Correlation between character of Portal Blood Flow and Post TIPS Incidence of Hepatic Encephalopathy (HE)

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ABSTRACT:

Background: Hepatic encephalopathy is one of the major complication that follow **TIPS** operatios in patients with different complications of portal hypertension as refractory ascites, refractory hydrothorax, bleeding varices, and hepatorenal syndrome, The aim of this study Was to clarify predisposing factors for post-TIPS incidence of HE in relations to Pre-TIPS hemodynamics.

Patients and method: fifty patients where enrolled in this study with different complications of portal hypertension most of them Child A and B, patients were assessed by Ultrasound Doppler for the flow inside the portal vein and divided into two groups: group 1; 31 patients with hepatopetal flow, group 2; 19 patients with hepatofugal flow then TIPS was performed and patients were Followed for one month for development of HE.

Results: There were no significant differences in multiple variables as age, gender, weight, etiology of liver disease, indication for TIPS. The incidence of HE post-TIPS was observed more at group 1 more than group 2. (P?)

Conclusion: Post-TIPS incidence of HE was closely related to Pre-TIPS flow in the portal vein (hepatopetal group more than hepatofugal group), also was closely related to child score and Pre-TIPS incidence of HE

Key words: Portal hypertension. Ultrasound Doppler, Flow inside the portal vein, TIPS, HE

Introduction:

The Transjugular Intrahepatic Portosystemic Shunt (TIPS) was developed in the 1980s for treatment of complications of portal hypertension. Once it was shown that the shunt could be placed with relative ease, TIPS was rapidly applied to the treatment of many of the complications of portal hypertension. These complications include actively bleeding gastroesophageal varices, control of refractory cirrhotic ascites and hepatic hydrothorax, and treatment of hepatorenal failure and hepatopulmonary syndrome. [1] Hepatic encephalopathy is a well-known complication of patient with liver Cirrhosis after TIPS, its pathogenesis not well understood [2] [3].In recent years TIPS has accepted as a minimally invasive therapy for complication of portal hypertension [4] [5] [6]. Because TIPS resembles as surgical side to side shunt, an increased rate of HE can be seen after TIPS. The incidence of HE after TIPS varies from 18%to45%[7] [8] and[9].

This high rate attracts researchers in investigating the causative factors for HE, beside, predicting factors of HE after TIPS which had been much controversial.

Aim of the Study

The aim of this study was to verify the relationship between pre-Transwajagular intrahepatic portosystemic shunt intrahepatic hemodynamics and the incidence of post-Transjagular intrahepatic portosystemic shunt hepatic enchephalopathy.

Patients and Methods: Fifty patients were included in this study with different causes of portal hypertension, patients underwent TIPS in National Liver Instute Menoufia University from 2015 to 2017 Patients were divided into two groups according to the flow inside the portal vein by Dopplar to Group I: 31 patients with hepatopetal flow (Toward the Liver), Group II: 19 patients with hepatofugal flow (Away from the liver).

TIPS: A catheter was inserted via the jugular vein past the right atrium and into the hepatic veins. A needle was then inserted into the hepatic parenchyma, and contrast

was injected as the needle was slowly withdrawn. When a branch of the portal vein was identified, a wire was inserted into the vein followed by a catheter. Pressures were obtained and portography was performed. A tract within the hepatic parenchyma was then created using a balloon and stent deployed. The used stents were self-expanding.

Follow Up: patients were followed at hospital for one week then discharged and followed for another three weeks for the incidence of HE.

Statistical analysis: The data collected were tabulated and analyzed by SPSS (statistical package for social science) version 22.0 on IBM compatible computer.

Two types of statistics were done:

Descriptive statistics:

- e.g. percentage (%), mean and standard deviation (SD).

Analytic statistics:

- e.g. Chi-square test (x2): was used to study association between two qualitative variables.
- Fischer exact test for 2 x 2 tables when expected cell count of more than 25% of cases was less than 5 and p-value < 0.05 was considered significant.
- Student t-test: is a test of significance used for comparison between two groups having quantitative variables.
- Mann-Whitney test (nonparametric test): is a test of significance used for comparison between two groups not normally distributed having quantitative variables.
- Paired t-test: is a test of significance used for comparison between two related groups having quantitative variables.

