

Dear Editor and Reviewers, Thank you very much for all your comment and suggestions. We have modified the manuscript according to your suggestions, and the revised parts are highlighted in the text. Our responses to the reviewers' comments are as follows:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: 1. The article's title should be changed and re-converted to be more appealing. 2. The study's abstract should be shortened because it contains a lot of information that can be omitted. 3. Keep in mind that only the most important findings from the study should be included in the results section of the study abstract. 4. Try to condense the study's introduction into two to three paragraphs at most. 5. Including related references in the method paragraph to provide additional support for the study protocol. 6. I would like the author(s) to include an explanation in the statistics section of the study methodology section that explains the justifications for selecting the statistical method that was used in data analysis. 7. Adding numerical values to the statistical images, specifically images 1-4, is required, so this must be considered. 8. Consider emphasizing the current study's strengths, weaknesses, and future directions in the discussion section. 9. If possible, I would like the author(s) to separate the conclusion from the discussion section. 10. I proposed that the total of 36 references is too many for a research paper. It can be reduced by removing references from before 2015, while keeping more important references and avoiding irrelevant ones. Good Luck.

1. The article's title should be changed and re-converted to be more appealing.

Response: Thank you for your comment. We have further condensed the title which presents the focus of the article.

2. The study's abstract should be shortened because it contains a lot of information that can be omitted.

Response: We have omitted some unnecessary contents.

3. Keep in mind that only the most important findings from the study should be included in the results section of the study abstract.

Response: We omitted some unnecessary contents in the results section of the Abstract.

4. Try to condense the study's introduction into two to three paragraphs at most.

Response: We shortened the INTRODUCTION to three paragraphs.

5. Including related references in the method paragraph to provide additional support for the study protocol.

Response: METHODS. Thank you for your suggestions. We have cited relevant references in METHODS. For TIPS procedure, we cited reference 11, and for the hepatic encephalopathy, we cited references 12,13.

6. I would like the author(s) to include an explanation in the statistics section of the study methodology section that explains the justifications for selecting the statistical method that was used in data analysis.

Response: We have added an explanation for the justifications for selecting the statistical method that was used in data analysis in the section of statistical analysis.

7. Adding numerical values to the statistical images, specifically images 1-4, is required, so this must be considered.

Response: We have added numerical values to the statistical images, specifically images 1-4.

8. Consider emphasizing the current study's strengths, weaknesses, and future directions in the discussion section.

Response: The last two paragraphs of the DISCUSSION pointed out the strength,

weakness, and future direction of the study .

9. If possible, I would like the author(s) to separate the conclusion from the discussion section.

Response: We have separated the conclusion from the DISCUSSION to the section of CONCLUSION.

10. I proposed that the total of 36 references is too many for a research paper. It can be reduced by removing references from before 2015, while keeping more important references and avoiding irrelevant ones.

Response: Two of the references before 2015 were reserved as guidelines. The remainder before 2015 has been removed, Some irrelevant references were also removed.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: Despite the using an expanded PTFE-covered stent graft (Viatorr) have improved patency rates and clinical outcomes compared to bare metal TIPS, hepatic encephalopathy remains a pertinent post-procedural complication as portosystemic shunt physiology can trigger or worsen hepatic encephalopathy. Given the potential relationship between portal decompression and hepatic encephalopathy, efforts have been made to develop techniques to balance the desired therapeutic effect while minimizing over-shunting. In this well planned a multicenter retrospective study, the authors found that patients who underwent TIPS with PSG reduced by one third of baseline and reduced to <12 mmHg had similar successful clinical outcomes, but the former had a lower rate of hepatic encephalopathy and liver damage. To reduce PSG by one third of basal value, the stent was not fully expanded, the diameter was retained, and the pressure was measured several times until it was reduced by one third. It should be noted that this

technique will only be effective if assuming that the not fully dilated stent will not expand significantly over time. For this reason, previously published studies have shown contradictory results of sub-maximally dilate a 10 mm TIPS. The present study is limited by its retrospective design, therefore, multicenter randomized controlled trials are required to confirm the results obtained.

Response: Thank you for your positive comment for accepting our article. We are planning to initiate a multicenter study to validate our results and to disseminate our findings to more clinicians.

Reduction of portosystemic gradient during transjugular intrahepatic portosystemic shunt achieves good outcome and reduces complications

批注 [MedE-QC1]: 此文题是我们最初给出的文题，也符合审稿人要求，建议采用

Luo SH *et al.* Reduction of portosystemic gradient during TIPS

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Author contributions: Chu JG designed the research; Luo SH and Zhou MM performed the research; Shen HW, Yao WX, Han SL, Zhang XQ analyzed the data;

Luo SH wrote the paper; Cai MJ revised the paper. All authors have read and approved the final version to be submitted.

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Air Force Medical Center of PLA, Beijing, China.

Informed consent statement: This is a retrospective study, and informed written consent was thus waived.

Conflict-of-interest statement: The authors declare that there is no conflict of interest related to this study.

Data sharing statement: No additional data are available.

Abstract

BACKGROUND

Transjugular intrahepatic portosystemic shunt (TIPS) is currently used for the treatment of complications of portal hypertension, there is still no suitable criterion for a reduction in PSG, which can both reduce PSG and maximize clinical results and minimize HE.

AIM

To compare the clinical outcome and incidence of hepatic encephalopathy (HE) after one-third portosystemic gradient (PSG) reduction during TIPS in patients with variceal bleeding and refractory ascites.

