Safety of ECT in patients receiving an oral anticoagulant

Nicolette R. Centanni, PharmD, BCPS, BCGP, BCPP; Wendy Y. Craig, PhD; Dena L. Whitesell, MD; Wesley R. Zemrak, PharmD, BCPS; Stephanie D. Nichols, PharmD, BCPS, BCPP, FCCP

Abstract

Introduction: This study assessed the use, tolerability, and safety of anticoagulation via direct oral anticoagulants or warfarin in medical and psychiatric inpatients receiving ECT.

Methods: This retrospective cohort study included 32 patients who received ECT while on either a direct oral anticoagulant (9) or warfarin (23) and spanned 247 encounters at Maine Medical Center between December 2012 and December 2018. Data are presented descriptively and analyzed using SPSS version 25 and Microsoft Excel version 2016.

Results: Among the 247 ECT patient encounters, there were few major adverse effects of ECT in this medically complex population. These adverse effects included headache during 4 encounters (1.6%), respiratory distress during 2 encounters (0.8%) and a cardiovascular event during 1 encounter (0.4%). One patient (3.1%) who was receiving concurrent rivaroxaban and venlafaxine experienced gastrointestinal bleeding that was determined to be unrelated to ECT. One patient on fluoxetine and warfarin experienced hemoptysis thought to be secondary to epistaxis. No other major bleeding or clotting event occurred during an ECT session nor for the duration of the hospitalization.

Discussion: Direct oral anticoagulants and warfarin appear safe in the treatment of patients with atrial fibrillation or acute venous thromboembolism who are receiving concomitant ECT. Prospective studies are needed to confirm these findings.

Keywords: direct oral anticoagulants, rivaroxaban, apixaban, warfarin, electroconvulsive therapy, safety, ECT

Introduction

ECT is an important treatment for patients with major depression, catatonia, and other psychiatric disorders and conditions. Among patients with depression, ECT is effective at attaining remission in 50% to 60%, compared with 10% to 40% remission rates with pharmacotherapy or psychotherapy. A recent review reported successful completion of ECT in 3 patients with cerebral aneurysms taking an anticoagulant or antiplatelet medication. Nevertheless, ECT may be associated with an increased risk of complications when used in patients with some medical conditions, including unstable or severe cardiovascular disease, aneurysm or vascular malformation,
increased intracranial pressure, recent cerebral infarct, pulmonary conditions, and those at high risk of complications associated with anesthesia.3

There is a theoretical risk of intracerebral hemorrhage when patients, particularly those on anticoagulants, undergo ECT and experience the typical postictal surge in blood pressure. It has been widely accepted that as long as patients on warfarin are within the desired international normalized ratio (INR) range (usually 2-3), it is safe to undergo ECT without an increased risk of intracerebral hemorrhage.3 One retrospective review4 evaluated 284 ECT treatments in 35 patients taking warfarin. For the duration of the study, patients were within the therapeutic INR range for 61%, subtherapeutic for 36%, and supratherapeutic for 3% of the time. The average course duration of ECT was 8 treatments per patient, and there were 0 instances of intracerebral hemorrhage during the study time frame of 8 years.4 There have also been multiple case reports5,5 of patients on warfarin who were successfully treated with ECT with no adverse events.

In addition to the potential risk of bleeding, there is a concern regarding the development of a pulmonary embolism (PE) during ECT. One proposed mechanism involves the mobilization of an already formed DVT secondary to muscle contraction as a result of the seizure elicited during the ECT.6 There have been at least 2 reports7-8 of PE occurring during ECT treatment, 1 of which was fatal. In an analysis9 of 8 patients receiving concomitant ECT and either edoxaban or apixaban for an acute DVT, 1 patient (12.5%) developed a PE during ECT. Reassuringly, other case reports5,10-12 have indicated that ECT sessions could be completed successfully and without complications after the development of a VTE. One published case report5 even described safe resumption of ECT as soon as 3 days after heparin initiation for acute PE.

