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LETTER TO THE EDITOR

Response to Porres-Aguilar et al., on ''Periprocedural and perioperative anticoagulation management strategies in liver cirrhosis''

Respuesta a Porres-Aguilar et al. «Estrategias de manejo perioperatorio y periprocedimiento de la anticoagulación en la cirrosis hepática»

We appreciate the comments and reflections of Porres-Aguilar, et al., in which they emphasize the existence of a significant prevalence of cardiovascular comorbidities in patients with cirrhosis, and the resulting increase in the prescription and use of direct oral anticoagulants (DOACs) from 20 to 77% between 2012 and 2019. Indeed, there are original studies on DOAC use in patients with cirrhosis and atrial fibrillation (AF) as a prophylactic strategy for preventing a cerebrovascular event that included: dabigatran, 24 patients; rivaroxaban, 32 patients (8 Child-Pugh A and 16 Child-Pugh B; Child-Pugh C was not included); and apixaban 32 patients (8 Child-Pugh A and B and 16 controls without cirrhosis). Based on that information, our guidelines recommend considering anticoagulation for cerebrovascular event prevention in patients with Child-Pugh A or Child-Pugh B cirrhosis that present with AF and a CHA_2DS_2-VASc score of 2 or more in men and 3 or more in women. There is no evidence for making recommendations regarding Child-Pugh C cirrhosis. Standard dose DOACs are suggested in patients with Child-Pugh A or B cirrhosis, instead of vitamin K antagonists (VKAs). Anticoagulation for pulmonary thromboembolism and deep vein thrombosis as treatment, but not as prophylaxis, is also mentioned. In addition, the guidelines underline the fact that patients with cirrhosis are excluded in the AMPLIFY, RECOVER, EINSTEIN, and HOKUSAI pivotal trials. Likewise, they recommend using DOACs in patients with Child-Pugh A or B cirrhosis, and enoxaparin in patients with Child-Pugh C cirrhosis, as a bridge to VKAs (in patients with a normal international normalized ratio).[1]

We should also clarify that there is a special section in our position paper that discusses anticoagulation in the cirrhosis population that has AF, and draws the following conclusions:[2,3]

a) In patients with Child-Pugh A or B cirrhosis and AF, oral anticoagulation is recommended in the absence of significant coagulopathy induced by liver failure or severe thrombocytopenia.
b) It is reasonable to prescribe DOACs (apixaban, dabigatran, or edoxaban), rather than warfarin, in patients with Child-Pugh A or B cirrhosis.
c) In patients with Child-Pugh B cirrhosis, rivaroxaban is contraindicated due to the potentially increased bleeding risk.

Porres-Aguilar, et al. also say they consider that special and meticulous multidisciplinary care (e.g., including a hematologist or a specialist in vascular medicine with experience in thrombosis and hemostasis) should be put forward in the position document, and that reasonable recommendations should be provided, not only with respect to thromboprophylaxis but also for patients currently taking DOACs for different cardiovascular indications. We agree that patients indicated for anticoagulation or those that are already taking anticoagulants should have a comprehensive evaluation by the vascular cardiologist, hematologist, and internist. As statement 4 of the scientific position paper says: ''Conducting a preoperative evaluation of non-hepatic comorbidities is recommended. It should include the habitual preoperative evaluation (electrocardiogram for estimating cardiovascular disease and the American Society of Anesthesiologists scale and Goldman index determinations)''. Likewise, statement 6 affirms: ''In patients with cirrhosis that require an elective surgical procedure, a multidisciplinary evaluation is recommended that should include specialists in hepatology or gastroenterology, internal medicine, nutrition, anesthesiology, and the area of surgery involved.''[2]

With respect to detailed recommendations on how to approach the significant adverse effects of anticoagulants, including DOACs, such as major and potentially fatal bleeding events, a multidisciplinary team is needed, as well as a combination of prevention, adequate monitoring, and management strategies for minimizing risks and treating complications. The main steps follow below:[4]

1 Risk evaluation before starting treatment
   - Thrombotic and bleeding risk stratification: Utilize tools, such as the CHA2DS2-VASc (for thrombotic risk in AF) and HAS-BLED (for bleeding risk).
   - Detailed clinical history: Identify comorbidities, such as kidney failure, liver failure, or a history of bleeding.
2 Adequate anticoagulant selection

- Consider patient characteristics: DOACs (such as rivaroxaban, apixaban, dabigatran, and edoxaban) have safety profiles different from that of warfarin. Choose the most appropriate, according to age, kidney function, medication interactions, etc.
- Dose adjustment: It is dependent on weight, kidney function (use creatinine clearance), and clinical indication.

