The effect of a short-term multi-modal prehabilitation intervention on the systemic stress response in patients undergoing semi-elective surgery for gastrointestinal cancer: a randomized controlled clinical trial

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Abstract

Objective

To evaluate the possible effects of short-term multi-modal prehabilitation intervention on the post-operative stress response in patients undergoing semi-elective surgery for gastrointestinal cancer.

Methods

A prospective and randomized clinical study was conducted in 84 patients with gastrointestinal cancers who underwent semi-elective surgery in a single university clinical hospital from June 2023 to October 2023. Patients were randomized into the standard (SD) group and the short-term prehabilitation (STP)group (1:1). The SD group received routine treatment and care, while the STP group received one-week prehabilitation including physical exercise, nutritional, and psychosocial interventions. Changes in post-operative stress response, outcome and recovery of patients in each group were observed.

Results

The two groups of patients were similar in terms of age, gender, body mass index, ASA grade and tumor type. After surgery, concentrations of epinephrine(6h), C-reactive protein(7d), and IL-6(6h) levels were significantly lower in the STP group than in the SD group($P < 0.05$). There were no significant differences in patients postoperative norepinephrine, insulin, glucose, IL-8 expression levels between the two groups at all time points. Besides, the time to first flatus($P = 0.02$), first diet($P = 0.01$) and ambulation($P = 0.01$) were significantly reduced in the STP group than those in the SD group. Differences in drainage removal time, postoperative hospital stay, postoperative complications were not statistically significant.

Conclusion

Our findings demonstrated that levels of certain metabolic(epinephrine), acute phase(CRP) and cytokine(IL-6) parameters were significantly lower in the STP group than in the SD group, which reflected a lesser degree of postoperative stress response in gastrointestinal cancer patients associated with the short-term prehabilitation. Furthermore, patients gastrointestinal function and exercise tolerance could recover more quickly.

Registration number

This randomized, and controlled clinical trial was approved by the ethics committee of our hospital and registered in Chinese Clinical Trial Registry in January 2022 with the registration number ChiCTR2200055764.

Background

Gastrointestinal cancers, such as gastric cancer and colorectal cancer, are the prevailing malignant tumors found in the digestive system[1].The latest data released in 2022 by the National Cancer Center shows that there were about 397, 000 new cases of gastric cancer and 408, 000 new cases of colorectal cancer in China in 2016, respectively ranking third and second nationwide.

Patients with gastrointestinal cancer are recommended to undergo surgical resection as the preferred treatment. However, surgical injury can lead to new issues such as a stress response. Gastrointestinal cancer surgery features large surgical trauma, evident stress response, and great risks for various postoperative complications [2]. The response of the body to trauma is an innate systemic response designed to maintain vital function and restore homeostasis [3]. Surgical stress response, along with metabolic, acute phase, cytokine, and catabolic responses, can activate the sympathetic nervous system and the hypothalamic pituitary adrenal axis(HPA), resulting in increased secretion of catecholamines(epinephrine and norepinephrine) and changes in a series of biochemical markers such as insulin, glucose, CRP, IL-6, IL-8 and so on. Stress response is usually adaptive and time-limited, and it is thought to provide survival advantages. However, the prolonged existence of this stress response may lead to deterioration of clinical and functional status even after the removal of destructive stimulus. Therefore, it is of positive significance to appropriately reduce the body's overstress response during the perioperative period for the postoperative rehabilitation of patients [4, 5].

