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Before-After Study of an Electronic Order Set for Reversal of Vitamin K Antagonist–Associated Intracerebral Hemorrhage

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Abstract

Background: Vitamin K antagonist (VKA)–associated intracerebral hemorrhages (ICHs) are more likely to expand and are associated with higher mortality than primary ICH. Prompt reversal of anticoagulant effect with prothrombin complex concentrate (PCC) may promote hemostasis and decrease hematoma expansion. The aim of this study was to evaluate the impact of an electronic order set designed to standardize and facilitate more timely reversal of coagulopathy in VKA-associated ICH. **Methods:** We identified all adults who received PCC for VKA-associated ICH from June 2012 to June 2015 at University of California San Francisco Medical Center, which included a period before and after an electronic order set became available in 2014. We abstracted baseline demographics and clinical data from electronic health records. The primary outcome was time from radiographic identification of ICH to administration of PCC. **Results:** Thirty-one patients received PCC for VKA-associated ICH, including 17 patients before and 14 patients after the order set became available. Baseline demographics and clinical features were similar. Order set use was associated with a significant decrease in the time from identification of ICH on imaging to the administration of PCC (median 83 vs 45 minutes; $P = .02$), more accurate dosing (29.4% vs 92.9%; $P < .01$), and a shorter time from the PCC order to follow-up international normalized ratio (INR) testing (median 164 vs 85 minutes, $P = .001$). **Conclusion:** An electronic order set for administering PCC for VKA-associated ICH was associated with significantly faster time to PCC administration and increased dosing accuracy.

Keywords

intracerebral hemorrhage, anticoagulation, reversal agents, vitamin K antagonist, warfarin, prothrombin complex concentrate

The increasing prevalence of atrial fibrillation, particularly as our population ages, has contributed to a growing number of patients using oral anticoagulant therapy.[1] Vitamin K antagonists (VKAs) remain the most widely prescribed class of oral anticoagulant to prevent thromboembolic events due to atrial fibrillation but are associated with an increased risk of hemorrhagic complications.[1,2] Intracranial hemorrhages are responsible for nearly 90% of deaths, as well as the majority of long-term disability associated with this class of medication.[2] Intracerebral hemorrhage (ICH), in particular, carries the highest burden of mortality and morbidity, and the incidence of VKA-associated ICH has steadily increased over the past several decades.[3,4] In a large national registry, the proportion of ICH admissions related to VKA therapy increased from 5.8% in 2005 to 7.8% in 2008.[4] Although mortality for non-VKA ICH has been steadily declining, mortality for VKA-associated ICH has remained around 40% to 60% for the past several decades, which corresponds to a 35% higher risk of death.[2,4,5]

Hematoma expansion occurs in 36% to 56% of patients with VKA-associated ICH, which is more common than with primary ICH and is a major determinant of mortality and

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functional outcomes.[6,8] Early administration of reversal agents such as prothrombin complex concentrate (PCC) in VKA-associated ICH is thought to promote rapid hemostasis through normalization of international normalized ratio (INR) and anticoagulant effect, thereby reducing hematoma expansion and final blood volume.[7,9,10]

In this setting, a standardized electronic order set for the reversal of VKA-associated ICH has the potential to reduce dosing variability, to mitigate delays associated with correcting or confirming dosing, and ultimately to accelerate the time from identification of the hemorrhage to administration of reversal agents. Therefore, our institution embarked on a collaborative interdisciplinary effort, including physicians, nurses, and pharmacists, to develop a mandatory electronic order set for VKA-associated ICH reversal that incorporated dosing guidelines for PCC and vitamin K. We then conducted a before and after analysis of the impact of this order set on key processes and outcomes.

Methods

Study Design

We conducted a before-after study of the impact of a mandatory electronic order set intervention on process measures for reversal of anticoagulation for VKA-related intracerebral hemorrhage. This study was approved by the local institutional review board under a waiver of informed consent.

Patient Selection

We retrospectively identified all adults (aged $\geq$18 years) who had received PCC for ICH between June 2012 and June 2015 at a tertiary care teaching hospital (University of California San Francisco Medical Center) using pharmacy records indicating any administration of PCC. Radiographic evidence of ICH on computed tomography (CT) and a history of VKA exposure with a recorded INR greater or equal to 1.5 at presentation was required for inclusion in this analysis. We excluded all patients with evidence of a primary subdural, epidural, or subarachnoid hemorrhage and all patients who were transferred in from another facility with a previously identified ICH.