Results:

The etiology of liver cirrhosis was more post HCV (70%), HBV (4%), HCV and HBV (8%) then Bilharizial periportal fibrosis (18%). There 20 males and 30 females with no significant difference in incidence of post-TIPS there was no statistically significant difference as regared gender (p value 0.41) The liver function has no significant difference except in calculating Child Score. The kidney function is important, the more increase in creatinine level and HRS the more the post-TIPS he. (P.value 0.14)

The patients weight was more at hepatofugal flow: Group than hepatopetal flow group, this indicate the more the cirrhosis and portal hypertension and ascites in this patients only, with no clinical important in post-TIPS HE.

The most common cause of TIPS is refractory ascites (64%) then refractory. hydrothorax (20%) then refractory. bleeding varices (12%) then HRS (4%), respectively as shown in^**(table 1)** Patient underwent TIPS with previous history **of** HE had HE post-TIPS (100%), and this show that pre-TIPS HE is a significant predictor for post-TIPS HEas in (table 2)

The more the Child Score the more the post-TIPS incidence of HE, none of Child A (0%), 9 patient of Child B (20%), the two patients of Child C (100%), this relationship can tell us that patients with Child score less than C are fit for TIPS with less predictors for post-TIPS HE.

All patients with hepatopetal flow or hepatofugal flow their Mean Arterial Blood Pressure decreased post-TIPS specialy in hepatopetal flow, and this indicate the change in the heamodynamics post-TIPS as shown in (table *3)* The Hepatic Artery RI was more in hepatofugal group than hepatpetal group before TIPS. The Hepatic Artery RI decreased significantly post- TIPS in hepatofugal group.

The pressure inside the inferior vein cava increased significantly post-TIPS due to shunting of the blood to new way through the shunt and IVC. The pressure inside the portal vein decreased significantly post-TIPS also due to shunting most of the blood that pass through it, to the IVC. The incidence of HE was less in Hepatofugal flow group (10%) than Hepatopetal flow group (29%).

Table (I): Comparison between studied groups regarding indication of TIPS.

Indication	Hepatofugal Group (no=19)		Hepatopetal group (no=31)		X^2 test	P value
	No	%	No	%		
Refractory Ascited	14	73.7	18	58.1	2.002	0.57
Refractory pleural Effusion	3	15.8	7	22.6		
Refractory Bleeding varices	2	10.5	4	12.9		
Hepatorenal Synrome	0	0.0	2	6.5		

Table (2): Comparison between studied groups regarding post HE.

		Hepatofugal group (no=19)		Hepatopetal group (no=30)		Fisher Exact test	P value
		No	%	No	%		
Post HE	**Negative**	17	89.5	22	71.0	2.55	0.12
	Positive	2	10.5	9	29.0		

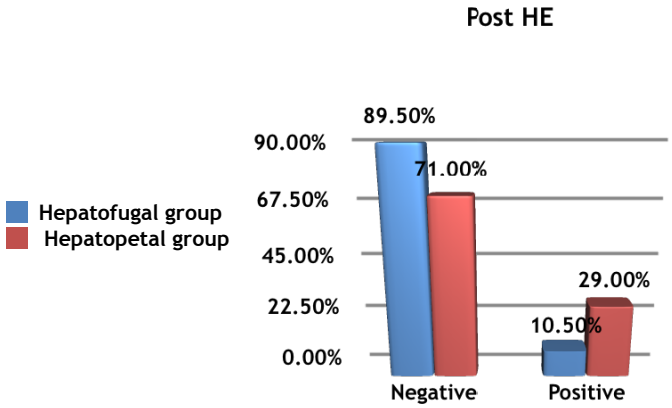
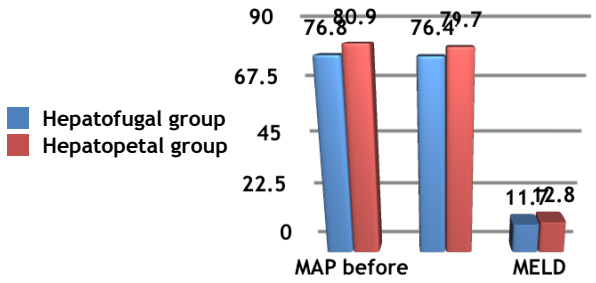


