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Original Article (Pages: 19254-19264)

Evaluation of the Effect of Rosuvastatin on Portal Hypertension and Variceal Bleeding in Children with Compensated Cirrhosis

* Maryam Marefat [1], Mohamad Ali Kiani [2], Masoud Mahdavirashed [3], Monavar Afzalagaie [4], Saeed Mohamadi [1], Hamidreza Kianifar [2], Seyyed Ali Jafari [2], Maryam Khalesi [5]

[1] Fellowship, Department of Pediatrics, Facility of Medicine, Mashhad University of Medical Science, Mashhad, Iran.
[2] Professor, Department of Pediatrics, Facility of Medicine, Mashhad University of Medical Science, Mashhad, Iran.
[3] Associate Professor, Department of Radiology, Facility of Medicine, Mashhad University of Medical Science, Mashhad, Iran.
[4] Assistant Professor , Department of Biological Statistics, Facility of Hygiene, Mashhad University of Medical Science, Mashhad, Iran.
[5] Associate Professor , Department of Pediatrics, Facility of Medicine, Mashhad University of Medical Science, Mashhad, Iran.

Abstract

Background: Portal hypertension, a complication of chronic liver disease in children, can lead to severe gastrointestinal bleeding and an increased need for hospitalization and endoscopic treatment, potentially resulting in death. Statins, known for their anti-inflammatory, antioxidant, and anti-fibrotic effects, are used in the treatment of many chronic diseases. This study aimed to investigate the effects of rosuvastatin on improving portal pressure and esophageal varices while reducing bleeding associated with these conditions in children with cirrhosis.

Methods: This randomized clinical trial was conducted in children with compensated liver cirrhosis at Akbar Children's Hospital in Mashhad, Iran, between March 2023 and November 2024. Initially, endoscopy and Doppler ultrasound were performed on 32 patients aged 7–17 years. The control group received standard treatments for portal hypertension, while the intervention group received rosuvastatin tablets in addition to standard treatments. After a 6-month period, Doppler ultrasound and control endoscopy were repeated. All clinical, laboratory, sonographic, and endoscopic data were analyzed by a statistician, and the results were reported.

Results: The study included 32 children with cirrhosis (16 in the control group and 16 in the intervention group). The number of cases showing a decrease in ultrasonographic parameters of portal hypertension (SA-RI and RRA-RI) was higher in the rosuvastatin group (p=0.14 and 0.37). The grades of esophageal varices decreased by 26.7% and 20% in the control and rosuvastatin groups, respectively (p=0.66). Esophageal variceal bleeding occurred in 13.3% of cases in the control group and in 25% of cases in the rosuvastatin group,with no statistically significant difference between the two groups (p=0.41).

Conclusion: Over the 6-month follow-up period, rosuvastatin did not demonstrate a beneficial effect in reducing portal hypertension and variceal bleeding in children with compensated liver cirrhosis.

Key Words: Pediatric Cirrhosis, Portal Hypertension, Statin.

* Please cite this article as: Marefat M, Kiani M.A, Mahdavirashed M, Afzalagaie M , Mohamadi S, Kianifar H.R , Jafari S.A , Khalesi M. Evaluation of the Effect of Rosuvastatin on Portal Hypertension and Variceal Bleeding in Children with Compensated Cirrhosis. J Ped Perspect 2025; 13 (1):19254-19264. DOI: **10.22038/jpp.2025.85036.5516**

Corresponding Author:

Maryam Marefat , Fellowship in Pediatric Gastroenterology and Hepatology, Department of Pediatrics, Facility of Medicine, Mashhad University of Medical Science, Mashhad, Iran. Tel: 09155594228, E-mail: marefatm4011@mums.ac.ir

1- INTRODUCTION

Cirrhosis in children is a complex and progressive liver disease that involves the replacement of healthy liver tissue with fibrous scar tissue. This process, called fibrosis, disrupts the normal architecture and function of the liver and leads to various complications (1). The etiology of cirrhosis in children varies with age. In infants and young children, hereditary conditions and biliary atresia are common causes (2). Conversely, older children may develop cirrhosis due to autoimmune hepatitis, Wilson's disease, or other metabolic disorders. Additionally, viral hepatitis, drug-induced liver injury, and non-alcoholic fatty liver disease can contribute to the development of cirrhosis in pediatric patients (3).