METHODS

A total of 1280 patients with portal-hypertension-related complications of refractory ascites or variceal bleeding who underwent TIPS from January 2016 to January 2019 were analyzed retrospectively. Patients were divided into group A (variceal hemorrhage and PSG reduced by one third, $n = 479$); group B (variceal hemorrhage

and PSG reduced to < 12 mmHg, $n = 412$); group C (refractory ascites and PSG reduced by one third, $n = 217$); and group D (refractory ascites and PSG reduced to < 12 mmHg of PSG, plus medication, $n = 172$). The clinical outcomes were analyzed.

RESULTS

By the endpoint of follow-up, recurrent bleeding was no different between groups A and B ($\chi^2 = 7.062$, $P = 0.374$), but recurrent ascites did differ significantly between groups C and D ($\chi^2 = 14.493$, $P = 0.006$). The probability of total hepatic impairment within 3 years was significantly different between groups A and B ($\chi^2 = 11.352$, $P = 0.005$) and groups C and D ($\chi^2 = 13.758$, $P = 0.002$). The total incidence of HE differed significantly between groups A and B ($\chi^2 = 7.932$, $P = 0.016$), groups C and D ($\chi^2 = 13.637$, $P = 0.007$). Survival rates were not different between groups A and B ($\chi^2 = 3.376$, $P = 0.369$, log-rank test), but did differ significantly between groups C and D ($\chi^2 = 13.582$, $P = 0.014$, log-rank test).

CONCLUSION

The PSG reduction by one third may reduce the risk of HE, hepatic function damage and achieve good clinical results.

Key Words: Portal hypertension; Transjugular intrahepatic portosystemic shunt; Portosystemic gradient

Core Tip: We analyzed a large cohort of patients with cirrhosis who underwent transjugular intrahepatic portosystemic shunt for recurrent variceal bleeding and refractory ascites. The reduction in portosystemic gradient (PSG) should be based on the original basal pressure and reduction by one third may reduce the risk of HE, hepatic function damage and achieve similar clinical results as for the refractory ascites patients. Appropriate reduction of PSG directly influences the patient prognosis.

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) is currently used for the

批注 [MedE-QC2]: 根据审稿人意见, 已改为 3 段。

treatment of complications of portal hypertension^[1]. It has been progressively recognized as an effective therapeutic option in a growing number of clinical situations^[2,3]. Measurement of portosystemic pressure gradient (PSG) is important during the TIPS procedure. Reduction of PSG can achieve good clinical results, but when PSG is too low, TIPS can have many complications, of which, hepatic encephalopathy (HE) and liver function damage are the most frequent^[4]. Post-TIPS HE could depend mainly on portocaval pressure gradient and volume of blood shunted through the liver^[5].

Several guidelines^[6-7] recommend that the PSG should be reduced to 12 mmHg after TIPS creation to achieve a better clinical outcome. In that situation, however, the incidence of HE is higher than in clinical practice. This has prompted many centers to anecdotally adopt the technique of dilation of stent grafts using balloons with a nominal diameter of ≤ 8 mm at TIPS positioning. Recently, a new controlled expansion stent has been introduced in clinical practice (Viatorr Controlled Expansion Endoprosthesis; Gore and Associates, Flagstaff, AZ, USA), which allows lasting diameter control within a range of 8–10 mm during implantation to reach a targeted portal pressure gradient^[8].

However, there is still no suitable criterion for a reduction in PSG, which can both reduce PSG and maximize clinical results and minimize HE, and few data are available to calculate an appropriate PSG value^[9]. Here, we report our multicenter retrospective study to compare the occurrence of HE and clinical results of one-third reduction of PSG with PSG reduced to < 12 mmHg in patients who required TIPS placement for portal-hypertension-related complications of variceal bleeding and refractory ascites.

MATERIALS AND METHODS

Patient information

This was a multicenter retrospective study. The Ethics Committee approved the study protocol and all procedures were conducted according to the guidelines approved by the Committee. Between January 2016 and January 2019, 1280 patients

were referred on an intention-to-treat basis and underwent a TIPS procedure. Indications for stent graft shunt were variceal hemorrhage or refractory ascites. The outcomes of HE, recurrent variceal bleeding and ascites, and mortality were compared between the groups. The patients' medical records and images were reviewed to gather information regarding underlying etiology, clinical presentation, age, sex, and severity of cirrhosis (Table 1).

Table 1. Baseline characteristics

Characteristics	Group A	Group B	<i>P</i> value	Group C	Group D	<i>P</i> value
Gender, M/F	256/223	237/175	0.369	126/91	93/79	0.319
Age (mean±SD) (yr)	54.616±17.27	56.39±12.19	0.319	56.24±13.67	58.27±13.25	0.246
Child-Pugh A/B/C	39/342/98	32/318/62	0.187	0/60/157	0/41/131	0.215
MELD score (mean±SD)	8.42±1.37	9.29±2.16	0.576	13.26±4.56	14.39±5.38	0.472
Viral hepatitis	324	276	0.528	136	107	0.632
Chronic ethanol consumption	102	87	0.317	55	38	0.258
Cryptogenic hepatitis	53	49	0.492	26	27	0.146
Variceal hemorrhage	479	412	0.721	0	0	0.000
Refractory ascites	0	0	0.000	217	172	0.562
Laboratory tests						
Alanine transaminase (U/L)	48.36±4.21	53.19±3.27	0.462	62.13±6.48	57.49±7.29	0.368
Aspartate Transaminase (U/L)	54.17±9.25	58.27±12.37	0.361	67.43±15.7	64.28±17.2	0.357
Alkaline phosphatase (U/L)	145.36±23.45	167.18±27.36	0.382	89.67±13.24	92.36±16.58	0.413