Table (3): Comparison between Studied groups regarding MAP before, MAP after

	Hepatofugal group (no=19)	Hepatopetal group (no=30)	t-test	P value
	Mean±SD	Mean±SD		
MAP before	76.8±7.1	80.9±7.5	1.91	0.06
MAP after	76.4±6.2	79.7±6.1	1.85	0.07
MELD	11.7±3.3	12.8±4.8	0.46#	0.64



Discussion

Transjugular intrahepatic portosystemic stent-shunts (TIPS) have been increasingly used for the treatment of the complications of portal hypertension. Meta-analysis of randomized controlled trials confirms the superiority of TIPS over endoscopic treatments in prevention of variceal rebleeding but without any improvement in mortality. [9]

Additionally, TIPS is effective in the resolution of refractory ascites in some patients.[10] But it remains unclear as to whether there is any survival advantage. [11]

Hepatic encephalopathy is thought to results from intestinally derived toxins that bypass the normal metabolic pathways of the liver, either because of shunting of portal vein blood flow away from the liver parenchyma as in TIPS patients or because of the inability of the liver to handle such substances because of chronic hepatocellular disease, Certainly, both of these factors may play a role in patients with cirrhosis, with either one being more important. [12]

Many studies have focused on the relevant factors of HE, but the effects of pre-/post-TIPS factors were found to be contradictory. The factors including pre- TIPS, age and liver function, Pre-TIPS HE, Child Score, The direction of Flow in the Portal vein. In this study we found that the occurrence of post-TIPS HE was closely related to the pre-TIPS portal blood flow direction, the low incidence of post-TIPS HE was observed in patients with hepatofugal portal blood flow (n=2) 10%, but the high incidence in those with prograde (hepatopetal) portal blood flow (n=9) 29%, indicating that the pre-TIPS pattern of blood flow may greatly affect the occurrence of post-TIPS HE. [13]

In the study done by Darryl A. Zuckerman, et al., 1997; occurrence of HE after TIPS was independent of central venous pressures; portosystemic gradients (before and after TIPS); direction of blood flow (before and after TIPS) in the right, left and main portal veins; and presence of encephalopathy after TIPS, and this contrary to our results. [14]

Similar study done by Dan Deng, et al., 2006; The incidence of post-TIPS HE in hepatofugal group 16% was lower than that in hepatopetal group 37%, that agree with our study. [15]

Many studies agree that age more than 60 years old increase the incidence of post-TIPS HE, Sanyal, et al., 1994. Stated that increasing age was significantly associated with encephalopathy, that agree with our study **(Sanyal et al., 1994).** [16]

In this study we found that Child Score was very important in post-TIPS incidence of HE, with increasing Child Score the more the post-TIPS incidence of HE, In this study 4 patient Child score A, none of them had post-TIPS HE, 44 patients Child score B, 9 had post-TIPS HE and 2 patients Child score C, the two had post-TIPS HE.

Similar Study Sanyal et al., 1994; Increasing Child Class as significantly associated with post-TIPS HE, that agree with our study. [17]

Another study Somberg KA, et al., 1995; post-TIPS HE associated with multivariate like hypoalbuminemia (Albumin as it's one of the main variable in assessing Child Score). [18]

In this study we found that pre-TIPS incidence of HE is associated with post-TEPS incidence of HE as two patients had pre-TIPS HE, and the two patients had post-TIPS HE.

In Another study, those patients who developed clinically evident HE were significantly more likely to have a past history of encephalopathy and tended to be male. [19][20]

Past history of encephalopathy along with increasing age have previously been identified as important variables increasing the risk of post-TIPS HE [17] that goes with our study.

Another study, although the mean age

difference between patients with TIPS-related encephalopathy and other patients was not statsitacally significant {P=0.11(>0.05)}.the statistical power of this test was only 0.35; therefore we cannot guarantee that TIPS-related encephalopathy id independent of age and large sample would be required. [21]

In this study we round that there were no significant difference between causes of TIPS in patients with portal hypertension and post-TIPS incidence of HE, except in HRS cases; we had 2 cases and the two cases developed post-TIPS HE.

