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ORIGINAL ARTICLE

Role of Prophylactic Vitamin K in Preventing Antibiotic Induced Hypoprothrombinemia

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Abstract
Objective To determine prophylactic role of single dose of vitamin K in prevention of antibiotic induced hypoprothrombinemia.
Methods This prospective comparative study included critically ill children in age group 2 mo to 12 y, admitted to a tertiary care hospital in India, likely to receive prolonged antibiotic therapy. One hundred twenty children, 60 in each group (A & B) were enrolled in the study. Patient allocation was done on alternate basis. Group A children received prophylactic vitamin K while group B did not. Baseline coagulation studies and other investigations were done in all children. Coagulation studies were repeated on day 10 and day 14 of antibiotic therapy and in between if required clinically. Children who developed deranged INR were given therapeutic vitamin K. If deranged INR returns to normal at 12 h of vitamin K administration then it indirectly confirms vitamin K deficiency. Analysis was done by fisher's *t* test and chi square test.
Results In children on prolonged antibiotic therapy, vitamin K deficiency was a common problem (15 %). It was common in male sex, severe grade of protein energy malnutrition (PEM), N-methylthiotetrazole (NMTT) group containing antibiotics use and duration of antibiotic more than 10 d. It was same in children whether they received or did not receive prophylactic vitamin K on day 1 of antibiotic therapy (95 % CI; *p* value 0.79).
Conclusions Vitamin K deficiency is common problem in patients on prolonged antibiotic therapy. There is no role of single dose of prophylactic vitamin K in preventing antibiotic induced hypoprothrombinemia.

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Introduction

The initial articles describing coagulopathy induced in humans by vitamin K deficiency were published in 1939 [1–4]. In 1952 Dam et al. recognized that administration of antibiotics increased the risk of hemorrhagic disease due to vitamin K deficiency in humans [5].

Two major hypotheses were proposed to explain the prolonged antibiotic use associated vitamin K deficiency. First is the use of broad spectrum antibiotic that suppresses the growth of intestinal flora [6, 7]. And second is antibiotic containing 1-N-methyl-5-thiotetrazole (NMTT) side group causes a more direct inhibition of the vitamin K dependent step in clotting factor synthesis *i.e.,* they inhibit gamma-carboxylation of glutamic acid residue of clotting factors [8, 9]. Conly et al. in their study found that patients who received intravenous fluids only for as long as 4 wk did not develop hypoprothrombinemia. But if they received concomitant antibiotics then they rapidly developed hypoprothrombinemia supporting role of antibiotic in causing vitamin K deficiency [10]. Vitamin K deficiency because of prolonged antibiotic use resembles with many other disorders of hemostasis so many cases remains unreported. This study was designed to study the status of hypoprothrombinemia in hospitalized children on prolonged antibiotics and role of prophylactic vitamin K in preventing the antibiotic induced coagulation abnormalities.

Material and Methods

This prospective comparative study was conducted at a tertiary care centre of a teaching hospital during a period of one

year from Dec 2011 to Dec 2012. The protocol of study was approved by the Institute Ethics Committee and written informed consent for inclusion was obtained from parents of each child. One hundred twenty patients in 2 mo to 12 y age group who received antibiotic for minimum of 14 d duration were enrolled. Patients with disseminated intravascular coagulopathy (DIC), thrombocytopenia, liver dysfunction, renal dysfunction and those in which coagulation profile was initially abnormal, had family history of bleeding tendency or history of bleeding tendency in the patient or who received prior vitamin K during this illness were excluded.

Patients with critical illness who were likely to receive antibiotics for a prolonged period (14 d) were enrolled. Patient with definite history of receiving antibiotics outside (with proper prescription) were also enrolled, but enrolled only in Group B as no vitamin K on day 1 of antibiotic therapy was given. Patients were divided into two groups, Group A and Group B by randomization on alternate basis. Detailed history and examination were recorded at time of admission. Investigations: CBC, bleeding time, clotting time, coagulation parameters (PT, APTT, INR), KFT and LFT of all patients were recorded on day 1 of admission. Group A patients received prophylactic vitamin K on day 1 of admission. Group B patients did not receive vitamin K on day 1 of admission. Both groups were followed and coagulation profile were done on day 10 and day 14 of antibiotic therapy. Coagulation profile and other necessary investigations were done in between in patients who manifested with bleeding tendency.

If INR was deranged in between or on day 10 or day 14 of antibiotic therapy, therapeutic vitamin K was given. Within 12 h of vitamin K administration, if coagulation profile returned to normal then vitamin K deficiency was diagnosed.

Group A patients were also evaluated for role of vitamin K as a prophylaxis for preventing hypoprothrombinemia in patients with prolonged antibiotic therapy.

All patients had severe infective illness and required prolonged antibiotic therapy. Indications for starting antibiotic were empyema, pyomeningitis, pneumonia, bronchopneumonia, brain abscess and infective endocarditis.

