Inhibiting effect of etomidate or propofol combined with remifentanil hydrochloride on adrenal cortex function in severe burn patients : a randomized, double-blind and controlled trial

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Abstract

Background: Etomidate is widely used for anesthetic induction in clinical practice. Adrenal insufficiency induced by etomidate has been demonstrated. However, a variety of studies present that etomidate plays an important role in patients with severe burn injuries.

Methods: Forty patients with severe burns were randomly divided into etomidate group (Group E) and propofol group (Group P). Etomidate, propofol and remifentanil hydrochloride were used for anesthesia induction and maintenance. General patient characteristics, mean arterial pressure (MAP), heart rate (HR) and bispectral index (BIS) value were measured and recorded at the baseline (t0), before the intubation (t1), 1, 3, 5, and 30 min following the intubation (t2–5), and the end of the surgery (t6). Before induction of anesthesia and at 30 min, 2h, 24h, and 48h after end of surgery (T0, T1, T2, T3 and T4), artery blood (2 ml) was collected and the concentrations of adrenocorticotropic hormone (ACTH), cortisol (Cor) and aldosterone (ALD) were measured.

Results: There were no significant difference in general patient characteristics between the two groups ($P>0.05$). The MAP values decreased significantly, the HR values decreased at the t1 and there was a statistical difference between the two groups; There was no statistical difference between the two groups at each time point. The patient's ACTH levels in two groups decreased significantly compared with that at preanesthesia, and the levels at T4 were apparently higher than T3 in Group E. The patient's Cor levels in Group E significantly decreased at T2, while that in Group P have no significant change. The differences were not statistical significance between the two groups. The patient's ALD levels in Group E were significantly lower than before induction; while the levels in Group P have no significant change at each time point; the levels in Group P were apparently higher than group E at T2, T3 and T4.

Conclusion: Propofol and etomidate for anesthesia induction and maintenance could cause hemodynamic changes, but the effect of etomidate was lighter. The propofol and etomidate both suppress adrenal cortex function, that inhibitory effect of etomidate was greater than propofol, therefore etomidate had a certain beneficial effect.

Background

Etomidate is a commonly used anesthetic induction agent in clinical practice, with fast onset (5–15 s), fast recovery (5–15 min), less adverse reactions to cardiovascular and respiratory functions, and less histamine release. [1] Etomidate may have a better hemodynamic outcome in critical patients, which is particularly useful for patients with cardiac-compromised and those who must avoid hypotension during induction of anesthesia. [2] In addition, myoclonus is one of the most common side-effects induced by etomidate anesthesia induction. Therefore, the use of etomidate in clinical anesthesia maintenance remains controversial.

Many authors described an elevation of cortisol levels in the early stage of treatment in burns. [3–4] Research has shown that the level of neuroendocrine hormone fluctuates in early burn patients, including hypothalamic-pituitary-adrenal axis (HPA) excitation. Excessive activation of the HPA axis can lead to severe secondary injuries and affect the prognosis of patients. [5] However, adrenal insufficiency induced by etomidate has been demonstrated in several studies. A variety of studies present that etomidate plays an important role in patients with severe burn injuries.

The response of HPA axis was widely used to biological marker of stress. [6] Serum was collected and ACTH, Cor and ALD were measured at different time points, which can reflect the severity of burn area or injury depth and inhibition degree of the adrenal cortex.

This study aims to observe the effect of propofol or etomidate on hemodynamics for anesthetic induction and maintenance; To compare the inhibitory effect of propofol or etomidate on the adrenal cortex in patients with severe burns.

Methods

General information

This study was approved by the Ethics Committee of Affiliated Hospital of Chengde Medical College (22029). This prospective, randomized, controlled, double-blinded study was performed from September 2015 to September 2016, and the hospitalization time of patients before operation was less than 1 week in the burn unit of our hospital. The total burn areas ranged from 31–50% of total body surface area (TBSA), with full-thickness burn surface area (FTBSA) 11–20% of the area. After voluntarily signed informed consents from patients or their legal representative, forty patients with severe burns, aged 18 to 65 years, ASA II or III, scheduled to receive elective general anesthesia with endotracheal intubation were included in the study. All patients were randomly assigned into etomidate group (Group E) (2 mg/mL, Jiangsu Nhwa Pharmaceutical, Xuzhou, China) and propofol group (Group P) (10 mg/mL, Fresenius Kabi Pharmaceutical Co. Ltd, Beijing, China) using web-based randomization software method. Exclusion criteria included: allergies to any of the study drugs; patients with epilepsy; body mass index (BMI) < 13 kg/m_2 or > 30 kg/m_2; history of heart, lung, liver or kidney dysfunction and adrenocortical insufficiency; airway abnormalities; administration of sedative or opioids within 24 hours; history of general anaesthesia within 7 days; pregnancy and mental disease.

