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A controlled multicentre study comparing early treatment with polytetrafluoroethylene (PTFE) covered stents (Viator) versus optimised medical treatment in patients with cirrhosis and a high risk variceal bleeding episode

Submission date
28/12/2005

Recruitment status
No longer recruiting

Registration date
24/03/2006

Overall study status
Completed

Last Edited
25/06/2010

Condition category
Digestive System

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title

Acronym
ETIPS

Study objectives
Early treatment with PTFE covered stents may be very effective in controlling the acute bleeding episode and in preventing variceal rebleeding. This will be especially relevant in high risk patients (Child-Pugh C patients or Child-Pugh B with active bleeding), where the potential deleterious effects of transjugular intrahepatic portosystemic stent (TIPS) worsening liver function are likely to be counterbalanced by its beneficial effects controlling and preventing complications due to portal hypertension.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Multicentre ethics approval from:
1. Spain: Barcelona - 20/04/2004
2. Italy: Palermo - 23/06/2004
3. Germany: Leipzig - 30/06/2004; Bonn - 28/07/2004; Halle - 31/01/2005; Stuttgart - 02/11/2005
4. Austria: Vienna - 18/08/2004
5. Belgium: Leuven - 14/10/2004
6. France: Toulouse - 23/11/2004

Study design
Multicentre randomised clinical study

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Liver cirrhosis

Interventions
Cirrhotic patients (previously diagnosed or suspected because of the presence of signs of portal hypertension) with an acute upper gastrointestinal bleeding of possible variceal origin will receive pharmacological treatment either with terlipressin or somatostatin/octreotide. Somatostatin will be given at a dose of 250 µg/hour after an initial bolus of 250 µg and octreotide at 50 - 100 µg/hour after an initial bolus of 50 µg. If terlipressin is chosen, it will be given at a dose of 2 mg/4 hours. As soon as possible, always within the first 24 hours, a diagnostic endoscopy will be performed and, if the variceal origin of the bleeding is confirmed, endoscopic band ligation (preferably) or sclerotherapy will be performed.

Active variceal bleeding at endoscopy will be defined, according to Baveno, as observing blood, spurting or oozing from a varix.

The Child-Pugh class will be determined from clinical characteristics at admission and on admission blood test for albumin, prothrombin activity, and bilirubin. Patients belonging to Child-Pugh class C (with a score of 10 - 13 points) or Child-Pugh class B (score of 7, 8 and 9) with active variceal bleeding at endoscopy will be considered eligible for the study. Patients fulfilling the inclusion criteria with no exclusion criteria and that give signed written informed consent will be enrolled in the study.

Patients will be allocated, as soon as possible, to receive optimized medical plus endoscopic treatment (group 1) or early treatment with TIPS with PTFE covered-stents (group 2). Allocation will be done centrally by the coordinating center, that will be contacted by phone, according to a computer-generated, blocked list. Allocated treatment will be kept in sealed, opaque envelops.

Medical treatment (group 1):
After endoscopy, if there is active variceal bleeding, if somatostatin is used, the dose will be doubled to 500 µg/hour. If the dose of somatostatin was doubled it can be decreased to the normal dose after 24 hours of being free of bleeding.

Pharmacological treatment will continue at least until getting 24 hours free of bleeding (preferably up to 5 to 7 days).

Then, patients will begin treatment with non-selective beta-blockers (either propranolol or nadolol). After an initial dose of 40 mg, the dose of propranolol/nadolol will be increased /decreased step by step to achieve a baseline heart rate of 55 bpm or up to the maximum tolerated dose, within the limit of 160 mg twice a day (bid) for propranolol or to a maximum of 160 mg for nadolol. After adjusting the dose of non-selective beta-blockers, isosorbide-5-mononitrate is initiated, starting with 10 mg at bedtime. Two days later the dose is increased to 10 mg at 8.00 and 18.00, and at day 4 - 5 the final dose of 20 mg at 8.00 and 18.00 is reached if tolerated. In case of contraindications or intolerance to beta-blockers, patients will not receive pharmacological treatment (beta-blockers but also mononitrate) and the only treatment to prevent rebleeding will be endoscopic band ligation.
The first elective session of endoscopic band ligation should be performed within the first 7-14 days. The following sessions will be performed at 14 + 3 days intervals until variceal eradication (defined as disappearance of the varix, impossibility of suctioning the varix, or a maximum of six continued sessions). Once eradication is achieved, a control endoscopy will be performed one month later for confirmation. The following endoscopies will be scheduled at 6 and 12 months of inclusion and yearly thereafter. If varices reappear, new band ligation will follow.

