Pre-emptive TIPS for the treatment of bleeding from gastric fundal varices: Results of a randomised controlled trial

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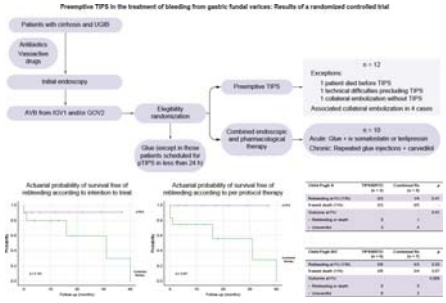
Graphical abstract



Highlights

- The study investigated whether an early decision for TIPS could improve the outcome of patients bleeding from fundal varices, a situation that carries a high risk of rebleeding and death.
- Patients treated with a pre-emptive TIPS (associated or not with collateral obliteration) had better outcome compared with those treated with standard therapy (drug therapy plus intravariceal glue injection) when analysed as per protocol, but failed to reach statistical significance on intent to treat, mainly because of the low number of patients in the study.
- The improved outcomes resulted from reduced rates of rebleeding and death in patients with Child-Pugh B and C scores, because prognosis in patients with Child-Pugh A scores was good irrespective of the treatment received.
- Our findings support the use of pre-emptive TIPS in patients with Child-Pugh B and C scores with acute bleeding from fundal varices, but are not conclusive because of the low number of patients included.

Impact and implications

The first-line treatment of gastric fundal varices (GOV2 and/or IGV1) is the combination of pharmacological therapy and endoscopic obliteration with glue. TIPS is considered the main rescue therapy. Recent data suggest that, in patients at high-risk of dying or rebleeding (Child-Pugh C or B scores + active bleeding at endoscopy) from esophageal varices, the use of pTIPS, performed during the first 72 h from admission, results in an increased rate of control of bleeding and survival compared with combined endoscopic and pharmacological therapy. Herein, we present a randomised controlled trial comparing pTIPS with combined endoscopic (injection of glue) and pharmacological therapy (first, somatostatin or terlipressin; carvedilol after discharge) in the treatment of patients bleeding from GOV2 and/or IGV1. Although we were not able to include the calculated sample size because of the scarcity of these patients, our results show that the use of pTIPS is associated with a significantly higher actuarial rebleeding-free survival when analysed as per protocol. This is because of the greater efficacy of this treatment in patients with Child-Pugh B or C scores.

https://doi.org/10.1016/j.jhepr.2023.100717

Short communication

JHEP|Reports

Pre-emptive TIPS for the treatment of bleeding from gastric fundal varices: Results of a randomised controlled trial

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JHEP Reports **2023.** https://doi.org/10.1016/j.jhepr.2023.100717

Background & Aims: Bleeding from gastric fundal varices (isolated gastric varices type 1/gastroesophageal varices type 2) represents a major problem because of a high incidence of rebleeding and death with standard-of-care therapy (endoscopic obliteration with tissue adhesives plus pharmacological therapy). Transjugular intrahepatic portosystemic shunts (TIPSs) are recommended as a rescue therapy. Pre-emptive 'early' TIPS (pTIPS) significantly improves control of bleeding and survival in patients at high-risk of dying or rebleeding from esophageal varices.
Methods: This randomised controlled trial investigate whether the use of pTIPS improves rebleeding-free survival in patients with gastric fundal varices (isolated gastric varices type 1 and/or gastroesophageal varices type 2) compared with standard therapy.
Results: The study did not achieve the predefined sample size because of low recruitment. Nevertheless, pTIPS (n = 11) was more effective compared with combined endoscopic and pharmacological therapy (n = 10) in improving rebleeding-free survival (per protocol analysis: 100 *vs.* 28%; p = 0.017). This was mainly because of a better outcome in patients with Child-Pugh B or C scores. There were no differences in serious adverse events or in the incidence of hepatic encephalopathy among the different cohorts.
Conclusion: The use of pTIPS should be considered in patients with Child-Pugh B or C scores bleeding from gastric fundal varices.
Impact and implications: The first-line treatment of gastric fundal varices (GOV2 and/or IGV1) is the combination of pharmacological therapy and endoscopic obliteration with glue. TIPS is considered the main rescue therapy. Recent data suggest that, in patients at high-risk of dying or rebleeding (Child-Pugh C or B scores + active bleeding at endoscopy) from esophageal varices, the use of pTIPS, performed during the first 72 h from admission, results in an increased rate of control of bleeding and survival compared with combined endoscopic and pharmacological therapy. Herein, we present a randomised controlled trial comparing pTIPS with combined endoscopic (injection of glue) and pharmacological therapy (first, somatostatin or terlipressin; carvedilol after discharge) in the treatment of patients bleeding from GOV2 and/or IGV1. Although we were not able to include the calculated sample size because of the scarcity of these patients, our results show that the use of pTIPS is associated with a significantly higher actuarial rebleeding-free survival when analysed as per protocol. This is because of the greater efficacy of this treatment in patients with Child-Pugh B or C scores.

Introduction

Bleeding from gastric fundal varices accounts for ~15% of overall variceal bleedings, but carries a higher mortality compared with bleeding from esophageal varices (including gastroesophageal varices [GOV] type 1 varices) (20–30% *vs.* 15% over 6 weeks). Baveno VII experts agreed that endoscopic therapy with tissue adhesives is recommended for acute bleeding from isolated gastric varices type 1 (IGV1) and GOV2 that extend beyond the cardia.[1] However, standard-of-care therapy is associated with rebleeding in over one-third of patients after reappearance of the varices. TIPS, with or without collateral embolisation, is recommended as rescue therapy after rebleeding. Several observational studies and meta-analysis have addressed the use of TIPS as initial therapy in patients bleeding from fundal varices. In the meta-analysis by Alqadi and coworkers, including 209 patients and excluding GOV1 bleeders or use of bare-metal stents for

Keywords: Cirrhosis; Portal hypertension; Tissue adhesive injection; Non-selective beta-blockers.
Received 15 December 2022; received in revised form 15 February 2023; accepted 18 February 2023; available online 1 March 2023
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TIPS, 15% of patients developed variceal rebleeding and 21% rebleeding resulting from any cause.[2] The association of variceal embolisation reduced the incidence of overall rebleeding to 16% (*vs*. 26% in those patients without collateral embolisation). Shah and coworkers presented a comparative single-centre study including 40 patients treated with the combined use of TIPS and collateral embolisation (n = 18) or TIPS alone (n = 22). The results showed a significantly higher rate of eradication of the varices with TIPS plus collateral embolisation and a trend toward reduced variceal rebleeding.[3] Lo and coworkers showed that TIPS (not pre-emptive but as secondary prophylaxis after initial control of gastric bleeding) proved more effective compared with glue injection in preventing rebleeding from gastric varices.[4] Finally, although pre-emptive TIPS (pTIPS) was more effective compared with combined endoscopic and pharmacological therapy in the prevention of both rebleeding and death in high-risk patients bleeding from esophageal varices, the role of pTIPS (± collateral embolisation) in patients with gastric fundal variceal bleeding has not been adequately investigated.

Patients and methods

The aim of this randomised, multicentre, controlled trial in patients bleeding from IGV1 and/or GOV2 was to investigate the efficacy of pTIPS (from 1 to 5 days after admission), combined or not with collateral embolisation, according to the results of immediate post-TIPS portography *vs*. standard of care. Both groups had similar initial therapy using vasoactive drugs + endoscopic variceal obturation with tissue adhesive. The main end-point was rebleeding-free survival of at 1 year of follow-up or until the last available control. Secondary objectives were reduced incidence of rebleeding and survival at 6 weeks and during the overall follow-up.

The study was conducted in accord with the Declaration of Helsinki and was approved by the ethical committee of the nine participating hospitals and by the Spanish Ministry of Health and fulfilled the guidelines of Good Clinical Practice in clinical trials. The study was registered in an independent clinical trial database (www.clinicaltrials.gov ID: NCT02364297). Written informed consent was obtained from each participant or legal representative or next of kin depending on the clinical condition of the patient.

The calculated sample size assumed an efficacy of pTIPS of 83% and 53% for the combined pharmacological and endoscopic therapy, with alpha = 0.05 and beta = 0.2 for the 30 patients in each group.

