BRIEF TECHNICAL REPORT

Clotting-Factor Concentrations 5 Days After Discontinuation of Warfarin

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Background: The American Society of Regional Anesthesia and Pain Medicine guidelines recommend discontinuation of warfarin and an international normalized ratio (INR) of 1.2 or less before a neuraxial injection. The European and Scandinavian guidelines accept an INR of 1.4 or less. We evaluated INR and levels of clotting factors (CFs) II, VII, IX, and X 5 days after discontinuation of warfarin.

Methods: Patients who discontinued warfarin for 5 days and had an INR of 1.4 or less had activities of factors II, VII, IX, and X measured. The primary outcome was the frequency of subjects with CF activities of less than 40%.

Results: Twenty-three patients were studied; 21 (91%) had an INR of 1.2 or less. In these 21 patients, the median (interquartile range) activities of factors II, VII, IX, and X were 66% (52%–80%), 114% (95%–132%), 101% (84%–121%), and 55% (46%–63%), respectively. Ninety-five percent (99% confidence interval, 69%–99%) had CF activities of greater than 40%. The patient who did not CF activities greater than 40% had end-stage renal disease. Two subjects had an INR of greater than 1.2; the activities of factor II, VII, IX, and X were 37% and 46%, 89% and 105%, 66% and 78%, and 20% and 36%, respectively. Neither patient had CF activities of greater than 40%.

Conclusions: Based on 40% activity of CFs, patients with INRs of 1.2 or less can be considered to have adequate CFs to undergo neuraxial injections. The number of patients with an INR of 1.3 and 1.4 is too small to make conclusions.

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The American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines on regional anesthesia recommend that in patients on warfarin, the drug is to be discontinued and an international normalized ratio (INR) of 1.2 or less be achieved before a neuraxial injection is performed.[1] This was to ensure that the activities of clotting factors (CFs) X and II, the CFs with the longest half-lives, are adequate (ie, at least 40%). The European and Scandinavian guidelines, on the other hand, accept an INR of 1.4 or less.[2,3] There has been no study on the levels of vitamin K–dependent CFs following warfarin discontinuation at slightly prolonged INRs (1.3–1.4) or at INRs of 1.2 or less, in the setting of patients who are to undergo regional anesthesia or pain interventional pain procedures. The purpose of this study was to evaluate the concentrations of CFs II, VII, IX, and X in relation to the INR in patients whose warfarin was stopped for 5 days before their surgery or interventional pain injection.

METHODS

The study was approved by the Northwestern University Institutional Review Board (STU00089581). The study was an observational cross-sectional trial conducted at Northwestern Memorial Hospital of the Northwestern University Feinberg School of Medicine, Chicago, Illinois. Inclusion criteria included patients presenting for surgery or who were on warfarin for at least 3 months and discontinued the drug for 5 days and had an INR of 1.4 or less. Exclusion criteria included patients with platelet counts of less than 100,000/μL, coagulopathies (partial thromboplastin time >35 seconds, fibrinogen <200 mg/dL), creatinine greater than 2.0 mg/dL, and liver function tests more than 2 times the upper limit of normal range.

After obtaining written informed consent, blood was drawn into sodium citrate Vacutainer tubes and centrifuged at 4°C to obtain plasma. The plasma was stored in aliquots at −70°C. The frozen samples were thawed at 37°C, and CFs II, VII, IX, and X were assayed using the STA Compact-Factors assay method (Diagnostica Stago, Parsippany, New Jersey).

Statistical Analysis

A sample size analysis was performed using the following assumptions: 95% of patients with an INR of 1.2 or less and 75% of patients with INRs of 1.3 to 1.4 would have CF activities levels greater than 40%. Based on the aforementioned assumption, a sample of 110 patients, 55 per group, would be required to have 80% power to detect a significant difference at $\alpha = 0.05$ in the number of subjects who did not have CF activities of greater than 40%.

