Challenge Journal of Perioperative Medicine

Research Article

The effects of pentoxyphiline on neurocognitive functions and neurobiochemical markers in coronary artery bypass graft surgery

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ABSTRACT

Aim: Neurocognitive dysfunction is a complication of cardiopulmonary bypass (CPB). Neuron-specific enolase (NSE) and S100ß protein are markers of cerebral injury. With its beneficial rheological and anti-inflammatory properties, pentoxyphiline (PTX) is an interesting agent in cardiac surgery patients. The study was designed to evaluate the influence of prophylactic use of PTX on cognitive function and S100ß and NSE in on-pump coronary artery bypass grafting (CABG) patients.

Method: In this prospective study, 40 patients undergoing on-pump CABG and received either PTX (bolus of 5 mg kg-1) after induction of anesthesia or saline are included. Neurological examination and neuropsychologic tests, including the mini-mental state examination test (MMSET) and Benton visual retention test (BVRT), were obtained preoperatively and on the seventh postoperative day. Blood samples for analysis of S100ß and NSE were collected before anesthesia, at the end of CPB, at the 3rd hour and 24th hour postoperatively.

Results: Demographic and perioperative data were similar for the two groups. Mean cross-clamping times were 67.86±22.22 and 66.32±27.84 min, respectively. In both groups, S100ß and NSE increased significantly ($p<0.01$) at the end of the CPB and remained slightly increased at T2 (at the CPB exit), and T3 (at the 3rd hour after surgery) than preoperative levels ($p>0.05$). MMSET and BVRT performances of the two groups were similar and did not change compared to preoperative scores.

Conclusions: Coronary artery bypass surgery caused a significant increase in NSE and S100ß serum levels but with no deterioration in neuropsychological outcome assessed in the first postoperative week. Although it was reported that PTX could be a promising agent to prevent post-CPB organ dysfunction in elderly cardiac surgery patients, prophylactic use of PTX appeared to offer no advantage for cerebral protection in the age group involved in this study.

ARTICLE INFO

Article history:
Received 12 June 2023
Revised 13 August 2023
Accepted 16 August 2023

Keywords:
Coronary artery bypass surgery
NSE
S100ß protein
Mini-mental state examination test
Benton visual retention test
Pentoxyphiline

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ISSN: 2980-292X / DOI: https://doi.org/10.20528/cjpm.2023.02.002

1. Introduction

Despite advances in surgical and anesthetic methods, temporary or permanent neurological and neuropsychological dysfunction continues as a problem after cardiac surgery with cardiopulmonary bypass (CPB) [1,2]. While the rate of neurocognitive dysfunction reaches 80% at discharge from the hospital after cardiac surgery, it is stated that this rate decreases to 10-35% in tests performed after six weeks and 10-15% after one year [3].

It has been reported that cognitive dysfunction after CPB may be due to many causes, such as cerebral microembolism, diffuse cerebral hypoperfusion, cerebral and systemic inflammation, cerebral hyperemia, cerebral edema, deterioration in the blood-brain barrier, pharmacological effects, and genetic characteristics [3,4].

Depending on CPB, the coagulation system, fibrinolytic system, complement system, leukocytes, endothelial cells and platelets are activated. Activation of the hemostatic system, developing systemic inflammatory response (SIRS), and ischemia-reperfusion injury are the most important factors in the pathogenesis of "post-perfusion organ damage" [3,5]. The organs most affected are the lungs, heart, brain, kidneys, and liver [6]. In addition to pharmacological agents such as corticosteroids, proteinase inhibitors such as aprotinin, and inflammatory cascade inhibitors to reduce CPB-related organ damage, methods such as "off-pump" surgery, leukocyte filter and ultrafiltration are tried [3,5].

Pentoxyphiline (PTX; 3,7-dimethyl -1-5-oxohexyl-xanthine) is a xanthine derivative that inhibits the 5' nucleotidase enzyme, reduces the loss of ATP in the tissue, and prevents cell damage by minimizing tissue energy consumption during the ischemia period [6]. It has been shown that PTX is protective in CPB-related peripheral organ damage due to its inhibition of the production of proinflammatory cytokines and its anti-inflammatory properties [6–8]. Its brain-protecting effect has been demonstrated in dogs [9]. No human studies have shown that PTX use is protective in preventing neurological damage in surgeries performed with CPB.

