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Use of a Neurometabolism-Targeting Drug in Prevention of Postoperative Cognitive Dysfunction

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Summary

Aim of the study: to evaluate the feasibility of preventing cognitive dysfunction after long-term surgery in elderly patients using an original neurometabolic succinate-containing drug.

Material and methods. A multicenter, double-blind, placebo-controlled randomized trial enrolled 200 patients aged 60–80 years who underwent elective cardiac or orthopedic surgery. The patients received either the study drug (inosine + nicotinamide + riboflavin + succinate) (treatment group, *n*=101) or a placebo (control group, *n*=99) intravenously for 7 days then orally for 25 days. Efficacy was assessed by the change in the Montreal Cognitive Assessment Scale (MoCA) score at the end of the treatment course compared with the preoperative level.

Results. Before surgery, the total MoCA score values did not differ between the groups. By the end of the treatment course (31 days after surgery), the MoCA total score was 26.4±1.96 in the main group and 25.0±2.83 in the control group (P<0.001). The intergroup difference in the mean change in the MoCA total score on day 31 was 1.56 points (95% CI 1.015; 2.113; P<0.0001) favoring the study drug in all randomized population. The lower limit of CI (1.015) exceeded the limit of superiority set by the protocol (0.97 points), which allowed acceptance of the hypothesis of superiority of the study drug over placebo with respect to the primary efficacy criterion. No significant differences in the frequency of adverse events were found between the groups.

Conclusion. The succinate-containing study drug demonstrated an acceptable safety profile and helped to reduce the severity of postoperative cognitive dysfunction in elderly patients who underwent a major surgery, which allows recommending the drug for prevention of postoperative cognitive impairment in high-risk patients.

Keywords: succinate-containing drugs; succinic acid; prevention of postoperative cognitive dysfunction

Identifiers. NCT03849664 Unique Protocol ID: CYT-COG-16

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Introduction

Postoperative cognitive dysfunction (POCD) manifests as impaired higher cortical functions and difficulty concentrating, which entail learning, performance, mood, and sometimes self-care problems. The cognitive impairment in the postoperative period can worsen the outcome, increase the length of stay in ICU and inpatient treatment, and reduce the quality of life of patients and their families, including in the long term after surgery [1]. POCD is a risk factor for mortality: its persistence 3 months after surgery correlates with an increased risk of death in the following 8 years [2].

Postoperative cognitive disorders occur more frequently in elderly patients undergoing major surgery. The prevalence of these conditions among elderly patients reaches 48–65% in abdominal, thoracic, orthopedic, and vascular surgical practice [3]. Age is a more significant risk factor than the type of surgery, but the issue of POCD is particularly relevant in cardiac and orthopedic surgery: the average incidence of this complication after cardiac surgery is 48–51% within the first 3 weeks, 21–26% within 6 months, 15–24% within a year, and, according to various data, from 24% to 42% within a year and beyond [4]. There is no single factor responsible for the development of POCD; randomized studies have shown that the use of a cardiopulmonary bypass during surgery [5] and the choice of anesthesia method [6] have no significant effect on the incidence of postoperative cognitive impairment. Apart from the patient's age, low level of education and preexisting cognitive deficit (in particular, associated with central nervous system diseases) predispose to this condition [7].

Despite the clinical and social impact of the problem, there are currently no drug regimens for the prevention or treatment of POCD with proven efficacy. A promising trend is the use of drugs with neuroprotective and neurotrophic effect. The concept of the neurocognitive reserve, which is defined as an active ability of the brain to effectively resist damaging factors, compensating for cognitive deterioration caused by various diseases, has been developed [8]. The potential capacity of strategy to increase cognitive reserve using chemical agents targeting neurometabolism was demonstrated in small groups of patients at high risk of developing postoperative cognitive impairment [9].

One of the drugs that may target neurometabolism has been tested during cardiac surgery (Cytoflavin®, OOO NTFF POLYSAN, Russia). The positive effect of this succinate-containing drug on cognitive functions has been revealed in patients undergoing cardiac surgery with cardiopulmonary bypass and on the beating heart. The use of the drug early after cardiac surgery reduced the likelihood and severity of cognitive, speech and attention impairment, promoted recovery of spontaneous activity, memory, emotional behavior, voluntary acts, and resulted in a rapid return of patients to active life [10, 11].