Anesthesia Protocol

All patients fasted for more than 8 hours before surgery and did not receive any premedication. On arrival at the operating room, the standard monitors consisted of heart rate (HR), electrocardiogram (ECG), pulse oximetry (SpO_2), invasive arterial pressure (IBP), end-tidal carbon dioxide ($PETCO_2$) and bispectral index (BIS) (BISTM XP sensor). In the meantime, an indwelling cannula was inserted into a large vein by nurse. Anesthesia was induced after ensuring that the blood pressure and HR were constant. Then, the patients were preoxygenated via a face mask and induction of anaesthesia intravenously was performed with midazolam 0.05 mg/kg, fentanyl 4ug/kg, etomidate 0.3 mg/kg or propofol 2 mg/kg with 20 s injecting time, respectively. After palpebral reflex loss, the BIS value reached to 50, a single dose of rocuronium 0.6 mg/kg was given and 1 min later the patient was orotracheally intubated. Continuous infusion of propofol 6–10 mg/kg/h or etomidate 0.6-1 mg/kg/h and remifentanil 0.1 μg/kg/min-0.3 μg /kg/min maintained anesthesia. The BIS value was used as a guide to adjust the infusion rate of propofol or etomidate and that was maintained between 40 and 50. Ventilation was adjusted to maintain $PETCO_2$ between 35–45 mmHg. To avoid the effects of diurnal changes in cortisol secretion, each study began between 8 AM to 9AM.

Observation Indicators

The patient characteristics (age, sex, weight, total burn areas, third-degree burns area), operation time and recovery time (time from drug stopping to orientation recovery (min)) of the two groups were recorded. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), HR and BIS were measured and recorded immediately at 7 different time points: the baseline (t0), before anesthesia induction (t1), 1, 3, 5, and 30 min following the intubation (t2–5), and the end of the surgery (t6). The remifentanil hydrochloride dosage was recorded during anesthesia maintenance in the two groups.

The number of patients with significant hemodynamic changes during the whole operation were recorded in the two groups: SBP or HR increases or decreases baselines by more than 30%, SBP < 90 mmHg or > 140 mmHg; HR < 50 beats/min or > 100 beats/min. Changes in MAP and HR fluctuated within 30% of the baseline values. Beyond this range, vasoactive drugs would be used for treatment (including ephedrine and atropine, etc.).

The clinical grade of myoclonic intensity was determined by the following scales for a period of two minutes: 0, no myoclonus; 1, mild myoclonus (short limb movements, such as fingers or wrists); 2, Moderate myoclonus (light movements of two different muscles, such as the face and arms); 3, Severe myoclonus (intense clonic movement of two two or more muscle groups, rapid adduction of limbs). [7]

Before induction of anesthesia, and at 30 min, 2 h, 24 h, and 48 h after end of surgery, artery blood (2 ml) was collected and placed in the PE tube (T0, T1, T2, T3 and T4). These samples were stored at -20℃ after centrifugation. Radioimmunoassay was used for quantifying serum concentrations of ACTH, Cor and ALD after all the samples were obtained.

Randomization

All the patients were randomly assigned into Group E and Group P using web-based randomization software. One researcher sealed envelopes in which had sequential study numbers, and they were opened just before anesthesia induction.

Another researcher performed total anesthesia according to the trial protocol and randomized table.

Blinding

The study was s a double-blind trial, the data collectors were blinded to which group each patient belong to and another study personnel gave the drugs intravenously. The patients also did not know which group they belong to.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or number, as appropriate.

SPSS statistical software was used for data analysis (SPSS 16.0, SPSS, Inc., Chicago, IL, USA). Kolmogorov-Simonov was used to test the normal distribution of data.