Electronic Order Set Intervention

An interdisciplinary group of physicians, nurses, and pharmacists developed a standardized electronic order set to provide an accessible and efficient method to calculate dosing, order reversal agents, and additional laboratory monitoring for patients requiring urgent anticoagulation reversal for VKA-associated hemorrhage. Based on guideline recommendations for best practices and institutional protocols, the electronic order set included preset weight–based PCC dosing for each baseline INR range, dose rounding instructions for pharmacists, prechecked intravenous vitamin K orders, repeat INR checks, and nursing instructions for administering PCC. For patients with known VKA exposure presenting with ICH, the order set called for an initial dose of 25 units per kilogram to be administered even before the first INR result becomes available in order to mitigate treatment delays. Once the actual INR result is available, the order set specified that a supplemental dose be given if necessary in order to achieve the total INR-based goal dose. Prior to the implementation of the electronic order set, a 3-factor PCC was available via a stand-alone medication order that required the clinician to manually enter the dose. On March 1, 2014, when the order set became available, the use of a 4-factor PCC was mandatory and was only available as part of the electronic order set bundle; a stand-alone medication order for PCC was no longer allowed. An attempt to order PCC directly would instead link to the newly implemented order set, thus mandating its use. A one-time competency examination on PCC administration for all pharmacists and e-mail notifications about the availability of new order set were sent to neurology, emergency medicine, and neurosurgery residents. No other interventions targeting the reversal of VKA-associated ICH took place during the entire study period.

Data Abstraction

We abstracted data on patient demographics, clinical parameters, and laboratory data through a review of each patient's comprehensive electronic health record. Clinical scores including Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), and ICH scores[11] were determined based on total scores as documented or imputed from clinical documentation of the constituent elements of each score. Time points captured included the time of initial imaging study, PCC order entry, PCC administration, and time of when the INR was collected before and after PCC administration. All time points were abstracted from the electronic health record by reviewing laboratory and medication administration records, and the methods for data abstraction were the same before and after implementation of the intervention. Calculations of a target weight–based dose were similarly derived from the comprehensive electronic health record.

Outcomes

The primary outcome was the time from identification of ICH on imaging to PCC administration. Time from completion of imaging study to PCC order and time from order entry to PCC administration were also calculated. Secondary outcomes included target PCC dosing, which was defined as an ordered dose that was within a margin of 20% of the target dose in units per kilogram. For 3-factor PCC, the institutional target dose was 75 units/kg. For 4-factor PCC, the target dose varied based on actual weight and initial INR: for an INR between 1.5 and 3.9, the target dose was 25 units/kg, for INR between 4 and 6, the target was 35 units/kg, and for INR >6, the target

Table 1. Baseline Characteristics and Outcomes of Patients With VKA-Associated ICH Treated With PCC.[a]

Baseline Characteristics	Preintervention (n = 17)	Postintervention (n = 14)	Entire Cohort (n = 31)
Age, median (IQR)	74 (12.0)	73 (12.0)	74 (9.0)
Female, n (%)	6 (35.3)	6 (42.9)	12 (38.7)
Presented to emergency department, n (%)	15 (88.2)	10 (71.4)	25 (80.6)
Initial INR, median (IQR)	2.0 (0.7)	3.2 (2.0)	2.6 (1.0)
NIHSS, median (IQR)	17 (22)	20 (13)	19 (18)
GCS, median (IQR)	10 (10)	9 (6)	9 (9)
ICH score, median (IQR)	2 (3)	3 (1)	2 (2)
Intraventricular hemorrhage, n (%)	9 (52.9)	8 (57.1)	17 (54.8)
Infratentorial location, n (%)	1 (5.9)	0 (0.0)	1 (3.2)
	Preintervention (n = 17)	Postintervention (n = 14)	*P* Value
Primary outcome			
Minutes from imaging to medication administration, median (IQR)	83 (52)	45 (35)	.02
Secondary outcomes			
Minutes from imaging to medication order, median (IQR)	28 (27)	15 (17)	.43
Minutes from medication order to medication administration, median (IQR)	55 (14)	28 (19)	.002
Dose within 20% of target dose, n (%)	5 (29.4)	13 (92.9)	.001
Percentage deviation from target dose, median (IQR)	31 (28.0)	10 (8.7)	.005
Minutes from medication order to follow-up INR, median (IQR)	164 (104)	85 (59)	.001
INR at follow-up, median (IQR)	1.1 (0.2)	1.3 (0.2)	.01
Absolute decrease in INR, median (IQR)	0.9 (0.5)	1.8 (2.1)	.01
Vitamin K administered, n (%)	16 (94.1)	14 (100.0)	.55
Modified Rankin Scale at discharge, median (IQR)	6 (3)	6 (1.75)	.59
In-hospital mortality, n (%)	9 (52.9)	8 (57.1)	.55

Abbreviations: GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; INR, international normalized ratio; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; PCC, prothrombin complex concentrate; VKA, Vitamin K antagonist.
[a]Data expressed in number, percent, median (IQR).

was 50 units/kg. If a patient weighed $\geq$100 kg, then 100 kg would be used to calculate the dose. Other secondary outcomes included time from PCC order to follow-up INR, INR at follow-up, modified Rankin Scale at discharge, and in-hospital mortality.

Statistical Analysis

Statistical analysis was performed using Stata (StataCorp LP, College Station, Texas). Summary statistics for normally distributed variables were expressed as mean (standard deviation [SD]) and compared using the unpaired *t* test, and nonnormally distributed variables were summarized as median (interquartile range [IQR]) and evaluated using the Mann-Whitney-Wilcoxon test. Categorical variables were evaluated with Fisher exact test. *P* values less than .05 were considered statistically significant. We evaluated for a trend in the time from imaging to PCC administration using linear regression.

Results

We identified 72 adults that received PCC between June 2012 and June 2015, of which 41 had received PCC for intracranial hemorrhage. Of these, 5 were excluded because the primary indication for PCC was not ICH, and 5 had an ICH identified prior to transfer from another facility, leaving a final analysis cohort of 31 patients with VKA-associated ICH that had received PCC. This included 17 patients treated before and 14 patients treated after the mandatory PCC order set was implemented.

The baseline demographic and clinical characteristics of the analysis cohort are listed in Table 1. The median age was 74 years (IQR: 9), and there were 19 men and 12 women. Most patients presented to the emergency department acutely (25, 81%), whereas the remaining patients developed ICH after already having been admitted to the hospital. The median NIHSS was 19 (IQR: 18), median GCS was 9 (IQR: 9), and median ICH score was 2 (IQR: 3). Slightly more than half of the patients had evidence of intraventricular extension (17, 55%) and only 1 (3.1%) patient had an infratentorial hemorrhage. Baseline demographics and clinical features of the patients were similar before and after implementation of the order set, except that the presenting INR was higher in patients following the implementation of the order set (median INR: 2.0 pre vs 3.2 post; $P = .002$).

The median time from the completion of CT imaging study that demonstrated ICH to administration of PCC was