During the last decade, several direct oral anticoagulants (DOAC) have been approved by the FDA for treatment and prevention of thromboembolism. Currently, there are 4 FDA-approved DOACs: dabigatran, which is a direct thrombin inhibitor, and apixaban, rivaroxaban, and edoxaban, which are Factor Xa inhibitors. The DOACs have an advantage over warfarin in that they don’t require intensive and long-term anticoagulant monitoring; furthermore, the risk of spontaneous CNS hemorrhage with DOACs is significantly less than with warfarin when dosed to target an INR of 2 to 3.13 One disadvantage, however, is that there is no standardized test available to monitor the anticoagulation effect or toxicity of these drugs.

To our knowledge, there is scant literature on the use and safety of ECT in patients on DOAC therapy. There have been 2 case reports14-15 on rivaroxaban. One of these cases14 was a 62-year-old male on rivaroxaban for stroke prevention who received ECT for 5 months with no adverse events reported. The other case15 was a 66-year-old female who during the same hospitalization was initiated on rivaroxaban for PE and had 6 ECT sessions performed with no adverse outcomes related to the anticoagulation. Another case series16 describes 2 patients on dabigatran for atrial fibrillation who successfully completed ECT sessions with no adverse outcomes. Finally, 1 retrospective review9 evaluated apixaban and edoxaban therapy for DVT in 8 patients receiving ECT with no adverse outcomes reported. The authors in all cases concluded that these medications may represent a safe and effective alternative to traditional warfarin therapy in atrial fibrillation and VTE treatment in patients receiving ECT, but further work is needed to confirm these findings in a larger groups of patients.

In this study, we assessed the use, tolerability, and safety of both DOACs and warfarin among patients receiving ECT in a large academic medical center and tertiary care facility in Maine.

**Methods**

**Patient Cohort**

All patients aged >18 years who received ECT while taking either a DOAC (apixaban, rivaroxaban, edoxaban, or dabigatran) or warfarin at Maine Medical Center between December 2012 and December 2018 were potentially eligible for inclusion in this retrospective cohort study. The study was approved by the Maine Health IRB. The start date was chosen for ease of data collection because of change of electronic health record system at that time.

**Data Collection**

One of the authors (N.C.) collected data from the medical record using a standardized protocol that included demographic data, details of anticoagulant use, concomitant medications that increase the risk of bleeding (ie, SSRIs, NSAIDs, aspirin) and prespecified laboratory findings such as serum creatinine, creatinine clearance, platelet count, and INR for those on warfarin. Additional information collected included the indication for ECT, treatment frequency, and procedural details for each ECT session. The adverse effects collected included number of bleeding episodes, number of hypercoagulable events, and other serious adverse effects of either ECT or anticoagulation therapy within 48 hours of each ECT session. Adverse effect data were reviewed and verified by a pharmacist board certified in pharmacotherapy and psychiatry. Laboratory and demographic data were considered to be current if they were obtained within 90 days of the ECT session.

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days of ECT. If ECT encounters spanned several years, the average weight and age for a given patient during their treatment period was calculated.

**Statistical Analysis**

Data are presented descriptively as mean ± SD, median (IQR) or frequency (n, %), as appropriate. Data were analyzed using SPSS version 25 and Microsoft Excel version 2016.

**Results**

We identified 32 patients with 247 ECT encounters while on either a DOAC (apixaban, rivaroxaban, edoxaban, or dabigatran) or warfarin during the study time period. Clinical and demographic characteristics of these patients are presented in Table 1. Twenty-three (71.9%) patients were on warfarin and 9 (28.1%) were on DOACs, including rivaroxaban (n = 5; 2 were prescribed 15 mg twice daily and 3 were on 20 mg daily) and apixaban (n = 4; all prescribed 5 mg twice daily); no patients were taking dabigatran or edoxaban. The DOAC dose was appropriate in each patient according to the FDA prescribing information. The median warfarin dose was 3 mg (SD 1.89 mg). Indications for anticoagulant use were acute VTE (14/32, 43.8%) and cardioembolic stroke prevention in the context of atrial fibrillation (18/32, 56.2%). In most patients, the anticoagulant therapy had been initiated before admission, however 1 patient (1/32, 3.1%) was initiated on rivaroxaban for an acute DVT 3 days prior to ECT treatment. Concomitant SSRI or SNRI therapy was recorded for 23/32 (71.9%) patients, with the most common medications being trazodone ≥150 mg (6/32, 18.8%) and sertraline (3/32, 9.4%); an additional 3 patients (9.4%) took both. Less commonly prescribed antidepressants included fluoxetine, paroxetine, citalopram, escitalopram, and venlafaxine. Patients also frequently received daily low dose aspirin (5/32, 15.6%) and in 19/247 (7.7%) encounters, patients received NSAIDs within 2 days of ECT.

