VITAMIN K DEFICIENCY BLEEDING IN THAILAND : A 32 - YEAR HISTORY

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Abstract. Vitamin K deficiency bleeding cases in Thailand from 1963 to 1995 were extensively studied. From 1963 to 1987 there were 499 reported cases from 10 papers including 102 cases of the authors' series. From March 1994 to April 1996, two subsequent nationwide surveys were conducted where questionnaires were sent to 714 and 732 hospitals located throughout Thailand. The responding rate was 58.2% and 67% respectively. 331 cases were found during 1988 to 1995. The total number was 830 cases of which 799 were indiopathic vitanink defreisncy in mfancy (IVKDI) and 31 were secondary types. IVKDI was found exclusively breast-fed infants (92%) who did not receive vitamin K prophylaxis at birth (90%). Bleeding and pallor were the common features. The occurrence of intracranial hemorrhage was strikingly high (82%); the fatality rates was 24%. However, the fatality rate among patients receiving either 1 mg of vitamin K, intramuscularly, (17%) or 2 mg, orally, (18%) were lower than those not receiving vitamin K prophylaxis (36%). The incidence of IVKDI significantly declined to 4.2-7.8 per 100,000 births between 1988 to 1995 which was in reverse proportion to the coverage of vitamin K prophylaxis ($r = -0.94$, $p < 0.05$).

INTRODUCTION

The bleeding problems caused by vitamin K deficiency can be divided into four groups : (i) early hemorrhagic disease of the newborn (HDN), (ii) classical HDN, (iii) late HDN or acquired prothrombin complex deficiency or idiopathic vitamin K deficiency in infancy (IVKDI) and (iv) secondary type. The early, classical HDN and secondary type are rather rare. IVKDI is commonly found in 2-8 week-old infants with life-threatening intracranial hemorrhage. It was first recognized in Thailand in 1963 (Bhanchet *et al,* 1966). Since then, more than one thousand cases of IVKDI have been reported from Thailand and other countries all over the world (Hanawa *et al,* 1990; Sutor and Hathaway, 1995). There were two longitudinal perinatal field work studies in a district of Ayutthaya Province which is located in the central part of Thailand (Khanjanathiti *et al,* 1987). The first study was conducted from 1977 to 1978 for a duration of 15 months. The incidences of the classical HDN and IVKDI were the same at 89 per 100,000 births. The second study was conducted from 1981 to 1984 for a duration of 33 months. The incidence of classical HDN and IVKDI were 54 per 100,000 births and 72 per 100,000 births, respectively. In 1983, a nationwide hospital - based survey in Thailand reported the incidence of IVKDI at 35 per 100,000 births (Ungchusak *et al,* 1988). The figure from the hospital-based survey will be lower than that of the longitudinal perinatal study since some affected infants died at home.

After the introduction of vitamin K prophylaxis at birth, the prevalence significantly declined (Isarangkura *et al,* 1986; Satayasai *et al,* 1987). The present study demonstrates the incidence, severity and outcome of vitamin K deficiency bleeding in Thailand in the past 3 decades from 1963 to 1995.

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MATERIALS AND METHODS

Vitamin K deficiency bleeding cases in Thailand from 1963 to 1995 were extensively collected. From 1963 to 1987, there were 499 cases of vitamin K deficiency bleeding reported in 10 papers including 102 cases of the authors' series. (Whitaker *et al,* 1969; Mitrakul *et al,* 1977; Isarangkura *et al,* 1984; Hirunyachote *et al,* 1987; Lerdsukprasert 1987; Mahasandana *et al,* 1987; Panjaroen *et al,* 1987; Panstienkul 1987; Satayasai *et al,* 1987; Maipang *et al,* 1988). In March 1994 and April 1996, two

subsequent nationwide surveys were conducted. Questionnaires were sent to 714 and 732 hospitals located throughout Thailand. The capacity of hospitalized beds varied from 10 to more than 1,000 beds. The questionnaires included the practice of routine vitamin K prophylaxis to all newborn infants and the occurrence of infants under one year of age with spontaneous bruising or bleeding which was not caused by an inherited coagulopathy. If such a case was reported, the physician was requested to complete another questionnaire giving the detailed data for each case, including age of onset, birth weight, type of delivery, vitamin K prophylaxis, type of feeding, site of bleeding , clinical manifestation, underlying disease, treatment, outcome and sequale.

