ARTICLE

Intramuscular vitamin K in the newborn and childhood cancer – a literature review of evidence for best practice

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Newborn infants are born deficient in vitamin K and its associated coagulation factors, and are therefore prone to developing vitamin K dependent bleeding (VKDB). This haemorrhagic disease is severe, but its incidence has been successfully reduced through a single dose of intramuscular Vitamin K given to newborns soon after birth. Oral administration is possible but requires repeated doses and is prone to failure due to poor feeding, regurgitation and cholestatic disease.

In 1992, a case-control study of two English maternity hospitals revealed a link between intramuscular vitamin K and childhood cancer (odds ratio 1.97 (confidence level 1.3-3.0)).[4] There was no link found with oral administration. A number of criticisms were made of the study, particularly its method of data collection, matching, and generalisablity. Nevertheless, its findings generated significant concern. Recommendations from the British Paediatric Association resulted in substitution of intramuscular for oral vitamin K, and the unfortunate recurrence of VKDB. Larger studies have been unable to satisfactorily confirm the proposed link between vitamin K and cancer, and it is felt the risk is extremely small, if real at all. As it is certain that the risk of VKDB is virtually eliminated with a single intramuscular dose of vitamin K, this remains the most prevalent practice worldwide.

In order to establish the influence of vitamin K on childhood cancer, the author carried out a literature review on the Medline database and discussed the matter with a Dunedin paediatrician. Further background material was provided by a New Zealand consensus statement, published in 2000, on the use of vitamin K in the newborn.[1] The following introduction includes a description of neonatal vitamin K deficiency, types and manifestations of VKDB, and a brief history of the use of supplemental vitamin K in the newborn. The article continues with critical appraisals of research and review articles published over the previous decade, in order to establish the validity of statements regarding the risks of supplemental vitamin K. The article concludes with a summary of the New Zealand consensus statement.

It is standard practice in Dunedin Public Hospital to administer a single dose of intramuscular vitamin K to all newborn infants, in order to prevent vitamin K dependent bleeding (VKDB),[1] a practice consistent with the world's major teaching hospitals. All newborn infants are deficient in vitamin K, detectable by an elevated prothrombin time and low plasma concentrations of vitamin K and the vitamin K-dependent coagulation factors II, VII, IX, and X.[2] As the concentration of vitamin K in breast milk is low and it has a half-life of only 24 hours, there is a high likelihood that deficiency will worsen if the baby feeds poorly, regurgitates excessively, or suffers from malabsorption.[3]

VKDB is typically separated into three categories: early, classic, and late. Early VKDB causes bleeding in the first 48 hours and is attributed to maternal anticonvulsant therapy,[3] particularly with barbiturates and phenytoin. Classic VKDB occurs in the first week of life in 0.4-1.7 per 100 births. It is associated with severe internal, gastrointestinal, and intracerebral bleeding. Bleeds may result in significant mortality and neurologic sequelae. Late VKDB is more rare, varying from 4.4-10.5 per 100 000 births, and occurs in infants 2-12 weeks of age. It is strongly associated with breast feeding and malabsorption, for example in cholestasis or biliary atresia.

The risk of VKDB is made negligible by a single intramuscular dose (1.0mg) of vitamin K at birth. This intervention was standard practice during the last 50 years. At times there were concerns raised that such an intervention may be harmful or unnecessary for the newborn. This led to varied practices including omission of therapy, treatment with oral vitamin K, or treatment reserved for 'at risk' babies ('at risk' implies babies born pre-term, with significant perinatal illness, or any delay in the onset of feeding). All

of these practices resulted in the recurrence of VKDB and an increase in perinatal mortality.[3]

In 1990 Golding et al reported results from the Oxford Survey of Childhood Cancers that suggested an increase in leukaemia and other cancers in children who received intramuscular vitamin K at birth.[4] These findings were supported by a case-control study published in 1992 by Golding et al[5] that found a statistically significant two-fold increase in risk of childhood cancer in children who received intramuscular vitamin K at birth. There was no association found between oral vitamin K and cancer.

