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Comprehensive preoperative regime of selective gut decontamination in combination with probiotics, and smectite for reducing endotoxemia and cytokine activation during cardiopulmonary bypass

A pilot randomized, controlled trial

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Abstract

Background: Both selective digestive decontamination (SDD) and probiotics have been reported to reduce endotoxemia. However, the available results are conflicting and few studies have investigated the combined effect of SDD and probiotics. This study aimed to examine the effectiveness of a comprehensive preoperative regimen of SDD in combination with probiotics and smectite on perioperative endotoxemia and cytokine activation in patients who underwent elective cardiac surgery with cardiopulmonary bypass (CPB) in a pilot, prospective, randomized, controlled trial.

Methods: Patients who underwent elective Aortic Valve Replacement or Mitral Valve Replacement surgery from July 2010 to March 2015 were included. In total, 30 eligible patients were randomly assigned to receive either the comprehensive preoperative regimen (n = 15) (a combination of preoperative SDD, probiotics, and smectite) or the control group (n = 15) who did not receive this treatment. The levels of endotoxin, IL-6, and procalcitonin were measured at the time before anesthesia induction, immediately after cardiopulmonary bypass (CPB), 24 hours after CPB, and 48 hours after CPB. The primary outcomes were changes in endotoxin, IL-6, and procalcitonin concentrations after CPB.

Results: The mean levels of change in endotoxin levels after CPB in patients receiving the comprehensive preoperative regimen was marginally significantly lower than those in control group ($F = 4.0$, $P = .0552$) but was not significantly different for procalcitonin ($F = .14$, $P = .7134$). An interaction between group and time for IL-6 was identified ($F = 4.35$, $P = .0231$). The increase in IL-6 concentration immediately after CPB in the comprehensive preoperative group was significantly lower than that in the control group ($P = .0112$). The changes in IL-6 concentration at 24 hours and 48 hours after CPB were not significant between the comprehensive preoperative group and control group.

Conclusion: The present pilot, prospective, randomized, controlled study in patients undergoing cardiac surgery with CPB demonstrated that 3 days of a comprehensive preoperative regime of SDD in combination with probiotics and smectite may reduce the endotoxin and IL-6 levels after CPB compared with the control group.

Abbreviations: CPB = cardiopulmonary bypass, ICU = intensive care unit, SDD = selective digestive decontamination.

Keywords: cardiopulmonary bypass, cytokine activation, endotoxemia, probiotics, selective digestive decontamination, smectite

1. Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) in combination with surgical trauma itself, anesthesia, extracorporeal circulation, and ischemia-reperfusion initiates a systemic inflammatory response syndrome.[1–3] This inflammatory reaction may contribute to an increased risk of organ dysfunction, infection, prolonged critical care stay, and morbidity after cardiac surgery.[4–6] The effect of endotoxin on the inflammatory response syndrome has been well studied since the 1990s. During CPB, hypoperfusion of the gut increases gut permeability[7] and the endotoxin levels produced by intestinal flora, mainly by aerobic gram-negative bacteria.[8,9] Thus, maintenance of gastrointestinal mucosal barrier function along with reduced bacteria, bacterial components, and endotoxin in the blood of patients during CPB has a significant effect on prognosis.

Selective digestive decontamination (SDD) is an antimicrobial prophylactic strategy that aims to control potentially pathogenic aerobic microorganisms in the gastrointestinal tract. Use of

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probiotics as an alternative to antimicrobials to restrain gut colonization by pathogens through competition with potential pathogens has also been assessed in several studies. Previous studies found that SDD or probiotics had a reduction effect on endotoxemia,[10–12] but the results were conflicting.[13] Smectite is a commonly used antidiarrheal drug administrated as an intestinal intervention to inhibit bacterial translocation. To our knowledge, few studies have investigated the effectiveness of a combination of preoperative SDD, probiotics, and smectite on decreasing endotoxemia and cytokine activation.

The aim of the present pilot, prospective, randomized, controlled trial was to examine the effectiveness of a comprehensive preoperative regimen of SDD in combination with probiotics and smectite on perioperative endotoxemia and cytokine activation in patients undergoing elective cardiac surgery with CPB.

2. Methods

2.1. Study design and patients

In this single-center, randomized, controlled trial, 67 patients undergoing elective Aortic Valve Replacement or Mitral Valve Replacement surgery were enrolled from July, 2010 to March, 2015 at the Department of Cardiothoracic Surgery in the first affiliated hospital of Nanchang University, China. The protocol was approved by the medical ethics committee of the first affiliated hospital of Nanchang University. All patients provided written informed consent before enrollment.

