Benefit of dual-chamber pacing with Closed Loop Stimulation (CLS) in tilt-induced cardio-inhibitory reflex syncope. A randomized double-blind parallel trial.

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Primary objective: The study has the primary objective of comparing the time to the first syncopal recurrence between · active group (CLS): CLS in addition to DDD pacing mode. · control group (CTL): sensing only, "ODO" mode (PM stimualtion…

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

Summary

ID

NL-OMON42000

Source
ToetsingOnline

Brief title
BIOSync CLS study

Condition

- Other condition
- Cardiac disorders, signs and symptoms NEC

Synonym
Tilt-Induced cardio-inhibitory reflex syncope

Health condition

Cardio-inhibitorisch reflex syncope

Research involving
Human

Sponsors and support

Primary sponsor: Biotronik
Source(s) of monetary or material Support: Biotronik SE & CO. KG

Intervention

Keyword: CLS, Syncope, Tilt-test, Vasovagal

Outcome measures

Primary outcome

Syncope

Secondary outcome

Pre-syncope

Study description

Background summary

The latest update of the European Society of Cardiology (ESC) guidelines for cardiac pacing has set a Class IIb (evidence B) indication for permanent cardiac pacing in patients with tilt induced cardio-inhibitory response with recurrent, frequent, unpredictable syncope and age >40 years after alternative therapy has failed. The reason behind the indication is that randomized clinical trials (RCTs) did not lead to a conclusive evidence due to some limitations in study design and controversial results.

Consequently, the status quo is that pacing may be considered (Class IIb indication) in patients with a cardio-inhibitory response to Tilt-Test (TT), after any cardiac dysfunction likely leading to loss of consciousness and other non-syncopal causes (including epilepsy, psychiatric, metabolic, drop-attack, etc.) have been excluded.

On the other hand, the 2009 ESC guidelines for diagnosis and management of syncope established that cardiac pacing showed higher evidence of benefit and should be considered (Class IIa indication) in patients with frequently recurrent reflex syncope, age >40 years and spontaneous cardio-inhibitory

episodes during long-term monitoring.

Recently, a sub-analysis of the ISSUE-3 showed that an asystolic response to TT predicts similar clinical forms of asystolic syncopal events during follow-up with an 86% probability, thus tracing back to a Class IIa indication for cardiac pacing. This is the main reason why pacing is currently preferred in structured Syncope Units and, more generally, in normal medical practice.

In most of the trials, a dual-chamber pacing mode was used with an automatic feature (rate-response: R) promptly responding to heart rate drops by rapid DDD pacing for a programmed interval (atrio-ventricular stimulation in DDD mode with R function: DDDR). However, few small studies have reported that the DDD-CLS mode may be effective as well. During the CLS mode intracardiac impedance curves are collected during systolic phases by injecting subthreshold high frequency current pulses. The waveforms of such rheometric signals are influenced by contractility, and this principle is exploited to adjust the pacing rate in normal rate responsive operation.

It has been hypothesized that the detection of an increase in contractility in the early stage of a vasovagal syncope could allow the system to activate atrio-ventricular pacing that may anticipate withdrawal of sympathetic tone and counterbalance vagal tone reaction. Therefore
CLS would react early during a first sympathetic phase of the reflex, while rate-drop response functions (R-function) would intervene after the vagal reaction (bradycardia) has been already triggered for a while.

In conclusion, further research is extremely important as it is very likely to have an important impact on recommendations.

Study objective

Primary objective:
The study has the primary objective of comparing the time to the first syncopal recurrence between
· active group (CLS): CLS in addition to DDD pacing mode.
· control group (CTL): sensing only, "ODO" mode (PM stimualtion function "OFF")

It is suspected that the 2-year survival rate of syncopal recurrence in the treatment arm is different from the 2-year survival rate of the control arm.

H0: SCLS(t=2 years) = SCTL(t=2 years)
H1: SCLS(t=2 years) * SCTL(t=2 years)

Secondary objective:
The Secondary endpoint will be the time to the first recurrence of pre-syncope

or syncope, whichever comes first, compared between the study groups during follow-up.

It is suspected that the 2-year survival rate to the combined event of pre-syncope or syncope is different in the two study groups.