S100ß protein and Neuron-Specific Enolase (NSE) are specific proteins that indicate brain damage [2,10–13]. In cardiac surgery, especially in the early postoperative period, a significant correlation was found between the increase in NSE level and the impairment in cognitive functions [2,14].

2. Materials and Methods

The study was conducted on patients who will undergo isolated coronary artery bypass graft (CABG) surgery with CPB in the Cardiovascular Surgery Operating Room at Istanbul University Cerrahpaşa Medical Faculty. Ethics committee approval, dated 16.09.2008 and numbered 27578, was obtained from Istanbul University Cerrahpaşa Medical Faculty for the study. This prospective, randomized, controlled and double-blind study included 40 patients. The patients were aged between 50-79 years old. The patients were at least primary school graduates. Written informed consent was obtained from the patients. Our exclusion criteria was: patients with psychiatric and cerebrovascular disease, carotid stenosis, EF <40% or emergency surgery, kidney failure, concomitant valve disease, or recent steroid or nonsteroidal anti-inflammatory drug use. The patients were given no steroid or nonsteroidal anti-inflammatory drug during the study.

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2.1. Randomization and blinding

The patients were randomly divided into Group P (n=20) and Group C (n=20). Group P patients were given pentoxyphiline, and Group C patients formed the control group. The psychologist and biochemist were blind to the study.

2.2. General anesthesia

Standard cardiac anesthesia monitoring (ECG, SpO_2, invasive arterial pressure, central venous pressure, $ETCO_2$, temperature, urine output, ACT) was applied to all patients taken to the operating room.

The anesthetic management was provided with premedication midazolam, anesthesia induction with 0.15 mg/kg midazolam, 5 mcg/kg fentanyl, 0.1 mg/kg morphine, and neuromuscular blockade with 0.1 mg/kg vecuronium, as in our standard clinical practices. Sevoflurane in an O_2-air mixture, midazolam, fentanyl and morphine were used when necessary for the maintenance of anesthesia. The operations were performed with the same surgical group and the same methods. After induction of anesthesia, 5 mg/kg pentoxyphiline in 500 mL 0.9% NaCl was administrated to the patients assigned to the pentoxyphiline group, while only 500 mL 0.9% NaCl was infused to the control group.

2.3. Measurements

A total of 40 patients, 30 male and 10 female, aged between 50 and 79, from Istanbul University Cerrahpaşa

Medical Faculty Cardiovascular Surgery operating room, were included in the study. Mean arterial pressure (MAP) and heart rate (HR) were recorded before and after pentoxyphiline infusion. The use of vasopressors and inotropic agents during and after CPB, central venous pressure (CVP) at the beginning and exit of the operation, operation time, CPB duration, aortic cross-clamp time, extubation time, and exit time from the intensive care unit were recorded.

Venous blood samples for S100ß protein and NSE blood level measurements were taken;

1. Before induction of anesthesia, (T1)
2. at the CPB exit, (T2)
3. at the 3rd hour after surgery, (T3)
4. at the 24th hour after surgery. (T4)

After the samples were taken, they were centrifuged, and the serums were separated into two. The samples were stored at -80 °C until the day of the study.

S100ß protein concentrations were measured by Enzyme-Linked Immunoassay (ELISA) technique using microplate wells coated with polyclonal S100ß antibodies (Human S100ß Elisa Biovendor Research and Diagnostic Products Cat. No.:RD192090100R). The detection limit of the method is 5 pg/ml. Samples with S100ß levels above 2000 pg/ml were diluted and studied again. It was recalculated considering the dilution coefficients. Intraassay and interassay coefficient of variation (CV) was 4.45% and 4.3%, respectively.

NSE levels were determined by the ELISA method using microplate wells coated with monoclonal antibodies working with the “sandwich” principle (DRG diagnostic EIA-4610 Germany). Its sensitivity is 4 ng/ml. Intraassay and interassay CV were 4.5% and 4.8%, respectively.

