Observational prospective study to evaluate the efficacy of Vitamin K Intravenously on the coagulopathy in patients with peroxisomal biogenesis disorders (PBD)

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Primary objective: To evaluate the effect of intravenous vitamin K therapy on the vitamin K dependent coagulopathy in patients with peroxisomal biogenesis disorders measured with APTT, PT, FV, FVII, fibrinogen, d-dimer, thrombocytes and PIVKA....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON42020

Source
ToetsingOnline

Brief title
VitKId

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Inborn errors of metabolism

Synonym
congenital metabolic diseases, Peroxisomal biogenesis disorder, zellweger syndrome spectrum

Research involving

Human

Sponsors and support

Primary sponsor: Kinderhematologie
Source(s) of monetary or material Support: Collectebusfonds MetaKids 18;000;-

Intervention

Keyword: Coagulation, Hemorrhages, Peroxisomal biogenesis disorder(PBD), Vitamin K

Outcome measures

Primary outcome

The lab results of APTT, PT, FV, FVII, fibrinogen, d-dimer, thrombocytes and

PIVKA will be shown descriptively and in scatter plots before and after iv

vitamin K.

Secondary outcome

Calibrated Automated Thrombogram (CAT) (= thrombin generation assay) will also

be presented desciptively.

Study description

Background summary

Patients with peroxisomal biogenesis disorders (PBD) have mutations in one of the PEX genes causing absent or dysfunctional peroxisomes. The biochemical characteristics of peroxisomal dysfunction are primarily accumulation of very long chain fatty acids and bile acid intermediates. The clinical spectrum of PBD ranges from the severe Zellweger syndrome to patients that survive into adulthood. Most patients have liver disease ranging from prolonged neonatal jaundice to liver failure. Patients with PBD often show abnormalities of the hemostatic system, and even have haemorrhagic complications, such as severe intracranial bleeding. The exact pathophysiology of liver disease and the coagulation disorder in PBD has not been elucidated. Most patients with PBD receive oral vitamin K (and other fat soluble vitamins), but the efficacy has not been systematically studied in a cohort of patients.
Since no literature is available on this subject, a retrospective cohort-study

in 38 patients (0 to 34 years old) with PBD was performed in the Emma Children*s Hospital Academic Medical Centre in Amsterdam (EKZ AMC) very recently (S. Zeynelabidin et al, unpublished data, attached document). This study showed that coagulopathy in PBD patients is multifactorial and probably at least partially caused by liver disease due to toxic bile acid intermediates resulting in reduced coagulation factors and by vitamin K deficiency due to malabsorption. Nowadays, the supplementation of oral vitamin K in PBD patients is non-uniform and orally given. The study S. Zeynelabidin et al. clearly shows that oral vitamin K therapy does not correct the coagulopathy caused by vitamin K deficiency sufficiently in most patients. The protein Induced by Vitamin K absence (PIVKA) levels are still increased after high oral dosages of vitamin K in 90% of the patients of our cohort. Furthermore, in the study group of 38 patients, four (10%) patients developed an intracranial haemorrhage. Two of them had increased PIVKA levels despite high oral dosages of vitamin K supplementation and normal platelet counts, pointing out a vitamin K deficient bleeding. PIVKAs of the third patient with intracranial haemorrhages was normal and the PIVKAs of the last patient were not measured.
Pereira et al. showed that intestinal absorption of oral vitamin K therapy was unreliable in patients with severe acute liver disease. They conducted a double blind randomized controlled trial in adults : only 20% developed a rise in vitamin K levels compared to 94% of the patients given intravenous vitamin K. A study in infants with hyperbilirubinemia revealed that oral vitamin K supplementation gave inconsistent changes in PIVKA levels, which did not occur in patients given intravenous vitamin K supplementation. In summary, oral supplementation of vitamin K does not seem to be effective in all our PBD patients and few studies suggest that intravenous vitamin K supplementation might be more effective in patients with liver disease. As a consequence, we want to evaluate the effect of intravenous vitamin K supplementation in patients with PBD disorders in order to reduce vitamin K deficient bleeding complications, including intracranial haemorrhages

Study objective

Primary objective: To evaluate the effect of intravenous vitamin K therapy on the vitamin K dependent coagulopathy in patients with peroxisomal biogenesis disorders measured with APTT, PT, FV, FVII, fibrinogen, d-dimer, thrombocytes and PIVKA.
Secondary objective: To evaluate the effect of intravenous vitamin K therapy on the Calibrated Automated Thrombogram (CAT) (= thrombin generation assay).

