ORIGINAL ARTICLE

Coagulopathy and its Correction by Vitamin K in Children with Celiac Disease

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ABSTRACT

Background: 25% of children with Celiac disease (CD) have coagulopathy at the time of presentation. Diagnosis of CD involves endoscopy and multiple duodenal biopsies. Risk of bleeding with endoscopy and biopsy is more if there is underlying coagulopathy.

Objective: to study the correlation of coagulopathy with grade of histology in CD and to assess the response of a single dose of vitamin K on coagulopathy in children undergoing upper GI endoscopy and duodenal biopsy for CD.

Study design: Non-randomized interventional study.

Settings: Department of Pediatrics, Fortis Escorts Hospital, Jaipur

Method: Children (<18 years) suspected to have CD referred for duodenal biopsies were prospectively recruited in study. During the first 6 months (Group A) Prothrombin time (PT) was tested prior to endoscopy. During the next 6 months (Group B)children were given one dose of Vitamin K (5 mg IM in <10 years and 10 mg IM in >10 years) 24 hour prior to endoscopy and PT was tested prior to endoscopy as in group A. A cut off of INR of >1.4 was labeled as abnormal (coagulopathy). Subsequently PT/INR was compared in both the groups and correlated with severity of histology.

Results: Of 133 recruited children, 100 had confirmed CD by histologyand were analyzed subsequently. Both groups (A and B) had 50 subjects in each. The male female ratio in CD was 1.6:1 and the mean age was 5 years and 4 months. Group A and B were identical in terms of degree of demography and histological abnormality. Coagulopathy was seen in 32% of children in group A and 14% of children in group B and the difference was statistically significant. More than 50% of subjects with coagulopathy had advanced (Marsh grade IIIc) histology in both the groups which was significantly higher than those who had no coagulopathy. None had any significant bleeding during the endoscopic procedure in the study population.

Conclusion: CD with coagulopathy at presentation predicts advanced histological Marsh grade on duodenal biopsy. Coagulopathy can be significantly improved by single dose of parenteral vitamin K administration a day prior to endoscopy.

Keywords: Celiac disease, Coagulation, Children, vitamin K

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INTRODUCTION

Celiac disease (CD) is an autoimmune disorder of the small intestine elicited by gluten and related prolamins in genetically predisposed people of all ages from middle infancy onward. CD is characterized by malabsorption of multiple nutrients, vitamin K being one of them. Vitamin K deficiency leads to deranged coagulation and bleeding manifestations.

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CD has a prevalence of 0.8% to 2.67% in the western world[1–3]. In one of the large population studies in India, CD was prevalent in 1.54% by serology and 1.04% by histology[4]. CD is characterized by coagulopathy in 27% of children in a recent study from our institute[5]. Considering the most probable cause of coagulopathy to be vitamin K deficiency.We planned to see the improvement in coagulopathy by giving a single dose of vitamin K to children with CD24 hours prior to endoscopic biopsy in a large cohort.

Vitamin K injection at birth to all newborns is standard practice all over the world[6]. This is to prevent Hemorrhagic disease of newborn (HDN) which has an incidence of 0.25–1.7%[7,8] in absence of prophylactic vitamin K. On the other hand, 27% children with CD have coagulopathy. Celiacs need duodenal biopsy for confirmation of diagnosis. Endoscopy and biopsy in coagulopathic state has more chance of bleeding. If our study shows a significant reduction in coagulopathy by giving one dose of inj. vitamin K, we would be able to recommend the administration of vitamin K to all celiac children before duodenal biopsy.

We took up this study to know the effect of vitamin K in correcting coagulopathy during endoscopic biopsy in children with celiac disease.

METHODS

Study Design

Non-randomized interventional study.

Sample size

In our study, sample size calculation was done by using Epi Infostatistical software version 7. The sample size was calculated at 80% study power and 5% alpha error assuming 35% reduction in coagulopathy with vitamin K administration (Group B) as compared to without vitamin K administration (Group A). With these parameters a sample size of 50 patients in each group was required.

Sample correlation coefficient	0.9
Population correlation coefficient	0.8
Power (1-beta)%	80
Alpha error (%)	5
One or two sided	2
Required sample size (each group)	50

Time frame

Study was done over10–month period. (June 2015 to March 2016)

Inclusion Criteria

1. Children aged 6 months to 18 years with suspected CD referred to Fortis Escorts Hospital for duodenal biopsy.
2. Children aged 6 months to 18 years were admitted in Pediatric ward and were seropositive for CD.
3. Those who gave written consent.

Group allocation and intervention

Study was designed asnon-randomized interventional study. Patients were recruited in two groups (A and B) following study protocol inclusion criteria.

For convenience initial group A recruitment was done followed by group B.

