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Effects of Obesity on Warfarin Reversal With Vitamin K

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Abstract

Phytonadione (vitamin K1, VK) is fat soluble and may be sequestered by adipose tissue, thus potentially altering drug distribution in obese patients requiring warfarin reversal. This single-center retrospective cohort study aimed to determine the effects of obesity (defined as body mass index [BMI] $\geq$ 30 kg/m^2) on warfarin reversal following administration of VK in adult patients. The primary outcome was complete or partial warfarin reversal (defined as an international normalized ratio [INR] $\leq$ 2.0) within 72 hours post-VK administration. Of 688 identified patients, 215 were included in primary INR analysis. Mean BMIs for obese (n = 84) and nonobese (n = 131) patients were 37.3 and 24.3 kg/m^2 ($P < .001$), and mean baseline INRs were 4.73 and 4.42 ($P = .534$), respectively. Within 72 hours post-VK administration, 70% and 69% of the obese and nonobese groups, respectively, achieved complete or partial warfarin reversal ($P = .904$). Multiple logistic regression determined baseline INR and concomitant fresh frozen plasma administration to be factors influencing warfarin reversal. These findings do not suggest obesity is significantly associated with a decreased likelihood of warfarin reversal within 72 hours post-VK administration.

Keywords

anticoagulants, bleeding, clinical pharmacology

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Introduction

Approved in 1954 in the United States, warfarin is a commonly used oral anticoagulant for prevention and treatment of thromboembolic events associated with venous thromboembolism and atrial fibrillation.[1] The anticoagulant effects of warfarin can be reversed with an antidote, phytonadione, or vitamin K1 (VK).[2,3] Since VK is fat soluble, it is easily distributed to tissues.[4] It has been proposed that VK can be sequestered by adipose tissue, thus contributing to lower circulating VK in those with higher body fat percentage.[5] To support this theory, Shea et al demonstrated VK accumulates in adipose tissue at higher concentrations than that of other organs known to store this vitamin (eg, liver). The authors also indicated an inverse relationship exists in women between body fat percentage and plasma VK. With potential sequestration by fatty tissue, the distribution and efficacy of administered VK may be affected.

Various factors have been determined to impact the efficacy of VK in international normalized ratio (INR) reversal. Tsu et al demonstrated VK dose, route, and baseline INR influenced reversal, whereas home warfarin dose did not.[6] Manufacturers recommend VK 2.5 to 10 mg initially for anticoagulant-induced prothrombin deficiency and 25 to 50 mg in rare occasions.[2,3] Current guidelines support the use of VK for warfarin reversal in patients with an INR greater than 10 or serious or life-threatening bleeding but not routine VK use in those with an INR between 4.5 and 10 and no evidence of bleeding.[7] Lower doses (2.5-5 mg) of oral VK are recommended in patients meeting reversal criteria with no evidence of bleeding, while higher doses (5-10 mg) of intravenous (IV) VK are preferred for major bleeding.[7,8] Further analysis by Tsu et al indicated IV doses larger than 2 mg did not result in more pronounced INR reductions at 12, 24, and 48 hours.[6] Higher doses can lead to prolonged effects on coagulation such as INR overcorrection and temporary warfarin refractoriness, which

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may necessitate bridging with parenteral anticoagulants to prevent thromboembolism.[2-4]

Warfarin reversal with VK may be affected by obesity in addition to VK route, dose, and baseline INR. Recent literature evaluating body mass index (BMI) in warfarin-related bleeding indicated higher bleeding risk in obese patients.[9] Obesity was an independent predictor of anticoagulation reversal failure (defined as INR $\geq$1.5) in a study evaluating prothrombin complex concentrate (PCC) for warfarin-related acute intracranial hemorrhage.[10] However, while other reversal agents such as fresh-frozen plasma (FFP) and PCC have specified weight-based dosing,[11,12] current guidelines and manufacturer recommendations for VK merely suggest a general dosing range.[2,3,7,8] Literature evaluating the impact of obesity on VK-induced INR reduction for warfarin reversal is lacking.

The primary aim of this study was to determine whether obesity affects warfarin reversal following administration of VK. If obesity is truly associated with an increased incidence of warfarin reversal failure post-VK administration, this may necessitate larger VK doses in obese patients. The secondary objective was to assess the impact of obesity on patient outcomes, such as bridging incidence and duration, in warfarin reversal with VK.

