Thrombin Generation during bleeding in orally anticoagulated patients: reversal can lead to hypercoagulability !

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INTRODUCTION

Bleeding during oral anticoagulant therapy is codified by expert proposals in France. The evaluation of the coagulation is challenging in these situations, overall during reversal with non specific procoagulant agents.

AIM

The aim was to compare thrombin generation (TG) in 3 populations under oral anticoagulants: patients with reversed bleedings, patients with non-reversed bleedings and anticoagulated patients without bleeding.

METHOD

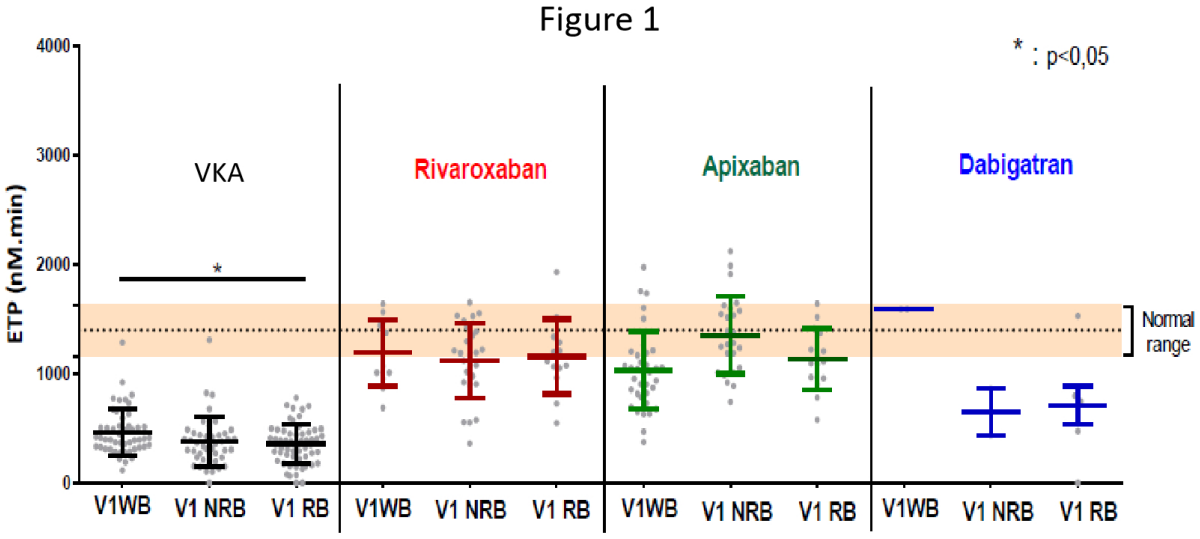
We conducted a prospective study to evaluate TG in anticoagulated patients (VKA, direct oral anticoagulants (DOACs) : rivaroxaban (R), dabigatran (D), apixaban (A)). TG was evaluated on platelet-poor plasma collected on arrival (V1), and 30min (V2), 6h (V3) and 2h (V4) after reversal (if indicated) after activation by 5 µM tissue factor.

RESULTS

307 patients were included: 98 patients with severe bleeding (61VKA, 13R, 17A and 7D), 95 patients with non reversed bleeding (44 VKA, 25 R, 24 A and 2 D) and 108 patients without bleeding.

At V1, patients VKA with reversed bleeding had a significant decrease in TG parameters (ETP and peak) compared to patients without bleeding (mean ETP±SD:357.2±177.7 vs 464.9±212 nM.min, p<0.05). ETP were significantly decreased in the reversal groups for VKA compared with DOACs (VKA-ETP: 357.2±177.7 nM.min, R:1156.3±342.3, A:1135.4±280.4, p< 0.05). No significant difference were found for ETP and peak between the 3 populations of DOACs at V1 (Figure 1).

