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APPEL 3: Algorithm to control Postprandial, Post exercise and night glucose Excursions in a portable closed Loop format

Submission date	Recruitment status	[_] Prospectively registered
18/12/2012	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
29/01/2013	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
21/01/2019	Nutritional, Metabolic, Endocrine	

Plain English summary of protocol

Background and study aims
Over the last decade insulin delivery and blood glucose monitoring have evolved facilitating better glucose control. Continuous Subcutaneous Insulin Infusion (CSII) and Continuous Glucose Monitoring (CGM) sensors combined with an insulin delivery algorithm results in a closed loop system: an artificial pancreas.
The aim of this study is to test the efficacy of a portable closed loop system first in the clinical research unit directly followed by testing at home.

Who can participate?
All adults diabetes mellitus (DM) type 1 treated with insulin pump

What does the study involve?
All participants will wear the artificial pancreas that will be compared to regular insulin pump use.

What are the possible benefits and risks of participating?
Benefits: This study will provide insight in glucose metabolism
Risk: hyperglycemia (high blood sugar) or hypoglycemia (low blood sugar)

Where is the study run from?
Academic Medical Center Amsterdam

When is the study starting and how long is it expected to run for?
Study started in January 2012 and will run till March 2013

Who is funding the study?
Academic Medical Center Amsterdam

Who is the main contact?
AC van Bon
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Protocol serial number
NL37969.018.11; U1111-1125-4086

Study information

Scientific Title
APPEL 3: Algorithm to control Postprandial, Post exercise and night glucose Excursions in a portable closed Loop format

Acronym
APPEL3

Study objectives
The aim of this study is to test the efficacy of a portable bi hormonal closed loop system first in the clinical research unit directly followed by testing at home compared to open loop.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical Committee of the Academic Medical Center Amsterdam, 18 October 2011, ref number 2011_292

Study design
Non randomized controlled trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Diabetes mellitus type 1 treated with insulin pump

Interventions
All participants have type 1 diabetes and are treated with an insulin pump. All participants start with open loop: the participants will wear CGM for 60 hours. This is followed after several weeks with the closed loop: the participants will wear the artificial pancreas.

Open loop arm: glucose control in daily life and measured via continuous glucose monitoring (CGM) for 60 hours

Closed loop arm: glucose control by artificial pancreas for 60 hours, the first 12 hours are for tuning and the last 48 hours participants are sent home. The closed loop contains of two CGM, two subcutaneous pumps for insulin and glucagon administration and portable computer with the algorithm.

The closed loop contains the algorithm, insulin pump, glucagon pump and CGM. These are similar to the software used in APPEL 2 (MEC09/263) [registered at CCMO http://www.ccmo-online.nl, ref: NL29814.018.09. The hardware of the closed loop system is changed compared to APPEL 2. The personal computer is changed in a small portable computer that contains two systems: a controlling system and an operating system. The interface is a wireless connection. Due to this connection, the glucose concentrations, insulin administration, glucagon administration and heart rate are read out continuously and visually during the whole experiment.

Insulin pump
The D-Tron+ (Disetronic Medical Systems, St. Paul, MN) is a CE marked infusion system. A plastic reservoir filled with short-acting insulin is connected to a catheter that is inserted into the subcutaneous tissue. The insulin catheter needs to be changed every three days. The device is driven by the algorithm to deliver insulin. Insulin will be administered if the glucose rises above 6.5 mmol/l. Depending of the rise in glucose concentration, an insulin bolus will be given.

Glucagon pump
The D-Tron+ (Disetronic Medical Systems, St. Paul, MN) is a CE marked infusion system. A plastic reservoir filled with glucagon is connected to a catheter that is inserted into the subcutaneous tissue. The device is driven by the algorithm to deliver glucagon. Glucagon will be administered when glucose falls below 6.5 mmol/l to regulate the glucose levels between the normal range. First a bolus glucagon is injected depending of the decrease in glucose concentration followed by glucagon delivery according to the formula. Below glucose concentration of 4.5 mmol/l, glucagon is administered in a rescue bolus.

Glucose sensor
The Continuous Glucose Monitoring System Gold (Medtronic Minimed, Sylmar, CA) is a needle-type sensor that quantifies interstitial glucose concentrations via the glucose oxidase reaction with the enzyme immobilized on a subcutaneously inserted electrode. Due to connection to the computer glucose values can be monitored in real time.

During closed loop two CGM sensors will be used: one primary and one back up in case of failure of the first sensor.