Results

Twenty-five patients were included in a 4-year inclusion period from give different treatment centres. The low incidence of fundal bleeding and technical aspects regarding pTIPS precluded the inclusion of the initially calculated sample size. One of the randomised patients was removed from the study as a result of a protocol violation because of identification of portal hypertension gastropathy as the cause of bleeding at second endoscopy to perform glue sclerotherapy.

Thus, we included 21 patients with a median age of 63 years (ranging from 34 to 73 years), 50% with alcoholic cirrhosis and a moderate-to-severe liver insufficiency (median Child-Pugh score: 8; ranging from 6 to 10). IGV1 was the cause of bleeding in 12 patients, whereas bleeding resulted from GOV2 in the remaining nine patients. All the included patients received vasoactive therapy and antibiotics from admission. Table 1 compares the two groups according to the randomised therapy received (TIPS n = 11; standard of care n = 10). Table 2 shows the same details according to per protocol analysis.

Table 1. Demographic and clinical variables in the overall series of patients and according to the Intention to Treat.

Variable	Pre-emptive TIPS (n = 11)	Standard of care (n = 10)	*p* value*
Age, years†	59 ± 11	64 ± 7	0.29
Sex (male/female), n	8/3	8/2	0.70
Etiology of cirrhosis (HCV/alcohol/HCV + alcohol/NASH/other), n	1/5/1/2/2	3/4/1/2/0	0.55
Cause of bleeding (IGV1/GOV2), n	5/6	7/3	0.26
Shock at admission (yes/no), n	8/3	4/6	0.13
Child-Pugh score at admission†	7.3 ± 1.9	7.7 ± 1.1	0.60
Child-Pugh class (A/BC), n	4/7	4/6	0.86
Haematocrit at admission (%)†	26 ± 6	28 ± 8	0.57
5-day failure (yes/no), n	1/10	2/8	0.47
Rescue therapy (yes/no), n	0/11	2/8	0.12
6-week death (yes/no), n	1/10	2/8	0.48
Outcome at 6 weeks, n:			0.48
Died or transplanted	1	2	
Alive without orthotopic liver transplantation	10	8	
Follow-up (months)†	14 ± 12	14 ± 13	0.93
Rebleeding at follow-up (yes/no), n	0/10‡	2/8	0.13
Outcome follow-up, n:			0.055
Rebleeding or death	1	5	
Uneventful	10	5	
Patients with SAE (yes/no), n	5/6	5/5	0.83
SAE (description), n:			
ACLF	2	1	
HE	2	4	
Portopulmonary syndrome	1	0	

Quantitative data were analyzed by Student's *t* test and qualitative data using Chi-square tests except for the outcome follow-up, for which a Fischer exact test was used.
ACLF, acute-on-chronic liver failure; AVB, acute variceal bleeding; GOV2, gastroesophageal varices type 2; HE, hepatic encephalopathy requiring admission; IGV1, isolated gastric varices type 1; NASH, non-alcoholic steatohepatitis; SAE, serious adverse event; TIPS, transjugular intrahepatic portosystemic shunt.
* Levels of significance: $p < 0.05$.
† Mean ± SD.
‡ Excluding one patient who died before the 5-day period.

Table 2. Demographic and clinical variables in the overall series of patients according to per protocol analysis.

Variable	Pre-emptive TIPS (n = 9)	Standard of care (n = 12)	*p* value*
Age, years†	59 ± 12	63 ± 7	0.42
Sex (male/female), n	6/3	10/2	0.37
Etiology of cirrhosis, n (HCV/alcohol/HCV + alcohol/NASH/other)	1/3/1/2/2	3/6/1/2/0	0.46
Cause of bleeding (IGV1/GOV2), n	4/5	8/4	0.31
Shock at admission (yes/no), n	6/3	6/6	0.44
Child-Pugh class (A/BC) at admission, n	3/6	5/7	0.69
Child-Pugh score at admission†	7.2 ± 1.6	7.8 ± 1.3	0.42
Haematocrit at admission†	26 ± 7	28 ± 7	0.55
5-day failure (yes/no), n	0/9	3/9	0.10
Rescue therapy (yes/no), n	0/9	2/10	0.19
6-week death (yes/no), n	0/9	3/9	0.105
Outcome at 6-week, n:			0.105
Died or OLT	0	3	
Alive w/o OLT	9	9	
Follow-up (months)†	17 ± 11	12 ± 13	0.38
Rebleeding at follow-up (yes/no), n	0/9	5/7	0.027
Outcome follow-up, n:			0.017
Rebleeding or death	0	6	
Uneventful	9	6	
Patients with SAE (yes/no), n	4/5	5/7	0.89
SAE (description), n:			0.30
ACLF	2	1	
HE	1	4	
Portopulmonary syndrome	1	0	

