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Abstract

Introduction: Neurological injuries remain a major concern following coronary artery bypass grafting (CABG) that offsets survival benefit of CABG over percutaneous coronary interventions. Among numerous efforts to combat this issue, is the development of off-pump CABG (OPCABG) that obviates the need for extracorporeal circulation and is associated with improved neurological outcomes. The objective of this study is to examine whether the neuroprotective effect of OPCABG can be further pronounced by the use of two state-of-the-art operating techniques.

Methods and analysis: In this randomised, controlled, investigator and patient blinded single center superiority trial with three parallel arms a total of 360 patients will be recruited. They will be allocated in a 1:1:1 ratio to two treatment and one control arms. Treatment arms undergoing either aortic no-touch OPCABG or OPCABG with partial clamp applying carbon dioxide surgical field flooding will be compared against control arm undergoing OPCABG with partial clamp. The primary endpoint will be the appearance of new lesions on control brain magnetic resonance imaging 3 days after surgery. Secondary endpoints will include the prevalence of new focal neurological deficits in the first 7 days after surgery, the occurrence of postoperative cognitive dysfunction at either 1 week or 3 months after surgery and the incidence of delirium in the first 7 days after surgery. Data will be analysed on intention-to-treat principles and a per protocol basis.

Ethics and dissemination: Ethical approval has been granted for this study. Results will be disseminated through peer-reviewed media.

Trial registration number: ClinicalTrials.gov NCT03074604

Article Summary

Strengths and limitations of this study

CANON study is the first study to evaluate the neuroprotective effectiveness of aortic no-touch off-pump coronary artery bypass grafting technique and the practice of carbon dioxide surgical field flooding using a prospective randomized controlled design.

Meticulous methodology of neurological injuries assessment employed in the CANON study will allow for a thorough evaluation of the studied surgical techniques influence on the central nervous system.

Data provided by the CANON study may impact clinical practice regarding the choice of the most favorable technique for surgical coronary revascularization.

CANON study is conducted within a single clinical setting which may influence the speed of participant recruitment.

In the CANON study loss to 3-month follow-up is possible.

Introduction

Background and rationale

Neurological complications of cardiac surgery are well recognized, common and clinically important. They have been classified into Types 1 and 2 by The American College of Cardiology and the American Heart Association [1]. Type 1 neurological injuries are overt and include stroke and transient ischaemic attack (TIA), whereas more subtle complications like delirium and postoperative cognitive dysfunction (POCD) are classified as Type 2 neurological injuries. The frequency of stroke associated with coronary artery bypass grafting (CABG) depends on patient variables and the type of surgery performed, ranging from 1.6 to 3% [2]. Meanwhile, the incidence of delirium and POCD during the first week after cardiac surgery was reported in up to 50 and 80% of patients respectively [3, 4]. Although, Type 2 neurological injuries are not as devastating as stroke, they are associated with negative hospital outcomes including a tenfold increased risk of death and a fivefold increased risk of nosocomial complications [5].

The principal etiology of intraoperative brain damage is embolic, followed by hypoperfusion and inflammation [2]. In order to reduce the negative impact of such mechanisms, various strategies have been proposed. Noteworthy among them are preventative operative techniques, especially the off-pump coronary artery bypass grafting (OPCABG). This method has been introduced to avoid potentially harmful effects of cardiopulmonary bypass (CPB) and involves performing surgery on a beating heart. In spite of its theoretical advantages, the neuroprotective effects of this approach remain a subject of intense debate [6]. However, an up-to-date meta-analysis, revealed no difference between OPCABG and CPB-CABG with respect to all-cause mortality and myocardial infarction while OPCABG was associated with a significant reduction in the odds of cerebral stroke [7]. Additionally, it is important to note that most studies reporting no difference in neurological complications between on- and off-pump procedures, do not take into account that OPCABG is not a homogenous technique. One of its modifications (i.e. aortic no-touch OPCABG a.k.a. “no-touch” OPCABG) avoids any kind of aortic manipulation by using both in-situ internal mammary arteries as the only source of blood supply to the coronary grafts. This may be effective in reducing particulate microembolism, because numerous studies have shown embolic showers in transcranial Doppler ultrasonography during clamping and unclamping of ascending aorta [8]. Recent meta-analyses found that “no-touch” OPCABG was associated

with lower risk of cerebrovascular accident as compared to OPCABG with partial clamp ("traditional" OPCABG) [9, 10]. Additionally, the neuroprotective value of the "no-touch" OPCABG has been preliminarily tested in our previous pilot study. This investigation showed a significantly lower incidence of POCD in patients who underwent "no-touch" OPCABG compared with "traditional" OPCABG [11].

While "no touch" OPCABG technique primarily reduces the number of solid microemboli, formation of gaseous microemboli remains a threat to the patients' central nervous system. However, the harmful impact of these factors may be limited by the practice of using carbon dioxide (CO_2) flooding to displace air in the surgical field. Carbon dioxide is 25 times more soluble in blood than air, does not form bubbles and is rapidly discharged from the system through breathing. It has been used in cardiac operations since 1950s, but remains relatively underutilized in CABG. Although the reports on the neuroprotective qualities of CO_2 surgical field flooding are sparse and do not focus distinctly on CABG, they consistently show its efficiency in reducing postoperative neurological injury following open heart surgery [12].

Objectives

The objective of this study is to investigate the value of employing the "no touch" OPCABG technique and the practice of CO_2 surgical field flooding for the prevention of type 1 and 2 neurological injuries following surgical coronary revascularization. In particular, we aim to assess the incidence of new lesions on control brain magnetic resonance imaging (MRI), new focal neurological deficits, delirium and POCD following different techniques of surgery. We hypothesize a reduction in postoperative brain dysfunctions in patients treated with both of the examined methods.

Trial design

The CArbon dioxide surgical field flooding and aortic NO-touch off-pump coronary artery bypass grafting to reduce Neurological injuries after surgical coronary revascularization (CANON) trial is designed as a randomised, controlled, investigator and patient blinded single center superiority trial with three parallel arms and a primary endpoint being the appearance of new lesions on control brain MRI 3 days after surgery.