**TABLE 1: Characteristics of patients on warfarin and direct oral anti-coagulants (DOAC) therapy**

| Variable                              | Overall | Warfarin | DOAC |
|---------------------------------------|---------|----------|------|
| N                                     | 32      | 23       | 9    |
| Age, y, mean ± SD                     | 71.5 ± 11.4 | 73.8 ± 11.1 | 65.8 ± 10.9 |
| Female gender, n (%)                  | 19 (59.4) | 12 (56.5) | 6 (66.7) |
| Weight, kg, mean ± SD                 | 84.2 ± 26.2 | 83.4 ± 29.4 | 85.7 ± 16.6 |
| BMI, kg/m², median (IQR)              | 29 (23.6-34.2) | 26.8 (22.9-33.1) | 30.7 (26.9-34.8) |
| ECT treatments/patient, n (IQR)       | 6.5 (5-10) | 7 (5-10) | 6 (4.9-5) |
| Anticoagulation for VTE, n (%)        | 14 (43.8) | 10 (43.5) | 4 (44.4) |
| Anticoagulation for atrial fibrillation, n (%) | 18 (56.2) | 13 (56.5) | 5 (55.6) |

**TABLE 2: Encounter-specific characteristics of patients on warfarin and direct oral anti-coagulants (DOAC) therapy**

| Variable                              | Overall | Warfarin | DOAC |
|---------------------------------------|---------|----------|------|
| Encounters, n                         | 247     | 188      | 59   |
| Serum creatinine, mg/dL, median (IQR) | 0.9 (0.76-1.78) | 0.9 (0.78-2.69) | 0.81 (0.76-1.19) |
| Platelet count, thousands/microliter, median (IQR) | 209 (169-247) | 205 (149-231) | 270 (228-325) |
| Mean INR, No., mean ± SD              | ...     | 2.1 ± 0.54 | ... |
| Therapeutic INR, n (%)                | ...     | 108 (57.4) | ... |

INR = international normalized ratio.

Data available for n = 243 encounters overall; n = 185 on warfarin and n = 58 on DOAC.
patients. Comparable to national averages of time within therapeutic range (53.7%), 57.5% of patient encounters involving warfarin had a therapeutic INR result. Only 8 patient encounters (4.3%) involved supratherapeutic INR readings and the maximum INR was 3.5 in a patient with a goal of 2 to 3. Of note, there were no patients with documented liver disease, and none were taking any medications known to have a pharmacokinetic drug-drug interaction with one of the DOACs. Patients were receiving ECT for treatment-resistant depression (32.3%), depression with psychosis (26.5%), neurocognitive disorder with behavior disturbances (17.6%), treatment-resistant bipolar disorder (8.8%), treatment-resistant schizophrenia (5.9%), treatment-resistant psychosis (5.9%), and catatonia (2.9%; Table 3). Most (93%) patients were in the acute induction phase of ECT and receiving at least 3 ECT treatments per week for a duration of 1 to 12 weeks. Electrode placement was unilateral only in 15 (46.9%) patients, unilateral and bilateral in 10 (31.2%), and bilateral only in 7 (21.9%) patients. Overall, adverse effects within 48 hours of ECT therapy were uncommon, with 9/247 (3.6%) encounters recording an event; frequency was 3/248 (1.2%) in the warfarin group and 6/59 (10.2%) in the DOAC group. In the DOAC group, headache accounted for 4/6 (66.7%) of the adverse events reported. Non-CNS bleeding during the course of ECT treatment was recorded in each group. One patient (3.1% of 32 patients) receiving concurrent rivaroxaban and venlafaxine experienced gastrointestinal bleeding that was determined to be unlikely related to ECT given the extracranial location, and 1 patient on fluoxetine 60 mg and warfarin (INR 1.9) experienced hemoptysis thought to be secondary to epistaxis. No other major bleeding, and notably, no CNS hemorrhage, occurred. Furthermore, despite the frequent history of acute VTE in these patients, with its associated risk for residual DVT and dislodgement, no patient developed an acute PE during an ECT session nor for the duration of hospitalization (Table 4).

