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Effect of Phytonadione on Correction of Coagulopathy in Pediatric Patients With Septic Shock

Katy Stephens, PharmD; Jamie L. Miller, PharmD; Maura Harkin, PharmD; Stephen B. Neely, MPH; Laura Haws, MD; and Peter N. Johnson, PharmD

OBJECTIVES The purpose of this study was to evaluate phytonadione in children with septic shock with disseminated intravascular coagulopathy (DIC). The primary objective was to identify the number of patients with an international normalized ratio (INR), defined as ≤1.2, following phytonadione. Secondary objectives were to compare patients who achieved a normalized INR versus those with INR >1.2 and to determine factors associated with a normalized INR.

METHODS A retrospective study of children <18 years of age receiving phytonadione from October 1, 2013, to August 31, 2020, with a diagnosis of septic shock, were included. Data collection included demographics, phytonadione regimen, INR values, Pediatric Index of Mortality 2 (PIM2) and Pediatric Risk of Mortality III (PRISM III) scores, fresh frozen plasma (FFP) and cryoprecipitate use. A logistic regression model and generalized linear model were used to explore factors associated with a normalized INR and evaluate phytonadione dosing.

RESULTS Data for initial phytonadione course for 156 patients were evaluated. Sixty-six (42.3%) patients had a normalized INR. Most patients (n = 145; 92.9%) received ≤3 phytonadione doses, with the largest reduction in INR occurring after the second dose. In the logistic regression model, baseline INR, FFP, cryoprecipitate, vasopressors, PIM2, PRISM III, or cumulative phytonadione dose were not associated with achieving a normalized INR.

CONCLUSIONS Less than half of patients achieved a normalized INR. The median cumulative dose of phytonadione and receipt of FFP or cryoprecipitate was not associated with an increased odds of a normalized INR. Future studies are needed to further explore phytonadione use in children with sepsis-induced coagulopathy.

ABBREVIATIONS APACHE II, Acute Physiology and Chronic Health Evalauation II Score; aOR, adjusted odds ratio; DIC, disseminated intravascular coagulopathy; ECMO, extracorporeal membrane oxygenation; EMR, electronic medical record; FFP, fresh frozen plasma; INR, international normalized ratio; IV, intravenous; PIM2, Pediatric Index of Mortality 2; PRISM III, Pediatric Risk of Mortality III; SQ, subcutaneous

KEYWORDS children; coagulopathy; international normalized ratio; phytonadione; septic shock; vitamin K

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Introduction

Critically ill children with septic shock are at high risk for developing disseminated intravascular coagulopathy (DIC). DIC is often identified with elevated clotting test values, including international normalized ratio (INR), prothrombin time, and activated partial thromboplastin time.[1] When patients develop sepsis, proinflammatory mediators trigger tissue factor expression and ultimately lead to procoagulant upregulation.[2,3]

The goal of treatment for sepsis-induced DIC is to identify and treat the underlying cause and to return clotting tests to normal parameters and manage serious bleeding. Treatment options include blood products (e.g., fresh frozen plasma [FFP], cryoprecipitate, platelets) and vitamin K (phytonadione). FFP contains all clotting factors, fibrinogen, plasma proteins, and physiologic anticoagulants (e.g., protein C, protein S, antithrombin).[4] Cryoprecipitate contains fibrinogen, factor VII, factor XIII, von Willebrand factor, and fibronectin.[5] It is recommended in the management of DIC that blood products be reserved for patients with active bleeding, and not based on laboratory derangements alone owing to their risk for adverse events (e.g., transfusion-associated lung injury, fluid overload).[6] Several clotting factors including factors II, VII, IX, and X are dependent on vitamin K concentrations. It has been noted that many critically ill hospitalized patients are deficient in vitamin K; thus, supplementation of exogenous

phytonadione could be indicated for patients with a suspected vitamin K deficiency, based on an elevated INR >1.5, without evidence of active bleeding.[7–9]

Phytonadione can be given via the oral, intravenous (IV), intramuscular, or subcutaneous (SQ) routes. Intravenous phytonadione has the most rapid onset, with a reduction in INR within 4 to 6 hours.[1] Most studies have evaluated the role of phytonadione in bleeding associated with warfarin anticoagulation. Limited studies have evaluated phytonadione dosing in other causes of coagulopathy in DIC.[6,10,11] Overall, there is a paucity of data evaluating the role of phytonadione in pediatric patients with sepsis-induced coagulopathy and its potential benefit to adequately reverse coagulopathy, while also limiting adverse effects. The purpose of this study was to evaluate the impact of phytonadione on INR in pediatric patients with septic shock.

