ORIGINAL ARTICLE

Intracranial haemorrhage due to late onset vitamin K deficiency bleeding in Hanoi province, Vietnam

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Background: In many developing countries vitamin K prophylaxis is not routinely administered at birth. There are insufficient data to assess the cost effectiveness of its implementation in such countries.
Objective: To estimate the burden of intracranial haemorrhage caused by late onset vitamin K deficiency bleeding in Hanoi, Vietnam.
Methods: Cases of intracranial haemorrhage in infants aged 1–13 weeks were identified in Hanoi province for 5 years (1995–1999), and evidence for vitamin K deficiency was sought. The data were compared with those on vitamin K deficiency bleeding in developed countries and used to obtain an approximation to the incidence of intracranial haemorrhage caused by vitamin K deficiency bleeding in Hanoi.
Results: The estimated incidence of late onset vitamin K deficiency bleeding in infants who received no prophylaxis was unexpectedly high (116 per 100 000 births) with 142 and 81 per 100 000 births in rural and urban areas respectively. Mortality was 9%. Of the surviving infants, 42% were neurologically abnormal at the time of hospital discharge. Identified associations were rural residence, male sex, and low birth weight. A significant reduction in the incidence was observed in urban Hanoi during 1998 and 1999, after vitamin K prophylaxis was introduced at one urban obstetric hospital.
Conclusions: Vitamin K deficiency bleeding is a major public health problem in Hanoi. The results indicate that routine vitamin K prophylaxis would significantly reduce infant morbidity and mortality in Vietnam and, costing an estimated US$87 (£48, €72) per disability adjusted life year saved, is a highly cost effective intervention.

Late onset vitamin K deficiency bleeding (VKDB) is a coagulopathy which occurs in young infants caused by inadequate plasma concentrations of active coagulation factors II, VII, IX and X.[1–4] First reports of this condition came from Asia,[5 6] and it became increasingly recognised in the 1980s as an important cause of morbidity and mortality in early infancy.[2 3] Late onset VKDB occurs after the first week of life (by definition),[4] has a peak incidence at 4–8 weeks, and is rare after 12 weeks.[7] It is a serious condition often presenting with an acute intracranial haemorrhage (ICH) in a previously healthy breast fed infant; in a recent review more than 60% of cases presented in this way.[7] The mortality is 10–15%, and at least 40% of the survivors have long term neurological handicaps.[2 7] Several studies have shown that vitamin K prophylaxis at birth greatly reduces the incidence of late onset VKDB.[2 3 8]

In infants who receive no vitamin K prophylaxis, late onset VKDB has been reported to be more common in Asian countries[9] and in warmer climates.[9 10] Estimates of the incidence show significant geographical variation—for example, the incidence in the United Kingdom and Germany was $>$ 5.0 and 7.2 per 100 000 births respectively,[2 3 11] whereas in Japan it can be calculated to be 20–25 per 100 000 births.[10 12] Each of these figures relates to infants who did not receive prophylaxis. In contrast, there are few published data on the incidence of late onset VKDB in developing countries. The only relevant study, from Thailand, reported an incidence in 1983 of 35 per 100 000 births,[13] suggesting that the condition may be more common in developing countries.[10]

Internationally recommended criteria for defining ''confirmed'' VKDB in epidemiological studies include the following: age between day 8 and the end of week 12, pretreatment coagulation studies which are grossly abnormal (Quick prothrombin value $<$ 15%), together with a normal platelet count and fibrinogen, or correction of coagulation results to normal after vitamin K administration.[14] However, in many areas of developing countries there are no facilities for such laboratory investigations, compounding the difficulties in defining the incidence of VKDB in these countries. Therefore a different approach was used in this study to identify infants with late onset VKDB in Vietnam, where the incidence of this condition has not previously been documented. We surmised that idiopathic intracranial bleeding in previously well infants may be largely or solely the result of vitamin K deficiency, and so be a guide to the incidence of late onset VKDB in this population.

