Effects of different methods of anesthesia on acute gastrointestinal dysfunction, postoperative cognitive impairment, and the immune status after laparoscopic radical rectal cancer surgery

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Research Article

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Abstract

Background

With an increase in the aged population in China, the annual incidence of rectal cancer is gradually increasing. This study compares the effects of two anesthesia methods on patients undergoing laparoscopic radical rectal cancer surgery.

Method

A total of 230 patients who underwent laparoscopic radical resection for rectal cancer in the Department of Anesthesiology, Huai'an First People's Hospital Affiliated to Nanjing Medical University from 2016 to 2021 were retrospectively analyzed. The general data, clinical symptoms, immune cell count, and cytokine count were collected on the first, third, and fifth postoperative days. In addition, the patients' Mini-Mental State Examination (MMSE) score was recorded, and dynamic analysis was performed to record gastrointestinal dysfunction after the operation.

Results

The postoperative awakening time (18.41 ± 2.88 vs. 23.23 ± 4.34), extubation time (27.84 ± 3.67 vs. 34.32 ± 5.73), and length of hospital stay (9.73 ± 1.32 vs. 12.32 ± 2.34) were shorter, while the postoperative MMSE score (25.43 ± 1.43 vs. 21.32 ± 2.32) was higher in patients administered general anesthesia plus epidural anesthesia than in those administered only general anesthesia. The proportion of CD4 + T lymphocytes was higher (39.45 ± 4.12 vs. 35.45 ± 4.56), and the proportion of CD8 + T lymphocytes was lower (25.34 ± 3.09 vs. 28.43 ± 3.43) in patients undergoing general anesthesia plus epidural anesthesia than in those undergoing only general anesthesia. Moreover, the count of natural killer (NK) cells was lower (0.104 ± 0.021 vs. 0.167 ± 0.024) and the level of human leukocyte antigen–DR isotype (HLA-DR) (66.43 ± 7.43 vs. 56.45 ± 6.43) was higher in patients administered general anesthesia plus epidural anesthesia. In addition, the levels of interleukin (IL)-6, IL-8, and IL-10 decreased with statistical differences ($P < 0.05$), and the probability of increased intra-abdominal pressure and acute gastrointestinal injury was lower ($P < 0.05$) in patients undergoing general anesthesia plus epidural anesthesia.

Conclusion

Addition of epidural anesthesia to general anesthesia can reduce the incidence of postoperative cognitive dysfunction, gastrointestinal injury, immunosuppression, postoperative awakening time, extubation time, and length of postoperative hospital stay.

Background

Due to a change in the social lifestyle and an increase in the aged population in China, the annual incidence of rectal cancer is gradually increasing, and it has a high mortality rate. Thus, it has become a major concern [1–3]. The treatment for rectal cancer can involve surgery, chemotherapy, radiotherapy, and immunotherapy; however, it is most commonly treated through laparoscopic radical resection [4–6].

Elderly patients often present with deteriorating organ function and immunity. As a result, they are often unable to tolerate several methods for anesthesia; furthermore, anesthetic drugs often produce various side effects [7]. General anesthesia is one of the most common pre-surgical procedures often accompanied by complications due to respiratory tract obstruction, including respiratory depression, pulmonary infection, and hypertension. Epidural anesthesia is a local anesthetic technique for blocking the nerve roots; it can reduce the postoperative revival time, accelerate the postoperative extubation time, and reduce pulmonary complications [8–10]. Combined anesthesia is the use of general and epidural anesthesia in patients, which may help achieve early postoperative awakening, reduced postoperative pain, and accelerated postoperative recovery.

In this study, we aimed identify the appropriate anesthetic technique for patients undergoing radical resection for rectal cancer by comparing the postoperative acute gastrointestinal, cognitive, and immune functions in patients administered general anesthesia and those administered general and epidural anesthesia.