Materials and Methods

Study Design. This was a retrospective chart review of children <18 years of age admitted to a pediatric intensive care unit or the cardiac intensive care unit at a tertiary care academic health system from October 1, 2013, to August 31, 2020, who had a diagnosis of septic shock and received IV phytonadione. Patients were identified by using the institution's electronic medical record (EMR) (Meditech [Medical Information Technology, Inc, Westwood, MA]). Additional points for data collection that were not available in the EMR were collected through the Virtual Pediatrics Systems (Virtual Pediatrics Systems, LLC, Los Angeles, CA). Patients were excluded if phytonadione was administered via oral, intramuscular, or SQ route, owing to variability in absorption from these routes. Patients were also excluded if they received warfarin; received chronic phytonadione, including within total parenteral nutrition, prior to coagulopathy; had a chronic liver or hematologic disease known to result in elevated INR; or had incomplete records. For patients who may have received more than 1 course of phytonadione for septic shock during the study period, only their initial course was included.

Study Objectives and Data Collection. Demographic data including age, sex, height, and weight were collected for all patients. Data collection also included the IV phytonadione dosing regimen, including dose, frequency, and number of doses received. At the time of this study, there was no standardized dosing protocol at our institution for phytonadione for sepsis-induced DIC. Patients' INR values were collected, including a baseline INR within 24 hours prior to phytonadione initiation, during therapy, and up to 24 hours post phytonadione administration, if available. When multiple INR values were obtained between phytonadione doses, the INR value closest to 24 hours post dose was collected. Pediatric Index of Mortality 2 (PIM2) and Pediatric Risk of Mortality III (PRISM III) scores were collected to evaluate severity of illness, because these scores are used to predict outcomes of pediatric patients admitted to intensive care units.[12,13] Hepatic and renal function were assessed as a surrogate marker of acuity in addition to the PIM2 and PRISM III. Hepatic function tests included baseline alanine aminotransferase, aspartate aminotransferase, total bilirubin, and albumin. For renal function assessment the baseline serum creatinine was used to calculate estimated glomerular function by using the Bedside Schwartz equation.[14] Administration of vasopressors, prothrombin complex concentrate, cryoprecipitate, and FFP were noted. Patients receiving enoxaparin or systemic heparin were noted to reflect thrombotic disease states. Additionally, use of extracorporeal membrane oxygenation (ECMO) was noted, as well as mortality during or within 24 hours of the phytonadione course. Active bleeding and phytonadione adverse events, such as anaphylaxis, were recorded by evaluation of patient care documentation within the medical record.

The primary objective was to identify the number of patients with sepsis-induced DIC who achieved a normalized INR, defined as an INR ≤1.2 following phytonadione treatment. Secondary objectives were to assess the median change in INR from pre versus post phytonadione administration and to compare demographics, phytonadione dosing regimens, and outcomes among patients who achieved a normalized INR versus those who did not. In addition, a comparison was made between those patients with a normalized INR versus INR >1.2 who received cryoprecipitate and/or FFP with phytonadione versus phytonadione alone. An additional secondary objective was to identify any patient and treatment factors associated with normalized INR.

Statistical Analysis. Descriptive and inferential statistics were performed. Continuous data were analyzed via Wilcoxon 2-sample test given that the data were not uniform. Nominal data were analyzed via chi-square, exact chi-square, or Fisher exact tests, as appropriate. A logistic regression model was used to assess the adjusted odds of a normalized INR with independent variables including FFP, cryoprecipitate, vasopressor use, cumulative phytonadione dose (mg/kg), baseline INR, PIM2, and PRISM III. A generalized linear model was used for the comparison of the adjusted cumulative dose and was used with these same independent variables for those who had a normalized INR versus INR >1.2. Data management and analyses were conducted via SAS v9.4 (Statistical Analysis System, Cary, NC) with the a priori alpha set at $p < 0.05$.

Results

Two hundred fourteen patients with a diagnosis of septic shock received IV phytonadione during the study period. Fifty-eight patients were excluded for

the following: SQ or oral phytonadione given prior to IV administration (n = 20), administered for warfarin reversal (n = 12), ordered but did not receive (n = 6), received total parenteral nutrition that contained phytonadione (n = 3), and received phytonadione as part of management for chronic liver disease (n = 17). The remaining 156 patients were included for further analysis.