The clinical presentation of cirrhosis in children varies and often depends on the underlying etiology and progression of the disease. Common signs include jaundice (yellowing of the skin and whites of the eyes), a distended belly caused by fluid accumulation (ascites), a heightened risk of bruising or bleeding due to decreased production of coagulation factors, and fatigue stemming from metabolic disturbances (4). As the disease advances, children may experience growth retardation, malnutrition, and cognitive impairment. Early detection and appropriate management are crucial for slowing the progression of the disease and preventing complications such as portal hypertension, esophageal varices, and hepatic encephalopathy (5). Treatment strategies typically focus on addressing underlying causes, managing symptoms, and providing supportive care. In cases of end-stage liver disease or severe complications, liver transplantation may be considered a life-saving intervention, offering the potential for improved quality of life, and long-term survival (6).

Portal hypertension in pediatric patients with compensated cirrhosis is a major clinical concern that requires careful monitoring and management. Compensated cirrhosis indicates that, despite fibrosis, the liver still functions adequately (7). However, increased pressure within the portal vein (portal hypertension) can lead to complications, such as variceal hemorrhage, ascites, and hepatic encephalopathy (8). Early detection and appropriate intervention, including the use of pharmacological agents such as beta-blockers, are essential to prevent progression to decompensated cirrhosis and optimize long-term outcomes (9).

In recent years, several epidemiological studies have demonstrated that statins provide benefits beyond those related to primary or secondary prevention of atherosclerotic disease, known as pleiotropic effects (10). These benefits have been observed in conditions such as chronic liver disease (CLD), chronic obstructive pulmonary disease (COPD), acute kidney injury, contrast-induced nephropathy, pancreatitis, and erectile dysfunction (11). Statins are recognized as a group of anti-inflammatory drugs with significant antioxidant and antifibrotic effects, making them valuable in the treatment of many chronic diseases (12).

Studies have suggested that rosuvastatin, a commonly prescribed statin medication, shows promise in treating portal hypertension in compensated cirrhosis (13-15). Evidence indicates that statins, including rosuvastatin, may reduce portal pressure and minimize the likelihood of variceal hemorrhage by improving endothelial function and decreasing liver fibrosis (10). However, additional studies are required to develop conclusive protocols and to confirm the long-term safety and effectiveness of rosuvastatin in this specific pediatric population. Based on the evidence demonstrating the effectiveness of this class of drugs in adults for reducing portal hypertension and

its complications, including variceal bleeding (16), this study aimed to investigate the effects of rosuvastatin on improving portal pressure, esophageal varices, and reducing bleeding associated with these conditions in children with cirrhosis.

2- METHODS

2-1. Study Population

This parallel, single-blind clinical trial included children with compensated liver cirrhosis who were referred to the pediatric gastroenterology department for inpatient admission or to the endoscopy department as outpatients at Akbar Children's Hospital in Mashhad, Iran, between March 2023 and November 2024. The inclusion criteria were children aged 7–17 years with a diagnosis of cirrhosis based on ultrasonography (liver echogenic pattern) or a prominent left lobe of the liver and other stigmata of chronic liver disease in the compensated stage (no history of recurrent bleeding from varices, hepatic encephalopathy, or impaired liver synthetic function), liver pathology consistent with cirrhosis (fibrosis and necrosis with regenerative nodules), and evidence of esophageal varices on esophagogastroduodenoscopy (grade 1 and above). Enclusion criteria included concomitant hypothyroidism (due to an increased risk of drug side effects), use of cyclosporine, and statin use in the past three months.

2-2. Study Protocol

In this study, 61 pediatric patients with liver cirrhosis who were referred to the endoscopy department or admitted to the gastroenterology department of Akbar Children's Hospital as outpatients were invited to participate. Thirteen parents did not consent to their children’s participation and sixteen children were deemed ineligible due to decompensated cirrhosis, a history of hypothyroidism, or prior use of statins. After meeting the study inclusion criteria, 32 children provided written informed consent from their legal guardians. Guardians were given comprehensive explanations of the treatment method and potential complications before enrolling in the study (Figure 1).

