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

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PROTOCOL OF STUDY

Preemptive TIPS in the treatment of bleeding from gastric fundal varices. RCT vs combined endoscopic and pharmacological therapy.

Short title: Preemptive TIPS in fundal variceal bleeding

Code: ET_VG15

Ethical committee Hospital Clínic: HCB/2014/0727

Clinical Trial PRS: NCT02364297

SUMMARY

Randomized controlled trial with a previously registered device.

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Design

Randomized, prospective, open, comparative and multicentric clinical trial.

Main end-point

To compare patients with liver cirrhosis and bleeding due to fundal varices (GOV2 or IGV1, see attached image) treated with conventional treatment (vasoactive drugs + obturation by injection of tissue adhesives) with respect to patients treated with conventional treatment + TIPS in the first 5 days regarding the probability of staying alive and free of recurrence of bleeding to the year of follow-up.

Patients

Patients of both genders, aged over 18 years, with liver cirrhosis and gastrointestinal bleeding due to fundal varices classified as GOV2 and/or IGV1.

Timetable and expected completion date.

The study inclusion period is expected to be approximately 24 months. Its total duration is estimated to be 30 months.

JUSTIFICATION, HYPOTHESIS AND OBJECTIVES

Justification

In recent years we have witnessed a very important advance in the treatment of acute variceal hemorrhage in liver cirrhosis. This progress has been reflected in a decrease in mortality related to this complication from 30 to 16%. And not only can we treat the haemorrhage episode more effectively when it occurs, we can also prevent its development. These statements are especially true when we refer to bleeding due to gastric varices,

especially in those of fundic location, the so-called GOV2 and IGV1 (1).

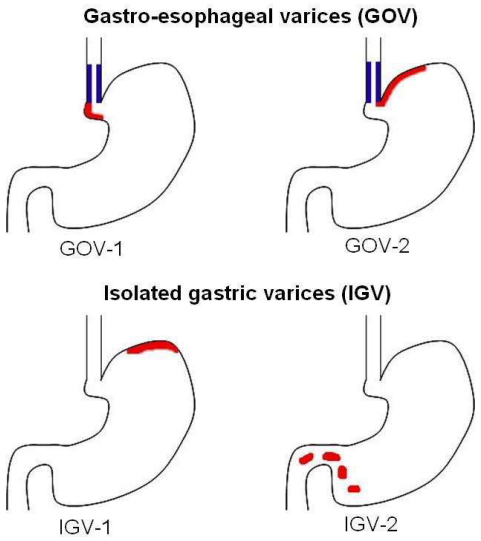

Fig. S1. Classification of varicose veins according to Sarin.

There were few studies focused specifically on this pathology, which does not allow to achieve reliably results (2). The pathophysiology of bleeding due to fundal varices is different, so it is not correct to extrapolate the data obtained in the treatment of esophageal varices, much more frequent, to define its management. Thus, esophagogastric varices GOV1, or subcardial prolongation of varicose veins, have an increase in their pressure more dependent on resistance than on flow. Gastric varices GOV2 and IGV1 (see attached image), usually have a large size and flow with low resistance, so that the pressure inside, which entails the rupture when exceeding a certain limit, depends more on the large blood flow they receive than on the resistance to that flow. This is because esophageal varices receive the flow of periesophageal collaterals, small vessels, while gastric varicose veins usually receive it from short gastric vessels, sometimes forming part of a large spontaneous spleno-renal shunt (3). From these physiopathological differences derives the fact that the endoscopic treatment of obliteration of the vessels that feed these collaterals (ligation or endoscopic sclerosis in the case of esophageal varices; obturation by injection of tissue glues in the case of gastric varicose veins) differed in terms of efficacy, i.e. it is much easier to block the flow of small vessels (periesophagic collaterals) than large vessels (short gastric vessels, splenorenal shunt).

To date, the available data mix results obtained in patients with GOV1 hemorrhage, with pathogenesis and treatment similar to esophageal varices, with that of GOV2 and IGV1, especially for the number of cases. Experts in the field of portal hypertension recommend

combined pharmacological and endoscopic treatment as a first choice in acute bleeding due to fundal varices (2,4,5).