The primary outcome was the incidence of subjects who failed to have a vitamin K–dependent CF activity greater than 40% 5 days after discontinuation of warfarin therapy. Because we were interested in the association of the INR with the CF activities, we stratified subjects according to the ASRA guidelines compared with the European and Scandinavian recommendations. Data are presented as median (interquartile range). Confidence intervals for the binomial outcome were calculated at 99% using the Clopper-Pearson method.

RESULTS

Study recruitment began in May 2014 and was closed on December 31, 2016. We were not able to perform a definitive

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study because only 23 patients were recruited after 2 years, and only 2 subjects had an INR of 1.3 or 1.4. The low recruitment rate was due to the rare occurrence of INRs of 1.3 to 1.4 after warfarin discontinuation because the surgeons were advising their patients to discontinue their warfarin 6 to 7 days preoperatively to ensure an INR of 1.2 or less. We also withheld recruiting patients with INRs of 1.2 or less by August 2016 until more patients with INRs of 1.3 and 1.4 were recruited. Because further patient recruitment appeared futile, we elected to terminate the study at the end of 2016 and present our initial results as a brief report.

Of the 23 subjects studied, all had discontinued their warfarin for 5 days prior to presentation for surgery or pain interventional procedure. Twenty-one subjects (91%) had an INR of 1.2 or less. Nine (43%) of the 21 subjects were male, and 12 (57%) were female. Subject characteristics for the 21 subjects, median (interquartile range), were as follows: age 72 (67–79) years, body mass index (BMI) 31 (25–27) kg/m^2, INR prior to discontinuation 2.4 (2.2–2.7), and warfarin dose 5 (5–5.5) mg. The levels, expressed as percent activities, of the vitamin K–dependent CFs II, VII, IX, and X were 66% (52%–80%), 114% (95%–132%), 101 (84%–121%), and 55% (46%–63%), respectively. Twenty of the 21 subjects, 95% (99% confidence interval, 70%–99%), had factors II, VII, IX, and X activities greater than the 40% recommended level of activity. Eleven of the 21 patients had neuraxial injections, 1 had a transforaminal epidural steroid injection, 6 had regional/pain blocks, and 3 had no block. Follow-up of the patients who had injections did not reveal any ecchymosis.

One of the 21 subjects had provided consent and had blood drawn before her preoperative laboratory values were available. She was 67 years old with a BMI of 33 kg/m^2 and an INR of 0.9 on the day of her surgery. Her blood urea nitrogen (BUN) was 64 mg/dL, creatinine was 5.3 mg/dL, and glomerular filtration rate (GFR) was 10 mL/min per 1.73 m^2. A left supraclavicular nerve block was performed under ultrasound guidance, and an arteriovenous fistula was placed uneventfully. The activities of factors II, VII, IX, and X were 41%, 159%, 55%, and 37%, respectively.

Subjects (n = 2) with an INR of greater than 1.2 activities of CFs II, VII, IX, and X were 37% and 46%, 89% and 105%, 66% and 78%, and 20% and 36%, respectively. Neither had CF activities greater than 40%; no injection was performed in these patients (Table 1).

DISCUSSION

The important finding of our study was the demonstration that the activities of the vitamin K–dependent CFs exceed 40% 5 days after discontinuation of warfarin when the INR is 1.2 or less. Although this finding is probably expected, there has been no study that looked into the activities of the CFs in patients who were being considered for a regional or interventional pain block. In contrast, patients with slightly increased INRs (1.3–1.4) had factors II and X activities of less than 40%, the CFs with the longest half-lives. In addition, despite a normal INR, CF activities may not be greater than 40% even after discontinuation of warfarin for 5 days in patients with end-stage renal failure.

Warfarin exerts its anticoagulant effect by interfering with the synthesis of the vitamin K–dependent CFs II, VII, IX, and X. The effects of warfarin are not evident until activities of the CFs fall less than 20% of normal, and this depends on the half-life of the CF. The half-lives of factors VII, IX, X, and II are 6 to 8, 24, 25 to 60, and 50 to 80 hours, respectively. The levels, expressed as percent activities, of the CFs required for in vivo hemostasis range from 10% for CF VII, 30% for CF IX, 20% for CF X, and 20% to 30% for prothrombin.[4] Studies to support these specific activities were not stated by the authors.

