Research Article

Is there Evidence for Vitamin K Prophylaxis in Pregnant Women taking Anticonvulsant Drugs?

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Abstract

Purpose: The objective of this study was to examine the need of vitamin K prophylaxis in women with epilepsy (WWE) taking anticonvulsant drugs (AED) during pregnancy to prevent neonatal bleeding.

Patients and methods: The study population (n=1037) consisted of two study groups: i) the epilepsy group including all neonates of WWE (n=51) taking AED of the Innsbruck EURAP register. Twenty-four of the 51 were taking enzyme-inducing AED (EIAED). ii) the control group of 986 newborns not exposed to AED.

Results: The two study groups did not differ regarding hemorrhagic complications in newborns. None of the newborns of WWE taking AED showed neonatal bleeding. Hemorrhagic complications were more prevalent in newborns with low birth weight ($p<0.01$) and in multiple birth ($p=0.02$).

Conclusion: Neonates exposed to AED, enzyme-inducing and non-enzyme-inducing, were not at a higher risk for hemorrhagic complications compared to unexposed newborns. Birth-weight and multiple birth - not AED - should be considered as risk factors of neonatal bleeding.

Keywords: Epilepsy; Pregnancy; Anticonvulsants; Vitamin K Prophylaxis

1. Introduction

There is controversy concerning prenatal vitamin K supplementation in women with epilepsy (WWE) taking certain anticonvulsant drugs (AED) to reduce neonatal haemorrhagic complication. On the one hand, case reports suggest that the use of enzyme-inducing AED (EIAED) might lead to a deficiency in vitamin K levels increasing the risk for neonatal bleeding due to altered coagulation [1-3]. Therefore, additional vitamin K prophylaxis was initially recommended for pregnant WWE taking EIAED [4]. On the other hand, several studies suggest that vitamin K prophylaxis does not influence the neonatal bleeding incidence [5, 6]. The first prospective study in this field compared 662 WWE using AED to healthy controls demonstrating that bleeding complications of newborns of WWE did not differ significantly from controls [5]. As a consequence of relevant articles published between 1985 and 2007, The American Academy of Neurology updated their recommendations concerning vitamin K supplementation in WWE because of inadequate evidence [7], but some studies still recommend vitamin K supplementation for WWE during the last month of pregnancy [8]. Due to the ongoing debate, the aim of the present study was to compare the occurrence of haemorrhagic complications in newborns of WWE taking AED versus neonates not exposed to AED.

2. Material and Methods

The study population (n=1037) comprises all neonates born between 2008 and 2010 at the University Hospital Innsbruck, divided in two study groups: i) the epilepsy group including all neonates of WWE (n=51) of the Innsbruck EURAP register and ii) the control group of 986 newborns not exposed to AED. The groups were compared with respect to hemorrhage complications in the neonates (yes/no), birth weight (low <2.500g, normal <2.500g), and multiple birth (single birth/multiple birth). No vitamin K prophylaxis was given to WWE during pregnancy, but all newborns (epilepsy group and controls) received vitamin K prophylaxis at delivery [9].

2.1 Statistics

Data are presented as absolute numbers and percentage in parenthesis when appropriate. Comparisons between groups were performed by using the Student's T-test for normally distributed data. Odds ratio was used with 95% confidence interval. All analyses were performed two-tailed with p-values ≤0.05 indicating statistical significance. Statistical analyses were performed using the Statistical Package for Social Sciences for Windows (SPSS Inc. Chicago, Illinois, version 19.0).

3. Results

Of 51 WWE taking AED, 41 women (80%) used monotherapy and 10 women (20%) used polytherapy. The exposure of 51 neonates to maternal AED is presented in Table 1. In 24 pregnancies of WWE (47%), EIAED were used. 10 women (19%) used Topiramate, nine women (17%) used Carbamazepine, two (4%) used Primidone, and there was one each using Oxcarbazepine (2%), Ethosuximide (2%), and Zonisamide (2%). In the remaining 27 pregnancies of WWE (53%), non-enzyme-inducing AED were used. The overwhelming

majority of bleedings in neonates was intracranial hemorrhage (98%), one bleeding was registered in the lung, and one newborn developed both, bleeding in the brain and in the gastrointestinal tract. Neonatal bleeding in the different groups is presented in Table 2. The study groups did not differ significantly regarding hemorrhagic complications in newborns ($p>0.05$).