Idiopathic vitamin K deficiency in infants was characterized by bleeding caused by vitamin K deficiency of unknown etiology in infants aged 2 weeks to 1 year. They had good responses to vitamin K therapy. No serious preceding or associated diseases were detected. Secondary vitamin K deficiency was defined when a patient had apparent causes such as hepatobiliary diseases, malabsorption resulting from chronic diarrhea or short - bowel syndrome.

Statistics the Student's *t*-test for proportion is used to differentiate between the mean of two groups. The correlation was studied by Pearson's correlation test. The p value of less than 0.05 was considered significant.

RESULTS

Responses were received from 433 hospitals in 1994 and 478 hospitals in 1996. The responding rate was 59.2% and 67%, respectively (Table 1). Three hundred and thirty-one cases of vitamin K deficiency bleeding were found from 1988 to 1995. With the addition of 499 reported cases from 10 papers from 1963 to 1987, the total number reached 830 cases of which 799 were idiopathic and 31 were secondary types. The incidence of IVKDI was calculated from the number of patients and births in each year. However the complete data of births in each hospital could not be complete obtained and the responding hospitals in the survey of 1994 and 1996 gave estimates of 59.2% and 67%, respec-

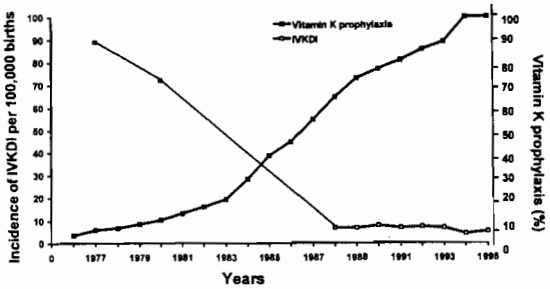

Fig 1–The declination of the incidence of idiopathic vitamin K deficiency in Thailand was in reverse proportion to the coverage of vitamin K prophylaxis.

Table 1

Response rate from hospitals with different capacity of beds.

Type	Capacity of bed	Survey 1994			Survey 1996		
		Total hospital	Response	%	Total hospital	Response	%
University	800-1,000	9	7	77.8	9	9	100
Regional	500-1,000	16	13	81.3	17	6	35.3
Provincial	90-500	69	29	42	69	28	40.6
District	10-90	542	339	62.5	519	384	73.9
Organizational	100-200	28	18	64.3	20	16	80
Private	100-300	68	27	40	80	35	43.8
Total		732	433	59.2	714	478	66.9

tively. Therefore, 59.2% and 67% of the annual birth rate of 1,000,000 births were used to correct the number of births in the periods of 1988 to 1993 and 1994 to 1995, respectively. The incidence of IVKDI from 1988 to 1995 of the hospital-based survey in this study was estimated to range from 4.2 to 7.8 per 100,000 births. The declination of the incidence of IVKDI was in reverse proportion to the coverage of vitamin K prophylaxis ($r = -0.94$, $p < 0.05$) as shown in Fig 1.

common features. The occurrence of intracranial hemorrhage was strikingly high, which was commonly found in the subdural and subarachnoidal spaces. However, multiple intracerebral hematomas and intraventricular hemorrhage were demonstrated in a few critical patients by computerized tomography of the brain. Most of the patients presented with signs and symptoms of intracranial hemorrhage, with convulsion in 65%; drowsiness 61%; vomiting 5%; irritability 2% and cardiopulmonary arrest 1%.

Table 2

The clinical findings of 691 cases of idiopathic vitamin K deficiency from 1963 to 1995.

