ORIGINAL ARTICLE

Cefoperazone-induced Coagulopathy in Critically Ill Patients Admitted to Intensive Care Unit

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Abstract

Background: N-methylthiotetrazole side chain (NMTT) of cefoperazone was attributed to inhibit the vitamin K epoxide enzyme. This mechanism is similar to warfarin; thus, vitamin K was suggested to antagonize the hematological effects of cefoperazone. The literature on critically ill patients receiving cefoperazone and its clinical significance on bleeding diathesis is sparse.

Objectives: To assess the incidence of cefoperazone-induced coagulopathy (CIC), its clinical impact on bleeding episodes, and transfusion requirements. Predisposing factors and the role of prophylactic and therapeutic vitamin K were evaluated.

Materials and methods: Prospective observational study of adult intensive care unit (ICU) patients (>18 years) receiving cefoperazone between December 2017 and December 2018. We excluded those on warfarin, those with preexisting elevated *prothrombin time*/international normalized ratio (PT/INR), and with bleeding manifestations. Relevant laboratory investigations and specific outcomes were noted for 6 days following therapy. Panel data regression was used to determine predictors of coagulopathy.

Results: Among 65 patients, 17 (26%) had probable CIC. Hypoalbuminemia and vancomycin co-administration were risk factors for CIC. Hemoglobin drops and blood transfusions were not different between INR non-elevated and elevated groups (11 vs 8 gm/dL; $p = 0.06$ and 11 vs 8 units; $p = 0.23$, respectively). Prophylactic vitamin K did not offer any benefit toward preventing INR elevation. Therapeutic vitamin K significantly reduced INR when elevated [absolute risk reduction (ARR):57.5% and number needed to treat (NNT):1.7].

Conclusion: Results of this study revealed that CIC is not uncommon in ICUs. Based on the findings of the study, we suggest INR monitoring in patients receiving nephrotoxic agents and patients with hypoalbuminemia. We also recommend vitamin K administration in patients with elevated INR.

Keywords: Cefoperazone, Coagulopathy, Critically ill adults, International normalized ratio elevation, Vitamin.

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Highlight

Cefoperazone-induced coagulopathy is common in ICU patients. However, clinical adverse events related to coagulopathy are rare. In patients with hypoalbuminemia and those taking nephrotoxic medications, INR monitoring is required. Vitamin K is most effective when given in patients with elevated INR.

Introduction

Cefoperazone is a third-generation cephalosporin. It has good bactericidal activity against most Enterobacteriaceae and *Pseudomonas* species, making it a reasonable choice for hospital-acquired and community-acquired infections where anti-pseudomonal activity is essential.[1,2] Ultrastructurally, cefoperazone contains an NMTT side chain, which has been attributed to causing deficiency of vitamin K-dependent factors (II, VII, IX, X) by inhibiting the reduction reaction of vitamin K epoxide leading to elevation of INR.[3,4] In 1980, Hooper et al. reported cases of bleeding associated with NMTT antibiotics. Later, Lipsky elaborated on the mechanism of coagulopathy in cefoperazone, cefamandole, and latamoxef.[4–6] Other proposed means by which cefoperazone induces coagulopathy were depletion of vitamin K-producing (menaquinone) flora in the intestine, drug-induced diarrhea leading to malabsorption and drug-induced impairment of ADP-induced platelet aggregation.[6]

Since the introduction of cefoperazone in 1977, there has been limited literature on hematological toxicity in the form of hypoprothrombinemia and bleeding manifestations. Most data were restricted to case reports, some case series, and a recent retrospective case-control study from Taiwan.[7–11] To our knowledge, there is limited literature on the clinical significance of such altered coagulation induced by this drug and the predisposing factors in the ICU population. This study is probably the first to be conducted on ICU patients of the Asian population, which aimed to evaluate whether the drug cefoperazone can predispose to bleeding diathesis in critically ill patients. The primary objective of our study was to measure the incidence of cefoperazone-induced elevation in

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INR ≥1.5. The secondary objectives were to evaluate risk factors for cefoperazone-associated coagulopathy, rescue treatment offered to patients, such as therapeutic vitamin K administration or blood product transfusions, and to measure the length of ICU and hospital stays and mortality in the ICU.