Algorithm
The algorithm is designed and patented by Inreda Diabetic B.V., Goor, The Netherlands. Both study devices will be connected via a personal computer embedded in a control unit (Robopump®, Inreda Diabetic B.V., Goor, The Netherlands), on which the algorithm is programmed. The most important assumption is that the algorithm makes use of the current blood glucose values of the patient. In the control unit blood glucose values are programmed between an upper and lower limit. These programmed values are continuously compared to the current, i.e. measured values which the glucose sensor transmits per time interval for programming.
The two D-Tron+pumps are controlled by the control unit. One pump contains a reservoir of short acting insulin analogue (NovoRapid, Novo Nordisk) and the other pump contains glucagon (Glucagen, Novo Nordisk).

The control unit has two operating ranges:
At glucose values below the programmed lower limit a sound signal will be generated. The patient is hereby warned that the lower limit is being approached or has been exceeded. He/she will be advised to eat and thereby correct the low glucose level. In the case of a further decrease of glucose levels, glucagon will be injected in accordance with the set values and a curve to be programmed according to: ml(E)/ fall mmol/l / time unit

At blood glucose values above the programmed upper limit insulin will be injected, as according to the set values and a curve to be programmed according to: ml(E)/rise mmol/l /unit of time (see figure 2), and a (different) sound signal is generated, whereby the patient is alerted that the upper limit is being approached or has been exceeded. If the fall in the blood glucose values starts at a determined speed (preferably adjustable) the supply of insulin is stopped.

The control unit contains a program that incorporates an adjustable curve corresponding to the amount of insulin or glucagon respectively introduced into the body of the patient and the nominal concentration of the glucose in the blood of the patient as a reaction thereto. The control unit stores in memory information relating to the introduced quantity of insulin or glucagon respectively, and in each successive case compare this information to the concentration of the glucose in the blood of the patient as a reaction thereto. Furthermore, this latter information is stored and used for metering the insulin or glucagon respectively. The algorithm is therefore a learning type, adapting to the specific patient.

Interface
The algorithm is incorporated in a portable computer. The voltage is low power and is provided by a rechargeable battery pack. Due to wireless internet connection, the glucose values, insulin administration, glucagon administration and heart rate can be read out immediately.

Intervention Type
Other

Phase
Not Applicable

Primary outcome(s)

To assess the efficacy of the closed loop system, defined as the time spent in euglycemia. Euglycemia is defined as glucose concentration between 3.5 mmol/l -10 mmol/l. The proportions of time spent in eu-, hypo and hyperglycaemia in closed loop will be compared to open loop.

Time points of measurement are the last 48 hours divided in first 24 hours and last 24 hours. Furthermore to analyze for a meal and three hours postprandial
Night: from 00.00 till 7.00 AM

Key secondary outcome(s))
1. Difference in overall mean sensor glucose comparing closed loop system to open loop
2. Difference in postprandial, post exercise and night sensor glucose excursions measured as area under the curve comparing closed loop to open loop
3. Difference in numbers of hypoglycaemias (glucose at or below 3.5 mmol/l) comparing the closed loop to open loop

Time points of measurement are the last 48 hours divided in first 24 hours and last 24 hours. Furthermore to analyze for a meal and three hours postprandial
Night: from 00.00 till 7.00 AM

Completion date
01/03/2013

Eligibility

Key inclusion criteria
1. Diabetes mellitus type 1 treated with continuous subcutaneous insulin infusion (CSII) for a minimum of 6 months
2. Age: 18-75, either sex
3. Willing and able to sign informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Key exclusion criteria

1. Impaired awareness of hypoglycaemia according to Gold [7] and / or Clarke [8] method
2. Body mass index (BMI) > 35 kg/m2
3. Glycated haemoglobin (HbA1c) > 11.0%
4. Use of heparin, coumarin derivatives or oral corticosteroids
5. Skin condition prohibiting needle insertion
6. Pregnancy and/or breastfeeding
7. Any condition that the local investigator feels would interfere with trial participation or the evaluation of results

Date of first enrolment
01/01/2012

Date of final enrolment
01/03/2013

Locations

Countries of recruitment
Netherlands

Study participating centre
Academic Medical Center (AMC)
Amsterdam
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Sponsor information

Organisation
Academic Medical Center (AMC) (Netherlands)

ROR
https://ror.org/03t4gr691

Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Academic Medical Center Amsterdam (Netherlands)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/03/2014	21/01/2019	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes