CARbon dioxide flooding for reduction of neurological injury following surgery for acute Type A aortic dissection. A prospective, randomized, blinded, controlled clinical trial.

The CARTA trial

NCT ID: 2021-02039

ORIGINAL DOCUMENT
SEPTEMBER 1st 2021

LAST UPDATE
OCTOBER 31st 2023

BACKGROUND

Aortic dissection is a life-threatening condition and a consequence of a tear of the innermost of the three aortic layers- the intima. When a tear occurs, blood surges through the tear and causes the flow of blood between the aortic layers, causing a "false lumen". This causes a weakening of the aortic wall and hinders the blood from reaching its target organs.

Type A aortic dissection affects the portion of aorta closest to the heart- the ascending aorta, and up to half of all afflicted patients die before reaching hospital care (1). This mainly occurs due to aortic rupture or bleeding into the pericardium, preventing venous return to the heart and thereby causing cardiac tamponade. An acute type A aortic dissection (ATAAD) requires immediate surgical treatment and patients are generally transferred to the operating room as soon as the diagnosis has been confirmed. Despite urgent surgical treatment, 15-20% of patients die during the operation or within the first 30 days after surgery (2).

The clinical symptoms associated with ATAAD may vary depending on which end organ is affected by circulatory compromise. Extremity malperfusion can lead to limb ischaemia or altered blood pressure measurements, gastrointestinal malperfusion may lead to intestinal ischaemia or necrosis and if the spinal circulation is compromised, patients may present with paraplegia.

In cases where patients are in hypotensive shock or if the carotid arteries are dissected, the patient may present with unconsciousness or hemiparesis. It has been demonstrated that 10-20% of the patients with ATAAD have neurological symptoms at initial assessment (3) and misdiagnosis is associated with increased risk of postoperative complications (2, 4, 5). In addition, we have previously shown that postoperative neurological injuries account for 10-15% of in-hospital deaths (6).

Several mechanisms may explain cerebral injuries following ATAAD surgery, the first being the patients' preoperative state. Preoperative neurological symptoms due to hypotensive shock or cerebral malperfusion related to carotid artery dissection are associated with a two-fold increase in risk of postoperative neurological injury (7).

Furthermore, the surgical procedure by itself includes several technical aspects that may cause cerebral injury. The foundation for all cardiac surgery is the use of cardiopulmonary bypass, which enables the re-routing of the circulation to enable cardiac arrest during surgery. Almost all ATAAD surgery is carried out in deep hypothermia (18-20°C) with complete circulatory arrest. This allows the surgeon to open the aorta and inspect the aortic arch for intimal tears. For the majority of patients, a short period of circulatory arrest (<30 min) is considered safe from a neurological standpoint, but a recent meta-analysis showed that cerebral injuries may be reduced by the use of retrograde cerebral perfusion (RCP), where the cerebral circulation is "flushed" by blood flowing retrogradely from the superior vena cava (8). It has been speculated that the protective effect of RCP is a result of the retrograde blood flow flushing out air that has been trapped in the aortic arch branch vessels during the circulatory arrest.

In association with other cardiac procedures where the left side of the heart is opened and air may be trapped within the arterial circulation, carbon dioxide flooding is used to displace open air from the surgical wound. In comparison to air, carbon dioxide is significantly more soluble in blood and may therefore decrease the risk of air embolism. In cardiac surgery, carbon dioxide flooding has been demonstrated to reduce levels of biomarkers of cerebral injury (9, 10), but carbon dioxide is not routinely employed in ATAAD surgery and has not been studied in association with these procedures.

Several biomarkers have been used to predict neurological injury, of which S100B and neuron-specific enolase (NSE) are the most commonly used in cardiac surgery. S100B has been shown to predict stroke after cardiac surgery but the usefulness of NSE has not been properly assessed (11). Furthermore, none of these biomarkers has been evaluated in the setting of ATAAD

surgery, and therefore, we do not have adequate information on the utility of these biomarkers in association with ATAAD surgery. Other biomarkers, including Neurofilament (NFL), Glial fibrillary acid protein (GFAP) and Tau-protein (TAU) have all showed to be valuable for predicting cerebral injury, but there is limited data on these biomarkers in cardiac surgery and none at all in association with ATAAD.