Efforts to reduce surgical stress are mainly concentrated in the intraoperative and postoperative stages. However, he postoperative period may not be the best time to require surgical patients to make significant changes in their care because they are exhausted and worried about disrupting the healing process[6, 7]. In contrast to sudden injury and severe illness, semi-elective surgery can be regarded as a"planned stress". As a result, the concept of preventing or reducing the surgical stress response before the operation appears to be a viable strategy. Prehabilitation is a comprehensive approach that aims to prevent or minimize the physical decline associated with surgery and its effects by utilizing the time before the operation[8]. Although a few studies have shown that prehabilitation plays an active role in enhanced recovery after gastrointestinal tumour surgery by advanced intervention in patients' functional ability, nutritional status and mental health, little has been carried out on the effect of prehabilitation on surgical stress response [9–12]. Additionally, there is currently no universally accepted definition, preferred protocol(s), or recommended duration for prehabilitation. Commonly employed prehabilitation techniques, aimed at enhancing physical conditioning before surgery, include exercise training, nutritional support, and anxiety reduction strategies.The duration of prehabilitation varies from 2 to 6 weeks according to the literature. [13, 14]. However, adherence to long-term projects remains a major obstacle to prehabilitation management. At the same time, whether the delay of definitive surgery by preoperative prehabilitation will lead to tumor progression and dissemination is still the focus of both doctors and patients.

Considering the imperfect medical structure and management system of community hospitals in China, with insufficient capabilities in prehospital patient referral, and pre-hospital optimization, the smooth implementation of prehospital prehabilitation cannot be guaranteed. Moreover, most patients who have been diagnosed with gastrointestinal cancer express a strong desire to undergo surgery without delay. In China, the duration of preoperative preparation in hospitals ranges from 3 to 12 days. Therefore, it is in the best interest to determine whether prehabilitation intervention is effective and feasible during this preoperative hospital stay, based on China's medical conditions. We refer to this type of preoperative optimization as short-term prehabilitation.

So far, there is no report on the application of short-term multi-modal prehabilitation in gastrointestinal tumor surgery and its effect on surgical stress and postoperative recovery. Hence, the aim of this study is to investigate the implementation and practicality of the multi-modal STP strategy for Chinese gastrointestinal cancer patients, as well as to examine the effect of short-term multi-modal prehabilitation on post-operative stress response, postoperative outcomes, and patient recovery following semi-elective surgery.

Methods

Study design

This study was a randomized, controlled clinical trial with two study groups, the standard (SD) group and the short-term prehabilitation (STP)group. We analyzed a cohort of 84 patients assigned different treatment and care regimens during the preoperative period . This randomized clinical trial was conducted with approval from the ethics committee of the Shanghai General Hospital Institutional Review Board(Ethical Approval No.[2023]079), and it was registered on the Chinese Clinical Trial Registry (ChiCTR2200055764).

Randomization

Patients who met all the inclusion criteria and none of the exclusion criteria from June to October 2023 were included consecutively. These patients were then randomly divided into one of the two study arms using a random allocation sequence generated by Software SPSS 24.0. Allocations were placed in sealed, opaque, consecutively numbered envelopes by an independent researcher. Allocations were concealed until the baseline assessment was complete and the envelope was opened in numerical order. Due to the nature of the intervention, blinding was not possible for both the patients and the intervenor. To reduce performance bias, patients were told that we had compared two perioperative intervention plans, and that one had not shown to be superior to the other.

Eligibility criteria

Inclusion criteria

The inclusion criteria are as follows:

• Prior written informed consent must be obtained before any assessment.

• Participants were Chinese male or female patients over 18 years old and under 85 years old.

• Participants were scheduled for semi-elective resection of none-metastatic gastrointestinal cancer.

Exclusion criteria

The exclusion criteria are as follows:

• Patients with co-morbid medical, physical, and mental conditions that contraindicate physical exercise or oral nutrition (eg. unstable angina or symptomatic severe aortic stenosis), disabled orthopedic and neuromuscular disease, dementia, psychosis

• Patients with severe cardiac abnormalities, severe end-organ disease such as cardiac failure, sepsis, severe liver or kidney failure.

• Patients unable to swallow, or being fed through tube feeding.

• Patient with poor Chinese comprehension.