The treatment of choice, therefore, combines vasoactive drugs (mostly somatostatin or terlipressin) with endoscopic treatment. Within the latter, published studies show that in the case of fundal varices, the endoscopic injection of tissue adhesives has a superior efficacy both to

sclerosis with other substances and to endoscopic ligation in the control of bleeding and in eradication of varices and in the prevention of haemorrhage recurrence. With this combined therapeutic strategy, acute bleeding control rates of 87-93% are achieved (5).

As already mentioned, the injection of tissue adhesives achieves the eradication of fundal varicose veins in a significant number of cases. However, about one-third of patients develop early or late rebleeding, which implies the application of rescue treatments (2,4,5). The salvage treatment in these cases is intrahepatic percutaneous portosystemic shunt, TIPS. The TIPS consist on performing a portosystemic anastomosis by percutaneous route with interventional radiology and guided by ultrasonography. In the first years of use of this technique, the main problem was the high risk of dysfunction due to stenosis or thrombosis of the intrahepatic stent. This problem, which affected almost all the TIPS carried out, was subsequently eliminated with the appearance of stents coated with polimers such as PTFE (6). Since its widespread use, TIPS dysfunction has become less of a problem.

However, TIPS still suffer from the same complications as conventional portosystemic anastomoses (although with much lower morbidity because it does not involve open surgery). The most serious problem we face is severe hepatocellular insufficiency due to hepatic ischemia in 10% of cases. In fact, TIPS derive portal vascularization towards the inferior vena cava obviating the sinusoidal circulation, so that the hep tic vascularization becomes dependent only and exclusively on the flow through the hepatic artery, not always sufficient. This is especially true in patients at high risk, with poor hepatocellular function, or in the context of a haemorrhage recurrence. On the other hand, the most frequent problem, although not so serious, is the development of hepatic encephalopathy secondary to the passage to the systemic circulation of all toxic products of splanchnic origin that escape hepatic metabolism. For hepatic

encephalopathy to appear, this increase in portosystemic shunting must be combined with a certain degree of hepatocellular insufficiency (6). The occurrence of severe hepatic encephalopathy after TIPS is always a medical dilemma, since reducing blood flow through

TIPS may resolve encephalopathy but would reappear the risk of the variceal hemorrhage.
In this sense, a recently published study showed that the performance of an early TIPS, within the first 72 hours after admission for bleeding, is not only able to increase the control of acute bleeding and survival at 42 days and at one year of follow-up, but also to reduce complications related to portal hypertension, namely ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, etc. (6). The authors contrast the beneficial results of performing a TIPS early with those of waiting for a hemorrhagic recurrence for the procedure. This is because early TIPS prevent deterioration of the patient's hepatocellular function that accompanies rebleeding (6).
It is not known whether performing a TIPS early during bleeding due to fundal varices imply a decrease in both the incidence of failure to control bleeding due to early and late recurrence as well as to increase survival, as has already been demonstrated in esophageal variceal bleeding in high-risk patients.
The analysis of this possibility, which would change the management and "fear" of a patient with bleeding due to fundal varices, is considered a priority. Thus, last consensus conferences on the treatment of complications of portal hypertension highlight the importance of conducting studies that evaluate the efficacy of TIPS against conventional treatment or as an adjuvant to it in the treatment of bleeding by gastric fundal varices (2,7).

Hypothesis of work

Performing an intrahepatic percutaneous portosystemic (TIPS) shunt in the first 5-day after the development of a fundal variceal bleeding (GOV2 or IGV1) in patients with hepatic cirrhosis should lead to a decrease in the incidence of both hemorrhage recurrence and complications related to portal hypertension as well as an increase in survival at one year of follow-up compared to conventional treatment (vasoactive drugs and obturation by injection of tissue adhesives). Objectives.

Primary objective.

To compare patients with liver cirrhosis and bleeding due to fundal varices (GOV2 or IGV1, see attached image) treated with conventional treatment (vasoactive drugs + obturation by
injection of tissue adhesives) with respect to patients treated with conventional treatment + TIPS

in the first 5 days regarding the probability of staying alive and free of recurrent bleeding on follow-up.

Secondary objectives.