Although much effort has been put into describing the long term outcomes of ATAAD few studies have addressed the late neurological effects of ATAAD repair and its impact om postoperative quality of life and cognitive function.

In summary, our hypothesis is that carbon dioxide flooding reduces cerebral air embolism and the aim of thos project is to evaluate whether carbon dioxide flooding may reduce neurological injuries following ATAAD surgery.

MATERIAL AND METHODS

Study design:
This is a prospective, randomized, controlled, patient- and reviewer blinded interventional study. Patients over the age of 18, presenting with ATAAD with symptom duration <14 days and are offered open heart surgery will be screened for inclusion. Those patients that have undergone previous open heart surgery or those who present with neurological symptoms will be excluded from the study.

Ethical approval for this study has been granted by the Swedish Ethical Review Agency (ref: 2021-02039, date: 5th of May 2021).

Endpoints:
Primary outcomes: Presence, number and volume of ischaemic lesions observed using magnetic resonance imaging (MRI) after ATAAD surgery.
Secondary outcomes: Clinical signs of neurological injury. Levels of biomarkers of neurological injury (S100B, NSE, NFL, GFAP, UCH-L1 and TAU) before and after surgery. Quality of life, postoperative recovery and neurological function after ATAAD surgery. Primary outcomes in relation to retrograde cerebral perfusion.

MRI:

”MRI Stroke” will be carried out within the first seven days of surgery, but as soon as the external pacemaker wires have been extracted. Daily assessment of the need for external pacemaker from postoperative day three and onward. If pacemaker wires cannot be extracted by postoperative day seven, the imaging will be carried out as soon as the wires are removed.

”MRI Stroke” includes diffusion weighted imaging “DWI”, Apparent diffusion coefficient (ADC) and a Flair-sequence.

A neuro-radiologist blinded to the randomisation arms and the clinical outcomes following surgery will analyse the images and quantify the ischaemic lesions with regard to number and volume of the lesions. Furthermore, the lesions will be described as focal- related to embolism, water-shed- related to hypoperfusion and its anatomical location. The volume of ischaemic lesions will be calculated using the formula (AxBxC)/2.

Biomarker analyses:

10ml of blood will be collected before surgery, immediately after surgery, four days and three months after the procedure. S100B, NSE, NFL, GFAP, UCH-L1 and TAU will be analysed. S100B and NSE will be analysed as routine analyses while remaining biomarkers will be analysed using the Simoa 4-plex analysis kit (NFL, T-tau, GFAP, UCH-L1). The analyses require <0.2mL of blood per analysis and will be analysed at the Biomedical centre (BMC) at Lund university. The samples drawn will be centrifuged at 2000g for 10 minutes and stored in a biobank until batch analysis.

Clinical follow-up:

Patients will be assessed using the NIH Stroke Scale (NIHSS), Modified Rankin scale for neurologic disability (mRS) and the Glasgow Outcome Scale Extended (GOSE) prior to hospital discharge. Three months after surgery, patients will be re-evaluated with regard to postoperative recovery and quality of life using the WHO-5 Well-being index, Postoperative recovery profile, Satisfaction with life scale and EQ5D-5L.Neurological function will be re-assesed using the Montereal cognitive assesment (MoCA) test, SDMT (Symbol digit modalities test), NIHSS, mRS and GOSE.

Power calculation:

To date, there are no studies to indicate the effect of carbon dioxide flooding on postoperative neurological outcomes following ATAAD surgery. However, Leshnower et al. recently published a study showing that RCP in conjunction with aortic surgery reduces the occurrence of lesions from 100% to 45% and the number of ischaemic lesions by 70% compared antegrade cerebral perfusion (12). Previous studies have shown that 61% of patients that have underwent routine aortic valve replacement have postoperative ischaemic lesions visualised by MRI (13). Provided that the beneficial effect of RCP showed by Leshnower et al. is due to a reduction of air-embolism, that data may be used as a basis for our power calculation. If one would use the finding by Leshnower et al. that the number of ischaemic lesions is reduced from 4 ±3.5 to 1.2 ±2.1, then a study sample of 25 patients in each arm would give a power of 80% to detect a significant difference between the groups with a 0.05 significance level (alpha). If instead, the calculation is based on a 50% reduction of presence of ischaemic lesions from a baseline prevalence of 70% (as in the study by Leshnower and colleagues), then 31 patients in each arm will be required to achieve similar statistical power. Given that 5-10% of patients die during or immediately after the surgical procedure, and therefore will not be eligible for postoperative assessment, we aim to include 40 patients in each arm. With an annual case volume of 30 patients, we expect an inclusion period over three years.