Allocation concealment was achieved using sealed opaque envelopes with a random sequence, dividing the participants into two groups: control (n=16) and intervention (n=16). Baseline endoscopy was initially performed by two pediatric gastroenterology subspecialist fellows under the supervision of four pediatric gastroenterology subspecialist professors. Additionally, a radiologist conducted baseline Doppler ultrasound using a Doppler ultrasound device to noninvasively assess portal pressure. Recorded results included the grade of esophageal varices observed during endoscopy, dumping criteria, splenic arterial resistive index (SA-RI), pulsatility index of the superior mesenteric artery (SMA-PI), and interlobar renal artery resistive index (RRA-RI) on Doppler ultrasound.

The control group received standard treatments for portal hypertension, including non-specific beta-blockers (propranolol) and endoscopic banding (EBL), under the supervision of a pediatric gastroenterologist. The intervention group, in addition to the standard treatments, was prescribed rosuvastatin tablets for six months. The dosage of rosuvastatin followed the UpToDate recommendations: for children aged 7–9 years, 5 mg daily for the first four weeks, then 10 mg daily for the following five months; for children aged 10 years and above, 10 mg daily for the first four weeks, and then 20 mg daily for the next five months. After this six-month period, Doppler ultrasound and control endoscopy were performed again by the aforementioned specialists.

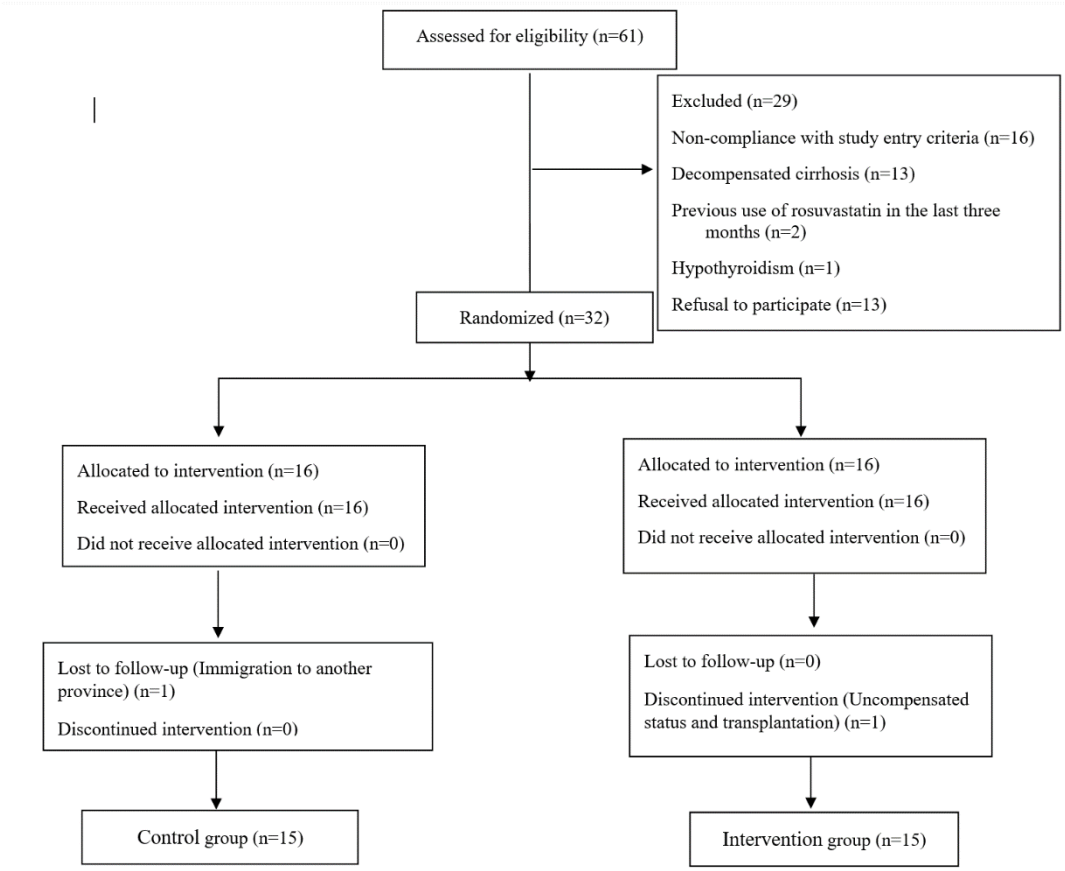

Figure-1: Flow Diagram of the Patients.

