension due to splenomegaly or myelodysplastic syndrome, which can lead to acute myeloblastic leukemia, an example of a myeloproliferative malignancy.

Keywords: esophagoduodenal varices, extrahepatic portal vein obstruction, myelodysplastic syndrome

Introduction

Esophagogastroduodenal varices are dilated submucosal of distal esophageal, gastric, and duodenal veins connecting the portal and systemic circulation.[1] Every minute, 1500 cc of blood circulates through the portal vein throughout the body. This large flow causes an increase in portal vein pressure. Several etiologies cause increased pressure in the portal vein, mostly due to complications from hepatic cirrhosis. Other etiologies unrelated to hepatic cirrhosis are extrahepatic portal vein obstruction (EHPVO), congestive heart failure (CHF), nodular regenerative hyperplasia (NRH), nonalcoholic fatty liver disease (NAFLD), hepatic sinusoidal obstruction syndrome (SOS), metabolic diseases (Gaucher's and Zellweger Syndrome), schistosomiasis, and hepatoportal sclerosis. [2,3] Due to this increase in portal vein pressure, the body will respond by forming collateral flows and dilating blood vessels. When the flow is higher, the varicose veins widen and rupture, leading to gastrointestinal bleeding.[1]

The clinical manifestations of non-cirrhotic portal hypertension are similar to those of patients with cirrhosis, namely the presence of collateral circulation, ascites, and splenomegaly in the absence of cirrhotic stigmata.[4] The main complication of this situation is bleeding from ruptured varices, this can be prevented by administering non-selective beta-blockers and varicose ligation per endoscopy.[5] The morbidity and mortality of non-cirrhotic portal hypertension are better than that of patients with liver cirrhosis.[6]

Pancytopenia may occur in patients with portal hypertension due to splenomegaly. Other causes of pancytopenia may result from myelodysplastic syndromes. This situation occurs due to ineffective hematopoiesis and can develop into acute lymphoblastic leukemia.[8]

In this case report, a 3-year-old girl with esophagogastroduodenal varices was reported without signs of hepatic cirrhosis. The patient underwent further examination, namely bone marrow puncture and the results were obtained. On further examination, it was found that the child also had myelodysplasia syndrome. Esophagogastroduodenal varices caused by myelodysplasia are rare and will be discussed in this case.

Case

A 3-year-old girl came to Hasan Sadikin General Hospital on April 3 2022, complaining of black stools 1 time per day for two days before admission. Complaints accompanied by vomiting of blood 2-3 times since the day before entering the hospital with a volume of half a glass. The patient looked paler and weaker. Patient experience purpura without any complaints of bleeding including nosebleed, bleeding of gums or bruising. There are no complaints of fever. The patient was previously taken to the

local hospital and then referred to our hospital for further examination and management.

Patients have experienced complaints of black stools and vomiting of blood since two years ago. Currently, the patient takes propranolol 5 mg every 24 hours orally. The patient had previously been diagnosed with esophagogastroduodenal varices since 2019 from an endoscopy examination on September 17 2019, with results of grade III-IV esophageal varices, fundal varices, gastroduodenitis, minimal grade II duodenal varices, gastric antral hypoperistalsis, duodenal a/r nodularity. The patient also had a CT angiography examination on October 15 2019, with the suspected results of duodenal varices starting from the superior mesenteric vein to the hepatic portal vein, and there may still be abnormalities in vein formation. Since then, the patient has been receiving propranolol 10 mg every 8 hours orally. The last time the patient had hematemesis and melena was in March 2020.

On initial examination, the patient was fully conscious and appeared pale. The patient weighs 15 kg and is 101 cm tall. The patient's nutritional status was within normal limits. On examination, blood pressure was 90/50 mmHg, respiratory rate 20 times per minute, heart rate 100 times per minute, 97% oxygen saturation in room air, and a temperature of 36.8 Celsius. The conjunctiva looked anemic, the sclera was not icteric. There is no enlargement of the lymph nodes. The liver was palpable 4 cm below the costal arch, and the spleen was palpable as far as Schuffner II. The acral feels warm, looks pale, and the capillary refill time is below 3 seconds. Other examinations are within normal limits. Laboratory examination showed a hemoglobin level of 5.8 mg/dl, hematocrit 21.3%, leukocytes 13,030/mm^3, and platelets 233,000/mm^3. **Table 1** showed the laboratory test results from admission to day-9 of admission. **Figure 1** showed endoscopic view of the patient and **Figure 2** showed CT angiography of the patient.

Table 1. Laboratory test results

	Admission	Day-2	Day-3	Day-4	Day-6	Day-9
Hemoglobin (mg/dl)	5.8	6.1	8.2	10.5	11.4	9.8
Hematocrit (%)	21.3	22.5	28.3	34.4	36.5	31.3
Leukocytes (mm^3)	13030	9640	3770	2910	5750	3490
Thrombocyte (mm^3)	233000	182000	93000	54000	113000	64000
MCV (fl)	57.7	60.2	66.4	69.8	66.7	67.7
MCH (pg)	60.2	16.3	19.2	21.3	20.8	21.2
MCHC (%)	27.2	27.1	29.0	30.5	31.2	31.3

The patient was initially diagnosed with upper gastrointestinal bleeding et causa esophageal rupture with anemia gravis et causa underlying disease. The patient was placed on a nasogastric decompression tube, given a blood transfusion for 250 ml (15 ml/kg body weight), gastric lavage, vasoactive octreotide maintenance therapy of 15 mcg/hour and a proton pump inhibitor. Once the patient could be given oral medication, we discontinued the vasoactive therapy and started beta blockers. The patient received propranolol 10 mg every 8 hours orally, omeprazole 20 mg every 12 hours, and sucralfate 10 cc every 6 hours. The patient's clinical condition improved, marked by the stopped bleeding.

On the second day of treatment, the patient found complaints of paleness without being accompanied by black stools and no blood vomiting. The patient was re-examined after the transfusion, and laboratory results were obtained. Laboratory tests showed a hemoglobin level of 6.1 mg/dl, hematocrit 22.5%, leukocytes 9640/mm^3, and platelets 182,000/mm^3. On the third day of treatment, there was a picture of pancytopenia. Laboratory tests showed 8.2 mg/dl hemoglobin levels, hematocrit 28.3%, leukocytes 3770/mm^3, and platelets 93,000/mm^3.