H0: SCLS(t=2 years) = SCTL(t=2 years)
H1: SCLS(t=2 years) * S CTL(t=2 years)

Study design

Multicenter, international, randomized, placebo controlled, double blind, interventional study.

Intervention

Patients will be randomized to the active or to the placebo group immediately after their enrolment and before any subsequent study-related procedure. Both patient groups will implanted with a Biotronik pacemaker with the capability of the CLS function.

- Active group: before post-implant hospital discharge, the pacemaker will be programmed in a dual-chamber DDD pacing mode with the CLS function ON.

- Control group: before post-implant hospital discharge, the pacemaker will be programmed in the "ODO" mode (sensing mode). During the "ODO" mode the pacemaker does not deliver any pacing therapy, while it maintains all the sensing and related diagnostic functions to monitor cardiac rhythm. The "ODO" mode is outside the intended use of the pacemaker. The investigators of the participating centers are able to program the pacemaker into the "ODO" mode via a special code. The only difference compared to standard therapy is the programming of the "ODO" mode in the control group (PM stimulation fucntion to "OFF").

Study burden and risks

The implantation of the investigational device systems and the follow-up procedures do not differ from the procedures in routine care with comparable systems. Only CE market medical devices will be used according to their IFU, only study sites and investigators with proven long-term experience in pacemaker implantation will be included, only study sites and investigators for whom the pacemaker therapy is routinely practiced in the patient population enrolled in the BIOSync CLS study will be selected.

Nevertheless, patients will undergo a randomization procedure which will assign each of them either to the treatment (pacing ON with CLS) or to the placebo.

Placebo will consist of the implantation of the investigational device and subsequent programming with only sensing and diagnostic functions activated ("ODO" mode). The potential risks linked to the use of the "ODO" mode are described in the CIP (section 6.2), the Investigator Brochure and the Risk Analysis Document. Additional protective measures will be adopted within the study setting in order to minimize the risks: programming of the "ODO" mode is only possible with a special release code, the "ODO" mode will be de-activated upon reaching the primary endpoint, there is an independent DSMB and 3 interim analysis will be performed.

Previous studies (e.g., the ISSUE 3 trial) have shown that "ODO" mode is safe in the study population: syncopal recurrences associated with trauma were rare and as frequent as in the active arm; no deaths were reported. However, in order to limit the risk of syncopal recurrences, a sequential study design will be adopted (see sections 11.6 and 11.7 of the protocol).

Based on this methodology, the study will be stopped immediately when the calculated number of events will be reached thus avoiding an unnecessary number of extra events.

Participating patients may optionally undergo a tilt-test (TT) examination one month after IPG implantation. TT is a safe procedure and often considered as part of normal clinical practice in the study population, even after pacemaker implant, to predict response to the therapy. There have been no reported deaths nor severe complications during the tests.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

*Age >40 years.
*significant limitation of social and working life due to unpredictable or frequent syncope recurrences: *2 within the last year.
*type 2B cardio-inhibitory response to TTT (according
to the VASIS classification).
*alternative therapies have failed or are not feasible.
*exclusion of other possible competitive causes of syncope.

Exclusion criteria

*Any other indication to IPG (pacemaker), implantable defibrillator (ICD), cardiac resynchronization therapy (CRT), according to current guidelines.
*Any cardiac dysfunctions possibly leading to loss of consciousness: overt heart failure; ejection fraction (LVEF) <40% (Echo-assessed within 3-month prior to study participation); myocardial infarction;...
*Symptomatic orthostatic hypotension diagnosed by standing BP measurement.
*Nonsyncopal loss of consciousness (eg, epilepsy, psychiatric, metabolic, drop-attack, cerebral transient ischemic attack, intoxication, cataplexy).
*Symptomatic cardioinhibitory carotid sinus hypersensitivity.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2016
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Pacemaker with Closed Loop Stimulation (CLS) from the Eluna 8 DR-T;Epyra 8 DR-T;Etrinsa 8 DR-T IPG f
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	27-07-2015
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	25-04-2016
Application type:	Amendment
Review commission:	METC Atrium-Orbis-Zuyd
Approved WMO Date:	20-09-2018
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

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
ClinicalTrials.gov	NCT02324920
CCMO	NL51328.096.15