METHODS

Patients

Patient records from the seven hospitals treating young infants in the province of Hanoi were examined retrospectively for cases of ICH occurring over five years, between January 1995 and December 1999. Infants who had been previously well but who presented with an unexplained ICH between day 8 and the end of week 13 were identified. In 1998 and 1999 only, vitamin K prophylaxis was given to all newborns at one large maternity hospital, the Hanoi Obstetric and Gynaecological Hospital. The preparation used was Konakion, Cremophor (Roche Pty Ltd, Basel, Switzerland), given in a dose of either 1 mg intramuscularly or 2 mg orally, soon after birth. The decision to begin vitamin K prophylaxis was made independently of the present study. Except for the infants born at the above hospital in 1998 and

Abbreviations: VKDB, vitamin K deficiency bleeding; ICH, intracranial haemorrhage; QV, Quick prothrombin value; DALY, disability adjusted life year; YLL, years of life lost; YLD, years lived with disability

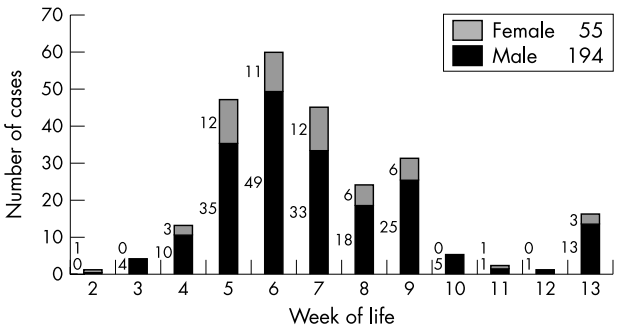

Figure 1 Idiopathic intracranial haemorrhage in Hanoi (rural and urban areas combined), 1995–1999: sex distribution and age at presentation. Cases occurring in week 13 are excluded from the statistical analysis (see text).

1999, no other infants in the study received vitamin K prophylaxis.

Study design

Idiopathic ICH was defined as one occurring without evidence of trauma, sepsis, or disseminated intravascular coagulation. The diagnosis was made on the basis of non-coagulating, macroscopically blood stained cerebrospinal fluid in infants presenting with an acute encephalopathy. Cranial imaging data (ultrasound or computed tomography) was available in about 20% of infants. Cerebrospinal fluid cell counts but not cultures were performed in all cases. Results of the Quick prothrombin value (QV), expressed as a percentage of normal clotting activity[14 15] (normal range 75–100%), were recorded where measured.

Data collected included presenting symptoms, investigations performed, treatment received, and clinical status at discharge. The seven hospitals involved in this survey were all those in the study area at which young infants were treated. Five were district hospitals that treated minor illnesses, but critically ill infants (such as those with an ICH) were referred to either of two major hospitals, the National Institute of Paediatrics or St Paul's Hospital. The infants were classified as living in an urban or rural area on the basis of the postal address of the mother. Using the Official Map of Hanoi, 2000 (Bando Cartographic Publishing House, Hanoi, Vietnam), we defined urban areas as those within the boundaries of the City of Hanoi and rural areas as those outside these boundaries but within the province of Hanoi. Urban areas were generally densely populated and had developing business and industry, whereas rural areas were more sparsely populated and predominantly used for farming.

Estimated incidence rates for late onset VKDB were calculated as the number of cases of idiopathic ICH per 100 000 births, using the number of cases ascertained as above as the numerator, and birth numbers obtained from the official birth statistics for Hanoi as the denominator.[16] Low birthweight rates (< 2500 g) were obtained from annual reports of the Mother and Child Health and Family Planning Department in Hanoi.

Cost effectiveness analysis

The cost effectiveness of vitamin K prophylaxis, which was assumed to prevent almost all cases of VKDB,[2 11] was modelled for a birth cohort of 100 000. Currency conversions from US dollars (US$) to pound sterling (£) and euro (€) were based on exchange rates obtained on 26 March 2004. The cost of the vitamin K (Phytomenadion; Rotexmedica, Trittau, Germany), together with syringe and needle, was estimated as US$0.50 (£0.28, €0.41) per infant. This estimate was doubled to allow for other indirect costs, assuming uncertainty as a uniform distribution ranging from US$0.75 (£0.41, €0.62) to US$1.25 (£0.69, €1.00). Disability adjusted life years (DALYs) were calculated to estimate the burden of late onset VKDB in Hanoi. Mortality was translated into age weighted and discounted (3%) years of life lost (YLL) using 2002 estimates of life expectancy in Vietnam.[17] Life long disability was estimated to occur in 40–60% of surviving infants. Between 50% and 70% of disabled survivors were estimated to have moderate disability (class 3), with the remainder severely disabled (class 4).[10 18] The years lived with disability (YLD) were calculated from the product of incidence, disability weight, and life expectancy, applying the same age weighting and discounting as for YLL. Uncertainty around the cost effectiveness ratio was examined in a Monte Carlo simulation model using the software program @RISK, version 4.0 (Palisade Corporation, New York, USA). The incidence, case-fatality ratio, and male to female ratio were entered as normal distributions with mean and standard error derived from observed data. Results are presented as point estimates with 95% uncertainty intervals (UI) based on 2000 iterations of the model.