During the first half of the study, Group A was assigned to the 50 consecutive children of confirmed CD and these were tested for PT at the time of duodenal biopsy without any prior vitamin K administration.

During the second half of study, Group B was assigned to the 50 consecutive children of confirmed CD who received a single IM dose of inj. vitamin K 24 hour prior to duodenal biopsy and PT was tested at the time of duodenal biopsy.

Sample Technique

Blood Sample (PT/INR) was taken during cannulation for IV sedation before biopsy. This tested at SRL laboratory at Fortis Escorts Hospital, Jaipur which is an NABL accredited laboratory. The test was funded by the Research Department of the hospital.

Group B patients received a single dose of vitamin K (5mg IM in children <10 years and 10mg IM in those >10 years). Name-Kenadion, Company-Samarth Life sciences Pvt Ltd. Strength of 10 mg/ml, use for IV/IM.

Before collection of samples, parents were counselled regarding participation in the study and oral and written consent was obtained.

STATISTICAL ANALYSIS

Data was analysed using software, STATA version 12.All the qualitative data was described as simple frequency with relative percentage. Quantitative data was expressed using descriptive statistics as mean, SD or percentages for categorical data. Statistical significant between different groups was evaluated by using appropriate statistical test. Intergroup difference among different group was evaluated by using independent t test for continuous variables while chi-square test was performed to differentiate categorical variables.A p-value ≤ 0.05 was taken as statistically significant. 95% confidence interval (CI) was estimated to understand the variability which can help to develop predictive models to estimate the risk of subsequent events in both group in concern to entitled problem.

RESULTS

We recruited 133 cases. Among them 100 had confirmed CD by histologyand were analysed subsequently (**figure 1**). Both groups (A and B) had 50 subjects in each. The male female ratio in CD was 1.6:1 and the mean age was 5 years and 4 months (**Table I**). Group A and B were identical in terms of degree of demography and histological abnormality. Coagulopathy was seen in 32 % of children in group A and 14 % of children in group B and the difference was statistically significant. More than 50% of subjects with coagulopathy had advanced (Marsh grade IIIc) histology in both the groups which was significantly higher than those who had no coagulopathy. None had any significant bleeding during the endoscopic procedure in the study population.

Description of various histological grades in the two groups of children with deranged PT/INR

We considered normal PT as 13–15 sec. and INR as <1.4[20]. In group A 16 children (32%) had deranged PT/INR (>1.40). We observed that of the 16 children with deranged PT, 9 had

TABLE 1. Demographic characteristics of CD children in Group A and B

		Group A (*n*=50)	Group B (*n*=50)	Total (*n*=100)(%)
Place of patient recruitment	OPD	50	49	99(98.5%)
	IPD	0	01	01(1.5%)
	Total	50	50	100(100%)
Mean age at presentation (95% CI)		4.9 ± 3.0 years (59.8 ± 36.2 months) (49.51–70.10)	5.8 ± 4.6 years (69.8 ± 55 .9 months) (53.94–85.73)	*P* value-0.29
Range (month)		13–192	12–192	
Sex	Male	31	29	60 (60%)
	Female	19	21	40 (40%)
	Total	50	50	100
Male to Female ratio		1.6:1	1.4:1	
(OPD- out patient department, IPD- in patient department)				

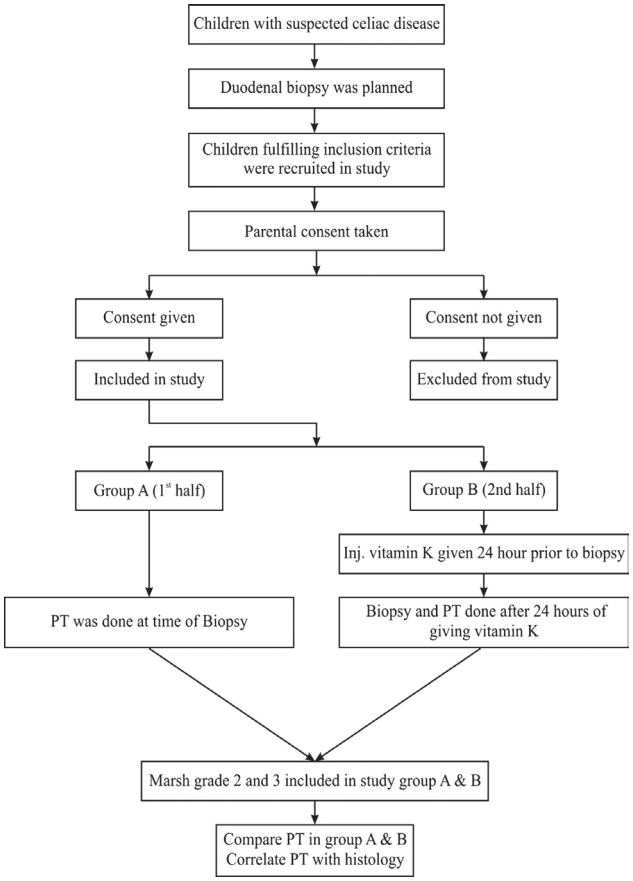

Figure 1: Study Flow Diagram

Marsh grade 3c histology (56.25 %)and 5 had Marsh grade 3b histology (31.25%).