	1994 - 1995 53 cases	1988 - 1993 150 cases	1963 - 1987 488 cases	Total 691 cases (%)
Sex				
Male : female	2 : 1	2.6 : 1	2.5 : 1	2.5 : 1
Age				
2 weeks - 2 months	46/53	139/150	237/294	422/497 (85)
> 2 months - 12 months	7/53	11/150	57/294	75/497 (15)
Infant feeding				
Breast	47/50	130/139	390/429	567/618 (92)
Breast and formula	2/50	8/139	23/429	33/618 (5)
Formula	1/50	1/139	16/429	18/618 (3)
Vitamin K prophylaxis				
Receiving IM	4/38	12/107	2/430	18/575 (3)
Receiving oral	21/38	17/107	4/430	42/575 (7)
Not receiving	13/38	78/107	424/430	515/575 (90)
Undetermined	15/53	43/150	12/488	70/691 (10)
Clinical manifestation				
Hemorrhage	52/52	150/150	439/439	641/641 (100)
- intracranial	38/52	129/150	357/439	524/641 (82)
- skin and muscle	19/52	46/150	105/439	170/641 (24)
- gastrointestinal tract	3/52	13/150	91/439	107/641 (17)
Anemia	33/52	90/150	350/439	473/641 (74)
Outcome				
Fatality rate	18/53	39/150	110/488	167/691 (24)
Sequelae				
- immediate	13/17	48/111	81/129	142/257 (55)
- long-term follow-up (> 1 year)	-	-	15/31	15/31 (48)

Six hundred and ninety-one cases of IVKDI with complete data were analyzed (Table 2). The male to female ratio was 2.5:1. Most of the patients were aged two weeks to two months and exclusively breast-fed. Bleeding and pallor were the

A few patients had a coagulogram study revealing prolonged activated partial thromboplastin time and prothrombin time. But the protein-induced by vitamin K absence (PIVKA) and level of vitamin K were not included. The comprehensive manage-

ment included supportive treatment, subdural tapping, blood component therapy as well as vitamin K administration. Forty out of 93 cases (43%) required a mechanical respirator to support their ventilation. The craniotomy for the removal of large hematomas were performed in 37 out of 246 cases (15%).

The overall fatality rate was 24% (167/691). Most of them succumbed to massive intracranial hemorrhage. The fatality rate among patients without intracranial hemorrhage was 6% (5/80) which was markedly lower than those with intracranial hemorrhage (116/462 = 25%). Moreover, the fatality rate among patients receiving 1 mg of vitamin K intramuscularly (3/18 = 17%) or 2 mg, orally (7/38 = 18%) were lower than those not receiving vitamin K (33/91 = 36%). The p-values were 0.1 and < 0.05, respectively. Permanent neurological deficits were found in 142 of 257 survivors (55%). They were seizure disorders 64%; muscle weakness 21%; mental retardation 15%; hemiparesis 13%; hydrocephalus 7%; and microcephaly 5%. A ventriculoperitoneal shunt was performed in four patients with hydrocephalus.

Regarding the history of vitamin K prophylaxis at birth, 90% of the patients did not receive vitamin K prophylaxis at birth while 10% received either 1 mg, intramuscularly, or 2 mg, orally. Eight of 18 patients who received 1 mg, intramuscularly were high-risk babies (three caesarean section, one vaccuum extraction, three low birth weight < 2,500 g and one was a six-month old baby who was exclusively breast-fed and did not receive any solid food). Ten of 42 patients receiving 2 mg, orally were high-risk babies (four caesarean section, four low birth weight < 2,500 g, one received only 1 mg of oral vitamin K prophylaxis at birth and one mother refused to eat green leafy vegetable during the first postpartum month). The improper practice of vitamin K prophylaxis was found in 48 of 478 surveyed hospitals (10%). The instance of an oral 1 mg dose of vitamin K given to normal full-term infants was found in 2 hospitals and an oral 2 mg dose of vitamin K given to both normal full-term and high-risk infants was found in 46 hospitals.

Thirty-one cases with secondary vitamin K deficiency were included. The age ranged from 0.5 to 10 months (mean ± SD 2.6 ± 2.2 months). The underlying diseases were hepatobiliary disease, malabsorption resulting from short-bowel syndrome or chronic diarrhea. Bleeding and anemia were also the common features. Intracranial hemorrhage was often found in the first two months of age. The fatality rate was 26% and permanent neurological deficits were found in 28% of the survivors (Table 3).