Materials and Methods

Study Design

We conducted a prospective observational study on ICU patients administered either cefoperazone or a combination of cefoperazone-sulbactam. This study was registered with the Institutional Ethics Committee (IEC/1/1113/2015) and Clinical Trials Registry India (CTRI/2017/12/010774).

Patient Selection and Data Extraction

STROBE guidelines have been followed for reporting the study data. The study was conducted from December 2017 to December 2018. The study population included all patients older than 18 years who were admitted to the ICU of tertiary care hospital and received either cefoperazone or cefoperazone-sulbactam therapy. The study included patients older than 18 years (no upper limit of age, as age is not a contraindication for cefoperazone therapy) and those who received cefoperazone for ≥3 days. We excluded patients on warfarin therapy, preexisting elevated PT/INR and clinical bleeding manifestations and those who received vitamin K 1 day before initiation of cefoperazone. All other patients with increased hepatic enzymes, sepsis with multiorgan failure, renal failure, and immunosuppressed with neutropenia were not excluded unless they had a preexisting derangement in INR and clinical bleeding manifestation.

After obtaining informed consent from the patient or a legally acceptable representative, patients were enrolled in this study, and the medical records were reviewed. The investigators captured all the data required for analysis in a structured format. Baseline variables and routine investigations on the day of admission or the day of initiation of cefoperazone were captured and followed till 6 days of therapy. Being an observational trial, the treating physician was not given suggestions on the drug's initiation, duration, and dosage, and the physicians are independent in choosing or refusing to investigate. The following investigations reports were captured: complete blood picture, liver function tests, renal function tests, and PT and INR.

Exposure

The exposure of interest was the drug cefoperazone administered to the ICU patient. The specific information collected from each subject included the dosage and duration of cefoperazone. Some patients received vitamin K either as a prophylaxis (i.e., before the INR elevation ≥1.5) or for treatment (i.e., after the INR elevation). Day of administration, dosage, and duration of vitamin K therapy was also noted.

Potential Confounding Variables

In the ICU, multiple confounding factors contribute to coagulopathy. To minimize this to a certain extent, we collected information on drugs that directly interfere with the coagulation cascade (unfractionated heparin, low-molecular-weight heparin) and those that indirectly interfere with renal and hepatic functions that contribute to coagulopathy.

Study Definitions and Outcome Measures

The primary outcome of interest was the incidence of cefoperazone-induced INR elevation of ≥1.5. The secondary outcomes analyzed were (1) risk factors associated with cefoperazone-associated coagulopathy, (2) number of patients with a decrease in hemoglobin (≥1 gm/dL/day), (3) rescue treatment offered to patients such as therapeutic vitamin K administration or blood product transfusions, and (4) length of ICU and hospital stay and mortality in ICU. As cefoperazone usually induces coagulopathy within 6 days,[12] we sought all the adverse events during this period. Any event that occurred on day 0 (day of initiation of cefoperazone) was considered insignificant and excluded from the analysis. For the study, coagulopathy was defined under the following categories: biochemically, derangement of INR (i.e., the elevation of INR ≥1.5) or clinically, if there is a spontaneous external bleed (or) decrease in hemoglobin (≥1 gm/dL/day). For patients who do not have baseline laboratory information on day 0, we substituted these laboratory values with the latest results obtained just before day 0. Measurement of PT and INR was done by the coagulometer clotting test, and the PT control in our laboratory was 11–14 seconds.