Methods

Study Design and Patients

This was an institutional review board–approved retrospective cohort analysis within a 495-bed academic teaching hospital. Patients were identified through a query of electronic medication orders for VK and confirmed by manual review. Patients were eligible for inclusion if they were at least 18 years of age, administered VK via any route for warfarin reversal, and admitted between January 1, 2014, and December 31, 2016. Patients were excluded if they were prisoners or wards of the state and if there was no documented baseline INR, subsequent INR post-VK administration, height, or weight.

Outcomes

The primary outcome was complete or partial warfarin reversal (defined as INR 2.0 or less) within 72 hours post-VK administration. In particular, complete warfarin reversal was defined as INR less than 1.5, whereas partial warfarin reversal was defined as INR between 1.5 and 2.0.[6,13] Secondary outcomes included incidence of anticoagulation bridging and duration, subsequent thromboembolic and hemorrhagic in-hospital events, length of stay, and in-hospital mortality. Bridging was defined as the temporary use of a parenteral anticoagulant during interruption of warfarin therapy typically when the INR is below therapeutic range.[14] Thromboembolic events included deep vein thrombosis, pulmonary embolism, myocardial infarction, arterial thrombosis, ischemic stroke, and transient ischemic attack. Major bleeding was defined as a hemorrhagic event that resulted in a reduction in hemoglobin of at least 2 g/dL, transfusion of 2 or more units of packed red blood cells, symptomatic bleeding in a critical area or organ, and/or death.[15] Minor bleeding was defined as all other bleeding not identified as major bleeding.

Data Collection

All patient data were maintained in a Microsoft Excel (Redmond, Washington) spreadsheet. To provide quality assurance, individuals responsible for data collection were trained in the use of the database and random audits were conducted. Baseline demographics collected included age, race, sex, height, weight, BMI, and home warfarin dose. Additional data obtained from patient medical records included concomitant drug interactions with warfarin (ie, amiodarone, sulfamethoxazole-trimethoprim, metronidazole, fluconazole), VK dose and route, baseline and subsequent INRs up to 72 hours post-VK administration, hemorrhagic and/or thrombotic events, and adjunct therapy (eg, FFP and PCC). If patients had multiple height and weight values documented within the study period, the data nearest to the time of initial VK administration were utilized. Obesity classifications were outlined according to the World Health Organization with obesity defined as $\geq$ 30 kg/m^2.[16]

To further isolate the effects of VK on INR reduction, data were processed to censor INRs and additionally exclude patients. In particular, those who received multiple doses of VK, received confounding adjunct therapy (eg, nonconcomitant FFP, PCC, or activated factor VII), or had an incalculable baseline INR were excluded after INR censoring. However, patients who received concomitant FFP, defined as receiving FFP within 1 hour of the initial VK dose, were included in this prespecified subpopulation. The primary outcome of complete or partial warfarin reversal was evaluated in the aforementioned subpopulation, termed as the "primary INR analysis." Conversely, the population before this second exclusion and censoring process was termed the "clinical cohort," in which all secondary outcomes were assessed.

Statistical Analysis

All statistical analyses were performed by SAS 9.4 software (Cary, North Carolina). Continuous variables for the obese and nonobese groups were compared using Student *t* test, whereas categorical variables were compared using χ^2, Fisher exact, and Mann-Whitney *U* tests. Comparisons of outcomes within subclasses of BMI were conducted via 1-way analysis of variance (ANOVA) and χ^2 test. Due to the variability in INR collection times, analysis of maximum likelihood estimates was used with logistic regression to assess factors associated with warfarin reversal failure in the primary INR analysis population. A post hoc sensitivity analysis was also completed for the primary outcome. Overall, a 2-sided α level of $< .05$ was considered statistically significant.