Study arms

• Standard(SD) group. Patients in this group received usual care according to the standard perioperative protocol of the Department of Surgery, Shanghai General Hospital. This group received general instructions on nutritional counselling and exercises (deep breathing, effective cough) during the hospital stay by a nurse.

• Short-term prehabilitation(STP) group. Patients in this group attended a one-week multi-modal prehabilitation program prior to surgery supervised by a multidisciplinary team in the hospital.

Components of prehabilitation

• **Exercise training**

a. Inspiratory muscle training (IMT)

After randomization, patients in the prehabilitation group received one session on inspiratory muscle training (IMT) and they were supervised to perform this exercise every day at the hospital prior to surgery. Patients were shown how to use the Carent Respiratory Exerciser as an inspiratory muscle training tool. The inspiratory muscles training duration was 15 min. Patients were supervised by a rehabilitation nurse and completed the IMT three times a day.

b. Aerobic exercise training

In addition to the IMT, patients attended an aerobic exercise training session once a day supervised by the kinesiologist at the hospital rehabilitation unit prior to surgery. Aerobic exercise training was completed on a stationary bicycle (LGT-5100, Guangzhou Longest Inc), starting with minimum resistance and gradually increasing according to the patient's heart rate. The aerobic exercise training duration was 30 min with a heart rate of 60-80% of the patient's maximal heart rate (maximal heart rate=220 - age).

- Nutritional supplementation

Malnutrition is common in patients with gastrointestinal cancer, where the prevalence of malnutrition is between 20%and 70%[15]. Studies[16,17]have shown that malnutrition is an independent risk factor for postoperative complications in patients with gastrointestinal cancer. Therefore, the primary goal of perioperative nutritional therapy was to optimize preoperative nutritional storage and provide sufficient nutrition to compensate for postoperative catabolic response.

The nutritional screening of all participants was implemented by a nutriology-trained nurse at their baseline appointment. Then, both study groups participated in the same counselling session(45 minutes total)provided by a registered dietitian. During this session, patients were provided with written dietary advice and viewed with a presentation on preoperative nutrition, emphasizing the importance of avoiding unintentional weight loss and increasing protein intake to maintain muscle mass prior to surgery.

Patients in the prehabilitation group were provided with an oral nutritional supplement(Nutrison, Milupa GmbH Inc) 1000 mL/d(3.28Kj, 0.03g of protein per mL) in addition to their normal diets. Patients were instructed to use these supplements within 1 hour after exercise training or before bedtime to maximize muscle protein synthesis. Patients in the standard group did not receive additional nutritional supplements beyond their normal diet. The nutriology-trained nurse was responsible for monitoring the patient's preoperative oral compliance and recording the patient's daily oral dose.

Psychological support

As might be expected, patients undergoing gastrointestinal surgery are anxious and fearful. All participants received an assessment by a psychology-trained nurse using the Hospital Anxiety and Depression Scale (HADS). If the assessment resulted in a high score (Anxiety Scale of 8 or higher, Depression Scale of 8 or higher), patients were considered high-risk and offered a referral to a psychologist.

Patients in the prehabilitation group received an extra booklet about the clinical pathway of gastrointestinal surgery during the preoperative period by the Department of Surgery, Shanghai General Hospital. Many pictures and photos were used in the booklet to explain various medical and nursing measures during the perioperative period of gastrointestinal surgery, such as preoperative examination, prehabilitation and early postoperative rehabilitation. Meanwhile, patients could also scan the QR code in the booklet to watch the relevant video. The possible underlying causes of pain, fatigue and anxiety during the perioperative period and the coping skills were also discussed. In addition, patients received a

log where all activities related to prehabilitation will be recorded, and the nurses provided adequate health education to the patients to eliminate the patients' misunderstanding.