Quantitative data were analyzed by Student's *t* test and qualitative data using Chi-square tests except for the outcome follow-up, for which a Fischer exact test was used.
ACLF, acute-on-chronic liver failure; AVB, acute variceal bleeding; GOV2, gastroesophageal varices type 2; HE, hepatic encephalopathy requiring admission; IGV1, isolated gastric varices type 1; NASH, non-alcoholic steatohepatitis; OLT, orthotopic liver transplantation; SAE, serious adverse event; TIPS, transjugular intrahepatic portosystemic shunt.
Excluding one patient who died before the 5-day period.
* Levels of significance: $p < 0.05$.
† Mean ± SD.

All 10 patients in the combined therapy group received endoscopic therapy (cyanoacrylate injection) and vasoactive drugs (initially somatostatin or terlipressin followed by propranolol or carvedilol at discharge and in the absence of refractory ascites and bradycardia <55 beats per minute). In the pTIPS group, three patients did not receive initial cyanoacrylate injection because TIPS was performed during the first 24 h following admission. One patient randomised to pTIPS died before TIPS could be performed (from massive bleeding despite the use of a Linton balloon); another patient did not receive TIPS because of technical difficulties (this patient was treated instead with combined endoscopic and pharmacological therapy); and in one case collateral vessels were embolised without the concomitant performance of TIPS (this patient was considered as having received pTIPS in both the randomisation and per protocol analyses because of the invasive character of the therapy). Four patients received collateral embolisation in addition to TIPS, in one case because of a final portal pressure gradient (PPG) >12 mmHg (13.5 mmHg) and, in the other three cases, because of post-TIPS portography showing persistent filling of large collaterals. PPG before pTIPS had a median value of 17 mmHg (ranging from 9 to 20 mmHg) and of 8.5 mmHg after pTIPS (range: 4.5–13.5 mmHg). pTIPS used polytetrafluoroethylene-covered stents (Gore-Viatorr prosthesis) dilated to either 8 or 10 mm in all cases. Median follow-up was 12 months (range 0 to 40 months).

On intent-to-treat analysis (Table 1), rebleeding-free survival was only just significantly higher in patients randomised to pTIPS compared with the control group (90% *vs.* 50%; p = 0.055). However, actuarial probability of rebleeding-free survival did not reach statistical significance (log-rank $p = 0.198$; Fig. 1A). Per protocol analysis showed that both overall rebleeding and rebleeding-free survival were significantly improved in the pTIPS group with the control group (100% *vs.* 50%; $p = 0.017$) (Table 2). The actuarial probability of survival without rebleeding was significantly higher in the pTIPS group compared with the control group (log-rank $p = 0.047$; Fig. 1B).

We repeated the analysis of the main end-point (rebleeding-free survival) excluding the patient treated with collateral embolisation without a concomitant pTIPS. In this analysis the results were the same as in the whole series [*i.e.* differences in outcomes between the two groups according to randomisation were not significant ($p = 0.051$), whereas a significant difference was observed when analysing patients as per protocol ($p = 0.017$].

Subanalysis according to Child-Pugh class showed that all patients with a Child-Pugh A score (n = 8) survived and all but one were free of rebleeding on follow-up, without significant differences between the two arms ($p = 0.28$). By contrast, among patients with Child-Pugh B/C scores (n = 13), only one patient in the pTIPS group *vs.* four patients in the standard-of-care group rebled or died on follow-up ($p = 0.053$). On per protocol analysis, there were no significant differences in the main outcome in patients with a Child-Pugh A score. However, no patient in the pTIPS group *vs.* five out of seven patients with Child-Pugh B/C scores receiving control therapy rebled or died on follow-up ($p = 0.008$).