Of the 67 patients, 21 declined to participate. Because cardiopulmonary bypass can trigger excessive immunological responses, leading to a severe systemic inflammatory response syndrome, resulting in organ dysfunction, patients with existing inflammatory diseases before surgery or those who were more likely to be complicated by multiple organ dysfunction after surgery were excluded. Therefore, we excluded patients who had endocrine diseases (n = 1), neurological diseases (n = 0), severe hypertension (n = 2), severe anemia (n = 1), liver dysfunction (n = 1), kidney dysfunction (n = 0), gastrointestinal ischemia (acute ulcerative gastrointestinal disease (n = 0), chronic ulcerative gastrointestinal disease (n = 1), Crohn's disease (n = 0), ulcerative colon inflammation (n = 1), necrotizing colitis (n = 0)), reflux esophagitis (n = 1), acute cholecystitis (n = 0), chronic cholecystitis (n = 1), obstructive jaundice (n = 1), severe pancreatitis (n = 1), diabetes (n = 1), and gastrointestinal cancer (n = 1). Patients with preoperative systemic infection symptoms (n = 1), infectious diarrhea (n = 0), coronary atherosclerotic heart disease (n = 1), acute or chronic myocardial infarction (n = 0), and left ventricular dysfunction (ejection fraction $<50\%$) (n = 1) were also excluded.

2.2. Interventions

In total, 30 patients were randomly assigned to receive either the comprehensive preoperative regimen (n = 15) (a combination of preoperative SDD, probiotics, and smectite) or the control group (n = 15) who did not receive this treatment. Randomization was performed by the hospital statistician using a computer-generated code for randomized allocation. Patients in the comprehensive preoperative regimen group received 0.2 g Levofloxacin twice daily, 2 capsules of probiotics containing bacterial strains of *Lactobacillus*, *Bifidobacterium*, and *Enterococcus*, twice daily at least 3 hours after receiving Levofloxacin, and 1 bag of smectite 3 times daily for 3 days before the surgery. The amount of each type of bacteria in 1 capsule of probiotics was 5×10^7 CFU/g. One day before surgery, the patients were required to eat light soft food such as porridge, noodles, or broth. Patients received an enema the night before surgery and were required to fast on the day of surgery. Patients in the control group were required to eat light soft food on the day before surgery. They received an enema the night before surgery and were required to fast on the day of surgery.

2.3. Outcomes

The primary outcomes were changes in endotoxin, IL-6, and procalcitonin concentrations after CPB. The secondary outcomes were duration of ventilator use in the intensive care unit (ICU), length of stay in the ICU, dosage of dopamine and adrenaline at 24 hours after surgery.

2.4. Sampling

Two milliliters arterial blood and 3 mL venous blood were drawn before anesthesia induction, immediately after CPB, 24 hours after CPB, and 48 hours after CPB. Arterial blood for endotoxin determination was collected in sterile non-pyrogenic heparinized tubes and serum was separated by centrifugation (3200 rpm/min for 6 minutes). Venous blood was prepared by centrifugation at 3000 rpm/min for 10 minutes at room temperature and the supernatant was stored at -20°C for IL-6 and procalcitonin measurement.

2.5. Endotoxin, IL-6, and procalcitonin assay

Plasma endotoxin concentration was measured using a commercially available Endotoxin Assay Kit based on the kinetic turbidimetric Limulus Amoebocyte Lysate assay (Zhanjiang Bokang Marine Biological Co, LTD., China) for qualitative detection of bacterial endotoxin following the manufacturer's protocol. Endotoxin concentration (EU/mL) was determined from a standard curve using pure endotoxin standards. The maximum sensitivity was 0.005 EU/mL.

IL-6 concentration was determined using radioimmunoassay kits (Sino-UK, Beijing, China) according to the protocols of the manufacturer. Briefly, 100 μL standard or samples were mixed with RIA buffer, 100 μL antibodies, and 100 μL ^{125}I-labeled IL-6 and incubated at 4°C for 24 hours. After mixing with 500 μL polyethylene glycol and incubating for 15 minutes at room temperature, the samples were centrifuged at 3500 rpm/min for 15 minutes. The supernatant was removed and a γ-counter was used to measure the counts per min of the precipitate. The IL-6 concentration was calculated according to a standard curve.