Methods

Study setting

The study will take place in the Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital, Bydgoszcz, Poland. This is a tertiary care centre that performs more than 400 CABG annually. The off-pump method is used as standard in all of these surgeries and both its "traditional" and "no-touch" variants are used regardless of the extent of required revascularization.

Eligibility criteria

Participants will be recruited among patients above 60 years of age and scheduled for elective and/or urgent CABG. They will be assessed with Mini-Mental State Examination (MMSE) and the Hospital Anxiety and Depression Scale (HADS) by a trained physician at the time of admission. Patients scoring below age- and education-adjusted cut-off scores in MMSE and/or above 8 on the subscales of HADS will be excluded from this research. Other exclusion criteria for this study will be as follows: neurologic deficit of any etiology, previous psychiatric illness, use of tranquilizers or antipsychotics, alcohol or drug abuse, history of cardiac surgery, preoperative left ventricular ejection fraction less than 30%, extracranial carotid artery stenosis of more than 70%, body mass index (BMI) of more than 35 kg/m^2, any contraindication for MRI (e.g., MRI-incompatible implantable device and claustrophobia), emergent and salvage setting. Additionally, patients with isolated left anterior descending coronary artery disease will be excluded from this study as in this condition standard of care requires performing "no-touch" OPCABG and prevents randomisation [13].

Interventions

Patients will be randomized into two treatment and one control arms. Treatment arms will undergo either "no-touch" OPCABG or "traditional" OPCABG applying CO_2 surgical field flooding. Control arm will undergo "traditional" OPCABG. To reduce the bias of surgeon's experience and preference all interventions will be carried out by two persons. The operators will be qualified specialist who performed at least five-hundred procedures of each type before joining this research.

All patients will undergo OPCABG through a median sternotomy. All the left anterior descending coronary artery lesions will be bypassed with left internal mammary artery graft (LIMA graft). Other coronary bypasses, for patients in study arm 2 (treatment group operated on with "traditional" OPCABG applying CO_2 surgical field flooding) and in study arm 3

(control group operated on with "traditional" OPCABG) will be performed with the use of vein grafts anastomosed proximally onto the aorta. For patients in study arm 1 (treatment group operated on with "no-touch" OPCABG) only the internal mammary artery grafts will be used (i.e. LIMA graft, right internal mammary artery graft - RIMA graft, or a Y-graft that uses RIMA anastomosed onto LIMA to allow for a wide territory of myocardial revascularization). However, in the rare event that the aforementioned approach is insufficient to reach all target vessels, a reversed (great) saphenous vein graft may be used to extend the LIMA or RIMA. In study arm 2 the chest cavity will be insufflated with CO_2 at a flow above 5 l/min during the entire surgical procedure.

All interventions in this study will be performed under the same anesthetic protocol. All patients will be treated before and after surgery according to the current European Society of Cardiology Guidelines.

Modifications

The final decision on the type of surgery to be performed will be based on patients safety and made by the surgeon after intraoperative assessment.

Outcomes

The primary endpoint of this study will be the appearance of new lesions on control brain MRI 3 days after surgery. Secondary endpoints will include the prevalence of new focal neurological deficits in the first 7 days after surgery, the occurrence of POCD at either 1 week or 3 months after surgery and the incidence of delirium in the first 7 days after surgery.

Participant timeline

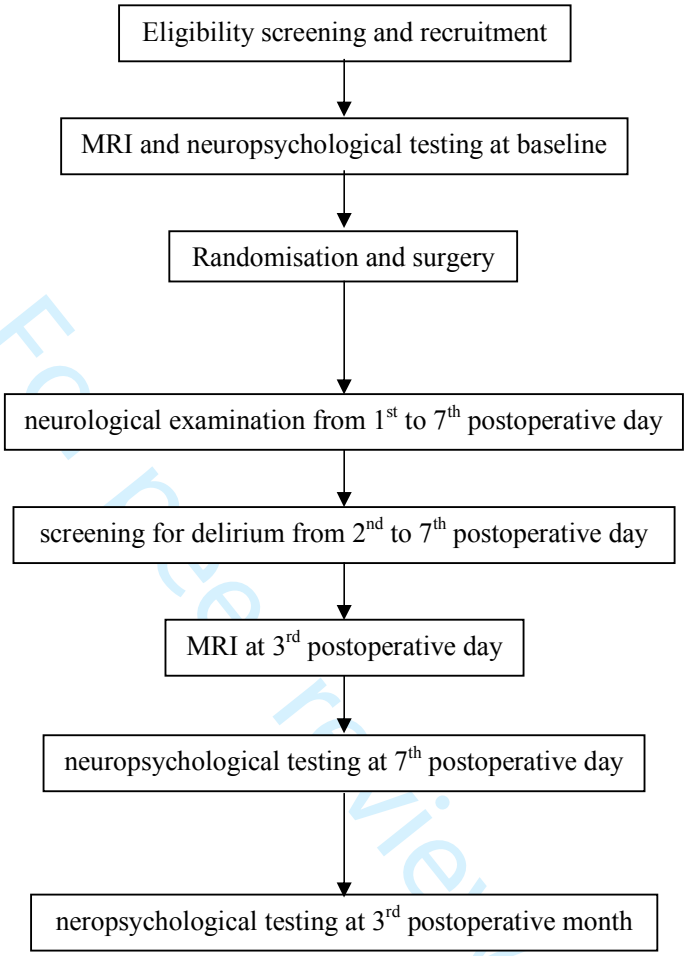

Figure 1. Single patient diagnostics process. MRI, magnetic resonance imaging.

Sample size

Sample size was calculated for the primary endpoint, i.e. the appearance of new lesions on control brain MRI. Prior data indicate that the incidence of this complication after cardiac surgical procedures is 30% [14]. Consequently, the expected failure rate is 0,3 in study arm 3 (control group operated on with "traditional" OPCABG). Based on our pilot research a 50% reduction in neurological injury in study arm 1 (treatment group operated on with "no-touch" OPCABG) is predicted [11]. Accordingly, the presumed true failure rate for experimental subjects in this group is 0,15. A sample size of 120 patients in study arm 1 and 120 patients in study arm 3 is needed to reject the null hypothesis that the failure rates for

experimental and control subjects are equal with probability (power) 0,8. The Type I error probability associated with this test of this null hypothesis is 0,05. An uncorrected chi-squared statistic will be used to evaluate this null hypothesis.