The CF activities that are acceptable for surgery and regional anesthesia are controversial. Clotting factor activity greater than 30% is the goal of fresh frozen plasma transfusions.[5] Surgeons consider CF activities less than 30% to be critical as surgical hemostasis appears to be compromised when CF levels fall below 30%.[6] The ASRA guidelines on neuraxial and regional procedures in patients taking anticoagulants, on the other hand, chose CF activities of less than 40% as indicating a significant risk of clinical bleeding.[1] Similar to the ASRA guidelines, we considered CF activities of less than 40% as the cutoff for increased risk of bleeding. This is because of the risk of spinal hematoma, realistic delays in its diagnosis, possible rapid progression of symptoms, and consequences that can be catastrophic. In contrast, bleeding is visualized and cauterized or ligated during surgery.

The European and Scandinavian guideline of an INR of 1.4 or less is supported by other investigators. The median CF VII activity was noted to be 57% in patients with INRs of 1.35 (1.3–1.7).[7] However, the range in the CF VII activities in this study was wide, 25% to 124%. Another study did not show increased rate of hemorrhagic complications after placement of an intracranial pressure monitor in patients with INRs of 1.3 to 1.6.[8] An evidence-based review concluded that there was a paucity of studies supporting increased bleeding in patients with abnormal coagulation test and undergo invasive procedures.[9] The invasive procedures that were reviewed included central vein cannulation, femoral arteriography, liver or kidney biopsy, paracentesis, and thoracentesis. Only 3 lumbar punctures were included in 1 of the studies reviewed. Therefore, the procedures in these publications did not have the devastating complication of paraplegia after neuraxial injections. Finally, a large observational study did not observe any complication related to warfarin in 2549 patients who had interventional pain treatments.[10] The procedures included transforaminal injection (880 patients), medial branch blocks (1090 patients), sacroiliac joint blocks (171 patients), radiofrequency neurotomy (29 patients), and interlaminar injections (25 patients). Unfortunately, the INRs of the patients were not stated.

Some of the factors associated with increased response to warfarin include age (>65 years), female sex, low weight (<100 lb), race (Asian ancestry), preexisting medical conditions (liver, cardiac, and renal disease), and drug interactions.[11] In a study of 12,202 patients receiving warfarin maintenance, it was noted that warfarin dose was inversely related to age and strongly associated with female sex.[11] This was also evidenced by a report of an 85-year-old female patient who developed a spinal hematoma after taking a 10-mg dose of warfarin preoperatively.[12] Patients with low body weight and low serum albumin (warfarin is >90% bound to plasma proteins) require lower doses.[13] There is synergism between warfarin and aspirin, nonsteroidal anti-inflammatory drugs, dong quai, and danshen.[1] On the other hand, ginseng reduces the effect of warfarin by increasing its clearance.

The patient in our study with impaired renal function, whom we unintentionally included, had barely acceptable activities of CFs X (37%) and II (41%). Patients with early-stage chronic kidney disease, even those who appear well nourished, often have poor dietary intake of vitamin K and biochemical evidence of vitamin K deficiency.[14] This is the most likely explanation for the reduced CF levels of our patient. Although warfarin is eliminated through hepatic metabolism and not directly excreted by the kidney, patients with chronic renal impairment have higher risk of hemorrhagic and ischemic episodes.[15] Studies reported that African, European, Asian, and Hispanic American patients with moderate and severe kidney impairment required reduction

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TABLE 1. Medical History of the Patients and Activities of Their Clotting Factors