For cognitive function measurement, one day before and seven days after the operation, SMMT and Benton tests, which are standardized for Turkish people, were applied [15,16].

2.4. Sample size estimation

In order to test the statistical significance of a difference of at least 20% between the groups in terms of the mean SMMT results at 95% power and 5% error level, it was observed that at least 15 subjects should be included in each group.

The sample size of the study was calculated with IBM SPSS Sample Power, since the universe was not known. A literature review was performed in accordance with the research hypotheses. With the reference to the study of Herrmann et al. [14], it was observed that at least 15 individuals should be included in each group to test the statistical significance of a difference of at least 20% between the groups in terms of mean MMST results at 95% power and 5% error level. In the study, it was decided to include 20 patients in each group to eliminate the possible dropouts.

2.5. Statistical analysis

Data are given as mean ± standard deviation. For statistical analysis, the chi-square test was used to compare demographic data, an unpaired t-test was used to compare data between groups, and "Repeated Measures ANOVA" tests were used for in-group comparison. $P<0.05$ was considered statistically significant.

3. Results

The control group (Group C) consisted of 20 patients, and the PTX group (Group P) consisted of 20 patients. Flow diagram of our study is presented in Fig. 1. The number of male patients was observed to be higher in both groups. There was no significant difference between the groups regarding age, weight, height, gender distribution and educational status ($p>0.05$). (Table 1) When the surgical parameters of the groups were compared, no significant difference was observed (Table 2).

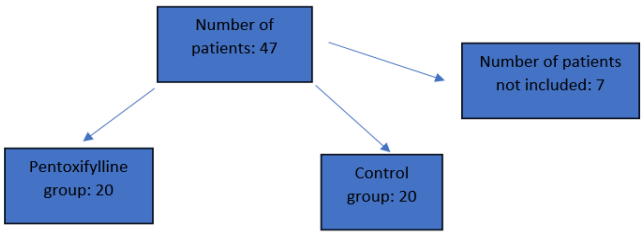

Fig. 1. The flow chart of the study.

Table 1. Patient characteristics in the groups.

		Control Group (n=20)	Pentoxyphiline Group (n=20)	*p-value*
Age (years)		61.48 ± 8.14	60.31 ± 7.69	0.619
Weight (kg)		77.08 ± 10.97	77.90 ± 14.80	0.827
Height (cm)		166.68 ± 9.33	167.18 ± 7.48	0.841
Male/Female		12/8	18/2	0.078
Educational Status	Primary School	12	7	0.563
	Middle School	5	3	
	High School	2	6	
	University	1	4	
Euroscore		4.24 ±1.76	4.5 ± 1.94	0.635

The data are presented as mean ± standard deviation or number.

Table 2. Surgical characteristics of the groups.

	Control Group (n=20)	Pentoxyphiline Group (n=20)
Surgery Time (min)	237.80±43.66	261.13±51.96
CPB Time (min)	93.92±33.01	99.18±38.73
Aortic Cross-Clamp Time (min)	66.32±27.84	67.86±22.22
Extubation Time (hour)	14.00±5.73	12.09±5.73
Discharge from ICU (hour)	62.08±37.22	46.77±9.03

The data are presented as mean ± standard deviation, CPB: Cardio-pulmonary bypass.

When the hemodynamic parameters of the cases were examined in the perioperative period, no significant difference was found between the CVP values measured at the beginning and end of the operation (p>0.05). There was no significant difference between the groups in the use of inotropic agents and vasopressors in the perioperative period according to the number of cases (p>0.05) (Table 3).

Although a decrease was observed in the HR and MAP values measured after 0.9% NaCl in Group C, they were not statistically significant compared with the initial values. A similar decrease was observed in HR and MAP values after infusion of 0.9% NaCl containing 5 mg/kg pentoxyphiline in Group P, but it was not statistically significant (p>0.05). No significant difference was found in the comparison between the groups.

Table 3. Peroperative hemodynamic properties.

		Control Group (n=20)	Pentoxyphiline Group (n=20)
Use of inotropes (n)		7	8
Vasopressor use (n)		8	13
CVP (mmHg)	Preoperative	7.56 ± 2.84	7.68 ± 2.83
	Postoperative	8.00 ± 3.12	7.90 ± 2.81
MAP (mmHg)	Before NS/PTX	83.08 ± 15.08	83.95 ± 18.02
	After NS/PTX	73.48 ± 14.20	77.00 ± 18.30
HR (beat/min)	Before NS/PTX	70.84 ± 13.64	66.40 ± 9.46
	After NS/PTX	65.20 ± 13.75	64.00 ± 13.75

The data are presented as mean ± standard deviation or number.
CVP: Central venous pressure; MAP: Mean arterial pressure; HR: Heart rate;
PTX: Pentoxyphiline; NS: %0.9 NaCl (Normal Saline).

S100ß protein measured at the CPB exit was significantly higher than the S100ß protein levels measured before induction, at the 3rd hour after surgery and at the 24th hour after surgery (p<0.001) (Table 4). NSE values measured at CPB exit were significantly higher than the pre-induction period (p<0.05). In the comparison between groups, S100ß and NSE values did not differ statistically in any period.

Table 4. S100ß (pg mL-1) and NSE (ng mL-1) values of the groups.

		Control Group (n=20)	Pentoxyphiline Group (n=20)
S100ß	Pre-induction	150.45±64.05	95.28±133.04
	CPB exit	840.90±578.05**	743.10±503.47**
	3rd hour after surgery	249.95±131.19	219.52±108.89
	24th hour after surgery	247.00±169.55	195.14±138.01
NSE	Pre-induction	22.81±11.61	23.04±11.32
	CPB exit	34.85±17.27*	31.70±13.04*
	3rd hour after surgery	26.28±14.61	30.11±11.74
	24th hour after surgery	26.23±13.49	26.53±13.00

The data are presented as mean ± standard deviation.
**p<0.001 Comparison with the intragroup CPB exit period.
*p<0.05 Comparison with the intragroup CPB exit period.

Standardized mini mental test (SMMT) and Benton test were used to evaluate the cognitive functions of the cases. There was no significant difference between the groups in the SMMT and Benton tests performed before and after the surgery (p>0.05). In the intragroup evaluation, although a decrease was observed in the Benton test scores after the operation in Group P, it was not statistically significant (p>0.05) (Table 5).

Table 5. Cognitive function test results of the groups.

		Control Group (n=20)	Pentoxyphiline Group (n=20)
Standardized Mini Mental Test	Before surgery	25.63 ± 3.40	24.76 ± 3.61
	After surgery	25.42 ± 3.45	24.41 ± 3.24
Benton Test	Before surgery	9.26 ± 3.08	9.52 ± 2.18
	After surgery	9.84 ± 3.51	8.29 ± 3.25

The data are presented as mean ± standard deviation.

4. Discussion

Our study found that S100ß and NSE levels peaked in both groups at CPB exit in patients who had undergone CPB operation and increased significantly compared to preoperative values. We found an approximate 5-6 fold increase in preoperative S100ß in the control group, while in the pentoxyphiline group, a 6-7 fold increase. NSE increased significantly from 22.81±11.61 ng/mL preoperatively to 34.85±17.27 ng/mL at CPB exit in the control group and from 23.04±11.32 ng/mL to 31.70 ± 13.04 ng/mL in the pentoxyphiline group. We could not find a significant difference between the postoperative 3rd and 24th hour values of NSE and S100ß and the preoperative values in both groups.

In a study on the prophylactic use of pentoxyphiline to preserve postoperative organ functions in elderly patients undergoing cardiac surgery, liver, kidney, and endothelial damage was found to be less in patients [6].

In another study investigating the effect of PTX on leukocytes and inflammation markers (TNFα, IL6, leukocyte count) in cardiac surgery and extracorporeal circulation, it was reported that PTX partially suppressed inflammation [17].