**Discussion**

The high efficacy of ECT for treating psychiatric disorders must be balanced against the fact that it is an invasive procedure with rare but potentially serious adverse effects. Using ECT for patients also taking oral anticoagulants needs special attention since intracranial hemorrhage can pose a serious risk. As described above, there have been few reports of safety profiles for ECT patients taking DOACs. To our knowledge this is the first study to date of anticoagulant safety among patients concomitantly receiving ECT that includes both patients taking warfarin and those taking DOACs.

Our findings suggest that anticoagulant-associated adverse events are rare in the context of ECT. DOACs and warfarin appear to be safe in the treatment of patients with atrial fibrillation or acute VTE who are receiving concomitant ECT. This understanding is important because there is emerging evidence that second-generation antipsychotics increase the risk of acute VTE, making the psychiatric population more vulnerable to this medical condition. This retrospective cohort study should be interpreted cautiously, and randomized-controlled studies should be conducted in the future to further elucidate this conclusion.

We acknowledge that our findings may have limited generalizability to other populations as this study did not evaluate patients with advanced liver or kidney dysfunc-

**TABLE 3:** Distribution of indications for ECT, stratified by individual patients and by encounters

| Indication                        | Frequency, n (%) | Patients n = 32 | Encounters n = 247 |
|----------------------------------|-----------------|----------------|--------------------|
| Depression, TR                   | 11 (32.3)       | 97 (39.3)      |
| Depression with psychosis         | 9 (26.5)        | 50 (20.2)      |
| Neurocognitive disorder with behavior disturbances | 6 (17.6) | 26 (10.5) |
| Bipolar disorder, TR             | 3 (8.8)         | 23 (9.3)       |
| Schizophrenia, TR                | 2 (5.9)         | 34 (13.8)      |
| Psychosis, TR                    | 2 (5.9)         | 15 (6.1)       |
| Catatonia (with bipolar disorder) | 1 (2.9)         | 2 (0.8)        |

TR = treatment resistant.

*One patient received ECT for depression with psychosis followed by ECT for TR bipolar disorder. A second patient received ECT for depression with psychosis followed by ECT for TR depression; thus the denominator used for calculating frequency was n = 34.

**TABLE 4:** Major adverse effects of ECT or anticoagulation therapy, stratified by anticoagulant type

| Variable                        | Frequency, n or n (%) | Overall | Warfarin | DOAC |
|---------------------------------|-----------------------|---------|---------|------|
| Encounters                      | 247                   | 188     | 59      |
| Headache                        | 4 (1.6)               | 0       | 4 (6.8) |
| Respiratory distress<sup>a</sup> | 2 (0.8)               | 2 (1.1) | 0       |
| Cardiovascular event<sup>b</sup>| 1 (0.4)               | 0       | 1 (1.7) |
| CNS bleeding                    | 0                     | 0       | 0       |
| Non-CNS bleeding                | 2 (0.8)               | 1 (0.5) | 1 (1.7) |
| Development of PE               | 0                     | 0       | 0       |
| Non-PE clotting event           | 0                     | 0       | 0       |

DOAC = direct-acting anticoagulant; PE = pulmonary embolism.

<sup>a</sup>Respiratory distress or aspiration.

<sup>b</sup>Cardiovascular event consisting of 30 seconds of pulseless electrical activity followed by full recovery.
tion, those taking dabigatran or edoxaban, nor those taking any medications known to have a pharmacokinetic drug-drug interaction with one of the DOACs. Future studies are needed in these patient populations to expand our knowledge of and guidance for the management of patients taking anticoagulants who receive ECT treatment. In conclusion, for patients in which they are otherwise appropriate, the DOACs rivaroxaban and apixaban, in addition to warfarin appear to be safe treatment options among patients receiving ECT.

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