The aim of the study was to evaluate the feasibility of preventing cognitive disorders after long-term surgery in elderly patients using an original neurometabolism-targeting succinate-containing drug.

Material and Methods

A multicenter double-blind placebo-controlled randomized trial was conducted under the supervision of the Ethics Council of the Russian Federation Ministry of Health in accordance with the ethical principles outlined in the Declaration of Helsinki of the World Medical Association (Fortaleza, 2013) and the regulatory documents in force in the Russian Federation. The study protocol CYT-cog-16 (clinicaltrials.gov: NCT03849664) was followed at 13 research centers in the Russian Federation from February 13, 2018 (screening of the first patient) until November 29, 2019 (date of closure of the last center). The study was sponsored by NTFF POLYSAN.

Men and women 60–80 years old who signed informed consent to participate in the study and were scheduled to undergo cardiac surgery without cardiopulmonary bypass or orthopedic surgery (hip arthroplasty, osteosynthesis for fractures of the proximal third of the femur, etc.) under general or combined anesthesia were included in the study. The other criteria for enrollment included mental capacity, absence of severe cognitive impairment (Montreal Cognitive Assessment (MoCA) score ⩾17 [12], Mini Mental State Examination (MMSE) score ⩾19 [13]), lack of reproductive potential or consent to use adequate contraceptive methods.

The non-inclusion criteria were intolerance to the components of the study drug; emergency character of surgery; repeated surgery; ASA anesthesia risk level ⩾5 [14]; severe visual and hearing impairments that prevent the performance of neuropsychological tests; surgery under general anesthesia in the previous 3 months; decompensated renal or hepatic failure; chronic obstructive pulmonary disease, diabetes mellitus; terminal chronic incurable disease; history of cancer, psychiatric diseases, HIV infection, syphilis, tuberculosis, alcohol, drug or medication abuse, consumption of 5 or more units of alcohol per week; documented psychiatric or neurodegenerative disease; continuous use of psychotropic drugs; use of nootropic drugs within the previous 3 months; communication,