Table 1 Incidence of idiopathic intracranial haemorrhage (ICH) in infants between day 8 and the end of week 12, in rural and urban Hanoi, 1995–1999

	1995	1996	1997	1998	1999	5 year totals
Rural areas*						
Total births	25290	24318	23652	22189	20301	115750
Number of cases of idiopathic ICH	38	32	33	39	22	164
Incidence of ICH per 100 000 births (no prophylaxis)	150	132	140	176	108	142 (122 to 165)‡
Urban areas						
Total births	18502	19383	20058	21817	19871	99631
Number receiving no prophylaxis†	18502	19383	20058	14613	12189	84745
Number receiving prophylaxis†	Nil	Nil	Nil	7204	7682	14886
Number of cases of idiopathic ICH	15	22	16	7	9	69
Incidence of ICH per 100 000 births (no prophylaxis)	81	114	80	48	74	81 (65 to 101)‡
Incidence of ICH per 100 000 births (total births)	81	114	80	32	45	69 (55 to 88)‡
Combined rural and urban areas						
Total births	43792	43701	43710	44006	40172	215381
Number receiving no prophylaxis	43792	43701	43710	36802	32490	200495
Number of cases of idiopathic ICH	53	54	49	46	31	233
Incidence of ICH per 100 000 births (no prophylaxis)	121	124	112	125	95	116 (102 to 132)‡
Incidence of ICH per 100 000 births (total births)	121	124	112	105	77	108 (95 to 123)‡

*Rural infants received no vitamin K prophylaxis in any year.
†Urban infants born at the Hanoi Obstetric and Gynaecological Hospital received vitamin K prophylaxis in 1998 and 1999 only.
‡Incidence per 100 000 births (95% confidence interval) based on five year totals.

Statistical analysis

Relative risks and 95% confidence intervals were calculated for all comparisons between groups. Only those cases presenting between day 8 and the end of week 12 were included in the statistical analysis, as recommended by Tripp *et al*[14] for the reporting of epidemiological studies of vitamin K prophylaxis. Cases presenting beyond week 12 are discussed separately (fig 1).

RESULTS

There were 233 infants (aged between day 8 and the end of week 12) with idiopathic ICH identified over the five year period (table 1). For rural and urban Hanoi the incidences of idiopathic ICH in infants receiving no vitamin K prophylaxis were 142 and 81 per 100 000 births respectively; for the entire province (rural and urban Hanoi combined) the figure was 116 per 100 000 births. The age distribution of cases of idiopathic ICH in Hanoi was almost identical with that of late onset VKDB reported from the United Kingdom[2] and Australia,[7] the majority occurring between 4 and 8 weeks of age with a median age at presentation of 5.5 weeks (fig 1). Presenting symptoms in our infants were also similar to those reported in studies of ''confirmed'' late onset VKDB;[2 7] most presented with an abrupt onset of seizures. Findings on admission included lethargy (89%), coma (10%), bulging fontanelle (92%), and pallor (97%). Twenty six (11%) had extensive skin bruising, and 22 (9%) had bleeding from other sites. In no case did the cerebrospinal fluid cell count suggest bacterial meningitis or viral encephalitis. There were 21 deaths (9%). In 110 (52%) of the survivors, neurological status was documented at the time of hospital discharge; 46 (42% of those documented) were neurologically abnormal with problems including continuing seizures, hemiparesis, and hydrocephalus.

Coagulation studies were not performed in all patients. Sixty seven had a QV measurement on admission. Forty two of these infants had received no treatment before coagulation was tested; in 40 (95%) the QV was $< 10\%$, consistent with profound vitamin K deficiency. The other two (5%) had QVs of 30% and 40%, values accepted as indicating ''probable'' VKDB.[14] The other 25 infants who had their QV measured had either already received treatment with vitamin K_1 (17 infants), or there was no information recorded on such treatment (eight infants). The QVs of these 25 infants ranged from 23% to 100% (median 85%). Eight of the infants with QVs $< 10\%$ had a repeat measurement within 24 hours of treatment with vitamin K_1, and in all it had normalised. Platelet counts were performed in all infants who had coagulation studies and in 11 others; all were normal ($> 150 \times 10^9$/l).