Even with high doses of vitamin K no adverse effects have been demonstrated; thus there is no upper limit for vitamin K uptake. So in group A patients on day 1 of admission, vitamin K was given in dose of 0.5 mg/kg/d (maximum of 10 mg/d) in single dose [7, 11–12].

In patients who developed hypoprothrombinemia, vitamin Kwas given in dose of 0.5 mg/kg/d (maximum of 10 mg/d) in OD dose for 3 d.

Hypoprothrombinemia is defined as INR value above the normal expected for that age [13, 14]. Abnormal INR was evaluated with respect to parameters like age, sex, malnutrition, group of antibiotic used and duration of therapy.

Considering vitamin K deficiency in healthy subjects as 1 % and with antibiotics as 25 % in previous studies, sample size calculated was 38. But the authors enrolled all eligible patients over study period of 1 year as more sample size adds to credibility, sensitivity and specificity. Thus, a total of 60 patients were enrolled in each group (open AP software version 2).

The data was compiled, analyzed and tabulated. The paired *t* test and chi-square test were used as test of significance. Statistical analysis was performed with the help of the software 'Graphpad Prism 5'.

Results

A total of 134 patients were studied; out of which 120 patients met the study criteria and 60 patients were enrolled in Group A and B respectively. A total of 18 children out of 120 developed hypoprothrombinemia (15 %). Children who were found to have hypoprothrombinemia (prolonged INR) received therapeutic vitamin K and repeat INR estimation was done at 12 h. In all these patients, hypoprothrombinemia was corrected, indirectly confirming vitamin K deficiency.

Table 1 shows distribution of hypoprothrombinemia in patients who received prolonged antibiotic therapy according to age groups. It shows that hypoprothrombinemia in patients receiving prolonged antibiotic therapy was equal in all age groups and difference of hypoprothrombinemia in age groups was statistically not significant (p 0.5152).

In the present study, out of 77 males enrolled 14 developed hypoprothrombinemia (18.18 %) and out of 43 females enrolled 4 developed hypoprothrombinemia (9.3 %). Thus, hypoprothrombinemia in patients receiving prolonged antibiotic therapy was common in males as compared to females.

Table 2 shows distribution of hypoprothrombinemia in patients according to IAP grade of PEM in under 5 children. Hypoprothrombinemia was more in patients receiving prolonged antibiotic therapy with PEM grade III & IV as compared to patients with no PEM, PEM grade I or PEM grade II and this difference was statistically not significant (p 0.0831).

Only 1 patient developed hypoprothrombinemia before 10 d of antibiotic therapy. All other patients developed it after 10 d of antibiotic therapy; 9 developing between 10 to 13 d (50 %) and 8 developing on 14 d of antibiotic therapy (44.45) (Table 3). Thus duration of antibiotic therapy more than 10 d is significant risk factor for development of hypoprothrombinemia in patients receiving prolonged antibiotic therapy.

Table 4 shows that a total of 18 children out of 120 developed hypoprothrombinemia (15 %). In Group A (who received prophylactic vitamin K), 8 children developed hypoprothrombinemia (13.32 %) while in Group B (without prophylactic vitamin K), 10 children developed hypoprothrombinemia (16.66 %). The difference in incidence

Table 1 Distribution of hypoprothrombinemia in patients according to age groups

Age (year)	Hypoprothrombinemia [n (%)]	No hypoprothrombinemia [n (%)]	Total [n (%)]
2 mo–1 y	06 (5)	28 (23.33)	34 (28.34)
> 1 y–5 y	07 (5.83)	31 (25.83)	38 (31.66)
> 5 y	05 (4.16)	43 (35.83)	48 (40)
Total	18 (15)	102 (85)	120 (100)

Table 3 Distribution of hypoprothrombinemia according to days of antibiotic therapy

Days of antibiotic therapy for deranged INR	Hypoprothrombinemia (%)
< 10	01 (5.55)
10–13	09 (50)
14	08 (44.45)
Total	18 (100)

of coagulopathy in both groups is statistically not significant (CI 95 %; *p* 0.79).

Table 4 also shows development of hypoprothrombinemia in relation to NMTT+other or other antibiotics used. It shows that development of hypoprothrombinemia in patients on prolonged antibiotic therapy in NMTT group was 22.72 % while in other group it was 13.26 %. So incidence of hypoprothrombinemia in NMTT group is higher than other group of antibiotics. But this difference was statistically not significant (*p* 0.32).

Discussion

The exact mechanism responsible for antibiotic associated vitamin K deficiency are not known with certainty. Most of the studies including the present one have shown a significant incidence of hypoprothrombinemia in children on prolonged antibiotic therapy. It is an important factor to be considered especially in those children who are critically ill. Mechanisms causing vitamin K deficiency include combined effect of diet low in vitamin K, loss of normal bowel flora due to prolonged antibiotic therapy which synthesize vitamin K1 and direct inhibition of synthesis of vitamin K dependent clotting factors due to NMTT group containing antibiotics.