When evaluating their initial course of phytonadione, 66 (42.3%) of the 156 patients achieved a normalized INR (i.e., INR ≤1.2) following IV phytonadione administration, and 80 (51.3%) did not achieve a normalized INR. An additional 10 (6.4%) patients did not have any follow-up INR values obtained after initiating phytonadione. Baseline characteristics and laboratory data are reported in Table 1. Statistical comparisons were conducted for the 146 patients who had follow-up INR values between those with a normalized INR and INR >1.2. Overall, 56% of all patients were male, and no difference in sex was found between those who achieved a normalized INR versus those who did not, p = 0.30. No significant difference in median (IQR) age was found between those who achieved a normalized INR and those with an INR >1.2, 5.33 (0.92–11.58) versus 3.56 (0.38–12.73) years, respectively, p = 0.45. There was no significant difference in PRISM III and PIM2 scores between groups. In addition, there was no significant difference in the number of patients with documentation of active bleeding between the normalized INR and INR >1.2 groups, 8 (12.1%) versus 4 (5.0%), p = 0.12. There was also no difference in patients between groups that received anticoagulant treatment with enoxaparin or heparin, p = 0.18. Additionally, a greater number of patients had an INR >1.2 than a normalized INR who required vasopressors during their admission, 57 (71.3%) versus 38 (57.6%), p = 0.08, but this was not statistically significant. There were no significant differences in mortality or in those who required ECMO between groups. Additionally, no difference was found between groups regarding hepatic or renal laboratory data.

Table 1. Baseline Characteristics, Clinical Outcomes, and Laboratory Data

Variables	All Patients (n = 156)	Patients Without a Follow-up INR (n = 10)	Patients With a Normalized INR ≤1.2 (n = 66)	Patients With INR >1.2 (n = 80)	P value[a]
	No. (%) or Median (IQR)				
Baseline demographics					
Males	87 (55.8)	5 (50.0)	34 (51.5)	48 (60.0)	0.30[b]
Age, yr	4.71 (0.48–12.5)	9.4 (0.93–14.6)	5.33 (0.92–11.5)	3.56 (0.38–12.7)	0.45[c]
Weight, kg	15.35 (5.95–41.4)	31.9 (6.82–58.3)	17.5 (8–41.8)	14.15 (4.8–37.4)	0.28[c]
Height, cm	101.6 (58–152)[d]	131.2 (61.0–160.3)	106 (68–152)[e]	93 (54–149)[f]	0.20[c]
Clinical characteristics and outcomes					
PRISM III score	12 (6–20)[g]	12.5 (4.25–19.5)	11 (7–19)[h]	15 (6–23)[i]	0.26[c]
PIM2 score	−3.1 (−4.49 to −1.79)[g]	−4.52 (−4.65 to −2.76)	−3.14 (−4.42 to −2.59)[h]	−2.94 (4.34 to −1.34)[i]	0.25[c]
Documented active bleeding	12 (7.7)	0	8 (12.1)	4 (5.0)	0.12[b]
Anticoagulants received (enoxaparin or systemic heparin)	10 (6.4)	1 (10.0)	2 (3.0)	7 (8.8)	0.18[j]
Vasopressors	100 (64.1)	5 (50.0)	38 (57.6)	57 (71.3)	0.08[b]
ECMO	6 (3.9)	0	3 (4.5)	3 (3.8)	1.0[j]
Mortality	8 (5.1)	2 (20.0)	5 (7.6)	1 (1.3)	0.22[j]
Baseline laboratory data and glomerular filtration rate					
AST, units/mL	63 (30–190)[k]	31.5 (21.3–41.0)	66.5 (30–185)[l]	62 (30–201)[m]	0.98[c]
ALT, units/mL	40 (20–152)[k]	17.5 (14.0–63.5)	44 (20–158)[l]	39 (21–150)[m]	0.91[c]
Total bilirubin, mg/dL	0.6 (0.3–1.45)[k]	1.15 (0.55–2.33)	0.6 (0.3–1.15)[l]	0.6 (0.3–1.5)[m]	0.63[c]
Albumin, mg/dL	3.1 (2.5–3.5)[m]	3.5 (2.3–3.6)	2.95 (2.4–3.5)[l]	3.1 (2.6–3.4)[n]	0.88[c]
Serum creatinine, mg/dL	0.48 (0.27–0.69)[m]	0.48 (0.22–0.52)	0.43 (0.28–0.69)[l]	0.48 (0.26–0.69)[n]	0.64[c]
eGFR, mL/min/1.73 m^2	94.0 (57.5–142.7)[o]	127.7 (120.9–148.3)[p]	96.4 (66.6–154.5)[q]	82.6 (50.3–136.1)[n]	0.12[c]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; PIM2, Pediatric Index of Mortality 2; PRISM III, Pediatric Risk of Mortality III