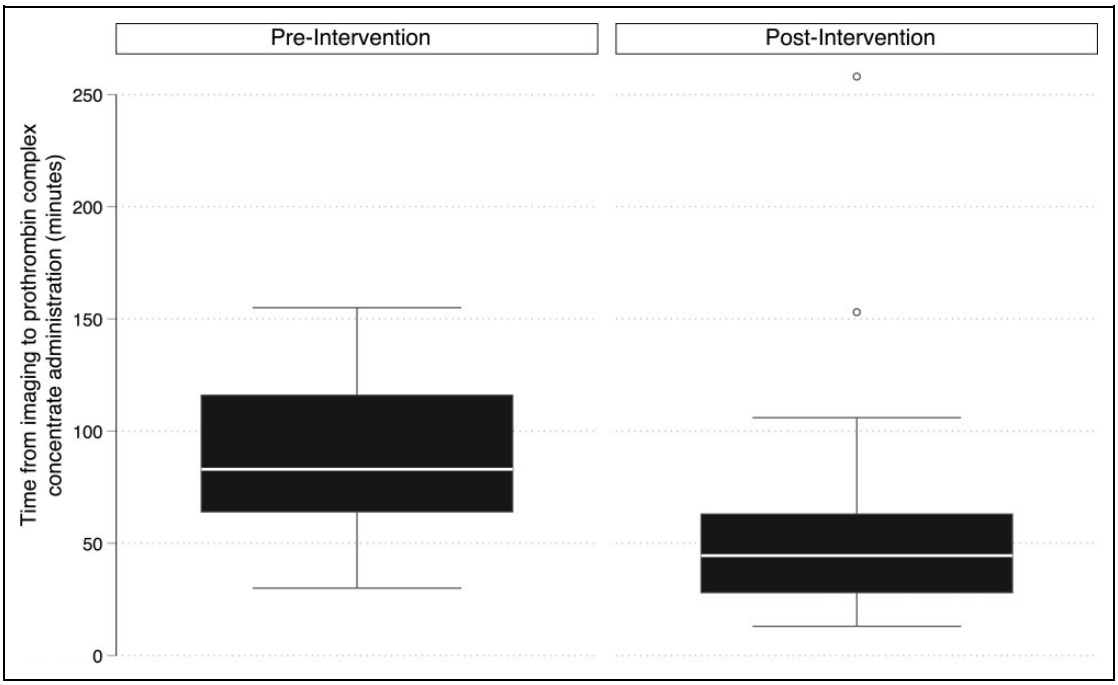

Figure 1. Time from imaging to administration of prothrombin complex concentrate for vitamin K-associated intracerebral hemorrhage before and after implementation of a mandatory electronic order set. The white line indicates the group median. The black box demonstrates the interquartile ranges. Bars represent upper and lower adjacent values. Circles represent specific outlier values.

significantly lower following the implementation of the order set (83 vs 45 minutes; $P = .02$; Figure 1). There was no evidence of a significant linear trend over time. There was no significant difference in the time from imaging to order entry (28 vs 15 minutes; $P = .43$), though the time from PCC order to administration was significantly lower (55 vs 28 minutes; $P = .002$; Table 1).

With the implementation of the electronic order set, patients were more likely to receive the target dose (29.4% vs 92.9%; $P = .001$). The median deviation from the target dose was also significantly decreased following the implementation of the order set (31% vs 10%; $P = .005$; Figure 2). All patients had a follow-up INR drawn after the administration of PCC except for 3 patients within the preorder set group, all of whom died. The time intervals from PCC order to INR follow-up were significantly lower with the order set as well (164 vs 85 minutes; $P = .001$). The median INR after PCC was somewhat higher in the postorder set group (1.1 vs 1.3, $P = .009$), though the overall decrease in INR after PCC was greater in the postorder set group (0.9 vs 1.4; $P = .01$). In-hospital mortality was high in both groups (53% vs 57%; $P = .55$) as was the median modified Rankin Scale at discharge (6 in each group; Table 1).

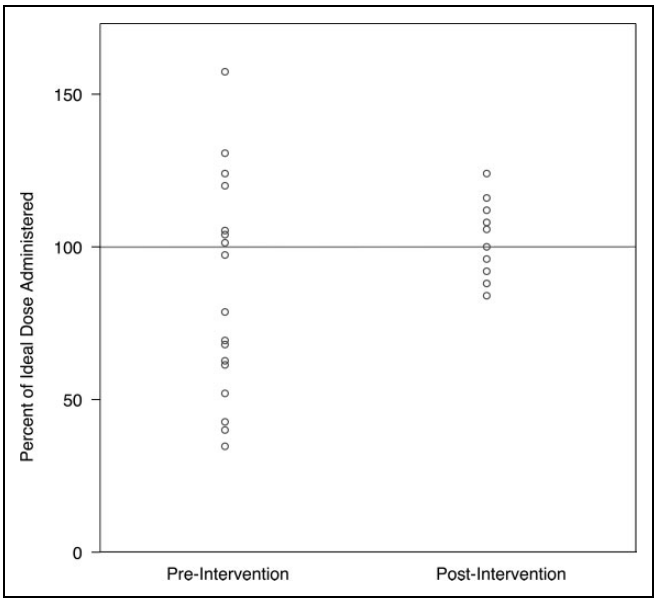

Figure 2. Percentage of ideal dose of prothrombin complex concentrate administered before and after implementation of a mandatory electronic order set. Each circle represents the percentage difference between the ideal versus the administered dose of prothrombin complex concentrate for each individual.