Statistical Methods

Since no previous studies are available to calculate sample size, we propose conducting consecutive sampling for 1 year. Descriptive statistics are reported using mean with standard error (SE) or median with interquartile range (IQR) depending on the data distribution for the continuous variables. Categorical variables were reported as numbers and percentages. The Chi-square test has been used to test the association between categorical variables, whereas the *t*-test is for continuous variables. $P < 5\%$ was considered statistically significant. Regression analysis for panel data was used to test if any important variables could be identified, predicting a rise in INR. Hausman test was used to compare random and fixed effect coefficients, and Wald tests for groupwise heteroskedasticity were performed to select an appropriate model ($p < 0.05$ is considered significant for both these tests). All the analyses were conducted using STATA™ v17.

Results

Among 77 potentially eligible patients (age >18 and cefoperazone therapy) during the study period, 12 patients were excluded. The study flowchart (Flowchart 1) shows the flow of patients. A total of 65 patients were finally included in the study. The study population's mean age, body mass index (BMI), and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores were 50.7 years (±17.7), 23 kg/m^2 (±3.3), and 16 (IQR 11–23), respectively. Our study had a male-to-female ratio of 1.8:1. Out of 65 patients, 17 (26%) had an elevation in INR over the 6-day study period. Baseline clinical characters and biochemical variables were compared between the INR non-elevated and INR elevated groups, as shown in Table 1.

Predictors of CIC

Bivariate Analysis

Baseline serum albumin levels and concurrent use of vancomycin are associated with INR elevation. The INR elevated group noted a significantly higher incidence of hypoalbuminemia and a significant number of vancomycin recipients than the non-elevated group (2.0 vs 2.4 gm/dL, $p = 0.04$, and 47vs 6.2%, $p < 0.001$, respectively).

Panel Data Regression Analysis

The results indicated a significant association between serum albumin and INR levels by performing a panel data regression

FLowchart 1: Study flowchart shows the flow of patients

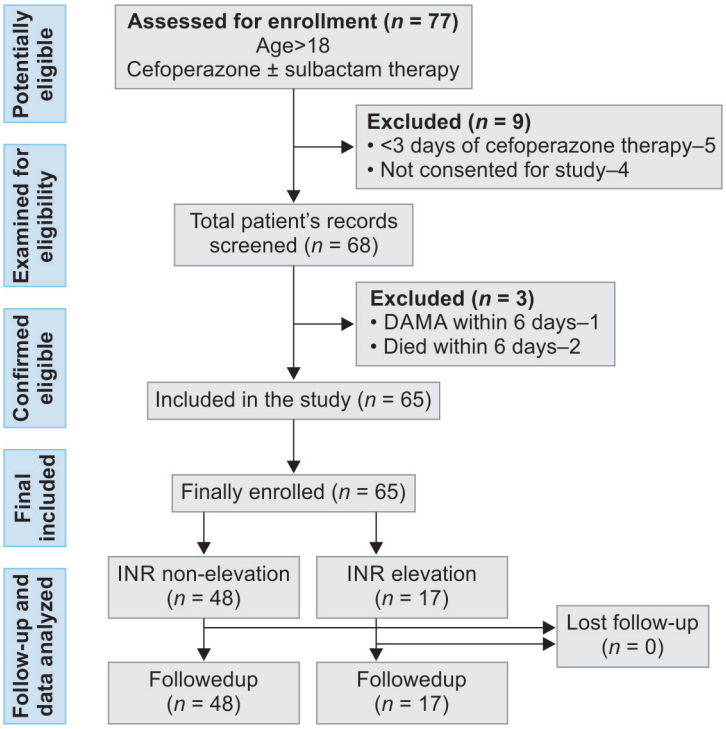


Table 1: Comparison of baseline clinical characteristics and biochemical variables in INR non-elevated and INR elevated groups