During this time period, the number of emergency room visits for gastrointestinal bleeding was documented using patient history and hospital records.

To ensure the safety of the drug, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine phosphokinase (CPK) were measured at baseline, four weeks after treatment began, and then every three months. Clinical symptoms of hepatopathy (jaundice) and myopathy (myalgia, muscle weakness, rhabdomyolysis) were assessed via telephone or in-person visits. If clinical symptoms, hypersensitivity reactions to statins, pregnancy in females, shunt or transjugular intrahepatic portosystemic shunt (TIPS) surgery, acute liver failure, decompensated cirrhosis (characterized by resistant ascites, recurrent bleeding from esophageal varices, hepatic encephalopathy, liver synthetic dysfunction), liver transplantation, or toxicity (myopathy and increased levels of CPK, AST, and ALT) occurred, the patient was excluded from the study.

2-3. Statistical Analysis

Descriptive data were characterized by means, standard deviations, and percentages. The Shapiro-Wilk test was used to ascertain the normality of the data before analysis. For continuous quantitative variables with normal distributions, the Simple t-test was employed, while the Mann-Whitney U test was used for non-normal distributions. Nominal variables were compared using the chi-squared test and Fisher's exact test. All analyses were performed using the SPSS software (version 24, Chicago, IL,

USA). Statistical significance was set at P < 0.05.

2-4. Ethical Considerations

The Ethics Committee of Mashhad University of Medical Sciences reviewed and approved the study protocol as part of thier review and approval of the research project (No: IR.MUMS.MEDICAL.REC.1403.129). Additionally, the study was registered at the Iranian Registry for Clinical Trials with the code IRCT20230301057580N1.

3- RESULTS

This study involved 32 children with cirrhosis. The intervention group consisted of 16 patients, with 37% (n=6) boys and 63% (n=10) girls. The control group also had 16 patients, with 56% (n=9) boys and 44% (n=7) girls. There was no statistically significant difference between the two groups in terms of gender (P=0.71). In total, 53% (n=17) of the patients had a known cause of cirrhosis, including 4 with Wilson's disease, 4 with congenital fibrosis, 3 with biliary atresia, and 1 with diabetes, cystic fibrosis, autoimmune hepatitis, primary sclerosing cholangitis, autoimmune sclerosing cholangitis, and vasooclusive disease . The remaining 46% (n=16) of patients had cirrhosis of an unknown cause. However, genetic testing was not performed in a significant percentage of the patients. The cause of cirrhosis was unknown in 50% of the control group and in 44% of the intervention group, with no significant difference in the cause of cirrhosis between the two study groups (P=0.59).

The demographic and clinical characteristics of the two groups are presented in Table 1. There were no significant differences between the two groups with respect to age (P>0.05), liver and muscle enzyme levels (P>0.05), or grade of esophageal varices (P>0.05) at the beginning of the study. There was also no significant difference between the two study groups in terms of the baseline ultrasound criteria for portal hypertension at the beginning of the study (P>0.05).

The frequencies of graded varicose veins at the start of the study and six months after the intervention are presented in Table 2. The analysis showed that there was no significant difference between the two groups regarding the frequency of graded varicose veins, both at the beginning of the study and six months after the intervention (P>0.05).

Table-1 : The demographic and clinical characteristics at baseline based on two groups.

Variable (Mean ± SD)		Control group (n=16)	Intervention group (n=16)	P-value*
Age (years)		3.4 ± 11.7	2.7 ± 11	0.49
Laboratory	AST (IU/L)	7 ± 41	12 ± 41	0.90
	ALT (IU/L)	7 ± 29	7 ± 30	0.78
	CPK (IU/L)	121 ± 400	106 ± 388	0.77
Grade of esophageal varices		2.06 ± 0.93	1.94 ± 1.00	0.31
Finding of doppler ultrasound	Dumping criteria	0.17 ± 0.69	0.11 ± 0.64	0.35
	SA-RI	0.10 ± 0.72	0.09 ± 0.66	0.06
	SMA-PI	0.18 ± 1.34	0.21 ± 1.37	0.68
	RRA-RI	0.11 ± 0.72	0.10 ± 0.72	0.57

Abbreviations: AST: Aspartate aminotransferase, **ALT:** Alanine aminotransferase, **CPK:** Creatine phosphokinase, **SA-RI:** Splenic arterial resistive index, **SMA-PI:** Pulsatility index of the superior mesenteric artery, **RRA-RI:** Interlobar renal artery resistive index

*T-test

Esophageal variceal grade reduction was observed in 26.7% of the cases in the control group (60% of these patients experienced a one-grade reduction and 40% a two-grade reduction) and in 20% of the cases in the rosuvastatin group (all with a one-grade reduction) (P=0.67).