Discussion

At our academic medical center, the implementation of a mandatory electronic order set reduced the time from recognition of ICH to administration of PCC by nearly half, chiefly by decreasing the time from physician order to reversal agent administration. Although there was a nonsignificant trend toward faster time from recognition of ICH to order entry, the most significant reduction in time occurred following order

placement. We suspect this was largely driven by a more efficient process in the pharmacy to validate standardized PCC dosing that in turn led to more expedited delivery of drug to the bedside.

The mortality and morbidity associated with VKA-associated ICH are high.[2,4,5] Although definitive trials that clearly demonstrate improved clinical outcomes using targeted reversal of anticoagulation are lacking, the recent INR Normalization in Coumadin-Associated Intracerebral Hemorrhage trial demonstrated a nonsignificant trend toward reduced mortality in patients treated with PCC, particularly within the first 48 hours.[10] Further large-scale randomized controlled trials are warranted to confirm this relationship, but several factors have the potential to improve outcomes, including blood pressure control and prompt reversal of coagulopathy to promote hemostasis.[7]

Within this context, computerized physician order entry (CPOE) has the potential to improve health-care delivery by facilitating process improvement, providing clinical decision support, facilitating communication among members of the health-care team, and reducing medical errors.[12] Computerized physician order entry has the potential to reduce variability in medication dose administration as well as to reduce pharmacy processing times that allow for more accurate and efficient delivery of interventions.[13-15] Disease-specific order sets may also streamline and standardize the process of bundling an intervention together with associated clinical and nursing orders, which has previously been demonstrated to improve adherence to evidence-based guidelines for patients with acute myocardial infarction and have led to more expedited fluid resuscitation and antibiotic administration and decreased in-hospital mortality in patients admitted with sepsis.[16,17] For acute ischemic stroke, CPOE systems have been associated with increased use of intravenous tissue-plasminogen activator when indicated, decreased the door-to-needle times, and improved adherence to dysphagia evaluations.[18,19] We are not aware of any previous study that has similarly evaluated the impact of an electronic order set on the acute management of ICH.

Prior to the implementation of an electronic order set at our institution, the indications and dosing for PCC were sometimes based on ad hoc literature searches, or dosing regimens used at other institutions, and not necessarily based on the most up-to-date versions of internal guidelines. This practice led to more variable dosing, inconsistent vitamin K administration, as well as delays in VKA reversal. The significant reduction in the PCC dose variability with the mandatory order set likely occurred because it specifically reflected institutional guidelines and did not allow for alternative dosing. There was also a statistically significant decrease in the interval from the time of PCC order to follow-up INR, which is an important measure to assess whether the coagulopathy has been sufficiently reversed.

However, our study has several limitations. Although process measures for VKA-associated ICH treatment improved, these data reflect observations at a single center with a relatively small sample size that may not be generalizable to other settings. Whether mandating the use of the order set alone, without the associated engagement for order set development and outreach, would result in similar impacts is unknown. Due to the retrospective nature of this study, there remains the possibility that other unknown factors may have influenced the results. For example, since baseline INR was higher in postorder set implementation period, it is possible that observed changes potentially reflect a difference in perceived risk. When total scores were not available in the clinical documentation, clinical scores were imputed from available documentation thereby potentially introducing measurement error. Furthermore, we were unable to assess for some clinically pertinent variables such as hematoma expansion as a sizable proportion of patients did not have a follow-up scan—most commonly due to death or a transition to comfort care. Consistent with prior studies, clinical outcomes for both patient populations were poor with a considerable majority who died during their hospital stay and many left with severe functional impairment at discharge.

Despite these limitations, our study illustrates the potential positive impacts of an electronic order set for the management of VKA-associated ICH. These findings parallel the results of other studies involving disease-specific order sets, including for acute ischemic stroke, where standardization and process improvement have led to more efficient delivery of targeted interventions and in some cases improved clinical outcomes. We demonstrated a significant decrease in time to administration of PCC as well as more accurate dosing and a shorter time interval to follow-up INR. Whether similar interventions within larger populations of VKA-associated ICH patients or within the context of a randomized clinical trial would result in decreased hematoma expansion or improved clinical outcomes remains to be seen.

Conclusion

An electronic order set for administering PCC for VKA-associated ICH was associated with significantly faster time to PCC administration and less variability in dosing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. ASK reports research grants from NIH/NINDS, NIH/NCATS, SanBio, and Biogen for unrelated work and serves on a clinical trial DSMB for Neuravi.

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