PTFE TIPS treatment (group 2):
TIPS will be performed as soon as possible once the patients are enrolled in the study, always within the first 72 hours after the diagnostic endoscopy (preferably in the first 24 hours).

Drug administration (either somatostatin, octreotide or terlipressin) will be maintained until TIPS is done.

TIPS will be performed according to the practice of each center. However, for homogeneity reasons the following will be adhered to:
1. A 10 mm Viator stent will be used, that will be dilated to 8 or 10 mm according to the hemodynamic response. The aim will be to reduce the portal pressure gradient (PPG) below 12 mmHg or by more than 50% of baseline if baseline PPG is greater or equal to 25 mmHg. Not paralleled TIPS or overdilatation are allowed.
2. Embolisation, either with coils or bucrylate, can be performed, if it is felt necessary, especially in patients where portography shows the filling of big portosystemic collaterals feeding the varices, in association with a PPG below 16 mmHg
3. After TIPS, anticoagulation will not be used as a rule, but is allowed if the attending physician thinks that it is warranted

US-Doppler will be performed at day 42 (this US only in the PTFE group), and in all groups at month 6 and every 6 months thereafter. TIPS revision will be performed whenever there is clinical recurrence of portal hypertension (portal hypertensive related bleeding, development of ascites) or when there is suspicion of TIPS dysfunction by Doppler-US: (for instance: portal blood flow velocity lower than 28 cm/s, or change in the direction of flow in intrahepatic portal branches from fugal to petal, or drop in portal blood flow velocity by more than 50%). If TIPS dysfunction is confirmed, angioplasty or PTFE re-stenting should be performed to achieve the previous haemodynamic goals.

Intervention Type
Other

Phase
Not Specified

Primary outcome measure
The major end-point of the present project is to evaluate, in patients with high risk of failure to control bleeding, whether early treatment with PTFE covered stents, in comparison with combined pharmacologic and endoscopic treatment, reduces the incidence of the main composed end-point: failure to control acute variceal bleeding or preventing significant variceal rebleeding within 1 year of inclusion.

Secondary outcome measures
Secondary end-points: To evaluate differences between these two treatment strategies in relation to:
1. The previous major composed end-point plus mortality
2. Failure to control acute variceal bleeding, early rebleeding and mortality at 5-days and at 6-weeks
3. Variceal rebleeding after day 5
4. Survival without liver transplantation
5. Bleeding related mortality

6. Development of other portal hypertension related complications on follow-up (ascites, hepatorenal syndrome, SBP, hepatic encephalopathy)
7. Transfusion requirements, days in hospital and use of alternative treatments over follow-up (5-days, 6-weeks, one-year)
8. Cost

Overall study start date
25/05/2004

Completion date
31/12/2006

Eligibility

Key inclusion criteria
1. Male and female patients 18 - 75 years of age
2. History of cirrhosis (clinical or by liver biopsy)
3. Admission due to acute bleeding from oesophageal or gastric (GOV1 or GOV2) varices
4. Child-Pugh Class C or Child-Pugh class B plus active bleeding at endoscopy under pharmacological treatment
5. Signed written informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
75 Years

Sex
Both

Target number of participants
64 eligible patients

Key exclusion criteria
1. Patients not fulfilling inclusion criteria
2. Pregnancy
3. Confirmed hepatocellular carcinoma with any of the following characteristics:
3.1. One nodule of more than 5 cm
3.2. More than 3 greater than 3 cm
3.3. Perihiliar
4. Creatinine greater than 3 mg/dl
5. Terminal hepatic failure (Child-Pugh score greater than 13)
6. Previous treatment with TIPS or combined pharmacological and endoscopic treatment to

prevent rebleeding
7. Fundal or ectopic gastric variceal bleeding (IGV1 or IGV2)
8. Portal vein cavernoma
9. Congestive heart failure New York Heart Association (NYHA) greater than III or medical history of pulmonary hypertension
10. Spontaneous recurrent hepatic encephalopathy

Date of first enrolment
25/05/2004

Date of final enrolment
31/12/2006

Locations

Countries of recruitment
Austria

Belgium

France

Germany

Italy

Spain

Study participating centre
Liver Unit
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Sponsor information

Organisation
Individual Sponsor (Spain)

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Sponsor type
Not defined

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Barcelona Hospital Clinic Villarroel (Spain)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	24/06/2010		Yes	No