Laboratory Tests in Assessing the Bleeding Risk in Patients Receiving Direct Oral Anticoagulants (DOACs)

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Abstract

Direct oral anticoagulants (DOACs)—apixaban, rivaroxaban and dabigatran have become the first line medications for patients with thromboembolism. However, DOAC therapy-associated bleeding complications remain the major clinical concern for these patients. This study compared laboratory test results from 82 patients with and 361 patients without DOAC-associated bleeding with the goal of determining the value of laboratory tests in assessing bleeding risk in these patients. There was no age or gender difference between patients with and without DOAC therapy-associated bleeding complications. Both prothrombin time (PT) and partial thromboplastin time (PTT) prolonged at the same time showed good correlation with bleeding complications for patients receiving dabigatran (91.7%) and rivaroxaban (41.2%). When comparing patients with bleeding and those without bleeding complications, impaired renal function showed high correlation (p < 0.01), impaired liver function showed moderate correlation (p = 0.03), and thrombocytopenia showed no correlation (p > 0.05) among patients with bleeding complications. A small population of patients had never experienced bleeding complications, despite the laboratory test results being similar to patients who suffered from bleeding complications. Laboratory tests may be useful in the assessment and prediction of bleeding complications in patients receiving DOAC therapy. However, it is important to incorporate both laboratory findings with the clinical information, such as concomitant antithrombotic agents and other underlying diseases in the decision making of DOAC therapy in order to reduce therapy-related bleeding risk.

Keywords

Direct Oral Anticoagulants, Prothrombin Time, Partial Thromboplastin Time, Apixaban, Rivaroxaban, Dabigatran, Bleeding Complications
1. Introduction

Apixaban, rivaroxaban and dabigatran are direct oral anticoagulants (DOACs), which are often indicated for the prevention of stroke caused by atrial fibrillation and the management of venous thromboembolism [1] [2] [3]. Dabigatran is a direct thrombin inhibitor, while apixaban and rivaroxaban are both direct factor Xa inhibitors [4] [5]. DOACs have gained wide use recently as alternatives to the traditional oral vitamin K antagonists (warfarin) therapy [6] [7]. However, the therapeutic benefit is not without risk of bleeding complications, such as hematuria and gastrointestinal bleeding [8] [9].

Anticoagulation therapy should be individualized based on both benefits and risks associated with this therapy [10] [11]. Concomitant antithrombotic agents, patient’s age and impaired liver and renal functions are amongst the risk factors associated with an increased bleeding complications in these patients [12] [13]. Multiple clinical trials on DOAC therapy have revealed valuable information on the risk factors of therapy-associated bleeding complications [14] [15] [16]; however, there are still limited studies on the risk factors of bleeding in the post-marketing general practice, especially on the roles of laboratory tests to determine the bleeding risk in patients receiving DOAC therapy. Insufficient laboratory evaluation before and/or during therapy may increase the risk of therapy-induced bleeding complications among certain patients. This study reviews the value of laboratory tests in assessing the bleeding risk in patients on DOAC therapy.

2. Materials and Methods

2.1. Patient Population

Using existing clinical laboratory data, patients with prolonged partial thromboplastin time (PTT) were selected at William Beaumont hospital, Troy, Michigan from August 2015 to April 2016. Among them, 443 patients were identified as receiving DOAC therapy during the same time period, including 82 patients with documented bleeding episodes and 361 patients without any bleeding episodes. The electronic medical charts from these patients were retrospectively reviewed. Bleeding complications and concurrent laboratory test results were collected, analyzed and compared amongst the two groups.

Patient population for this study consisted mainly of local residents in the suburban region of a major US metropolitan city. A pilot study was performed initially to determine the number of patients, laboratory tests and clinical information to be included in this study in order to perform meaningful statistical analysis. Patients younger than 19 years and older than 90 years were excluded.

2.2. DOAC Therapy Information

The clinical indications and dosing regimen of DOAC therapy were based on the clinically established as well as United States Food and Drug Administration (FDA) approved guidelines [17] [18]. The clinical indications for DOAC therapy
include atrial fibrillation, deep vein thrombosis and pulmonary embolism. Patients received one of the following: apixaban 2.5 mg or 5.0 mg bid; dabigatran 75 mg or 150 mg bid; or rivaroxaban 15 mg or 20 mg once daily. No patient received more than one DOAC medications concurrently.

2.3. DOAC Therapy-Associated Bleeding Complications

The electronic medical charts of patients with DOAC therapy-associated bleeding complications were reviewed. Some patients had bleeding with multiple organ system involvement; in which case, we recorded the total number of patients with bleeding as opposed to the total number of bleeding episodes.

