Double blind placebo controlled randomized intervention study to validate the beneficial effect of hydrocortisone on dexamethasone-induced neurobehavioral side effects in pediatric acute lymphoblastic leukemia

Published: 09-01-2018
Last updated: 21-12-2024

The primary aim is to validate the finding that addition of physiological doses of hydrocortisone reduces dexamethasone-induced clinically relevant neurobehavioral problems. The secondary aims are to study the role of genetic variation, psychosocial...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON50327

Source
ToetsingOnline

Brief title
DexaDays-2 study

Condition

- Leukaemias

Synonym
Acute lymphoblastic leukemia; blood cancer

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: KiKa

Intervention

Keyword: Dexamethasone, Intervention, Leukemia, Side-effects

Outcome measures

Primary outcome

The primary outcome parameter of the intervention study (RCT - now closed):

- The occurrence of neurobehavioral problems after 5 days of dexamethasone treatment with or without hydrocortisone addition. These neurobehavioral problems will be measured with the parent-reported strength and difficulty questionnaire (SDQ).

Secondary outcome

The secondary outcome parameters of the Intervention study (RCT - now closed) are

- The occurrence of dexamethasone related sleeping difficulties after 5 days of dexamethasone treatment with or without hydrocortisone, measured by the Sleep Disturbance Scale for Children (SDSC) and actigraphy.

- Quality of life after 5 days of dexamethasone treatment with or without hydrocortisone, measured with the Pediatric Quality of Life questionnaire (PedsQL).

- The degree of frailty in pediatric ALL patients with or without hydrocortisone addition, measured through bio-impedance, ultrasonography,

activiy questionnaire, timed Up and Go test, fatigue (PedsQL), hand grip and musculus rectus femoris strength (dynamometer) and 'Time to rise from floor' test.

Other study parameters, investigated in Identification part, include:
- The influence of carrier status of single nucleotide polymorphisms (SNPs) on the development of dexamethasone induced clinically relevant neurobehavioral problems.
- The effect of dexamethasone kinetics on the development of dexamethasone induced clinically relevant neurobehavioral problems
- The impact of psychosocial and environmental factors on the development of dexamethasone induced clinically relevant neurobehavioral problems.
- The prevalence of frailty in pediatric ALL patients and the effect of dexamethasone on the different frailty parameters.
- The prevalence of vitamin D and B as well as other nutrient/hormone (e.g. leptin, myokines) deficiencies, the effect of dexamethasone on these deficiencies and the association between nutrient deficiencies and frailty occurrence.

Study description

Background summary

Dexamethasone, a highly effective drug in treating pediatric acute lymphoblastic leukemia (ALL), can induce serious neurobehavioral side effects. These are experienced as extremely detrimental with respect to quality of life by patients and parents. For a long time, the underlying mechanism of

dexamethasone induced neurobehavioral side effects was poorly understood. However, recent studies emphasized that cortisol depletion of the mineralocorticoid receptor (MR) in the brain might play an important role. This depletion occurs due to the fact that dexamethasone has a low affinity for the MR and suppresses the endogenous cortisol production. Addition of cortisol (hydrocortisone) to dexamethasone treatment could overcome this depletion. In our recent randomized controlled trial, the Dexadagen study, we found that clinically relevant neurobehavioral and sleeping problems decrease by hydrocortisone addition during dexamethasone treatment. Validation is required in a selected larger sample size. The inclusion for this part of our study closed on 5-8-2020 since enough patients were entered in the study.

There are big differences in the amount of experienced dexamethasone induced problems. There are possible determinants that could explain these differences. We will study 3 possible determinants of the inter-patient variability in the occurrence of dexamethasone induced neurobehavioral problems:
1. Genetic predisposition: throug SNP array polymorphisms of the mineralocorticoid receptor and glucocorticoïd receptor genes which are associated with behavioral and sleeping problems will be investigated in a large sample size (105 children).
2. Dexamethasone kinetics will be studied through peak and trough levels.
3. Environmental and psychosocial factors such as parental stress, family background, education and support will be investigated through several questionnaires.

Besides neurobehavioral problems, dexamethasone therapy is known to cause metabolic side effects. Furthermore, children with ALL experience muscle wasting during treatment, and it has recently been shown that childhood cancer survivors have a high risk of frailty. Frailty is a state of reduced physiologic reserve that is associated with increased susceptibility to chronic disease and disability and is mostly described in older adults. It is characterized by a combination of three of the following five measurements of physical abilities: poor muscle mass, poor muscle strength, fatigue, slow walking performance and physical inactivity .
So far, frailty has never been examined in childhood cancer patients during their treatment. In our previous study, we showed that merely 4 days of dexamethasone treatment can induce metabolic toxicity on three components of the metabolic syndrome in children with ALL. In our current study, we want to examine the acute effect of dexamethasone treatment on frailty. Futhermore, we want to determine the prevalence of vitamin D and B as well as other nutrient and hormone (e.g. leptin) deficiencies, the effect of dexamethasone on these deficiencies and the association between nutrient deficiencies and frailty occurrence.