Afterwards, the patient was consulted to the hemato-oncology division regarding suspicions of bleeding from other sources and underwent a bone marrow puncture in relation due to complaints of purpura and pancytopenia from laboratory examination on April 12, 2022, according to suspicions towards pancytopenia the bone marrow puncture was performed. The result of bone marrow puncture was myelodysplastic syndrome. The final diagnosis for the patient was esophagogastroduodenal varices et causa myelodysplastic syndrome.

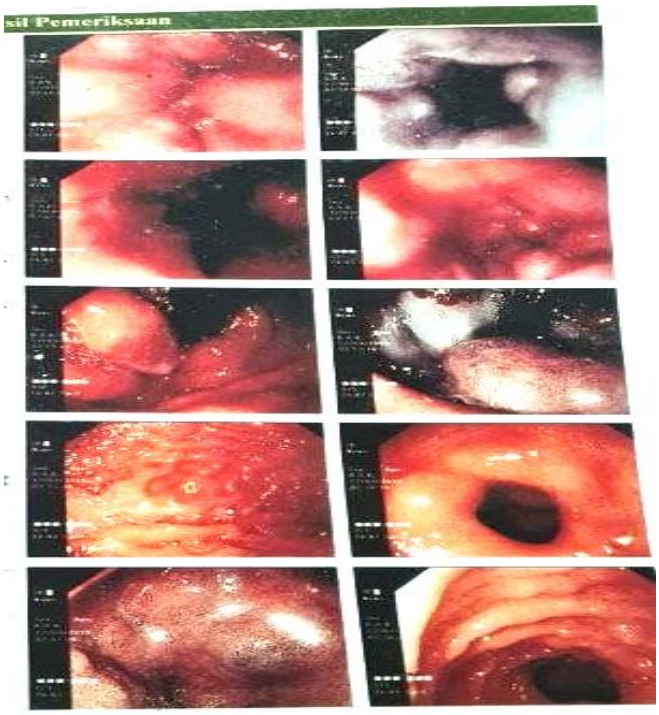

Figure 1. Endoscopic View

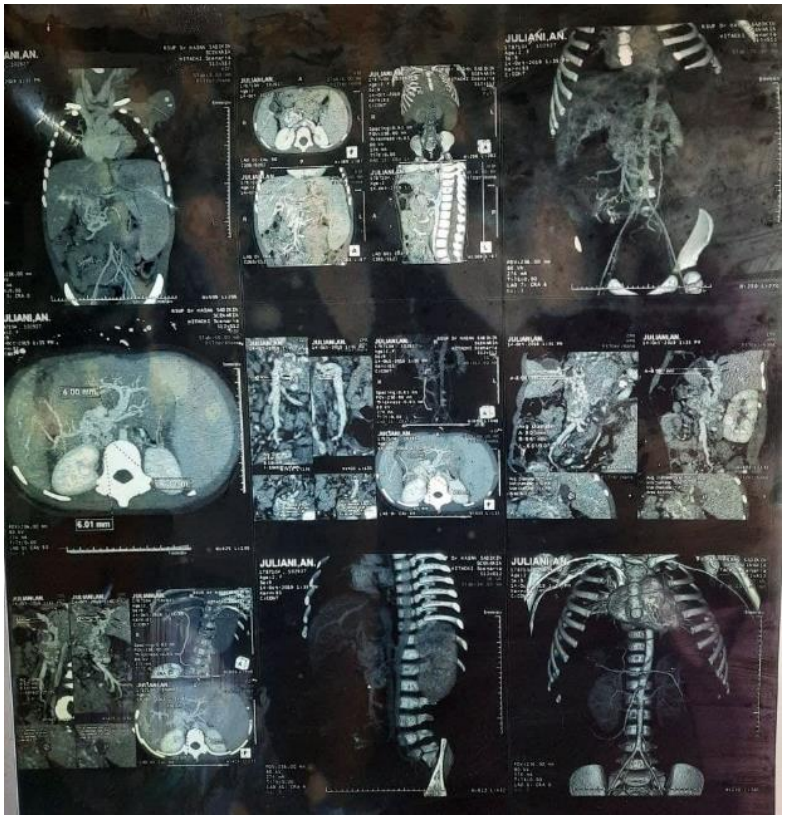

Figure 2. CT angiography of the patient

Discussion

Non-cirrhotic portal hypertension (NCPH) is a condition of increased portal pressure without signs of cirrhosis. Diagnosis of NCPH is challenging because there is no gold standard for diagnosing this condition. NCPH can occur due to EHPVO (54%), others can occur due to CHF, NRH, NAFLD, SOS, metabolic diseases (Gaucher's and Zellweger Syndrome), schistosomiasis, and hepatoportal sclerosis, or occur idiopathically. Liver biopsy is the main examination for diagnosing patients with suspected NCPH to rule out hepatic fibrosis and cirrhosis.[2,3,4]

Clinical manifestations of NCPH include the presence of collateral circulation, ascites, and splenomegaly without any signs of cirrhotic stigmata. In western countries, the main manifestation of INCPH is splenomegaly and/or increased liver function, whereas in India, most present with gastrointestinal bleeding. The prognosis of patients with NCPH depends on the underlying disease. Complications from increased portal venous pressure must be managed, such as administering diuretics in patients with ascites, administering non-selective beta-blockers, and/or varicose veins ligation.[4,13]

Idiopathic non-cirrhotic portal hypertension (INCPH) is a diagnosis of exclusion if no signs of hepatic cirrhosis are found, and must meet the following 5 criteria, namely: (1) clinical manifestations (splenomegaly, esophageal varices, ascites, increased hepatic vein pressure gradient (PG), or the presence of collateral portal vein flow), (2) no signs of cirrhosis were found on liver biopsy, (3) the absence of chronic liver diseases such as hepatitis B or C, steatohepatitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, or primary biliary cirrhosis, (4) non-cirrhotic diseases that cause increased portal pressure such as CHF, sarcoidosis, schistosomiasis were not found, (5) portal and hepatic vein patency from Doppler ultrasound or CT scan results.[4] INCPH is more common in Asia than in western countries. Several things can be associated with this event: immune disorders, infections, drugs and toxins (thiopurine derivatives, arsenic, vitamin A), genetic disorders, and prothrombotic disorders (thrombophilia, myeloproliferative malignancy, antiphospholipid syndrome). In this patient, since the bone marrow puncture revealed MDS, we diagnosed the patient as NCPH due to Myelosysplastic Syndrome.[7,13]