Esophageal variceal bleeding occurred in 13.3% and 25% of cases in the control and rosuvastatin groups, respectively, with no statistically significant difference between the two groups (P=0.41). In the control group, 25% of cases required band ligation; one-third were banded once, one-third twice, and one-third thrice. In the rosuvastatin group, 46.6% of cases required band ligation, all banded only once (P=0.12).

Although the number of cases with a reduction in the sonographic criteria SA-RI and RRA-RI was higher in the rosuvastatin group six months after the intervention, the two groups did not show a significant difference in terms of these sonographic criteria (P>0.05). Additionally, when comparing the means of the mentioned criteria after adjusting for the baseline level and removing the confounding effect of the baseline state (using the ANOVA test), the means became closer to each other and the difference between the two groups diminished (P>0.05) (Table 3).

Table-2: The frequencies of graded varicose veins based on two groups.

Grade of esophageal varices		Control group	Intervention group	P-value*
At the beginning	Grade 1	50%	37.5%	0.71
	Grade 2	6.25%	18.75%	
	Grade 3	43.75%	43.75%	
Six months after the intervention	Grade 1	60%	33.33%	0.33
	Grade 2	26.67%	40%	
	Grade 3	13.33%	26.67%	

Table-3: The clinical characteristics six months after the intervention based on two groups.

Variable (Mean ± SD)		Control group (n=15)	Intervention group (n=15)	P-value*
Dumping criteria	Without correction*	0.11 ± 0.66	0.13 ± 0.62	0.44
	With correction**	0.08 ± 0.65	0.08 ± 0.64	0.68
SA-RI	Without correction*	0.11 ± 0.70	0.11 ± 0.65	0.21
	With correction**	0.11 ± 0.69	0.11 ± 0.68	0.88
SMA-PI	Without correction*	0.17 ± 1.28	0.20 ± 1.40	0.09
	With correction**	0.17 ± 1.29	0.17 ± 1.39	0.66
RRA-RI	Without correction*	0.08 ± 0.68	0.10 ± 0.71	0.40
	With correction**	0.09 ± 0.68	0.09 ± 0.71	0.57
Grade of esophageal varices	Without correction*	1.93 ± 0.8	1.53 ± 0.74	0.19
	With correction**	0.07 ± 0.7	0.33 ± 0.81	0.06

Abbreviations: SA-RI: Splenic arterial resistive index, **SMA-PI:** Pulsatility index of the superior mesenteric artery, **RRA-RI:** Interlobar renal artery resistive index
*T-test; **Anova test

Table 4 presents the percentage change in varicose vein grade and sonographic criteria for hypertension over a six-month follow-up period in all patients. When comparing the mean values of these variables, there was no significant difference between baseline and six months after the intervention.

Based on these results, all instances of variceal bleeding occurred in patients with initial grade 3 esophageal varices (Figure 2).

Table-4: Comparison of mean sonographic and endoscopic criteria of all patients at baseline and after 6 months.

Variable (Mean ± SD)	At the beginning (n=32)	Six months after the intervention (n=30)	Mean difference	P-value*
Grade of esophageal varices	0.95 ± 1.97	0.77 ± 1.74	-46 ± 1.1	0.11
Dumping criteria	0.14 ± 0.66	0.12 ± 0.64	-19 ± 0.3	0.31
SA-RI	0.10 ± 0.69	0.11 ± 0.68	-16 ± 0.6	0.61
SMA-PI	0.20 ± 1.37	0.19 ± 1.34	-19 ± 0.9	0.56
RRA-RI	0.02 ± 0.71	0.02 ± 0.70	-21 ± 0.3	0.47

Abbreviations: SA-RI: Splenic arterial resistive index, **SMA-PI:** Pulsatility index of the superior mesenteric artery, **RRA-RI:** Interlobar renal artery resistive index
*Paired test