γ-Glutamyl	278.54±37.	259.74±46.	0.463	364.27±58.	382.17±47.	0.482
transpeptidase (U/L)	47	37		74	26	
Total bilirubin	29.45±3.17	32.46±4.28	0.147	37.18±7.69	35.24±8.54	0.367
(μmol/L)						
Albumin (g/L)	31.28±1.47	32.07±1.25	0.106	28.07±1.29	29.36±1.48	0.294
Prothrombin time (s)	14.02±1.35	15.04±1.19	0.236	18.12±2.39	19.23±2.41	0.241
Clinical presentations						
Abdominal distention	89	93	0.261	217	172	0.562
Abdominal pain	48	52	0.273	134	97	0.183
Weakness	364	314	0.148	189	154	0.136
Poor appetite	373	362	0.302	196	153	0.324
Jaundice	28	24	0.532	21	16	0.214
Splenomegaly	264	249	0.357	205	168	0.436
Lower limbs edema	47	62	0.159	189	157	0.327
Ascites paracentesis	0	0	0	217	172	0.562
Endoscopic therapy	453	407	0.372	0	0	0.000

No difference ($P > 0.05$) could be seen in terms of age, sex, Child–Pugh score, MELD score, laboratory tests, and clinical presentations. MELD: Model of End-Stage Liver Disease.

Study design

This was a multicenter retrospective study that compared the rate of HE and clinical outcomes after TIPS with PSG reduced by one third with PSG reduced to < 12 mmHg in patients who required TIPS placement for portal-hypertension-related complications of ascites or variceal bleeding. The patients were divided into four groups^[10]: group A (variceal hemorrhage and PSG reduced by one third, $n = 479$); group B (variceal hemorrhage and PSG reduced to < 12 mmHg, $n = 412$); group C (refractory ascites and PSG reduced by one third, $n = 217$); and group D (refractory ascites and PSG reduced to < 12 mmHg, plus medication, $n = 172$). The clinical

outcomes were analyzed .

The inclusion criteria were: recurrent variceal bleeding after a session of variceal sclerotherapy, and refractory ascites that required TIPS placement with portal-hypertension-related complications. Only *de novo* TIPS procedures using Viatorr stent grafts (Gore & Associates) were included. We excluded: TIPS procedures performed with bare stents, TIPS with bare stents followed by revision with Viatorr stent grafts, and TIPS performed with other types of stent grafts; variceal bleeding as an emergency indication; portal vein thrombosis; history of HE; severe right-sided heart failure; severe liver failure (bilirubin > 4 mg/dL), polycystic liver disease, and dilated biliary ducts; age >75 years; Child-Pugh score > 11; MELD score > 18; hepatic carcinoma; sepsis spontaneous bacterial peritonitis; and liver transplantation.

TIPS procedure

TIPS was performed under standard local anesthesia as described previously^[11]. The entire length of the intrahepatic tract was covered by the stent graft. Hepatic venous pressure gradient and portal venous pressure were measured during the procedure, and the shunts were dilated to an appropriate diameter to reach a target PSG of < 12 mmHg or reduced by one third. To reduce PSG by one third of basal value, the stent was not fully expanded, the diameter was retained, and the pressure was measured several times until it was reduced by one third. Obvious gastroesophageal collateral vessels observed during the TIPS procedure were embolized with coils (Cook Inc., Bloomington, IL, USA; or Interlock Coil, Boston Scientific Corporation, Natick, MA, USA). Subsequent direct portography was performed to evaluate whether the portal venous system was completely patent.

After the TIPS procedure, intravenous Dalteparin Sodium Injection (5000 U/d; VetterPharma-Fertigung, Germany) was administered for 3 d. No patients had portal vein thrombosis, and oral warfarin was not given.

Follow-up

After TIPS deployment, baseline duplex sonography was performed. Shunt velocities were compared with this baseline result during follow-up. Patients were placed into a routine follow-up protocol identical for each group. They were seen as outpatients 1 mo after the procedure and then at 3 and 6 mo and 1 and 3 years, or whenever needed. Each consultation included a clinical examination, blood chemistry, upper abdominal ultrasonography, and assessment of HE.

TIPS angiography was performed in patients with recurrent symptoms or suspected shunt dysfunction. TIPS revision was performed when hemodynamically significant shunt stenosis ($> 50\%$) was present with recurrent variceal bleeding, or recurrent or gradually worsening ascites. HE was defined according to the practice guidelines of the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD)^[12,13]. Patients lost to follow-up were censored at the time of the last known imaging of the shunt (duplex ultrasonography or shunt venography).

Statistical analysis

Data measurements results of the four groups were normally distributed, and expressed as mean \pm standard deviation, and their differences were determined using t test. Categorical variables were expressed as frequencies and compared using χ^2 test, and their differences among the four groups were determined by one-way ANOVA. A P value of less than 0.05 was considered significant. The statistical analyses were performed with SPSS version 22.0 (SPSS, Armonk, NY, USA).

批注 [MedE-QC3]: 注意是否回答了审稿人意见。

RESULTS

All TIPS procedures demonstrated similar efficacy by decreasing PSG before and after TIPS placement in all four groups. PSG was reduced after TIPS placement from 24.58 ± 2.41 to 15.72 ± 1.04 mmHg in group A ($P = 0.012$), 25.37 ± 2.54 to 11.27 ± 2.04 mmHg in group B ($P = 0.004$), 25.12 ± 3.16 to 16.15 ± 1.37 mmHg in group C ($P = 0.016$), and 24.48 ± 3.24 to 10.28 ± 1.18 mmHg in group D ($P = 0.003$) (Table 2). It showed that there were significant differences between groups A and B ($P = 0.017$)

and groups C and D ($P = 0.026$).