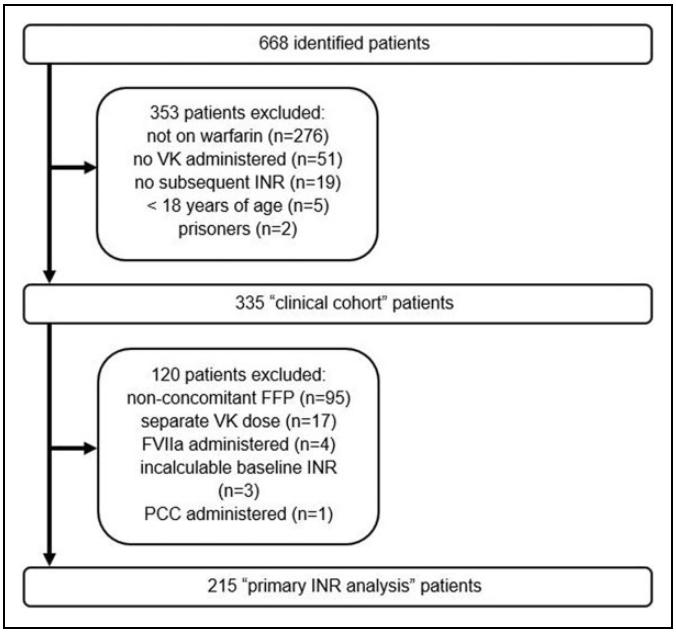

Figure 1. Flow diagram of patient population. FFP indicates fresh frozen plasma; FVIIa, recombinant human coagulation factor VIIa; INR, international normalized ration; PCC, prothrombin complex concentrate; VK, phytonadione.

Results

Of 688 identified patients who had an electronic order for VK within the prespecified time range, 335 and 215 patients were included into the clinical cohort and primary INR analysis, respectively (Figure 1).

Primary INR Analysis

The baseline characteristics of the primary INR analysis patients (N = 215) are outlined in Table 1. In this population, obese patients were generally older than nonobese ones (66.9 [12.9] vs 73.9 [12.9] years, $P < .001$) and less likely to receive concomitant amiodarone (n = 6; 7% vs n = 31; 24%, $P = .002$). The mean weight and BMI of obese patients were 110.9 kg and 37.3 kg/m^2, whereas that of nonobese patients were 71.5 kg and 24.3 kg/m^2, respectively ($P < .001$ for both). Of the 84 obese patients, 34 (40%), 28 (33%), and 22 (26%) were categorized as class I, II, and III obesity, respectively. Of the 131 nonobese patients, 8 (6%) were categorized as underweight (defined as BMI <18.5 kg/m^2).[16] Mean baseline INR was similar between obese and nonobese groups (4.73 [1.94] vs 4.42 [1.40], $P = .534$). A majority of the population was being anticoagulated for atrial fibrillation. Within the obese and nonobese groups, 18 (21.4%) and 20 (15.3%) patients received concomitant FFP, respectively ($P = .247$). For those who received concomitant FFP, with each unit of FFP estimated to contain approximately 200 mL, the mean weight-adjusted dose of administered FFP was lower in obese patients (6.01 [3.95] vs 9.25 [5.09] mL/kg, $P = .036$).

Table 1. Baseline Characteristics for Primary INR Analysis Patients (N = 215).[a]

Characteristic	Obese, n = 84	Nonobese, n = 131	*P* Value
Age, years	66.9 (12.9)	73.9 (12.9)	<.001
Weight, kg	110.9 (25.3)	71.5 (14.1)	<.001
BMI, kg/m^2	37.3 (7.1)	24.3 (3.6)	<.001
Baseline INR	4.73 (1.94)	4.42 (1.40)	.534
Female	40 (48)	55 (42)	.373
White	73 (87)	109 (83)	.889
Atrial fibrillation	46 (55)	131 (63)	.253
Major bleeding	21 (25)	33 (25)	.703
Minor bleeding	12 (14)	13 (10)	
No bleeding	51 (61)	85 (65)	
Amiodarone	6 (7)	31 (24)	.002
Concomitant FFP	18 (21)	20 (15)	.247

Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; INR, international normalized ratio.
[a]Expressed as mean (SD) or n (%).