Variables	*INR non-elevated group (N = 48)*	*INR elevated group (N = 17)*	*p-value*
Age–years, $\bar{x}$ (SE)	49.5 (±2.4)	54 (±4.7)	0.37
Male sex, *n* (%)	29 (60)	13 (76.4)	0.23
BMI, $\bar{x}$ (%)	23.4 (±0.5)	21.9 (±0.4)	0.12
APACHE II score, $\bar{x}$ (SE)	17.8 (±1.6)	18.5 (±1.6)	0.80
DM, *n* (%)	17 (35.4)	8 (47)	0.39
CKD, *n* (%)	9 (18.7)	3 (17.6)	0.92
AKI, *n* (%)	16 (33.3)	8 (47)	0.31
Albumin*, median (IQR)	2.4 (1.8–2.8)	2.0 (1.6–2.3)	0.04
AST*, median (IQR)	39.5 (25–87)	32.5 (22–76)	0.38
ALT*, median (IQR)	32 (19–91)	26.5 (19–81)	0.38
Cefoperazone dosage, *n* (%)			
≤4 gm/day	26 (54)	10 (58.8)	0.74
5–7 gm/day	22 (45.8)	7 (41.1)	0.74
Prophylactic vitamin K	18 (37.5)	4 (23.5)	0.29
Medications, *n* (%)			
Vancomycin	3 (6.2)	8 (47)	<0.001
Amikacin	3 (6.2)	3 (17.6)	0.16
Netilmicin	2 (4)	0	0.39
Furosemide	2 (4)	0	0.39
UFH	35 (73)	12 (70.5)	0.85
LMWH	10 (21)	3 (17.6)	0.85
Indication for cefoperazone therapy, *n* (%)			
Respiratory infections	22 (45.8)	14 (82.3)	0.009
Urinary tract infections	7 (14)	0	–
Abdominal infection	6 (12.5)	1 (5.8)	0.45
Others	13 (27)	2 (11.7)	–

*Values at admission; AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; IQR, interquartile range; LMWH, low-molecular-weight heparin; M, median; N, number of patients; UHF, unfractionated heparin; UTI, urinary tract infection; $\bar{x}$, mean

Table 2: Outcomes observed in INR non-elevated and INR elevated groups

Variables	*INR non-elevated group (N = 48)*	*INR elevated group (N = 17)*	*p-value*
Hemoglobin drop ≥1 gm/dL/day, *n* (%)	11 (22.9)	8 (47)	0.06
Patients received packed cell, *n* (%)	10 (20.8)	6 (35.3)	0.23
Total packed cell requirement, *n* (%)	11 (23)	8 (47)	0.21
LOS ICU, median (IQR)	15.5 (7–23.5)	15 (11–22)	0.53
LOS hospitalization, median (IQR)	22 (16–49)	30 (17–47)	0.22
Death in ICU, *n* (%)	20 (41.6)	7 (41.1)	0.97

ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; N, number of patients

analysis using a robust fixed effects model. The findings suggest that with lower serum albumin levels, there is a higher probability of an increase in INR levels (slope: −0.402; 95% CI −0.641 to −0.163; $p = 0.002$) (supplementary analysis). We preferred a fixed effects model over a random effects model due to significant coefficient differences (Hausman test $p < 0.05$). The modified Wald test for groupwise heteroskedasticity in the fixed effect regression model was significant ($p < 0.05$); therefore, a robust option was chosen to correct the regression model.

Secondary Outcomes

In the 17 patients with INR elevation, the APACHE scores were compared before and after the INR derangement, and the scores were not significantly different (18.5 vs 19.9, $p = 0.91$). The incidence of coagulopathy in the elderly population was identified as 6 out of 16 patients (37.5%, $p = 0.23$). As shown in Table 1, cefoperazone dosage did not significantly influence the INR levels. Prophylactic vitamin K administration has not offered any protection against the elevation of INR. A significant number of patients who had received cefoperazone for respiratory tract infection were found in INR elevated group (82.3 vs 45.8%, $p = 0.009$).