[a] p value represents comparison between patients with a normalized INR (≤1.2) or >1.2. [b] Chi-square test. [c] Wilcoxon 2-sample test. [d] n = 153. [e] n = 65. [f] n = 79. [g] n = 141. [h] n = 58. [i] n = 75. [j] Fisher exact test. [k] n = 148. [l] n = 64. [m] n = 75. [n] n = 76. [o] n = 147; [p] n = 9; [q] n = 63.

Table 2 describes the phytonadione dosing regimen and additional factors affecting INR values. In the 146 patients who had follow-up INR values, there was no significant difference in the median number of phytonadione doses with a normalized INR versus those with an INR >1.2, p = 0.76. When evaluating all patients, most (n = 145; 92.9%) received ≤3 phytonadione doses, with 90 (58%) of these receiving 2 phytonadione doses. All of these doses were administered once daily. Eleven (7.1%) received >3 doses, with 1 patient receiving 9 phytonadione doses. There was no significant difference in the median initial mg/dose or mg/kg/dose in those with a normalized INR versus INR >1.2: 1.0 (1.0–5.0) versus 1.0 (1.0–2.75), p = 0.56 and 0.12 (0.05–0.23) versus 0.13 (0.05–0.26), p = 0.50, respectively. Additionally, there was no statistical difference in the cumulative dose (IQR) in patients with a normalized INR versus INR >1.2: 0.27 (0.12–0.60) versus 0.30 (0.11–0.79) mg/kg, p = 0.47, respectively. After adjusting for PIM2, PRISM III, FFP, cryoprecipitate, vasopressor use, and baseline INR values in a generalized linear model, the median (IQR) cumulative dose in patients with a normalized INR versus INR >1.2 was 0.39 (0.31–0.54) versus 0.53 (0.42–0.74) mg/kg, respectively, p < 0.001. No adverse events related to phytonadione administration were identified in either group.

Eighty-seven (55.8%) patients received either FFP or cryoprecipitate (Table 2). Eighty-three (53.2%) patients received FFP, and 20 (12.8%) received cryoprecipitate in addition to phytonadione for management of their sepsis-induced coagulopathy. Sixteen (10.3%) patients received both FFP and cryoprecipitate. Additionally 2 patients received prothrombin complex concentrate, with one receiving it in addition to FFP and the other receiving it in addition to both FFP and cryoprecipitate. There was a significantly higher number of patients receiving FFP in the normalized INR versus >1.2 groups, 50 (62.5%) versus 28 (42.4%), p = 0.016 (Table 2). However, there was no significant difference in cryoprecipitate in the normalized INR versus >1.2 groups, p = 0.65. In addition, there was no difference in the number of patients receiving both in the normalized INR versus INR >1.2 groups, 7 (10.6%) versus 9 (11.3%), p = 0.90. Most (n = 64; 73.6%) patients who received these agents did not have documentation of active bleeding.

Table 3 provides a comparison of the baseline INR and phytonadione dosing in those who received cryoprecipitate and/or FFP with phytonadione versus phytonadione alone. There was a significantly higher median (IQR) baseline INR in patients who received cryoprecipitate and/or FFP with phytonadione versus phytonadione alone, 1.9 (1.6–2.5) versus 1.7 (1.5–2.0), p = 0.03. For the cumulative phytonadione dosing these patients received, there was no significant differences in the median cumulative mg/kg or mg/dose between groups. However, patients who received FFP and/or cryoprecipitate with phytonadione versus phytonadione alone had a higher median (IQR) number of phytonadione doses received, 3 (2–3) versus 3 (1–3), p = 0.005.