Compare other aspects such as:

- Incidence of variceal rebleeding at 42 days and at one year of follow-up.
- Survival at 42 days and at one year of follow-up.
- Incidence of serious adverse effects at one year of follow-up.
- Requirement of blood derivatives (packed red cells, fresh plasma and platelets) during follow- up.
- Hospital stays.
- Use of hospital resources (additional treatments and readmissions).

PATIENTS AND METHODS

Patients:

Inclusion criteria

All those patients with acute bleeding due to fundal varices (GOV2 and/or IGV1) defined according to the criteria of the Baveno II consensus conference who are admitted to the Hospital and who have received pharmacological treatment (somatostatin 3 mg/12h iv perfusion or terlipressin, 2mg/4h iv) and in which endoscopic treatment (obturation by injection of tissue adhesives) has been scheduled. In the event that the patient, by randomization, corresponds to treatment with TIPS and this can be performed in the following 24 hours after it, it will be considered that endoscopic or treatment is not essential. Otherwise, endoscopic treatment will always be performed as part of conventional treatment.

Exclusion criteria

- Age < 18 years and > 75 years.
- Known Hepatocarcinoma without therapeutic option (according to the Milan criteria).
- Portal thrombosis or portomesenteric axis that prevents the performance of a TIPS.
- Multiple liver cysts that prevent TIPS from being performed.
- Platelet count < 20,000/mm^3.
- Pre-treatment with portosystemic shunt.
- Previous treatment by sclerosis or endoscopic ligation of the fundic varicose

veins responsible for the current episode.

- Pregnancy.
- Decompensated congestive heart failure.
- Sepsis or systemic infection that is uncontrolled or has not received at least 48 hours of appropriate antibiotic treatment.
- Complete biliary obstruction.
- Previously known severe pulmonary hypertension.
- Arterial insufficiency of the hepatic artery (thrombosis, stricture).
- Prior randomization for this study.
- Patient in the terminal phase of the hepatopathy (bilirubin > 10 mg / dL and / or prothrombin index < 30% and / or Child-Pugh score > 13); or other diseases.
- Refusal to participate in the study. All patients or their relatives will be asked for their consent prior explanation of the characteristics and objective of the study (Annex I).

Sample size: The calculation of the sample has been made based on previous studies that have estimated the incidence of variceal rebleeding in patients treated with conventional treatment of

47% and those treated with TIPS of 17%. The data are indicative since they are related to populations with liver cirrhosis and advanced hepatocellular insufficiency (Child BC) which, in theory, should not differ from those included in the present study. To detect a satisfactory increase in the achievement of the primary objectives of the study, with an alpha error rate of

0.05 and beta of 0.20, assuming 5% of losses in follow-up, it is necessary to include a total of 60 patients (30 per group).

Data of analysis

It shall be carried out in a data collection notebook. In all cases, the following variables will be collected:

- Demographic data: age, sex, etiology of cirrhosis and years of evolution, previous decompensations,

  severity of cirrhosis (Child-Pugh), current decompensations and associated diseases.
- Analytical (at admission and inclusion): complete blood count, hemostasis profile, electrolytes, renal function, liver function.
- Blood data (admission and inclusion): arterial tension, heart rate, vasoactive drug requirements (other than those used in the treatment of gastrointestinal bleeding) and

plasma expanders, transfusional requirements.

- Data regarding the pre-endoscopy period: manifestation of bleeding, admission to the first hospital and the reference hospital, hemodynamic impact, transfusion need, need for orotrachea l intubation, administration of antibiotics.
- Data concerning pharmacological treatment: pharmacological agent (somatostatin, terlipressin),
  dose, period of administration, associated complications.
- Data concerning endoscopy: date and time of endoscopic procedures and therapy, characteristics of varicose veins, endoscopic treatment, complications during the procedure.
- Evolution: episodes of rebleeding, complications related to liver disease (encephalopathy, bacterial peritonitis, ascites and renal failure), antibiotic requirements, orotracheal intubation days, ICU stay, hospital stay, hospital readmissions.
- Survival: during hospitalization and up to one year of follow-up.