There was no difference in serious adverse events leading to patient readmission during follow-up among the two groups, with two patients in the pTIPS group and four control patients developing overt hepatic encephalopathy. One patient in the pTIPS group developed portopulmonary syndrome.

Discussion

In patients bleeding from gastric fundal varices, TIPS, associated or not with collateral embolisation, has been recommended as rescue therapy in cases of failure of endoscopic therapy with

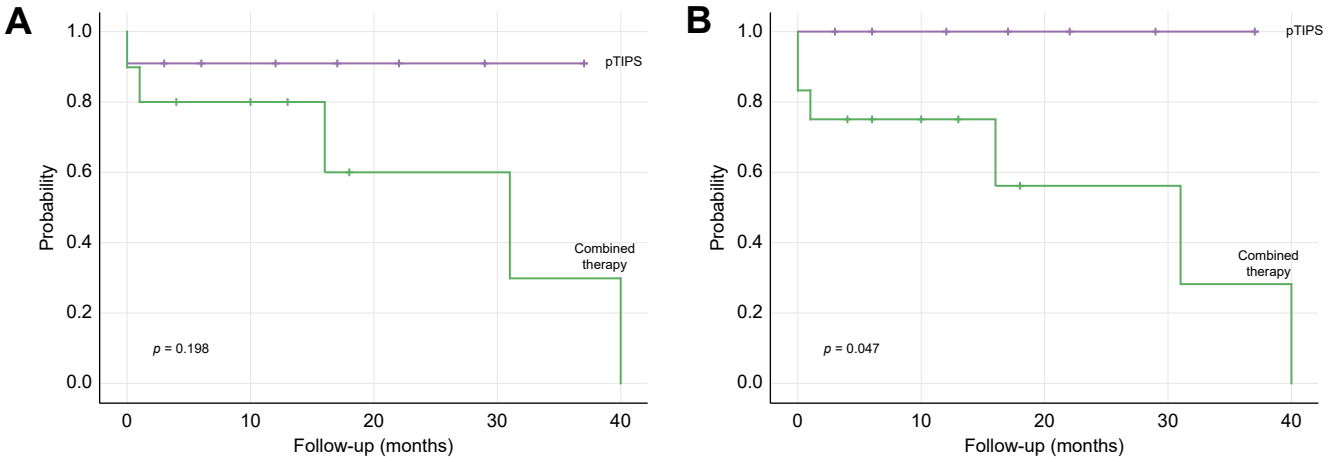

Figure 1. Actuarial probability of survival free of rebleeding (A) according to intention to treat (curves constructed with the Kaplan-Meier method and compared with the Mantel-Cox test), (B) according to per protocol analysis (curves constructed with the Kaplan-Meier method and compared with the Mantel-Cox test).

tissue adhesives plus pharmacological therapy (vasoactive drugs during the acute bleeding episode; non-selective beta-blockers thereafter).[1,5] Its role as a first-line therapy in acute gastric variceal bleeding has been suggested in single-centre studies and meta-analyses including low number of patients (largest: 209 patients).[3,6] Moreover, TIPS performed after initial control of gastric variceal bleeding (secondary prophylaxis) proved to be more effective compared with glue injection in the prevention of rebleeding from gastric varices.[4]

As far as we know, this is the first randomised controlled trial in Western countries comparing the standard-of-care therapy with pTIPS in fundal variceal bleeding. Standard-of-care therapy was the combination of endoscopic cyanoacrylate injection plus intravenous somatostatin or terlipressin, followed by repeated cyanoacrylate injection (until variceal obliteration) concomitantly with non-selective beta-blockers (carvedilol in our patients). Patients in the pTIPS group also received initially combined endoscopic and pharmacological therapy, followed by TIPS performed during days 1 to 5 post admission, except in the three patients, in whom pTIPS was performed during the first 24 h after admission (according to that specified in the protocol).