2.4. Concurrent Laboratory Test Results

Laboratory test results from all patients receiving DOAC therapy were reviewed with a focus on platelet count (reference range: 150 - 400 bil/L), prothrombin time (9.3 - 12.4 seconds), PTT (23.0 - 30.0 seconds), renal function tests: creatinine (0.60 - 1.40 mg/dL) and blood urea nitrogen (8 - 22 mg/dL) and liver function tests: aspartate aminotransferase (10 - 37 U/L), alanine aminotransferase (8 - 37 U/L), and alkaline phosphatase (30 - 110 U/L). Abnormal test results were defined by values outside of the reference ranges set by the Beaumont Hospital laboratory. Abnormal renal and liver function test results were interpreted in the context of data trend analysis in order to assess the likelihood of significant organ dysfunction.

2.4.1. Laboratory Test Results in Patients with Bleeding Complications

The concurrent laboratory test results in patients at the time of bleeding complications while receiving DOAC therapy were collected and reviewed. All bleeding incidences documented in the electronic medical charts were recorded, including gastrointestinal bleeding, hematuria, epistaxis, bruises, and hematomas. These were discussed in our previous study on DOAC agents [9].

2.4.2. Comparison between Patients with and without Bleeding Complications

While receiving DOAC therapy, the laboratory test results between patients with and without bleeding complications were compared and analyzed. Then, the laboratory test results were further compared and analyzed among patients receiving different DOAC agents.

2.4.3. Laboratory Test Results in Patients without Bleeding Complications

Of those patients who experienced no bleeding complications during DOAC therapy, some of them had significantly abnormal laboratory test results. These patients were further evaluated with clinical correlations and their laboratory test results were compared with patients who had bleeding complications.

2.5. Statistical Analysis

Student’s T test was used for the calculation of p value to determine the signi-
ficance of the difference between different patient groups.

3. Results

3.1. General Patient Information and DOAC Therapy-Associated Bleeding Complications

There were 443 patients included in this study, 228 males and 215 females, with the age range between 20 and 90 years old. The overall incidence of bleeding complications associated with DOAC therapy was 18.5% (82/443) in this patient population. The age and gender distribution was similar between patients with and without DOAC therapy-associated bleeding complications (Table 1). The bleeding incidence in patients receiving apixaban was 10.8% (19/175), significantly lower (p < 0.01) than patients on rivaroxaban and dabigatran, 22.7% (51/225) and 27.9% (12/43) respectively. Additional analysis on the incidence of bleeding complications, comparison with different DOAC agents, related clinical information and follow-ups were published in our previous study [9].

3.2. Laboratory Test Results in Patients with DOAC Therapy-Associated Bleeding Complications

Both prothrombin time (PT) and PTT prolonged at the same time had an overall high association with bleeding incidence (42.7%), especially for patients receiving dabigatran (91.7%) and rivaroxaban (41.2%); however, this was not seen with apixaban (15.6%). In patients with bleeding complications, abnormal renal function, liver function and thrombocytopenia were seen in 34.1%, 29.3% and 23.2% of the patients respectively.

3.3. Laboratory Test Results between Patients with and without Bleeding Complications (Table 2)

Overall, patients with DOAC therapy-associated bleeding complications had a

| Bleeding Complications | Total | Males (%) | Females (%) | Median age (years) | Range of age (years) |
|------------------------|-------|-----------|-------------|--------------------|---------------------|
| Positive               | 82    | 42 (51.2%)| 40 (48.8%)  | 73                 | 26 - 89             |
| Negative               | 361   | 186 (51.5%)| 175 (48.5%)| 72                 | 20 - 90             |

| Bleeding complications | Both PT/PTT Prolonged | Abnormal renal function | Abnormal liver function | Thrombocytopenia |
|------------------------|------------------------|-------------------------|-------------------------|------------------|
| Positive               | Total                  | 35 (42.7%)              | 28 (34.1%)              | 24 (29.3%)       | 19 (23.2%)       |
| Negative               | 82                     | 62 (16.7%)              | 51 (14.1%)              | 67 (18.6%)       | 69 (19.1%)       |
| P value                | 361                    | <0.01                   | <0.01                   | =0.03            | >0.05             |
significantly higher incidence of prolonged PT and PTT at the same time (p < 0.01) as well as impaired renal functions (p < 0.01), when compared with patients without bleeding. The percentage of impaired liver function was moderately increased in patients with bleeding (p = 0.03). There was no significant difference in the incidence of thrombocytopenia between patients with and without bleeding (p > 0.05).