In this case, apart from NCPH, the patient also experienced pancytopenia. Pancytopenia can be caused by many diseases including malignancy, Evans syndrome, malaria infection and chronic liver disease.[12] Portal hypertension can also cause pancytopenia due to splenomegaly, but in this case, the patient had BMP performed due to myelodysplastic syndrome. Patient was diagnosed with myelodysplastic syndrome after BMP was performed.[8]

Myelodysplastic syndrome (MDS) is a condition where ineffective hematopoiesis occurs and can lead to blood malignancy, especially acute myeloblastic leukemia. In this patient, present of unequivocal of hypertension gastroesophageal varisces, splenomegaly absence of fibrosis and thrombocytosis supporting subsequent diagnosis of INCPH but on the other hand, NCPH is probably caused by MDS. [11] MDS is more common in adults, and cases in children are around 1.8 – 4 cases per 1,000,000 population. MDS in children can occur due to the deletion of chromosome 5q and/or sideroblasts. Children with MDS can be managed by administering a hematopoietic stem cell transplant (HSCT).[9] About 20% of MDS can turn into acute myeloblastic leukemia.[10]

Our weakness in managing this patient is that we have not performed a liver biopsy to rule out liver fibrosis or cirrhosis. It is necessary to carry out periodic follow-ups of patients to prevent varicose rupture and evaluate the possibility of malignancy in patients.

Conclusion

In conclusion, NCPH is a condition that is rarer than portal hypertension with cirrhosis. Treatment of NCPH is similar to therapy in portal hypertension patients with liver cirrhosis. A histopathological examination needs to be done to rule out liver fibrosis or cirrhosis. Myeloproliferative malignancies can be a cause of INCPH. Pancytopenia often occurs in patients with portal hypertension due to splenomegaly or MDS, which can lead to acute myeloblastic leukemia, an example of a myeloproliferative malignancy.

Conflict of Interest

None declared

Funding Statement

There is no specific grant from any funding agency involved in this study.

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APGHN
Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Case Report

Nutritional Approach of Neonatal with High Output Stoma Due to Long Segment Hirschsprung Disease: A Case Report

Aris Primadi[1], Filla Reviyani Suryaningrat[1]

[1]Neonatology Division, Department of Child Health, Faculty of Medicine Padjadjaran University, Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

Corresponding author:
Aris Primadi
aris.primadi@yahoo.co.id

Published:
31st August 2023

DOI:
https://doi.org/10.58427/apghn.2.3.2023.33-8

Citation:
Primadi A, Suryaningrat FR. Nutritional Approach of Neonatal with High Output Stoma Due to Long Segment Hirschsprung Disease: A Case Report. *Arch Pediatr Gastr Hepatol Nutr*. 2023;2(3):33-8.

Abstract:

Background: High Output Stoma (HOS) continues to be one of the most challenging problems for pediatrician especially in neonates. One of the most common causes in neonatal HOS is post resection long segment Hirschsprung disease.

Case: We reported a case of three-day-old baby boy diagnosed as Hirschsprung diseases with peritonitis possibility and did laparotomy with ileal resection, double barrel ileostomy and biopsy. Nutritional management is a major subject on taking care of this type of neonatal patient. We share our experience in limited facilities with all the patient uniqueness

Discussion: Loss of a significant length of the small bowel results in interrelated physiologic events as a result of decreased small intestinal mucosal absorptive cell. This leads to a lesser fraction of ingested food and intestinal secretion thus causing an excessive volume loss. The introduction of early enteral feeds promotes intestinal adaptation, with subsequent weaning off parenteral nutrition. Most off patient with high output stoma will require parenteral nutrition which is associated with acute and long-term complications. In our case, we did early nutritional intervention using parenteral and enteral nutrition, counting ongoing fluid loss trough stoma and adjust it to total daily fluid requirement. We found weight loss during hospitalized due to HOS, and we do catch up at the end. We found difficulties to adjust comparation between enteral and parenteral intake to maintain the weight gain.

Conclusion: Although parenteral nutrition is often necessary, at least initially, the therapeutic goal should be to enhance intestinal adaptation and enteral nutrient assimilation, and thereby reduce parenteral nutrition requirements. Daily monitoring for ongoing fluid loss very crucial for adjusting nutrition.

Keywords: high output stoma, hirschsprung, neonatal, nutrition

Introduction

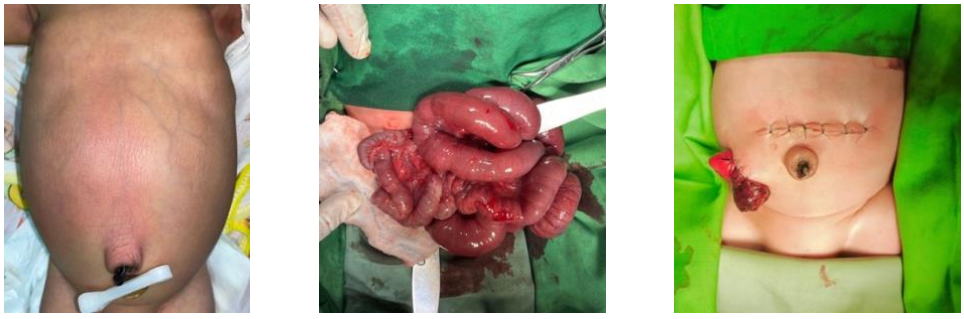
High Output Stoma (HOS) continues to be one of the most challenging problems for pediatrician especially in neonates. One of the most common causes in neonatal HOS is post resection of long segment Hirschsprung disease. Nutritional and metabolic effects ensue from diminished intraluminal digestive capacity and rapid intestinal transit leading to an excessive loss of fluids, nutrients, electrolytes and bile salts. Nutritional support should begin promptly, either by the parenteral route or the enteral route.

In our case, we describe the nutritional management that we provide to neonatal HOS patients with all the uniqueness and limited facilities.

Case

A 4-day-old term infant transferred to our referral hospital due to abdominal distention in the last 3 days with brownies vomit and has never defecated since birth. Baby was born spontaneously by midwife, crying immediately with birth weight 3450 grams. Mother did prenatal care every month and three times ultrasonography with normal result. There was no risk factor on pregnancy, mother nor delivery. Baby's weight at arrival 3025.

