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REPORT

ROUTINE NEONATAL VITAMIN K ADMINISTRATION AT BIRTH

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EXECUTIVE SUMMARY

HDN (Haemorrhagic disease of newborn) was first described in 1894, and only in 1940 was its relationship with vitamin K deficiency documented. Currently the preferred term for HDN is 'Vitamin K Deficiency Bleeding' (VKDB). Vitamin K is an anti-hemorrhagic factor that is capable of correcting clotting defects caused by obstructive jaundice and other biliary diseases in humans. HDN is an acquired coagulopathy secondary to reduction of Vit K- dependent coagulation factors below haemostatic levels. It is characterized by prolonged prothrombin time with normal fibrinogen and platelet count and elevated levels of Proteins Induced by Vitamin K Absence-II(PIVKA-II). The coagulopathy and/or clinical bleeding can be corrected early within 30-120 minutes by Vit K administration parenterally.

The causes of VKDB can either be primary (idiopathic) , usually associated with exclusive breastfeeding, or secondary to underlying disorders like diseases causing cholestasis, malabsorption or due to drugs. The condition can be classified according to the age of onset - early (first 24 hours), classical (first week of life) or late (after day 8 until 6 months age).

Vitamin K prophylaxis is required to prevent VKDB, and is administered intramuscularly at birth at a dosage of 1 mg. In the absence of vitamin K prophylaxis the incidence of classical VKDB has been reported to vary between 0.4% to 1.7%. When routine administration of parenteral Vit K was introduced to newborns, VKDB cases ceased. The objective of this assessment is to determine the effectiveness, safety and cost implication of routine administration of vitamin K at birth.

The main concern was the association between IM vitamin K and leukemia raised in a study in England. However, subsequent studies showed that there is sufficient evidence to refute the carcinogenic risk of parenteral vitamin K.

From this assessment, it can be concluded that there is sufficient evidence on the safety of vitamin K. With respect to effectiveness there is sufficient evidence to support vitamin K in preventing VKDB. A selective policy of vitamin K administration after screening is not appropriate since relatively high incidence of both classic and late VKDB occurred without prophylaxis. The evidence on a comparison of parenteral with intramuscular route of administration appears inconclusive, however there is sufficient evidence to show that oral regimens are effective. In relation to starting oral regimen, ethnical and geographical differences in vitamin K metabolism and absorption, incidence of underlying disease, breastfeeding patterns and uptake would need to be considered. In the area of cost implications, there is insufficient evidence, although there is some evidence that it is cost effective.

It is recommended that an intramuscular dose of vitamin K be given to all newborns at birth as prophylaxis to prevent VKDB

1. BACKGROUND

'Haemorrhagic disease of the newborn' (HDN) was first described in 1894, and only in 1940 was its relationship with vitamin K deficiency documented. The incidence of late HDN in developed countries ranges from 5 to 225 per 100,000 births with a median of 7.1. In less developed countries, an estimate of this incidence is 35 (with a range 7 to 72) per 100,000 births. Currently, the preferred term for HDN is 'vitamin K deficiency bleeding' (VKDB).

The American Academy of Pediatrics recommended in 1961 that vitamin K be given to all newborns intra-muscularly (Vitamin K Ad Hoc Task Force, AAP). In 1990, the Ministry of Health of Malaysia endorsed intra-muscular vitamin K to be given to all babies at birth.

2. INTRODUCTION

HDN was first described by Charles Townsend in Boston more than a century ago. In 1929, Henrik Dam, a Danish biochemist, observed massive haemorrhages in chickens fed on a cholesterol-free diet. This has led to the discovery of a new fat-soluble vitamin, to which Dam gave the letter K, because of its effect on coagulation.

HDN is an acquired coagulopathy secondary to a reduction of vitamin K- dependent coagulation factors below haemostatic levels. It presents as unexpected bleeding, often with gastrointestinal hemorrhage, ecchymoses and sometimes, intracranial haemorrhage. It is characterized by prolonged prothrombin time with normal fibrinogen and platelet count and elevated levels of proteins induced by vitamin K absence-II (PIVKA-II). The coagulopathy and/or clinical bleeding in HDN can be corrected early (within 30-120 minutes) by administration of vitamin K parenterally, which also confirms the condition.