A number of significant associations were identified. ICH occurred more commonly in infants from rural than urban areas (relative risk 1.7; 95% confidence interval (CI) 1.3 to 2.3; $p = 0.0001$), in boys than girls (3.3; 95% CI 2.5 to 4.6; $p < 0.0001$), and in those with birth weight < 2500 g (2.1; 95% CI 1.3 to 3.2; $p = 0.001$). Urban areas of Hanoi had a higher incidence of idiopathic ICH in 1995–1997 than in 1998–1999 (2.4; 95% CI 1.4 to 4.2; $p = 0.002$), when some infants received vitamin K prophylaxis (table 1). However, among those given no prophylaxis, the incidence did not differ significantly between the two time periods, whether comparing infants from urban (1.5; 95% CI 0.9 to 2.7; $p = 0.13$) or rural (1.0; 95% CI 0.7 to 1.3; $p = 0.90$) areas.

At a cost of US$100 000 (£55,200, €82,400) vitamin K prophylaxis administered to a birth cohort of 100 000 infants could prevent 11 deaths, 340 YLL, and 53 cases of life long disability, or 820 YLD. The cost effectiveness ratio is US$87 (£48, €72) per DALY saved; 95% UI US$60 to 120 (£33 to 66, €49 to 99). A sensitivity analysis was performed based on the rather unlikely scenario that 33 of our cases had diseases other than VKDB. This yielded a cost effectiveness ratio of US$100 (£55, €82), 95% UI US$69 to 140 (£38 to 77, €57 to 115) (table 2).

DISCUSSION

The reported data indicate an unexpectedly high incidence of late onset VKDB in Hanoi (table 1). Estimated incidences from different countries in infants who have not received vitamin K prophylaxis vary widely. Wariyar *et al*[8] summarised the published data from developed countries, noting the highest incidence to be in Japan, namely 20–25 per 100 000 births.[8 10 12] In 1983 a higher incidence was reported from Thailand, then a developing country, namely 35 per 100 000 births.[13] Because there are few published data on VKDB incidence in developing countries, no meaningful analysis of the cost effectiveness of vitamin K prophylaxis in these countries has been performed.[10] Possible reasons for the wide variation in reported incidences include the following: in developed countries where routine vitamin K prophylaxis is almost universally practised, estimates of the small number of infants who do not receive vitamin K may be inaccurate; also, reports from developed countries have usually applied strict diagnostic criteria for ''confirmed'' cases, thereby excluding some ''true'' cases in which full laboratory investigation was not performed.[10 14] Identification of cases in developing countries will often be incomplete because of poor record keeping or inadequate investigation, leading to an underestimate of the number of affected infants.[10]

The strict criteria recommended to confirm a case of late onset VKDB[14] could not be applied in the present study but, working within the constraints of research in a developing

Table 2 Cost effectiveness analysis based on reported data (primary analysis), and sensitivity analysis based on a worst case scenario considering the maximum predicted number of incorrect diagnoses

	Primary analysis	Sensitivity analysis*
Incidence	116 (102 to 132)	100 (87 to 115)
Deaths	11 (7 to 14)	9 (6 to 13)
Years of life lost	340 (220 to 470)	290 (200 to 410)
Life long disability	53 (41 to 66)	45 (35 to 57)
Years lived with disability	820 (630 to 1000)	700 (540 to 890)
Cost of prophylaxis (US$)†	100000 (76000 to 124000)	100000 (76000 to 124000)
Cost effectiveness ratio (US$)†	87 (60 to 120)	100 (69 to 140)

Values are mean (95% confidence interval or uncertainty interval) per 100 000 births.
*Excludes 33 cases of possible incorrect diagnoses, including five predicted cases of haemorrhagic stroke/arteriovenous malformation, and an estimated 28 cases with normal prothrombin values in whom prior administration of vitamin K could not be established with certainty (see text).
†Currency conversion rates (26 March 2004): US$1.00 = £0.55, €0.82.

country, we have attempted to follow them as far as is possible. Many patients were treated empirically and appropriately on the suspicion of late onset VKDB, and some did not have coagulation studies beforehand. However, of the 42 infants who had a QV measured and had definitely received no prior treatment, 95% met the coagulation criteria for a diagnosis of ''confirmed'' VKDB; the other 5% fulfilled the criteria for ''probable'' VKDB.[14]

