Author's response to reviews

Title: Portal Vein Thrombosis; Risk factors, Clinical presentation and Treatment

Authors:

Kirstine K Sogaard (kks@dce.au.dk)
Lone B Astrup (loast@as.aaa.dk)
Hendrik Vilstrup (hvils@as.aaa.dk)
Henning Gronbaek (henning.gronbaek@dadlnet.dk)

Version: 3 Date: 27 June 2007

Author's response to reviews: see over
Cover letter

Dear Dr Annabel Phillips

Thanks for the final comments and suggestions to our manuscript. We have dealt with the specific points raised by you and the reviewers, and made corrections accordingly. The manuscript has been corrected by our English proof-reader, and hopefully you will find the linguistic improved. Please see the revised version of the manuscript, and the comments. We have been through the checklist to ensure that the revised manuscript conforms to all of the points. The only point that is not quite clear is which type of character and size you prefer in the tables. Also in the instructions it says that borders of tables must be visible black lines, however if looking in already printed articles there are no visible borders.

We thank you and the reviewers for the comments; we find that they have contributed with great improvements, and hope that you will find the revised manuscript of interest to publication in your journal.

Yours Sincerely,
Kirstine Kobberøe Søgaard

Comments to the editors

According to your suggestions we have toned down any recommendation on treatment.

1. In the revised manuscript we have changed the conclusion in the abstract from:

“Most patients had a combination of local and systemic risk factors for PVT. We suggest early anticoagulation therapy to avoid further thrombosis and to favour recanalization, especially in patients with prothrombotic disorders. Pharmacological treatment of portal hypertension and active endoscopy may be considered in the treatment of oesophageal varices.”

To:

Most patients had a combination of local and systemic risk factors for PVT. We observed that partial/complete recanalization was more frequent in patients treated with anticoagulation therapy, and that regression of varices was more pronounced in patients who where treated with active endoscopy combined with pharmacological treatment.

2. In the revised manuscript we have changed the discussion paragraph on anticoagulant therapy from:

“Spontaneous resolution of the thrombosis did happen in some cases, but the frequency of partial/complete recanalization seemed to be higher in patients treated with anticoagulation therapy. The effect was seen in patients with both acute and chronic PVT. There is no consensus on the indication for anticoagulant therapy (13), but since one study showed no increased rate of bleeding episodes in patients with established PVT who received anticoagulant therapy (6), anticoagulation therapy may be considered in non-cirrhotic patients with PVT, especially in patients with prothrombotic disorders. The aim is both to prevent further thrombosis and potentially lead to recanalization, thereby preventing the development of portal hypertension and its complications. It has been suggested that interventional recanalization should be performed whenever the result of anticoagulation is unsatisfactory, and furthermore should TIPS be implanted in patients with cirrhosis (18).”

To:

Spontaneous resolution of the thrombosis did happen in some cases, but the frequency of partial/complete recanalization seemed to be higher in patients treated with anticoagulation therapy. The effect was seen in patients with both acute and chronic PVT. The aim of anticoagulation therapy is both to prevent further thrombosis, and potentially lead to
recanalization, thereby preventing the development of portal hypertension and its complications. It has been suggested that interventional recanalization should be performed whenever the result of anticoagulation is unsatisfactory, and furthermore, that TIPS should be implanted in patients with cirrhosis [20]. One study showed no increased rate of bleeding episodes in patients with established PVT who received anticoagulant therapy [6]. However, to our knowledge, there is yet no consensus on the indication for anticoagulant therapy [9].

3. In the discussion we have revised the paragraph on treatment of varices from: Endoscopy and VBL remain central to the acute management of variceal haemorrhage, whereas both VBL/sclerotherapy and β-blockers ± nitrates are used in the secondary prevention of rebleeding (7,8,19,20). However, there are at the moment not sufficient data on whether β-blockers or endoscopic therapy should be preferred in the primary prophylaxis. In the secondary prophylaxis, endoscopic therapy is effective, whereas evidence to recommend β-blockers is insufficient. (13). We observed regression of the varices in patients who were treated with sclerotherapy and/or VBL combined with β-blockade.
To:
For primary prophylaxis, β-blockade is standard for cirrhotic portal hypertension, but the effect is not documented in PVT, and VBL may be preferable. In the acute management of variceal bleeding, vasoactive substances, antibiotics, and VBL remain central. For secondary prophylaxis of re-bleeding we used combined VBL and β-blockade ± long-acting nitrates [7,8,21,22] although evidence to support β-blockers is sparse [9]. In any case, our patients showed regression of their varices when given this combination preventive treatment.

4. In the discussion we have deleted the following suggestions on treatment of varices: “It may be suggested that PVT patients with varices are treated with VBL as secondary prophylaxis and it may be used also as primary prophylaxis in selected patients with large oesophageal varices. Addition of beta-blockers ± nitrates are controversial but may be added in selected cases.”