Serum procalcitonin level was measured using an enzyme-linked immunosorbent assay according to the manufacturer's instruction (RayBiotech, Inc. Norcross, Georgia and Diagnostic Biochem Canada Inc.). Briefly, the 96-well plates pre-coated with an antibody specific to human procalcitonin were loaded with 50 μL of standard and plasma samples. After incubation at 37°C for 30 minutes with the biotinylated tracer antibody, 50 μL horseradish peroxidase-avidin in the conjugate was added and absorbance was measured at 450 nm. The concentration of procalcitonin in each sample was quantified against the standard curve. Values were expressed as nanogram procalcitonin protein per mL plasma.

2.6. Data analysis

The sample size was calculated by the mean difference in endotoxin and IL-6 concentrations after treatment between groups, as reported in the study by Martinez-Pellus, with a α level of 0.05 and a β level of 0.8.[10] The design had an estimated power of 69% for detecting a difference in endotoxin and a power of 95% for IL-6 with a significance level of 0.05 (2-sided test). Categorical baseline data and recovery characteristics of participants in the comprehensive preoperative group and control group were reported as numbers and percentages. Continuous variables were summarized as means with standard deviations. Comparisons between groups were performed using the *t* test or Fisher's exact test. Repeated-measures analysis of variance (ANOVA) was used to compare the changes in endotoxin, IL-6, and procalcitonin levels after CPB between the comprehensive preoperative group and control group as well as the difference over 3 time points (T1: immediately after CPB, T2: 24 hour after CPB and T3: 48 hour after CPB). The probability of post hoc tests was corrected for multiple testing using the Bonferroni correction. A nominal significance level of 5% was used in the 2-sided tests. All analyses were performed using SAS 9.2 software (SAS Institute, Cary, NC).

Table 2

Endotocin, IL-6, and procalcitonin concentrations in the comprehensive preoperative group and the control group before anesthesia induction, immediately after CPB, 24 hours after CPB and 48 hours after CPB.

	Comprehensive preoperative (n = 15)	Control (n = 15)
Plasma endotoxin concentration (EU/mL)		
Before anesthesia induction	0.017 ± 0.008	0.025 ± 0.009
Immediately after CPB	0.075 ± 0.041	0.110 ± 0.039
24 hours after CPB	0.029 ± 0.013	0.038 ± 0.022
48 hours after CPB	0.021 ± 0.011	0.037 ± 0.016
Serum IL-6 concentration(pg/mL)		
Before anesthesia induction	20.73 ± 4.81	24.98 ± 5.93
Immediately after CPB	58.79 ± 7.24	72.39 ± 5.38
24 hours after CPB	39.02 ± 2.58	44.87 ± 5.99
48 hours after CPB	28.37 ± 5.44	35.30 ± 5.47
Serum procalcitonin concentration (ng/L)		
Before anesthesia induction	53.15 ± 5.10	50.15 ± 3.54
Immediately after CPB	87.98 ± 5.25	92.10 ± 2.61
24 hours after CPB	54.34 ± 6.61	54.15 ± 5.29
48 hours after CPB	50.34 ± 5.67	52.47 ± 8.17

CPB = cardiopulmonary bypass.

3. Results

3.1. Baseline characteristics of participants in the comprehensive preoperative group and control group

In total, 30 eligible patients were randomly assigned to either the comprehensive preoperative group (n = 15) or control group (n = 15). Table 1 shows the baseline characteristics of 2 groups. Patients receiving the comprehensive preoperative regimen did not differ from those in the control group with respect to age, sex, weight, and surgical procedure (including duration of cardiopulmonary bypass and aorta clamp time) (Table 1).

3.2. Effect of comprehensive preoperative treatment on changes in plasma endotoxin, procalcitonin, and IL-6 concentrations after CPB

The mean concentrations of endotoxin, IL-6, and procalcitonin before anesthesia induction, immediately after CPB, 24 hours after CPB, and 48 hours after CPB are presented in Table 2. Figures 1 to 3 show the changes in plasma endotoxin, procalcitonin, and IL-6 concentrations after CPB in the comprehensive preoperative group and control group. There was no significant interaction between treatment effects and time effects for endotoxin and procalcitonin ($F = 2.08$, $P = .1468$ for endotoxin and $F = 1.06$, $P = .3541$ for procalcitonin). The mean levels of change in endotoxin and procalcitonin after CPB in patients receiving the comprehensive preoperative regimen were not significantly lower than those in the control group ($F = 4.0$, $P = .0552$ for endotoxin and $F = .14$, $P = .7134$ for procalcitonin, Fig. 1 and Fig. 2). An interaction between group and time was identified for IL-6 ($F = 4.35$, $P = .0231$). Multiple comparison tests show that the increase in IL-6 concentration immediately after CPB in the comprehensive preoperative group was significantly lower than that in the control group ($P = .0112$, Fig. 3). The changes in IL-6 concentration at 24 hours and 48 hours after CPB were not significant between the comprehensive preoperative group and control group.