T test was used for comparison between the two groups. Repeated measures analysis of variance (RM-ANOVA) was used to compare the difference within the group and post hoc tests (Least Significant Difference, LSD). Count data were analyzed by Chi-square test. A P value of < 0.05 was considered statistically significant.

Sample Size

The study was designed to be a non-inferiority trial, and the aim of that was to assess whether etomidate is superior to propofol in severe burn patients. When calculating the sample size, the maximum risk was 5% and the significance level was 5%. According to the previous results, we determined that the sample size for each group should be 20 for proper reproducibility.

Results

Forty patients were included in the trial. None was excluded during the study period. (Fig. 1) The demographic data, operation time and recovery time of the patients were summarized in Table 1. The difference between the two groups was not significant ($P > 0.05$).

The dosage of remifentanil hydrochloride during the perianesthetic period was not significantly different in the two groups ($P > 0.05$). There was no significant difference in the time from drug withdrawal to eye opening between the two groups (Group P 10.34 ± 0.15; Group E 9.25 ± 0.23; $P = 0.64$).

Table 2 summarize the MAP changes during the perianesthetic period in two groups. In Group P, compared with t0, MAP of t1, t2, t3, t4, t5 and t6 decreased significantly, and the difference was statistically significant ($P = 0.045$, $P = 0.009$, $P = 0.007$, $P = 0.005$, $P = 0.008$, $P = 0.006$, respectively). In Group E, compared with t0, MAP of t3, t4 and t6 decreased significantly ($P = 0.021$, $P = 0.022$, $P = 0.026$, respectively). But the MAP at other time points was not different in both groups. In addition, there was no significant difference between the two groups at any time point.

Table 3 summarize the HR changes during the perianesthetic period in two groups. The HR was significantly decreased at t1 in two groups, compared with t0 ($P = 0.000$, $P = 0.000$). Compared with t1, the HR was significantly increased at t2(Group P: $P = 0.004$; Group E: $P = 0.010$), t3 (Group P: $P = 0.013$; Group E: $P = 0.033$), t4 (Group P:$P = 0.035$) and t5 (Group P:$P = 0.042$). However, there was no significant difference between the two groups at any time point.

Figure 2 shows the ACTH changes and comparisons. The ACTH level of the patients in Group P and Group E significantly decreased at T1, T2, T3 and T4 compared with those at T0 ($P = 0.004$, $P = 0.000$, $P = 0.000$, $P = 0.000$; $P = 0.001$, $P = 0.000$, $P = 0.000$, $P = 0.000$, respectively). In Group E, the ACTH level significantly increased at T4 compared with T3 ($P = 0.017$). At the time points T2 and T3, the difference between Group P and Group E were statistically significant ($P = 0.010$ and 0.000, respectively).

Figure 3 shows the Cor changes and comparisons. In Group E, the Cor level decreased significantly at T2 compared with T0 ($P = 0.022$). However, there was no statistical difference in Group P. The Cor level was not different between the two groups at any time point.

Figure 4 shows the ALD changes and comparisons. The ALD level of the patients in Group E decreased significantly at T1, T2, T3 and T4 compared with those at T0 ($P = 0.002$, $P = 0.000$, $P = 0.000$, $P = 0.000$, respectively). But there was no statistical difference in Group P. The ALD level at T2, T3 and T4 were significantly higher in Group P than those in Group E.

There was no myoclonic case in Group P, and there was only one case of mild myoclonus and one case of moderate myoclonus in Group E (Table 4). Incidence of myoclonus was 10% in Group E.

Discussion

This study aims to observe the effect of propofol or etomidate on hemodynamics for anesthetic induction and maintenance; To compare the inhibitory effect of propofol or etomidate on the adrenal cortex in patients with severe burns. Our results concluded that the MAP was significantly decreased in the Group P and Group E compared to that of base value and there were no intergroup differences in the two groups. However, etomidate has less effect on hemodynamics than propofol. Both propofol and etomidate are commonly used to intravenous induction and maintenance. Hypotension is known to occur with propofol because sympathetic activity is reduced, leading to vasodilation. The effect of etomidate on hemodynamic stability may be due in part to its lack of unique effects on sympathetic nervous system and baroreceptor function.[8] Thus, etomidate appears to be an appropriate drug to provide hemodynamic stability and more is appropriate for critical ill patients. We also demonstrated that the HR decreased significantly at the t1 time point in the two groups and then the HR was significantly increased at t2, t3, t4 and t5. The reason for HR's return may be due to pain and sympathetic nerve stimulation caused by intubation and operation.

A burn wound is perhaps the most intense stress that a human body can suffer. [9] The biological response to stress covers the endocrine, immune and autonomic nervous systems; however, the most widely used biomarker of stress is the HPA axis response. [10] Changes in neuroendocrine hormone levels are highly correlated with burn area and the depth of injury.[5] Pileri D et al. [9] studies reported that high cortisol levels are predictors of the severity of sepsis and clinical outcome. Elevated cortisol levels have been shown to reflect the severity of the traumatic injury.

Etomidate is a short-acting hypnotic anesthetic agent commonly used for induction and maintenance. However, etomidate reversibly inhibits adrenal function.[11] The present study showed that the ACTH level of the patients in Group P and Group E decreased significantly at T1, T2, T3, T4 compared with those at T0. However, that levels of T2 and T3 were significantly lower in Group E than those in Group P. In Group E, the ACTH level significantly increased at T4 compared with T3. The Cor level decreased significantly at T2 compared with T0 in Group E, and then recovering gradually. The ALD level of the patients in Group E decreased significantly at T1, T2, T3, T4 compared with those at T0, and that also gradual recover at T3. But the ALD level at T2, T3 and T4 were significantly higher in Group P than those in Group E. Similarly, Das D et al. [12] reported that etomidate inhibits the enzyme 11 hydroxylase in a dose-dependent manner which converts function for up to 24 h.

Myoclonus is one of the adverse side effects induced by etomidate anesthesia induction. Increased risk of reflux and aspiration can be caused by myoclonus in full stomach patients and increased oxygen consumption in the myocardial also can be caused by myoclonus. [13] When etomidate was used without premedication, the incidence of myoclonus could can be as high as 50–80%. [14] In our study, only one mild myoclonus and one moderate myoclonus were observed in 20 patients. The reasons for that we used midazolam, fentanyl and remifentanil. Other studies reported that several drugs could effectively prevent the occurrence of the myoclonus induced by etomidate, such as dezocine, lidocaine and midazolam, fentanyl and remifentanil. [15–16]

This study has two limitations: we could not track long-term mortality or survival rate and did not compare the effects of propofol or etomidate in non-burn patients.

Conclusions

Propofol and etomidate for anesthesia induction and maintenance could cause hemodynamic changes, but the effect of etomidate was lighter. The propofol and etomidate both suppress adrenal cortex function, that inhibitory effect of etomidate was greater than propofol. There were no related serious adverse during this study. Therefore, etomidate may have a certain beneficial effect in severe burn patients.

Abbreviations

HR: heart rate; MAP: mean arterial pressure; BIS: bispectral index; ACTH: adrenocorticotropic hormone; Cor: cortisol; ALD: aldosterone; HPA: hypothalamic–pituitary–adrenal; TBSA: total body surface area; FTBSA: full-thickness burn surface area; ASA: American Society of Anesthesiologists; BMI: body mass index; ECG: electrocardiogram; SpO2: pulse oximetry; IBP: invasive arterial pressure; PETCO2: end-tidal carbon dioxide; SD: standard deviation; RM-ANOVA: Repeated measures analysis of variance; LSD: Least Significant Difference.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Affiliated Hospital of Chengde Medical College (22029) according to the Declaration of Helsinki. Chairman of the ethics committee: Qing Zhang. Tel: +86 03142279322. All patients or their legal representative voluntarily signed informed consents.

Consent for publication

Not applicable.

Availability of data and materials

The datasets during the current study were available from the first author.

Competing interests

The authors declare that they have no competing interests.

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No funding was obtained for this study.

Authors' contributions

XLL participated in study design, data collection, drafting of the manuscript, and the statistical analysis. GYJ participated in the statistical analysis and helped draft the manuscript. HBL participated in study design, data collection, and drafting of the manuscript. JMZ participated in data collection, and drafting of the manuscript. RHL participated in study conception and design. JLL participated in study design and the statistical analysis. HMZ participated in study conception and design, data collection. All authors read and approved the final manuscript.

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Tables

Due to technical limitations, Tables 1-4 are provided in the Supplementary Files section.

Figures

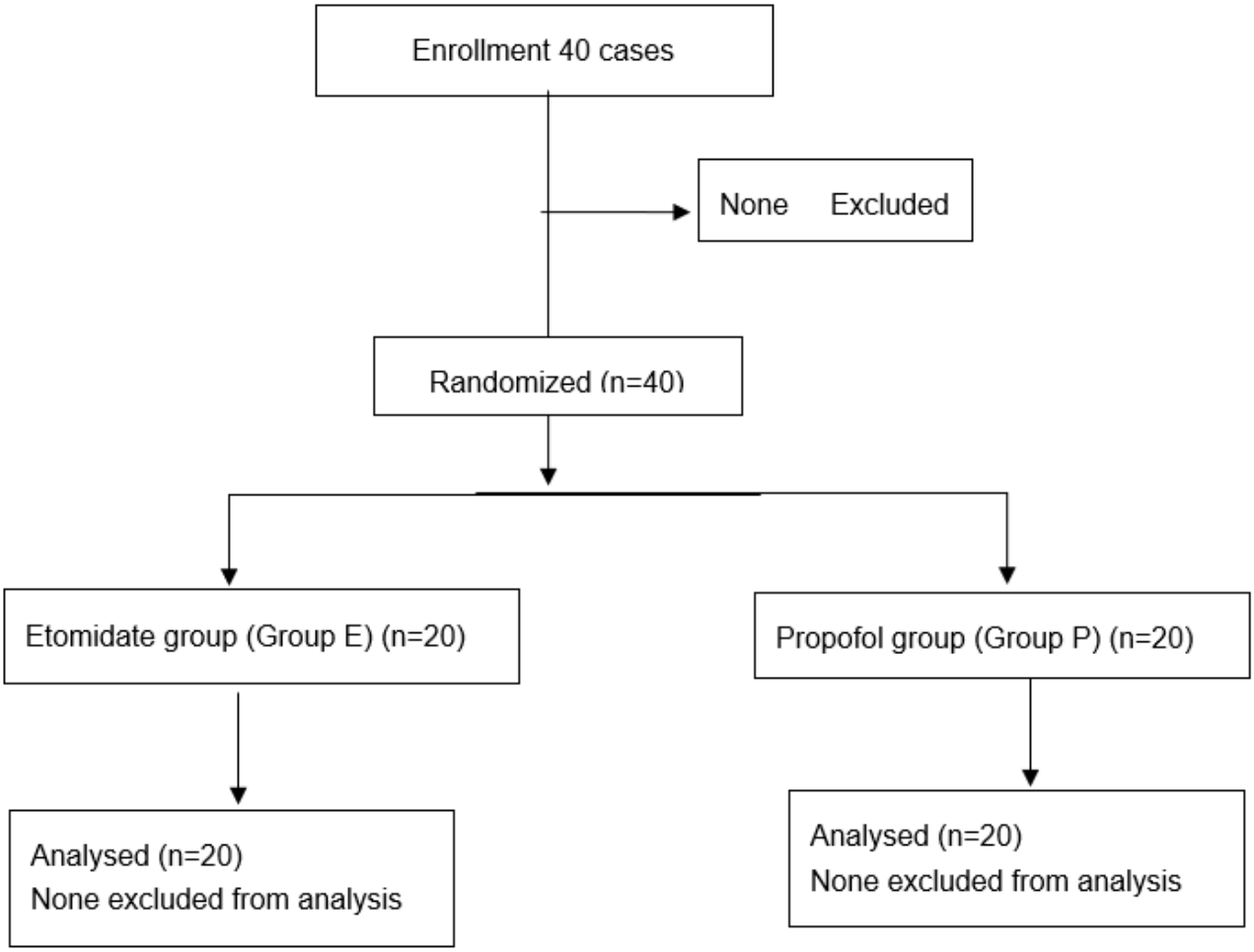
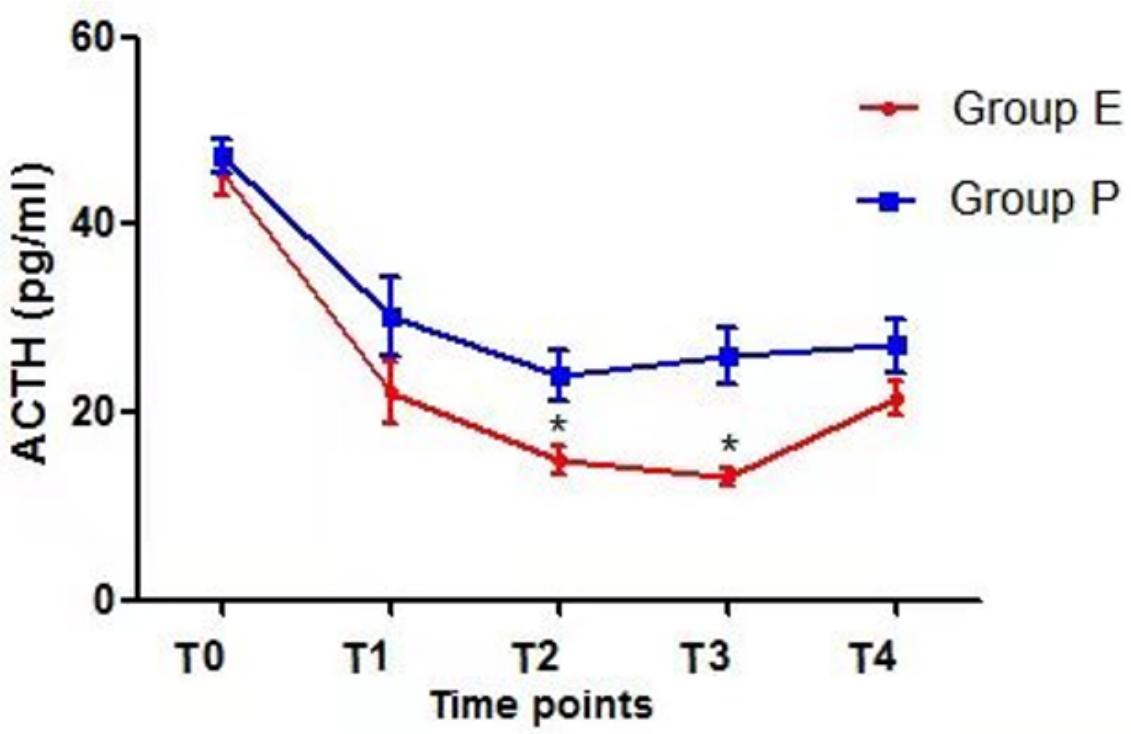