Answers and comments to the 1 reviewers report

1. According to the suggested we have changed the paragraphs regarding follow-up time. Changes have been made in following sections: methods line 7 and basic data line 5 and 9. Thank you for pointing this out.
2. The study reports data on 67 patients; however, as stated in the first paragraph of risk factors patients can have more than one risk factor, and therefore some patients are reported to have both local and systemic risk factors.
3. According to the comment on sensitivity on MRI sensitivity, we have deleted this, and instead specified in imaging methods line 5-6 that all MRI performed were positive.
4. In imaging methods lines 8-11 we describe the location of the thrombosis. 65 cases had extrahepatic thrombosis; but the majority of these patients also had thrombosis either intrahepatic and/or in the splenic vein and/or in the superior mesenteric vein – therefore the percentages are more than 100%.
5. We have inserted “were” in the sentence on page 8, line 10. Thank you for pointing this out.
6. We have corrected the spelling of renal insufficiency.
7. We have deleted the sentence “but in most other cases fairly good”.
8. According to a comment from the second reviewer we deleted the sentence on gastrointestinal bleeding.
9. In table 1 we have corrected the spelling of idiopathic and removed the bracket after portal vein phlebitis. It was the causation of portal vein phlebitis, but since it seemed to confuse more than help, we deleted it.

Answers and comments to the 2 reviewers report

1. We have added “retrospective” in the second sentence in the abstract. The discussion starts with the sentence “we retrospectively report…”, but in the second paragraph we have added a discussion of limitations, including the retrospective nature and the incomplete screening. “The main limitation of this study is lack of generalizability due to its retrospective nature; however, large-scale randomised trials of such rare conditions can not be conducted, and, to our knowledge, this is one of the larger retrospective studies of PVT.”

2. Regarding methodology; in the following you can read how all the tests are performed: “Thrombophilia investigation was performed by using citrated plasma and heparin-flouride containing plasma collected by venipuncture and kept at -80ºC until analysis. Total homocysteine in plasma (tHcy) was recorded by combined gas chromatography-mass spectrometry analysis as previously reported (Rasmussen et al. 1996). The Factor V Leiden mutation was detected using PCR amplification (Bertina et al. 1994). The APC-resistance functional test was determined using the ACL-3000 Coagulyzer (Instrumentation Laboratory, Milan, Italy), employing the Coatest (Chromogenix, Mölndal, Sweden) kit method, as originally devised with no prior addition of Factor V depleted plasma (reference ratio >2.0). Functional Protein C was measured using the IL Test TM Proclot (Instrumentation laboratory) on the ACL-3000 analyzer (reference interval 0.72–1.44 U/ml), whereas the amidolytic function was measured by a Coamatic Protein C kit (Chromogenix) (reference interval 0.60–1.33 U/ml). If the Protein C anticoagulant function was lower than 0.75 arbitrary Units per ml, the antigenic concentration of Protein C antigen was quantified with an in-house ELISA method using polyclonal rabbit antibodies (Dakopatts, Roskilde, Denmark) (reference interval 0.60–1.40 U/ml). The anticoagulant function of Protein S was measured using IL test TM Protein S (Instrumentation Laboratory) (reference interval 0.73–1.36 U/ml). The antigen of protein S was measured by an inhouse method utilising polyclonal antibodies from Dakopatts (reference interval 0.60–1.40 U/ml). The free Protein C was measured using the same methodology after precipitation of C4b-bound Protein S with polyethylene glycol 10% at 4¾C by an in–house method (reference interval 0.13–0.32 U/ml). Antitrombin was measured by using a Coamatic Antitrombin kit (Chromogenix, and an ACL-3000 Coagulation analysis system (Instrumentation Laboratory) (reference interval 0.89–1.25 U/ml). The antithrombin antigen was estimated by nephelometry utilising a Behring BNA-100 instrument (Behring Diagnostika AG, Marburg, Germany) and specific rabbit antibodies (Behring AG) (reference interval 0.80–1.20 U/ml). Antibodies to phospholipid and β-2 glycoprotein-1 were recorded using an ELISA kit method, Asserachrom APA, STAGO (Asnieres, France) (reference interval <5U/ml). The spontaneous fibrinolytic capacity was determined by a routine fibrin plate technique. However, we found this was too detailed, so in the manuscript we inserted the following: “Thrombophilia investigation was performed by using citrated plasma and heparin-flouride containing plasma collected by venipuncture and kept at -80ºC until analysis. The protocol for sample collection and processing, as well as data interpretation, has been reported in previous publications. Thrombophilia testing included collection for antithrombin (AT), homocystein, protein C, free protein S, factor V (FV) Leiden, prothrombin G20210A, Von Willebrand-factor, activated protein C resistance, β-2 glycoprotein-1 (APA), phospholipid antibody, and lupus anticoagulant (LA). The spontaneous fibrinolytic capacity was determined by a routine fibrin plate technique.”
3. We have removed increased von Willebrand factor as a risk factor, as suggested.

4. According to the suggestions we have deleted the section and table on laboratory findings, and in the discussion line 2-9, and the sentence on sigmoidoscopic examination.

5. We have also discussed our finding of high frequency of ascites. “The high presenting occurrence of ascites among our patients may be due to the fact that we registered ascites both when detected by physical examination and by ultra sound, so that cases of slight ascites were included. The ascites was in no case tense (although some were treated with paracentesis to speed up recovery). Ascites in such patients is most likely caused by intestinal venous congestion, whereas the mechanisms leading to massive fluid retention are not activated as at sinusoidal portal hypertension.”