Table 2. Portosystemic gradient changes in the two groups

Groups	PSG (mmHg)		<i>t</i> value	<i>P</i> value
	Before	After		
Group A	24.58±2.41	15.72±1.04	11.48	0.012
Group B	25.37±2.54	11.27±2.04	14.25	0.004
	(<i>T</i> value) 0.649	6.382		
	(<i>P</i> value) 0.483	0.026		
Group C	25.12±3.16	16.15±1.37	12.43	0.016
Group D	24.48±3.24	10.28±1.18	15.47	0.003
	(<i>T</i> value) 0.367	5.734		
	(<i>P</i> value) 0.534	0.017		

There are differences before and after transjugular intrahepatic portosystemic shunt in the four groups: group A compared with B, and group C compared with D. PSG: Portosystemic gradient.

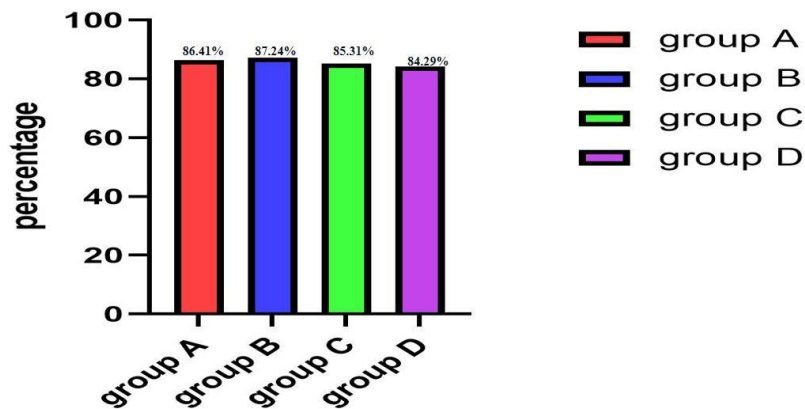
None of the patients died within 30 d after TIPS placement, with an early survival rate of 100%. None of the patients in groups A and B had recurrent bleeding within the first week. The symptoms of ascites in 198 (91.24%) patients in group C and 161 (93.60%) in group D disappeared or were relieved within the first week, without paracentesis, and there was no significant difference between the groups ($P = 0.327$).

During 3-years' follow-up, the total primary unassisted patency rates in groups A and B were 86.41% versus 87.24% ($\chi^2 = 4.486$, $P = 0.257$), and in groups C and D were 85.31% versus 84.29% ($\chi^2 = 4.529$, $P = 0.248$), with no significant differences (Figure 1).

Figure 1. Total primary unassisted patency rates of four groups. The total primary unassisted patency rates were not significantly different.

批注 [MedE-QC4]: 图表应统一放到文后，为何又放回文内？图说明应放到图下方。

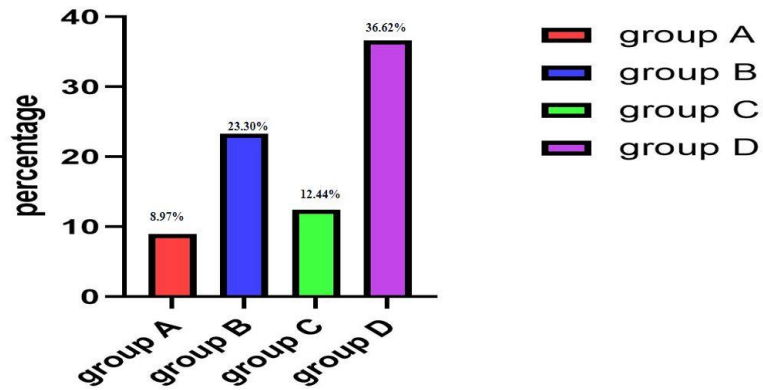
Primary unassisted patency rate



Forty-three (8.97%) patients in group A, 96 (23.30%) in group B, 27 (12.44%) in group C and 63 (36.62%) in group D developed hepatic function compromise after TIPS placement. The probability of total hepatic impairment within 3 years differed significantly between groups A and B ($\chi^2 = 11.352$, $P = 0.005$) and groups C and D ($\chi^2 = 13.758$, $P = 0.002$) (Figure 2). Mean aspartate transaminase, alanine transaminase, and total bilirubin concentrations were elevated, albumin levels decreased, and prothrombin time was prolonged compared with pre-TIPS.

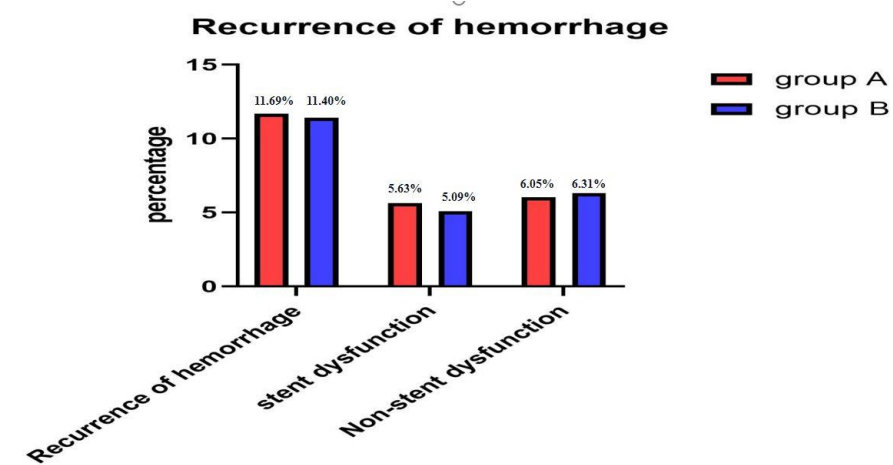
Figure 2. Hepatic function compromise after transjugular intrahepatic portosystemic shunt. The probability of total hepatic impairment differed significantly between groups A and B, and C and D.