Statistical analysis:

The results will be analyzed according to the intention to treat. The comparison of the data obtained will be carried out by means of the Student's t test or the Chi-square tests according to whether they are quantitative or qualitative variables, respectively. The probability and survival curves will be constructed with the Kaplan-Meier method and compared with the Mantel-Cox test. To identify the predictor variables of survival and complications, a univariate analysis will be carried out (using the Student's t test for quantitative variables and Chi-square tests for qualitative variables, respectively) and a multivariate analysis through regression or logistic
analysis. All calculations will be carried out with the SPSS program.

WORK PLAN.

Baseline.

Patients with hepatic cirrhosis admitted with gastrointestinal bleeding will receive pharmacological treatment with somatostatin or terlipressin. Subsequently, after its hemodynamic stabilization, an upper endoscopy will be performed where the origin of the hemorrhage and the characteristics of the gastroesophageal varices will be evaluated. If it is considered that the origin of the bleeding is fundal varices (GOV2 and / or IGV1), we will proceed:

- Endoscopic treatment by injection of tissue adhesives, if the physician who performs the diagnostic endoscopy is trained to perform this technique and the appropriate conditions are given for its realization
- or to the programming of endoscopic treatment by injection of tissue adhesives within 12 hours of the patient's admission. If active bleeding occurs during this period, tamponade should be placed by Linton-Nachlas balloon.

Pharmacological treatment should be maintained for 5 days. If the patient meets the inclusion criteria in the study, without the presence of any exclusion criteria, he will be randomized. The technique for performing therapeutic endoscopy is described below.

In the event that randomization corresponds to the realization of a TIPS, it will be scheduled as soon as possible, always within the first 5 days of admission. If the TIPS is scheduled within 24 hours after the randomization of the patient, endoscopic treatment may be waived. The TIPS will be performed according to the usual technique under sedation and adequate analgesia and radiological and ultrasound control (see https://intranet.clinic.cat/?q=ca/hemodinamica-hepatica/documents/tecnica-de-tips-hemodinamica-hepatica-clinic).

Randomization

Randomization of the patient in the present study should be carried out as soon as possible after diagnostic endoscopy of bleeding due to fundal varices, whether or not treatment with tissue adhesives injection has been performed.

Randomization will be centralized and carried out by telephone contact with the phone provided by the IP on a 24/7/365 basis.

Follow-up

The patient will be monitored during the period of admission until discharge or death. In patients randomized to TIPS, follow-up endoscopies will not be necessary unless they develop rebleeding. On the other hand, a follow-up Doppler ultrasound is scheduled 4 weeks after the proxcedure. Patients randomized to SMT will undergo a follow-up endoscopy 4 weeks after injection and proceed to a second injection of the adhesive in case of persistence of fundal varices greater than 5 mm in diameter and/or red wall signs. In all patients, after hospital discharge, an out-patient follow-up will be carried out every 2 months until completing the 12 months of inclusion. In the study and ultrasound follow-up for screening for hepatocarcinoma

and vascular alterations of the spleno-portal axis at 6 and 12 months after inclusion. In case of subsequent bleeding the patient will undergo an endoscopy evaluating the presence and characteristics of resildual varices and ulcers as well as an echographic and hemodynamic control to assess the possible dysfunction of the TIPS if applicable.

Rescue treatment.

In case of significant rebleeding due to fundal varices, emergency derivative treatment will be carried out (repermeabilization of the TIPS or realization of the same if it has not been done previously).

In case of massive hemorrhage, and as a bridge to derivative treatment, tamponade with Linton- Nachlas balloon can be used. This probe has a single large capacity balloon (600 ml) that, once swollen, must be impacted into the cardia by continuous tracing. In our unit a pulley with a stroke of a weight of 1 Kg is used.

The tolerance is poor and the risk of aspiration high so it is advisable to intubate the patient and provide sedoanalgesia.

In addition, numerous complications have been described with this technique, the most serious and frequent being aspiration pneumonia and esophageal rupture. Therefore, this method of hemostasia should only be used as a temporary measure ($\leq$24 hours!) pending more definitive treatment when bleeding cannot be controlled by conventional methods and only by highly experienced personnel, since in inexperienced hands it is extremely dangerous.

Treatment of concomitant esophageal varices.

If the patient has concomitant esophageal varices, which do not constitute the cause of the bleeding, these will be treated following the accepted guidelines for primary prophylaxis (if they have never bled) or secondary (if they have previously bled).

