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Original Research Article

Role of prophylactic Vitamin K in preventing antibiotic induced hypoprothrombinemia

***Abdullah Qadri and Amanullah Arifzai**

Shiekh Zayed University Medical Faculty Pediatrics Department, Khost, Afghanistan

***Corresponding Author E-mail: abdullahqadri08@gmail.com; Tel: 0093708802019.**

Abstract

To find out the prophylactic role of single dose of vitamin K in prevention of antibiotic induced hypoprothrombinemia. This is comparative cross sectional study included critically ill children in age bracket 4 months to 11 years, admitted to a tertiary care hospital in Afghanistan, likely to receive prolonged antibiotic therapy. 100 children, 50 in each group (A & B) were enrolled within the study. Patient allocation was done on alternate basis. A children received prophylactic vitamin K while B didn't. Baseline coagulation studies and other investigations were wiped out all children. Coagulation studies were repeated on day 10 and day 15 of antibiotic therapy and in between if required clinically. Children who developed deranged INR got therapeutic vitamin K . If deranged INR returns to normal at 11 hour of vitamin K administration then it indirectly confirms vitamin K deficiency. Analysis was done by fisher's t test and chi square test. In children on prolonged antibiotic therapy, vitamin K deficiency was a standard problem (17 %). it had been common in male sex, severe grade of protein energy malnutrition (PEM), Nmethylthiotetrazole (NMTT) group containing antibiotics use and duration of antibiotic quite 9 days. it had been same in children whether or not they received or didn't receive prophylactic vitamin K on day 1 of antibiotic therapy (95 % CI; p value 0.77). Vitamin K deficiency is common problem in patients on prolonged antibiotic therapy. there's no role of single dose of prophylactic vitamin K in preventing antibiotic induced hypoprothrombinemia.

Keywords: Antibiotics, Hypoprothrombinemia, Vitamin K.

INTRODUCTION

The initial articles describing coagulopathy induced in humans by vitamin K deficiency were published in 1939. In 1952 a study recognized that administration of antibiotics increased the danger of hemorrhagic disease but advantage of vitamin K deficiency in humans (Warner et al., 1939). Two major hypotheses were proposed to elucidate the prolonged antibiotic use associated vitamin K deficiency (Waddell et al., 1939). First is that the use of broad spectrum antibiotic that suppresses the expansion of microorganism (Kark and Lozner, 1939). 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 coagulation factor synthesis i.e., they inhibit gammacarboxylation of glutaminic acid residue of clotting factors (Dam et al., 1939; Dam et al., 1952). Similar s in their study found that patients who received intravenous fluids just for as long as 4 wk didn't develop hypoprothrombinemia (Nicholas et al., 1987). But if they received concomitant antibiotics then they rapidly developed hypoprothrombinemia supporting role of antibiotic in causing vitamin K deficiency. vitamin K deficiency due to prolonged antibiotic use resembles with many other disorders of hemostasis numerous cases remains unreported (Kliegman et al., 2011). This study was designed to review 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 1 year from March 2019 to March 2020. The protocol of study was approved by the Institute ethics panel and written consent for inclusion was obtained from parents of every child. 100 patients in 4 months to 11 years age bracket who received antibiotic for minimum of 14 d duration were enrolled. Patients with disseminated intravascular coagulopathy (DIC), thrombocytopenia, liver dysfunction, renal dysfunction and people during which coagulation profile was initially abnormal, had case history of bleeding tendency or history of bleeding tendency within 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 protracted period (14 days) were enrolled. Patient with definite history of receiving antibiotics outside (with proper prescription) were also enrolled, but enrolled only in B as no vitamin K on day 1 of antibiotic therapy was given. Patients were divided into two groups, A and B by randomization on alternate basis. Detailed history and examination were recorded at time of admission. Investigations: CBC, bleeding time, time period , coagulation parameters (PT, APTT, INR), KFT and LFT of all patients were recorded on day 1 of admission. A patients received prophylactic vitamin K on day 1 of admission. B patients didn't 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 wiped out 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. 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 are demonstrated; thus there's no upper limit for vitamin K uptake. So in 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. 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 traditional expected for that age. Abnormal INR was evaluated with reference to parameters like age, sex, malnutrition, group of antibiotic used and duration of therapy. Considering vitamin K deficiency in healthy subjects as I Chronicles and with antibiotics as 25 you bored with 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 complete of 60 patients were enrolled in each group (open AP software version 2). The info 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 assistance of the software 'Graphpad Prism 5'.