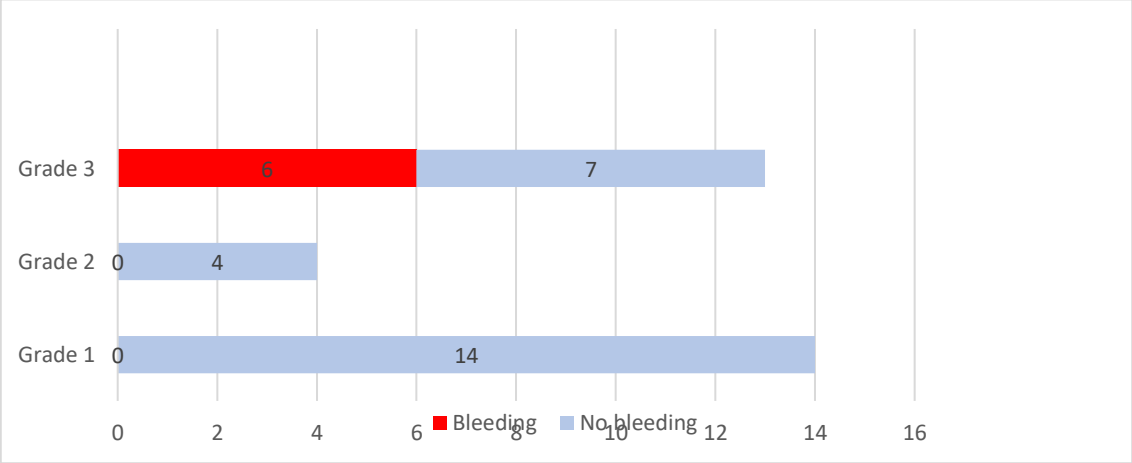

Figure-2: Comparison of bleeding incidence in each grade of esophageal varices in all patients.

4- DISCUSSION

This randomized clinical trial aimed to examine the therapeutic effects of rosuvastatin in children with compensated liver cirrhosis. At the start of the project, data collected from the two groups, including demographic characteristics (age and gender), severity of esophageal varices, ultrasound criteria for hypertension, and liver enzyme levels, showed no significant differences between the intervention (rosuvastatin) and control groups. Regarding the RRA-RI criteria after the intervention, 66% of the control group and 60% of the rosuvastatin group still had severe portal hypertension (> 0.6, equivalent to HVPG greater than 12). Similarly, based on the SA-RI criteria, 80% of the control group and 60% of the

rosuvastatin group had severe portal hypertension after the intervention. Although these findings were not statistically significant, they may have been clinically significant. Consequently, this study could not demonstrate the effect of rosuvastatin on reducing portal hypertension within a given sample size. When comparing the severity of esophageal varices, 43.75% of the patients in both groups had grade 3 varices before the intervention. After intervention, the prevalence of grade 3 varices decreased to 26.6% and 13.3% in the rosuvastatin and control groups, respectively. However, this reduction in variceal grade was not significant between the two groups, suggesting that the effect of rosuvastatin in reducing the grade of esophageal varices could not be confirmed. Additionally, patients taking rosuvastatin did not experience more benefits regarding variceal bleeding than those receiving standard treatment, and rosuvastatin did not reduce the need for banding.

Portal hypertension, a severe complication of liver disease, has significant clinical and hemodynamic implications in individuals with compensated cirrhosis. This condition is characterized by increased pressure within the portal venous system, leading to a range of potentially life-threatening complications (17). Elevated risks associated with portal hypertension include the development of ascites (accumulation of fluid in the abdominal cavity), variceal hemorrhage (bleeding from dilated blood vessels in the esophagus or stomach), and hepatic insufficiency (reduced liver function). These clinical onset events can significantly impact a patient's quality of life and overall prognosis (18).

Recent research has focused on potential therapeutic interventions to address portal hypertension and its associated complications. Rosuvastatin, a medication primarily used to lower cholesterol levels, has shown promise in this regard (19). Its ability to reduce liver scarring and dermis-intima thickening in non-cirrhotic individuals with cardiovascular syndromes has led researchers to investigate its potential in modifying liver scarring extension, which has recently been implicated in the clinical manifestations of portal hypertension. This approach represents a novel strategy for managing portal hypertension, potentially offering new avenues for treatment and improved outcomes in patients with liver diseases (20).