Our study was geographically restricted to urban Hanoi and surrounding rural districts. This area was chosen because health records there were accurately maintained, and infants with acute neurological symptoms were almost certain to be treated at one of the seven hospitals included in the study. It is unlikely that the number of cases of presumed late onset VKDB with ICH has been overestimated because most of the QVs when measured before treatment were grossly abnormal and the age distribution of the affected infants (fig 1) is almost identical with that in other reports of ''confirmed'' VKDB.[2 7] This age distribution is different from that of ICH caused by cerebral arteriovenous malformations, which usually occurs soon after birth or later in childhood.[19] Presenting symptoms and signs, including the incidence of skin bruising, in our idiopathic ICH cases were also similar to those reported in studies of ''confirmed'' VKDB.[2 7] With the methodology used, it was not possible to document long term neurological sequelae, but at the time of hospital discharge more than 40% of the survivors had obvious neurological abnormalities. It is likely that most or all of these would suffer significant long term disability. This is similar to the rate of sequelae reported by others.[2 7]

The incidence of late onset VKDB reported here is likely to be an underestimate because only 60–70% of cases present with ICH,[7 13] and some infants may have died before reaching hospital.[10] Further studies are needed to ascertain whether the high incidence in Vietnam occurs in many developing countries or is peculiar to countries in Asia. Furthermore, the incidence rates reported here only include cases occurring between 1 and 12 weeks as was recommended for reports of epidemiological studies of vitamin K prophylaxis.[14] If the data collected for week 13 (an additional 16 cases) are included, the calculated incidences are higher still; rural 151, urban 87 per 100 000 births, and combined rural and urban 124 per 100 000 births.

Possible explanations for different susceptibilities to this condition in different populations include genetic variation affecting vitamin K absorption,[1] variation in the incidence of chronic liver disease and malabsorptive conditions,[7] and differences in breast feeding rates[10 20] and in dietary intake of vitamin K in its various forms.[21] With the methodology used here it was not possible to determine the reason for the increased incidence of late onset VKDB in infants from rural areas. Features of residents in rural compared with urban areas include the following: higher levels of poverty, less adequate diet, increased occurrence of enteric diseases, and lower standards of medical care. In this setting the increased incidence in rural areas could be explained by a decreased dietary intake of vitamin K_1 in breast feeding mothers or impaired absorption of menaquinones (vitamins K_2) caused by altered bowel flora in young infants.[21] Another highly significant association for late onset VKDB in this study was male sex. This has been reported previously from several other Asian countries including Taiwan,[9] Japan,[12] and Thailand,[13] but is not a feature of reports from the United Kingdom and Germany.[2 11] The reason for this higher incidence in male infants in Asian countries is unknown.

Although this study was not primarily designed to evaluate efficacy, the observed decrease in the incidence of idiopathic ICH after the introduction of prophylaxis strongly suggests that vitamin K administration was protective in infants born at one large urban obstetric hospital. This further supports the hypothesis that most cases of idiopathic ICH were indeed presentations of late onset VKDB.

It is important to consider the cost effectiveness of introducing routine vitamin K prophylaxis in developing countries. In a recent review, Victora and Van Haecke[10] attempted to calculate the cost effectiveness in terms of DALYs lost through late onset VKDB. Lacking reliable frequency data for the condition in developing countries, they derived an estimate. Taking a median (seven per 100 000 births) of the incidences reported from several developed countries,[10] they doubled it for the effect of a warm climate, and doubled it again for the higher breast feeding rate—hence the incidence of 28 per 100 000 births used in their evaluation. Other assumptions in their calculation were: a mortality of 25%, age at onset 6 weeks, male infants affected twice as commonly as female infants, and life long disability in 50% of survivors. This translated to a cost of US$133 (£73, €110) per DALY saved by introducing vitamin K prophylaxis, assuming a cost of US$1.00 (£0.55, €0.82) per injection.[10] Despite our lower case fatality, because of the high incidence of VKDB in Hanoi (116 per 100 000 births), our estimate of the cost per DALY saved by prophylaxis is US$87 (£48, €72) (table 2). This is well below the figure, US$100 (£55, €82), that the World Bank regards as indicating a high priority for implementation.[10 22] Costs may be reduced by combining the vitamin K dose with the neonatal hepatitis B vaccine already used in many developing countries (K Mulholland, personal communication).

ICH caused by vitamin K deficiency is a major public health problem and its importance in Vietnam and possibly other developing countries may be underestimated. We argue that most of our reported cases of idiopathic ICH are, in fact, instances of late onset VKDB. The data strongly indicate, furthermore, that vitamin K prophylaxis is protective and highly cost effective and would significantly reduce infant morbidity and mortality if it were to be introduced throughout the study area. Further studies are required to determine whether this would hold true in other developing countries.

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