Similar study: Darryl A. Zuckerman, et al., 1997: The cause of liver disease had no interrelationship with the patients with TIPS-related HE, that agree with our study in general**.** [14]

Another study Oliviero Riggio, et al., 2008: Serum creatinine level was the only variable related to the development of refractory HE at the logistic multivariate analysis. That agree also with our study in the HRS cases, but we think that this issue need more studies with more cases for more accurate results. [22]

According to the Hepatic artery **RI,** normally when portal perfusion decreases, hepatic arterial blood may increase to maintain the relative invariableness of liver blood supply. This mechanism is called Hepatic Arterial Buffer Response (HABR). In this study we found that before TIPS the hepatic artery RI of patients of hepatopetal flow (0.61±0.11) was significantly lower than that of hepatofugal group (0.75±0.79) (P value 0.005).

Similar study, Dan Deng, et al., 2006; the hepatic artery RI of the ptients before-TIPS was lower than that of the patients with prograde flow, indicating the difference of post TIPS intrahepatic hemodynamics, and this agree with our study **.** [15]

Also we found in this study that the hepatic artery RI in hepatopetal group decrease after TIPS (0.6U0.11 before to 0.59±0.07 after) but less than that of the hepatofugal group (0.75±0.79 before to 0.57±0.07 after) {P=002}, this indicate that there is a great change in the hemodynamics in the patient of hepatofugal group after TIPS.

Similar study, Dan Deng, et al., 2006; hepatic hemodynamics of patients with hepatofugal portal flow only changed a little after TIPS and was still dependent on the hepatic artery perfusion. Therefore, the RI of the hepatic artery was changed a little before and after TIPS, and this contrary to our study; although in patients with hepatofugal flow, large spontaneous portosystemic anastomosis could be found, and more importantly, the long-term existence of small to large Pre-TIPS spontaneous portosystemic anastomoses might enable the cerebrum to adapt to some neurotoxic substances in blood, which cause HE. [15]

According to Post-TIPS hemodynamics and mean arterial blood pressure (MAP) before and after in this study we found that, the patients with hepatofugal flow the MAP (76.8±7.1) was less than of hepatopetal flow (80.9±7.5), also we found that the MAP decreased after TIPS, and the decrease was more in the patient with hepatopetal flow more than that of hepatofugal flow, all this results indicate that there is alteration in the hemodynamic in the patients post-TIPS more in patients with hepatopetal flow and this may explain the high rate of post-TIPS HE.

Another study L A Colombato, et al., 1996: the average of MAP was (92 mmHg) before TIPS, a tendency of MAP to increase after TIPS replacement was noted (100 mmHg) but the difference was not significant; two months later it decreased to a value lower than baseline (85 mmHg), and this agree with our study**.** [23]

Conclusion

Patients with hepatofugal flow in the portal vein are perfect candidate for TIPS than patients with hepatopetal flow in the portal vein. Patient with previous history of HE are contraindicated for TIPS except as a bridge for Liver transplantation.

Recommendation

Further research should be done to analyze the efficacy of TIPS in HRS cases. Further research should be done to standardize the use of Child Score and Pre-TTPS HE as good predictors of post-TIPS HE.

Reference:

1. **Thomas d. Boyer, Conn HO., et al**, Hepatology: a textbook of liver disease (4ail Philadelphia: Saunders (2003) 21:627-628.
2. **Notle W.Ramadori G**. Diagnosis of hepatic encephalopathies. Dtsch Mod Wochenschr (1996) l21:665-669.
3. Butteworth RF Neurotransmitter dysfunction in hepatic encephalopathy: new approaches and new findings. Metab Brain Dis (2001) 16:55 -65.
4. Gerber Tand Schomerus H. Hepatic encephalopathy in liver cirrhosis; pathogenesis. Diagnosis and management. Drugs 2000; 60:1353-1370.
5. MamiyaY ,Kanazawa H ,Kimura Y,Narahara Y ,Yamte Y, Nakatsuka K, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Hepatol Res 2004; 30:162-168.
6. Stefankova J, Fejfar T, Safka V, Hulek P, Krajina A, Fendrichova M, Hepatic encephalopathy after TIPS retrospective study. Vnitriek 2002; 48:390-395.
7. Tripathi D, Helmy A, Macbeth K, Balata S, Lui HF, Stanley AJ, et al. Ten years[9] follow-up of 472 patients following transj ugular intrahepatic portosystemic stent-shunt insertion at a single centre. Eur J GastroenterolHepatol 2004; 16:9-18.
8. Ong JP, Mullen KD, Hepatic encephalopathy. Eur JGastroenterolHepatol 2001; 13:325-334.
9. Khan S, Tudur SC, Williamson P, Sutton R. Porto systemic Shunts Versus Endoscopic therapy for Variceal rebleeding in patients wuth cirrhosis. Cochrane Database Syst Rev 2006; CD000553
10. **Salerno F, Camma C, Enea M, Rossle M, Wong F.** Transjugular intrahepatic portosystemic shunt for refractory ascites: A meta-analysis of individual patient data. Gastroenterology 2007: 133:825-834.
11. Saab S, **Nieto JM, Lewis SK, Runyon BA.** TIPS versus paracentesis for cirrhotic patients with refractory ascites. Cochrane Database Syst Rev 2006; CD004889.
12. Spiro H. ed. Clinical gastroenterology, 4th ed. New York: McGraw-Hill, 1993:1184-1188.
13. **Kramer L, Bauer E, Gendo** A, **Funk G, Madi C, Pidlich J, et al.** Neurophysio logical evidence of cognitive impairment in patients without hepatic encephalopathy after transjagular intrahepatic portosystemic shunts. Am J Gastroenterol 2002; 97:162-166.
14. **Darryl A. Zuckerman, Michael D. Darcyi, Thomas P. Bocchini, Charles F. Hildebolt,** AJR1997; 169:1727-1731.
15. **Dan Deng, Ming-Song Liao, Jian-Ping Qin and Xiao-An Li.** Hepatobiliary pancreat Dis Int 2006; 5:232-236.
16. **Sanyal AJ, Freedman AM, Luketic VA, Purdum P III, Shiffman M, Cole P, Tisnado J, Simmons S.** Transjugular intrahepatic portosystemic shunts compared with endoscopic sclerotherapy for the prevention of recurrent variceal hemorrhage. A randomized, controlled trial. Ann Intern Med 1997; 126:849-857.
17. **Sanyal AJ, Freedman AM, Shiffman ML, Purdum PP. 3rd, Luketic VA. Cheatham AK.** Portosystemic encephalopathy after transjugular intrahepatic portosystemic shunt: results of a prospective controlled study. HEPATOLOGY 1994; 20:46-55.
18. **Somberg KA, Riegler JL, LaBerge JM, Doherty-Simor MM, Bachetti P,**

Roberts J, Lake JR. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunts: incidence and risk factors. Am J Gastroenterol 1995- 90:549-555

19. **Jalan R, Eiton RA, Redhead DN, Finlayson ND, Hayes PC.** Analysis of prognostic variables in the prediction of mortality, shunt failure, variceal rebleeding and encephalopathy following the transjugular intrahepatic portosystemic stenpshunt for variceal haemorrhage. J Hepatol 1995; 23:123-128.
20. Tripathi D, Helmy A, Macbeth K, Balata S, Lui HF, Stanley AJ, et al., Ten years` follow-up of 472 patients following transjugular intrahepatic portosystemic stent-shunt insertion at a single centre. Eur J Gastroenterol Hepatol 2004; 16:9-18.
21. Garcia-Villarreal l, Martinez-lagares F, Sierra A, Guevara C, Marrero J, Jimenez E, Monescillo A. Trans jugular intrahepatic Porosystemic shunt versus endoscopic sclerotherapy for the prevention of variceal rebleeding after recent variceal hemorrhage. HEPATOLOGY 1999; 29:27-32
22. Oliviero R, Stefania A, Filippo S, Adriano D, Federica C, Alessin F, Adolfo F, Manuela M, AJG 2008:2738-2746.
23. **A Colombato, L Spahr, J-P Martinet, M-P Dufresne, M lafortune, D Fenyves, G Pomier-layrargues, Gut 1996;39:600-604.**