Our study faced more difficulties in recruitment than we had foreseen. This was mainly because of the scarcity of patients bleeding from IGV1 or GOV2. In fact, most previous studies used for estimating feasibility of recruitment included as gastric varices patients with GOV1, which is more frequent but behaves and should be treated as bleeding from esophageal varices according to Baveno VI and Baveno VII recommendations.[1,7] Another limitation in previous studies was the use of TIPS using bare stents, with much poorer outcomes compared with current covered stents. Moreover, patients randomised to pTIPS were not all treated on the first 2 days post admission (the ideal situation) but had to use the full bracket of 5 days in some centres because of difficulties in scheduling early TIPS. This is likely to add heterogeneity of outcomes, but closely reflects real life practice in many centres.[8] Patients were stratified according to the Child-Pugh score (*i.e.* Child-Pugh A or B/C). Thus, the two series were not different regarding the Child-Pugh score.

The main result of the study was that patients randomised to receive pTIPS showed a close to significant higher rebleeding-free survival compared with those randomised to receive combined pharmacological and endoscopic therapy. Given the low number of patients, the results should be considered supportive rather than strongly conclusive. In fact, the actuarial probability of being free of death or rebleeding did not reach statistical significance, except when using a per protocol approach. Nevertheless, the different outcomes in the two arms exceeded the assumptions used in the sample size calculation and are of undeniable clinical relevance.

Importantly, the benefit of pTIPS was limited to patients with Child-Pugh B or C scores. Therefore, as in bleeding from esophageal varices, pTIPS should probably be restricted to these patients, indicating that, contrary to our assumption, bleeding from gastric fundal varices does not change the indication for early TIPS per se.

The low number of patients included precluded any conclusion of whether adding variceal embolisation to pTIPS contributes to a higher efficacy of TIPS. However, a recently published randomised controlled trial showed that concomitant collateral embolisation did not significantly reduce the incidence of variceal rebleeding in patients with cirrhosis receiving TIPS for bleeding gastro-esophageal varices.[9]

Low numbers also precluded evaluation of the impact of therapy on ascites. However, the incidence of overt hepatic encephalopathy did not differ between the two groups. It may be that collateral embolisation, performed in half of the patients receiving pTIPS, contributed to the low incidence of hepatic encephalopathy in pTIPS-treated patients, as shown in another recent randomised controlled trial.[10] As already discussed above, the main limitation of our study was the low number of patients included. We initially planned to expand the duration of the trial to minimise this problem; however, this was not possible because of the Coronavirus 2019 pandemic. However, even in the context of the low number of patients included, this trial suggests that pTIPS is more effective compared with combined endoscopic and medical therapy in patients bleeding from GOV2 or IGV1 varices, without a significant increase in the incidence of hepatic encephalopathy, in analogy with that demonstrated for patients with cirrhosis bleeding from esophageal varices.

Abbreviations

ACLF, acute-on-chronic liver failure; AVB, acute variceal bleeding; GOV, gastroesophageal varices; HE, hepatic encephalopathy requiring admission; IGV1, isolated gastric varices type 1; NASH, non-alcoholic steatohepatitis; OLT, orthotopic liver transplantation; PPG, portal pressure gradient; pTIPS, pre-emptive transjugular intrahepatic portosystemic shunt; SAE, serious adverse event; TIPS, transjugular intrahepatic portosystemic shunt.

Financial support

This work was supported by grant number PI 043484 from the Fondo Sanitario de la Seguridad Social, Instituto de Salud Carlos III, Spain, and from the CIBERehd. The CIBERehd is an initiative of the Instituto de Salud Carlos III. The trial is registered at www.clinicaltrials.gov (NCT02364297).

Conflicts of interest

AE/CV: travel grant from Gore. JCGP: Cook advisory board member, travel grants from Gore and Mallinkrodt; JB: consultant/advisory board member for Astra Zeneca, BioVie, Boehringer Ingelheim, NovoNordisk, and Resolution Therapeutics.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors made substantial contributions and satisfy the criteria for authorship. Inclusion and follow-up of included patients: JCGP, EAT, CA, HM, and CV. AE was the principal investigator and, with JB, analyzed the results and prepared the manuscript.

Data availability statement

The data shown in this article are available from the corresponding author upon request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2023.100717.

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