Currently, there is not enough evidence to allow for prediction of neurological injury rate in study arm 2 (treatment group operated on with "traditional" OPCABG applying CO_2 surgical field flooding). Consequently, the number of patients who will be operated using this technique is arbitrarily set at 120 in line with study arm 1 and 3.

Recruitment

At the time of admission to the hospital, patients who meet the criteria of eligibility for this study will be invited to enter the trial in a one-on-one interview with the principal investigator.

Allocation

Patients will be assigned in a 1:1:1 ratio to the three arms of the study according to a computer-generated list of random numbers. The allocation sequence will be concealed from the researchers enrolling and assessing participants in consecutively numbered, opaque and sealed envelopes. The sequence generation and the envelopes will be prepared by an investigator with no clinical involvement in the trial. They will be stored in a closed locker in the operating block. The randomisation will take place after the completion of all baseline assessments, immediately before surgery. A member of the surgical team will open the next consecutively numbered envelope and perform the designated intervention.

Blinding

Investigators and patients will be blinded to study arm allocation. Unfortunately, some participants may deduce that they were assigned to the study arm 1 (treatment group operated on with "no-touch" OPCABG) due to the absence of vein harvest wounds on their lower limbs. On the contrary, presence of vein harvest wounds is not indicative of any surgical procedure, as even patients treated with "no-touch" OPCABG may receive vein grafts. Considering that this potential for unblinding may also affect the investigators, patients will be instructed not to disclose any information about the surgery, and to cover their legs during

the follow-up assessments. Any comprises of blinding will be recorded with their reasons and reported along with the trial's results.

Data collection methods

Magnetic resonance imaging assessment

Brain MRI will be performed at baseline and 3 days postoperatively. A 1.5 T scanner will be used (Optima MR450w, GE Healthcare, Waukesha, USA) with a 12-channel coils. Both examinations will consist of morphological imaging and functional imaging. The morphological imaging will be the same for both scans. A high resolution three dimensional inversion recovery fast spoiled gradient echo T1-weighted images (3D FSPGR T1WI) will be used for the brain volumetric assessment and anatomical reference. Chronic white matter lesions will be assessed with a high resolution 3D fluid attenuated inversion-recovery (FLAIR) sequence [15]. Both chronic and new microbleeds will be detected using a susceptibility-weighted imaging (SWI) sequence [16].

The functional imaging will include an analysis of the diffusion and perfusion within the brain tissue. A multi b-value single shot echo-planar imaging scan (b = 0, 20, 50, 100, 200, 400, 600, 800, 1000, 1500 s/mm^2) will be used to perform both a conventional diffusion-weighted image analysis and an imaging based on the intravoxel incoherent motion (IVIM) theory [17]. Conventional DWI images, including apparent diffusion coefficient (ADC) maps, will be used to count acute ischemic lesions. Biexponential fits will be applied to calculate pseudo-diffusion coefficient (D*), perfusion fraction (f) and pure molecular diffusion coefficient (D) on the basis of the IVIM model [18]. Whole brain perfusion will be assessed with the use of a non-contrast enhanced 3D pseudo-continuous arterial spin labelling (ASL) technique [19]. Additionally, the baseline examination will include an analysis of microstructural white matter integrity with diffusion tensor imaging (DTI) scan at 25 directions [20].

The MRI scans will be evaluated independently by 2 experienced neuroradiologists blinded to patients' group allocations, with disagreements resolved by consensus. Brain lesions detected on postoperative DWI and SWI that are not present on pretreatment images, will be classified as new. The location, number, and volume of these lesions will be evaluated. FLAIR, SWI, and conventional DWI images will be analyzed using a dedicated custom clinical software READY View (GE Healthcare, Waukesha, USA). For post-processing and

calculations of IVIM parameters IVIM AW 4.6 (GE Healthcare, Waukesha, USA) and Olea Sphere 3.0 (Olea Medical, La Ciotat, France) will be applied. Voxel-based brain volumetry as well as ASL and DTI analysis will be performed using FMRIB Software Library v. 5.0 (Analysis Group, FMRIB, Oxford, UK).

Neurological assessment

Clinical neurological status will be examined by a neurologist preoperatively and once every day until 7 day after surgery. The occurrence of postoperative transient ischaemic attack (TIA) will be defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord or retinal ischemia, without acute infarction, while stroke will be diagnosed on the basis of the presence of acute infarction in postoperative MRI or the persistence of symptoms for at least 24 hours [21]. National Institutes of Health Stroke Scale (NIHSS) will be used to categorize severity of stroke (none, minor, moderate, moderate/severe, severe) andmodified Rankin Scale (mRS) will be used to measure disability.

Neuropsychological assessment

A single experienced neuropsychologist blinded to patients' group allocations will perform neurocognitive assessment. Examination will be conducted preoperatively, as well as 7 days and 3 months after surgery in the same quiet and seclude environment with a battery of well-established tests chosen according to the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery [22]. It will include the Stroop test (consisting colors' names with meaning incongruent with ink they are printed in) comprising of two subtasks, part A (time required to read the words aloud ignoring the ink color) — assessing speed of processing and part B (time required to name the colors of the ink in which the words are printed) — assessing attention, automaticity and parallel distributed processing; the Trail Making Test part A (time required to connect numbered circles in ascending order) – assessing psychomotor speed; the Trail Making Test part B (time required to connect circles containing numbers and letters in ascending and alternating order) – assessing selective attention and shifting ability; the Digit Span Test forward (number of correctly recalled digit strings in original order of presentation) — assessing auditory attention and short-term retention; the Digit Span Test backward (number of correctly recalled digit strings in reverse order of presentation) – assessing verbal working memory; Rey Auditory Verbal Learning Test (number of correctly recalled words on five trials) – assessing learning and immediate and delayed memory functions. The same form of each test will be used pre- and

postoperatively. Currently there is no one definition of POCD. In this research it will be described as a decline from preoperative performance of more than 20% on two or more tests according to the definition provided by Martens et al. (2008) [23] and used in our pilot study [11].