Table 2. Indications for Warfarin Reversal for Primary INR Analysis Patients (N = 215).[a]

Indication	Obese, n = 84	Nonobese, n = 131	*P* Value
Major bleeding	21 (25)	33 (25)	.412
Minor bleeding; urgent procedure	2 (2)	2 (2)	
Minor bleeding; no urgent procedure; INR $\geq$ 4.5	5 (6)	7 (5)	
Minor bleeding; no urgent procedure; INR < 4.5	5 (6)	4 (3)	
No bleeding; urgent procedure	18 (21)	28 (21)	
No bleeding; no urgent procedure; INR > 10	3 (4)	5 (4)	
No bleeding; no urgent procedure; INR 4.5-10	26 (31)	35 (27)	
No bleeding; no urgent procedure; INR < 4.5	4 (5)	17 (13)	

Abbreviation: INR, international normalized ratio.
[a]Expressed as n (%).

Indications for warfarin reversal are portrayed in Table 2 and distinguished by degrees of bleeding and INR elevation in addition to the need for INR normalization for an urgent procedure, such as an orthopedic surgery.[7] The most common warfarin reversal indications for obese and nonobese patients were: (1) an elevated INR between 4.5 and 10 without evidence of bleeding or tentative urgent procedure requiring INR normalization (n = 26; 31% vs n = 35, 27%) and (2) major bleeding with any INR (n = 21; 25% vs n = 33, 25%). The distribution of reversal indications was similar for both groups ($P = .412$). As depicted in Figure 2, routes of VK administration did not significantly differ between groups ($P = .107$). Dose distribution of administered VK is provided in Table 3 with VK doses categorized as low ($\leq$ 1.25 mg), medium (2-5 mg), and high ($\geq$ 10 mg).[6]

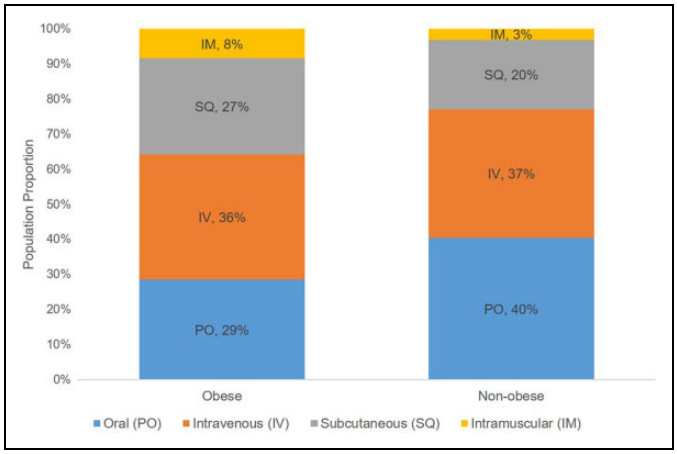

Figure 2. Route of phytonadione administration in primary INR analysis. INR indicates international normalized ratio.

Table 3. Phytonadione Dosing Distribution Within Different Routes of Administration.[a]

	Obese, n = 84	Nonobese, n = 131	*P* Value
Oral, mg			
≤ 1.25	4 (17)	1 (2)	.083
2-5	19 (79)	43 (81)	
≥ 10	1 (4)	9 (17)	
Intravenous, mg			
≤ 1.25	1 (3)	0 (0)	.711
2-5	15 (50)	29 (60)	
≥ 10	14 (47)	19 (40)	
Subcutaneous, mg			
≤ 1.25	1 (4)	2 (8)	.555
2-5	7 (30)	4 (15)	
≥ 10	15 (65)	20 (77)	
Intramuscular, mg			
≤ 1.25	1 (14)	1 (25)	> .05[b]
2-5	1 (14)	0 (0)	
≥ 10	5 (71)	3 (75)	

[a]Expressed as n (% within subgroup).
[b]*P* value for comparisons of intramuscular phytonadione dose distributions was unable to be approximated with Mann-Whitney *U* test due to small sample sizes.

Of the 215 patients included in the primary outcome analysis, 59 (70%) obese patients achieved complete or partial warfarin reversal (INR ≤ 2.0) within 72 hours post-VK administration compared to 91 nonobese patients (69%; $P = .904$). Complete or partial warfarin reversal rates within 24 and 48 hours post-VK administration did not significantly differ between the 2 groups (24 hours: n = 41; 49% vs n = 67; 51%, $P = .738$; 48 hours: n = 58; 69% vs n = 86; 66%, $P = .605$). The complete warfarin reversal rates (INR < 1.5) within 72 hours post-VK administration were 56% and 50% for obese and nonobese groups, respectively ($P = .424$). When comparing the primary outcome in patients within each subclass of obesity to that of the nonobese group, no significant difference was detected (class I: 23/34 [68%], class II: 20/28 [71%], class III: 16/22 [73%]; $P = .976$).

Table 4. Warfarin Reversal Failure via Multiple Logistic Regression.

	Adjusted Odds Ratio	95% Confidence Interval	*P* Value
Baseline INR	1.22	1.09-1.36	<.001
Age	0.99	0.96-1.01	.446
IV vs SQ route	0.54	0.22-1.32	.107
Phytonadione dose	0.98	0.88-1.09	.753
Concomitant FFP	0.68	0.48-0.94	.021
Obesity	0.73	0.37-1.44	.374

Abbreviations: FFP, fresh frozen plasma; INR, international normalized ratio; IV, intravenous; SQ, subcutaneous.

Results from multiple logistic regression are shown in Table 4. Two statistically significant predictors of warfarin reversal failure (INR > 2.0 within 72 hours) were identified. Patients with increased baseline INR were more likely to experience warfarin reversal failure (odds ratio [OR] 1.223; 95% confidence interval [CI], 1.097-1.363; $P < .001$). Alternatively, patients given concomitant FFP had a much lower odds of warfarin reversal failure compared to those who did not (OR 0.68; 95% CI, 0.489-0.0944; $P = .021$). Further analysis indicated obesity and BMI were not significant predictors of warfarin reversal failure (OR 0.736; 95% CI, 0.374-1.449; $P = .374$ and OR 0.98; 95% CI, 0.94-1.02; $P = .340$, respectively). Intravenous VK administration in comparison to subcutaneous (SQ) administration did not exhibit a statistically significant influence on warfarin reversal failure (OR 0.549; 95% CI, 0.227-1.325; $P = .107$).

A post hoc sensitivity analysis was completed on the primary INR analysis subpopulation who did not receive concomitant FFP. Consequently, the complete or partial warfarin reversal rates within 72 hours post-VK administration did not differ between obese and nonobese patients in this particular subpopulation (44/66 [67%] vs 73/111 [66%], $P = .902$].

Clinical Cohort Analysis

The baseline characteristics of the clinical cohort (N = 335) are summarized in Table 5. These findings were generally comparable to those of the primary INR analysis, featuring statistically significant differences between obese and nonobese patients in age (67.5 [13.4] vs 73.5 [13.4], $P < .001$) and concomitant amiodarone (n = 15; 12% vs n = 41; 20%, n = 0.043). Over half of the clinical cohort received FFP at least once during admission (obese: n = 68; 52% vs nonobese: n = 114; 56%; $P = .554$). In-hospital patient outcomes are described in Table 6. Anticoagulation bridging incidence and duration did not significantly differ between obese and nonobese groups (35% vs 41%, $P = .266$ and 3.6 [2.7] vs 4.3 [3.3] days, $P = .183$, respectively). In both groups, SQ enoxaparin was the most commonly used parenteral anticoagulant for bridging (27/46 [59%] vs 53/85 [62%], $P = .681$).

The obese group in the clinical cohort was comprised of 65 (50%), 36 (28%), and 29 (22%) patients of class I, II, and III obesity, respectively. The bridging incidences and durations of

Table 5. Baseline Characteristics for Clinical Cohort Patients (N = 335).[a]

Characteristic	Obese, n = 130	Nonobese, n = 205	*P* Value
Age, years	67.5 (13.4)	73.5 (13.4)	<.001
Weight, kg	109.0 (22.4)	71.7 (27.2)	<.001
BMI, kg/m^2	36.7 (7.9)	24.5 (7.8)	<.001
Baseline INR[b]	5.01 (3.59)	5.03 (3.60)	.961
Female	58 (45)	89 (43)	.829
White	100 (77)	170 (83)	.175
Atrial fibrillation	73 (56)	121 (59)	.604
Major bleeding	46 (35)	64 (31)	.587
Minor bleeding	16 (12)	22 (11)	
No bleeding	68 (52)	119 (58)	
Amiodarone	15 (12)	41 (20)	.043
FFP administration	68 (52)	114 (56)	.554

Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; INR, international normalized ratio.
[a]Expressed as mean (SD) or n (%).
[b]One obese and 2 nonobese patients with incalculable INRs were excluded from this calculation.