Patient Information	Daily Warfarin Dose, mg	INR		Relevant Laboratory Results	Factor Activities			
		Before Discontinuation	5 d After Discontinuation		II	VII	IX	X
Subjects with INR ≤1.2								
61 y, F, BMI 35 kg/m^2, PE, general anesthesia	5 alternate with 2.5	3.7	1.2	Platelets 281	64	134	134	42
86 y, F, BMI 39 kg/m^2, AF, PE, ankle block	6 alternate with 3	1.6	1.2	BUN 16, creatinine 1.8	72	114	99	46
67 y, F, BMI 53 kg/m^2, AF, PE, CSE	6	2.6	1.1	BUN 20, creatinine 1.2	80	172	153	63
71 y, F, BMI 33 kg/m^2, PE, TPI	5 alternate with 2.5	2.3	1.1		93	156	151	81
63 y, M, BMI 42 kg/m^2, AF, spinal anesthesia	7	5.1	1.1	Platelets 226	85	121	122	68
67 y, M, BMI 28 kg/m^2, AF, genitofemoral nerve block	5	2.3	1.1		88	127	100	64
73 y, F, BMI 31 kg/m^2, AVR, general anesthesia	5	2.6	1.1	Platelets 161	50	95	66	40
79 y, F, BMI 38 kg/m^2, AF, PE, spinal anesthesia	5	2.6	1.0	Platelets 236	72	114	97	57
72 y, M, BMI 26 kg/m^2, AF, MVR, transforaminal ESI	6 alternate with 3	2.4	1.1		52	87	68	41
72 y, M, BMI 27 kg/m^2, AF, MVR, cervical ESI	7.5	2.0	1.0	Platelets 151	93	126	120	61
72 y, F, BMI 23 kg/m^2, AF, epidural anesthesia	4 alternate with 2	3.0	1.2		76	74	108	55
83 y, M, BMI 27 kg/m^2, AF, CSE	5	4.3	1.2	Platelets 204	49	69	72	43
80 y, M, BMI 18 kg/m^2, AF, ESI	5	2.2	1.2	Platelets 147	60	96	51	55
70y, F, BMI 31, AF, PE, SIJ injection	3.5	2.3	1.1		75	107	107	73
73y, F, BMI 28, AF, spinal anesthesia	5	2.7	1.1	BUN 33, creatinine 1.3, platelet 170	58	111	101	52
47 y, F, BMI 34 kg/m^2, PE, sciatic-saphenous nerve block	5	2.7	1.1		92	122	127	79
94 y, M, BMI 24 kg/m^2, VTEs, TPI	5 alternate with 2.5	2.3	1.1	Platelets 234	60	132	121	54
70 y, M, BMI 47 kg/m^2, VTE, spinal anesthesia	5	2.4	1.1	Platelets 182	52	141	117	49
79 y, M, BMI 22 kg/m^2, AF, ESI	2.5	1.8	1.0	Platelets 201	50	85	96	63
79 y, F, BMI 21 kg/m^2, MVR, ESI	5	2.0	1.1	BUN 21, GFR 57 mL/min per 1.73 m^2	66	89	84	52
67 y, F, BMI 33 kg/m^2, AF, ESRD, CAD, s/p stent placement, no procedure	5	2.2	0.9	Platelets 305, BUN 64, creatinine 5.3, GFR 10 mL/min per 1.73 m^2	41	159	55	37
Subjects with INR values of 1.3 or 1.4								
85 y, F, BMI 29 kg/m^2, AF, MVR, no procedure	4 alternate with 2	3.1	1.3	BUN 30, creatinine 1.3, platelet 179, PTT 40.8	46	105	78	36
75 y, F, BMI 32 kg/m^2, AF, CVA, aspirin 81 mg, no procedure	2 alternate with 1	2.5	1.4	BUN 23, creatinine 1.03, GFR 52 mL/min per 1.73 m^2, platelet 169	37	89	66	20

Normal values in our laboratory: CF VII: 67% to 162%, CV IX: 65% to 165%, CF X: 82% to 155%, CF II: 82% to 148%. The levels of clotting factors are noted as percent activities; there is no specific unit.

Units of measurement: Platelets: per mcL (microliter); BUN: mg/dL; Creatinine: mg/dL.

AF indicates atrial fibrillation; AVR, aortic valve replacement; CAD, coronary artery disease; CSE, combined spinal-epidural; CVA, cerebrovascular accident; ESI, epidural steroid injection; ESRD, end-stage renal disease; F, female; M, male; MVR, mitral valve replacement; PE, pulmonary embolism; PTT, partial thromboplastin time; SIJ, sacroiliac joint; TPI, trigger point injection; VTE, venous thromboembolism.