Delirium assessment

Two psychologists trained in delirium assessment and blinded to the type of surgery performed will screen all participants after surgery. The initial examination will take place no sooner than 24 hours postoperatively. The purpose of this timing is to avoid confounding results with post-anaesthetic emergence delirium which is usually of short duration and minimal clinical consequence [24]. Following examinations will be performed twice daily at 0800 and 2000 hours until 7 day after surgery. The diagnosis of delirium will be based on Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [25]. It is valid, reliable and recommended by the current 2013 Pain, Agitation, and Delirium Clinical Practice Guidelines for adult ICU patients [26]. The polish version of CAM-ICU employed in this study is available at www.proicu.pl.

Immediately before each screening for delirium, assessment of sedation or agitation will be performed using Richmond Agitation-Sedation Scale (RASS) [27]. Based on its results, 3 motoric subtypes of delirium will be determined. According to the classification provided by Peterson et al. (2006) [28], hypoactive delirium will be diagnosed when RASS is consistently negative or neutral (RASS -3 to 0), hyperactive delirium will be diagnosed when RASS is consistently positive (RASS +1 to +4) and mixed delirium will be diagnosed when during the episode RASS is alternately negative or neutral (RASS -3 to 0) and positive (RASS +1 to +4). Patients who are unresponsive (RASS -5 to -4) will be defined as comatose and excluded from further assessment.

Statistical analysis

The statistical analysis will follow the intention-to-treat approach, with each patient being analyzed as a member of the study arm assigned by randomisation, regardless of treatment subsequently received. The treatment arms undergoing either “no-touch” OPCABG or “traditional” OPCABG applying CO_2 surgical field flooding will be compared against the control arm undergoing “traditional” OPCABG for all analyses. To calculate primary and

secondary outcomes chi-squared test will be applied. Up-to-date version of STATISTICA (StatSoft, Inc., Tulsa, OK, USA) will be used to conduct all statistical analyses.

Data monitoring

A Data Monitoring Committee (DMC) will not be established for this study due to known minimal risks of all applied interventions.

The progress of the study will be evaluated every 6 months. The principal investigator has the right to terminate or modify the trial according to certain circumstances (e.g. danger to participants' safety or insufficient recruitment).

Harms

There are no safety concerns related to this study. Currently all interventions evaluated in this research are considered equivalent and are routinely used in contemporary medicine. There are no known harmful side-effects of using MRI scanners on patients without contraindications to this diagnostic method, and there were many studies that used MRI in this clinical setting before [14]. Neurological, neuropsychological and delirium assessment designed for this study is entirely non-invasive. Nevertheless, if any adverse effects occur, they will be reported to the principal investigator.

Ethics and dissemination

This study obtained the approval of the Bioethics Committee at Collegium Medicum in Bydgoszcz (KB 60/2017) and will be completed according to the standards established in the Declaration of Helsinki. Modifications to the protocol will require a formal amendment and permission from the aforementioned Bioethics Committee.

The principal investigator will introduce the trial to potential participants. Patients will be provided with both verbal and written information about the study. They will then be able to have an informed discussion about its details. Written consent will be required to partake in this research.

Results will be disseminated in peer-reviewed media using the CONSORT statement recommendations.

Funding

This study will be financed by a statutory activity grant from the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń. We also requested funding from the Polish National Science Center, which is a government grant-making agency. Our application to the latter institution is currently under review. Both funders had no role in study design and they will not be involved in data collection, data analysis, decision to publish, or preparation of the manuscript.

Contributors

SK conceived the study and is guarantor. SK, PW, SZ, KM, TR, PD, SM, TM, AL and BA designed the trial. SK drafted the protocol aided by SZ and KM. All authors decided to submit this final version of the protocol.

Competing interests

None declared

Discussion

At this point, there is very little research on the neuroprotective effectiveness of individual OPCABG techniques. Given this lack of data, studies that compare the frequency of neurological injuries following CPB and off-pump procedures usually use "traditional" OPCABG as their reference. However, in this clinical situation "traditional" OPCABG may in fact be the least favorable of all off-pump methods. Therefore, the debate between supporters and critics of performing surgery on a beating heart may be greatly influenced by the results of this investigation. If the studied techniques prove to have better neuroprotective value than "traditional" OPCABG, they should be considered the standard of off-pump surgery to which the CPB-CABG needs to be compared. Consequently, the advantages of avoiding CPB may become more apparent.

Essentially, data provided by this study may impact clinical practice regarding the choice of the most favorable technique for surgical coronary revascularization. If the research demonstrates outstanding neuroprotective effectiveness of any studied treatment, it should be considered state-of-the-art for reducing neurological injuries following CABG. Taking into account that such complications threaten a substantial number of people undergoing CABG every year, results of this investigation may reduce their extensive economic and societal impact.

Finally, the meticulous design of neurological injuries assessment employed in this study needs to be emphasized. Combined with a thorough analysis of clinical data, it may give insights into the underlying mechanisms of postoperative neurological complications that are beyond the initial assumptions of this research. For example, apart from testing its hypothesis, our preliminary investigation has yielded some interesting results regarding the predictive value of a recently developed angiographic grading tool for short term cognitive outcomes of OPCABG [29]. Therefore, by providing a vast wealth of neuropsychiatric and radiological data, this project may have a profound impact on the research field in pioneering and facilitating its further development.

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	13

Introduction

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	13
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

CArbon dioxide surgical field flooding and aortic NO-touch off-pump coronary artery bypass grafting to reduce Neurological injuries after surgical coronary revascularization (CANON): protocol for a randomised, controlled, investigator and patient blinded single center superiority trial with three parallel arms.