The cause of VKDB can either be primary (idiopathic), usually associated with exclusive breastfeeding, or secondary to underlying disorders like diseases causing cholestasis, malabsorption, or due to drugs. The condition can be classified according to the age of onset - early (within the first 24 hours), classical (first week of life) or late (after day 8 till 6 months of age). Early VKDB cannot be prevented by postnatal vitamin K prophylaxis.

As vitamin K crosses the placental barrier poorly, its concentration at birth in the newborn is considerably lower than that of the mother. Although the vitamin K deficiency state intensifies in the first few days of life, especially in breastfed babies, the majority of babies do not experience bleeding. On the other hand, formula-milk fed infants achieve vitamin K levels that are ten times higher than those exclusively breastfed, and it appears that these babies are protected against both classical and late VKDB. Vitamin K levels gradually reach adult values in babies by six weeks of age.

Vitamin K prophylaxis is required to prevent VKDB, and is administered intramuscularly at birth at a dosage of 1 mg. In the absence of vitamin K prophylaxis, the incidence of classical VKDB has been reported to vary between 0.4% and 1.7%. However, with

routine administration introduction of parenteral vitamin K to newborns, VKDB has ceased to occur. For late VKDB, in infants who are not given prophylactic vitamin K the incidence ranges from 4.4 to 7.1/100,000 births, usually involving infants who are exclusively breast-fed.

2.1 Issues in relation to vitamin K

While the problem of VKDB appeared to have been resolved when oral vitamin K prophylaxis was made available, there was setback somewhere in the 1950s when a water-soluble preparation of the synthetic vitamin K₃ was found to cause hemolysis with consequent kernicterus in many neonates. However, this problem seemed to have been overcome after vitamin K₃ was replaced with vitamin K₁ (phytomenadione).

Apart from this, it was discovered that a single oral dose of vitamin K does not always prevent late VKDB. However, with the introduction of intra-muscular vitamin K prophylaxis, the problem appears to have been resolved.

Subsequently, there were suspicions raised that parenteral Vitamin K could increase the risk of childhood cancer. This prompted many countries to move to oral vitamin K prophylaxis. However, this trend has recently been associated with a resurgence of late VKDB, especially with a single oral dose of vitamin K at birth.

3. OBJECTIVE

To determine the effectiveness, safety and cost implications of routine administration of vitamin K at birth.

4. METHODOLOGY

The electronic databases of Medline, HealthSTAR, EMBASE, Cochrane library, International Pharmaceutical Abstracts, US Guidelines Clearing House, the Canadian Medical Association, Health Canada, the US Centers for Disease Control, the Australian Department of Health & Aged Care, and the Aggressive Research Intelligence Foundation at the University of Birmingham were searched from 1966-2000. The following were the keywords used, either singly or in combination - *vitamin k deficiency, neonate(s), neonatal, newborn, infant(s), administration, routine, therapeutic, screening, dosage, route, frequency, timing, cancer, leukaemia, safe, safety, cost-benefit analysis, costs, cost analysis, economic and cost-effectiveness*. The search was limited to studies carried out on human subjects only. From the various titles retrieved, only 71 papers were relevant and were critically appraised.

5. TECHNICAL FEATURES

Vitamin K is an anti-hemorrhagic factor that is capable of correcting clotting defects caused by obstructive jaundice and other biliary diseases in humans. The name stems from the German word *Koagulationsvitamin*, which means *clotting vitamin*. The term Vitamin K includes several related compounds that have in common a methylated naphthoquinone ring structure, that vary in the aliphatic side chain.

Vitamin K is found in both plants and animals. Those found in plants is known as vitamin K₁, whereas the multiple forms synthesized by bacteria is referred to as vitamin K₂. The Subcommittee on Nomenclature of Quinones has since recommended that vitamins K₁ and K₂ be called *phylloquinones* and *menaquinones*, respectively. Phylloquinone is found throughout the plant kingdom and in cyanobacteria (blue-green algae), while menaquinones represent a diverse family of compounds all synthesized by bacteria. Since *naphthoquinone* is the functional group, the mechanism of action is similar for all K vitamins. Substantial differences may be expected, however, in intestinal absorption, transport, tissue distribution, and bio-availability. These differences are caused by the different lipophilicities of the various side chains and by the different food matrices in which they occur.