RESULTS

A total of 112 patients were studied; out of which 100 patients met the study criteria and 50 patients were enrolled in A and B respectively. A complete of 18 children out of 120 developed hypoprothrombinemia (18%). Children who were found to possess hypoprothrombinemia received therapeutic vitamin K and repeat INR estimation was done at 11 hours. Altogether these patients, hypoprothrombinemia was corrected, indirectly confirming vitamin K deficiency. Table 1 shows distribution of hypoprothrombinemia in patients who received prolonged antibiotic therapy consistent with age groups. It shows that hypoprothrombinemia in patients receiving prolonged antibiotic therapy was equal altogether age groups and difference of hypoprothrombinemia in age groups was statistically not significant (p 0.5261). In . 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). just one patient developed hypoprothrombinemia before 11 days of antibiotic therapy. All other patients developed it after 11 d of antibiotic therapy;developing between 10 to 13 d (50 %) and eight developing on 14 d of antibiotic therapy (44.45) (Table 2 shows that a complete of 19 children out of 120 developed hypoprothrombinemia (27%). In A (who received prophylactic vitamin K), 8 children developed hypoprothrombinemia (13.32 %) while in B (without prophylactic vitamin K), 09 children developed hypoprothrombinemia (15.67 %). The difference in incidence of coagulopathy in both groups is statistically not significant (CI 95 %; p 0.76). It also showed that also shows development of hypoprothrombinemia in reference to NMTT+other or other antibiotics used. It shows that development of hypoprothrombinemia in patients on prolonged antibiotic therapy in NMTT group was 21.72 take a while in other group it had been 18.26 %. So incidence of hypoprothrombinemia in NMTT group is above other group of antibiotics. But this difference was statistically not significant (p 0.43).

Table 1. Distribution of hypoprothrombinemia in patients according to age groups.

Age (Year)	Hypoprothrombinemia (n (%)	No Hypothrombinemia (n (%)	Total (n (%)
04 mo- 1 year	06 (6)	29 (22.33)	30 (29.34)
>1years- 6Years	06(6.73)	33 (29.83)	32 (30.66)
> 7 Years	06(6.73)	45 (34.83)	40(40)
Total	18(15)	107 (97)	100 (100)

Table 2. Hypoprothrombinemia in each group and its distribution according to antibiotic-used with or without NMTT side chain.

Group	Hypoprothrombinemia (n (%)	No Hypothrombinemia (n (%)	Total (n (%)
Group A	10 (12.32)	50 (85.67)	62 (100)
Group B	09 (15.66)	53 (83.42)	64 (100)
NMTT+	04 (21.72)	18(76.37)	20 (100)
Other	12 (12.27)	85 (87.75)	99 (100)

DISCUSSION

The exact mechanism liable for antibiotic associated vitamin K deficiency aren't known with certainty. Most of the studies including this one have shown a big incidence of hypoprothrombinemia in children on prolonged antibiotic therapy. it's a crucial factor to be considered especially in those children who are critically ill (Lipsky, 1984; Welage et al., 1989). Mechanisms causing vitamin K deficiency include combined effect of diet low in vitamin K, loss of normal bowel flora thanks to prolonged antibiotic therapy which synthesize vitamin K 1 and direct inhibition of synthesis of vitamin K dependent clotting factors thanks to NMTT group containing antibiotics (Conly et al., 1984). Within the present study authors found that incidence of antibiotic associated hypoprothrombinemia was more in males as compared to females almost like the study by Conly et al. (Human vitamin and mineral requirements, 1998; Nutrient reference values for Australia and New Zealand including recommended dietary intakes [internet] (2006) this might be explained on the idea of influence of sex hormones on prothrombin. Prothrombin is made sooner and at a lower effective concentration of vitamin K in presence of oestrogen (Nathan et al., 2003). Prothrombin levels are higher in females than in males and therefore the dietary requirement for vitamin K in females is additionally less (Nathan et al., 2003; Hypoprothrombinemia workup [internet] (2008). As patients up to age bracket 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 better incidence of hypoprothrombinemia, a finding almost like Bhat and Deshmukh, Ehsanipour and Zarifian, Kark et al. and Pineo et al. Possible explanation might be that malnutrition limits the supply of oral phylloquinone causing hypoprothrombinemia. within the present study it had been found that antibiotic associated hypoprothrombinemia was more common with NMTT side chain containing antibiotic than other group of antibiotics, a finding almost like Shearer et al., Conly et al. and Nicholas et al. this might be explained by direct inhibition of biosynthesis of the vitamin K dependent clotting factors by the N-methylthiotetrazole (NMTT) moiety. Unlike this study Bhat and Deshmukh (Matschiner and Bell, 1973). Ehsanipour and Zarifian and Williams et al. reported that antibiotic associated hypoprothrombinemia is analogous in children receiving NMTT group of antibiotic or other groups (Bhat and Deshmukh, 2003; Ehsanipour and Zarifian, 2002). Within the present study a greater incidence of hypoprothrombinemia was found in children with quite 10 d of antibiotic therapy, a finding almost like Bhat and Deshmukh and Ehsanipour and Zarifian. So it might be prudent to watch coagulation parameters in every patient receiving antibiotics for quite 10 d (Pineo et al., 1973). Unlike this study Nicholas et al. and Pineo et al. found that incidence of hypoprothrombinemia wasn't associated with duration of antibiotic therapy (Williams et al., 1991). Vitamin K prophylaxis in patients whose nutrition is insufficient, who are treated with intravenous antibiotics and are on intravenous fluids for prolonged periods of your time is vital as shown by many authors .

CONCLUSIONS

Thus, antibiotic induced hypoprothrombinemia is common in children on prolonged antibiotic therapy and one dose (0.5 mg/kg, max 8 mg) of prophylactic vitamin K given on day 1 of antibiotic therapy doesn't prevent antibiotic induced hypoprothrombinemia. However further research is required to understand role of vitamin K and other factors, prophylactic doses and frequency of

vitamin K administration for prevention of antibiotic induced hypoprothrombinemia.

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