Study objective

The primary aim is to validate the finding that addition of physiological doses

of hydrocortisone reduces dexamethasone-induced clinically relevant neurobehavioral problems. The secondary aims are to study the role of genetic variation, psychosocial factors, and pharmacokinetics as determinants of dexamethasone induced neurobehavioral problems and to investigate sleeping problems, quality of life, frailty and vitamin/nutrient deficiencies after 5 days of dexamethasone treatment with or without hydrocortisone addition.

Study design

We will perform a prospective double blind placebo-controlled randomized cross-over study. Patients with clinically relevant neurobehavioral problems (defined as an increase of *5 points on the Strengths and Difficulties Questionnaire (SDQ)) will receive hydrocortisone or placebo during 2 consecutive 5 day courses of dexamethasone and thereafter cross over. We will investigate clinically relevant sleeping problems (defined as an increase of *7 points on the Sleep Disturbance Scale for Children (SDSC)) and quality of life (measured with the Pediatric Quality of Life questionnaire (PedsQL)). Frailty will be evaluated both in the RCT as in the Identification study. Vitamin/nutrient deficiencies will be studied in all patients. The RCT was closed on 5-8-2020 since 50 patients were included.

Besides the RCT we want to investigate possible determinants of the inter-patient variability of dexamethasone induced neurobehavioral side effects in an identification study:
1. The influence of several polymorphisms using a candidate SNP approach
2. The role of dexamethasone pharmacokinetics
3. The impact of psychosocial and environmental factors

The prevalence of frailty and several vitamin/nutrient/hormone deficiencies will be studied as well. Frailty is defined as having 3 or more of the following 5 physical indicators:
1. Sarcopenia, measured with bio-electrical impedance analysis, muscle ultrasonography and leg circumference.
2. Fatigue, measured with PedsQL fatigue questionnaire
3. Slow walking performance, measured with the 'Timed up and go' test
4. Physical inactivity, measured with an activity questionnaire
5. Poor muslce strength, measured with handheld dynamometer and the 'rise from the floor' test.

We will also ask 5 sarcopenia screening questions (SARC-F) to assess whether these questions can predict sarcopenia.

Intervention

During 2 identical periods of 5 days of dexamethasone treatment, in addition, patients will receive either a physiological dose of hydrocortisone

(intervention) or placebo. In the consecutive 2 periods of dexamethasone treatment the intervention or placebo will be reversed.

Study burden and risks

Extent and burden is low. The intervention drug (hydrocortisone) will be given in a physiological dose, not in a pharmacological dose, which is the equivalent of a normal cortisol production of the body. We have ample experience with hydrocortisone in physiological dose in other patient groups, and no side effects are expected. Our previous pre-clinical in vitro study in leukemic blasts showed no adverse effect on the antileukemic effect of adding hydrocortisone to dexamethasone. Furthermore, the RCT (Dexadays 1 study) did not show any adverse events or side effects during the intervention. Blood sampling will be done using the existing vascular access ports, during regular hospital visits only when blood must be drawn or intravenous medication must be given, therefore minimizing the risk of infection. Patients have one extra visit to the hospital. Parents and patients will have to fill in questionnaires, but this will be reduced to minimum and will all be accessible through one online portal. Furthermore all questionnaires will be filled in together with the researcher when possible. The frailty measurements are short and non-invasive. They will take place when a child has a regular visit at the hospital. The potential benefit of this study is an improvement in quality of life for patients with clinically relevant dexamethasone induced neurobehaviroural side effects.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 25
Utrecht 3584 CS
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 25
Utrecht 3584 CS
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Written informed consent
- Age 3-18
- Histologically or cytologically confirmed acute lymphoblastic leukemia (ALL)
- Inclusion in DCOG ALL medium risk group protocol
- Able to comply with scheduled follow-up

Exclusion criteria

- Patient or parent refusal
- Anticipated compliance problems
- Underlying conditions which affect the absorption of oral medication
- Pregnant or lactating patients
- Current uncontrolled infection or any other complication which may interfere with
dexamethasone treatment
- Language barrier
- Pre-existing mental retardation
- Current oral hydrocortisone treatment
- Current risperidone treatment

Study design

Design

Study type:	Interventional
Intervention model:	Crossover

Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-05-2018
Enrollment:	105
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hydrocortisone
Generic name:	Hydrocortisone
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	09-01-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	02-03-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	09-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	15-05-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 22781
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2017-002738-22-NL
CCMO	NL62388.078.17
OMON	NL-OMON22781

Study results

Date completed: 27-03-2021

Actual enrolment: 106