Table 6. Patient Outcomes Within Clinical Cohort (N = 335).[a]

	Obese, n = 130	Nonobese, n = 205	*P* Value
Bridging incidence	46 (35)	85 (41)	.266
Bridging duration, days	3.6 (2.7)	4.3 (3.3)	.183
New thrombus	2 (2)	8 (4)	.326
Length of stay, days	8.1 (6.9)	7.9 (6.1)	.789
In-hospital mortality	8 (6)	10 (5)	.613

[a]Expressed as mean (SD) or n (%).

class I, II, and III obese patients were similar to that of the nonobese group ($P = .476$; $P = .435$ via ANOVA). Hospital lengths of stay for class, I, II, and III obese patients were 7.6 (7.1), 7.3 (5.0), and 10.1 (8.1) days, respectively ($P = .285$ when compared to that of nonobese group via ANOVA).

Discussion

The results suggest obesity may not be associated with an increased likelihood of warfarin reversal failure within 72 hours post-VK administration. Warfarin reversal rates among 3 obesity subclasses also did not differ. Conversely, concomitant FFP administration and baseline INR were factors that significantly influenced warfarin reversal, which is consistent with previously published literature.[6] The sensitivity analysis, which excluded patients who received concomitant FFP, produced similar results to that of the primary INR analysis.

The multiple logistic regression indicated that IV VK administration was trending toward decreased likelihood of warfarin reversal failure when compared to SQ administration (OR 0.549), but this was not statistically significant. This may be due to the prespecified, longer INR follow-up time of 72 hours as an elevated INR will generally normalize over time, regardless of VK administration, as warfarin's pharmacologic activity wanes and the liver produces clotting factors, ultimately leading to potential for negative confounding. Previously published literature supports this finding as Nee et al demonstrated IV VK caused a greater INR reduction at 24 hours when compared to SQ VK but both routes led to similar INR reductions at 72 hours.[17]

Regarding route of VK administration, our study found an extensive use (23%) of SQ VK in the primary INR analysis population. However, oral and IV VK are preferred over SQ VK due to its erratic absorption and effects on warfarin reversal.[4,7] This result may be due to the study setting where resident physicians enter a large proportion of medication orders. Additionally, provider concerns of hypersensitivity reactions associated with IV VK administration may partially contribute to the unexpectedly frequent utilization of SQ VK for warfarin reversal.[2] Historically, IV VK-associated anaphylaxis rates were very low with an estimated incidence of 3 per 100 000 doses.[18] Our study included 1 suspected anaphylaxis case out of 174 doses of IV VK.[18] In theory, high use of SQ VK should decrease the rate of warfarin reversal in obese patients relative to that of nonobese patients due to increased capacity of adipose tissue to sequester fat-soluble VK in obese patients, but this finding was not supported by our results in the subset of patients who received SQ VK (obese: 17/23 [74%] vs nonobese: 17/26 [65%], $P = .517$). A separate pharmacokinetic theory to explain these nonsignificant results is VK sequestration by adipose tissue can lead to prolonged effects of VK on coagulation as the antidote is redistributed in the body over time, allowing for gradual INR reduction and warfarin reversal over 72 hours.[4] Moreover, obese individuals typically have higher prevalence of hepatic steatosis and nonalcoholic fatty liver disease (NAFLD), which may hypothetically facilitate delivery of administered, fat-soluble VK to the liver, thus promoting clotting factor production and increasing warfarin reversal probability.[19] Of 130 obese patients in the clinical cohort, 4 (3%) had documented chronic liver disease with none being attributed to NAFLD. It is still plausible that many obese patients had some degree of hepatic steatosis, which can consequently affect drug distribution of VK. However, VK administration routes did not significantly differ between obese and nonobese groups, and biological plausibility of the original theory of VK sequestration by adipose tissue should be unchanged. Furthermore, comparison of obese and nonobese groups who received oral or IV VK yielded no difference in the primary outcome (36/54 [67%] vs 73/101 [72%], $P = .466$).

Multiple logistic regression via analysis of maximum likelihood estimates did not indicate increasing BMI was associated with increasing likelihood of warfarin reversal failure ($P = .340$), as it trended toward the opposite outcome, albeit with a clinically insignificant reduction in likelihood of warfarin reversal failure (OR 0.98).

As shown in Table 5, obese and nonobese patient in-hospital outcomes did not differ in regard to bridging incidence and duration, new thrombus incidence, length of stay, and mortality. However, patients with class III obesity, occasionally

known as "morbid obesity," had a statistically nonsignificant increased mean length of stay of 10.1 days compared to those of other BMI categories (mean length of stay ranging from 7.3 to 7.9 days). This may be attributed to the higher number and severity of comorbidities associated with class III obesity.[20]

The mean weight-adjusted FFP dosing for both groups was below the recommended dosing range of 10 to 15 mL/kg, but FFP underdosing appears to be common in clinical practice.[11,21] In addition to provider lack of FFP dosing familiarity, provider-individualized goals in warfarin reversal can contribute to this underdosing as providers may aim for different INR goals (eg, complete and immediate INR normalization for major bleeding vs INR reduction to 1.9 or less in 24 hours for elective procedures in the absence of bleeding).

Although the current study provides additional data related to factors associated with VK reversal, there are limitations. First, the variability of provider-individualized goals in warfarin reversal is frequent. Patients are likely to have different indications for warfarin reversal with VK, and this inevitably leads to different decisions on administration and dosing of VK and FFP. In effect, despite exhibiting a similar distribution of author-categorized warfarin reversal indications between obese and nonobese groups in the primary INR analysis, the study population can still be heterogeneous, thus increasing the potential for confounding and bias. This was partially accounted for via multiple logistic regression. In addition, the retrospective and observational nature of this study increases data heterogeneity as it did not allow for uniform INR monitoring frequencies and timing post-VK administration. Depending on how often and when INR labs were drawn, warfarin reversal rates within shorter time frames, such as those evaluated in previously published literature (eg, 12 and 24 hours), can be indeterminate if INR labs are infrequent.[6] Hence, these outcomes within shorter time frames were not reported. The authors also deemed interpolation and extrapolation of INR values to specific time points (eg, 12, 24, and 48 hours) using preexisting INR values to be inappropriate as there is no evidence to suggest INRs decrease in a linear or other well-modeled manner post-VK administration over such time periods. Recognizing the high probability for INR timing issues, the authors designated an INR follow-up time of 72 hours for the primary outcome, albeit this 72-hour follow-up time also allows more time for INRs to normalize, thus potentially influencing the primary outcome. A prospective study design with prespecified times for INR lab draws can resolve this limitation.

In clinical practice, if the initial dose of VK does not provide adequate INR reduction in warfarin reversal with or without adjunct therapy such as FFP, providers can opt to repeat VK administration with the theoretical potential for consequent warfarin refractoriness with frequent administration of high VK doses ($\geq$ 10 mg).[2-4,6] In result, this can be associated with increased bridging incidence and duration.[4,6] At this time, there is little to no published evidence to adequately support individual VK doses, initial or subsequent, greater than 10 mg in patients requiring warfarin reversal (excluding superwarfarin poisoning), regardless of obesity class.[4,22]

Conclusion

A retrospective, observational evaluation of warfarin reversal within 72 hours post-VK administration at an academic teaching hospital suggests complete or partial INR reversal within 72 hours post-VK administration is not affected by obesity status. Also, BMI as a continuous variable did not significantly influence this result. Although weight-based dosing for FFP and other treatment modalities exists for reversal of warfarin-induced coagulopathy,[11,12] little to no evidence exists in clinical literature to support increasing VK doses solely based on body weight or BMI. These results underscore the need for more research on the efficacy and safety of anticoagulation antidotes in patients at extremes of body weight as their pharmacokinetic differences can theoretically affect outcomes.

Authors' Note

Ethical approval to conduct this research was obtained from the Texas Tech University Health Sciences Center Amarillo Institutional Review Board (IRB# A17-3994). Informed consent for patient information to be published in this article was not obtained because Institutional Review Board review found this research to meet prespecified criteria, such as minimal risk, and in accordance with 45 CFR 45.116 (d) waived the requirement for documentation of consent. This work was presented as a poster (Abst. # 44108) at the American College of Clinical Pharmacy Conference, Phoenix, AZ, October 9, 2017.

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