In group B 7 (14%) had deranged PT/INR (>1.40). Among the 7 children, 4 had marsh grade 3c histology (57.14%) and 3 had Marsh grade 3b histology (42.85%).

We observed that in both groups, advanced histological picture (higher Marsh grade) was associated with greater number of children with deranged PT/INR.

TABLE 2. Comparision of PT / INR in CD children between Groups A & B

INR	Group A (*n*=50)	Group B (*n*=50)	*P* value
INR<1.4	34	43	
INR>1.4	16	7	0.032
Total	50	50	
INR- international normalised ratio			

The difference of deranged PT/INR in both the groups was statistical significant (p value 0.032)(**Table II**)

Description of degree of derangement of INR in different Marsh grades in group A & B

Derangement of INR was categorized as mild (1.40–2.50), moderate (2.51–5.00) and severe (>5.00). In group A 16 children (32%) had deranged PT/INR (INR>1.40). 15(30.0 %) children had mildly deranged INR while 1 (2.0%) had moderately deranged PT/INR.

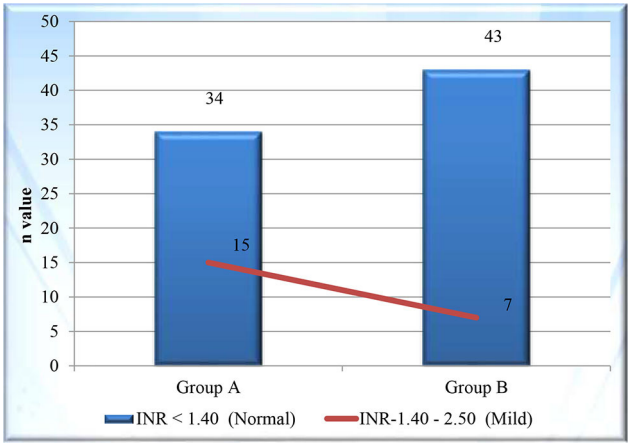

Figure 2: Bar diagram illustrating the decrement in the numbers of children with deranged PT/INR after injecting vitamin K

TABLE 3. Clinical features and lab parameter of CD in low vs high degree villous atrophy

Clinical feature	Low degree villous atrophy (%)	High degree villous atrophy (%)	Total (%)	*p* value
Chronic diarrhea	7(16)	36(84)	43(100)	0.27
Abdomen distension	9(14)	55(86)	64(100)	0.11
Failure to thrive	12(16.4)	61(83.6)	73(100)	0.13
Short stature	11(17.7)	51(82.3)	62(100)	0.48
Abdominal pain	9(25)	27(75)	36(100)	0.30
Pallor	14(19)	60(81)	74(100)	0.79
Cheilitis	1(33)	2(67)	3(100)	0.72
Frontal bossing	1(16.6)	5(83.4)	6(100)	0.61
Hepatomegaly	0(0)	11(100)	11(100)	0.18
Deranged PT/INR	12(24)	28(76)	50(100)	0.012
(Low degree villous atrophy - Marsh grade 2 and 3a, High degree villous atrophy- Marsh grade 3b and 3c)				

In group B, 7(14%) had deranged INR (INR>1.40) (**figure 2**)

All had mildly deranged INR while none had moderate and severe deranged INR. In both the groups, most children with deranged INR were with Marsh grade 3c hence the more severe the Marsh grading on histology, the more chances of coagulation abnormality.There wasstatistical significant difference between the two groups in term of number of children with mildly deranged PT/INR (*p* value 0.04).

Clinical features and lab parameters of CD in different histological grades

We defined low degree villous atrophy as marsh grade 2 and 3a, while high degree villous atrophy included marsh grade 3b and 3c. Among 100 total children with CD, children presented with pallor (74.0%), failure to thrive (73.0%), abdominal distention (64.0%), short stature (62.0%), chronic diarrhea (43.0 %) and abdominal pain (36.0%). Frontal bossing, dry skin and hepatomegaly was found in 6 %, 14 % and 11% respectively. No case of sibling celiac, IDDM, pedal edema, purpura and petechiae was seen. Deranged PT/INR was observed in 50 % children.We observed that clinical features and deranged lab parameters (PT/INR) were more pronounced in high degree villous atrophy grades. (**Table III**).

DISCUSSION

CD is a chronic inflammatory disorder of the small bowel that results in malabsorption of nutrients. Because vitamin K is a fat soluble vitamin absorbed from the small bowel, malabsorption leads to vitamin K deficiency, coagulative deficit of the vitamin K dependent factors resulting in prolonged PT.