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CArbon dioxide surgical field flooding and aortic NO-touch off-pump coronary artery bypass grafting to reduce Neurological injuries after surgical coronary revascularization (CANON): protocol for a randomised, controlled, investigator and patient blinded single center superiority trial with three parallel arms.

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Abstract

Introduction: Neurological injuries remain a major concern following coronary artery bypass grafting (CABG) that offsets survival benefit of CABG over percutaneous coronary interventions. Among numerous efforts to combat this issue, is the development of off-pump CABG (OPCABG) that obviates the need for extracorporeal circulation and is associated with improved neurological outcomes. The objective of this study is to examine whether the neuroprotective effect of OPCABG can be further pronounced by the use of two state-of-the-art operating techniques.

Methods and analysis: In this randomised, controlled, investigator and patient blinded single center superiority trial with three parallel arms a total of 360 patients will be recruited. They will be allocated in a 1:1:1 ratio to two treatment and one control arms. Treatment arms undergoing either aortic no-touch OPCABG or OPCABG with partial clamp applying carbon dioxide surgical field flooding will be compared against control arm undergoing OPCABG with partial clamp. The primary endpoint will be the appearance of new lesions on control brain magnetic resonance imaging 3 days after surgery. Secondary endpoints will include the prevalence of new focal neurological deficits in the first 7 days after surgery, the occurrence of postoperative cognitive dysfunction at either 1 week or 3 months after surgery and the incidence of delirium in the first 7 days after surgery. Data will be analysed on intention-to-treat principles and a per protocol basis.

Ethics and dissemination: Ethical approval has been granted for this study. Results will be disseminated through peer-reviewed media.

Trial registration number: ClinicalTrials.gov NCT03074604

Date and version indentifier: 10-Mar-2017 Original

Article Summary

Strengths and limitations of this study

CANON study is the first study to evaluate the neuroprotective effectiveness of aortic no-touch off-pump coronary artery bypass grafting technique and the practice of carbon dioxide surgical field flooding using a prospective randomized controlled design.

Meticulous methodology of neurological injuries assessment employed in the CANON study will allow for a thorough evaluation of the studied surgical techniques influence on the central nervous system.

Data provided by the CANON study may impact clinical practice regarding the choice of the most favorable technique for surgical coronary revascularization.

CANON study is conducted within a single clinical setting which may influence the speed of participant recruitment.

In the CANON study loss to 3-month follow-up is possible.

Introduction

Background and rationale

Neurological complications of cardiac surgery are well recognized, common and clinically important. They have been classified into Types 1 and 2 by The American College of Cardiology and the American Heart Association [1]. Type 1 neurological injuries are overt and include stroke and transient ischaemic attack (TIA), whereas more subtle complications like delirium and postoperative cognitive dysfunction (POCD) are classified as Type 2 neurological injuries. The frequency of stroke associated with coronary artery bypass grafting (CABG) depends on patient variables and the type of surgery performed, ranging from 1.6 to 3% [2]. Meanwhile, the incidence of delirium and POCD during the first week after cardiac surgery was reported in up to 50 and 80% of patients respectively [3, 4]. Although, Type 2 neurological injuries are not as devastating as stroke, they are associated with negative hospital outcomes including a tenfold increased risk of death and a fivefold increased risk of nosocomial complications [5].

The principal etiology of intraoperative brain damage is embolic, followed by hypoperfusion and inflammation [2]. In order to reduce the negative impact of such mechanisms, various strategies have been proposed. Noteworthy among them are preventative operative techniques, especially the off-pump coronary artery bypass grafting (OPCABG). This method has been introduced to avoid potentially harmful effects of cardiopulmonary bypass (CPB) and involves performing surgery on a beating heart. In spite of its theoretical advantages, the neuroprotective effects of this approach remain a subject of intense debate [6]. However, an up-to-date meta-analysis, revealed no difference between OPCABG and CPB-CABG with respect to all-cause mortality and myocardial infarction while OPCABG was associated with a significant reduction in the odds of cerebral stroke [7]. Additionally, it is important to note that most studies reporting no difference in neurological complications between on- and off-pump procedures, do not take into account that OPCABG is not a homogenous technique. One of its modifications (i.e. aortic no-touch OPCABG a.k.a. “no-touch” OPCABG) avoids any kind of aortic manipulation by using both in-situ internal mammary arteries as the only source of blood supply to the coronary grafts. This may be effective in reducing particulate microembolism, because numerous studies shown embolic showers in transcranial Doppler ultrasonography during clamping and unclamping of ascending aorta [8] while avoiding this maneuver by using devices for proximal venous graft

anastomoses shown reduction in neurological injury compared to CPB-CABG [9]. Recent meta-analyses found that "no-touch" OPCABG was associated with lower risk of cerebrovascular accident as compared to OPCABG with partial clamp ("traditional" OPCABG) [10, 11]. Additionally, the neuroprotective value of the "no-touch" OPCABG has been preliminarily tested in our previous pilot study. This investigation showed a significantly lower incidence of POCD in patients who underwent "no-touch" OPCABG compared with "traditional" OPCABG [12].

While "no touch" OPCABG technique primarily reduces the number of solid microemboli, formation of gaseous microemboli remains a threat to the patients' central nervous system. However, the harmful impact of these factors may be limited by the practice of using carbon dioxide (CO_2) flooding to displace air in the surgical field. Carbon dioxide is 25 times more soluble in blood than air, does not form bubbles and is rapidly discharged from the system through breathing. It has been used in cardiac operations since 1950s, but remains relatively underutilized in CABG. Although the reports on the neuroprotective qualities of CO_2 surgical field flooding are sparse and do not focus distinctly on CABG, they consistently show its efficiency in reducing postoperative neurological injury following open heart surgery [13].

Objectives

The objective of this study is to investigate the value of employing the "no touch" OPCABG technique and the practice of CO_2 surgical field flooding for the prevention of type 1 and 2 neurological injuries following surgical coronary revascularization. In particular, we aim to assess the incidence of new lesions on control brain magnetic resonance imaging (MRI), new focal neurological deficits, delirium and POCD following different techniques of surgery. We hypothesize a reduction in postoperative brain dysfunctions in patients treated with both of the examined methods.