Table 1

Characteristics of the Participants at Baseline.

	Comprehensive preoperative (n = 15)	Control (n = 15)	*P* value
Age, mean ± SD, yr	45.6 ± 2.8	45.7 ± 4.2	.945
Sex			.690
male	5 (33.3)	4 (26.7)	
female	10 (66.7)	11 (73.3)	
Weight, Kg	57.1 ± 8.4	51.8 ± 8.4	.068
Cardiopulmonary bypass time, min	111.1 ± 9.5	110.0 ± 12.1	.968
Aortic cross-clamp time, min	48.1 ± 16.3	42.9 ± 17.7	.407

3.3. The main effect of time on changes in plasma endotoxin, IL-6, and procalcitonin levels after CBP

The main effect of time on endotoxin, IL-6, and procalcitonin was significant ($F = 53.90$, $P < .0001$ for endotoxin, $F = 297.57$, $P < .0001$ for IL-6, and $F = 419.79$, $P < .0001$ for procalcitonin). Multiple comparison tests shows that the increase in endotoxin, IL-6, and procalcitonin concentrations immediately after CPB in the 2 groups was significantly higher than that at 24 hours and 48 hours after CPB (all $P < .0001$), whereas, the changed levels of endotoxin and procalcitonin at 24 hours and 48 hours after CPB were not significantly different ($F = 1.27$, $P = .2695$ for endotoxin and $F = 3.15$, $P = .0866$ for procalcitonin). The changed levels of IL-6 at 24 hours after CPB were higher than those at 48 hours after CPB ($F = 93.13$, $P < .0001$).

3.4. Effect of comprehensive preoperative treatment on other clinical outcomes

No differences between the groups were observed regarding the duration of ventilator use in ICU and the length of stay in the ICU. Patients who received the comprehensive preoperative regime received lower dosage of dopamine and adrenaline at 24 hours after surgery (Table 3).

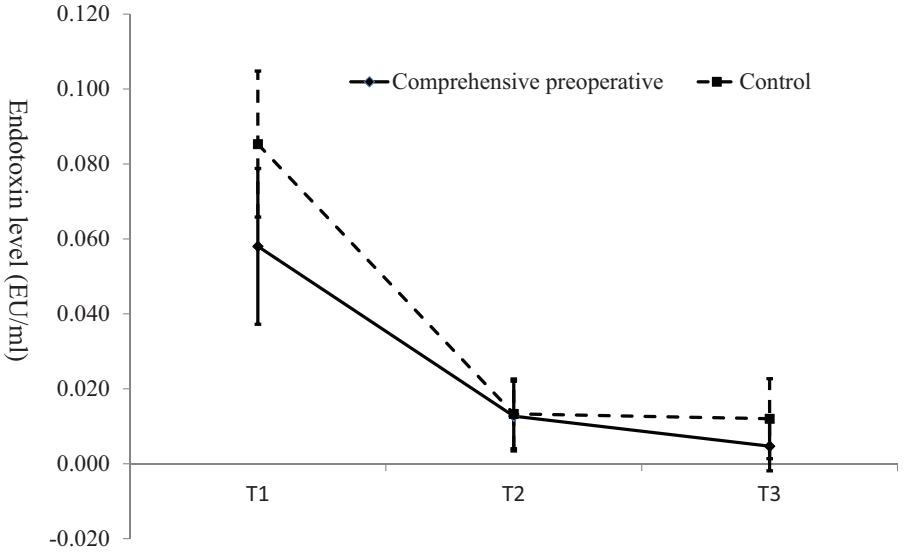

Figure 1. Changes in plasma endotoxin concentration after CPB in the comprehensive preoperative group and control group. Mean endotoxin concentration and 95% confidence intervals for patients in the comprehensive preoperative group and control group over time. Where T1: immediately after CPB, T2: 24 hours after CPB, and T3: 48 hours after CPB. CPB = cardiopulmonary bypass.