These findings created an uproar in the field, as any increase in cancer would far outweigh a reduced risk of VKDB. A flood of studies emerged over the decade, some finding no link and others inconclusive.

Childhood cancer, intramuscular vitamin K and pethidine given during labour

A retrospective case-control study was used to assess the relative risk of childhood cancer in babies given oral or intramuscular vitamin K at birth.[5] Cases included 195 children with cancer born in the two major Bristol (England) maternity hospitals, and controls were 558 children identified from the delivery books. A significant association was found in children receiving intramuscular vitamin K when compared to oral vitamin K or no vitamin K. The odds ratio was 1.97 (1.3-3.0, p = 0.002). There was no increased risk found with oral vitamin K.

There were a number of limitations to the study in its collection of data and selection of subjects. It used only two hospitals for drawing its subjects, meaning the study population may not have been a fair representation of the general population. The cases and controls were unmatched for age and sex, making it less likely for the two groups to be comparable. Finally data collection was often unable to assess by what route vitamin K had been given, if at all. In identifying the probable route of administration the clerks used the practice endorsed by the hospitals at the particular time when the child was delivered. This method may have introduced a significant uncertainty in data collected.

Despite its drawbacks, the Golding study could be considered a pilot study that generates a hypothesis, for larger, more rigorous, population-based studies to confirm.

Vitamin K and childhood cancer: a population-based case-control study in Lower Saxony, Germany[5]

Von Kries et al[6] made it their objective to confirm or refute the possible association of parenteral vitamin K prophylaxis and childhood cancer. The authors labelled this a 'population-based study' as subjects were taken from 162 different hospitals. Therefore any results from the study may be generalisable to the wider population. The cases included 272 children with leukaemia and other cancers, and the controls included 334 children matched for sex and age from a broad population base. Their results found no significant associations between vitamin K and cancer, with an odds ratio of 1.04 (0.74-1.48). The risk of leukaemia only was 1.24 (0.68-2.25). These results were almost unchanged with adjustment for potential confounders.

The design of this study lends it more credibility than that of Golding et al, yet it is also comparable because it assessed the same preparation of vitamin K. It included data from 162 hospitals, whereas Golding et al used only two, matching cases to both local and general population controls and matching for age and sex. Golding et al did not age and sex match, and it may be that the certainty of vitamin K delivery is more reliable than Golding's.

In accurately assessing the mode of exposure to vitamin K, the data clerks took a systematic approach. If the dose and route were not documented in the child's records the clerks would instead use the information of the child nearest it in the book, given the same perinatal morbidity. If this was unavailable, a nurse, doctor of midwife who worked at the hospital at the time said what would have been given, according to the birth and type of delivery. The vitamin K history was 'unknown' if nothing was recorded and nothing remembered. The authors did not consider the results to be due to the inclusion of cases or controls with an uncertain vitamin K history, as the results remained the same when analyses were performed with those particular subjects excluded.

Review articles and evidence-based medicine

In 1996, Professor A. Zipursky summarised the evidence for use of vitamin K, the clinical actions that were taken in response to findings, and results of these actions.[2] He outlines the biological plausibility of vitamin K as a carcinogen.

Israels and Israels reported the addition of vitamin K to lymphocyte suspensions increased the rate of sister chromatic exchange, correlating to mutagenicity. However, other tests for mutagenicity have found no link.[8] For example, a study of the incidence of chromosomal abnormalities in a small number of newborn babies given vitamin K found no change. Therefore, there is no conclusive and repeated experimental evidence for vitamin K as a potential carcinogen in humans.