General procedure and monitoring

Data collection and management

Treatment-related data were collected at baseline (beginning of prehabilitation period), and immediately prior to surgery (end of prehabilitation period). Follow-up data was followed from 6 hours postoperative (6h) to 7 days (7d) postoperative. Data collection started from the date when a participant signed the informed consent form and continued until the trial was terminated, or until the participant withdrew from the trial at any time for any reason. If participants stop or deviate from the study protocol, the researchers will try their best to minimize all missing data. All original data were kept in chronological order for verification. The original data were transferred to the paper-based case report form (CRF) and an electronic database system located in the guarded facility at the trial site in time.

Study outcome variables

Primary outcome measure

The primary outcome is the post-operative stress response. The stress response is the term for changes in hormones and metabolism after injury or trauma. This is an important result of surgery as it leads to metabolic response and inflammatory response, mediated by catecholamines, insulin, acute phase proteins, and cytokines. When combined with surgical trauma and increased metabolism, stress response may adversely affect clinical outcomes. Peripheral blood was sampled on the day of surgery, 6 hours (6h), 2 days (2d), 5 days (5d) and 7 days (7d) after the surgery. The centrifuged serum was stored at -80℃ until analysis. Indexes of systemic stress responses such as epinephrine, noradrenaline, insulin, glucose, C-reactive protein (CRP), interleukin-6 (IL-6) and interleukin-8 (IL-8) were determined.

Secondary outcomes measure

Secondary outcome measures included changes in postoperative outcome and recovery of patients such as time to first flatus, time to first diet, time to first ambulation, drainage removal time, postoperative hospital stay, and postoperative complications.

Statistical Analysis

SPSS 24.0 and Prism 5.0 were applied for statistical analysis. Measurement data were shown as the mean±standard deviation. Enumeration data were shown as the percentage(%). T test or U test was applied for the comparison of measurement data between groups. The Chi-squared test or Fishers exact test was applied for comparison of enumeration data between groups. Overall, differences were considered significant at a P level of <0.05.

Results

Patients Clinical Baseline Level

84 patients were randomly assigned to the SD group (n = 42) or the STP group (n = 42). For the SD group, the average age was 66.98 ± 9.58 years, and the BMI was 22.97 ± 2.90. There were 25 men and 17 women. 40 patients were identified as ASA grade II based on the American Society of Anesthesiologists physical status classification with the other 2 as . 15 patients were diagnosed with gastric cancer, and 27 patients were diagnosed with colorectal cancer. For the STP group, the average age was 67.26 ± 8.95, and the BMI was 24.20 ± 5.23. There were 21 men and 21 women. 35 patients were identified as ASA grade II and 7 were . 12 patients were diagnosed with gastric cancer, and 30 patients were diagnosed with colorectal cancer. Differences in each baseline characteristic (Table 1) between groups had no statistical significance (P > 0.05), and the factors were comparable.

Table 1
Clinical baseline characteristics of the two groups

Baseline characteristics	SD group (42)	STP group (42)	P value
Age (years)	66.98 ± 9.58	67.26 ± 8.95	0.89
BMI (kg/m^2)	22.97 ± 2.90	24.20 ± 5.23	0.19
Gender			
Men (n (%))	25(59.5)	21(50.0)	0.38
Women (n (%))	17(40.5)	21(50.0)	
ASA grade (n (%))			
≤ 2	40(95.2)	35(83.3)	0.08
> 2	2(4.8)	7(16.7)	
Tumor type			
Gastric cancer (n (%))	15(35.7)	12(28.6)	0.48
Colorectal cancer (n (%))	27(64.3)	30(71.4)	

3.2 Systemic Stress Response

3.2.1 Metabolic response

Metabolic response in stress response mainly involves catecholamine secretion(epinephrine and norepinephrine) and glucose homeostasis(insulin and glucose). Changes in plasma levels of epinephrine, norepinephrine, insulin and glucose are presented in Fig. 1. For the SD group, epinephrine levels peaked at 6h at 48.11 ± 22.01 pg/mL after operation. For the STP group, they peaked at 2d at 42.49 ± 19.94 pg/mL.