Table 3

The clinical findings of 31 cases of secondary vitamin K deficiency from 1963 to 1995.

	Total 31 cases (%)
Sex	
Male : female	1.2 : 1
Age	
2 weeks - 2 months	18/31 (58)
> 2 months - 12 months	13/31 (42)
Vitamin K prophylaxis	7/31 (22)
Underlying diseases	
Malabsorption	11/31 (35)
Hepatobiliary disease	20/31 (65)
Clinical manifestation	
Hemorrhage	31/31 (100)
- intracranial	20/31 (65)
- skin and muscle	7/31 (22)
- gastrointestinal	9/31 (29)
Anemia	21/31 68
Outcome	
Fatality rate	8/31 (26)
Sequelae	7/25 (28)

DISCUSSION

Vitamin K prophylaxis at birth by giving 1 mg intramuscularly was first initiated in Thailand in 1964. However, less than 10% of the surveyed hospitals gave vitamin K prophylaxis at birth during the 1970s. Since the availability of oral vitamin K preparation in 1984, vitamin K prophylaxis at birth either by 1 mg of intramuscular or 2 mg of oral route has been widely promoted. Vitamin K prophylaxis by oral route is simple, practical and of low cost. It can be given to newborn infants by physicians, nurses or traditional midwives. In Thailand, 30% of deliveries are still carried out by traditional midwives in the remote rural areas. The practice of vitamin K prophylaxis at birth has gradually ex-

tended to cover 89% of the surveyed hospitals in 1993. Complete coverage was achieved in 1994 when the health authorities integrated vitamin K prophylaxis into the national health care program. The incidence of IVKDI among Thai infants dramatically declined in reverse proportion to the coverage of vitamin K prophylaxis at birth. However, misunderstanding of the improper practice of vitamin K prophyaxis in 48 surveyed hospitals should be clarified in order to achieve the effective protection of bleeding disorder in all newborn infants.

There was a strikingly high incidence of intracranial hemorrhage of IVKDI, as well as secondary type in the first two months of age. The high prevalence of intracranial hemorrhage in vitamin K deficiency has not been satisfactorily explained. The rapid development of the brain at this age with the disproportional growth of surrounding supportive tissue and blood vessels may be one of the contributing factors. Patients in a vitamin K deficient state will have markedly low levels of factor II, VII, IX and X. The deficient state of factor VII and/or factor X has been shown to associatedly occur with serious bleeding in the first year of life (Girolami *et al,* 1970; Ragni *et al,* 1981). The deficient state of specific coagulation factors may be another contributing factor of intracranial hemorrhage.

Although comprehensive management was given to the patients, the fatality rate and permanent neurological deficits among the survivors were high. The cost-benefit of management was not as efficient as that of vitamin K prophylaxis at birth (Kajornpadungkitti *et al,* 1988). However, in this study, 60 cases had received prophylaxis either intramuscularly or orally at birth. Eleven of them were preventable cases. Oral vitamin K prophylaxis should not be given to high-risk infants (8 cases), moreover, the appropriate dose of oral vitamin K prophylaxis is 2 mg. The dose of 1 mg is inadequate since the level of prothrombin complex in infants receiving 1 mg orally at birth was significantly lower than those receiving 2 mg orally at the age of 1-2 months (Isarangkura *et al,* 1986). One normal full-term infant, who received 1 mg of oral vitamin K at birth, developed IVKDI at the age of one and a half months. Improper feeding in infants and lactating mothers was also a precipitating etiology (2 cases). However, the actual deficient state of vitamin K is another possible etiology. Even though vitamin K prophylaxis at birth cannot totally prevent bleeding disorders, the fatality rate in patients receiving vitamin K prophylaxis at birth is lower than those not receiving. Vitamin K administration at birth may be helpful in decreasing the extent of serious bleeding. Therefore, at least one appropriate dose of vitamin K prophylaxis at birth to all newborn infants should be completely achieved in Thailand. The intramuscular route is more effective than the oral route. In cases of giving oral vitamin K at birth, additional dose of vitamin K at the age of 4-7 days and/or 30 days in exclusive breast-fed infants should be considered in order to obtain the completeness of prevention.

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