Overall, 639 neonates of the study population (61.5%) had low birth weight (<2.500g). In 39 newborns (3.8%) with low birth weight hemorrhagic complications were registered. Only 4 neonates (0.3%) with birth weight of more than 2.500 g showed neonatal bleeding. Odds ratio (OR) between the groups was 6.4 (CI 95% 2.2 – 21.2, $p<0.01$) representing a significant influence of birth weight on neonatal bleeding. In between the group of low birth weight (<2.500g) OR between neonates exposed to AED and unexposed AED showed no significant influence on neonatal hemorrhagic complications. Within the study population, 227 newborns (21.8%) were multiple birth. Thereof, 16 neonates (0.02%) showed hemorrhagic complications. 27 neonates (0.03%) of single birth had neonatal bleeding. OR between single birth and multiple birth was 2.2. (CI 95% 1.1 – 4.3, $p=0.022$) representing a significant influence of multiple birth on neonatal hemorrhagic complications.

4. Discussion

The most important finding of the present study is that neonates exposed to AED, enzyme-inducing and non-enzyme-inducing, were not at a higher risk for hemorrhagic complications compared to unexposed newborns. Our results are in line with other studies reporting no association of neonatal bleeding with maternal exposure to EIAED [5, 6]. Previous studies suggested that neonates exposed to EIAED during pregnancy might be at greater risk for vitamin K deficiency bleeding [1-3]. AED could potentially induce enzymes in the fetus degrading vitamin K, potentially leading to reduced concentrations of clotting factors in newborns. Possible deleterious consequences include bleeding within 24 hours after delivery, intracranial, and intra-abdominal hemorrhages [1-3]. However, there are several limitations concerning the cases reported previously. Mostly, newborns only suffered from mild symptoms and developed bleeding more than 48 hours after birth. Neonatal bleeding due to side effects of maternal AED usually occurs within the first 24 hours after birth. Consequently, these cases might not be counted as bleeding due to maternal use of EIAED. In 2009 the American Academy of Neurology evaluated studies between 1985 and 2007 and updated their recommendation that “evidence is inadequate to determine if prenatal vitamin K supplementation in WWE reduces neonatal hemorrhagic complications” [7]. Additionally, clinical practice has changed. There is a general consensus, that vitamin K prophylaxis is given at birth which is considered to prevent symptomatic bleeding. Furthermore, the rate of caesarean sections is increasing, potentially reducing the incidence of birth trauma and symptomatic bleedings in neonates.

Moreover, medication of WWE has changed over the last years [8]: First, polytherapy was more common and the monitoring of drug levels was irregular formerly. Second, the most common drugs used, and prescribing patterns have changed. This is backed up by the fact that WWE used Valproate, Lamotrigine, Topiramate, and Carbamazepine predominantly on monotherapy in this study. In a systematic review, the use of older AED like Valproate was associated with an increased risk of malformations leading to the recommendation to avoid Valproate in women with childbearing potential [10].

Two factors showed significant influence on neonatal bleeding. Hemorrhagic complications were more prevalent in neonates with low birth weight and in multiple birth comparable to previous findings [11].

5. Conclusion

To sum up, newborns exposed to AED, enzyme-inducing and non-enzyme-inducing, were not at a higher risk for hemorrhagic complications compared to unexposed neonates. Birth-weight and multiple birth - not AED - should be considered as risk factors of neonatal bleeding.

Disclosure

The author reports no conflicts of interest in this work.

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Appendix Tables

Maternal drug	Monotherapy (n=41)	Polytherapie (n=10)
Valproic acid	12	2
Lamotrigine	12	2
Topiramate	9	1
Carbamazepine	6	3
Levetiracetam	2	7
Primidone	0	2

Table 1: Exposure of 51 neonates to maternal AED.

	Neonatal bleeding	No neonatal bleeding
All neonates exposed to AED	0	51
Neonates exposed to enzyme-inducing AED	0	24
Neonates exposed to non-enzyme-inducing AED	0	27
Unexposed neonates	43	943

Table 2: Neonatal bleeding in the different study groups.