Data And Methods

General data and grouping

We retrospectively studied the data of patients who underwent laparoscopic radical resection for rectal cancer in the Department of Anesthesia and Surgery, Huai 'an First People's Hospital Affiliated with Nanjing Medical University, from 2016 to 2021. A total of 230 laparoscopic radical colorectal cancer surgery cases with complete records were identified; this included 148 male and 82 female patients, with an average age of 68.32 years. The patient's general information was collected, including age, gender, medical history, length of hospital stay, type of anesthesia, postoperative extubation time, and postoperative revival time. They were divided into general and compound anesthesia groups according to the mode of anesthesia.

Inclusion criteria

Laparoscopic resection for rectal cancer; age ≥ 50 years; and complete postoperative medical records, which could be evaluated after surgery.

Exclusion criteria

History of cognitive disorders, such as mental abnormalities, mental retardation, etc.; history of open or laparoscopic surgery; and incomplete patient data.

Data collection

Gastrointestinal symptoms were recorded, including abdominal pain, diarrhea, constipation, and increased intra-abdominal pressure. Acute gastrointestinal injury classification was used to grade gastrointestinal function. Lymphocyte subsets and cytokine counts were recorded on the first, fourth, and seventh postoperative days. The Mini-Mental State Examination (MMSE) scores were recorded on the first, third, and seventh postoperative days.

Flow cytometric analysis

Peripheral blood mononuclear cells were isolated using Ficoll gradient centrifugation. The antibodies used included anti-CD19 (HIB19), anti-CD3 (UCHT1), anti-CD4 (OKT4), anti-CD8 (SK1), anti-CD16 (3G8), anti-CD56 (5.1H11) and anti-human leukocyte antigen–DR isotype (HLA-DR) (L243). Antibodies were purchased from eBioscience, Biolegend, or MD Bioproducts. FACSAria III with 3-laser (BD Biosciences, New York, USA) was used for flow cytometry analysis.

Measurement of cytokines

The cytokines concentrations in different patients' serums were determined by LEGENDplex beading-based multiplex assay (Biolegend) according to the manufacturer's protocol.

Data analysis

Data analysis was performed by using SPSS version 19.0. Mean and standard deviations were used when data were normally distributed, and median and quartile were used when data were not normally distributed. An independent sample t-test or Mann-Whitney U test was used to compare the data between the two groups according to the normality test results. Enumeration data were expressed as N (%), comparison between groups was performed by chi-square test, continuous dynamic indicators were analyzed by continuous dynamic analysis, and a P value of ≤ 0.05 was considered statistically significant.

Results

General patient data

The postoperative recovery time (18.41 ± 2.88 vs. 23.23 ± 4.34), postoperative extubation time (27.84 ± 3.67 vs. 34.32 ± 5.73), length of hospital stay (9.73 ± 1.32 vs. 12.32 ± 2.34) and bed rest time (1.79 ± 0.41 vs. 2.12 ± 0.32) were shorter in the combined anesthesia group than in the general anesthesia group. Furthermore, there was a lower risk of acquiring pneumonia and developing deep vein thrombosis in the combined anesthesia group ($P < 0.05$). There were no differences in age, height, and past medical history, as shown in Table 1.

Table 1
Baseline data of both groups

Variable	General anesthesia(n = 130)	Compound anesthesia (n = 100)	P
Male	85 (65.4%)	63 (63%)	0.7082
Female	45 (34.6%)	37 (37%)	
Age	68.43 ± 13.24 yrs	67.32 ± 11.73 yrs	0.9082
Height	1.68 ± 0.142 m	1.73 ± 0.135 m	0.8643
Hypertension	74 (56.9%)	63 (63%)	0.8324
Diabetes	67 (51.5%)	54 (54%)	0.7012
Coronary heart disease	58 (44.6%)	42 (42%)	0.6916

Length of hospital stay and other complications

The awakening time (18.41 ± 2.88 vs. 23.23 ± 4.34), postoperative extubation time (27.84 ± 3.67 vs. 34.32 ± 5.73), length of hospital stay (9.73 ± 1.32 vs. 12.32 ± 2.34) and time required for bed rest (1.79 ± 0.41 vs. 2.12 ± 0.32) were shorter in the combined anesthesia group than in the general anesthesia group. In addition, the combined anesthesia group showed a lower risk of hypostatic pneumonia and deep venous thrombosis ($P < 0.05$), as shown in Table 2.