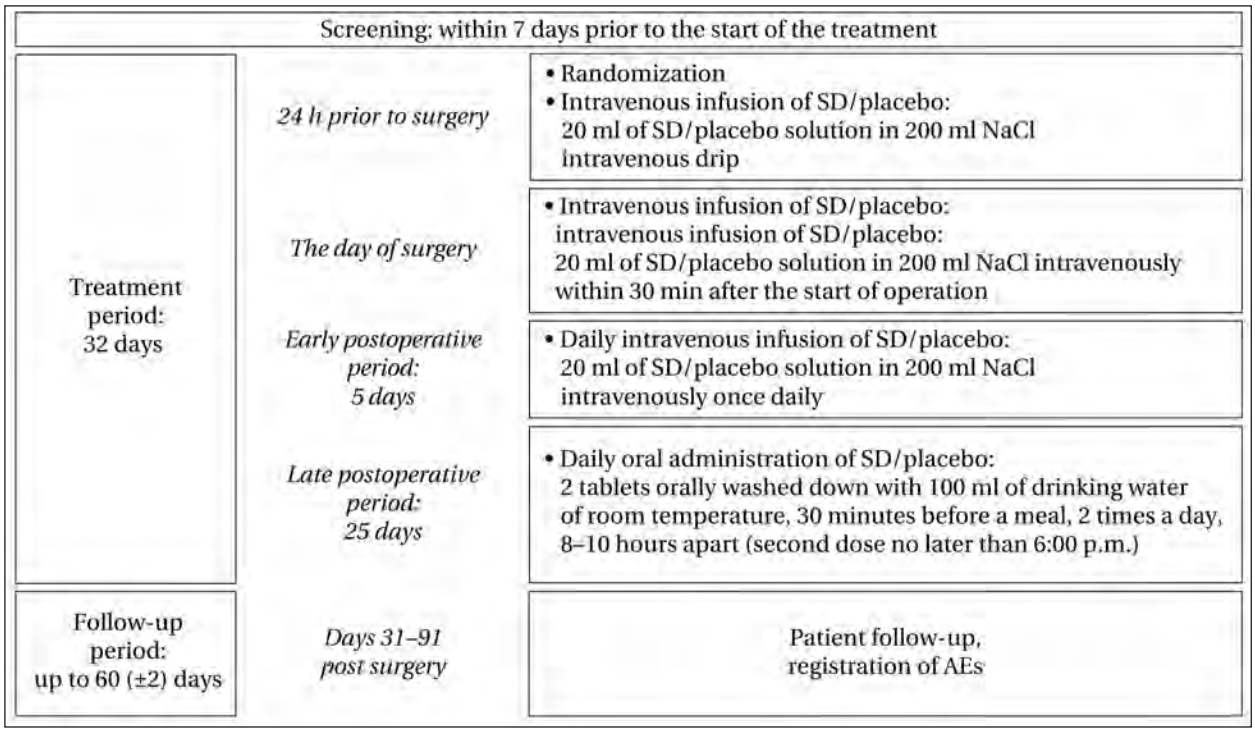

Fig. 1. The flowchart of the study.
Note. SD — studied drug; AEs — adverse effects.

sensory, motor, or any other deficit that prevents the patient from complying with the study protocol; history of any other significant condition preventing study participation (according to the investigator's opinion).

The patients were allocated to the main group, which included those receiving the study drug Cytoflavin® (succinate + nicotinamide + inosine + riboflavin, manufactured by LLC NTFP «POLYSAN», Russia) according to the chart in Fig. 1, and the control group who received placebo according to the same scheme by 1:1 block randomization.

The primary efficacy endpoint was the change in the MoCA score [12] by the end of the treatment course (day 31 days post surgery) versus the preoperative level. The MoCA score was assessed before surgery, at the end of the treatment period, and at the end of the follow-up period. The forms with different task options were used to avoid the memorization effect.

Secondary efficacy endpoints included change in the MMSE cognitive status score [13] at the end of the treatment course (day 31 post surgery) and at the end of the follow-up period (day 91 post surgery) compared to preoperative levels; change in the MoCA score at the end of the follow-up period compared to preoperative levels; proportion of patients who developed postoperative delirium during the first 96 h after surgery; length of ICU and hospital stay; change in the total score on the European Quality of Life Questionnaire (EQ-5D) at the end of the follow-up period compared to baseline values; the percentage of postoperative deaths; the percentage of patients with reduced scores on two and more neuropsychological tests by more than 20% of baseline values at the end of the treatment course and at the end of the follow-up period.

The neuropsychological test battery [15] included the TMT test A, the 10 word recall test, the Schulte table, the Wechsler memory scale, as well as the MoCA and MMSE scales, for which a decrease of more than 20% from the initial score was considered significant. Psychodiagnostic assessment was performed by a psychologist with appropriate professional qualifications. Preoperative risks were assessed using ASA scales, delirium risk assessment scales in general surgery [16] and cardiac surgery [17], fragility index [18]. Blood loss volume and hematocrit value, delirium development according to CAM-ICU (Confusion Assessment Method Intensive Care Unit) scale [19], severity of postoperative pain according to visual analogue scale, episodes of clinically significant BP changes and blood oxygen saturation (SpO_2) <90%, depression and anxiety according to Hospital Anxiety and Depression Scale (HADS) [20] were registered in early postoperative period; in the late postoperative period, the degree of dependence in the performance of daily functions according to the Katz index was assessed [21].

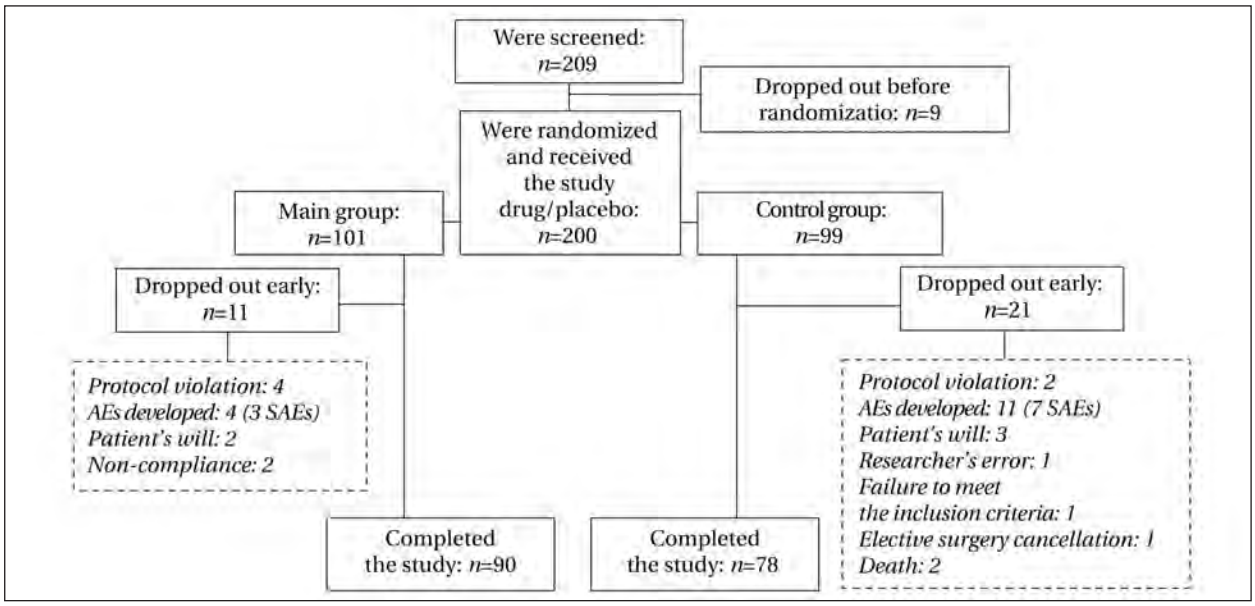

Figure 2. Flow diagram of subject recruitment and retention in the CYT-cog-16 clinical trial.
Note. AE — adverse effect; SAE — serious adverse effect.

Safety analysis was performed based on the frequency of adverse events (AEs), serious adverse events (SAEs); abnormal vital signs (BP, HR, respiratory rate, body temperature, SpO_2), laboratory parameters, ECG findings were recorded as AEs. Coding of AEs and preexisting diseases/comorbidities was performed using Medical Dictionary for Regulatory Activities (MedDRA, version 22.1), coding of previous and concomitant treatments was performed using the ATC classification.

SAS 9.4 software (SAS Institute Inc, USA) was used for statistical analysis. For qualitative variables, comparisons between groups were made using Pearson's χ^2 test or Fisher's exact test. For quantitative variables subject to normal distribution, comparison between groups was performed using Student's *t*-test or Student's *t*-test for dependent samples; for quantitative variables with non-normal distribution, Mann–Whitney *U*-test (for independent samples) or Wilcoxon *T*-test (for dependent samples) were applied. The Shapiro–Wilk test was used to verify the normality of the data distribution. The changes in the variables were assessed using the mixed-model analysis of variance with repeated measures (ANOVA MMRM). Differences were considered significant at $P<0.05$.

To assess the primary efficacy endpoint, we calculated the 95% confidence interval (95% CI) for the differences in the group mean values of the individual MoCA score changes at the end of the treatment compared with the preoperative level. To prove the hypothesis of superiority of the study drug compared with placebo, the lower limit of the 95% CI for the difference in the group mean values of individual changes was required to be higher than the limit of superiority of 0.97. To test the hypothesis of superiority of the study drug over the comparison drug at a significance level of 0.05 (5%) and with a power of 0.8 (80%), we calculated the minimum number of randomized patients who would complete the study per protocol to be 98 (49 patients per group). Given the high probability of patient dropout during the study, we planned to randomize at least 200 patients.

To study efficacy criteria in individual patient subpopulations, given the large number of subpopulations of interest and the large number of studied efficacy criteria, we chose the decision tree method, which allowed us to evaluate the potential effect of all factors of interest on the efficacy of the studied treatment, omitting the missing values.

Results

We screened 209 patients, randomized 200 patients who received at least one dose of study drug/placebo, and composed the ITT (Intent-To-Treat — all randomized patients who received at least one dose of study drug) population; 168 patients who completed the study according to protocol were included in the per-protocol (PP) population (Fig. 2).

The study groups were comparable in terms of demographic characteristics, comorbidities, med-

Table 1. Baseline patient characteristics.

Parameter	Values in groups		*P* value
	Main, *n*=101	Placebo, *n*=99	
Age, years (*M*±*SD*; *Me* [Q25; Q75])	68±5.23 67 [65; 71]	68±5.8 66 [63; 72]	0.949
Female sex, *n* (%)	66 (65.3)	55 (55.6)	0.157
Body mass index (*M*±*SD*; *Me* [Q25; Q75])	29.3±4.42 28.9 [26.4; 32.2]	28.7±4.85 28.0 [25.7; 32.2]	0.362
Any comorbidity, n (%)	100 (99.01)	98 (98.99)	>0.999
Cardiac disorders	90 (89.1)	92 (92.9)	0.460
Vascular disorders	33 (32.7)	24 (24.2)	0.212
Nervous system disorders	27 (26.7)	24 (24.2)	0.747
Any treatment within the previous 30 days	77 (76.2)	77 (77.8)	0.796
Preoperative ASA score	Class II 31 (30.7) Class III 63 (62.4) Class IV 7 (6.9)	Class II 26 (26.3) Class III 65 (65.7) Class IV 8 (8.1)	0.772
Surgical Risk Scale, mean points (±SD; n; *Me* [Q25; Q75])	0.9 (±0.83; 74) 1 [0; 2]	1.3 (±1.01; 70) 1 [0; 2]	0.042
Delirium risk assessment in cardiac surgery, mean points (±SD; n; *Me* [Q25; Q75])	0.4 (±0.69; 27) 0 [0; 1]	0.4 (±0.63; 29) 0 [0; 1]	0.681
Frailty index, mean points (±SD; n; *Me* [Q25; Q75])	0.9 (±0.83; 101) 1 [0; 1]	1.1 (±0.81; 99) 1 [0; 2]	0.265

Note. *M*±*SD* — arithmetic mean ± standard deviation; *Me* [Q25; Q75] — median [lower quartile; upper quartile]; *n* — number of subjects in the group.

Table 2. Distribution of patients according to the surgical intervention type.

Parameter	Values in groups		*P* value
	Main, *n*=101	Placebo, *n*=99	
Elective surgery performed, *n* (%)	99 (98.0)	96 (97.0)	0.982
Cardiac surgery	26 (25.7)	28 (28.3)	0.686
Orthopedic surgery	73 (72.3)	68 (68.7)	0.578
Endoprosthetic reconstruction	66 (65.3)	59 (59.6)	0.678
Osteosynthesis	6 (5.9)	9 (9.1)	0.489
Other	1 (1.0)	0 (0.0)	0.972

Note. *n* — number of subjects in the group.

ical history and the frequency of concomitant treatment, as well as the general anesthesia risk class (Table 1).

Elective surgery was performed on 99 patients in the main group and 96 patients in the placebo group (Table 2); 2 and 3 patients, respectively, dropped out of the study prematurely in the preoperative period.

Patient compliance at the stage of intravenous infusion of the SD/placebo solution was 100% (SD/placebo was administered by medical professionals); further on, in both study groups, the average compliance was above 80%.

The results of the analysis of the MoCA score and its change at the end of the treatment course (day 31) and the follow-up period (day 91) compared with the preoperative level are presented in Table 3. The difference between the SD group and the placebo group in terms of mean change in the total MoCA score at day 31 was 1.564 points (95% CI 1.015; 2.113). Thus, the lower limit of this CI (1.015) exceeded the limit of superiority set by the protocol (0.97 points). Based on the above results, the superiority of Cytoflavin® SD over placebo was confirmed with regard to the primary efficacy endpoint in the study populations. At the end of the treatment period (day 31), the groups also differed significantly in the absolute value of the total MoCA score in favor of the study drug.

When analyzing the changes in the total score on the MoCA scale (ANOVA MMRM) at the end of the treatment course (day 31) and at the end of the follow-up period (day 91) compared with the preoperative level with the inclusion of age group (younger than 70 years/70 years or older) and type of surgery (cardiac surgery/orthopedic surgery) cofactors, we found that these had no significant effect on achieving the primary efficacy endpoints.

On day 91 post surgery, the changes in the MMSE score versus the preoperative level significantly differed between groups in favor of the study drug and were 1.2±2.06 (1; [0; 2]) in the main group and 0.7±2.26 (1; [0; 2]) in the placebo group (*P*=0.0027, ANOVA MMRM), we also observed a small difference between the groups in terms of

Table 3. Group mean values of MoCA scores and their changes by the end of the treatment and follow-up periods.

MoCA score, points	Values in the groups				*P* value
	Mean, *n*=101		Placebo, *n*=99		
	M±*SD*	*Me* [Q25; Q75]	*M*±*SD*	*Me* [Q25; Q75]	
ИBaseline total	24.9±2.76	25 [23; 27]	24.9±2.63	25 [23; 27]	0.941
On day 31	26.4±1.96	27 [25; 28]	25.0±2.83	25 [24; 27]	<0.001
On day 91	26.6±1.81	27 [25; 28]	26.3±1.69	26 [25; 27]	0.299
Change in total score vs preoperative value					
On day 31	1.7±2.4	2 [0; 3]	–0.1±2.5	1 [–1; 2]	<0.001
On day 91	1.9±2.60	2 [0; 4]	1.2±2.02	1 [0; 2]	0.121
Difference in MoCA score change between patients in the main group and the placebo group:					
in ITT population	1.564 points			(95% CI 1.015; 2.113)	
in PP population	1.556 points			(95% CI 1.005; 2.106)	

Note. *M*±*SD* — arithmetic mean ± standard deviation; *Me* [Q25; Q75] — median [lower quartile; upper quartile]; ITT — intent-to-treat (all randomized patients who received at least one dose of the study drug); PP — per protocol population (all randomized patients who completed the study without protocol violations).

Table 4. Summary table of adverse events and serious adverse events.

Parameter	Values in groups		*P* value
	Main, *n*=101	Placebo, *n*=99	
Any AEs (including SAEs), *n* (%), number of AEs	63 (62.40%), 151	67 (67.68%), 156	0.433
AEs with no criteria for severity, *n* (%), number of AEs	59 (58.42%), 144	57 (57.58%), 141	>0.999
SAEs, *n* (%), number of AEs	4 (3.96%), 7	10 (10.10%), 15	0.103

Note. n — number of subjects in the group; AE — adverse event; SAE — serious adverse event.

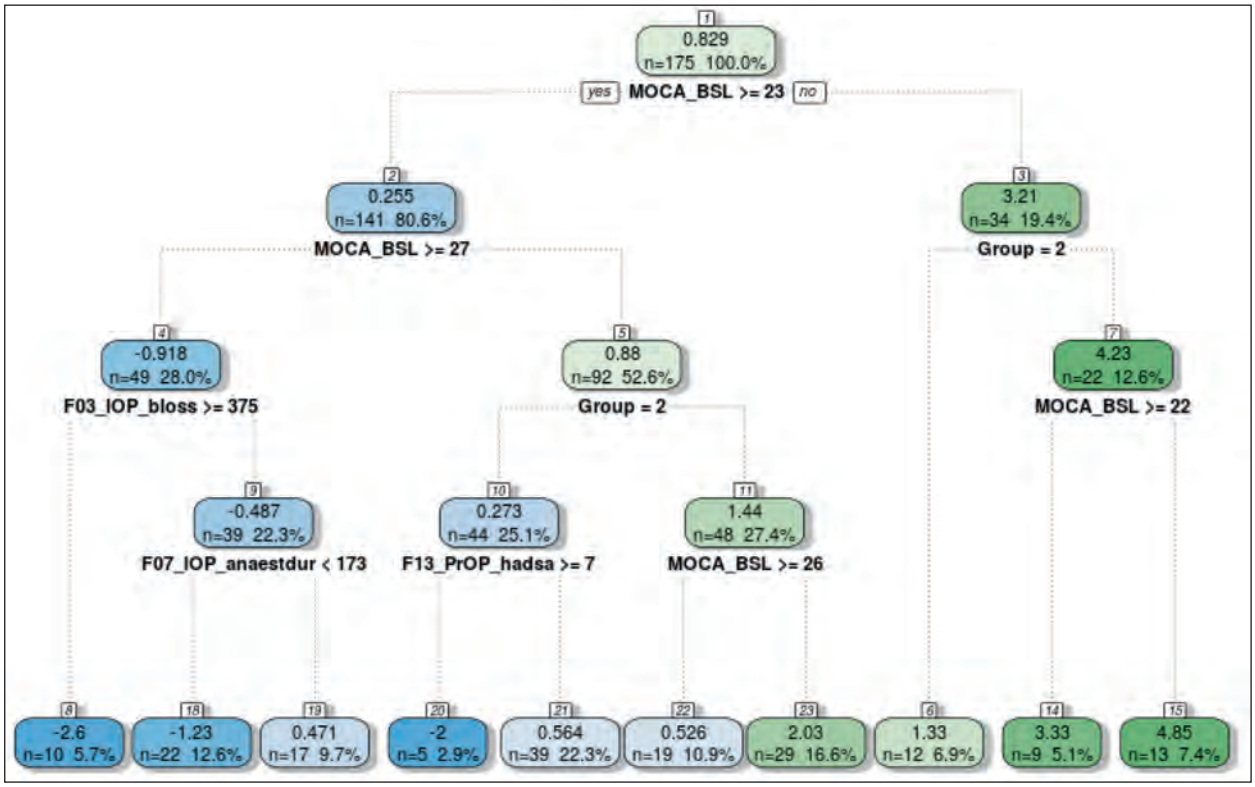

Fig. 3. Decision tree for the primary efficacy endpoint. Changes in the MoCA score by the end of the treatment period.
Note. MOCA_BSL — baseline MoCA score; F03_IOP_bloss — intraoperative blood loss; F07_IOP_anaestdur — duration of anesthesia; F13_PrOP_hadsa — preoperative HADS (Hospital Anxiety and Depression Scale) assessment.

the mean group MMSE score in favor of the study drug, 28.8±1.34 (29; [28; 30]) in the main group and 28.0±1.92 (28; [27; 30]) in the placebo group (P=0.003, ANOVA). At the end of the treatment course (day 31 post surgery), the percentage of patients with a reduction of more than 20% from baseline in two or more neuropsychological tests was lower in the Cytoflavin® group, 6.9% (7/101) of patients versus 16.2% (16/99) in the placebo group (P=0.041). At the end of the follow-up period (day 91), this proportion was 4.0% (4/101) and 9.1% (9/99) in the Cytoflavin® and placebo groups, respectively; the differences between the groups did not reach significance though (P=0.141). The odds ratio for «no worsening on two or more neuropsychological tests» was 2.5886 (95% CI for OR 1.0153; 6.6001) at Visit 9 and 2.4250 (95% CI for OR 0.7215; 8.1503) at Visit 10. For other secondary efficacy endpoints, no significant differences were found between the study groups. Postoperative delirium did not occur in all patients in both groups at each assessment point.

Analysis of the effect of various potential factors on the achievement of primary and secondary efficacy endpoints using the decision tree method revealed no significant effects of the study drug/placebo on the rate of intraoperative episodes of clinically significant hypotension and decreased oxygen saturation (SpO_2<90%), intraoperative blood loss, duration of anesthetic care, number of episodes of clinically significant BP changes (which required additional antihypertensive treatment) during ICU monitoring, postoperative hematocrits level, as well as the preoperative delirium risk scores, postoperative pain severity, anxiety, depression, and dependence in daily activities. At the same time, the MoCA baseline score before the start of therapy had the highest significance with respect to MoCA scores: patients with more severe (<23 points) cognitive impairment at the study start (n=34, 19.4%) had greater MoCA score changes at the end of the treatment period (day 31) — 3.21 points versus 0.255 points for patients with baseline MoCA scores ⩾23 (n=141, 80.6%). All other factors had significantly lower significance (Fig. 3) and had no major effect on achieving the primary efficacy endpoint, but the subgroup of patients with greater baseline cognitive impairment tended to have stronger MoCA score changes at the end of the treatment period if administered with SD versus placebo.

Safety analysis was performed in the ITT population. During this study, a total of 307 AEs were recorded after the first dose of the study drug/placebo (Table 4).

All 22 SAEs were unrelated to the study drug/placebo or had only a presumptive or doubtful relation. The outcome of 5 SAEs was fatal (2 cases in the main group and 3 cases in the placebo group). A total of 8 AEs with at least a possible relation to the administered drug were recorded. Among them, there was 1 case of hypersensitivity definitely related to the drug administration. There was also 1 case of leukocytosis, probably related, and 1 case of urinary incontinence, possibly related to the study drug. In the placebo group, there were 5 AEs with possible relation to placebo administration, including leukocytosis, asthenia, dizziness, abdominal pain, and diarrhea (one case of each). All intergroup differences in the incidence of AEs with at least a possible relation to placebo or study drug administration were not significant. Single cases of clinically significant abnormalities in several laboratory parameters, heart rate and overall ECG evaluation were recorded, while no significant intergroup differences in the frequency of clinically significant abnormalities were found either.