Epinephrine levels were significantly higher at 6h in the standard group than in the prehabilitation group (P = 0.02). The postoperative norepinephrine levels increased from 93.49 ± 46.88 pg/mL at baseline and peaked at 2d at 93.45 ± 46.88 pg/mL in the standard group with 96.53 ± 52.35 pg/mL at 5d in the prehabilitation group. There was no significant difference in postoperative plasma epinephrine levels between the two groups. For the SD group, the postoperative insulin levels reach the trough at 2d at 5.62 ± 4.03 uIU/mL. For the STP group, the insulin levels touched the bottom at 24 hours at 5.67 ± 4.40 uIU/mL. After the operation, the glucose levels peaked at 6h at 10.09 ± 4.40mg/dL in the SD group and at 9.17 ± 4.09mg/dL in the prehabilitation group. There was no significant difference in insulin and glucose levels between the two groups.

3.2.2 Inflammatory response

Inflammatory responses in stress response mainly involved changes of acute phase proteins (CRP) and cytokines (IL-6, IL-8). Changes in plasma levels of CRP, IL-6 and IL-8 are illustrated in Fig. 2. The postoperative CRP levels increased from mg/dL at baseline and peaked at 2d at 51.09 ± 48.74mg/dL in the SD group and at 30.95 ± 30.20 mg/dL. CRP levels were significantly higher at 7d in the SD group than that in the STP group (P = 0.04). There was no significant difference in postoperative CRP levels between the two groups. For the SD group, IL-6 levels peaked at 6h at 113.08 ± 142.42 pg/mL after the operation. For the STP group, they peaked at 6h at 48.64 ± 54.56 pg/mL. IL-6 levels were significantly higher at 6h in SD group than in STP group (P = 0.01). The postoperative IL-8 levels peaked at 5d at 13.63 ± 13.42 pg/mL in SD group and at 27.64 ± 10.77 pg/mL at 5d in STP group. There was no significant difference in postoperative plasma IL-8 levels between the two groups.

3.3 Postoperative outcomes

Compared with the SD group, there were no statistically significant differences in drainage removal time and postoperative hospital stay in the STP group. However, time to first flatus, time to first diet and time to first ambulation were significantly reduced in the STP group than those in the SD group. We performed a two-week follow-up visit on patients in each group and recorded their complications during the period. The severity of postoperative complications was graded using the Dindo-Clavien classification system[18], as shown in Table 2. The SD group had 8 postoperative complications (Grade I, II: 6, Grade ≥ III: 2), including three chyle leakages, three ileuses, and two hemorrhages. The STP group had 6 postoperative complications (Grade I, II: 5, Grade ≥ III: 1), including two chyle leakages, one anastomotic fistula, one ileuse, and two hemorrhages. Postoperative complications were less developed in both groups.

Table 2
Postoperative outcomes of the two groups

Variable	SD group (42)	STP group (42)	P value
Time to first flatus (d)	3.21	2.67	0.02
Time to first diet (d)	3.29	2.43	0.01
Time to first ambulation (d)	3.64	2.98	0.01
Drainage removal time (d)	8.14	8.81	0.46
Postoperative hospital stay (d)	9.29	9.57	0.79
Postoperative complications (n (%))	8(19.0)	6(14.3)	0.56
Grade of complications (n (%))			
I, II	6(75.0)	5(83.3)	0.70
≥III	2(25.0)	1(16.7)	

Discussion

Surgical intervention is a form of deliberate trauma, accompanied by hormonal and inflammatory responses that may become key factors affecting the final clinical outcome of patients [19]. It is evidently confirmed that reducing perioperative stress can reduce catabolism and promote anabolic metabolism so that patients can recover faster and better from surgery [20]. Thus, it is of great importance in reducing stress by new structured preoperative intervention.