We did rectal touché, radiologic barium enema examination and suction biopsy. We suspected this patient as Hirschsprung disease with peritonitis possibility and did laparotomy with ileal resection, double barrel ileostomy and biopsy on the day after. Intraoperatively, the patient was found to have total colon non-ganglion with multiple impending rupture. The patient was subsequently admitted to the neonatal high care unit after surgery. Post operative examination found the patient was stable, without respiratory support and normal lab results. **Figure 1** showed pre-operation, intra-operation and post-operation condition of the patients.



(a) (b) (c)

Figure 1. Physical examination (a) abdominal distention; (b) intestinal dilatation with spastic of colon; (c) stoma post operation.

Total Parenteral Nutrition (TPN) was already performed before operation, and we also correct the dehydration. Central venous line was established. Ongoing fluid losses

were calculated and added in TPN solution with daily adjustment. Fluid maintenance on 4 days of age were given 120 ml/kg body weight/day. Adequate quantities of micronutrients and fat-soluble vitamin also added.

Enteral feeding was given after we found residue on stoma on post operation day (POD)-3 starting at 10ml/ kg body weight /day every 3 hours with protein extensively hydrolysate formula. Combination of enteral and parenteral nutrition was done, as soon as enteral feeding reached 70 ml/kg body weight/day we decrease the parenteral nutrition. We use full concentration of 0.67 Calories/ml. High output stoma start at POD-4 with 28 ml/kg body weight/day but getting better on the next day. Therefore, we continue to increase the volume every 1-3 days as tolerated. Tolerance to enteral feeding is determined by monitoring volume and consistency of stoma production. We still cannot evaluate for specific nutrition, vitamins nor mineral malabsorption. **Figure 2** showed high output stoma post operative day 4 and day 16.

(a) (b)

Figure 2. High output stoma (a) post operative day 4; (b) post operative day 16.

Appropriate enteral feeding device are selected base on the patient condition and the duration of expected adaptation interval. In our case we use oral feeding, but we start continues feeding on POD-18 due to repeated high output stoma. Details on post operative enteral feeding and body weight are provided in **Table 1.**

Table 1. Record for calculation ongoing fluid losses and enteral nutrition

Post Operative Day (POD)	Feeding	Body Weight (Gram)	Output Stoma
POD 4	8x8 cc (20cc/kg/day)	3235	86 cc (28cc/kg)
POD 5	8x16 cc (40cc/kg/day)	3315	56 cc (16,9cc/kg)
POD 6	8x25 cc (60cc/kg/day)	3315	56 cc (16,9 cc/kg)
POD 7	8x25 cc (60cc/kg/day)	3320	35 cc (10,5cc/kg)
POD 8	8x33 cc (80cc/kg/day)	3240	35 cc (10,9 cc/kg)
POD 9	8x33 cc (80cc/kg/day)	3199	58 cc (18,1 cc/kg)
POD 10	8x40 cc (100cc/kg/day)	3210	62 cc (19,3 cc/kg)
POD 11	8x50 cc (120cc/kg/day)	3155	93 cc (30 cc/kg)
POD 12	8x50 cc (120cc/kg/day)	3170	61 cc (19,6 cc/kg)
POD 13	8x50 cc (120cc/kg/day)	3155	93 cc (30 cc/kg)
POD 14	8x55 cc (130cc/kg/day)	3145	57 cc (18,3 cc/kg)
POD 15	8x55cc (130cc/kg/day)	3085	40 cc (13,3 cc/Kg)
POD 16	8x55 cc (130cc/kg/day)	2980	127 cc (43,7 cc/Kg)
POD 17	8x40 cc (100cc/kg/day)	2985	313 cc (107 cc/Kg)
POD 18	8x40 cc (100cc/kg/day) Start continuous feeding	3070	102 cc (34 cc/Kg)
POD 19	8x40cc (100cc/kg/day)	2995	122cc (40,6 cc/Kg)
POD 20	8x40 cc (100cc/kg/day)	3012	70cc (23 ,3 cc/Kg)
POD 21	8x40 cc (100cc/kg/day)	3130	75 cc (24,19 cc/Kg)
POD 22	8x55 cc (130cc/kg/day)	3185	57 cc (18,3 cc/kg)
POD 23	8x55 cc (130cc/kg/day)	3220	40 cc (13,3 cc/Kg)
POD 24	8x60 cc (150cc/kg/day)	3268	35 cc (10,9 cc/kg)
POD 25	8x60 cc (150cc/kg/day)	3315	35 cc (10,5cc/kg)

Electrolyte monitoring was done by blood examination every 5-7 days. Our patient experience mild hyponatremia that did not require special management. Other electrolyte was normal during our treatment. Optimal growth is very difficult to achieve under HOS conditions, on our monitoring, we found weight decreased during 2 weeks of treatment with optimal nutrition including lipids and protein each 4 grams/kg body weight/day. Weight gain catch up start after POD-19

Discussion

Loss of a significant length of the small bowel results in interrelated physiologic events as a result of decreased small intestinal mucosal absorptive cell. This leads to a lesser fraction of ingested food and intestinal secretion thus causing an excessive volume loss.[1] In our case we did laparotomy with long segment ileal resection, double barrel ileostomy and biopsy thus give possibility of high output stoma acquired.

The introduction of early enteral feeds promotes intestinal adaptation, with subsequent weaning off parenteral nutrition.[2] Most patients with high output stoma will require parenteral nutrition. This associated with a host of acute and long-term complication. Malabsorption of non-essential and essential nutrition, fluids and electrolyte if not compensated for by increased intake, leads to diminish body stores, subclinical and clinical deficiencies.[1,3] In our case we did early nutritional intervention using parenteral and enteral nutrition, counting ongoing fluid loss trough stoma and adjust it to total daily fluid requirement. We found weight lost during hospitalized due to HOS, and we do catch up at the end. We found difficulties to adjust comparation between enteral and parenteral intake to maintain the weight gain.

Impaired fat absorption leads to deficiency of fat-soluble vitamins.[1] In our center we do not assess vitamin levels, so there is no data to confirm this, yet we still give fat-soluble for our patient. The overall morbidity and mortality are extremely high with complication like sepsis, electrolyte imbalances, thrombosis or infection of the catheter, TPN related cholestasis, weight/ age deficit greater than 40% and malabsorption syndrome.[2,4] Central venous access needs to be performed in this patient. We did routine blood examination for all the risk evaluation and only mild hyponatremia experienced.