Table 2
Comparison of postoperative complications and length of hospital stay between the two groups

Variable	General anesthesia (n = 130)	Compound anesthesia (n = 100)	P
Operation time	94 ± 13.24	89.3 ± 15.23	0.328
Awakening time	23.23 ± 4.34	18.41 ± 2.88	**< 0.001**
Extubation time	34.32 ± 5.73	27.84 ± 3.67	**< 0.001**
Length of stay	12.32 ± 2.34	9.73 ± 1.32	**0.0432**
Time in bed	2.12 ± 0.32	1.79 ± 0.41	**0.0243**
Hypostatic pneumonia	18(13.8%)	5(5%)	**0.0266**
Deep venous thrombosis in the lower limbs	21(16.2%)	6(6%)	**0.017**

Comparison of postoperative MMSE scores between the two groups

The MMSE scores of patients undergoing laparoscopic radical resection for rectal cancer were measured on the first, third, and seventh postoperative days. The results showed that the MMSE scores of patients in the combined anesthesia group on the first postoperative day were significantly better than those in the general anesthesia group (25.43 ± 1.43 vs. 21.32 ± 2.32). There was no significant difference in MMSE scores on the third and seventh postoperative days. However, the combined anesthesia group still had higher scores than the general anesthesia group. In addition, the MMSE scores of patients on the seventh postoperative day in the combined anesthesia group were higher than those on the first postoperative day, as shown in Fig. 1.

Comparison of immune function status between the two groups

The proportion of CD4 + T lymphocytes (39.45 ± 4.12 vs. 35.45 ± 4.56) was higher, the proportion of CD8 + T lymphocytes (25.34 ± 3.09 vs. 28.43 ± 3.43) and NK cell count (0.104 ± 0.021 vs. 0.167 ± 0.024) were lower, and HLA-DR concentration (66.43 ± 7.43 vs. 56.45 ± 6.43) was higher in the combined anesthesia group than in the general anesthesia group, as shown in Table 3. In terms of dynamic analysis, the proportion of CD3 + T lymphocytes, CD4 + T lymphocytes, and HLA-DR in the combined anesthesia group continued to increase after surgery, while the proportion of CD8 + T lymphocytes and B lymphocytes continued to decrease, and the NK cell count was in dynamic balance. The proportion of CD3 + T lymphocytes, CD4 + T lymphocytes, and HLA-DR in the general anesthesia group continued to rise gradually after surgery. However, the counts of CD8 + T lymphocytes and NK cells continued to decline, and the B lymphocyte count was in dynamic balance, as shown in Table 3 and Fig. 2. A total of 93 patients had complete data on inflammatory factors, 56 from the general anesthesia group and 37 from the combined anesthesia group. It was found that the levels of IL-6, IL-8, and IL-10 in the combined anesthesia group continued to decrease and returned to the normal range on the third postoperative day. In contrast, interferon (IFN)-α level decreased slowly and returned to normal on the fifth postoperative day. In the general anesthesia group, the level of IL-8 continued to decrease, but it was still higher than the upper limit of the normal range on the fifth postoperative day. IL-10 and IFN-α were in dynamic equilibrium, both higher than the upper limit of the normal range, and the level of IL-6 increased initially and then decreased, as shown in Fig. 3.

Table 3
Baseline values of immune cells and inflammatory cytokines in postoperative patients

Variable	General anesthesia group (n = 84)	Compound anesthesia group (n = 53)	P
CD3 + T lymphocytes	63.23 ± 7.43	68.43 ± 8.43	0.243
CD4 + T lymphocytes	35.45 ± 4.56	39.45 ± 4.12	**0.043**
CD8 + T lymphocytes	28.43 ± 3.43	25.34 ± 3.09	**0.039**
B leukomonocyte	0.234 ± 0.054	0.243 ± 0.043	0.524
NK cell	0.167 ± 0.024	0.104 ± 0.021	**0.028**
HLA-DR	56.45 ± 6.43	66.43 ± 7.43	**< 0.001**
IL-6	187.63 ± 21.34	165.4 ± 24.3	**0.043**
IL-8	95.43 ± 13.24	78.43 ± 14.6	**0.035**
IL-10	56.73 ± 8.45	43.2 ± 7.43	**0.0564**
IFN-α	24.54 ± 4.87	18.76 ± 4.34	**< 0.001**
NK; natural killer, HLA-DR; human leukocyte antigen–DR isotype, IL; interleukin, IFN- α; interferon-alpha			

Comparison of gastrointestinal dysfunction between the two groups

Following the classification of gastrointestinal function proposed by Li [13] et al., the appropriate classification was made according to the clinical manifestations of patients. Compared with patients undergoing surgery under general anesthesia, patients undergoing surgery under combined anesthesia were less likely to have elevated intra-abdominal pressure and acute gastrointestinal dysfunction ($P < 0.05$). At the same time, there were no statistically significant differences in the clinical manifestations such as abdominal distension, abdominal pain, dyspepsia, and poor defecation, as shown in Table 4.

Table 4
Evaluation of postoperative gastrointestinal symptoms and gastrointestinal loss of function in the two groups

Variable	General anesthesia group (n = 130)	Compound anesthesia group (n = 100)	P
Abdominal distension	38	24	0.3755
Abdominal pain	25	17	0.6642
Indigestion	46	35	0.9517
Poor defecation	27	13	0.1233
Elevated intra-abdominal pressure	15	4	**0.04**
AGI classification			
I	16	4	**0.027**
II	15	3	**0.024**
III	8	1	**0.045**
IV	2	0	0.213
AGI; Acute gastrointestinal injury			

Discussion

In recent years, the incidence of rectal cancer has been increasing. Although the age of onset has a downward trend, the elderly are still a high-risk group for rectal cancer. Rectal cancer is commonly treated with laparoscopic radical resection [1–3]. Postoperative complications such as cognitive and gastrointestinal dysfunction and immunosuppression often exist in elderly patients. Choosing appropriate anesthesia methods can reduce these complications and improve immune function and survival rates.

In this study, we compared the effects of general anesthesia and general anesthesia combined with epidural anesthesia on patients undergoing laparoscopic radical resection of rectal cancer. The postoperative recovery time, postoperative extubation time, hospitalization time, and the time for bed rest (1.79 ± 0.41 vs. 2.12 ± 0.32) were all lower in the combined anesthesia group than in the general anesthesia group; furthermore, there was a lower risk of hypostatic pneumonia and deep venous thrombosis; There was no significant difference in age, height, past medical history, and other aspects, which was consistent with previous studies [14–15].

Postoperative cognitive dysfunction is the most common complication after surgery and anesthesia, which can manifest as anxiety, speech disorder, and poor orientation [16–17]. Several studies have confirmed that postoperative cognitive dysfunction can be related to advanced age, prolonged operative time, cardiovascular and cerebrovascular system diseases, type of surgery, and anesthesia [18–20]. Surgical anesthesia is the most significant influencing factor. This study compares two anesthesia methods to assess their influence on postoperative cognitive function; the MMSE score was used to evaluate postoperative cognitive impairment. Our results showed that general anesthesia combined with epidural anesthesia could reduce postoperative anxiety and speech disorders. The MMSE score on the first postoperative day was significantly lower in the combined anesthesia group than in the general anesthesia group. Although there was no significant difference in MMSE scores on the third and fifth postoperative, the absolute value of MMSE was still lower than that in the general anesthesia group, which was consistent with the results of previous studies [21–22]. This study showed that using general anesthesia combined with epidural anesthesia could reduce the incidence of postoperative cognitive dysfunction in surgical patients. Previous studies have shown that postoperative cognitive dysfunction may be related to the abnormal activation of cholinergic neurons [23]; however, this study could not evaluate this aspect.

Gastrointestinal dysfunction is a common complication after radical resection of rectal cancer. Postoperative patients often present with dyspepsia, abdominal pain, abdominal distension, nausea, vomiting, elevated intra-abdominal pressure, and other manifestations. [24–25]. Compared with patients in the general anesthesia group, those in the combined anesthesia group were less likely to have increased intra-abdominal pressure and acute gastrointestinal dysfunction (P< 0.05), while there was no significant difference in clinical manifestations such as abdominal distension, abdominal pain, dyspepsia, and poor defecation, which was consistent with the results of previous studies [26–27]. Postoperative gastrointestinal injury is related to postoperative bleeding or surgical injury to the intestinal mucus barrier. When the intestinal mucus barrier is destroyed, a large number of endotoxins cause the release of inflammatory factors [28–29]. Previous studies have suggested that increased IL-6 level is an independent risk factor for acute gastrointestinal injury in surgical patients [30]. This study found that the levels of proinflammatory cytokines such as IL-6 and IL-8 in patients in the general anesthesia group were significantly higher than those in the combined anesthesia group, the downward trend was slower, and the values were higher than the upper limit of normal value. The continuous IL-6 and IL-8 cytokine storm may be the reason behind more serious gastrointestinal injury in patients in the general anesthesia group.

There are many reasons for immunosuppression in surgical patients, such as intraoperative injury of immune organs, the release of several immunosuppressive factors into the blood, postoperative nutritional dysfunction, etc. [31–32]. T lymphocytes are the main functional cells behind cellular immunity, among which CD8 + T lymphocytes are killer T lymphocytes play a significant role. They can secrete killer cytokines such as TNF-α and IFN-γ. On the other hand, CD4 + T lymphocytes mainly play a helper role. They can differentiate into T helper cells under the action of a variety of precursors to participate in immune regulation [33–34]. In this study, on dynamic analysis, compared with patients in the general anesthesia group, those in the combined anesthesia group had higher CD4 + T and CD8 + T

lymphocyte count. In the compound anesthesia group, CD4 + T and CD8 + T lymphocytes continued to rise postoperatively; Il-10, an immunosuppressive cytokine, has been shown to inhibit secondary lymph node formation by affecting the function of follicular helper T cells and affecting the expression of transcription factors Bcl-6 and BLAMP-16 [35–36], thereby achieving immunosuppression. In this study, the general anesthesia group had higher levels of IL-10 cytokines than the combined anesthesia group. In the dynamic analysis, the patients in the general anesthesia group had higher levels of IL-10 in dynamic equilibrium. In contrast, in the combined anesthesia group, the levels of IL-10 went down faster; on the third postoperative day, they were below the normal limit. Therefore, general anesthesia combined with epidural anesthesia can reduce the injury due to CD4 + T lymphocytes and CD8 + T lymphocytes, reduce the release of immunosuppressive cytokine IL-10, and thus reduce the incidence of postoperative immunosuppression.

There were also several limitations in this study. First, this study was a single-center study and included 230 surgical patients; therefore, it had a relatively uniform and small sample size. Second, some patients in this study had partially incomplete data for immune function and cytokine level evaluation. Therefore, future large-scale research is needed to prove the beneficial effects of general anesthesia combined with epidural anesthesia.

Conclusion

General anesthesia combined with epidural anesthesia can reduce the incidence of postoperative cognitive dysfunction, alleviate damage to gastrointestinal function, improve postoperative immunosuppression, shorten the postoperative awakening time and extubation time, and reduce the length of hospital stay in patients undergoing radical laparoscopic surgery for colorectal cancer.

Abbreviations

MMSE; Mini-Mental State Examination

NK; natural killer

HLA-DR; human leukocyte antigen – DR isotype

IL; interleukin

IFN; interferon

Declarations

Authors' contributions

All work was approved by the co-authors. DCW made significant contributions to conception and study design. Data acquisition was completed by XH and XQZ . Data analysis and interpretation were

performed by DCW and XH; DCW and XH have written the draft of the article and critically revised it. No conficts of interest exist in the submission of this manuscript. I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously and is not under consideration for publication elsewhere, in whole or in part. All authors read and approved the fnal manuscript.