DEFINITIONS

Failure of initial control of bleeding. Failure occurs in the first 120h (5 days) and is defined as death or need for therapeutic modification based on any of the following criteria:

- hematemesis or NGT aspiration of $\geq$ 100 ml of fresh blood in $\geq$ 2 hours after the start of pharmacological or endoscopic treatment
- hypovolemic shock

- drop in 3g of Hb (9% hematocrit) in 24h (without transfusion in this period of time)

The transfusion threshold shall be defined by a hemoglobin < 7 g/dl or a haematocrit < 21% (6).

Failure of pharmacological or endoscopic treatment. It is defined as the appearance of the criteria of therapeutic failure despite having received pharmacological treatment (somatostatin 3 or 6 mg / 12h in perfusion continuous iv or terlipressin, 2mg / 4h iv) and endoscopic (minimum a session of injection of tissue adhesives).

Massive gastrointestinal bleeding. It is defined as gastrointestinal bleeding due to fundal varices where, despite the pharmacological treatment initiated at any time, whether or not endoscopic treatment has been performed, it is not possible to achieve hemodynamic stability (systemic arterial tension> 70 mmHg and heart rate < 100 bpm).

Early rebleeding. Any recurrence that occurs after day 5 and during the first 6 weeks is considered early recurrence and is defined by the presence of melena or hematemesis that conditions any of the following situations:

- Hospital admission
- transfusion of 2 PRC
- loss of 3g of Hb
- death during the first 6 weeks

TIPS dysfunction

TIPS dysfunction should be suspected when Doppler ultrasonography shows a maximum portal velocity (mVPmax) < 28 cm/s if the flow is hepatofugal or mVPmax < 39 cm/s if the flow is

hepatopetal. The suspicion of dysfunction implies the realization of a catheterization of the TIPS with measurement of pressures, confirmation or not of the suspicion of dysfunction and correction of the same if it exists.

TECHNIQUES AND PROCEDURES UNDER STUDY

Injection of tissue adhesives

How to use

1. Purge the sclerosis needle with distilled water.
2. Open the vial of Lipiodol.
3. Remove the 3 vials of Histoacryl® from their sealed sachets.

4. With the help of the intravenous needle, load into a 5cc syringe: 1.5cc of Lipiodol + 1.5cc of Histoacryl®.
5. With the sclerosis needle purged with distilled water, start endoscopy and locate the point to be treated.
6. During endoscopy and until the right moment of injection, keep the loaded syringe (Histoacryl® + lipiodol) in the hands of the helper without connecting it to the sclerosis needle and shake it gently. This maneuver prevents premature polymerization of the glue.
7. Once the point to be treated is located, connect the syringe (Histoacryl® + lipiodol) to the sclerosis needle, inject 1cc and then push by injecting 1cc of distilled water.
8. This maneuver is repeated at as many points as you want to treat.
9. A control FGS should be performed at 4-6 weeks with reinjection of tissue adhesives in case of persistence of varicose veins that remain soft to the touch.
11. After the eradication of varicose veins, control endoscopies will be performed 3 and 6 months after the same and in any case in the event of suspicion of rebleeding or treatment failure.

TIPS placement

The TIPS will be carried out with radiological and ecographic support and the participation of hepatologists, radiologists and anaesthetists. The prosthesis will always be coated (PTFE). In summary, the technique will consist of:

1. Anesthesia: HVPG measurement without anesthesia or with midazolam 0.02 mg/kg. Subsequently, sedation and analgesia will be maintained with continuous perfusion of propofol and remifentanil iv.
2. Antibiotics: ceftiaxone + teicoplanin is administered in single doses iv 30 min before placement of TIPS.
3. Catheterization of the hepatic vein, puncture of the portal vein and deployment of prosthesis.
4. PPG measurement: measurement of the gradient between portal vein and inferior vena cava, not between porta and right atria.
5. Final value of the PPG: final measurement without effect of sedation (waiting until the patient is awake).
6. The goal is to achieve a PPG between 10 and 12 mmHg except in those patients who

have bled with PPG < 12 mmHg in whom a PPG between 8 and 10 mmHg will tend to be achieved.