Study design

An observational prospective pilot study with five patients will be conducted. We include the five patients in three months and it will take place in the EKZ AMC.

Patients with known vitamin K deficiency will be treated with vitamin K intravenously.

Before administration of vitamin K, blood will be collected for determination of baseline level of APTT, PT, FV, FVII, fibrinogen, d-dimer, thrombocytes, PIVKA and Calibrated Automated Thrombogram (CAT) (= thrombin generation assay). (2x 2.7 ml citrate whole blood). The needle or line that has already been inserted to take blood will be utilised for the insertion of vitamin K, so that the number of *jabs* is kept to the minimum.

To evaluate the effect of vitamin K, a second sample of blood will be taken for determination of APTT, PT, FV, FVII, fibrinogen, d-dimer, thrombocytes, PIVKA and CAT after 3 to 7 days. (The half-life of prothrombin is 60 hours) (2x 2.7 ml citrate whole blood)

These patients normally receive oral vitamin K and have routinely check ups to evaluate the effect of vitamin K, and other medication, through blood samples. Therefore these patients will only be punctured one time extra, the first time we take blood and insert vitamin K, since the check up is routine.

Intervention

Before administration of vitamin K, blood will be collected for determination of baseline level of APTT, PT, FV, FVII, PIVKA, thrombocytes, d-dimer fibrinogen and Calibrated Automated Thrombogram (CAT) (= thrombin generation assay). (2x 2.7 ml citrate whole blood). The needle or line that has already been inserted to take blood will be utilised for the insertion of vitamin K, so that the number of *jabs* is kept to the minimum.

To evaluate the effect of vitamin K, a second sample of blood will be taken for determination of APTT, PT, FV, FVII, PIVKA, thrombocytes, d-dimer, fibrinogen and CAT after 3 to 7 days. (The half-life of prothrombin is 60 hours) (2x 2.7 ml citrate whole blood)

Study burden and risks

The study S. Zeynelabidin et al. clearly shows that oral vitamin K therapy does not correct the coagulopathy caused by vitamin K deficiency sufficiently in most patients with PBD. The Protein Induced by Vitamin K Absence (PIVKA) levels are still increased after high oral dosages of vitamin K in 90% of the patients of our cohort. Furthermore, in the study group of 38 patients, four (10%) patients developed an intracranial haemorrhage. Two of them had increased PIVKA levels despite high oral dosages of vitamin K supplementation and normal platelet counts, pointing out a vitamin K deficient bleeding. Studies suggest that intravenous vitamin K supplementation might be more effective in patients with liver disease, which these patients also have.

The patients will have one extra visit. They normally have a routine check up of their medication, so only their first visit where they receive vitamin K will be different. Since children usually don*t prefer punctures, emla crème will be used. Intravenous vitamin K rarely causes an allergic reaction but this risk is minimal when injected slowly.
This study can only be done using this patient group since these specific children show no response to oral vitamin K therapy for their coagulopathy. The risk they have of a brain haemorrhage is 10%. We therefore think that the risks of this intervention are negligible and the burden minimal. As a consequence, we want to evaluate the effect of intravenous vitamin K supplementation in patients with PBD disorders in order to reduce vitamin K deficient bleeding complications, including intracranial haemorrhages.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Patients with PBD over five years of age
2. Coagulopathy with prolonged PT, low FVII concentration and increased PIVKA level due to vitamin K deficiency.

Exclusion criteria

1. No oral or written informed consent of the parents.
2. No coagulopathy as measured by PT.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-04-2015
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	18-03-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL51866.018.14