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Effect of Cerebrolysin on Cognitive Function and Delirium in Coronary Artery Bypass Graft Patients

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Background: The occurrence of delirium in the first days after cardiac surgery is associated with a worse prognosis. We studied the effect of cerebrolysin (CBL) given to patients undergoing elective coronary artery bypass grafting surgery (CABG) under extracorporeal circulation, on the postoperative results in the Montreal Cognitive Assessment score (MoCA) results, and the rate of delirium detected by using the Confusion Assessment Method (CAM).

Material/Methods: Adult patients undergoing elective CABG surgery under propofol-based anesthesia were divided into 2 groups: the study group received 50 ml of CER preoperatively and on the 4 subsequent consecutive days, and the control group did not receive CER. MoCA was used to assess cognition, and CAM was applied to detect delirium. Both tests were performed preoperatively, as well as on the 2nd and 5th postoperative days.

Results: The study [n=29] and control [n=26] groups were well-balanced in terms of basic demographic, psychological, and clinical variables. Although significantly lower values of the MoCA (medians: 27 vs 24, respectively; *P*=0.0083) were detected in the study group in the second assessment, the pre- and postoperative MoCA values did not differ between the analyzed groups. Delirium occurred in 3 cases, and only in the control group, and the difference was not statistically significant.

Conclusions: Patients maintained their cognitive status. The lack of delirium in the study group prompts us to develop a plan for a large-scale multicenter study assessing the potential ability of CER to reduce the risk of delirium in cardiac surgery patients.

Keywords: Delirium • Cognitive Dysfunction • Cardiac Surgical Procedures

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Introduction

Neuropsychological disorders, especially severe delirium, are common complications observed in the perioperative period, after cardiac surgery [1]. These disorders present a serious problem in the Cardiac Intensive Care Unit (CICU). The incidence of delirium ranges from 26% to 52%, depending on the type of procedure and the methodology applied to detect delirium [2].

Elective coronary artery bypass grafting (CABG) surgery performed under cardiopulmonary bypass (CPB) involves specific circulatory conditions and exposure to certain risk factors stemming directly from use of CPB, which enables complex cardiac operations but increases the inflammatory response and oxidative stress, such as by contact of patient blood with external surfaces (eg, tubes, connections, membrane oxygenator) of the heart-lung machine, excessive phosphorylation of tau protein, decreased blood volume or perfusion and oxygen in the cerebral cortex, which affect the pathophysiology of postoperative cognitive dysfunction (POCD) and delirium in the postoperative period [3,4]. Moreover, leakage through the blood–brain barrier and subsequent brain edema, thromboembolism, fat embolism, air bubbles, and embolism of atherosclerotic plaques are not uncommon during cardiac surgery, upsetting brain homeostasis. CPB produces a laminar flow profile distinct to the physiological pulsatile flow, which is responsible for maintenance of sufficient microcirculation. The robust links in the brain pathology involve ischemia-reperfusion, caspase-independent intrinsic pathway of apoptosis, and increased activity of matrix metalloproteinases, with subsequent loss of blood–brain barrier integrity [5]. CPB is strongly associated with, but not solely responsible for, neurological complications after cardiac operations, including stroke, seizures, delirium, coma, cognitive disturbance, visual loss, saccadic abnormality, phrenic nerve palsy, and chorea. Specifically, POCD and postoperative delirium remain influential sequelae, as the rate of these complications is 42% and 50%, respectively, of surgical patients [6]. POCD is a specific cognitive impairment that involves functional impairment of the nervous system's activities, such as selective attention, vigilance, perception, learning, memory, executive function, verbal and language abilities, emotion, visuospatial, and visuomotor abilities [7]. The word "delirium" is a very specific term for the state of acute confusion, and is a physiological consequence of an intervention, treatment, or medical condition/s and develops within hours to days [8]. It has been reported that the occurrence of delirium in the first days after cardiac surgery is associated with a worse prognosis, prolonged hospitalization, and increased mortality [9]. In addition, patients with delirium after cardiac surgery have worse cognitive impairment, memory problems, and tend to need long-term hospital care [10].