Multi-modal prehabilitation was known as physical exercise, nutritional, and psychosocial interventions to optimize physical and mental health before major surgery [21]. Recent studies have demonstrated that prehabilitation can reduce hospital length of stay in major surgery [22, 23]. Despite the potential advantages of prehabilitation to improve patient outcomes after cancer surgery, the effect of surgical stress and its benefits relating to gastrointestinal cancer are less clear. The regular range of prehabilitation was from 4 to 8 weeks if the disease permits [24]. Concern about project adherence and tumor progression during long-term prehabilitation remains a major obstacle. However, it is unclear whether short-term prehabilitation in gastrointestinal tumor surgery could improve surgical stress and postoperative recovery. In our study, we explored the short-term multi-modal prehabilitation strategy for gastrointestinal cancer patients in China and its effect on postoperative stress response, postoperative outcome and recovery of patients undergoing semi-elective surgery.

Postoperative stress response is associated with a significant metabolic reaction. A major component of the metabolic response to operative injury is stimulation of the adrenal medulla by the sympathetic nervous system. In response to surgical stress, the activation of the hypothalamic-pituitary-adrenal axis leads to an elevation in counter-regulatory hormones including epinephrine, norepinephrine, insulin and

so on. In our study, we did not observe any difference in norepinephrine levels between the two groups, but epinephrine levels (6h) were significantly lower in the STP group than in the SD group, and the peak was also delayed which suggested a more gradual postoperative hormone release and a reduced neuroendocrine response after short-term prehabilitation. The hyperglycemic response is also an important metabolic reaction in surgical stress, and a state of insulin insensitivity has been shown to occur consistently after injury. In our study, postoperative glucose was significantly increased in both the SD and the STP group, but no significant difference in insulin and glucose levels was found between the two groups.

Another component of the systemic stress response to operative injury is an inflammatory stress response. The elevated inflammatory response after surgery leads to increased generation of reactive oxygen species (ROS) that can damage lipids, proteins, and even DNA leading to impaired vascular permeability which eventually results in delayed gastrointestinal function in colorectal operations [25]. CRP is the most sensitive acute-phase protein which has been used as an objective biochemical marker to reflect the degree of operative injury. Our study demonstrated elevation of CRP levels peaked at 6h postoperatively and decreased afterwards in both the SD and the STP group. CRP levels were significantly lower at 7d in the SD group than in the STP group. The lower CRP response at 7d reflects a reduced long-term effect of operative trauma in the STP group. Operative trauma also stimulates the release of a variety of cytokines which are produced at the site of injury as mediators of the host response to operative injury. Of these cytokines, interleukin-6 is the major regulator of the cytokine-mediated inflammatory response, and its levels have been shown to correlate with the severity of operative injury. In our study, IL-6 levels peaked at 6h, with levels nearly three-fold higher in the SD group than in the STP group. A reduced IL-6 may have contributed to the lower inflammatory stress responses observed in the STP group. Other proinflammatory cytokines released after operative injury include interleukin-8 (IL-8). IL-8 is released by endothelial cells and serves as a poly-mononuclear activator and potent chemoattractant. In our study, the release of IL-8 was fluctuant in both groups and their levels did not differ between the two groups.

A recent study showed that prehabilitation in hepatobiliary, colorectal, and upper gastrointestinal cancer surgery was associated with reduced hospital length of stay but had no effect on postoperative complications or mortality rates [26]. In our study, we tracked postoperative outcomes and complications of patients in each group and found that time to first flatus, time to first diet and time to first ambulation were significantly reduced in the STP group than those in the SD group, suggesting short-time prehabilitation could accelerate the recovery of gastrointestinal function and exercise tolerance after operation. The overall postoperative complication incidence of patients in the two groups was relatively low, which means short-term multi-modal prehabilitation intervention was safe to improve patients' postoperative recovery.