Several studies demonstrated improved pharmacokinetic properties of a new formulation of vitamin K i.e. mixed micellar preparation (Amadee-Maresme et al, 1992, Schubiger et. al., 1997; Schubiger et. al., 1999).

The vitamin K₁ currently being used in Malaysia is marketed by Roche as Konakion™ 1mg/0.5ml. It is a cremophor formulation containing propylene glycol, phenol and polyethylated castor oil.

6. RESULTS & DISCUSSION

6.1 Safety

Golding et. al. (1990) studied relevant information collected prospectively in over 16,000 pregnancies in 1970 in relation to subsequent cancer in childhood. There was an unexpected statistically significant association between drugs given to infants (odds ratio 2.62, 95% CI 1.31 to 5.21) and childhood cancer (all types) identified when the child was 10 years old. Thus, a possible association between intra-muscular vitamin K and leukaemia (OR 2.65, 95% CI 1.34 to 5.24) was established (Golding et at 1992).

Draper (1992) mentioned the lack of an increase in the incidence of leukaemia in the more recent period studied, leading to considerable doubt on the risks ascribed to intra-muscular vitamin K. Chayen (1992) has indicated that the phenol in vitamin K is both mildly carcinogenic by itself as well as being a strong promoter of carcinogenic action.

Parker et al (1998) showed that there was no association between intra-muscular vitamin K and the development of all childhood cancers (OR 0.89, 95% CI 0.69 to 1.15) as well as for all Acute Lymphoblastic Leukaemia (OR 1.20, 95% CI 0.75 to 1.92). However, the OR for Acute Lymphoblastic Leukaemia (ALL) developing 1 to 6 years after birth was 1.79 (95% CI 1.02 to 3.15). A separate ecology based study by the same author did not show any association in the rates of ALL in babies that received vitamin K compared to those where less than 30% received prophylaxis.

Von Kries (1996), found that the adjusted OR for 'intra-muscular' and 'sub-cutaneous' versus 'oral and no vitamin K' for common ALL compared with local controls was 2.28 (95% CI 0.94 to 5.54, p=0.03).

A study by Klebanoff (1993) showed an odds ratio of 0.84 (95% CI 0.41 to 1.71) for vitamin K versus no vitamin K for all cancers, while for leukaemia the OR was 0.47 (95% CI 0.14 to 1.55). An ecological study done by Ekelund (1993) showed the OR for all childhood cancers occurring after intra-muscular versus oral vitamin K was 1.01 (95% CI 0.88 to 1.17), and for leukaemia it was 0.90 (95% CI 0.70 to 1.16). Olsen (1994) also did an ecological study, which did not show an increase of childhood cancers with intra-muscular versus no vitamin K. Other studies also indicated that there was no association of cancer with intra-muscular versus combined 'none/oral/no record' of vitamin K (Ansell, 1996; Passmore et.al, 1998).

In a case-control study of childhood cancers including ALL by McKinney et al (1998), the OR for subset of ALL aged 1 to 6 years was 1.16 (95% CI 0.62 to 2.15) for recorded data and 1.33 (95% CI 0.70 to 2.53) for imputed data. This result is contradicts that of Parker.

The American (Vitamin K Ad Hoc Task Force, AAP 1993), Canadian (Brousseau 1996, JPS 1997) and Australian (JPS 2000) expert committees did not support Golding's findings and they quoted the results of some of the above findings. The Australian Joint Statement (NHMRC, Oct 2000) stated that the production of the cremophor preparation has ceased. They recommended a new preparation Konakion Mixed Micellar (MM) Paediatric preparation, administered preferably intra-muscularly with the alternative of three oral doses.

A few studies showed marginal increased risk, but these were unable to totally refute the possibility of a carcinogenic effect - all cancers odds ratio 0.89 to 1.44 (95% CI: 0.05 - 1.15), all ALL/leukemia odds ratio 1.2 to 1.53 (95% CI: 0.17 -1.92), ALL onset from 1 to 6 years odds ratio 1.03 to 1.79 (95% CI: 1.02 -3.15) (Parker et. al., 1998; Passmore et al., 1998). Passmore et al., 1998, also mentioned that there is a slight, though not significant, increased risk of developing cancer from vitamin K.