Hepatic function compromise



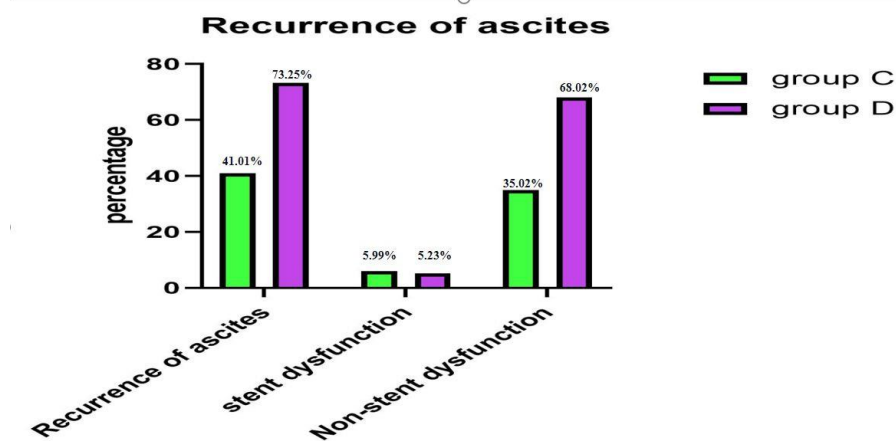
At the end of follow-up, 56 (11.69%) patients in group A and 47 (11.40%) in group B had recurrent variceal bleeding, which was not a significant difference ($\chi^2 = 7.062$, $P = 0.374$) (Figure 3).

Figure 3. Recurrent variceal bleeding after transjugular intrahepatic portosystemic shunt. Patients in groups A and B had recurrent variceal bleeding, and there was no significant difference between the groups.



There were 89 (41.01%) patients in group C and 126 (73.25%) in group D with recurrent ascites, which was a significant difference ($\chi^2 = 14.493$, $P = 0.006$) (Figure 4).

Figure 4. Recurrent ascites after transjugular intrahepatic portosystemic shunt of groups C and D. Patients in groups C and D had recurrent ascites, with a significant difference between the groups.



Of these, 27 (5.63%) patients in group A, 21 (5.09%) in group B, 13 (5.99%) in group C and nine (5.23%) in group D were caused by stent dysfunction, and after stent revision, the symptoms disappeared, and there was no significant difference between the groups ($\chi^2 = 834$, $P = 0.358$; $\chi^2 = 4.574$, $P = 0.375$).

The bleeding in patients in groups A and B that was not caused by stent dysfunction was relieved after medical treatment. However, 76 (35.02%) patients in group C and 117 (68.02%) in group D was not caused by stent graft dysfunction but rather hepatic dysfunction and hypoalbuminemia, which differed significantly between the two groups ($\chi^2 = 13.356$, $P = 0.006$). After medication and albumin supplementation, the symptoms recurred many times (Table 3).

Table 3. Outcomes of symptoms in the four groups

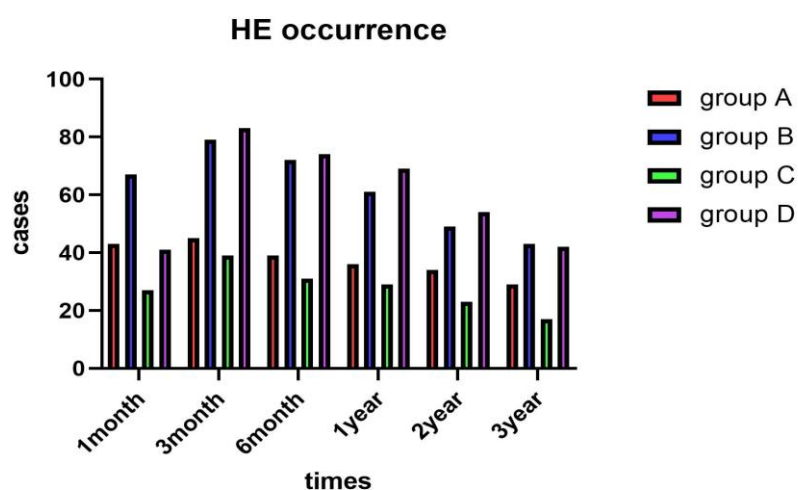
Symptoms	Group A	Group B	χ^2	P	Group C	Group D	χ^2	P
Ascites within 1wk	/	/		/	198(198/217, 91.24%)	161(161/172, 93.60%)	0.327	
Hemorrhage within 1 wk	000	000		000	/	/		/
Primary unassisted patency rate	86.41%	87.24%	4.486	0.257	85.31%	84.29%	4.529	0.248
Hepatic function compromise	43(43/479, 8.97%)	96(96/412, 23.30%)	11.352	0.005	27(27/217, 12.44%)	63(63/172, 36.62%)	13.758	0.002
Recurrence of hemorrhage	56(56/479, 11.69%)	47(47/412, 11.40%)	7.062	0.374	/	/	/	/
stent dysfunction	27(27/479, 5.63%)	21(21/412, 5.09%)	6.834	0.358	/	/	/	/
Non-stent	29(29/479)	26(26/412)	6.4	0.36	/	/	/	/

dysfunction	, 6.05%)	6.31%)	86	2								
Recurrence of	/	/	/	/	89(89/217,	126(126/1	14.	0.00				
ascites					41.01%)	72,73.25%)	493	6				
stent	/	/	/	/	13(13/217,	9(9/172,	4.5	0.37				
dysfunction					5.99%)	5.23%)	74	5				
Non-stent	/	/	/	/	76(76/217,	117(117/1	13.	0.00				
dysfunction					35.02%)	72,68.02%)	356	6				

Symptoms of variceal bleeding in groups A and B disappeared within 1 wk, and symptoms of ascites in groups C and D disappeared or were relieved within 1 wk without paracentesis, and total primary unassisted patency rates were not significantly different. The probability of total hepatic impairment and recurrent symptoms was significantly different between the groups.