The incidence of drop in hemoglobin, packed cell transfusions, length of stay (LOS) ICU and LOS hospital, and ICU mortality were compared in both groups and are shown in Table 2. However, patients in the INR elevated group had a decreasing trend in hemoglobin levels but were not statistically significant ($p = 0.06$). The number of patients who received packed cell transfusion was also not significantly higher (10 vs 6 units, $p = 0.23$) in the INR elevated group. Out of 17 patients who had an elevation in INR, 11 received therapeutic vitamin K; among them, 10 had a subsequent decrease in INR to the normal range, and this was statistically significant ($p = 0.013$), whereas only two out of six patients who had not received vitamin K and had a spontaneous resolution in INR. The ARR was 57.5%, and the number needed to treat (NNT) to normalize the elevated INR was 1.7.

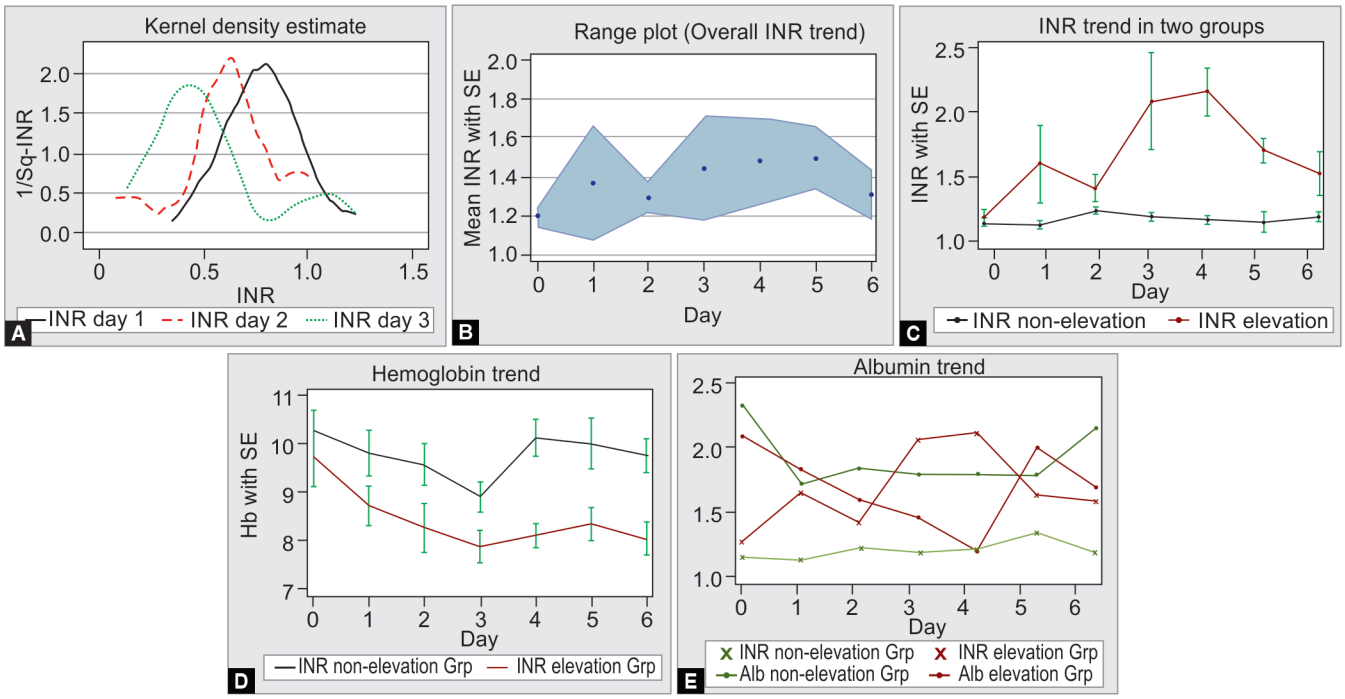
We noticed a rise in the mean INR in the study population over the 6-day follow-up period, as shown in the INR Kernel density estimate and range plot (Figs 1A and B). Mean INR trends in the INR elevated and non-elevated groups are graphed separately (Fig. 1C), while (Figs 1D and E) trends in mean hemoglobin and serum albumin. The line graphs of mean albumin and INR (Fig. 1E) show a diverging trend in the INR-elevated patients.