However, there have been numerous studies refuting the risk of carcinogenesis of leukemia from parenteral vitamin K (Odds ratio 0.47 - 1.3; 95% CI: 0.14 - 2.03) (McKinney et. al. 1998; Klebanoff et. al., 1993; McMillian et. al. 1996; Bousson et. al. 1996; Von kries et. al. 1996; Ekchund et al 1993, Pizer et.al 1995; Cornelissen et. al.

1991) ALL (Odds ratio 0.60 -1.21; 95% CI: 0.3 – 1.97) (McKinney et. al. 1998; Von Kries et. al. 1999; Roman et. al 1997) and all cancer like lymphoma, CNS tumours and solid tumours (Odds ratio 0.59 - 1.08; 95% CI: 0.37 – 2.61) (McKinney et. al. 1998; Klebanoff et. al., 1993; McMillian et. al. 1996; Bousson et. al. 1996; Von kries et. al. 1996; Ekchund et al 1993; Pizer et.al 1995; Cornelissen et. al. 1991).

Thus, there is sufficient evidence to refute the carcinogenic risk of parenteral vitamin K and these studies are more widespread in their representation from Scotland, Europe, USA and Canada, whereas the studies postulating a carcinogenic effect are limited to England alone.

Other side effects of minor concern are biochemical effects like increased hemolysis from the oxidative stress from Vitamin K demonstrated in G6PD susceptible red blood cells. There have also been few case reports of scleroderma-like lesions at the site if IM Vitamin K injection named as Texier's disease.

6.2 Effectiveness

6.2.1 Routine vs selective vitamin K

There is little data available on comparing a routine with a selective strategy for the administration of Vitamin K in the newborn. A study by Nishiguchi et. al. (1996) using prothrombin levels as a basis for administering vitamin K found that mass screening was complicated and did not appear to be sensitive. The appropriate screening test to indicate the neonates at risk for bleeding could not be determined, as this study did not correlate low PT activity with bleeding.

6.2.2 Parenteral vs. oral route of administration

With respect to plasma vitamin K levels, it was found that I/M Vitamin K results in peak levels that are 20 times higher than that after 1mg oral vitamin K, within the first 24 hours (McNinch et al, 1985). In addition, the incidence of late VKDB for babies given a single oral dose of Vitamin K 1mg was found to be 6 times higher than for those given I/M 1mg Vitamin K at birth (von Kries *et. al.*, 1992). The relative risk for late VKDB in those receiving a single oral vitamin K was estimated to be 13 times than that for those receiving I/M vitamin K at birth (McNinch et. al. 1991; Canadian Paediatric Society, 1997).

However, another study determining plasma vitamin K levels at 4-5 days of life, found no difference in the mean vitamin K levels for those given I/M vitamin K 1mg and those given oral 2mg at birth (Gupta et al, 1994). There was also no difference in activity of coagulation factors and PIVKA-II levels at 3 days of age between those given 1mg oral Vitamin K and those given 1mg I/M at birth, with no episode of bleeding in either group at 5 days follow-up (Jorgensen et al 1991). Similarly, although it was found that infants given vitamin K 1mg I/M at birth had significantly higher plasma levels at 2 weeks, 1 month and 3 months compared to those given single oral 1mg at birth in an exclusively breastfed population sample, there was no difference in the activity of coagulation factors, and PIVKA-II was detectable in almost equal proportion of cases in both groups

at 1 and 3 months (Cornelissen et. al. 1992). A small RCT also found no difference in the mean vitamin K levels in the groups given a single oral dose of 2mg or 5mg and I/M 1mg at 1 month of age (Hathaway et al,1991). 3 oral doses of mixed micellar vitamin K 2 mg at birth, at 7 days and at 30 days appeared to provide at least equal or even higher levels of Vitamin K monitored at 14, 30 and 56 days compared with the I/M group(Greer et. al,1998).

There were only a few clinical trials that compared the efficacy of the parenteral route of Vitamin K prophylaxis with the oral route. Most had small samples with total numbers varying from less than 100 to 300 babies. These studies utilized biochemical indicators of vitamin K deficiency, namely, plasma vitamin K levels, prothrombin activity or PIVKA-II levels. There is no direct evidence to suggest that these biochemical indices bear a relationship to the occurrence of VKDB. In addition, in most of these studies, randomization procedures were not described, and loss to follow-up was high. Most of these studies had limited periods of follow-up, and most compared only a single oral dose with an intra-muscular(I/M) dose at birth. There was only one trial comparing a multiple oral dose regimen to a single I/M dose of vitamin K. Some studies used more than the commonly employed oral 1mg of vitamin K viz. 2mg and 5mg. However there was no evidence that a higher dose of vitamin K improved coagulation status more than the usual dose of 1mg.