During the 3-year follow-up period, 46 (9.60%) patients in group A, 67 (16.26%) in group B, 47 (21.65%) in group C and 69 (40.11%) in group D developed HE, and the incidence of HE in group A compared with group B, and group C compared with group D differed significantly ($\chi^2 = 7.932$, $P = 0.016$; $\chi^2 = 13.637$, $P = 0.007$, respectively). There were significant differences in the occurrence of HE between groups A and B at 1 mo ($\chi^2 = 6.463$, $P = 0.027$), 3 mo ($\chi^2 = 5.0368$, $P = 0.023$), 6 mo ($\chi^2 = 6.473$, $P = 0.017$), 1 year ($\chi^2 = 4.538$, $P = 0.027$), 2 years ($\chi^2 = 5.452$, $P = 0.026$) and 3 years ($\chi^2 = 5.467$, $P = 0.028$). There were also significant differences in HE occurrence between groups C and D at 1 mo ($\chi^2 = 14.673$, $P = 0.014$), 3 mo ($\chi^2 = 17.478$, $P = 0.009$), 6 mo ($\chi^2 = 13.957$, $P = 0.011$), 1 year ($\chi^2 = 14.576$, $P = 0.014$), 2 years ($\chi^2 = 11.476$, $P = 0.013$) and 3 years ($\chi^2 = 8.473$, $P = 0.017$) (Figure 5).

Figure 5. Incidence of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. The incidence of HE differed significantly in group A compared with group B, and in group C compared with group D at different times. HE: hepatic encephalopathy.



The incidence of HE in the four groups showed a downward trend. After drug treatment, the symptoms disappeared in patients with covert and grade II HE. In patients with grade III or IV HE, the symptoms disappeared after shunt reduction, but five patients who underwent shunt reduction still had hepatic myelopathy (Table 4).

Table 4. Hepatic encephalopathy occurrence in the four groups

Time	Group	HE occurrence		Occurrence rate (%)	χ^2	<i>P</i>
		Yes	No			
1 mo	A	43	436	8.97	6.463	0.027
	B	67	345	16.26		
	C	27	190	12.44	14.673	0.014
	D	41	131	23.83		
3 mo	A	45	434	9.39	5.368	0.023
	B	79	333	19.17	17.478	0.009
	C	39	178	17.97		

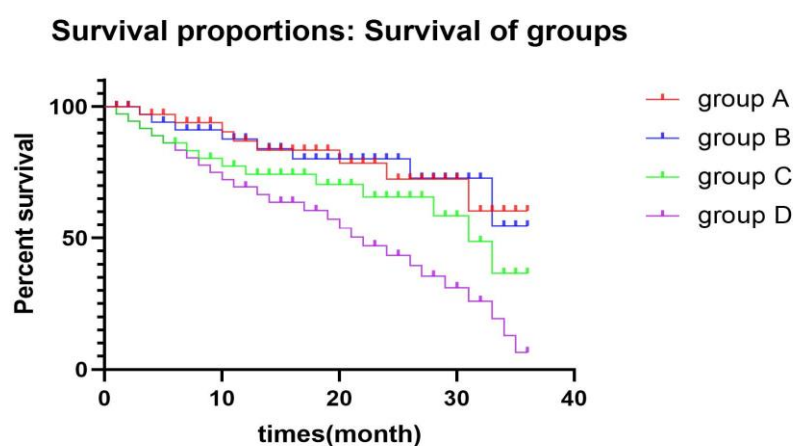
6 mo	D	83	89	48.25	6.473	0.017
	A	39	440	8.14		
	B	72	340	17.47		
	C	31	186	14.28		
1 yr	D	74	98	43.02	13.957	0.011
	A	36	443	7.51		
	B	61	351	14.80		
	C	29	188	13.36		
2 yr	D	69	103	40.11	14.576	0.014
	A	34	445	7.09		
	B	49	363	11.89		
	C	23	194	10.59		
3 yr	D	54	118	31.39	11.476	0.013
	A	29	443	6.14		
	B	43	369	10.43		
	C	17	155	9.88		
Total HE rate	D	42	130	24.41	8.473	0.017
	A	46	433	9.60		
	B	67	158	16.26		
	C	47	170	21.65		
	D	69	103	40.11	13.637	0.007

There were significant differences in incidence of HE in group A compared with groups B-D at 1, 3, 6 and 9 , mo, and 1, 2 and 3 years ($P < 0.05$). HE: Hepatic encephalopathy.

During 3 years' follow-up, 262 patients in group A, 234 in group B, 189 in group C and 160 in group D were lost to follow-up. The total survival rates were no different between groups A and B ($\chi^2 = 3.376$, $P = 0.369$, log-rank test), but there were

significant differences between groups C and D ($\chi^2 = 13.582$, $P = 0.014$, log-rank test) (Figure 6).

Figure 6. The survival rates of four groups. The total survival rates were not different between groups A and B, but differed significantly between groups C and D.



The 3-mo, 6-mo, and 1-, 2-, and 3-year survival rates were different between groups A and B ($\chi^2 = 5.368$, $P = 0.425$; $\chi^2 = 4.557$, $P = 0.436$; $\chi^2 = 4.562$, $P = 0.427$, $\chi^2 = 5.487$, $P = 0.382$, and $\chi^2 = 4.582$, $P = 0.375$, respectively); and significantly different between groups C and D ($\chi^2 = 13.364$, $P = 0.012$; $\chi^2 = 12.463$, $P = 0.013$; $\chi^2 = 12.568$, $P = 0.016$; $\chi^2 = 11.467$, $P = 0.017$, and $\chi^2 = 10.367$, $P = 0.027$, respectively). Four hundred and forty-nine patients died of multiorgan failure, 127 of hepatic tumor, and 298 of other causes (Table 5).