Three key factors, referred to as the "3-strike" paradigm can increase the risk of delirium after cardiac surgery:

a) baseline brain sensitivity in older adult cardiac patients, which results in lower psychological, sociological, and physiological reserves;
b) experiencing an acute cardiac stressor (a new event, such as cardiac surgery);
c) a further increase in stress factors after surgery, related to care, including in the CICU [11,12].

The combination of the "3-strike" paradigm in the context of direct central nervous system (CNS) damage indicates the complexity of abnormal processes. The most accepted theory underlying the pathophysiology of delirium is a systemic response to stress (trauma) and inflammation, leading to damage in the blood–brain barrier (BBB), metabolic disorders in the CNS, and activation of glial and neuronal cells, leading to increased inflammation and, ultimately, cell death. Episodes of transient cerebral ischemia are also important in the pathogenesis of delirium [13].

Given the complexity of the many potential causes of delirium, it is not surprising that the treatment and prevention of delirium is multimodal and difficult. Several pharmacological and nonpharmacological methods have been proposed to prevent it, including early mobilization, improved intensive care unit (ICU) conditions, antipsychotics, melatonin, and dexmedetomidine or preoperative statin therapy [14-16].

However, numerous meta-analyses have not confirmed the independent beneficial effect of any therapy on the causes and treatment of postoperative delirium [17,18]. Therefore, it seems reasonable to search for a novel method to reduce the risk of severe delirium in patients after cardiac surgery.

Cerebrolysin (CBL) is an enzymatically processed peptide obtained from porcine brain. It contains the following neurotrophic factors: brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and ciliary neurotrophic factor (CNTF) [19]. The protective effect of CBL is caused by reducing the concentration of glutamate in the synaptic gap. Moreover, CBL reduces oxidative stress and damage to cells of the central nervous system, increasing antioxidant activity and reducing the level of cytokines [20,21].

Importantly, Sarode et al showed that CBL inhibits the upregulation of extra-synaptic NR2B, which is responsible for triggering apoptotic pathways. It reduces the expression of apoptotic proteins such as JNK, PTEN, calpain, and caspase-3. Additionally, they showed that CBL significantly reduces SREBP1 expression, which increases after around 6 hours of ischemia. They showed that CBL, by inhibiting apoptotic protein activation,

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reduces excitotoxicity and protects neuronal cells during subsequent ischemic reperfusion injury [22]. Current indications for CBL therapy are hemorrhagic or/and ischemic stroke, traumatic brain injury (TBI), and dementia caused by Alzheimer's disease (AD) or of vascular origin [23].

The European Academy of Neurology and European Federation of Neurorehabilitation Societies guideline on pharmacological support in early motor rehabilitation after acute ischemic stroke, published in 2021, highlights CBL's superior effects compared to standard care [24].

CBL was assessed by Jarosz et al in 10 studies involving 8749 patients and the authors concluded CBL is beneficial in TBI cases, although without improvements in length of stay or mortality [25].

The final conclusion of an updated umbrella review on the efficacy and safety of CBL treatment in AD is that the AChE inhibitors, Ginkgo biloba, and CBL are the optimum cognitive and activities of daily living medication for patients with AD [26]. The Cochrane analysis of 6 studies assessing the application of CBL in vascular dementia in 597 people, although using different CBL treatments, showed beneficial effects on cognition and measures of daily living, although the supporting evidence base was weak. No serious adverse effects were noted [27]. Al-Kuraishy et al performed a meta-analysis of studies on use of CBL application in vascular dementia, which includes small-vessel disease, thromboembolism, and hypoperfusion, directly linked with reduced cerebral blood flow [28]. The resultant triad of hypoxia, oxidative stress, and inflammation trigger the white-matter damage and demyelination, oligodendrocyte damage, neurodegeneration, neuroinflammation, and apoptosis, which finally develops the clinical symptoms of vascular dementia. The authors described the findings from the preclinical and clinical studies assessing the positive role of CBL in this type of pathology with a robust pathophysiological background of neuroinflammation, BBB integrity, chronic cerebral hypoperfusion, oxidative stress, and neurogenesis. They concluded that CBL is an effective therapeutic strategy in preventing and treating VD by targeting several of the above-mentioned mechanisms [28]. These studies suggest that use of CBL can improve postoperative outcomes and reduced the risk of POCD and delirium in patients undergoing CABG. Therefore, the present study assessed pre- and postoperative cognitive function measured using Montreal Cognitive Assessment (MoCA), and the occurrence of postoperative delirium detected using the Confusion Assessment Method (CAM), in 29 patients with and 26 patients without adjunctive treatment with CBL before elective CABG surgery requiring extracorporeal circulation. We combined those 2 diagnostic tools, as postoperative cognitive dysfunction and postoperative delirium share risk factors and can co-occur; their relationship is not well-established, but they may be considered as distinct manifestations of perioperative neurocognitive deficits [29]. By using 2 different psychological tools (MoCA and CAM), we applied a double approach to patient status allowing both cognitive assessment and detection of delirium. To the best of our knowledge, this is the first study analyzing such a use of CBL.

Material and Methods

The study protocol was approved by the local bioethics committee (Consent No. KE-0254/235/11/2022) and was supported by the Medical University in Lublin (Grant: DS 352). The study was also registered in the Clinical Trial Registry: NCT05864677. All participants were informed about the main hypothesis and the aim of this study and signed the written informed consent form.

Inclusion and Exclusion Criteria

Adult patients (aged 18 years and over) undergoing elective CABG with cardiopulmonary bypass were included to this study. The exclusion criteria were:

- no consent for participation;
- chronic neurological and psychiatric conditions (eg, status post stroke, CNS neoplasm, epilepsy, diagnosed and treated psychiatric conditions: schizophrenia, depression, bipolar affective disorder);
- ejection fraction <30%;
- allergy to CBL or its components.

Groups of Patients

Following the initial qualification, the patients were assigned to 2 groups: the study group consisted of patients receiving CBL in the method described below, and the control group was composed of patients not receiving CBL. The patients were randomly assigned to the groups prior to their preoperative visit, by means of sealed envelopes. The CBL patients were provided detailed information on CBL and gave their written consent to its administration during their procedures. CBL was administered intravenously (iv) at the dose of 50 ml in 250 ml of 0.9% NaCl as a 15-20-minute bolus infusion, immediately after admitting the patient into the operating room prior to the surgical procedure, and also on 4 subsequent consecutive days postoperatively once daily in 24-h break periods (5 doses in total).

General Anesthesia Protocol

All patients received the same premedication with morphine (Morphini sulfas, WZF, Poland) at the dose of 0.1-0.15 mg/kg body weight administrated intramuscularly 30-60 minutes prior to the surgery (diazepine-free

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premedication). Before anesthesia, as preemptive analgesia, the patients received acetaminophen (Paracetamol Fresenius Kabi, Germany) at the dose of 1.0 g iv.

All patients were monitored in accordance to the local rules. Continuous systolic, diastolic, and mean arterial blood pressure (MAP), heart rate (HR) and expiratory CO_2 tension were monitored using CARESCAPE Monitor B650 (GE Healthcare, Helsinki, Finland). Masimo Root monitor (Masimo, Irvine CA, USA) with SEDLine was used for continuous measurement of regional cerebral saturation (SrO_2) and frontotemporal electroencephalography with Patient State Index (PSI) to control the depth of anesthesia and disorders in cerebral oxygenation.

The anesthesia was induced using an iv fentanyl injection (Fentanyl WZF, Polfa SA, Poland) at the dose of 5-7 mcg/kg/body weight, and etomidate (Etomidate-Lipuro, B. Braun Melsungen AG, Germany) at the dose of 0.15-0.3 mg/kg body weight. Perioperative analgesia was followed by a remifentanil infusion (Ultiva Aspen Pharma Trading Limited, Ireland) at the dose of 0.2-0.5 µg/kg/min. The anesthesia was maintained with continuous infusion of propofol (Propofol 1% MCT/LCT Fresenius Kabi, Germany) at the dose of 2-5 mg/kg/h with its depth controlled by PSI (recommended level: 25-50). The patients were intubated following achievement of complete muscle relaxation with a single dose of pancuronium bromide (Pancuronium Jelfa, Jelfa, Poland) at 0.04-0.1 mg/kg body weight administrated iv. The patients were mechanically ventilated in IPPV mode with the TV of 6-8 ml/kg of ideal body weight, PEEP of 3-5 mmHg (Primus Dräger, Germany). During the total extracorporeal circulation, the ventilation was modified into low-volume at 1-3 ml/kg and frequency of 20-30/min or, when necessitated by procedure complications, discontinued with the maintained PEEP of 5 cmH_2O.

Postoperative Protocol

Following the surgical procedure, the patients were transferred to the Cardiothoracic Intensive Care Unit (CICU). Until their admission into the recovery room, they had continuously received propofol and remifentanil iv at sedative and analgesic doses. At the CICU, the patients continued to be carefully monitored, as initiated in the OR, with additional monitoring of the hourly postoperative drain output and hourly diuresis.

Oxycodone (Oxycodone Kalceks, Poland) was the primary analgesic used in postoperative pain management. It was administered in the initial continuous infusion of 1-2 mg/h iv, supplemented by additional doses of acetaminophen (Paracetamol Fresenius Kabi, Poland) at 1.0 g iv every 6 h, as well as, in the case of severe pain requiring additional treatment, by doses of metamizole (Metamizole Kalceks, Poland) at 2.5 g iv every 12 h.

Extubation was performed once the patients had met the following criteria: their respiratory function had been fully restored, and there were no abnormalities in their mental state, muscle strength, hemodynamics, body temperature, electrolyte and glucose levels, and they were not presenting a risk of postoperative hemorrhaging (understood as postoperative drain output of over 100 ml/h).

Psychological Assessment and Diagnosing Postoperative Delirium

The patients underwent psychological testing for neuropsychological dysfunctions, including postoperative delirium. The tests were carried out 1 day prior to their surgical procedure, as well as on the second and fifth postoperative days (with day 0 being the day of the surgery).

We used the following tests:

MoCA. The test is composed of 8 parts: visuospatial function, naming, memory, attention, speech, abstract reasoning, delayed recall, and orientation. Within these areas, long-term and short-term memory function is evaluated, together with the ability to correct and monitor actions, verbal fluency, visual processing, and allopsychic orientation. The MoCA is a screening tool detecting minor cognitive impairment, and it takes 10 minutes to complete. The sensitivity of the MoCA score in the Polish population was determined to be at 55.56% and its specificity was 99.08% [30,31]. Kaustov et al list MoCA as one of the standardized psychometric tools used in perioperative patient assessment, but emphasized that no single cognitive screening test is ideal for every clinical setting, and several factors must be considered when selecting an appropriate test [32].

CAM. An interviewer fills in the assessment form based on their observations and an interview with the subject. The following elements are observed: acute onset or fluctuation of symptoms, inattention, disorganized thinking, disorientation, memory impairment, perceptual disturbances, psychomotor agitation, psychomotor retardation, and altered sleep-wake cycle. It takes 5 minutes to complete. It has a sensitivity of 94-100%, specificity of 90-95%, positive predictive value of 91-94%, and negative predictive value of 90-100% [33,34].

Statistical Analysis

The collected data were analyzed using Statistica 13 PL and MedCalc 15.8 software. Categorized variables are expressed using absolute numbers and percentages. The Shapiro-Wilk test was used to examine the normality of the distribution of data of the analyzed variables [35]. Since most continuous variables showed a distribution other than normal, nonparametric tests were used in further analyses. For the same

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Table 1. Characteristics and comparison of the 2 groups in terms of demographic, psychological, and clinical variables.

Variable	Study group [n=29]	Control [n=26]	p
	Median [IQR] (min.-max.) or n (%)	Median [IQR] (min.-max.) or n (%)	
Age [years]	69 [66.8-74.3] (53-79)	67 [64-71] (47-82)	0.2114
Sex Female Male	 8 (27.6%) 21 (72.4%)	 9 (34.6%) 17 (65.4%)	0.7864
Height [cm]	168 [162.3-170.3] (148-180)	169.5 [160-175] (152-186)	0.4267
Weight [kg]	73 [69-89] (47-121)	84.5 [70-100] (54-115)	0.2182
BMI [kg/m^2]	27.3 [24.9-31.2] (16.3-40.9)	29 [24.2-33] (21.4-40.6)	0.6858
EuroSCORE II	1.1 [0.9-1.5] (0.6-3.9)	1 [0.8-1.4] (0.6-3.9)	0.6130
ECC duration [minutes]	54 [46.5-76] (32-112)	56 [46-64] (936-108)	0.7614
Aortic cross-clamp duration [minutes]	33 [26.8-42.3] (19-72)	34 [29-40] (20-63)	0.9798
Surgery duration [minutes]	145 [132.5-176.3] (100-250)	152.5 [140-175] (120-230)	0.5207

BMI – body mass index; ECC – extracorporeal circulation.

reason, continuous data are presented as median (measure of clustering), interquartile range, and minimum-maximum range (measures of dispersion). The Mann-Whitney U test was used to assess the significance of differences in continuous variables in the compared groups [36]. The comparison of categorized variables was performed using Fisher's exact test [37]. In all analyses, the results whose significance level did not exceed the threshold of $P<0.05$ were considered statistically significant. A power of analysis was calculated using Statistica 13 PL software.

Results

Characteristics and Comparison of the Study Group and Control Group in Terms of Demographic, Psychological, and Clinical Variables

Table 1 presents detailed data on the characteristics and comparison of the study group and control group in terms of demographic, psychological, and clinical variables. The study [n=29] and control [n=26] groups were well-balanced in terms of basic demographic, psychological, and clinical variables. Both groups mainly consisted of men (72.4% and 65.4%, respectively) with no differences between the groups ($P>0.05$). Median (and range) ages were 69 (53-79) and 67 (47-82) years, respectively, while the median (and range) BMI was 27.3 (16.3-40.9) and 29 (21.4-40.6) kg/m^2, respectively ($P>0.05$). There were no significant differences between the 2 groups in terms of fear of pain or fear of complications ($P>0.05$). Similarly, no significant differences were observed in terms of EuroScore II, duration of ECC, duration of aortic cross-clamp, and duration of surgery ($P>0.05$). The only statistically significant difference observed between the study group and the control group was the occurrence of a lower level of fear of anesthesia in the study group (medians and IQR, respectively: 0 [0-0] vs 0 [0-5]; $P=0.0318$).

Characteristics and Comparison of the Study Group and Control Group in Terms of Cognitive Function Assessment Results

Detailed data on the characteristics and comparison of the analyzed groups in terms of cognitive function assessment results are presented in **Table 2**. The 2 groups did not differ significantly in terms of cognitive function in the first and third assessment ($P>0.05$). However, in the second assessment, significantly lower values of the MoCA (medians: 27 vs 24, respectively; $P=0.0083$) were noted in the study group.

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Table 2. Characteristics and comparison of the 2 groups in terms of cognitive function assessment results.

Variable: MoCA	Study group [n=29]	Control [n=26]	*p*
	Median [IQR] (min.-max.) or n (%)	Median [IQR] (min.-max.) or n (%)	
1st assessment	24 [22-26] (19-28)	25.5 [23-28] (22-29)	0.1126
2nd assessment	24 [22-26] (19-28)	27 [24-28] (2-29)	0.0083*
3rd assessment	25 [24-28] (22-30)	27 [25-29] (5-30)	0.1529

MoCA – Montreal Cognitive Assessment; * statistically significant result.

Table 3. Characteristics and comparison of the subsequent assessments in terms of cognitive function in the 2 groups.

	1st assessment	2nd assessment	3rd assessment	*p* (1st vs 2nd)	*p* (1st vs 3rd)	*p* (2nd vs 3rd)
	Median [IQR] (min.-max.) or n (%)	Median [IQR] (min.-max.) or n (%)	Median [IQR] (min.-max.) or n (%)			
Study group [n=28]#						
MoCA	24 [22-26] (19-28)	24 [22-26] (19-28)	25 [24-28] (22-30)	0.8321	0.1162	0.0773
Control [n=24]#						
MoCA	25.5 [23-28] (22-29)	27 [24-28] (2-29)	27 [25-29] (5-30)	0.2954	0.1209	0.4753

MoCA – Montreal Cognitive Assessment; # The number of cases is lower due to pairwise comparisons.

Table 4. Characteristics and comparison of the subsequent assessments in terms of delirium occurrence in the 2 groups.

Variable	Study group [n=29]	Control [n=26]	p
	Median [IQR] (min.-max.) or n (%)	Median [IQR] (min.-max.) or n (%)	
CAM 2nd assessment No delirium Delirium *Missing data: Control [n=2]*	 29 (100%) 0 (0%)	 22 (91.7%) 2 (8.3%)	0.3894
CAM 3rd assessment No delirium Delirium *Missing data: Study: [n=1]*	 28 (100%) 0 (0%)	 24 (92.3%) 2 (7.7%)	0.4386
Throughout the study we observed 3 cases of delirium.			

CAM – Confusion Assessment Method.

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The power analysis showed the differences in MOCA: 1.3384; SD-K: 5.8885; SD-B: 2.6795, and the ratio K/B: 0.9. Based on these calculations, 185 patients should be included to the study group and 166 in the control group. We recorded patient characteristics and compared subsequent assessments in terms of cognitive function in the 2 groups.

Detailed data on characteristics and comparison of the subsequent assessments in terms of cognitive function in the analyzed groups are presented in **Table 3**. There were no significant differences in cognitive functions between the subsequent assessments in the study group ($P>0.05$). Similarly, there were no significant differences in MoCA between the subsequent assessments in the control group ($P>0.05$).

Postoperative Delirium

Three cases of delirium were detected, and all 3 were in the control group (11.54%). One patient had positive CAM scores from the 2nd postoperative day throughout the whole period of study observation. The second patient presented short-term delirium only on the 2nd postoperative day, whereas the third one had a positive CAM on the 5th postoperative day, with a full recovery on the day after (**Table 4**). No patients required intubation or mechanical ventilation. All patients survived the postoperative period. Unfortunately, the number of delirium cases did not achieve statistical significance. Patients were treated with oral quetiapine 50-100 mg daily, with a positive response.

Discussion

CBL has considerable neuroprotective potential and is used in various therapeutic approaches, including in patients with mild cognitive impairment (MCI). A previous study assessed the influence of CER on cognitive outcome in 19 patients who received 20 iv infusions of 30 ml CER, and the authors found increases in test results when assessed at 4, 10, and 26 days after the last infusion [38]. CER also was shown to reduce the rate of transitions of MCI to dementia after 2.5 years of observation of the first-degree relatives of patients with Alzheimer's disease (AD) [39]. Gavrilova and Alvarez in their review article summarizing 30 years of clinical experience with CBL concluded that the medication is safe and efficacious in the treatment of AD, and can enhance and prolong the efficacy of cholinergic drugs, particularly in moderate-to-advanced AD patients [40]. Positive response to CBL treatment was also shown in 87 severe brain trauma patients with nonoperative lesions, and the authors noticed an increase in GCS/GOS scoring and shortened length of stay (although with no reduction in 28-day mortality) [41]. In that study, patients received CBL doses of 30 ml for 14 days, and the received 10 ml for next 14 days). The assessment was performed 21 days after the treatment, much later than in our study. An interesting use of CBL was published by Khasanova and Kalinin, who used CBL as an early add-on to reperfusion therapy (the CEREHETIS Study). They showed that CBL was safe and significantly decreased the rate of symptomatic hemorrhagic transformation and early neurological deficit, and had beneficial effects in patients treated for failed recanalization therapy [42]. CBL as add-on therapy was reported to be beneficial and safe for patients with acute stroke in terms of lowering risk for hemorrhagic complications after recanalization therapy [43]. CBL has potential in patients with the vascular basis of pathology, which is of interest in cardiac surgery and anesthesia.

Unfortunately, the perioperative utility of CBL has been not well documented. A pilot study assessed the neurological effect of CBL in patients undergoing surgery due to degenerative cervical myelopathy, finding significantly greater improvement in hand function in patients treated with CBL at the dose 5 mL CBL diluted in 100 mL normal saline over 30 minutes once a day for 21 days postoperatively compared to those receiving placebo. However, the 2 groups of patients were of very different sizes (the CBL group included 60 patients, and the placebo group consisted of only 30 participants) [44]. Not all clinical perioperative CBL applications had positive results. Mracek et al assessed perioperative changes in S100B, glycemia, lactate, pH, and jugular vein bulb oxygen saturation (SvjO2) in patients receiving CBL as a broad neuroprotective component of preoperative a broad neuroprotective mixture (Sendai cocktail: Mannitol, Phenhydan, Solumedrol, Tocopherol; Cerebrolysin; fraction of inspired oxygen (FiO2)=1, mean arterial pressure (MAP)=100 mmHg) did not found a superior clinical outcome in patients undergoing total intravenous anesthesia (TIVA) for carotid endarterectomy anesthetized with [45].

The present preliminary report is one of the first studies on use of CBL in patients undergoing CABG. We enrolled typical myocardial patients, and both of our groups were mostly composed of men. According to the European Society of Cardiology (ESC) data, although females accounted for more new cases of cardiovascular disease across ESC member countries compared with males (10.3 million vs 9.6 million), after age-standardization, the median rates per 100 000 people were lower in females than in males (1006 vs 1291) [46]. We found that CBL reduced the occurrence of POCD as reflected in neuropsychological tests. The topic is important, and as Fiani et al stated in their conclusion after reviewing material on use of CBL in stroke, neurodegeneration, and TBI, it potentially can play a major role in their treatment, but much more clinical data are needed to reach a consensus on its therapeutic role [23]. Unfortunately, there are no published reports on perioperative use of CBL in CABG patients written in English. A similar study was only published in Russian by Polushin et al, who studied 38 patients undergoing CABG, of whom 15 were treated with

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preoperative CBL [47]. The psychological testing included MoCA. A basic protocol for Doppler examination of the vessels of the head and neck was performed. In addition, the components of the MoCA scale – "attention" and "counting" tests – were analyzed, since during the dynamic examination participants had difficulties in completing these items. In contrast to our study, CBL was administered earlier and in lower doses; they used a lower volume of 10 ml for 3 days before the procedure and during the surgery. The anesthesia protocol also differed from our methodology, as they used desflurane/sevoflurane (as opposed to our choice of propofol) in their anesthesia.

A review of the literature by Zhu et al did not find a relationship between POCD and the method of anesthesia used (intravenous or inhalation) [48], and the discrepancies in the research results may be due to different sample sizes and assessment tools [48].

Polushin et al chose different timing of assessment. All examinations were carried out before surgery (1st visit) and on the 10th (2nd visit) and 30th (3rd visit) days after surgery, much later than in our study. In the group of patients receiving neuroprotection, the quantitative parameters of cerebral blood flow were stable, with a slight increase on the 10th day after surgery, which may indicate an increase in the stress resistance of CNS cells after appropriate pharmacological protection [47].

The authors used a different type of MoCA analysis – the proportion of patients with a decrease – in the assessment. The raw MoCA results in the chosen time periods show the mean MoCA results are comparable to ours despite different timing of assessment. The results of that study should also be interpreted cautiously due to the low number of participants.

In our study we noted significantly lower scores in MoCA in the CBL group in comparison with the control group. This decline was transient, and the patients exhibited normal results in the next assessment, which was a positive outcome in both groups. It is difficult to find a possible explanation and to discuss the problem based on the available literature, especially since the studies cited above analyzed the problem in completely different populations. The pharmacokinetic/pharmacodynamic interactions with the multiple medications (including anesthetics) should be considered. The manufacturer's drug characteristic data only provide information on the possible central nervous overstimulation with dizziness or grand-mal seizures. None of these adverse effects were noted in the study participants. Most of the studies assessed patient cognition after at least 7 days following the operation. An interesting study was performed by Nurcahyo et al, who tested patients in similar periods of time (after 72 h), analyzing the possible relationships between MoCA-INA (the Indonesian version of MoCA) results and GFAP levels [49]. They found that POCD patients had higher GFAP levels than non-POCD patients. The number of patients included in the study was comparable to ours, and the mean MoCA results were similar, although our population was older, and the durations of anesthesia, surgery, CPB, and aortic cross-clamping were shorter. Another difference was the chosen scheme of anesthesia (we used propofol, while Nurcahyo et al used sevoflurane), which may have resulted in different patterns of postoperative neuroinflammation.

The postoperative MoCA results were generally good, and comparison of the pre- and the final postoperative results in both groups showed satisfactory outcomes, with no significant differences, but further research with larger samples is needed. MoCA is basically a screening tool, but the strict anesthesiologic approach may improve final cognitive outcomes and warrants further exploration in the future.

The only cases of delirium were in the control group (11.54%). The result did not reach the statistical significance, probably due to the low number of study participants, but the result is worth further observation. A retrospective Polish study on delirium by Kotfis et al found delirium in 21.4% of cardiac surgery patients ≥65 years of age, which was higher than in our study [50]. The authors chose a different tool for detecting delirium, the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), and the anesthesia was sevoflurane-based. We included also patients younger than 65 years of age, which could have influenced the final outcome. Unfortunately, we could not find any reports in the literature on use of CBL in CABG patients, so we cannot compare our results with those of other studies. We are planning a prospective multicenter study focusing on this topic in a wider population covering the whole spectrum of cardiac surgery, as it could change pharmacological perspectives on prevention and treatment of postoperative delirium.

Conclusions

CBL did not improve postoperative scoring in MoCA, although patients in both groups maintained the initial preoperative results. There were no cases of delirium in the study group, which warrants further analysis in larger groups of participants. This preliminary report, although not providing strong statistical evidence due to the low number of participants, prompts us to develop a plan for a large-scale multicenter study assessing the potential reductive role of CBL in delirium in cardiac surgery patients in the context of severity of neuroinflammation.

Limitations of the Study

Our study has several limitations. First, the small number of participants significantly reduced the power of statistical

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analysis. For the studied group we would need 185 patients, and for the control group 166 participants. Second, we did not support the study with the changes specific for perioperative brain injury and POCD biomarkers. An analysis of correlations between blood biomarkers and neuropsychological findings would allow assessment of the beneficial effect of CBL much better than using a neuropsychological test alone. Therefore, further study is necessary to confirm our findings.

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