Discussion

Bleeding episodes are reported with different β-lactam antibiotics, especially those with NMTT side-chain-containing antibiotics, by inducing hypoprothrombinemia, leading to INR elevation.[6] Our results indicate that INR derangement in ICU patients receiving cefoperazone is not uncommon, with an incidence as high as 26%. This was comparatively higher than the previously noted incidence of 12.3% in a large retrospective cohort study.[13] The higher incidence in this study could be partly because of differences in the study populations. This study was performed on ICU patients where the baseline risk of coagulopathy itself could have been higher.[14] Furthermore, the studies' cut-off to define coagulopathy differed. In the former study by Strom et al., any elevation in PT more than 5 sec from the upper limit of normal was taken as a cut-off to define coagulopathy or hypoprothrombinemia. While in another study, Cohen et al. reported that 4% of the study population had an increase in PT; however, they have not mentioned the cut-off chosen for the same.[13,15] In our study, we preferred INR instead of PT to define coagulopathy, as INR provides a definitive standardization method and consistency in interpreting results. Any INR elevation ≥1.5 was considered coagulopathy in this study. We followed INR values for 6 days following the initiation of cefoperazone therapy as the existing literature mentions that the maximal suppression of vitamin K epoxide occurs 1–2 days after the initiation of treatment and, after that, a gradual recovery within six days.[12] We also found a similar trend; our study population had shown a peak in mean INR on day 5 and then a gradual decline.

Since our data fit into a panel data model with each patient having observations over a 6-day study period, a panel data regression was performed. On a panel data regression, an important baseline variable that predicted CIC was the presence of low serum albumin while a patient was receiving cefoperazone therapy. The proposed mechanism was that a low serum albumin level could increase the free drug level, enhancing the adverse effect of cefoperazone.[13] Once the free drug releases NMTT moiety, this can inhibit the production of clotting factors, leading to INR elevation. This was reflected in the diverging trends of albumin and INR in our 6-day study period. We could not analyze the effect of baseline hepatic dysfunction as we did not have patients with hepatic failure during this study period. Impaired renal functions can increase the biliary excretion of the drug, suppressing the intestinal vitamin K-producing bacteria and thus increasing the bleeding tendency.[9] However, in this study, we did not observe increased bleeding episodes or derangement of INR in patients with impaired renal functions.

Our study population showed a definite coagulopathy predicate when patients simultaneously received vancomycin. This can be attributed to a higher incidence of acute kidney injury (AKI) and chronic kidney disease (CKD) in these patients that could have predisposed them to coagulopathy rather than synergy between



Figs 1A to E: (A) Kernel density estimates of INR on days 1, 3, and 5. This graph illustrates that the inverse square of INR is normally distributed. The progressive shift to the left signifies a rise in INR over the study period; (B) Trends in the mean INR over the study period. The graph shows that the mean INR of all patients peaks on the 5th day and subsequently decreases; (C) Compares trends in the mean INR between the two groups. Mean INR peaks on the 3rd and 4th day in the INR-elevated group; (D) Comparison of trends in the mean hemoglobin between the two groups; (E) Comparison of trends in the mean albumin between the two groups. On day 4, in the INR elevated group, the mean serum albumin was lowest, whereas the mean INR was at its peak; this reveals an inverse relationship between the two

the two drugs. We do not have sufficient patients co-administered with other nephrotoxic agents for statistical analysis. We found a significant association between patients who received cefoperazone for respiratory tract infections and INR elevation. We could not find the biological plausibility of this association; hence we postulate that this could be a spurious finding.

Previous studies have mentioned that elderly age, undernourished, or patients with renal failure are risk factors that predispose them to CIC.[10,16–23] Our study did not show a significant impact of elderly age, preexisting renal failure or AKI during the ICU stay in the development of coagulopathy in patients receiving cefoperazone. We could not comment on the role of BMI as our study population had a minimal number of patients with a BMI of less than 18.5.