The previous study from same centre demonstrated that deranged coagulation profile (INR≥1.40) is seen in 27% of children with CD[5]. There is a significant correlation between progression of Marsh Grade and number of children with deranged PT/INR as well as severity of coagulopathy..

We observed that of 50 CD children in group A 16 (32%) had deranged PT/INR. Of 50 CD children in group B 7 (14%) had deranged PT/INR. The difference between the two groups was significant (*p* value 0.03).

We also observed that of 16 children with deranged PT/INR in group A 15 children had mild coagulopathy and 1 child had moderate coagulopathy. In group B all 7 children had mild coagulopathy. There was significant difference between the two groups in term of number of children with mildly deranged PT/INR (*p* value 0.04).

As two groups were comparable in terms of demography, serology, histology and anthropometry the significant improvement in coagulopathy can be attributed to vitamin K therapy.

Battaro G *et al*[9] studied the effect of the therapy with vitamin K on coagulation factors in CD in Italian children. The Authors carried out a study on 37 untreated celiac children to investigate the behavior of K-dependent factors after vitamin K administration. They demonstrated that vitamin K administration resulted in a rapid increase in clotting activity of all K-dependent factors after 24 hours.

Mitterstieler *Get al*[10] studied 4 children with hemorrhagic diathesis in CD. In all 4 cases the hemorrhagic diathesis could be explained by a low prothrombin complex. After the administration of vitamin K1 there was an immediate rise in the prothrombin complex and bleeding quickly stopped.

Djuric Z *et al*[11] described a 4 years old girl with CD with diffuse cutaneous bleed due to vitamin K deficiency. Test showed considerably prolonged PT and aPTT. A coagulation profile showed a decrease in clotting factors II, VII, IX, and X. The patient was given intravenous vitamin K 5 mg daily for 3 days. All coagulation tests were normalized and bruising started to disappear.

Cavallaro *et al*[12] carried out a cross sectional analysis on 390 adults with untreated CD. Of 390 untreated CD 72 (18.5%) had prolonged PT (INR ≥1.4). 5 of them (7%) had an INR ≥ 5, 15(21%) had an INR between 4.9 and 2.5, and 52 (72%) had an INR between 2.4 and 1.4. Parenteral vitamin K was required in those who had INR >2.4.

Chen CS *et al*[13] presented a case with coagulopathy due to CD presenting as non traumatic intramuscular hemorrhage associated with prolongation of both PT and aPTT. He was treated with 5 mg oral vitamin K, FFP and cryoprecipitate which resulted in resolution of bleeding. Coagulopathy was attributed to vitamin K deficiency due to malabsorption.

FO Hosnut *et al*[14] stated that children with CD are predisposed to coagulopathy secondary to vitamin K deficiency. Correction of coagulopathy with vitamin K is necessary before endoscopic biopsy in patients with suspected CD. However, since vitamin K causes hemolysis in G6PD deficiency, possibility of hemolysis following vitamin K administration should be kept in mind.

Marta Eusebio *et al*[15], **Avery RA *et al*[16]**, **David R Graham *et al*[17]**, **McNicholas BA *et al*[18]**, **Lubel JS *et al*[19]** have published case reports suggesting improvement in coagulopathy by injectable vitamin K. In order to document similar response in a larger cohort we planned this study.

CONCLUSIONS

- CD with coagulopathy at presentation predicts advanced histological Marsh grade on duodenal biopsy.
- As two groups were comparable in terms of demography, serology, histology and anthropometry the significant difference in coagulopathy can be attributed to only vitamin K therapy

LIMITATIONS

- We have compared the effect of vitamin K on PT/INR by comparing PT/INR in groups who had received vitamin K (group B) and who had not (group A). It would have been better to compare PT/INR in same subject pre and post vitamin K to see the effect of vitamin K on each child.
- This was a study with a small sample size. A well designed RCT with a large sample size is recommended.

WHAT IS ALREADY KNOWN

- Endoscopic biopsy in children with underlying coagulopathy increases risk of bleeding complications.
- Children with seropositive CD had elevated PT/INR at the time of endoscopic duodenal biopsy.

WHAT THIS STUDY ADDS

- CD with coagulopathy at presentation predicts advanced histological Marsh grade on duodenal biopsy.
- Coagulopathy can be significantly improved by single dose of parenteral vitamin K administration a day prior to endoscopy.

Authors' contributions:

- SK,LB, DS: Contributed to conception and design of the study, drafting and critically reviewed the content.
- SSS: Contributed in collecting data, analysis, interpretation of data and drafting the manuscript.

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Ethical clearance: *study was approved by Institutional ethics committee.*

Conflict of Interest: No

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