Using objective biochemical markers, we quantified the stress response after surgery. Our findings demonstrated that levels of certain metabolic (epinephrine), acute phase (CRP) and cytokine (IL-6) parameters were significantly lower in the STP group than in the SD group, which may reflect a lesser

degree of postoperative stress response in the gastrointestinal cancer patients associated with the short-term prehabilitation. Furthermore, patients' gastrointestinal function exercise tolerance could recover more quickly.

Conclusion

The short-term multi-modal prehabilitation has been proven to be significantly effective and safe,achieving a lower level of epinephrine in the early postoperative period,and decreasing the level of CRP in the late postoperative period. In addition, it has significantly reduced the time to first flatus, time to first diet and time to first ambulation, suggesting short-time prehabilitation could accelerate the recovery of gastrointestinal function and exercise tolerance after operation.

Furthermore, the prominent issue is the cost-benefit analysis of short-term multi-modal prehabilitation plans, the improvement of compliance of patient.

Declarations

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Author contribution Fang Fang: conceptualization, investigation, and writing — original draft. Rui Tai: investigation and formal analysis. Chao Han: investigation and formal analysis. Chen Huang: supervision and project administration. Yaqing Zhang: conceptualization, supervision and writing — review and editing, and visualization.

Availability of data and materials The datasets generated during and/or analyzed during the current study are not publicly available because of the limitations of the law of data protection of our country but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Ethics approval This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the ethics committee of Shanghai General Hospital.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication The patients were informed that the data obtained during the study could be used for publications in scientifc journals.

Conflict of interest The authors declare no competing interests.