In the present study authors found that incidence of antibiotic associated hypoprothrombinemia was more in males as compared to females similar to the study by Conly et al. [10]. This could be explained on the basis of influence of sex hormones on prothrombin [15]. Prothrombin is formed more rapidly and at a lower effective concentration of vitamin K in presence of oestrogen. Prothrombin levels are higher in females than in males and the dietary requirement for vitamin K in females is also less. As patients upto age group of 12 y were enrolled incidence of antibiotic associated hypoprothrombinemia was found more in males as compared to females.

Children with severe malnutrition had a higher incidence of hypoprothrombinemia, a finding similar to Bhat and Deshmukh [16], Ehsanipour and Zarifian [17], Kark et al. [3] and Pineo et al. [18]. Possible explanation could be that malnutrition limits the availability of oral phylloquinone causing hypoprothrombinemia.

In the present study it was found that antibiotic associated hypoprothrombinemia was more common with NMTT side chain containing antibiotic than other group of antibiotics, a finding similar to Shearer et al. [19], Conly et al. [10] and Nicholas et al. [6]. This could be explained by direct inhibition of biosynthesis of the vitamin K dependent clotting factors by the N-methylthiotetrazole (NMTT) moiety. Unlike the present study Bhat and Deshmukh [16], Ehsanipour and Zarifian [17] and Williams et al. [20] reported that antibiotic associated hypoprothrombinemia is similar in children receiving NMTT group of antibiotic or other groups.

In the present study a greater incidence of hypoprothrombinemia was found in children with more than 10 d of antibiotic therapy, a finding similar to Bhat and Deshmukh [16] and Ehsanipour and Zarifian [17]. So it would be prudent to monitor coagulation parameters in every patient receiving antibiotics for more than 10 d. Unlike the present study Nicholas et al. and Pineo et al. found that incidence of hypoprothrombinemia was not related to duration of antibiotic therapy.

Vitamin K prophylaxis in patients whose nutrition is inadequate, who are treated with intravenous antibiotics and are on intravenous fluids for prolonged periods of time is important as shown by many authors [10, 21].

Table 2 Distribution of hypoprothrombinemia according to PEM in under 5 children

PEM (IAP grade)	Hypoprothrombinemia [n (%)]	No hypoprothrombinemia [n (%)]	Total [n (%)]
No PEM or Grade I, II PEM	06 (8.33)	42 (58.33)	48 (66.66)
Grade III-IV (Severe PEM)	07 (9.72)	17 (23.61)	24 (33.33)
Total	13 (18.05)	59 (81.94)	72 (100)

PEM Protein energy malnutrition

Table 4 Hypoprothrombinemia in each group and its distribution according to antibiotic used with or without NMTT side chain

Group	Hypoprothrombinemia [n (%)]	No hypoprothrombinemia [n (%)]	Total [n (%)]
Group A	08 (13.32)	52 (86.68)	60 (100)
Group B	10 (16.66)	50 (83.32)	60 (100)
NMTT+ other	05 (22.72)	17 (77.28)	22 (100)
Other	13 (13.26)	85 (86.74)	98 (100)

Thus it is concluded that a single dose of prophylactic vitamin K given on day 1 of antibiotic therapy has no role in preventing antibiotic induced hypoprothrombinemia. In the present study, hypoprothrombinemia was corrected in all cases after administration of vitamin K, however the authors did not reassess recurrence of hypoprothombinemia after administration of therapeutic doses of vitamin K.

In the present study after initial prophylactic dose of vitamin K the assessment for hypoprothombinemia was done on 10th day of antibiotic therapy except whenever there was clinical manifestation. However, hypoprothrombinemia after prophylactic vitamin K might have occurred before 10th day of antibiotic therapy and this needs further research. The duration of prophylaxis provided by single dose of vitamin K may be shorter than 10 d due to interference by some unknown factor which can be antibiotic itself which may be directly or indirectly affecting the duration of action of vitamin K and may necessitate administration of vitamin K at shorter intervals or at higher dose. This is an issue for further research in this area. Usui et al. showed that two third of hepatic vitamin K was lost in 3 d in patients who were on low vitamin K diet and received antibiotics [22]. Other studies showed vitamin K body pool turnover of about 1.5 d [23, 24].

Other factors like malnutrition and NMTT side chain of antibiotic in addition might be responsible for hypoprothrombinemia. Thus, mechanism of development of hypoprothrombinemia because of prolonged antibiotic therapy is complex and continues to be poorly understood.

Conclusions

Thus, antibiotic induced hypoprothrombinemia is common in children on prolonged antibiotic therapy and a single dose (0.5 mg/kg, max 10 mg) of prophylactic vitamin K given on day 1 of antibiotic therapy does not prevent antibiotic induced hypoprothrombinemia. However further research is needed to understand role of vitamin K and other factors, prophylactic doses and frequency of vitamin K administration for prevention of antibiotic induced hypoprothrombinemia.

Conflict of Interest None.

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