3 Patient education
- Clear instructions about adherence: DOAC efficacy and safety depends on a constant administration of the drug.
- Recognizing alarm symptoms: Teach patients to identify bleeding symptoms (blood in urine, stools, or gums, and abnormal hematomas).
- Avoid certain medications and foods: Avoid the concomitant use of NSAIDs, anti-platelet drugs (with no indication), and certain supplements/herbal agents that increase the risk of bleeding.

4 Adverse effect management

Bleeding:
- Mild-to-moderate:
  - Temporarily suspend the DOAC.
  - Manage the cause of the bleeding (such as gastric ulcer).
- Severe or potentially life-threatening:
  - Use of reversal agents:
- Dabigatran: idarucizumab.
- Factor Xa inhibitors (rivaroxaban, apixaban): andexanet alfa (if available).
- Others: Prothrombin complex concentrates (PCCs) or fresh frozen plasma, in cases without specific reversal agents.
  - Fluid replacement and transfusions, as needed.

Other complications:
- Anticoagulant-induced thrombocytopenia: Rare but possible, it requires drug suspension and the use of non-heparin alternative anticoagulants, if necessary.
- Kidney or liver dysfunction: Regular monitoring and dose adjustment or treatment change, if necessary.

5 Continuous monitoring

Even though DOACs, unlike warfarin, do not require routine INR monitoring, the following should be periodically evaluated:
- Kidney and liver function: Especially in the elderly or patients with comorbidities.
- Adverse events: New medication interactions or changes in clinical status that increase the risk for bleeding.

6 Strategies in special situations
- Surgeries or invasive procedures: Temporarily suspend the DOAC according to the bleeding risk and kidney function of the patient. Restart as soon as it is safe to do so.
- Accidental overdose: Start support measures and consider using reversal agents if there is evidence of active bleeding.

A preventive focus, proactive complication management, and close communication with the patient are key to minimizing the risks involved in anticoagulant use, including DOACs.

Porres-Aguilar, et al. commented that an updated guideline was recently published on DOAC reversal strategies,[4] but said guideline was not yet available at the time our Mexican position paper was prepared.[2]

And lastly, Porres-Aguilar, et al. stated they did not agree with the recommendation of using low-molecular-weight heparins (LMWHs), instead of unfractionated heparin, for thromboprophylaxis, especially in clinical settings with coexisting advanced chronic kidney disease (stage 4 or 5, according to the KDIGO classification, defined by a GFR < 30 ml/min/1.73 m^2) and advanced cirrhosis of the liver (e.g., Child-Pugh class C or MELD score > 20 points). In addition, Porres-Aguilar, et al. stated that there was a scarcity of randomized prospective data addressing those clinically relevant topics.[5,6] They also said they preferred unfractionated heparin due to its secretion through the reticuloendothelial system, including the liver, thus preventing bioaccumulation and bleeding complications. We should point out that in patients with severe chronic kidney disease treated with LMWHs, adjusting the doses and closely monitoring the anti-Xa levels is recommended in a meta-analysis. Certainly, in those specific cases, and some others, using unfractionated heparin or alternative anticoagulants, such as DOACs, could be safer, but solid evidence on that population is still limited.[7]

Regarding the patients with important liver function deterioration, a recent study showed that there was insufficient evidence on the risks and benefits of anticoagulation for preventing stroke in AF, in patients with Child-Pugh C cirrhosis. In cases of acute deep vein thrombosis or pulmonary embolism, anticoagulation is recommended. In patients with Child-Pugh A or B cirrhosis, using DOACs or LMWHs/VKAs is suggested. In patients with Child-Pugh C cirrhosis, LMWH, alone, or as a bridge to VKAs in patients with a normal baseline international normalized ratio is preferred.[1]

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Conflict of interest

The authors declare that they have no conflict of interest.

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