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in their maintenance dose of warfarin.[16] In fact, investigators have excluded patients with creatinine greater than 150 μmol/L (1 mg/dL = 88.4 μmol/L) in their studies on INR after discontinuation of warfarin.[17]

Most publications focused on the INR values, and not the CF activities, after warfarin is discontinued. Warfarin is usually stopped 5 days preoperatively in patients with INRs between 2.0 and 3.0 because it takes 4.7 days to achieve an INR of 1.1 or less.[18] It is interesting that 5 (23%) of the 22 patients in the study of White et al[18] had INRs of 1.2 or greater 5 days after warfarin was stopped. Another study showed 15 (7%) of 224 patients had INRs greater than 1.5 at 5 days after the warfarin was stopped.[17] The results of this latter study may explain why some investigators stop warfarin 5 days before invasive procedures in patients with INRs of 2.0 to 3.0 but 6 days before invasive procedures in patients with slightly higher INRs of 2.5 to 3.5.[19] In this study,[19] the warfarin was stopped an average of 5.7 days before the procedure. In this study, the INR levels were not stated at the end of 5 or 6 days, when the invasive procedure was performed. Later studies and the recent American College of Chest Physicians guidelines recommended stoppage of the warfarin for 5 days.[20] At any rate, this brings into question whether the duration of warfarin discontinuation should be revisited (ie, 5 days for INRs of 2.0–3.0 and 6 days for INRs of 2.5–3.5) This is to increase the probability of the INR being 1.2 or less on the day of the patient's surgery or neuraxial injection.

The ASRA recommendation on the requisite normalization of the INR has been rigidly followed, but such recommendation has not been backed up by a study on the activities of the relevant CFs in patients who were scheduled for regional or interventional pain procedures. Except in a patient with severe renal disease, we noted that the activities of CF II, VII, IX, and X were within normal limits when then INR is normal. None of the patients with INRs of 1.2 or less had bruising after the block. Our numbers, however, are very small. It should also be noted that spinal hematoma can occur in patients with normal coagulation values. Clotting factor activity, an in vitro study, is only 1 factor in the development and progression of spinal hematoma. Other considerations include the number of neuraxial attempts, presence of vascular abnormality, and spinal stenosis.

After 2½ years, we enrolled only 2 patients with INRs of 1.3 to 1.4. Both patients had less than 40% activities of CF X and II. The numbers are extremely small for us to conclude that these INRs are associated with CF activities of less than 40%. Neither can we make statements on the safety of administering regional blocks in patients with these INRs, as CF activities is only 1 factor in the development of spinal hematoma. A multi-institutional study on this issue is recommended.

Although only 24 patients were included in this study, the activities of the vitamin K–dependent CFs in each patient were determined. We decided to publish our results to support the ASRA recommendation about the INR being normal after warfarin is stopped, except in patients with severe renal disease. Our surgeons have pushed for neuraxial injections in these patients commenting that a slight prolongation of the INR by 0.1 or 0.2 should not make a difference in the activities of the vitamin K–dependent CFs. We want to inform clinicians that the activities of CFs X and II in patients with INRs of 1.3 to 1.4, 5 days after discontinuation of warfarin, are below the levels recommended by ASRA. This does not imply that administering regional nerve blocks, especially superficial injections, is not safe. We recommend discussion of the risk and benefits of neuraxial and deep regional/plexus blocks performed in these patients

Future studies should continue to examine the activities of CFs in patients with INRs of 1.3 to 1.4, regardless of the duration of discontinuation of warfarin. The ideal duration of interruption, 5 or 6 days, should also be investigated. The concentration of CFs should be determined in patients who are at risk of an exaggerated response to warfarin but have a normal INR. These include elderly women and patients with severe liver or kidney disease.

In summary, this study showed adequate activities of the vitamin K–dependent CFs in patients with INR of 1.2 or less 5 days after discontinuation of warfarin, with the exception of a patient in chronic renal failure. The CF activities in patients with INRs of 1.3 to 1.4 require further evaluation.

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