Table 5. Survival at 3 and 6 mo, and 1, 2 and 3 years

Time	Group	Survival		Survival rate (%)	χ^2	P
		Yes	No			
3 mo	A	470	9	98.12	5.368	0.425

		B	401	11	97.33	13.364	0.012
		C	184	33	84.79		
		D	127	45	73.83		
	6 mo	A	442	37	92.27	4.557	0.436
		B	381	31	92.47		
		C	162	55	74.65	12.463	0.013
		D	107	65	62.20		
		A	397	82	82.88		
	1 yr	B	335	77	81.31	4.562	0.427
		C	117	100	53.91		
		D	65	107	37.79		
	2 yr	A	293	186	61.16	5.487	0.382
		B	245	167	59.46		
		C	59	158	27.18	11.467	0.017
		D	26	146	15.11		
3 yr		A	229	250	47.80	4.582	0.375
		B	193	219	46.84		
		C	32	185	14.74	10.367	0.027
		D	16	156	9.30		
Total survival rate		A	217	262	45.30	3.376	0.369
		B	178	234	43.20		
		C	28	189	12.90	13.582	0.014
		D	12	160	6.97		

Survival rates showed no significant differences between groups A and B ($P > 0.05$), but there were significant differences between groups C and D.

DISCUSSION

During the TIPS procedure, measuring PSG is an important step because reducing

PSG can achieve good clinical results, in which a conduit is constructed within the liver between the systemic venous and portal systems, with the aim of decreasing portal systemic pressure^[14]. However, too low portal pressure can lead to some complications, and to avoid the recurrence of bleeding and uncontrolled ascites induced by excess reduction of portal vein pressure, appropriate PSG levels are required^[15].

Most guidelines recommend^[16,17] that the upper threshold of the post-TIPS PSG for a patient with variceal bleeding is < 12 mmHg or 50% of baseline, and the AASLD practice guidelines suggest a gradient of ≤ 8 mmHg^[18]. Most centers presently use the thresholds for TIPS procedures.

The complications of TIPS are classified as related to the TIPS procedure itself, the stent, portosystemic shunting, etc.^[19]. Among them, HE and deterioration of liver function, as complications related to portosystemic shunting, are associated with reduced PSG. Some of the patients with low PSG after TIPS have complications such as worsening of HE, which causes multiple admissions to hospital and increased liver enzymes and bilirubin, even though they are ultimately medically controlled^[20].

This creates a paradoxical dilemma in which low PSG results in complications such as severe HE or liver function failure, and inappropriate reduction of PSG also leads to recurrence of symptoms of portal hypertension, such as variceal bleeding and ascites. The current concept of small balloon expansion is intended to reduce PSG appropriately to reduce portal hypertension without associated serious complications^[21].

Self-expandable stents may continue to dilate until achieving their nominal diameter^[22]. This means that if PSG is 11 mmHg after dilating a 10-mm stent to only 8 mm, the stent may continue to self-dilate until reaching ~10 mm in diameter, leading to a further decrease in PSG and an increased risk of HE. How frequently this spontaneous expansion is clinically relevant is a matter of debate, but certainly represents a limitation. This led to a further technical improvement, the controlled-expansion stents, that cannot spontaneously dilate over preset limits. More crucially, the exact reduction of PSG is unknown.

However, we do not have an answer for simple questions such as how large the shunt should be, or what PSG reduction should be targeted to prevent recurrent bleeding or ascites during TIPS. PSG should be decreased to ≤ 12 mmHg, or by $> 50\%$ of baseline (which in most cases means < 12 mmHg) to prevent the complications of portal hypertension^[23]. This comes from observations that recurrent bleeding and ascites occurred almost exclusively when patients had a PSG of at least 12 mmHg after TIPS^[24].

A study has suggested that despite a traditional PSG reduction to below 12 mmHg or $>50\%$ of baseline, a PCG decrease to 14 mmHg or $>30\%$ of baseline would be appropriate when uncovered stents are used^[25]. This goal is achieved in a large proportion of patients with small diameter TIPS such as 7 or 6 mm dilated shunts that are likely to result in less worsening of portosystemic shunting and hence a lower likelihood of severe HE and post-TIPS liver failure^[26]. Of note, in high-risk situations, such as refractory ascites, the recent EASL guidelines recommended small diameter TIPS, although not as small as 6 mm^[27].

It has been shown that complementing a small diameter TIPS with drugs can be converted into a satisfactory one by adding propranolol, even at low doses^[28]. The synergistic effect of combining two different mechanisms decreases PSG by bypassing liver resistance to portal flow, and propranolol decreases PSG by reducing splanchnic blood flow. This approach achieves good clinical results and lower incidence of HE. Post-TIPS HE is a complex condition that is determined by TIPS diameter and many nonhemodynamic factors. Age, degree of liver and kidney failure, chronic inflammation, urease-producing intestinal bacteria, bacterial translocation and malnutrition/sarcopenia, are other important factors that can modulate the therapeutic effect^[29]. Several of them are associated with post-TIPS HE and survival^[30]. Therefore, appropriate reduction of PSG can reduce the occurrence of TIPS-related complications, such as HE. Combined with drugs, if good clinical results are achieved, it is not necessary to reduce PSG too low to produce higher TIPS-related complications.