An interim analysis will be performed once 20 patients have been included in each arm. Apart from the primary endpoints, the safety arm including intraoperative mortality, 30-day mortality, reoperation for bleeding, stroke, myocardial infarction and other thromboembolic events will be analysed by a statistician that has previously not been involved in the study. The external statistician and the PI will hereafter decide for the study to proceed or be terminated due to harms, effect or futility.

Statistical analysis:

Groups will be compared using independent sample t-test and Mann-Whitney U-test depending on distribution of the data. Chi-squared test will be used for categorical data or Fisher's exact test in samples with fewer than 5 observations. Subgroup analyses will be performed comparing patients operated using RCP versus those undergoing surgery under straight hypothermic circulatory arrest.

Time plan:

Study design, acquisition of ethical approval and registration during 2021. Start of inclusion Jan 1st, 2022 or earlier if possible. We aim to start the writing of a manuscript describing the study methods and study objectives in 2021 and our ambition is to write the final manuscript during 2025.

IMPACT

Acute type A aortic dissection is one of the most devastating conditions that we face in clinical practice. Even if the patient arrives safely to the hospital and is treated surgically, mortality is significant and often associated with chronical neurological impairment. Neurological injuries can occur preoperatively, but it is clear that the surgical techniques employed and clinical decisions during surgery have a major impact on the development of cerebral injuries. Despite intensive research, our local database shows that approximately 25% of patients develop neurological , and that up to 15% of the early mortality is caused by cerebral injury. Thus, neurological injuries account for a significant portion of morbidity and mortality associated with ATAAD surgery and apart from its effects on the patients' neurological function and quality of life, it is associated with a significant consumption of health care resources. Postoperative stroke is associated with prolonged stay both in the intensive care unit and in the postoperative ward (14). This in turn causes crowding-out effects and thus poorer availability for other types of cardiac surgical care.

When analysing our data in association to a previous study, we observed that the vast majority of patients who suffered a postoperative stroke had ischaemic lesions in the right cerebral hemisphere. This implies that the lesions observed are the consequence of air-embolism, since there are no calcifications or thrombi to explain other types of embolic material. Therefore, we believe that air-embolism is a significant cause of neurological morbidity following ATAAD surgery. This has previously not been studied in detail and if our hypothesis is correct, our findings would contribute to a significant change of the surgical technique in ATAAD repair.

In the field of cardiovascular surgery, neurological injuries are a hot topic. Intensive research is addressing how modifications in surgical management may reduce the frequency of neurological injury, but the main focus is aimed towards cannulation strategies and selective cerebral perfusion. To the best of our knowledge, the effects of carbon dioxide have not been studied in ATAAD patients and therefore, any positive findings from our study would have a major impact within the cardiac surgical community. Furthermore, a positive finding could confirm our hypothesis of air-embolism being a significant cause of cerebral injury, and thus serve as a basis for new studies on how to reduce air-embolism during ATAAD surgery.

BUDGET

MRI scans	229 600 SEK(2870 SEK/scan)
Salary for personnel conducting clinical follow-up (339 SEK/h, 3h per patient)	81 360 SEK
Biomarker analyses Simoa 4-plex analysis kit (1000 SEK per patient)	360 000 SEK
Processing and storage of blood samples	100 000 SEK
Medical freezer	110 000 SEK
Disposable material for sample collection	20 000 SEK
Statistical services	100 000 SEK
Conference expenses	100 000 SEK
Hardware	80 000 SE
Software and licensing	20 000 SEK
Sum	**1 200 960 SEK**
Overhead (Lund University 21%)	252 200 SEK
Total	**1 453 160 SEK**

Referenser

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