Trial design

The CArbon dioxide surgical field flooding and aortic NO-touch off-pump coronary artery bypass grafting to reduce Neurological injuries after surgical coronary revascularization (CANON) trial is designed as a randomised, controlled, investigator and patient blinded single center superiority trial with three parallel arms and a primary endpoint being the appearance of new lesions on control brain MRI 3 days after surgery.

Methods

Study setting

The study will take place in the Department of Cardiac Surgery, Dr Antoni Jurasz Memorial University Hospital, Bydgoszcz, Poland. This is a tertiary care centre that performs more than 400 CABG annually. The off-pump method is used as standard in all of these surgeries and both its "traditional" and "no-touch" variants are used regardless of the extent of required revascularization.

Eligibility criteria

Participants will be recruited among patients above 60 years of age and expecting elective and/or urgent CABG for multivessel coronary disease. They will be assessed with Mini-Mental State Examination (MMSE) and the Hospital Anxiety and Depression Scale (HADS) by a trained physician at the time of admission. Patients scoring below age- and education-adjusted cut-off scores in MMSE and/or above 8 on the subscales of HADS will be excluded from this research. Other exclusion criteria for this study will be as follows: neurologic deficit of any etiology, previous psychiatric illness, use of tranquilizers or antipsychotics, alcohol or drug abuse, history of cardiac surgery, preoperative left ventricular ejection fraction less than 30%, extracranial carotid artery stenosis of more than 70%, body mass index (BMI) of more than 35 kg/m^2, any contraindication for MRI (e.g., MRI-incompatible implantable device and claustrophobia), emergent and salvage setting. Additionally, patients with isolated left anterior descending coronary artery disease will be excluded from this study as in this condition standard of care requires performing "no-touch" OPCABG and prevents randomisation [14].

Interventions

Patients will be randomized into two treatment and one control arms. Treatment arms will undergo either "no-touch" OPCABG or "traditional" OPCABG applying CO_2 surgical field flooding. Control arm will undergo "traditional" OPCABG. To reduce the bias of surgeon's experience and preference all interventions will be carried out by two persons. The operators will be qualified specialist who performed at least five-hundred procedures of each type before joining this research.

All patients will undergo OPCABG through a median sternotomy. To obtain heart exposure deep pericardial traction sutures (Lima stitch) will be applied. Target vessels will be

stabilized using Octopus Medtronic coronary stabilizer and occluded with bulldog clamp. All the left anterior descending coronary artery lesions will be bypassed with left internal mammary artery graft (LIMA graft). Other coronary bypasses, for patients in study arm 2 (treatment group operated on with "traditional" OPCABG applying CO_2 surgical field flooding) and in study arm 3 (control group operated on with "traditional" OPCABG) will be performed with the use of vein grafts anastomosed proximally onto the aorta. For patients in study arm 1 (treatment group operated on with "no-touch" OPCABG) only skeletonized internal mammary artery grafts will be used (i.e. LIMA graft, right internal mammary artery graft - RIMA graft, or a Y-graft that uses RIMA anastomosed onto LIMA) to allow for complete arterial myocardial revascularization. However, in the rare event that the aforementioned approach is insufficient to reach all target vessels, a reversed (great) saphenous vein graft or a radial artery graft may be used to extend the LIMA or RIMA. In study arm 2 the chest cavity will be insufflated with CO_2 at a flow above 5 l/min during the entire surgical procedure. To accurately assess the anastomotic quality of all grafts in every study arm intraoperative transit time flow measurement will be used.

All interventions in this study will be performed under the same anesthetic protocol. All patients will be treated before and after surgery according to the current European Society of Cardiology Guidelines.

Modifications

The final decision on the type of surgery to be performed will be based on patients safety and made by the surgeon after intraoperative assessment.

Outcomes

The primary endpoint of this study will be the appearance of new lesions on control brain MRI 3 days after surgery. Secondary endpoints will include the prevalence of new focal neurological deficits in the first 7 days after surgery, the occurrence of POCD at either 1 week or 3 months after surgery and the incidence of delirium in the first 7 days after surgery.

Participant timeline

(FIGURE 1)

Figure 1. Single patient diagnostics process. MRI, magnetic resonance imaging.

Sample size

Sample size was calculated for the primary endpoint, i.e. the appearance of new lesions on control brain MRI. Prior data indicate that the incidence of this complication after cardiac surgical procedures is 30% [15]. Consequently, the expected failure rate is 0,3 in study arm 3 (control group operated on with "traditional" OPCABG). Based on our pilot research a 50% reduction in neurological injury in study arm 1 (treatment group operated on with "no-touch" OPCABG) is predicted [12]. Accordingly, the presumed true failure rate for experimental subjects in this group is 0,15. A sample size of 120 patients in study arm 1 and 120 patients in study arm 3 is needed to reject the null hypothesis that the failure rates for experimental and control subjects are equal with probability (power) 0,8. The Type I error probability associated with this test of this null hypothesis is 0,05. An uncorrected chi-squared statistic will be used to evaluate this null hypothesis.

Currently, there is not enough evidence to allow for prediction of neurological injury rate in study arm 2 (treatment group operated on with "traditional" OPCABG applying CO_2 surgical field flooding). Consequently, the number of patients who will be operated using this technique is arbitrarily set at 120 in line with study arm 1 and 3.

Recruitment

At the time of admission to the hospital, patients who meet the criteria of eligibility for this study will be invited to enter the trial in a one-on-one interview with the principal investigator.

Allocation

Patients will be assigned in a 1:1:1 ratio to the three arms of the study according to a computer-generated list of random numbers. The allocation sequence will be concealed from the researchers enrolling and assessing participants in consecutively numbered, opaque and sealed envelopes. The sequence generation and the envelopes will be prepared by an investigator with no clinical involvement in the trial. They will be stored in a closed locker in the operating block. The randomisation will take place after the completion of all baseline assessments, immediately before surgery. A member of the surgical team will open the next consecutively numbered envelope and perform the designated intervention.