4. Discussion

The present prospective, randomized, controlled pilot study in patients undergoing cardiac surgery with cardiopulmonary bypass demonstrated that 3 days of a comprehensive preoperative regime comprising SDD in combination with probiotics and smectite has a reducing effect on IL-6 levels after CPB compared with that in the control group, but not on decreasing the procalcitonin concentration. A marginally significant decrease was found in the level of endotoxin in the intervention group.

Reduction of endotoxemia and inflammatory reactions is one of the main concerns of surgeons during CPB. Martinez-Pellus et al first examined the effect of SDD on endotoxemia during CPB. [10,14] They found significantly lower levels of rectal bacteria, blood endotoxin, and IL-6 in the SDD group ($P = .01$). Several systematic reviews and meta-analyses have found that SDD significantly reduces lower airway infection and blood stream infection due to gram-negative bacteria.[11,15] However, results from randomized clinical trials were conflicting. Bouter et al found no reduction of perioperative endotoxemia, TNF-α, IL-10, and IL-6 levels in SDD-treated patients, although a significant reduction of rectal aerobic gram-negative bacteria was observed ($P < .001$).[13] Some recent studies have also demonstrated a reduction in endotoxemia and pro-inflammatory

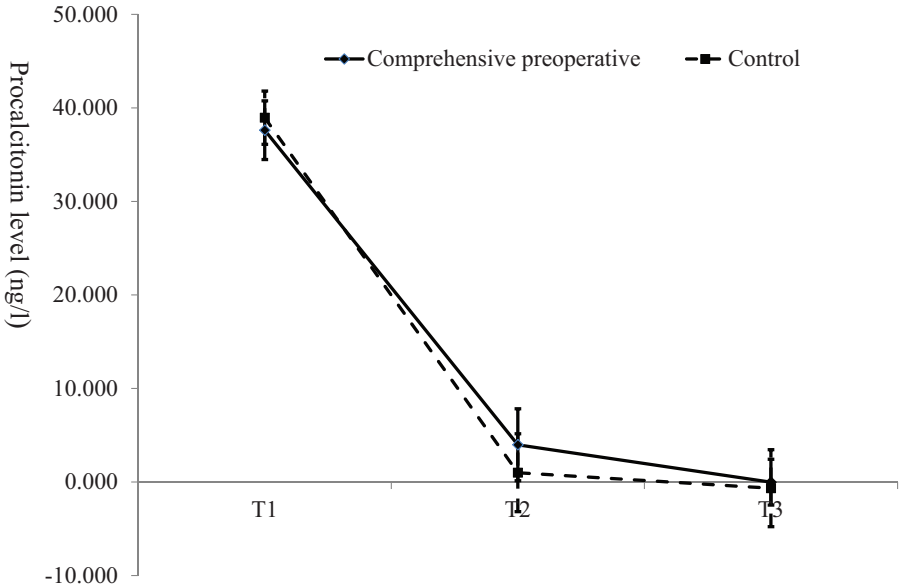

Figure 2. Changes in serum procalcitonin concentration in the comprehensive preoperative group and control group. Mean procalcitonin concentration and 95% confidence intervals for patients in the comprehensive preoperative group and control group over time. Where T1: immediately after CPB, T2: 24 hours after CPB, and T3: 48 hours after CPB. CPB = cardiopulmonary bypass.