Tolerance to enteral feeds is determined by testing for reducing substances in stools and monitoring volume and consistency of stool. Malabsorption of fat, protein, carbohydrate, vitamins and heavy metal deficiency should be monitored.[5] In our center we cannot do routine examination for this but still we try to calculate the ongoing fluid loss.

Continuous feeds give more advantages for HOS with poor tolerated bolus feeds.[5] In our case we give oral feeding at the beginning after surgery due to good appetite of the patient but we change to continuous feeds after recurrent HOS and got improvement.

Conclusion

Although parenteral nutrition is often necessary, at least initially, the therapeutic goal should be to enhance intestinal adaptation and enteral nutrient assimilation, and thereby reduce parenteral nutrition requirements. Daily monitoring for ongoing fluid loss very crucial for adjusting nutrition.

Conflict of Interest

None declared.

Funding Statement

There is no specific grant from any funding agency involved in this study.

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APGHN Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

Review Article

The Role of Mesenchymal Stem Cells in Liver Regeneration

Hardian Gunardi[1]

[1]Department of Pediatric Surgery, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Corresponding author:
Hardian Gunardi
hardian312@gmail.com

Published:
31st August 2023

DOI:
https://doi.org/10.58427/apghn.2.3.2023.39-51

Citation:
Gunardi H. The Role of Mesenchymal Stem Cells in Liver Regeneration. *Arch Pediatr Gastr Hepatol Nutr.* 2023;2(3):39-51.

Abstract:

Background: Inflammation of the liver caused by cholestasis, viral infection, alcohol, autoimmune reactions, toxins, or metabolism will result in a prolonged immune response. As a result, simultaneous inflammation and tissue remodelling occur, resulting in fibrosis and eventually leading to cirrhosis. The main treatment for end-stage liver cirrhosis is liver transplantation. However, it is often not possible for patients to undergo this life-saving procedure. On the other hand, stem cell transplantation may be a potential strategy to prevent disease progression and improve the degree of fibrosis.

Discussion: Inflammation of the liver activates hepatic stellate cells, which are perisinusoidal cells in the Disse cavity that contain vitamin A. Hepatic stellate cells activation results in retinoid storage loss and transformation into myofibroblast-like cells that express α-smooth muscle action (α-SMA) and produce collagen which plays a major role in fibrosis. Liver regeneration due to chronic liver damage is played by mesenchymal cells through the mesenchymal-epithelial or epithelial-mesenchymal transition (MET/EMT) process. Administration by the intrahepatic route is thought to be the ideal route because fewer cells are lost in the circulation and more mesenchymal stem cells differentiates into hepatocytes in the damaged liver area. However, intrasplenic route maybe an alternative with easier administration technique. There are special considerations regarding the risks, including the risk of carcinogenesis and viral transmission.

Conclusion: Mesenchymal stem cells transplantation may be a potential therapeutic strategy for patients with end stage liver disease in the future. However, future research is needed regarding the risk of carcinogenesis and viral transmission following the procedure.

Keywords: mesenchymal stem cells, liver regeneration, fibrosis

Liver Fibrosis and Regeneration

Inflammation of the liver caused by cholestasis, viral infection, alcohol, autoimmune reactions, toxins, or metabolism will result in a prolonged immune response. As a result, simultaneous inflammation and tissue remodelling occur, resulting in fibrosis and eventually leading to cirrhosis. Inflammation activates hepatic stellate cells, which are perisinusoidal cells in the Disse cavity which contain vitamin A.[1] Hepatic stellate cells activation results in retinoid storage loss and transformation into myofibroblast-like cells that express α-smooth muscle action (α-SMA) and produce collagen which plays a major role in fibrosis. In addition, there was an increase in tissue inhibitor of metalloproteinase-1 (TIMP-1) which inhibited extracellular matrix resolution thereby increasing collagen deposition.[2]

Matrix deposition due to liver damage is a transient process, thus optimal recovery will eliminate the matrix.[3] Fibrosis occurs when a substantial amount of collagen matrix accumulates, producing scars and distorting the architecture and consistency of the liver; thus, it is known as cirrhosis. If the injury or inflammatory response persists, the parenchyma will be replaced by a connective tissue matrix containing collagen and elastin fibers that bond progressively, leaving the scar difficult to break down by enzymes.[4]

Regeneration and fibrosis are linked by a cascade that is triggered by an injury and then branches out depending on the severity or duration of the damage. This cascade involves the interaction of epithelial, mesenchymal, endothelial, and immune cells.[3] During the liver damage, dead hepatocytes or foreign antigens are recognized by Kupffer cells. Recruited monocytes are activated into macrophages, which then produce tumor growth factor-β (TGF-β). TGF-β induces transcription of collagen types I and III through the Smad signalling pathway.[5] Furthermore, these cells will release pro-inflammatory cytokines such as interleukin (IL)-1β and tumor necrosis factor-α (TNF-α), which will mediate activated hepatic stellate cells survival (positive SSH α-SMA) and cause hepatic collagen deposition.[6]

Mesenchymal cells initiate an inflammatory response by increasing the number of leukocytes that recruit chemokines and adhesion molecules, perform phagocytosis, antigen presentation, and T cell activation.[3] Liver sinusoidal endothelial cells (LSEC) also play a role in inflammation by acting as a conduit for pro-inflammatory chemicals. in the regeneration and fibrosis of the liver. In response to acute injury, LSEC activates the chemokine receptor CXCR7, which collaborates with CXCR4 signals via the DNA-binding protein inhibitor ID1 to produce pro-regenerative signals such as hepatocyte growth factor (HGF), which promotes hepatocyte enlargement. In chronic damage, constitutive signals from fibroblast growth factor receptor 1 (FGFR1) will reduce the ratio of CXCR7 to CXCR4 expression, take over the

activation of inhibitor of DNA binding 1 (ID1), and trigger SSH proliferation by triggering the secretion of cytokines such as TGF-β, bone morphogenetic protein 2 (BMP2), Platelet-Derived Growth Factor (PDGF).[2]

Macrophages in the liver also play a role in the fibrogenesis and extracellular matrix resolution process. Proinflammatory macrophages will transform into restorative macrophages, increasing the production of matrix metalloproteinases (MMP), including MMP9 and MMP12, as well as genes related to phagocytosis and growth factor.[5] As a result, alterations in macrophage phenotype and the elimination of profibrotic macrophages play an important role in extracellular matrix resorption and liver regeneration during acute inflammation.[2] Changes in macrophage phenotype do not occur in chronic inflammation, yet there is persistent interaction between various inflammatory agents. This allows the process of liver fibrosis to occur concurrently with regeneration.

The Role of Stem Cells for Liver Regeneration

The main treatment for end-stage liver cirrhosis is liver transplantation. Facilities that can perform liver transplants in Indonesia are still very limited and often with long waiting times or queues for transplants as well as very high costs. Therefore, it is often not possible for patients to undergo liver transplantation.[7] On the other side, stem cell transplantation may be a potential strategy to prevent disease progression and improve the degree of fibrosis. Studies show that liver cells can regenerate, although it requires a balance between secreted matrix proteins and matrix metalloproteinase (MMP).[8]

Stem cells can divide and differentiate into various derivatives, thus, can be an option in regenerative medicine, especially in the liver. Various stem cell derivatives that have been studied include pluripotent embryonic stem cells, hematopoietic stem cells, mesenchymal stem cells, and so on.[8] Administration of embryonic stem cells has the potential for malignancy such as splenic teratoma so that its application is limited.[9] Hematopoietic stem cells are only sourced from the hematopoietic system thus its clinical application is also limited.[8]

Liver regeneration due to chronic liver damage is also played by mesenchymal cells through the mesenchymal-epithelial or epithelial-mesenchymal transition (MET/EMT) process.[8,10] The liver consists of mesenchymal and epithelial cells, and successful liver regeneration occurs when damaged liver epithelial cells are replaced by new epithelial cells. Epithelial cells are adherent and have apico-basal polarity, while mesenchymal cells are non-polar and can migrate due to a lack of intercellular connections. During regeneration a MET/EMT process will occur which results in changes in cell properties, especially its plasticity.[11]

There are 3 types of MET/EMT processes. Type 1 occurs during implantation, embryogenesis and organ development where mesodermal and endodermal mesenchyme occurs which will form secondary epithelium that forms the organs. Type 2 is associated with cell damage and inflammation, a process involving fibroblastic cells which, if inflammation persists, will accumulate and cause progressive fibrosis. Type 3 occurs due to genetic or epigenetic changes that occur in cancer cells and promote invasion and spread of tumor cells. In liver regeneration in general, EMT/MET type 2 occurs which can cause fibrosis, while the desired process is EMT/MET type 1. This is the basis for trans-differentiation of mesenchymal stem cells into hepatocytes, so it can be considered as an alternative therapy for liver regeneration.[12]

The interaction between hepatic progenitor cells and mesenchymal cells is important in liver remodelling, thus, mesenchymal stem cells have therapeutic potential in liver damage.[8] Mesenchymal stem cells can differentiate into hepatic cells and help regenerate liver function, which is characterized by apoptosis of hepatic stellate cells, decreased TGF -β1, and α-SMA gene expression.[13] Damaged liver cells will be surrounded by an extracellular matrix into which the mesenchymal stem cells is embedded, and this matrix will trigger the differentiation of the mesenchymal stem cells into hepatocyte cells assisted by various cytokines and growth factors.[7] Apart from differentiation into hepatocyte cells , various trophic factors are also secreted by mesenchymal stem cells, thereby preventing apoptosis of hepatocytes with the help of antiapoptotic factors, such as: hepatocytes growth factor (HGF), insulin-like growth factor (IGF)-1, angiogenetic factors (vascular endothelial growth factor/VEGF), mitogenic factors (epidermal growth factor/EGF , nerve growth factor/NGF), and TGF-α.[8]

The advantages of mesenchymal stem cells as a therapeutic agent in liver fibrosis include the ability to self-repair, implant in the target area (engraftment), immunomodulation, dual differentiation as well as ability to secrete trophic factors and help restore damaged tissue.[14] Various sources of mesenchymal stem cells have been discovered from various studies , such as from bone marrow, adipose cells, umbilical cord, peripheral blood, synovial membrane, cartilage and amniotic fluid.[7,8] Of these various sources, the most common source that has shown therapeutic potential in liver disease is bone marrow mesenchymal stem cells, umbilical cord mesenchymal stem cells and adipose tissue mesenchymal stem cells.

Long-term outcomes in patients with liver cirrhosis using umbilical cord mesenchymal stem cells show satisfactory results, although in terms of short-term effectiveness bone marrow mesenchymal stem cells is preferred.[15-18] Zhang et al. demonstrated that when using umbilical cord mesenchymal stem cells in humans with follow up period for one

year, showed improvement in liver function as indicated by increased albumin levels, decreased bilirubin levels, and reduced ascites, without any significant side effects.[18] Another study showed that in patients who showed an incomplete response to uresodeoxycholic acid in biliary cirrhosis, there was a decrease in alkaline phosphatase and gamma glutamyl transferase (GGT) within 48 weeks.[17]

Routes of Administration of Mesenchymal Stem Cells

The route of administration of mesenchymal stem cells is very important in therapeutic effectiveness. Mesenchymal stem cells administration can be given through a peripheral vein, intrahepatic, or intrasplenic. Although in vivo studies show good migration of mesenchymal stem cells through peripheral veins into chronically damaged liver parenchyma, mesenchymal stem cells engraftment is limited in acute liver damage.[19] Intravenous administration will result in large cell loss in the capillaries, especially in the lung, resulting in cell shorter lifespan.[7,8] Vascular patency is very influential for mesenchymal stem cells levels in target organs. When given together with heparin, the level of mesenchymal stem cells trapped in the lungs will decrease so that the number of cells going to the liver becomes greater.[8] Another risk of administering mesenchymal stem cells by intravenous route is procoagulant activity, which is related to the expression of tissue factor that when comes into contact with blood, will coagulate and result in thrombosis.[20] In research conducted by Coppin et al., intravenous administration of mesenchymal stem cells resulted in thrombogenic events in one in eleven patients, namely thrombus in the portal vein.[21]

Administration by the intrahepatic route is thought to be the ideal route because fewer cells are lost in the circulation and more mesenchymal stem cells differentiates into hepatocytes in the damaged liver area.[7] Administration via the intrasplenic route can be an alternative, because the splenic vein flows into the portal vein, with easier administration techniques.[22] There are not many studies comparing mesenchymal stem cells administration routes simultaneously. Amer et al. conducted a preliminary study by comparing intrahepatic and intrasplenic mesenchymal stem cells injections in 40 patients with chronic liver failure due to hepatitis C, and showed a significant increase in liver function compared to controls.[23] His study showed that the intrahepatic route was more effective than the intrasplenic route, which was marked by reductions in fatigue and MELD scores, although this effect was only seen in the first month and these differences disappeared in the following months.[22,23] This shows that the intrahepatic pathway allows faster engraftment, but does not affect the total engraftment cells. Technically, intrasplenic injection is easier to do, but has more minor side effects, namely fever that subsides with antipyretics.[23]