7. To achieve this objective, a first angioplasty of the TIPS will be performed at 8 mm in diameter, the PPG will be measured without the effect of anesthesia. If the desired goal has not been achieved, an angioplasty will be performed at 10 mm. In no case will an overdilation to 12 mm be performed.
8. The length of the prosthesis will be determined by the length of the hepatic vein, from its origin in the IVC and the hepatic tract. The segment of uncoated prosthesis will be housed inside the punctured portal branch.
9. Portosystemic collateral embolization should be considered if the final PPG is not less than or equal to 12 mmHg and/or when a predominant flow directed towards a gastric collateral is identified following low-pressure contrast injection into the splenic vein.

A measurement of the PPG is recommended 24-48 hours after the procedure.

A month, 6 and 12 months after the placement of the TIPS will perform a Doppler ultrasound in order to assess its permeability. In case of suspected dysfunction of the TIPS (see definition), a hemodynamic examination should be performed in order to confirm or not its correct functioning and rule out other complications.

EXPECTED RESULTS

Percutaneous intrahepatic portosystemic shunt (TIPS) in the first 5 days after development of fundic variceal bleeding (GOV2 or IGV1) in patients with liver cirrhosis should involve:

- decrease in the incidence of hemorrhagic recurrence
- Decrease in the incidence of complications related to portal hypertension
- Increased survival at one year of follow-up

compared to conventional treatment (vasoactive drugs and injection of tissue adhesives).

ETHICAL ASPECTS.

The study will be carried out following the rules of Good Medical Practice in accordance with current ethical standards (Declaration of Helsinki; revision of Hong Kong 1989 and Spanish Code of Ethics). This protocol must be approved by the Clinical Research Ethics Committee. Patients should freely give informed consent before being included in the study.

The responsible investigator shall obtain signed written informed consent from each patient

or his/her next of kin. Each patient will be provided with an information sheet and will be informed by the responsible investigator of the benefits and risks of participating in the study and of their right to withdraw at any time.

The Ethics Committee's approval letter must be kept in the study file before it begins. The Ethics Committee should be informed of all changes to the protocol that may affect the safety of the subjects or the conduct of the trial. All unexpected serious adverse reactions and other information that may alter the study design or pose a risk to the patient should be reported to the Committee. In the study files, a list of the members of the Ethics Committee indicating those who participated in the discussion will also be kept.

The patient's date of birth will be used as identification, along with an individual code. A patient information sheet will be completed and filed in the hospital.

Information and written informed consent.

All patients who are candidates for participation in the study (and their legal representative if incapable) will be adequately informed of the characteristics of the study, requesting their free and voluntary authorization. Each selected patient (and his/her representative) will be explained the nature, purpose and procedures of the study and the possible risks resulting from the study.

The patient (and his/her representative) must be informed that participation is voluntary and that he/she may withdraw at any time without any consequences. They shall also be informed that the sponsor, its representatives and the responsible authorities may have access to the clinical data.

The researcher must also sign and date this consent, indicating that informed consent has been obtained and that the patient (and his/her representative) have had the opportunity to ask questions and that these have been properly answered.

The patient or legal representative will receive a copy of the information and the consent form. The original sheet will be filed with the study documentation.

Clinical Research Ethics Committee.

The protocol has been approved by the Hospital Clinic Research Committee (HCB/2014/0727).

CONFIDENTIALITY

The confidentiality of each patient's data will be maintained in accordance with Organic Law 15/99 on the Protection of Personal Data. In this sense, any reference to patients will be

made using their code and tracking number to maintain their confidentiality.

There will be a file for each subject participating in the study, where the researcher must include all the information related to the patient or treatment. The personal information of each patient required for the study (age, gender, information about their health...) is confidential and the identity of the patient will never be revealed unless it is necessary to meet the objectives of the trial or in case of medical emergency or legal requirement. The personal information obtained will be stored and processed in a computer system that ensures confidentiality.

The investigator agrees that the sponsor has the right to use the results of the clinical trial, including notebook sheets or copies thereof, or reports with or without comments and with or without analysis to deliver them to the licensing authorities and may disclose them if necessary to other investigators. To allow the use of the information obtained in the clinical trial, the investigator understands that he is obliged to provide complete test results and all information developed during the study to the sponsor.

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