Figure 1

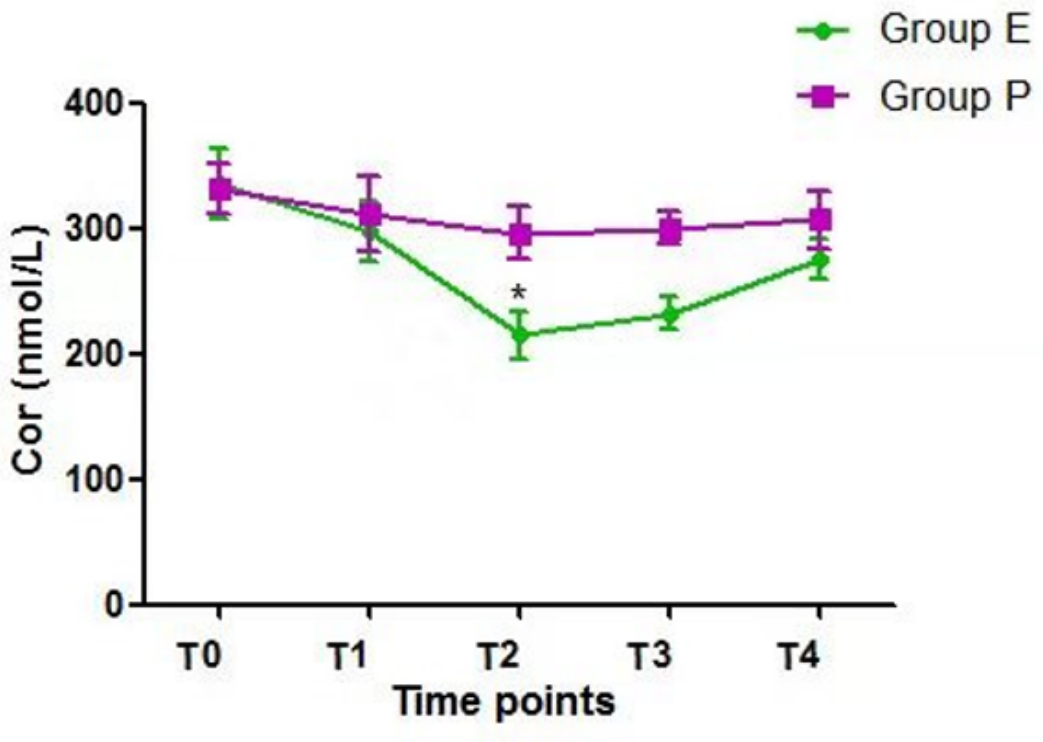
The inclusion of patients



Notes: Compared with group P, * P <0.05.

Figure 2

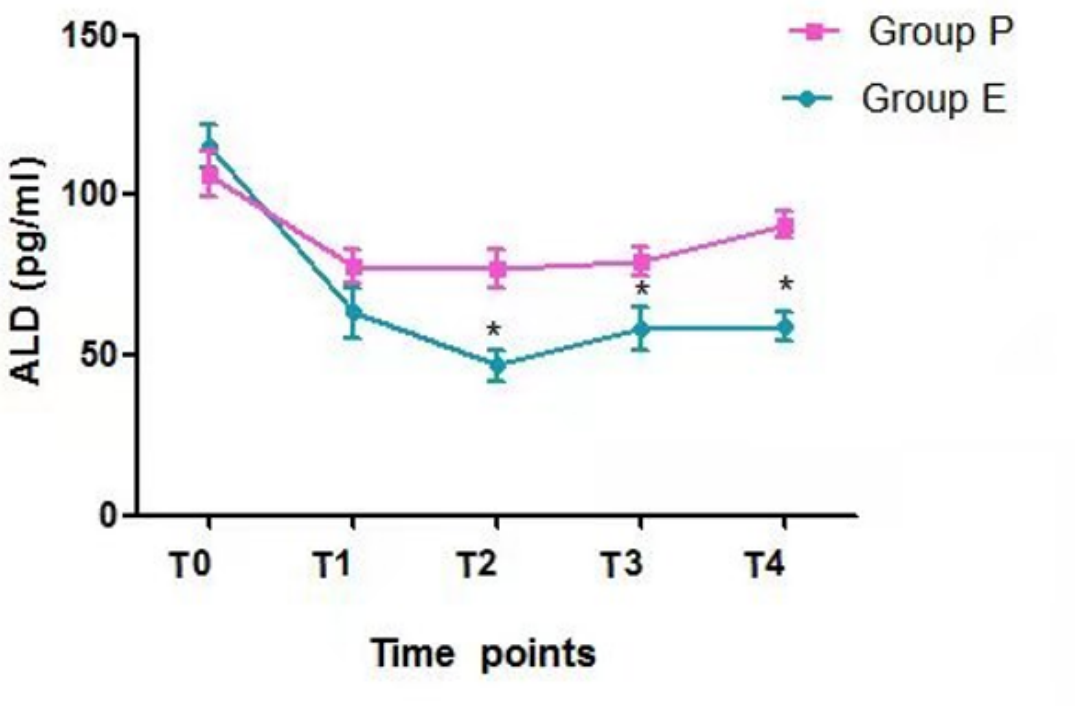
The ACTH level of the patients in group P and group E. Data are presented as the mean and SD.



Notes: Compared with T0 in group E, * P <0.05.

Figure 3

The Cor level of the patients in group P and group E. Data are presented as the mean and SD.



Notes: Compared with group P, * P <0.001.

Figure 4

The ALD level of the patients in group P and group E. Data are presented as the mean and SD.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTFlowDiagram.doc
- CONSORT2010Checklist.doc
- Tables.docx