3.4. Laboratory Test Results in Patients without Bleeding Complications

In patients without documented bleeding complications while receiving DOAC therapy, a small population (17.5%) of them was found to have both PT and PTT prolonged at the same time. These patients also had higher incidence of impaired renal and liver functions and thrombocytopenia similar to that observed in patients with bleeding, even though they did not experience bleeding complications during this study period.

The incidence of impaired renal and liver function in patients who never had PT and PTT prolonged at the same time was much lower than in patients who had both prolonged PT and PTT (Table 3).

4. Discussion

Bleeding complications remain the major concern for patients receiving DOAC therapy [19] [20]. In our patient population, the overall bleeding incidence was 18.5% among patients with prolonged PTT while on DOAC therapy. There was no difference in age and gender distribution between patients with and without DOAC therapy-associated bleeding complications in this study. Patients receiving apixaban had a lower bleeding incidence than those on dabigatran or rivaroxaban. Apixaban has been shown to have the benefit of lower bleeding incidence than dabigatran and rivaroxaban in other studies as well [21].

PT and PTT are commonly used coagulation laboratory tests to evaluate the hemostasis status in patients with bleeding disorders [22] [23]. It was common to see prolonged PT and PTT in patients with bleeding complications while receiving DOAC therapy during this study. It was especially interesting that both PT and PTT prolonged at the same time was highly associated with bleeding complications in patients receiving dabigatran or rivaroxaban, but not necessarily with apixaban. Prolonged PT and PTT not only reflect the therapeutic effects of DOACs, but also may indicate a significant underlying coagulopathy, which could be a contributing factor to the bleeding complications in these patients.

Table 3. Laboratory test results in patients without bleeding complications.

| Both PT/PTT prolonged | Total | Abnormal renal function | Abnormal liver function | Thrombocytopenia |
|------------------------|-------|-------------------------|-------------------------|------------------|
| Positive               | 63    | 18 (28.6%)              | 21 (33.3%)              | 13 (20.6%)       |
| Negative               | 298   | 34 (11.4%)              | 44 (14.8%)              | 56 (18.8%)       |
Impaired renal function was a significant risk factor in the development of bleeding complications in patients receiving DOAC therapy [24] [25] [26]. When compared with non-bleeding patients in this study, patients with DOAC therapy-associated bleeding complications had a significantly higher incidence of impaired renal function (p < 0.01). Given that all three DOAC medications have a component of renal excretion, abnormal renal function can alter the metabolism of these medications, and thus, increase the bleeding risk. Impaired liver function, to a less extent, had only moderate correlation with bleeding complications (p = 0.03). Thrombocytopenia, on the other hand, showed no significant difference between patients with and without DOAC therapy-associated bleeding complications.

It was noted in this study that a small population of patients receiving DOAC therapy had both PT and PTT prolonged at the same time, as well as impaired renal and liver functions similar to the bleeding patients, but never experienced bleeding complications during this study period. This suggests that the bleeding complications in patients receiving DOAC therapy have multiple factors involved. Concomitant antithrombotic agents and other underlying diseases, such as peptic ulcer disease and bladder lesions, may also be important in the development of bleeding complications.

Clinical trials provide important information and guidelines in the assessment and management of DOAC therapy-associated bleeding complications. However, patient characteristics studied in clinical trials may differ from that of general patient population and the time frame of clinical trials is typically short. These limitations may underestimate the true bleeding risk [14]. Our study provides some insight into the laboratory evaluation of DOAC therapy-associated bleeding complications among the general patient population. However, the heterogeneity of patients in general practice makes it very challenging, if not impossible, to have complete clinical and laboratory information from these patients. Long-term clinical follow up, adequate laboratory testing, well documented medical conditions and complications will be helpful in future studies for better understanding of DOAC therapy-associated bleeding complications.

5. Conclusion

Laboratory tests may be useful in the assessment and prediction of bleeding risk in patients receiving DOAC therapy. Both PT and PTT prolonged at the same time had high association with bleeding, especially in patients receiving dabigatran or rivaroxaban. Impaired renal and liver functions had strong and moderate correlation, respectively, with DOAC therapy-associated bleeding complications in this study. Thrombocytopenia showed no significant difference between bleeding and non-bleeding patients. It is important to incorporate both laboratory findings and clinical information, such as concomitant antithrombotic agents and other underlying diseases, in the decision making of DOAC therapy in order to reduce therapy-related bleeding risk.
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