Therapeutic Mechanisms of Mesenchymal Stem Cells Transplantation in Liver Disease

Hepatocyte-like cells derived from mesenchymal stem cells are considered as a surrogate source for liver regeneration.[14] Mesenchymal stem cells differentiation into liver cells is influenced by several factors such as: hepatocytes growth factor (HGF), fibroblast growth factor (FGF)-2/4, epidermal growth factor (EGF), oncostatin M, leukemia inhibitory factor, dexamethasone, insulin-transferrin-selenium, or nicotinamide.[24] Damaged liver tissue is surrounded by extracellular matrix which is the location for mesenchymal stem cells engraftment and differentiation. Co-culture with liver cells and pellet culture can induce differentiation into hepatocyte like cells.[25,26] Differentiation of mesenchymal stem cells into hepatocytes occurs in less than 1% of the total liver mass.[27] To increase this number, it is necessary to develop better techniques to trigger the differentiation of mesenchymal stem cells into hepatocytes in the management of liver disease.

Chronic liver damage caused by inflammation is marked by infiltration of T cells, B cells and monocytes, thus, immunosuppressive agents can help liver regeneration before and after liver transplantation.[28,29] The immunomodulatory properties of mesenchymal stem cells can help in a similar way, namely by inhibiting T cells by releasing various factors such as nitric oxide, prostaglandin E (PGE)-2, indoleamine 2, 3-deoxygenase, IL-6, IL-10, and human leukocyte antigen G, thus controlling the proliferation and function of various immune cells.[30] The immunosuppressive ability of mesenchymal stem cells is produced by various combinations of cytokines such as interferon-γ, IL-1α, and TNF-α. In addition, mesenchymal stem cells can inhibit B cell activation, reducing immunoglobulin levels.[31] Mesenchymal stem cells co-culture was associated with significant reduction of chemokine receptors (CXCR4, CXCR7, and CXCR5).[32] Mesenchymal stem cells also induce polarization of inflammatory macrophages into alternative macrophages that produce factors such as IL-10 and IL-1Ra that repair liver damage.[33]

Chronic liver damage also causes trans-differentiation of quiescent mesenchymal stem cells into fibrogenic myofibroblasts that produce excessive matrix proteins that result in fibrosis.[7] Proliferation of activated mesenchymal stem cells and collagen deposition can be inhibited by mesenchymal stem cells by direct cell contact. Through an indirect contact mechanism, mesenchymal stem cells produces several factors such as TGF-β3, TNF-α, IL-10, and HGF which inhibit collagen synthesis, and HGF and NGF promote mesenchymal stem cells apoptosis.[34-36] Mesenchymal stem cells co-cultured with mesenchymal stem cells will inhibit mesenchymal stem cells proliferation and α-SMA expression through cell contact. Mesenchymal stem cells also increase the expression of MMPs that degrade the extracellular matrix, and reduce the expression of TIMPs that inhibit the process.[35]

Risks of Mesenchymal Stem Cells Transplantation

Several studies regarding the administration of mesenchymal stem cells for chronic liver disease have been conducted, and there are special considerations regarding the risks, including the risk of carcinogenesis and viral transmission.[7] Mesenchymal stem cells can secrete various trophic factors and growth factors that trigger the growth of tumor cells such as carcinoma-associated fibroblasts (CAF).[37] Previous animal studies suggest that the risk of malignancy is related to the number of breeding cycles (passages).[37] Although malignant transformation in humans has not been reported, most follow-up periods are still too short for tumors or malignant transformation to occur. For this reason, it is necessary to analyze the integrity of the chromosome before mesenchymal stem cells transplantation.[38]

In the case of allotransplantation, there is a risk of transmitting the virus to the patient. Although transmission of parvovirus B19 to mesenchymal stem cells has been studied in vitro, B19-induced viremia resulting from mesenchymal stem cells transplantation in humans has not been reported. There is no information regarding the transmission of herpes simplex virus (HSV) and cytomegalovirus (CMV) via mesenchymal stem cells in vivo. For this reason, it is necessary to screen for parvovirus B19, HSV, and CMV in both donors and allotransplant recipients because of the possibility of infection, especially in patients who are immunodeficient.[7]

Liver Fibrosis and Regeneration Parameters

Various tests to evaluate liver fibrosis and regeneration have been developed. Aminotransferases, such as alanine transaminase (ALT) and aspartate transaminase (AST), are hepatocellular damage indicators. These two enzymes contribute to gluconeogenesis by catalyzing the transfer of amino groups from aspartic acid or alanine to ketoglutaric acid, which results in the formation of oxaloacetic and pyruvic acids. As the AST enzyme is found in the cytosol and mitochondrial isoenzymes of the liver, heart and skeletal muscle cells, kidneys, brain, pancreas, lungs, and blood cells, the increase in this enzyme is not specific nor sensitive to the liver. Due to its high concentration in the liver, the ALT enzymes are more specific.[39]

Cholestasis parameters include elevated bilirubin levels, particularly direct bilirubin, alkaline phosphatase, and GGT, which are not proportional to AST and ALT levels. Bilirubin is a derivative of hemoglobin that is an end product of heme catabolism. Indirect (unconjugated) bilirubin is transported to the liver by binding to albumin, where it is conjugated to form bilirubin glucuronide (direct bilirubin). Direct bilirubin is then excreted in the urine after being released into the bile. Alkaline phosphatase is a zinc metalloenzyme found in the microvilli of the biliary canaliculus as well as other tissues such as bone, gut, and the placenta. These parameters might rise as a result of hepatobiliary disorders including bile duct obstruction, as well as non-hepatic causes

like bone disorders, pregnancy, kidney disorders, and malignancy. Since it is not found in bones, Gamma-Glutamyl Transferase (GGT) is an enzyme found in cell membranes that catalyzes the transfer of the gamma-glutamyl group from peptides to other amino acids. It is more specific in detecting biliary diseases than ALP.[39]