According to a review article by Gratacós-Ginès et al., statins were found to reduce portal pressure regardless of whether they were used in conjunction with propranolol (10). However, a study by Vijayaraghavan et al. failed to demonstrate a significant decrease in portal pressure; this particular trial used simvastatin along with carvedilol instead of propranolol. The use of carvedilol for bleeding prevention in this study may have influenced these negative outcomes. Nevertheless, additional controlled studies are needed to evaluate the potential effects of this combination (21). While a study by Wani et al. yielded promising results regarding the reduction in portal pressure using simvastatin and carvedilol, it lacked a control group. Consequently, these findings should be interpreted with caution (22).

In a study by Bishnu et al., which examined the effect of atorvastatin over a one-month period, the data showed that the drug reduced portal blood pressure, but the bleeding rate did not decrease (23). Similarly, in the study by Vijayaraghavan et al., the effect of simvastatin administration for one month on any of the study objectives (reduction of portal pressure, reduction of banding, and reduction of bleeding) was not proven (21). However, a study by Pollo-Flores et al. demonstrated that a three-month administration of simvastatin successfully reduced portal blood pressure (24). Alsaeid

et al. investigated mortality and bleeding due to portal hypertension. Despite the effect of simvastatin on the survival rate of patients with cirrhosis, the drug did not reduce the rate of variceal bleeding (25). Additionally, a systematic review by Wan et al. found that statins may improve hypertension and decrease the risk of variceal hemorrhage, although further large randomized controlled trials are needed to confirm these findings (26). Lastly, Pfisterer et al. reported that statins, metformin, and renin-angiotensin system (RAS) inhibitors did not reduce the risk of variceal bleeding and mortality in a large cohort of cirrhotic patients. It appears that the beneficial effects of statins become more pronounced over an extended follow-up period (27).

Recent studies have explored the therapeutic potential of rosuvastatin in children with compensated liver cirrhosis, particularly with respect to portal hypertension and variceal bleeding. While rosuvastatin is well known for its cholesterol-lowering effects and benefits in adult cardiovascular conditions, its application in pediatric cirrhosis aims to reduce portal hypertension, a significant complication in liver diseases (28). The findings of this study suggest that although rosuvastatin showed some reduction in the sonographic criteria for portal hypertension, the differences were not statistically significant. However, the clinical implications may still be worth considering, as a higher percentage of patients in the rosuvastatin group demonstrated improvements in certain Doppler ultrasound metrics.

The results indicated that rosuvastatin did not significantly reduce the incidence of variceal bleeding compared to standard treatments. The occurrence of variceal bleeding remained comparable between the control and intervention groups, suggesting that the impact of rosuvastatin on this specific complication may be limited. Nevertheless, the observation that variceal grades decreased in both groups, although not significantly different, suggests a possible therapeutic role of rosuvastatin that might warrant further investigation with larger sample sizes or longer follow-up periods to draw more definitive conclusions.

In summary, although this study could not definitively prove the efficacy of rosuvastatin in reducing portal hypertension or preventing variceal bleeding in children with cirrhosis, it highlights the need for more extensive research. The modest improvements observed in some patients suggest that rosuvastatin may still have potential benefits. Future studies should focus on larger cohorts and explore combination therapies to enhance the overall treatment strategy for pediatric liver cirrhosis. Ongoing research is crucial to better understand and manage the complex challenges associated with pediatric portal hypertension and variceal bleeding.

This study had several limitations, including the lack of parental consent, which may have caused selection bias and limited sample representativeness. The restriction to children over 7 years of age, as required by the Food and Drug Administration (FDA), excluded younger children, potentially affecting the comprehensiveness of the findings. Additionally, the high variability in liver cirrhosis causes complicated robust conclusions among the participants. Despite being a referral center, the diversity of cases may have masked important associations. Future research should consider larger sample sizes and more focused inclusion criteria for better insight into pediatric liver cirrhosis.

5- CONCLUSION

Based on the study results, it cannot be conclusively determined that rosuvastatin administration in pediatric

patients with cirrhosis effectively reduces portal hypertension and associated hemorrhage. Despite recommendations for statin use in the adult cirrhotic population to mitigate cirrhosis progression and portal hypertension, this effect was not observed in our study. Therefore, it is recommended that additional studies be conducted with larger sample sizes, extended follow-up periods, and more homogeneous populations to elucidate the etiology of cirrhosis in pediatric patients.

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