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Figures

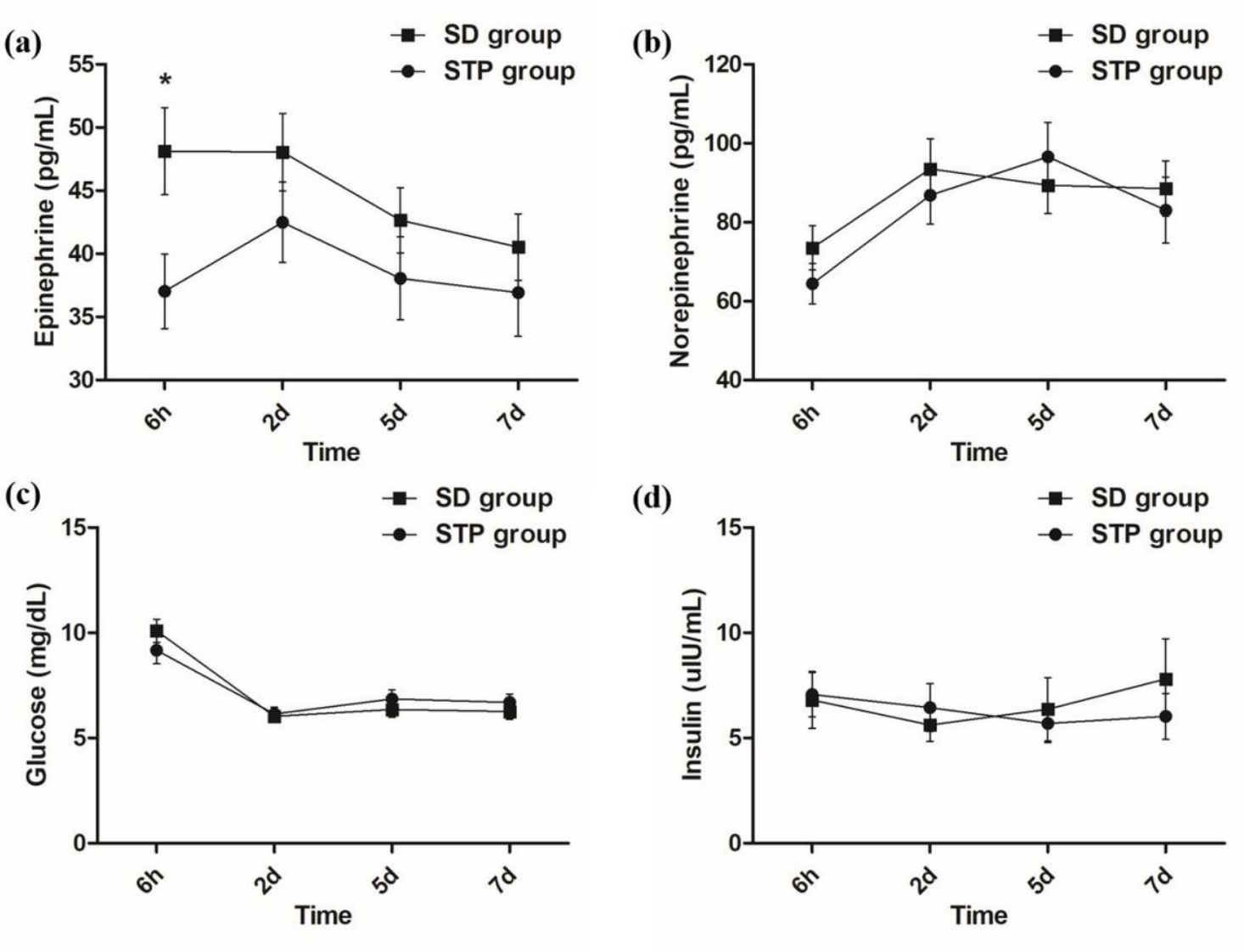

Figure 1

Postoperative metabolic response parameters of the two groups: (a) postoperative epinephrine expression level in each group at all time points; (b) postoperative norepinephrine expression level in each group at all time points; (c) postoperative glucose expression level in each group at all time points. (d) postoperative insulin expression level in each group at all time points. ∗ p< 0:05

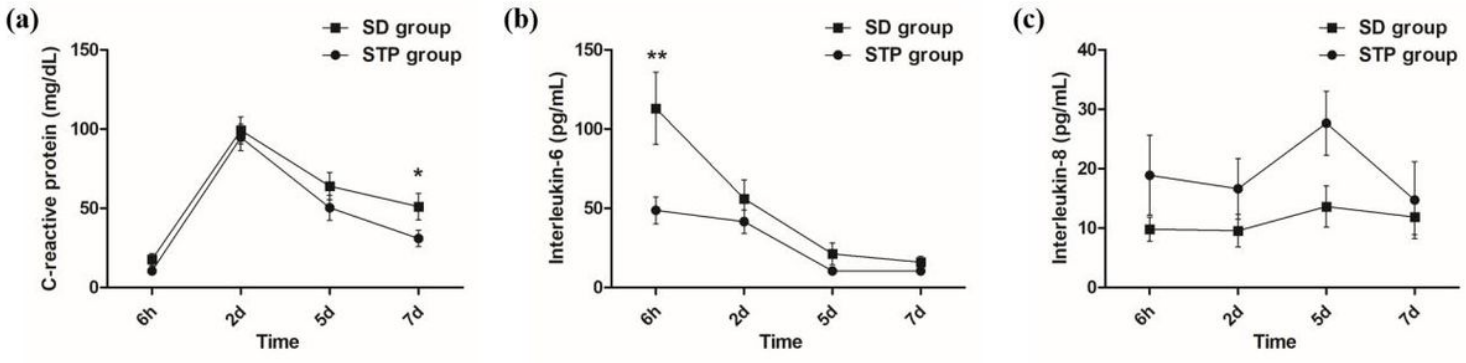

Figure 2

Postoperative inflammatory response parameters of the two groups: (a) postoperative CRP expression level in each group at all time points; (b) postoperative IL-6 expression level in each group at all time points; (c) postoperative IL-8 expression level in each group at all time points. ∗p< 0:05, ∗∗ p <0:01