Figure 1

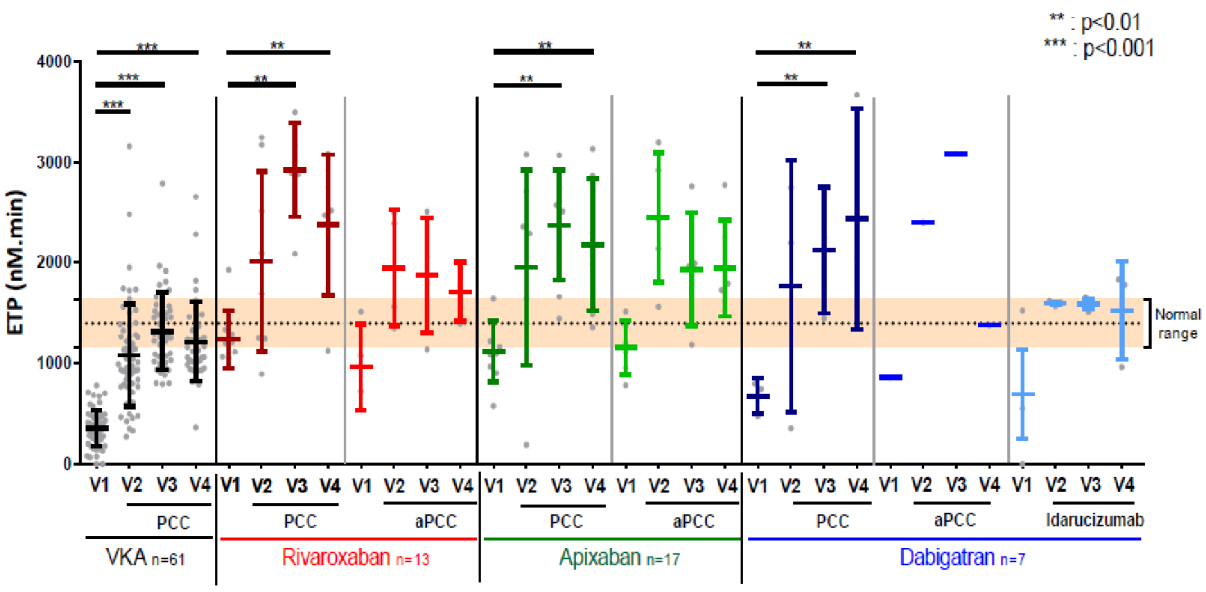


V1WB: Without Bleeding on arrival; **V1NRB**: Non Reversal Bleeding on arrival; **V1RB**: With Reversal Bleeding on arrival

Endogenous Thrombin Potential with Thrombin generation test on arrival

For VKA patients, the PCC (25 IU/kg) reversal restored a normocoagulable state at V2,V3 and V4 without hypercoagulability (healthy controls ETP: 1398.86±235.77 vs ETP V2: 1083.38±507.12, ETP V3: 1328.44±384.35, ETP V4: 1215.42±394.64 nM.min, p=NS). For DOACs reversed by PCC (46.2IU/kg) or aPCC (49,5IU/kg), a significant hypercoagulability was demonstrated as early as V3 (R-ETP:2922.15±466.81, A: 2372.46±548.33, D: 2126.75±627.16 nM.min,p < 0.01) and similarly to V4. For the dabigatran patients reversed by idarucizumab, we found a normalization of the coagulation, without hypercoagulable state from V2 to V4. (Idarucizumab ETP, V2:1596.88±25.3, V3:1592.80±73.38 V4:1525.90±486.84 nM.min, p=NS) (Figure 2).

Figure 2



Effect of PCC or aPCC or idarucizumab on Endogenous Thrombin Potential with Thrombin generation test.

CONCLUSIONS

Patients on VKA regained a normocoagulable state as healthy subjects after reversal therapy, whereas patients treated with DOACs and reversed with PCC or aPCC displayed a hypercoagulable state. This hypercoagulable state could be probably minimized by reducing the doses of PCC or aPCC or be circumvented by using specific antidotes.

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