In response to the concerns raised by Golding et al, the British Paediatric Association recommended that newborns receive supplemental vitamin K orally rather than intramuscularly. It was felt this would not only reduce

the risk of cancer, but also avoid invasive procedures, pain, infection, bleeding and errors. However, by 1993 there were five reports of late VKDB in babies who received only oral vitamin K.

Important evidence was brought to light by Olsen et al , who used data from the Danish national cancer registry to determine whether the incidence of cancer in children had increased since the introduction in 1975 of intramuscular vitamin K to all newborns. Before 1975, no Danish babies received vitamin K. No difference in the rate of cancer during the period of 1975-90 was found.[8 9]

Zipursky concludes that although late VKDB may be prevented with repeated oral doses in the first two months of life, "compliance for such a regimen has been shown to be poor, leaving infants at risk".[2] The overall tone of his review is strongly in favour of intramuscular vitamin K for all newborns as evidence against its use is inadequate.

By comparison, von Kries[6] is more circumspect. As vitamin K concentrations in the blood following intramuscular administration "exceed endogenous levels by a factor of up to 10 000" he points out the need for clarification of vitamin K's potential for harm. He considered two recent studies reassuring, though two others concerned him.

One found a significant two-fold increase for leukaemia in one to six-year olds has some important biases, including a lack of blinding in the data collectors to the case/control status of the subject, and only half of the eligible cases being included. Another study found a 'borderline' significant result of 1.44 (1.00-2.08) for all cancers, principally for acute lymphoblastic leukaemia. However, it was felt to be a questionable analysis, as the increased risk of leukaemia was associated with abnormal deliveries in hospitals with a policy to give vitamin K only to those babies deemed 'at risk'.

It is presumed that 'at risk' refers to those babies who suffered from prematurity, birth asphyxia or other conditions which may delay feeding and hence worsen vitamin K deficiency, or whose mothers were on anticonvulsant medications. There was no increased cancer risk where hospitals were not selective – where vitamin K was either given to all newborns or to none. This suggests that babies deemed 'at risk' and given intramuscular vitamin K may have developed cancer due to their perinatal morbidity (for example, perinatalhypoxia), rather than to the vitamin K. Here perinatal morbidity operates as a potential confounder. It is felt that the practice of giving vitamin K only to those 'at risk' is poor practice as VKDB is as common in babies born by normal delivery.[3] The review concluded that "almost all cases of late VKDB are preventable with intramuscular vitamin K prophylaxis, with a potential risk for some forms of leukaemia that seem more hypothetical than real".

Vitamin K prophylaxis in the newborn: Consensus statement

This consensus statement of the recommended practice for vitamin K prophylaxis in New Zealand points out that the risk of leukaemia is small but "does nevertheless influence the decision making of some families".[1] The report reiterates that several large studies in Europe and North America have been unable to prove the association found by Golding et al, and that the oral route for vitamin K was not as successful for preventing the late VKDB.

The report cites recent data from Australia that place the risk of late VKDB at 34.4 per 100 000 babies given no vitamin K (Konakion brand), 4.1 with three oral doses of vitamin K, and 0.2 with intramuscular vitamin K at birth. The report recommends that the lead maternity carer must discuss vitamin K prophylaxis with parents, that all babies should receive vitamin K and the preferred route is intramuscular (1mg Konakion MM).

Conclusion

All babies are born deficient in vitamin K and the vitamin K dependent coagulation factors. They are therefore at risk of developing VKDB, previously known as haemorrhagic disease of the newborn. This risk is virtually eliminated with a single dose of intramuscular vitamin K at delivery. Oral vitamin K is more difficult to administer and is proven to be less effective at reducing late VKDB.

Many have argued that low levels of vitamin K at birth may be somehow protective against disease as yet unidentified. Since Golding et al's findings[4] there has been no consistent evidence vitamin K increases the risk of childhood cancer. However, there is good evidence for the efficacy of intramuscular vitamin K in preventing VKDB, which outweighs the insubstantial evidence for its carcinogenicity.

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