For the first time, Aberg et al. reported that increased levels of protein S100β were associated with cerebral damage [18]. Westaby et al. emphasized that protein S100β level increases as the duration of cardiopulmonary bypass increases, and Taggart et al. emphasized the relationship between neurocognitive tests and protein S100β [19,20]. Jönsson et al. reported that neurocognitive tests were negatively affected as protein S100β increased [21].

Neuron-specific enolase (NSE) is another marker to determine neurological survival in cardiac surgery. It has increased in central nervous system damage and head traumas [10].

In a study examining the variation of protein S100β and NSE over time during CPB and their relationship with each other, it was observed that both of them increased rapidly and proportionally, especially during the warm-up period (10-fold in protein S100β, 3-fold in NSE), while a 50% decrease was observed in NSE and a 79% decrease in protein S100β on the first postoperative day, and decreased to pre-bypass levels on the second postoperative day [11].

In the studies of Farsak et al., neurological survival in cardiac surgery was evaluated by a mini-mental test, and its relationship with protein S100β was examined. It was found that protein S100β peaked when the skin was closed after CPB and increased in direct proportion to the duration of CPB; a weak correlation was found in age, and there is a significant relationship between protein S100β elevation and neurocognitive tests. Protein S100β decreased to its normal level after 24 hours in half of the patients and 48 hours in the others [22].

In our study, these markers decreased significantly (60-70%) from the 3rd hour to the 24th hour after surgery, and we could not find a significant difference between them when compared with the preoperative values.

Wimmer-Greinecker stated they could not find a relationship between postoperative neuropsychological evaluation and S100ß and NSE in CPB operations [23].

In the study of Heinze et al., it was stated that a single dose of 5 mg/kg PTX given before the operation to patients scheduled for CPB could alleviate the inflammatory response. It was also reported that there was a shortening in ventilation and intensive care unit length of stay depending on this dose [24].

In the study of Das et al., in which 400 mg of pentoxyphiline was administered twice a day orally to patients scheduled for CPB operation from the day of hospitalization, a neurocognitive assessment was evaluated one day after hospitalization and on the seventh postoperative day. Although the perioperative use of PTX did not make a neurocognitive difference, it was stated that it reduced the early postoperative neurocognitive decline after CPB due to the decrease seen in the control group [25].

In our study, we could not find a significant difference between the results of the SMMT and Benton test performed on the seventh day after the operation and the preoperative period. Also, no difference was found between the groups. The absence of major comorbidities in our patients, the inclusion of only CPB patients in the groups except for valve surgeries reported in some studies, and the younger age of our patients compared to the average age reported in the literature affect our results. No significant neurological damage developed in any of our patients. There are also publications reporting a weak relationship between neurocognitive dysfunction

and these biochemical markers, apart from apparent neurological damage. There are also studies using various complicated neuropsychological and neuropsychiatric tests. In our study, we applied the SMMT and Benton tests because they can be done quickly in daily practice and are easy to apply. The specificity and sensitivity of the tests we used should also be considered since there was no difference between our groups regarding neurocognitive functions.

The limitations of our study are the insufficient number of patients in evaluating the effect of PTX, the younger average age compared to other studies, and the necessity of studies involving more elderly patients to evaluate the long-term effects of pentoxifylline use on cognitive functions.

In conclusion, our study found that NSE and S100ß protein significantly increased in CPB exit, consistent with the literature. Since there was no difference between the groups in neurocognitive functions, it can be said that this is not an indicator of neuron damage in the early period. We found that pentoxyphiline, which is effective in organ preservation, but we could not find any information on cerebral protection except for an experimental study in the literature, did not make a significant difference between the groups regarding early cerebral damage and neurocognitive dysfunction.

Author Contributions

All of the authors made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; they have been involved in drafting the manuscript or revising it critically for important intellectual content; have given final approval of the version to be published.

Acknowledgements

None declared.

Funding

The authors received no financial support for the research, authorship, and/or publication of this manuscript.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this manuscript.

Data Availability

The datasets created and/or analyzed during the current study are not publicly available, but are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of İstanbul University-Cerrahpaşa Faculty of Medicine. Written informed consent was obtained from the participants. All methods were performed in accordance with relevant guidelines and regulations.

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