Blinding

Investigators and patients will be blinded to study arm allocation. Unfortunately, some participants may deduce that they were assigned to the study arm 1 (treatment group operated on with "no-touch" OPCABG) due to the absence of vein harvest wounds on their lower limbs. On the contrary, presence of vein harvest wounds is not indicative of any surgical procedure, as even patients treated with "no-touch" OPCABG may receive vein grafts. Considering that this potential for unblinding may also affect the investigators, patients will be instructed not to disclose any information about the surgery, and to cover their legs during the follow-up assessments. Any comprises of blinding will be recorded with their reasons and reported along with the trial's results.

Data collection methods

Magnetic resonance imaging assessment

Brain MRI will be performed at baseline and 3 days postoperatively. A 1.5 T scanner will be used (Optima MR450w, GE Healthcare, Waukesha, USA) with a 12-channel coils. Both examinations will consist of morphological imaging and functional imaging. The morphological imaging will be the same for both scans. A high resolution three dimensional inversion recovery fast spoiled gradient echo T1-weighted images (3D FSPGR T1WI) will be used for the brain volumetric assessment and anatomical reference. Chronic white matter lesions will be assessed with a high resolution 3D fluid attenuated inversion-recovery (FLAIR) sequence [16]. Both chronic and new microbleeds will be detected using a susceptibility-weighted imaging (SWI) sequence [17].

The functional imaging will include an analysis of the diffusion and perfusion within the brain tissue. A multi b-value single shot echo-planar imaging scan (b = 0, 20, 50, 100, 200, 400, 600, 800, 1000, 1500 s/mm^2) will be used to perform both a conventional diffusion-weighted image analysis and an imaging based on the intravoxel incoherent motion (IVIM) theory [18]. Conventional DWI images, including apparent diffusion coefficient (ADC) maps, will be used to count acute ischemic lesions. Biexponential fits will be applied to calculate pseudo-diffusion coefficient (D*), perfusion fraction (f) and pure molecular diffusion coefficient (D) on the basis of the IVIM model [19]. Whole brain perfusion will be assessed with the use of a non-contrast enhanced 3D pseudo-continuous arterial spin labelling (ASL) technique [20]. Additionally, the baseline examination will include an analysis of

microstructural white matter integrity with diffusion tensor imaging (DTI) scan at 25 directions [21].

The MRI scans will be evaluated independently by 2 experienced neuroradiologists blinded to patients' group allocations, with disagreements resolved by consensus. Brain lesions detected on postoperative DWI and SWI that are not present on pretreatment images, will be classified as new. The location, number, and volume of these lesions will be evaluated. FLAIR, SWI, and conventional DWI images will be analyzed using a dedicated custom clinical software READY View (GE Healthcare, Waukesha, USA). For post-processing and calculations of IVIM parameters IVIM AW 4.6 (GE Healthcare, Waukesha, USA) and Olea Sphere 3.0 (Olea Medical, La Ciotat, France) will be applied. Voxel-based brain volumetry as well as ASL and DTI analysis will be performed using FMRIB Software Library v. 5.0 (Analysis Group, FMRIB, Oxford, UK).

Neurological assessment

Clinical neurological status will be examined by a neurologist preoperatively and once every day until 7 day after surgery. The occurrence of postoperative transient ischaemic attack (TIA) will be defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord or retinal ischemia, without acute infarction, while stroke will be diagnosed on the basis of the presence of acute infarction in postoperative MRI or the persistence of symptoms for at least 24 hours [22]. National Institutes of Health Stroke Scale (NIHSS) will be used to categorize severity of stroke (none, minor, moderate, moderate/severe, severe) andmodified Rankin Scale (mRS) will be used to measure disability.

Neuropsychological assessment

A single experienced neuropsychologist blinded to patients' group allocations will perform neurocognitive assessment. Examination will be conducted preoperatively, as well as 7 days and 3 months after surgery in the same quiet and seclude environment with a battery of well-established tests chosen according to the Statement of Consensus on Assessment of Neurobehavioral Outcomes after Cardiac Surgery [23]. It will include the Stroop test (consisting colors' names with meaning incongruent with ink they are printed in) comprising of two subtasks, part A (time required to read the words aloud ignoring the ink color) — assessing speed of processing and part B (time required to name the colors of the ink in which the words are printed) — assessing attention, automaticity and parallel distributed processing;

the Trail Making Test part A (time required to connect numbered circles in ascending order) – assessing psychomotor speed; the Trail Making Test part B (time required to connect circles containing numbers and letters in ascending and alternating order) – assessing selective attention and shifting ability; the Digit Span Test forward (number of correctly recalled digit strings in original order of presentation) — assessing auditory attention and short-term retention; the Digit Span Test backward (number of correctly recalled digit strings in reverse order of presentation) – assessing verbal working memory; Rey Auditory Verbal Learning Test (number of correctly recalled words on five trials) – assessing learning and immediate and delayed memory functions. The same form of each test will be used pre- and postoperatively. Currently there is no one definition of POCD. In this research it will be described as a decline from preoperative performance of more than 20% on two or more tests according to the definition provided by Martens et al. (2008) [24] and used in our pilot study [12].

Delirium assessment

Two psychologists trained in delirium assessment and blinded to the type of surgery performed will screen all participants after surgery. The initial examination will take place no sooner than 24 hours postoperatively. The purpose of this timing is to avoid confounding results with post-anaesthetic emergence delirium which is usually of short duration and minimal clinical consequence [25]. Following examinations will be performed twice daily at 0800 and 2000 hours until 7 day after surgery. The diagnosis of delirium will be based on Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [26]. It is valid, reliable and recommended by the current 2013 Pain, Agitation, and Delirium Clinical Practice Guidelines for adult ICU patients [27]. The polish version of CAM-ICU employed in this study is available at www.proicu.pl.