Table 4 describes INR changes following each phytonadione dose. A baseline INR value was not

Table 2. Phytonadione Dosing and Additional Factors Affecting International Normalized Ratio

Characteristics	All Patients (n = 156)	Patients Without a Follow-up INR (n = 10)	Patients With a Normalized INR ≤1.2 (n = 66)	Patients With INR >1.2 (n = 80)	P value
	No. (%) or Median (IQR)				
Total number of phytonadione doses		2.0 (1–3)	3 (2–3)	3 (2–3)	0.58*
Phytonadione dosage:					
Initial dose, mg	1.0 (1.0–5.0)	2.8 (1.3–5.0)	1.0 (1.0–5.0)	1.0 (1.0–2.75)	0.56*
Initial dose, mg/kg	0.12 (0.05–0.26)	0.15 (0.09–0.30)	0.12 (0.05–0.23)	0.13 (0.05–0.26)	0.50*
Cumulative dose, mg	3.00 (2.01–9.00)	6.75 (3.00–10.00)	3.00 (2.50–10.00)	3.00 (2.00–8.50)	0.60*
Cumulative dose, mg/kg	0.27 (0.12–0.71)	0.19 (0.12–0.57)	0.27 (0.12–0.60)	0.30 (0.11–0.79)	0.47*
Total number of INRs collected†	–	1 (1)	4 (3–6)	4 (3–7)	0.40*
FFP	83 (53.2)	5 (50.0)	28 (42.4)	50 (62.5)	0.02‡
Cryoprecipitate	20 (12.8)	0	10 (15.2)	10 (12.3)	0.65‡
FFP and cryoprecipitate	16 (10.3)	0	7 (10.6)	9 (11.3)	0.90§

FFP, fresh frozen plasma; INR, international normalized ratio

* Wilcoxon 2-sample test.
† Data presented as median (IQR).
‡ Chi-square test.
§ Exact chi-square test.

available in 2 patients prior to phytonadione initiation. In addition, several INR values were missing with some of the subsequent phytonadione doses as noted in Table 4. In 154 patients with a baseline INR, the mean baseline INR was 1.99 ± 0.64. Table 4 also provides the mean INR during the phytonadione regimen, for up to 4 doses, and depicts the changes in INRs from baseline and changes in INR between phytonadione doses. There was a decline in overall mean changes in INR from baseline with each dose that ranged from −0.18 to −0.55, with the largest reduction in INR following the second phytonadione dose. Additionally, there was a decrease in INR between doses that ranged from −0.08 to −1.0. In the 66 patients with a normalized INR, 65 (98.5%) patients achieved a normalized INR by their third dose. The median (IQR) number of phytonadione doses that were associated with a decrease in INR ≤1.2 was 2 (1–2), corresponding to a median (IQR) cumulative phytonadione dose of 0.17 (0.075–0.415) mg/kg.

A logistic regression model was used to assess the relationship of a normalized INR and independent variables including use of baseline INR, FFP, cryoprecipitate, or vasopressors, PIM2, PRISM III, and cumulative phytonadione dose. The adjusted odds of achieving a normalized INR was not associated with receipt of FFP (adjusted odds ratio [aOR], 0.494; 95% CI, 0.230–1.069, p = 0.07), cryoprecipitate (aOR, 2.07; 95% CI, 0.70–6.1; p = 0.19), and cumulative phytonadione dose (aOR, 0.69; 95% CI, 0.35–1.3; p = 0.27). In addition, there was no association with baseline INR, vasopressor use, or PIM2 and PRISM III scores in the adjusted odds of achieving a normalized INR.

Discussion

This is one of the few studies to evaluate phytonadione use in children with sepsis-induced DIC. To our knowledge, only 3 reports have evaluated the use of IV phytonadione for coagulopathy in DIC in children and adults.[9–11] Our primary objective was a reduction in INR ≤1.2. It is important to note that no previous reports evaluating the use of phytonadione for DIC included a specific INR target.[9–11] Previous reports have noted that supplementation of phytonadione is indicated for patients with a suspected vitamin K deficiency with an INR >1.5 and no evidence of bleeding.[7–9] At the time of this study, our institution did not have a specific protocol for phytonadione for sepsis-induced coagulopathy.