Discussion

In a multicenter, double-blind, placebo-controlled randomized trial evaluating the effect of daily use of a succinate-containing neurometabolism-targeting agent on cognitive function, the efficacy of the drug in preventing cognitive impairment after major surgery in elderly patients was shown for the first time to exceed that of placebo. In theory, pharmacological perioperative neuroprotection should reduce the likelihood of neurological, including cognitive, deficits in the postoperative period. In clinics, it has not been demonstrated earlier: the use of lidocaine, ketamine, and magnesium sulfate produced inconsistent results (either questionable effect, or no effect), while there were no differences for the other drugs tested (thiopental, propofol, nimodipine, glutamate/aspartate, xenon, atorvastatin, erythropoietin, piracetam, rivastigmine, estradiol) with respect to POCD between the groups of patients receiving the drug and the control group [22]. Given the ambiguity of POCD diagnostic criteria [23], not the individual neuropsychological tests but an integral MoCA scale, which can assess different cognitive domains (attention and concentration, executive functions, memory, language, visual constructive skills, abstract thinking, counting and orientation) were chosen to evaluate effectiveness, i.e., changes in the total score on this scale occur in any type of cognitive dysfunction. The MoCA scale has high sensitivity and specificity (100% and 87%, respectively) for moderate cognitive dysfunction [13], and has an advantage over other tests in detecting mild cognitive impairment [24]. The results obtained in this study

are consistent with those of previous minor studies that have shown a positive effect of Cytoflavin on cognitive function in patients undergoing cardiac surgery with cardiopulmonary bypass and on the beating heart [10, 11].

To confirm POCD, extensive neuropsychological testing before and after surgery, which should reveal a decrease in cognitive functions in two or more functional domains for at least two weeks, is necessary [15]. However, the extent of this decrease to be considered as clinically significant is controversial, and therefore, there is a strong variation in the frequency of diagnosis of this condition according to different researchers [23]. In this study, we used the proportion of patients with more than a 20% decline in two or more neuropsychological tests at the end of the treatment course as a separate parameter based on the results of a battery of neuropsychological tests including 10 subscales to assess various cognitive domains, which corresponds to the consensus recommendations [15]. The incidence of POCD, according to this definition, on day 31 post-surgery was 11.5% (6.9% of patients in the Cytoflavin® group and 16.2% of patients in the placebo group). This incidence is somewhat lower than in earlier studies [25], which may be due to the smaller portion of patients who underwent cardiac surgery in the study group, exclusion of patients operated with a cardiopulmonary bypass, improvements in general anesthesia techniques and perioperative management. Nevertheless, it is important to note that a significant intergroup difference in favor of the study drug was also observed for this parameter.

Numerous risk factors for postoperative cognitive impairment have been previously described [26], and in addition to older age, initial cognitive deficit, and low educational level, the negative effect of perioperative adverse effects (hypovolemia and cerebral hypoperfusion, arrhythmias, inflammatory reactions, intraoperative blood loss and massive hemotransfusion, reduction of hematocrit after surgery <30%, etc.) were also mentioned [26, 27]. All these factors were considered in this study and studied in a multivariate outcome analysis, which confirmed the relationship between baseline cognitive status and the development of clinically manifest POCD. Other factors had no significant effect on the outcome, probably due to their uncommon occurrence and low severity of adverse intraoperative factors in modern elective surgery.

The results of the study suggest acceptable safety profile of Cytoflavin®: no significant intergroup differences in the frequency of both non-serious and serious AEs were found, and the patterns of AE outcomes were comparable in the study groups. This study limitation is the non-inclusion of cardiac surgery patients operated with extracorporeal circulation, due to lack of an unified protocol of intraoperative extracorporeal circulation in different centers. Although this limitation excluded patients with the highest risk of postoperative cognitive impairment, it helped avoid significant variation in the baseline risk level in the groups, as well as a significant impact of the «center effect» on the final outcome. In addition, patients with postoperative stroke were excluded from the study, since the mechanisms of cognitive dysfunction development in these patients were fundamentally different due to morphological damages to various areas of the brain.

Conclusion

The study drug Cytoflavin® (Inosine + Nicotinamide + Riboflavin + Succinate) demonstrated an acceptable safety profile and helped reduce the severity of cognitive dysfunction in the postoperative period in elderly patients after major surgery, which suggests using the drug for prevention of postoperative cognitive impairment in high-risk patients.

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