Immediately before each screening for delirium, assessment of sedation or agitation will be performed using Richmond Agitation-Sedation Scale (RASS) [28]. Based on its results, 3 motoric subtypes of delirium will be determined. According to the classification provided by Peterson et al. (2006) [29], hypoactive delirium will be diagnosed when RASS is consistently negative or neutral (RASS -3 to 0), hyperactive delirium will be diagnosed when RASS is consistently positive (RASS +1 to +4) and mixed delirium will be diagnosed when during the episode RASS is alternately negative or neutral (RASS -3 to 0) and positive (RASS

+1 to +4). Patients who are unresponsive (RASS -5 to -4) will be defined as comatose and excluded from further assessment.

Statistical analysis

The statistical analysis will follow the intention-to-treat approach, with each patient being analyzed as a member of the study arm assigned by randomisation, regardless of treatment subsequently received. The treatment arms undergoing either "no-touch" OPCABG or "traditional" OPCABG applying CO_2 surgical field flooding will be compared against the control arm undergoing "traditional" OPCABG for all analyses. To calculate primary and secondary outcomes chi-squared test will be applied. Up-to-date version of STATISTICA (StatSoft, Inc., Tulsa, OK, USA) will be used to conduct all statistical analyses.

Data monitoring

A Data Monitoring Committee (DMC) will not be established for this study due to known minimal risks of all applied interventions.

The progress of the study will be evaluated every 6 months. The principal investigator will consolidate data acquired by individual researchers and thus be the only person with access to the entire data-set. He will review source documents and indentify any problems with data gathering (e.g. insufficient recruitment or retention of participants, inadequate or insufficient research staff, missing data). The principal investigator has the right to terminate or modify the trial according to certain circumstances (e.g. danger to participants' safety or insufficient recruitment).

Harms

There are no safety concerns related to this study. Currently all interventions evaluated in this research are considered equivalent and are routinely used in contemporary medicine. There are no known harmful side-effects of using MRI scanners on patients without contraindications to this diagnostic method, and there were many studies that used MRI in this clinical setting before [15]. Neurological, neuropsychological and delirium assessment designed for this study is entirely non-invasive. Nevertheless, if any adverse effects occur, they will be reported to the principal investigator during research staff's briefings held in the morning of every working day.

Ethics and dissemination

This study obtained the approval of the Bioethics Committee at Collegium Medicum in Bydgoszcz (KB 60/2017) and will be completed according to the standards established in the Declaration of Helsinki. Modifications to the protocol will require a formal amendment and permission from the aforementioned Bioethics Committee.

The principal investigator will introduce the trial to potential participants. Patients will be provided with both verbal and written information about the study. They will then be able to have an informed discussion about its details. Written consent will be required to partake in this research.

All study-related information will be stored in locked file cabinets while electronic databases will be password-protected. Coded identification numbers will be used to conceal personal information on all laboratory specimens and data collection forms. Participants' study information will not be released outside of the study, except as necessary for monitoring by the Bioethics Committee at Collegium Medicum in Bydgoszcz.

Results will be disseminated in peer-reviewed media using the CONSORT statement recommendations.

Funding

This study will be financed by a statutory activity grant from the Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń (ul. Jagiellońska 13-15, 85-067 Bydgoszcz, Poland, tel. +48525853895, e-mail: org@cm.umk.pl). We also requested funding from the Polish National Science Center, which is a government grant-making agency. Our application to the latter institution is currently under review. Both funders had no role in study design and they will not be involved in data collection, data analysis, decision to publish, or preparation of the manuscript.

Contributors

SK conceived the study and is guarantor. SK, PW, SZ, KM, TR, PD, SM, TM, AL and BA designed the trial. SK drafted the protocol aided by SZ and KM. All authors decided to submit this final version of the protocol.

Competing interests

None declared

Discussion

At this point, there is very little research on the neuroprotective effectiveness of individual OPCABG techniques. Given this lack of data, studies that compare the frequency of neurological injuries following CPB and off-pump procedures usually use "traditional" OPCABG as their reference. However, in this clinical situation "traditional" OPCABG may in fact be the least favorable of all off-pump methods. Therefore, the debate between supporters and critics of performing surgery on a beating heart may be greatly influenced by the results of this investigation. If the studied techniques prove to have better neuroprotective value than "traditional" OPCABG, they should be considered the standard of off-pump surgery to which the CPB-CABG needs to be compared. Consequently, the advantages of avoiding CPB may become more apparent.

Essentially, data provided by this study may impact clinical practice regarding the choice of the most favorable technique for surgical coronary revascularization. If the research demonstrates outstanding neuroprotective effectiveness of any studied treatment, it should be considered state-of-the-art for reducing neurological injuries following CABG. Taking into account that such complications threaten a substantial number of people undergoing CABG every year, results of this investigation may reduce their extensive economic and societal impact.

Finally, the meticulous design of neurological injuries assessment employed in this study needs to be emphasized. Combined with a thorough analysis of clinical data, it may give insights into the underlying mechanisms of postoperative neurological complications that are beyond the initial assumptions of this research. For example, apart from testing its hypothesis, our preliminary investigation has yielded some interesting results regarding the predictive value of a recently developed angiographic grading tool for short term cognitive outcomes of OPCABG [30]. Therefore, by providing a vast wealth of neuropsychiatric and radiological data, this project may have a profound impact on the research field in pioneering and facilitating its further development.

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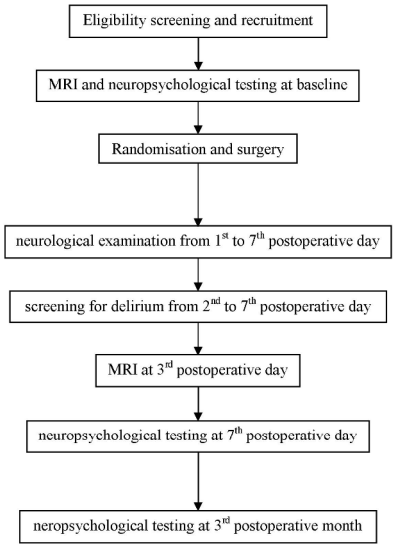

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	3
Funding	4	Sources and types of financial, material, and other support	15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5
Objectives	7	Specific objectives or hypotheses	6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	8
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____10____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____10____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____10____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____10____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____10____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____10____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____11____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.