Table 3. Comparison of International Normalized Ratio and Phytonadione Data in Patients Who Received Cryoprecipitate and/or Fresh Frozen Plasma With Phytonadione or Phytonadione Alone

Variables	FFP, Cryoprecipitate, or Both (n = 87)	Phytonadione Alone (n = 69)	p value
	Median (IQR)		
Baseline INR	1.9 (1.6–2.5)*	1.7 (1.5–2.0)†	0.03‡
Median cumulative phytonadione dose, mg/kg	0.14 (0.06–0.27)	0.11 (0.04–0.23)	0.19‡
Median cumulative phytonadione dose, mg	3.0 (3.0–9.0)	3.0 (2.0–10.0)	0.33‡
Number of phytonadione doses patients received	3.0 (2.0–3.0)	3.0 (1.0–3.0)	0.005‡

FFP, fresh frozen plasma; INR, international normalized ratio

*Baseline INR only available for 84 patients.
†Baseline INR only available for 67 patients.
‡Wilcoxon 2-sample test.

Table 4. International Normalized Ratio Changes Following Phytonadione Doses

Variables	After Dose 1	After Dose 2	After Dose 3	After Dose 4
	No. (%) or Mean ± SD			
INR after each phytonadione dose				
	n = 136	n = 98	n = 71	n = 8
INRs	1.69 (0.65)	1.55 (0.57)	1.66 (1.01)	1.91 (0.53)
Normalized INR (≤1.2)	29 (21.3)	35 (35.7)	21 (29.6)	0 (0.0)
INR >1.2	107 (78.7)	63 (64.3)	50 (70.4)	8 (100.0)
Changes in INR from baseline and previous dose				
	n = 135	n = 97	n = 70	n = 7
Change from baseline INR	−0.34 ± 0.65	−0.56 ± 0.64	−0.51 ± 1.09	−0.14 ± 0.76
		n = 90	n = 62	n = 8
Change from previous INR	–	−0.28 ± 0.48	−0.07 ± 0.45	−1.13 ± 1.84

INR, international normalized ratio

However, anecdotally many of our providers use an INR target of ≤1.2 for this indication.

In addition to IV phytonadione, 87 (55.8%) patients in our study received either cryoprecipitate or FFP. MacLaren and colleagues[9] also noted a similar number of patients initiated on phytonadione who also received FFP or platelets (47.9%). They did not comment on the number of patients who had active bleeding during phytonadione administration. However, they noted that patients with an elevated APACHE II (Acute Physiology and Chronic Health Evalauation II Score) score and coagulation products were associated with an increased baseline INR ($p < 0.05$). We found that patients who received cryoprecipitate and/or FFP with phytonadione versus phytonadione alone had a higher median baseline INR, 1.9 versus 1.7, $p = 0.03$. However, we did not compare the baseline INR in patients with a higher PIM2 or PRISM III. We did include baseline INR, PRISM III, and PIM2 in our logistic regression model, and none of these variables was associated with a normalized INR. MacLaren and colleagues[9] noted that coagulation products were not independently associated with a reduction in INR in their regression analyses. Similarly, as noted in our logistic regression, we found that cryoprecipitate and FFP were not associated with a normalized INR. Recommendations for the management of DIC note that use of these products is indicated for patients with coagulation laboratory derangements and active bleeding.[6] Selection of these coagulation products was dependent on providers, and we did not explore the indication for initiation. However, we did note that 26% of patients who received FFP or cryoprecipitate had documentation of active bleeding during their phytonadione therapy. These findings suggest that while the role of phytonadione in sepsis-related DIC remains undefined, many providers may use it in an attempt to avoid blood products or select it in combination with cryoprecipitate and/or FFP in severe cases, such as patients with active bleeding.

Additionally, limited evidence is available for the dosing of phytonadione in this setting. Our study found that 66 (42.3%) achieved our definition of a normalized INR (≤1.2) after a median of 2 IV doses with a cumulative phytonadione dose of 0.17 mg/kg. After adjusting for PIM2, PRISM III, FFP, cryoprecipitate, vasopressor use, and baseline INR value, there was also a significantly lower median cumulative dose in patients with a normalized INR versus INR >1.2: 0.39 versus 0.53 mg/kg, respectively, $p < 0.001$. A study by Koshel and colleagues[10] reported a wide variability in dosing of phytonadione in critically ill children with a mean dose of 0.18 ± 0.14 mg/kg/dose; however, they did not report the cumulative dose or number of doses received. It should also be noted that in their study only 53% of patients were thought to have sepsis-related coagulopathy, and the remainder of patients had other underlying causes for coagulopathy.