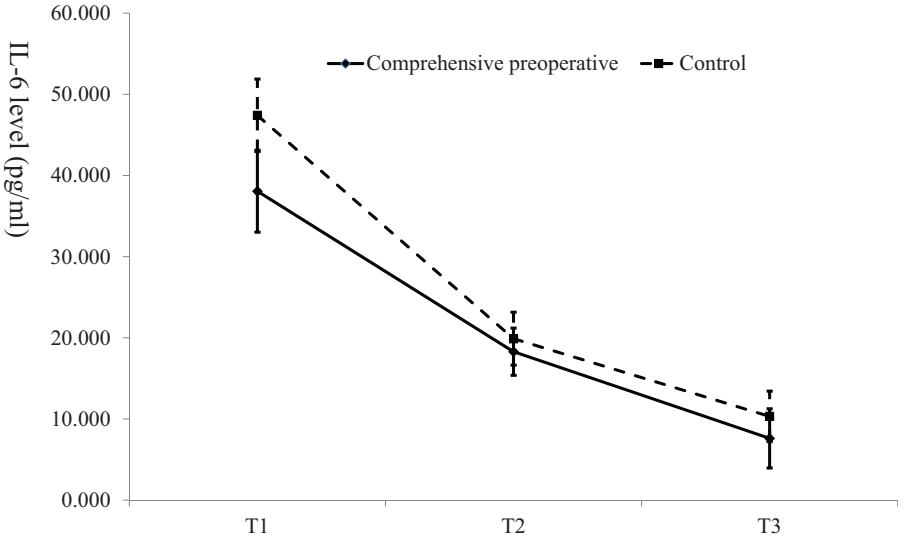

Figure 3. Changes in serum IL-6 concentration in the comprehensive preoperative group and control group. Mean IL-6 concentration and 95% confidence intervals for patients in the comprehensive preoperative group and control group over time. Where T1: immediately after CPB, T2: 24 hours after CPB, and T3: 48 hours after CPB.*$P = .0112$. CPB = cardiopulmonary bypass.

cytokines (TNF-α and IL-6) after administration of probiotics in patients with acute pancreatitis, non-alcoholic fatty liver disease, peritoneal dialysis, and cirrhosis.[12,16–18] There were few studies that investigated the effect of probiotics in patients undergoing CPB. An animal study showed that pre-administration of probiotics can improve intestinal barrier function by inhibiting the CPB-induced inflammatory response in rats. Several experimental studies showed that smectite can improve intestinal barrier function in *Escherichia coli* infected pigs, reduce bacterial translocation, and decrease the mRNA levels of TNF-α and IL-6.[19,20] A marginally significant decrease in the levels of endotoxin was found in the present study, which may be attribute to the small sample size, resulting in a lack of power to detect a difference. However, the study revealed that the comprehensive preoperative regime of SDD in combination with probiotics and smectite resulted in reduced IL-6 levels immediately after CPB. Further studies with enough samples are needed to confirm these results.

Procalcitonin, a marker of postoperative infection,[21–23] showed no significant difference between the intervention group and control group, suggesting that the intervention cannot decrease the risk of bacteremia during CBP. Endotoxin can cause release of 5-hydroxytryptamine, prostaglandins, and kinins, leading to circulatory disorders such as dilation of peripheral blood vessel beds, decreased blood pressure, insufficient perfusion of important organs and tissues, and metabolic acidosis of tissues.[14,24,25] In circulatory disorders, the most common way for doctors in intensive care is to use positive muscle drugs. Lower dosages of dopamine and adrenaline administered to patients in the comprehensive regime group at 24 hours after surgery, indirectly suggests that the comprehensive regime of intervention may have an effect on reducing circulatory disorders via decreasing endotoxin levels and the inflammatory reaction.

Previous studies either investigated the effect of SDD or probiotics. To our knowledge, there was no study investigating the combined regime of preoperative SDD, probiotics, and smectite for decreasing endotoxemia and cytokine activation during cardiopulmonary bypass. This study has some limitations. First, given the obvious nature of the method, it would not be possible to blind clinicians to the intervention. Second, the statistic power might not enough to detect the diffidence of endotoxemia and procalcitonin concentration because of the small sample size in the present study. Third, the endotoxemia, procalcitonin, and IL-6 concentrations were not measured before the intervention, which limited evaluation of the baseline difference. However, we examined the difference of changes in endotoxin, IL-6, and procalcitonin levels after anesthesia induction but before CPB, which could largely decrease the bias of baseline difference.

5. Conclusions

The present prospective, randomized, controlled pilot study in patients undergoing cardiac surgery with cardiopulmonary

Table 3

Recovery characteristics of the participants.

	Comprehensive preoperative (n = 15)	Control (n = 15)	*P* value
Ventilator use time in ICU, min	549.8 ± 72.7	569.4 ± 67.3	.449
ICU stay, days (d)	3.3 ± 0.3	2.8 ± 1.4	.211
Dosage of dopamine 24 hours after surgery, mg	320.30 ± 53.23	618.10 ± 75.06	<.001
Dosage of adrenaline 24 hours after surgery, mg	0.71 ± 0.10	1.84 ± 0.59	<.001

ICU = intensive care unit.

bypass demonstrated that 3 days of the comprehensive preoperative regime comprising SDD in combination with probiotics and smectite may have an effect on reducing the concentration of endotoxin and IL-6 after CPB compared with the control group, but not on decreasing the procalcitonin concentration.

Author contributions

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