It was thought that patients with adequate stores of vitamin K do not manifest with bleeding diathesis, whereas those with depleted stores are at a higher risk of bleeding. Hence, administering vitamin K uniformly as prophylaxis to those initiated on cefoperazone therapy could prevent coagulopathy. This suggestion was based only on a few case reports and case series.[9,24–26] Contrary to these findings, we did not find the protective role of prophylactic vitamin K in our study population. Sattler et al. investigated 35 renal failure patients treated with cefoperazone and reported hypoprothrombinemia in 64% of patients who had not been given prophylactic vitamin K.[22] No such relationship has been established in our study. This study had a more significant number of patients with vitamin K prophylaxis (33.8%), probably because of increased awareness of coagulopathy with cefoperazone among the treating physicians. While we found that prevention with vitamin K had a limited clinical benefit, our findings strongly favored the therapeutic administration of vitamin K. Nearly all our patients except one had normalized INR after therapy with vitamin K ($p = 0.013$).

Strengths and Limitations

This study has certain limitations. Since this is an observational study, daily reports of all necessary laboratory investigations were unavailable as the decision to send lab investigations was left to the primary physician's discretion. Hence some data was missed, which can potentially alter the statistical inference. We had not measured the study population's activity of factors II, VII, IX, or X. Similarly, drug levels of cefoperazone were not measured. Furthermore, the vitamin K dose was not standardized, and patients received different amounts ranging from 10 to 30 mg for 1–3 days. Vitamin K assay was not performed before the administration of cefoperazone; hence we could not predict patients at risk for bleeding diathesis. We might have missed some subclinical bleeding episodes from the urinary and gastrointestinal tract. Lastly, this study was restricted to a single-center ICU.

On the other hand, this study has several strengths. This study was done in an ICU population, focusing on the most vulnerable subset of the patient population. Our results did not show significant adverse consequences of elevated INR, such as bleeding episodes and blood transfusion requirements. The rate of packed cell transfusion in our study was 24.6%, which was not different from the overall transfusion requirements in the ICU, as mentioned in major multicenter trials, such as TRICC, ABC, and CRIT.[27–29] Our study delineated the role of prophylactic and therapeutic vitamin K administration in CIC.

Clinical and Cost Implications of the Study Findings

Overall, the results showed a decreasing trend in hemoglobin, but this has not been translated to either significantly higher bleeding episodes or increased transfusion requirements. Length of stay in ICU and hospital and ICU mortality were not different in INR elevated and non-elevated groups. Lastly, many confounding factors exist in ICU, primarily sepsis, which predisposes patients to coagulopathy. Hence, we measured APACHE scores before and after the elevation of INR in the INR elevated group, and we did not find a significant difference. This probably excludes sepsis as a major confounder in our study.

A cost analysis of injection vitamin K was done, and the cost for each ampule (10 mg) of intravenous vitamin K in our hospital was ₹17. The average cost incurred by each patient by administering vitamin K as a therapeutic approach was nearly ₹50. Although our analysis did not reveal a significant impact of therapeutic vitamin K on decreasing the number of packed cell transfusions, it was observed that a considerable number had subsequent normalization of INR with an NNT of 1.7. Hence, it may be sensible to consider the therapeutic role of vitamin K in the case of CIC. Moreover, the risk of bleeding with subsequent blood transfusions and healthcare burden is always higher than the risk of vitamin K administration, which is believed to be one of the harmless drugs.

Conclusion

The study's results indicate that the administration of cefoperazone in critically ill ICU patients could increase INR levels. However, this has not been translated to increased bleeding episodes or transfusion requirements. Baseline hypoalbuminemia and vancomycin co-administration alongside cefoperazone were identified as significant risk factors predisposing to CIC. Therapeutic administration of vitamin K can significantly reduce elevated INR. Based on study results, we recommend vitamin K administration when INR is elevated, and we would not suggest prophylactic vitamin K in patients receiving cefoperazone. However, we recommend close monitoring of INR when patients receive nephrotoxic agents, such as vancomycin and in patients with hypoalbuminemia.

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