

Perioperative pentoxifylline therapy attenuates early postoperative neuro-cognitive decline in patients undergoing coronary artery bypass grafting surgery using cardiopulmonary bypass

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Abstract

Background: Postoperative cognitive decline (POCD) after coronary artery bypass grafting (CABG) is a common problem. Studies show that pentoxifylline administration reduces inflammation induced by cardiopulmonary bypass and brain injury after ischaemia. Hence the perioperative use of pentoxifylline in attenuating POCD was evaluated in the study. **Materials and Methods:** Eighty patients were divided randomly into two groups from 106 patients scheduled for CABG surgery. The study group was administered pentoxifylline 400 mg twice daily orally from day of admission to 7th day after surgery, whereas the control group patients received placebo. Neurocognitive assessment was assessed by an independent clinical psychologist one day after admission to hospital and again on 7th postoperative day. The data was analyzed and a $P < 0.05$ was considered significant results. **Results:** Pentoxifylline-treated group showed no statistically significant difference in animal naming test scores (10.3 ± 2.2 versus 9.4 ± 2.5 , $P = 0.07$), digit symbol substitution test (26.1 ± 7.47 vs 22.2 ± 6.07 , $P = 0.09$) and 8 subtests of Post Graduate Institute-memory scale. The control group had significant POCD as detected by animal naming test (10.5 ± 3.7 versus 8.6 ± 3.9 , $P = 0.008$), digit symbol substitution test (20.2 ± 8.2 versus 14.7 ± 8.9 , $P = 0.008$) and five subtests of memory scale ($P = 0.01, 0.04, 0.003, 0.005$ and 0.02). The incidence of POCD was 50% in placebo-treated group compared to 22.5% in pentoxifylline group. **Conclusions:** The perioperative use of pentoxifylline attenuates the early postoperative neurocognitive decline after CABG using cardiopulmonary bypass.

Key words: Cardiopulmonary bypass, coronary artery bypass grafting, neurocognitive assessment tests, pentoxifylline, postoperative neurocognitive decline

INTRODUCTION

The number of patients undergoing coronary artery bypass grafting (CABG) for the management of coronary

artery disease is increasing every year. Postoperative neurocognitive decline (POCD) and stroke are associated with CABG using cardiopulmonary bypass (CPB).^[1,2] Zamvar *et al* estimated that around 63% of patients undergoing CABG on CPB and 27% of patients undergoing CABG off pump show signs of cognitive decline at the time of discharge.^[3] Cerebral injury after CABG increases the length of hospital stay, cost of medical expenditure, morbidity and mortality of the patients.^[1,4]

Various attempts in attenuating the POCD have been tried by improvements in biomaterials, pharmacological,

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anaesthetic and surgical managements.^[5] The complete attenuation of POCD is not achieved so far. Therefore some new effective intervention is necessary to overcome POCD. Recently few studies show that pentoxifylline (PTX) administration reduces inflammation generated from CPB.^[6] Pentoxifylline with blood viscosity lowering and immunomodulatory property improves microcirculation and oxygenation of brain.^[7] Few animal studies have shown that PTX protects brain by reducing inflammation and hypoxic – ischaemic injury.^[8,9]

To the authors' best knowledge, there are no studies on PTX in preserving POCD after CABG with CPB in the English language. We hypothesised that perioperative therapy of PTX will attenuate the POCD in patients undergoing CABG. Hence the objectives of the study were to assess the impact of perioperative PTX therapy on POCD, by using neurocognitive assessment (NCA) tests in patients undergoing CABG surgery with CPB.

MATERIALS AND METHODS

Study Design

The prospective randomised clinical trial was conducted between October 2009 to September 2012 in the Cardiothoracic Centre of All India Institute of Medical Sciences; a tertiary care hospital at New Delhi in India. It received ethical approval from the institutional ethics committee. Written informed consent was obtained from all patients to participate in the study and they were free to withdraw at any time.

Patient selection

One-hundred and six patients age between 40 and 65 years scheduled for elective on pump CABG were considered for the study. Patients with neurological, psychiatric, carotid artery disease, renal disease, liver disease, emergency surgery, recent myocardial infarction, repeat surgery, coagulation disorder, use of anti-inflammatory drug like steroid, patients with a history of allergy to PTX and uncontrolled diabetes mellitus were excluded from the study. Twenty-six patients were excluded for various reasons, 80 patients were allocated into two groups by using a computer-generated randomised list according to CONSORT guidelines [Figure 1]. Groups PTX ($n = 40$) received PTX 400 mg twice daily orally from the day of admission to 7th day after surgery. The control group was administered matching placebo prepared by a pharmaceutical company (Group placebo). The PTX and placebo tablet was given to the patients and checked by nurses who were unaware to the study.

Statistical analysis and sample size calculation

There is lack of published study on effect of PTX on POCD in cardiac surgical patient. The incidence of POCD

after CABG using CPB is 63% in a study by Zamvar *et al.*^[3] We assumed 50% reduction of POCD after PTX treatment and the probable incidence would be 31.5%. Taking α of 0.05 and 80% power, for a two-tailed study the estimated minimum sample size for each group would be 38. In order to achieve better power of study we increased the sample size to 40 in each group.

Data analysis was performed using SPSS 15.0 (Chicago, IL) software package. Data were recorded and tabulated with excel software (Microsoft Corp, Redmond, WA). Data are presented as mean and standard deviation (SD), percentage and frequency unless otherwise indicated. Demographic details, illness variables, anaesthesia and surgical details were recorded using a semi-structured pro-forma. All the quantitative baseline variables were compared using paired t-test or unpaired t-test between the two groups, whereas all the categorised variables was compared using χ^2 or Fisher's exact test while change within groups was seen by paired t test or Wilcoxon Signed ranks or McNemar test as applicable. Rest of the biostatistical tools was used as per the requirement. $P < 0.05$ were considered significant results.

Anaesthesia technique

All patients were kept fasting 6-8 hours for solid food and 3-4 hours for liquid before surgery. Patients were pre-medicated with oral diazepam 5 mg night before and on morning of surgery. In addition all patients received injection morphine 0.1 mg/kg and promethazine 0.5 mg/kg intramuscularly, 45 minutes before shifting to operation room. Anaesthesia technique was standardised for all patients. Induction of anaesthesia consisted of fentanyl 2 μ g/kg, thiopentone sodium 4 mg/kg and rocuronium 0.9 mg/kg. Maintenance of anaesthesia included intermittent doses of midazolam, fentanyl, pancuronium and oxygen in air and isoflurane. Monitoring included continuous 5 lead ECG, invasive arterial blood pressure, central venous pressure, pulmonary capillary wedge pressure (PCWP), transoesophageal echocardiography, end tidal carbon dioxide, pulse oximetry (SpO_2), near infrared spectrometry (NIRS), core temperature, hourly urine output, intermittent arterial blood gases, electrolytes and blood glucose. Haemodynamic parameters and cerebral oximetry were maintained within normal range in both the groups. Any patient from either of the two groups, showing persistence hypotension (systolic BP < 90 mmHg), dysrhythmias (ventricular tachycardia, fibrillation and fast rate atrial fibrillation) and low oxygen saturation ($PaO_2 < 50$ mmHg and $SpO_2 < 90\%$) in -CPB period were decided to be excluded from the study.

Surgical technique and cardiopulmonary bypass

Median sternotomy and pericardiotomy was performed to expose the heart. Saphenous vein and left internal

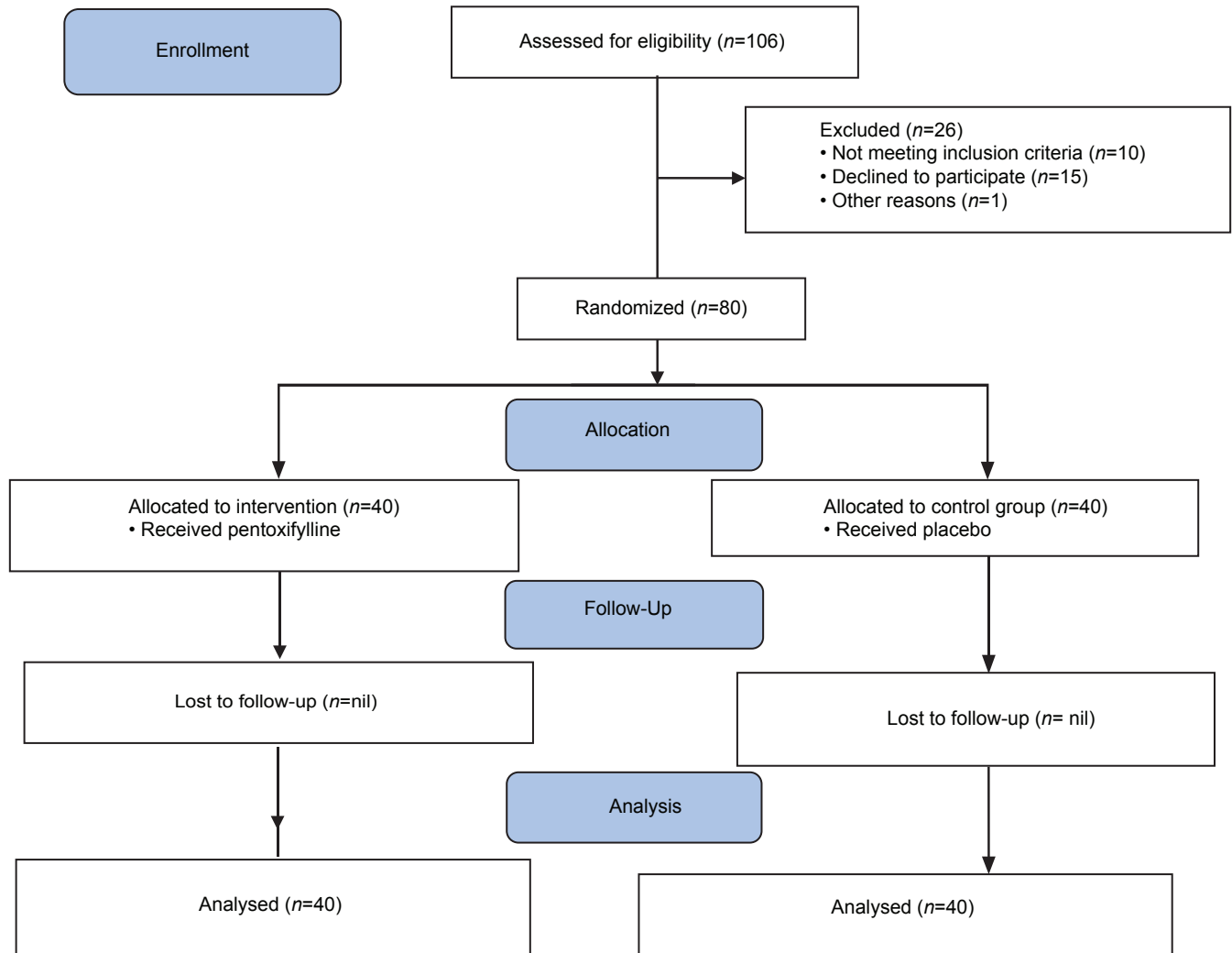


Figure 1: CONSORT Flow diagram for designing the study

mammary artery grafts were harvested. Systemic heparinisation was achieved with 400 IU/kg dose of heparin and ACT > 480 seconds. Cardiopulmonary bypass was established with ascending aorta and two stage right atrial venous cannulation. The bypass circuit, hard-shell reservoir and membrane oxygenator were primed with 1.5 liters of ringer's solution, 0.5 mg/kg of mannitol and 5000 IU of heparin, non-pulsatile flow of 2.2 to 2.4L/min/m² with hypothermia up to 32°C. The mean perfusion pressure was maintained between 60 and 80 mmHg on pump. Cardiac asystole was achieved with multiple dose cold St. Thomas cardioplegia solution after application of aortic cross clamp. Haematocrit was maintained around 24% during CPB. Patients were rewarmed to 36-37°C and heparin was neutralised with protamine sulfate in the ratio of 1: 1.5. All operations were performed by the same surgical team. Duration of CPB, number of vessels grafted, any perioperative use of blood, blood products, inotropes and use of IABP were noted. The decision for extubation and discharge from the intensive care unit was made according to the preset criteria.

Neurocognitive assessment procedure

All patients underwent neurocognitive testing with a battery of evaluations preoperatively at admission to hospital (baseline) and post operatively on 7th day. All evaluations were carried out by a trained and dedicated psychologist who was blinded to intervention and serological testing. The standardised battery induced three tests.

Post Graduate Institute memory scale (PGI-MS): The scale is part of the PGI battery of brain dysfunction developed by Pershad and Verma (1990).^[10] The battery is administered in Hindi, the first language of most patients, and has been developed and validated for use in the Hindi speaking population. It includes 10 subtests; of which all were used. These included remote and recent memory, forward and backward digit spans, delayed recall of a word list, immediate recall of sentences, visual recognition, visual retention, retention of similar word pairs and retention of dissimilar pairs. The procedure involved asking questions asked to patients as per

subtest and the score assigned was the number of correct answers.

Digit symbol tests

The digit symbol substitution test (Wechsler, 1981) is a test of visuomotor coordination, motor persistence, sustained attention and response speed.^[11] Rapid information processing is required in order to substitute the symbols accurately and quickly. The test consists of a sheet in which numbers 1-9 were randomly arranged in 4 rooms of 25 squares each. The subject substitutes each number with a symbol using a number-symbol key given on the top of the page.

Procedure

Test sheet is placed in front of the subject. The principle of substituting symbols for digits is explained. Practice is given for the first ten squares after which the test commences for a period of 90 seconds. The score assigned was the number of correct substitution.

Animal naming test

It consists of recalling maximum number of names of animals within one minute. The test assesses the fluency power and early cognitive impairment. Instructions followed are those of Rosen (1980).^[12]

Procedure

The subject is asked to generate the names of as many animals as possible in one minute. The subject is asked to exclude the names of fish, birds and snakes. The score assigned was the total number of names generated.

Postoperative neurocognitive decline

Patients were considered to have POCD if they showed a deterioration of 1 standard deviation (SD) or more in two or more tests in the postoperative score compared to preoperative score.^[3]

Other parameters

Any major cardiovascular, pulmonary, renal and neurological complications were recorded and those patients were excluded. Patients with re-exploration for bleeding were also excluded from the study. Time of discharge from ICU and hospital were recorded. Any serious adverse effects because of pentoxifylline administration was also noted and recorded.

RESULTS

A total of 80 patients were enrolled for the study, 40 patients in PTX group and 40 patients in placebo group [Figure 1]. All 80 patients cooperated to complete the study. The mean age of the control group (58.1 ± 6.7) was slightly higher than the study group (56.4 ± 7.7) and there were fewer patients in the from the urban area in the study group (73%) as compared to control (84%); however, the

difference was not statistically significant. There were a greater proportion of males in both the groups, as can be seen in [Table 1]. In the PTX group the minimum education was class IX. The difference between the two groups in terms of education was marginal ($P = 0.05$). Most patients belonged to the middle socio-economic status and were married as shown in [Table 1]. Both the groups were found to be comparable in terms of number of diabetics, CPB time, number of grafts used during CABG, number of packed red blood cells used during and after CPB, hospital discharge time, IABP support and requirement of high inotropes [Table 2]. The extubation time (7.25 ± 1.12 h vs 8.5 ± 1.68 h, $P = 0.001$) and ICU stay (28.2 ± 4.9 h vs 32.4 ± 7.0 h, $P = 0.01$) were increased in placebo treated group. The nausea, vomiting and abdominal distension was similar (15% vs 12.5%, $P = 0.55$) [Table 2].

Cognitive function

Results are reported according to the test used.

Animal naming test (ANT)-The animal naming test noted no statistically significant difference in pre and post-operative period in the PTX-treated group ($P < 0.07$). However, patients of placebo group showed significant difference in ANT, ($P < 0.008$) [Table 3].

Table 1: Demographic data

Variables	Group PTX (n=40)	Group Placebo (n=40)	P
Age, mean (SD)	56.4±7.7	58.1±6.7	0.36
Weight, mean (SD)	69.6±10.3	64.6±8.1	0.04*
Marital status			
Married	39 (96.7)	40 (100)	0.46
Single	1 (3.3)	0 (0)	
Male	36 (86.7)	37 (90)	0.54
Female	4 (13.3)	3 (10)	
Education			
5 th and below	5 (12.5)	7 (17.5)	0.15
6 th - 8 th	6 (15)	5 (12.5)	
9 th -12 th	14 (35)	12 (30)	
Graduate	13 (32.5)	11 (27.5)	
Professional	2 (5)	5 (12.5)	
Socioeconomic status			
Lower middle	5 (12.5)	5 (12.5)	0.21
Middle	28 (70)	30 (75)	
Upper middle	7 (17.5)	5 (12.5)	
Domicile			
Urban	30 (75)	28 (70)	0.26
Rural	10 (25)	12 (30)	

Continuous variables are presented as mean±SD; discrete variables are presented as number (%), SD: Standard deviation, PTX: Pentoxifylline

The digit symbol substitution test detected statistically significant difference in pre and post-operative period in placebo group [Table 3]. However, the decline in the values was less and cognitive functions were more preserved in intervention or PTX-treated group.

PGIMS- The preoperative base line 10 subtests of PGIMS of both groups showed no statistical significance on comparison [Table 4]. In the placebo group a significant difference was noted pre and post-operatively with increase in memory deficits in remote memory ($P < 0.01$), recent memory ($P < 0.04$), mental balance ($P < 0.002$), attention and concentration ($P < 0.005$) and visual retention ($P < 0.02$) [Table 5]. In contrast POCD was less in PTX-treated patients. Only two subtests were noted to have significant decline in the study group [Table 5].

The deterioration in cognitive score from admission to 7th postoperative day was detected in nine (22.5%) patients in the PTX group and 20 (50%) patients in the placebo group when 1SD or more was defined as POCD.

DISCUSSION

The present study was carried out to estimate the effect of PTX on neurocognitive dysfunction in patients undergoing CABG. All the 3 NCA tests detected a significant reduction of POCD in intervention or PTX group in comparison to placebo-treated group. The incidence of POCD is 22.5% in PTX group and 50% in placebo group on the 7th day postoperative period. The findings of our study replicate numerous well-documented studies that have demonstrated the presence of neurocognitive deficits after CABG.^[3,4] Decline in categorical verbal fluency by animal naming test was noted in the placebo group. The digit substitution test proved marked decline in motor persistence and response speed after surgery in placebo group. Poor performance by patients on remote memory, recent memory, mental balance, attention and concentration and visual retention functions was observed by PGIMS in the placebo group. However, in the PTX-treated group, the pre and post-operative difference was not significant on animal naming test, digit symbol substitution test and eight subtests of memory functions by PGIMS. The extubation time and ICU discharge time was higher in placebo group. This might be explained by reduction in pulmonary and tissue inflammation by PTX as proved by the study of Hering lake *et al* and Heinze *et al.*^[13,14] But the hospital discharge time from hospital was similar and not statistically significant.

Cognitive function is the intellectual, memory and skillful activities of a person generated from the activities of brain. Cognition is a set of abilities, skills or processes that are part of nearly every human action. They have more to do with the mechanisms of how we learn, remember, problem-solve, and pay attention rather than with any actual knowledge. Post-operative cognitive decline after CABG will create problem in daily life activities.^[2] The person's abilities to react or solving the problems will be slower and hence the quality of life will be poor than prior to CABG. Hence, the hospital stay might be more and cost would increase. The person after CABG with higher POCD will resume the preoperative level of cognitive activity later.^[2]

Brain injury from cardiac surgery has a range of manifestations, including stroke, encephalopathy, and/or neurocognitive dysfunction.^[1] A major area where the field has not made great progress in improving patient outcomes is brain injury following CPB. While stroke (type 1 deficit) is the most serious and carries an incidence of 1.5% to 5.2%, neurocognitive dysfunction (type 2 neurologic deficit) is arguably the most common complication following cardiac surgery, with a short-term incidence of 33-83% as well as a long-term incidence of 20-60%.^[15,16] The present study detected the incidence

Table 2: Perioperative variables

Parameters	Group PTX	Group Placebo	P
Diabetes mellitus	12 (30)	14 (35)	0.51
CPB time	48.6±11.1	47.38±14.5	0.66
Number of grafts	3.2±0.6	3.18±0.6	0.6
Number of PRBC used during and after CPB	2.3±0.9	2.2±0.7	0.5
Extubation time (hrs.)	7.25±1.12	8.5±1.68	0.001
ICU discharge (hours)	28.2±4.9	32.4±7.0	0.01
Hospital discharge (days)	7.9±0.7	8.0±0.8	0.82
IABP and high inotropes	7 (17.5)	7 (17.5)	1
Nausea, vomiting and abdominal distension	6 (15)	5 (12.5)	0.55

Continuous variables are presented as mean±SD; discrete variables are presented as number (%). Abbreviations: CPB: Cardiopulmonary bypass, ICU: Intensive care unit, IABP: Intra-aortic balloon pump, PTX: Pentoxifylline

Table 3: Pre and post-operative comparison of both groups on animal naming test and digit symbol substitution test (mean±SD)

Time point	Mean±SD			
	Group PTX		Group Placebo	
	ANT	DST	ANT	DST
Pre-op	10.3±2.2	(26.1±7.47)	10.5±3.7	(22.3±7.7)
Post-op	9.4±2.5	(22.2±6.07)	8.6±3.9	18.4±8.9
P	0.07	0.09	0.008	0.004

Abbreviations: ANT: Animal naming test, DST: Digit symbol tests, SD: Standard deviation, PTX: Pentoxifylline

of POCD of 50% on 7th postoperative period in placebo group.

Pentoxifylline is xanthine derivative.^[7] Pentoxifylline is almost completely absorbed after oral administration. The 400 mg PTX sustained release tablet showed an initial peak plasma concentration after 2 to 3 h. The active main metabolite 1-(5-hydroxyhexyl)-3,7-dimethyl-xanthine is measurable in twice the concentration of its parent substance.^[7] Biotransformation products are almost exclusively eliminated by the kidneys. It belongs to a group of vasoactive drugs which improve peripheral blood flow and thus enhance peripheral tissue oxygenation. The mechanism by which PTX achieves this effect has not been determined, but it is likely due to improvement of red blood cell flexibility, vasodilatation and platelet disaggregation.

The preservation of cognitive function in PTX-treated group could be because of the rheological benefits of PTX.^[7] PTX improves blood flow through cerebral blood vessels of the brain and improves red blood cell deformability, reduces blood viscosity and decreases the potential for platelet aggregation and thrombus formation in the moment of hypothermic non-pulsatile flow during CPB.^[8,9] The better cognitive function in the PTX group might be also because of reduction of inflammation; as proved by Cagli *et al* and Heringlake *et al.*^[6,14] The adverse effects of PTX treatment are nausea, vomiting, abdominal distension and hypotension and tachycardia induced by vasodilation.^[7] But we did not observe any major haemodynamic and gastro-intestinal events with 400 mg twice daily dose of PTX comparing the two groups.

Table 4: Comparison of preoperative PGI memory scores

PGI memory subtests	Group PTX	Group Placebo	P
Remote memory	5.69±0.549	5.5±0.86	0.426
Recent memory	4.96±0.196	4.9±0.24	0.664
Mental balance	7.23±1.751	6.6±02.15	0.352
Attention and concentration	8.31±1.087	8.2±1.57	0.616
Delayed recall	8.50±1.175	8.16±1.26	0.382
Immediate recall	9.69±1.738	9.4±1.63	0.471
Verbal retention (similar)	4.27±0.778	3.9±1.14	0.286
Verbal retention (dissimilar)	8.04±3.376	7.6±3.89	0.658
Visual retention	8.54±1.964	8.1±2.19	0.352
Recognition	6.61±1.888	6.8±1.82	0.398

PGI: Post graduate institute, PTX: Pentoxifylline

Study Limitations

The present study had not included elderly patients of age more than 65 year. Patients were only coronary artery disease with less co-existing diseases. The inflammatory markers like tumour necrosis factor (TNF) or interleukins were not measured to observe the anti-inflammatory property of PTX. The patients were small in number; a larger population will strengthen the finding. The neurocognitive functions were assessed only by three batteries of tests, which might not have examined all the neurocognitive functions. More number and different category of neurocognitive tests is required to give better verdict on the effect of PTX to reduce POCD.

In conclusion the present study suggests that pentoxifylline is useful in attenuating the early postoperative neurocognitive decline in patients undergoing coronary artery bypass grafting surgery using cardiopulmonary bypass.

Table 5: Pre and post-operative scores comparison of both groups (frequency) on subtest of PGI-MS (mean±SD)

Subtest	Group PTX		P	Group Placebo		P
	Pre	Post		Pre	Post	
Remote memory	5.7±0.55	5.3±0.74	0.03*	5.5±0.86	4.2±1.1	0.001*
Recent memory	4.9±0.19	4.7±0.62	0.05	4.9±0.24	3.8±0.40	0.004*
Mental balance	7.2±1.75	6.9±01.61	0.43	6.6±02.15	5.9±02.22	0.003*
Attention and concentration	8.3±1.08	7.8±1.27	0.019*	8.2±1.57	7.5±1.50	0.005*
Delayed recall	8.5±1.17	8.7±1.19	0.30	8.16±1.26	7.8±1.46	0.17
Immediate recall	9.7±1.74	9.0±2.19	0.10	9.4±1.63	9.1±2.04	0.35
Verbal retention (similar)	4.3±0.77	4.1±1.07	0.50	3.9±1.14	3.6±1.18	0.09
Verbal retention (dissimilar)	8.04±3.38	7.1±3.84	0.05	7.6±3.89	7.4±4.01	0.68
Visual retention	8.5±1.96	8.5±2.61	0.91	8.1±2.19	7.4±2.51	0.02*
Recognition	6.6±1.88	6.3±2.0	0.42	6.8±1.82	6.6±2.10	0.62

SD: Standard deviation, PTX: Pentoxifylline

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