Based on the above, we hypothesize that for patients with gastrointestinal

bleeding and refractory ascites requiring TIPS, one-third reduction of PSG of the baseline is appropriate, which was supplemented by drug-lowering portal pressure therapy. We should reduce portal hypertension as much as possible, achieve good therapeutic results, and minimize complications, especially the incidence of HE and compromise of liver function.

In this study, we divided the patients with gastrointestinal bleeding and refractory ascites who required TIPS into four groups, to make a detailed evaluation of the clinical effects. The results showed that, as for patients with variceal bleeding who required TIPS placement, PSG reduced by one third compared with < 12 mmHg baseline, the two groups had a similar effect on variceal bleeding, but the incidence of HE and compromise of liver function differed. During the TIPS procedure, to achieve the goal of reducing PSG by one third, a small balloon was required for gradual dilatation, slowly from 6 mm to 8 mm, which would also be useful for the controlled expansion stent that has been introduced in clinical practice. During the dilatation process, the operating procedure will be slower, PSG measurement will take ~30 min longer, and two more balloons will be used, resulting in increased cost. However, the cost should be worthwhile in comparison to the cost of complications.

For patients with refractory ascites who required TIPS, the incidence of HE and compromise of liver function were obviously different. In the short term, the symptoms of ascites disappear or subside, but in the medium and long term, PSG drops less, ascites still recurs in some cases, and drug therapy is necessary. Post-TIPS HE is a complex condition that is determined by TIPS and many nonhemodynamic factors. The liver function reserve of patients with refractory ascites and survival rate are poor, and the patients are prone to hypoproteinemia and electrolyte disturbances, which are likely to cause recurrence of ascites and require drug treatment^[31]. In this circumstance, to reduce TIPS-related complications and liver function damage, it is not necessary to reduce PSG drastically, one-third PSG reduction plus drug therapy would be appropriate.

As a retrospective analysis, this study had several limitations. First, randomized

controlled trials are needed to verify our results. Second, to achieve the goal of reducing the PSG by one third, it requires gradual balloon dilatation from 6 mm to 8 mm, the operating procedure will be slower, PSG measurement will take ~30 min longer, and two more balloons will be used, resulting in increased cost. Finally, our hypothesis needs to be validated by a comparative study on the results of small balloon dilatation.

CONCLUSION

This multicenter retrospective study showed that patients who underwent TIPS creation with PSG reduced to one third of baseline or to < 12 mmHg or 50% of baseline had similar successful clinical outcomes. However, PSG reduced to < 12 mmHg had a lower rate of HE and liver compromise. Given that the PSG will become more controllable in the future with the advent of controllable stents, we believe that our concept is worthy of clinical application.

ARTICLE HIGHLIGHTS

Research background

Transjugular intrahepatic portosystemic shunt (TIPS) is currently used for the treatment of complications of portal hypertension. Measuring the portosystemic pressure gradient (PSG) is important during the TIPS procedure. Reducing PSG can achieve good clinical results, but when PSG is too low, TIPS leads to many complications. Factors associated with post-TIPS complications depend mainly on portocaval pressure gradient and the volume of blood shunted through the liver. Several guidelines recommend that PSG reduced to 12 mmHg after TIPS creation achieves better clinical outcomes. However, in that situation, the incidence of HE was higher in clinical practice. There is still no suitable criterion for a reduction in PSG, which can both reduce PSG and maximize clinical results and minimize HE, and few data are available to calculate an appropriate PSG value.

Research motivation

We report our multicenter retrospective study to compare the rate of HE and clinical results of reducing PSG by one third of baseline with PSG reduction to < 12 mmHg in patients with portal hypertension who required TIPS placement for portal-hypertension-related complications of variceal bleeding and ascites.

Research objectives

The main objective was to establish that patients who underwent TIPS PSG reduced by one third of baseline compared with PSG reduced to < 12 mmHg of baseline were associated with similar successful clinical outcomes.

Research methods

We hypothesized that reducing PSG by one third of baseline compared with < 12 mmHg of baseline would result in a lower rate of HE and liver compromise. The patients were divided into four groups: group A (variceal hemorrhage and PSG reduced by one third, $n = 479$); group B (variceal hemorrhage and PSG reduced to < 12 mmHg, $n = 412$); group C (refractory ascites and PSG reduced by one third, $n = 217$); and group D (refractory ascites and PSG reduced to < 12 mmHg, plus medication, $n = 172$). The clinical outcomes, rate of HE, recurrent variceal bleeding and ascites, and mortality were compared and analyzed between the groups. Data measurements results of the four groups were normally distributed, and expressed as mean \pm standard deviation, and their differences were determined using t test. Categorical variables were expressed as frequencies and compared using χ^2 test, and their differences among the four groups were determined by one-way ANOVA. A P value of less than 0.05 was considered significant. The statistical analyses were performed with SPSS version 22.0 (SPSS, Armonk, NY, USA).

Research results

This study showed that during TIPS placement, when PSG was reduced by one third compared with < 12 mmHg of baseline, recurrent bleeding showed no significant

difference, but recurrent ascites did differ significantly. The probability of total hepatic impairment within 3 years was significantly different. During follow-up, the total incidence of HE differed significantly. The total survival rates were no different for the variceal bleeding patients, but were significantly different for the patients with refractory ascites.

Research conclusions

We found that patients who underwent TIPS PSG reduced by one third of baseline compared with reduced to < 12 mmHg of baseline were associated with similar successful clinical outcomes, but PSG reduced by one third resulted in a lower rate of HE and liver compromise.

Research perspectives

Measuring PSG is important during the TIPS procedure. Reducing PSG can achieve good clinical results, but when PSG is too low, TIPS leads to many complications. Reduction of PSG by one third of baseline is recommended to decrease the probability of liver function impairment after TIPS, decrease the incidence of HE, and increase survival in patients with refractory ascites.

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