6.2.3 Oral vitamin K

Infants given a single oral dose of 1mg of vitamin K at birth were found to have undetectable PIVKA-II at 5 days of age while 48% of those not given any vitamin K had detectable levels (von Kries, 1987). Higher rates and higher levels of PIVKA-II were found in one month old babies not given vitamin K as well as in those given a single oral 5mg dose, compared to babies given 2 oral 5mg doses, at birth and at 2 weeks (Motohara et. al. 1986). In another study of breast-fed infants given oral 1mg vitamin K weekly for 12 weeks following a 1mg dose at birth showed normal coagulation status, there were undetectable PIVKA-II and raised vitamin K levels at all time points till the age of 3 months (Cornelissen et. al.; 1993). In addition, no case of late VKDB was seen in babies given weekly 1mg oral vitamin K for 3 months following an oral dose of 2mg at birth while there were 4.5/100 000 cases in those given a single oral 1mg at birth (Hansen et al, 1996). It was found that three oral 2mg doses (at birth, first week and at week 5-6) resulted in a much reduced incidence of late VKDB as compared to three oral 1mg doses (at birth, 4-10 days and 4-6 weeks) (Von Kries 1995; 1999). In the Netherlands, a regimen of oral vitamin K 1mg at birth and 25 micrograms daily till the age of 13 months reported the lowest failure in comparison to 3 oral 1mg doses or 2 oral mixed micellar 2mg doses (Cornelissen, 1997). A prospective cohort study demonstrated that 4 spaced doses of oral 1mg vitamin K did not protect those with underlying liver disease (Wariyar et al, 2000). In a 3-dose regimen oral vitamin K, the uptake of the third dose was found to be only 90.6% (Hill, 1994).

No randomized control trials that compared the efficacy of the different oral regimens in preventing classical or late VKDB were found. Most RCTs compared a single oral dose of vitamin K with an I/M dose at birth and most studies utilised biochemical indicators as

secondary outcome measures. The different oral regimens however were compared in small size descriptive studies using biochemical indicators. Large scale epidemiologic data in the form of birth cohort studies were also available which compared rates of VKDB with different oral regimens.

Epidemiologic data in general provided evidence that multiple oral doses provide better protection than a single oral dose at birth

6.3 Cost Implications

A review of the cost implications of vitamin K administered intra-muscularly, indicates that saving one disability adjusted life year (DALY) would cost \$533 in the 'low', \$133 in the 'intermediate' and \$52 in the 'high' incidence scenario. Based on the World Bank classification of interventions costing under \$100 as 'cost-effective' while those costing between \$250-999 per DALY as 'moderately cost-effective', vitamin K prophylaxis can be said to be cost effective only in the high incidence scenario (Cesar et al, 1998)

An analysis of cost and quality adjusted life expectancy years (QALEY) in intra-muscular vitamin K prophylaxis for HDN found that the cost of each life saved by an oral programme is \$4500 and \$11 000 for intra-muscular prophylaxis, while the QALEY gained though small, has been said to be worthwhile (Brown, 1989).

7. CONCLUSION

There is sufficient evidence on the safety of vitamin K. With respect to effectiveness, there is sufficient evidence of vitamin K in preventing vitamin K deficiency bleeding. A selective policy of vitamin K administration after screening is not appropriate since there is a relatively high incidence of both classic and late VKDB without prophylaxis. The evidence on a comparison of parenteral with intramuscular route of administration of vitamin K appears to be inconclusive. However, there is sufficient evince that oral vitamin K regimens are effective. In relation to this, ethnical and geographical differences in vitamin K metabolism and absorption, incidence of underlying diseases, breastfeeding patterns and uptake, would need to be considered. In the area of cost implications, there is insufficient evidence, although there is some evidence that it is cost effective.

8. RECOMMENDATIONS

It is recommended that an intramuscular dose of vitamin K be given to all newborns at birth as prophylaxis to prevent VKDB.

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