Albumin is a protein that is produced in the liver. When there is a disruption, albumin production is diminished. Low albumin levels with normal liver function occur in conditions such as insufficient protein intake in malnutrition or excessive protein loss in nephrotic syndrome, malabsorption, or enteropathy.[39] Prothrombin time (PT) measures the rate at which prothrombin is converted to thrombin and represents the liver synthesis. In addition to factor VIII, coagulation factors are produced in the liver, therefore prolonged PT may occur in hepatic diseases, indicating the activity of factors II, V, VII, and X.[39]

A histopathological examination could determine the extent of liver fibrosis. Fibrosis plays a role in chronic inflammation in the liver. Persistent inflammation leads to the deposition of connective tissue in the parenchyma, which replaces the normal liver architecture.[3] Histopathological examination with hematoxyllin-eosin staining or histochemical staining (Masson's trichrome or Sirius Red) demonstrates the liver fibrosis with varying degrees of deformation of liver architecture.[40] Various scoring systems measuring the degree of fibrosis have been established over time, including the Scheuer system, Batts- Ludwig, Ishak, and METAVIR.[40] The Laennec system is a modified version of the METAVIR system that categorizes stage 4 into 4A, 4B, and 4C based on the thickness of the septa and the size of the nodules on the liver biopsy.[40] The Laennec criteria can be seen in **Table 1** below. [41]

Table 1. Laennec Scoring System for Liver Biopsy Fibrosis[41]

Stage	Classification	Septa (thickness and amount)	Criteria	Score
0	No definite fibrosis			0
1	Minimal fibrosis	+/-	Absent septa or thin septa are uncommon, portal expansions or mild sinusoidal fibrosis may be present.	1
2	Mild fibrosis	+	Some septa are thin; portal expansion or mild sinusoidal fibrosis may occur	2
3	Moderate fibrosis	++	Moderately thin septa; to	3

			partial cirrhosis	
4A	Cirrhosis, mild, definite or probable	+++	Septation is significant with a round contour or visible nodule. The majority of septa are thin	4
4B	Moderate cirrhosis	++++	At least two broad septa, although not very extensive, and tiny nodules occupy less than half of the length of the sample	5
4C	Severe cirrhosis	+++++	At least one very large septum and more than half of the length of the sample comprised of tiny nodules (micronodular cirrhosis)	6

Fibrosis regression may occur, which is characterized as a decrease in the fibrosis score on consecutive biopsies using any scoring system. This regression can be used as a benchmark for final outcomes in numerous therapeutic clinical trials, however, it has limitations in terms of sample size and number of portal tracts (minimum 2 cm or longer, with a minimum of 11 complete portal tracts).[40]

At the cellular level, liver regeneration consists of compensatory hypertrophy followed by hepatocyte hyperplasia. The regeneration process is divided into three stages: initiation (0-5 hours after injury), proliferation (up to day 6), and termination.[42] This injury will initiate a signal cascade that mobilizes immune cells to remove dead tissue, alter metabolic processes, and promote regeneration through the action of numerous cytokines and growth factors.[43]

Initial hemodynamic alterations result from changes in portal venous flow quantity and quality, which activate the regeneration cascade. Increase in portal volume causes shear stress and reduces arterial blood flow. The concentration of lipopolysaccharide (LPS) produced from intestinal bacteria in the portal circulation increases with innate immune activation, promoting growth factors such as HGF and EGF, as well as cytokines such as IL-6 and TNF. Furthermore, intrahepatic volume and shear stress increase urokinase plasminogen activator (uPA), activate the extracellular matrix that binds to HGF, and activate HGF and EGF receptors. Quiescent hepatocytes will then begin the cell cycle, progressing from G0 to G1. Hepatocytes will then produce VEGF, FGF-1 and -2, and angiopoietin-1 and -2 to stimulate endothelial cells; PDGF to activate SSH; and TGF-α to stimulate biliary epithelial cells.[43]

In the proliferation phase, hepatocytes and cholangiocytes proliferate within 72 hours. Angiogenesis begins within 2-3 days as a result of SSH, EC, and Kupffer cells growing in response to hepatocyte cytokines and growth factors. In order to preserve appropriate liver mass and function, antiproliferative substances such as TGF-β produced by SSH and Kupffer cells prevent autonomous proliferation of hepatocytes during the termination phase.[43]

Various cytokines, growth factors, and biological markers derived from the various complex interactions in regeneration may indicate the liver regeneration. Hepatocyte growth factor is a mitogen produced by mesenchymal cells that promotes liver cell proliferation and angiogenesis, therefore its levels in blood rise during acute injury and return to normal after seven days.[43] Tumor necrosis factor- and interleukin-6 (IL-6) are proinflammatory cytokines that aid in liver regeneration.[44] Heparin-binding EGF-like growth factor is a form of EGF produced by endothelial cells and Kupffer cells that aids in liver regeneration, particularly on the fifth to seventh day following liver injury.[43] Vascular endothelial growth factor promotes angiogenesis and neovascularization during liver regeneration and rises in the advanced phase.[45]

Insulin-like growth factor has mitogenic properties that play a role in liver regeneration, especially in chronic liver damage.[46] Fibroblast growth factor is important in biliary homeostasis.[43] Angiopoetin has a role in angiogenesis through Tie-signal 1 and Tie-2 receptor tyrosine kinases.[47] Platelet-Derived Growth Factor promotes cell growth, however blocking its receptor does not totally disrupt liver regeneration, therefore its role appears to be taken over by other growth factors[48].

Proliferating cell nuclear antigen (PCNA) and Ki-67 are biochemical indicators that are able to predict liver regeneration. Proliferating cell nuclear antigen is a non-histone protein found in the nucleus that aids in DNA synthesis and cell cycle progression. Studies on animals found an accumulation of PCNA-positive cells in post-hepatectomy animals, indicating liver growth or regeneration.[49] Ki-67 is a cell cycle core protein whose expression signifies cell division. [43]

Studies show that several proteins such as the specific protein on the bile duct cytokeratin 19 (CK19) and the hepatocyte specific protein HepPar1 are progenitor cells in liver morphogenesis and thus active in liver regeneration.[50] These proteins may serve as indicators of liver regeneration.

Conflict of Interest

None declared.

Funding Statement

There is no specific grant from any funding agency involved in this study.

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Archives of Pediatric Gastroenterology, Hepatology, and Nutrition

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Volume 2 / No. 3
August 2023

Published by
Indonesian Society of Pediatric Gastroenterology, Hepatology, and Nutrition