MacLaren and colleagues[9] evaluated phytonadione dosing in 48 adult critically ill patients with coagulopathy; 8 (16.7%) patients had their coagulopathy attributed to sepsis. All patients received phytonadione doses of 10 mg IV, and most (77.1%) received 3 total doses.[9] We reported the initial and cumulative dosing in mg/dose and mg/kg. There was no significant difference in the phytonadione cumulative mg/kg and mg/dose that patients received between those with and without a normalized INR. However, it is difficult to compare our findings with those of MacLaren and colleagues[9] owing to differences in population (i.e., adults versus children) and given that they did not report the cumulative dosing and did not report dosing in mg/kg. MacLaren and colleagues[9] did note that INR significantly decreased after at least 2 doses of phytonadione, likely suggesting a single dose is not sufficient in adequately reducing INR. Similar to their findings, we noted that in those patients with a normalized INR, 62% achieved resolution with 2 phytonadione doses. Additionally, we noted the largest reduction in INR from baseline occurred following a second phytonadione dose. However, it should be noted that we found that the median cumulative phytonadione dose was not associated with a higher odds of a normalized INR when controlling for independent variables. These findings suggest that higher dosing and longer duration of phytonadione may not be beneficial. So providers may consider that if no benefit in INR reduction is seen with 2 to 3 phytonadione doses, additional doses of phytonadione may not provide further benefit, and they should consider further workup and other options for management of coagulopathy.

Our study demonstrated that only 42.5% of courses had their INR normalized post treatment. However, 10 courses had no follow-up INR values obtained, and an INR value was not collected after each additional phytonadione dose (Table 4). Koshel and colleagues[10] noted a similar issue with 27% of patients not having INR values available. This finding should prompt providers to ensure resolution of sepsis-induced coagulopathy after initiation of phytonadione.

Adverse events have been documented with phytonadione, including anaphylaxis.[15] The overall incidence of anaphylaxis with phytonadione is not well defined. A study by Riegert-Johnson and colleagues[15] evaluated the incidence of anaphylaxis after IV phytonadione at their institution during a 58-month period. They reported the incidence of anaphylaxis with IV phytonadione at 3 per 10,000 doses (95% CI, 0.04–11 per 10,000).[15] In our study, no documented adverse events including anaphylaxis were noted. Additionally, the studies by McLauren and colleagues[9] and Koshel and colleagues[10] described above also noted no documented adverse events. It is important to note that all of these studies have limited sample sizes, but it could be speculated that adverse effects, such as anaphylaxis, are not dose dependent, given the variability of dosing discussed in these studies. However, caution should still be taken when administering phytonadione, especially when given through the IV route.

Limitations must be considered for this study. First, this study was conducted at a single center with a small sample size. To account for the limited sample size, a logistic regression analysis was conducted to identify factors associated with a normalized INR. Second, the retrospective nature of this study made it difficult to determine documentation of active bleeding or adverse events attributed to phytonadione according to the EMR. Additionally, at the time of this study there was no dosing protocol at our institution for phytonadione. In addition, INR values were not routinely obtained from all patients, which may have affected results evaluating INR changes. Therefore, these findings may have likely contributed to the variability of the results in this study.

Conclusions

Resolving coagulopathy in critically ill children with septic shock can be challenging. Less than half of patients in our study achieved a normalized INR following IV phytonadione. In those with a normalized INR, most achieved resolution after receipt of 2 phytonadione doses. The median cumulative dose and receipt of either FFP or cryoprecipitate was not associated with an increased odds of a normalized INR. Consistent monitoring of INRs should be performed throughout therapy to determine if dosing should be altered in order to obtain an INR ≤1.2 and resolve coagulopathy. Future studies with larger sample sizes are needed to further explore the role of phytonadione in critically ill children with sepsis-induced DIC and its efficacy in resolving coagulopathy.

Article Information

Affiliations. Department of Pharmacy (KS, MH), Oklahoma Children's Hospital at OU Health, Oklahoma City, OK; Department of Pharmacy: Clinical and Administrative Sciences (JLM, SBN, PNJ), College of Pharmacy, University of Oklahoma Health Sciences Center, Oklahoma City, OK; Department of Pediatrics (LH), College of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Correspondence. Peter N. Johnson, PharmD; peter-johnson@ouhsc.edu

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