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Ethics approval and consent to participate

All experiments in this study were carried out in accordance with the Declaration of Helsinki.

This study was approved by the Ethical Committee of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University. The data used in this study was anonymised before its use and were collected during routine procedures, which did not pose any additional risk to the patients. The requirement for informed consent by individual patients was waived by the Ethical Committee of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University given the retrospective nature of the study.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Consent for publication

Not applicable.

Competing interest

The authors declare that they have no confict of interest.

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Figures

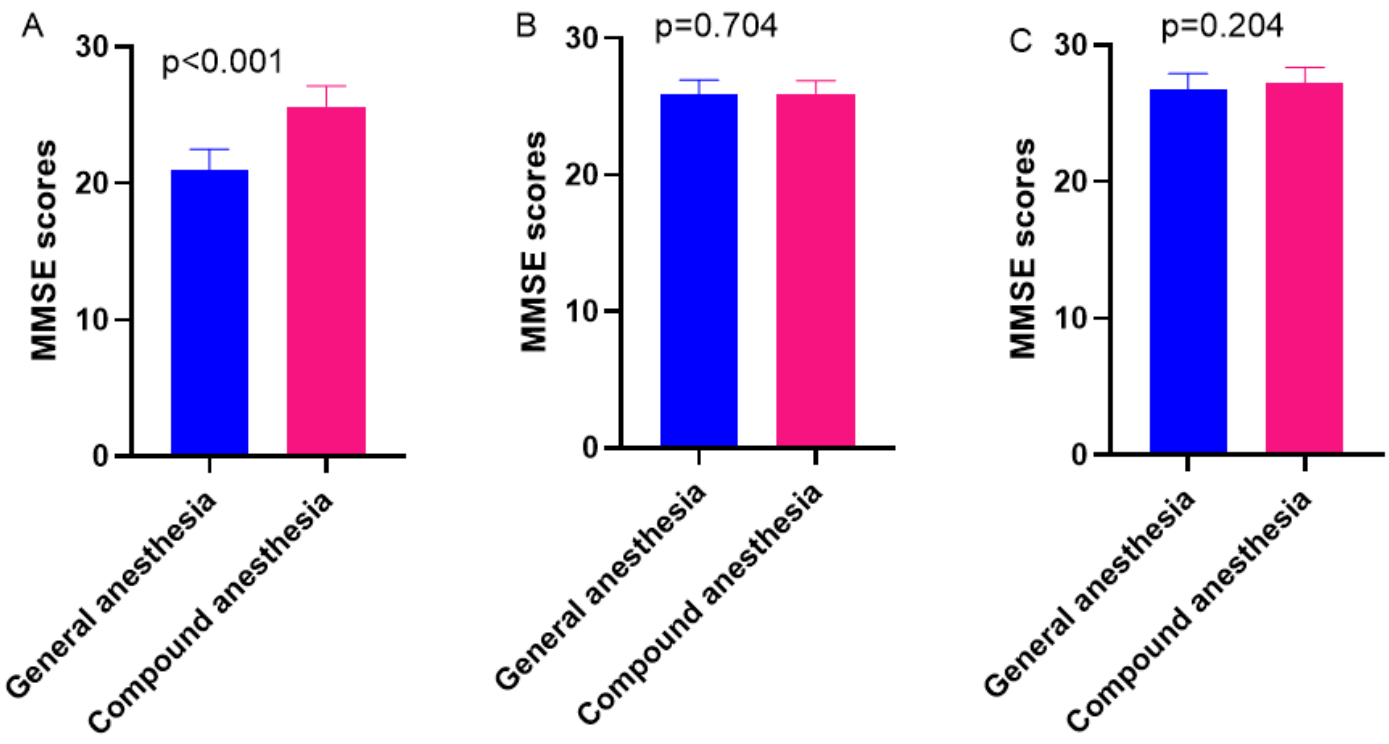

Figure 1

Dynamic changes in cognitive function scores after surgery

A: The MMSE score on the first postoperative day; B: The MMSE score on the third postoperative day; C: The MMSE score on the seventh postoperative day.

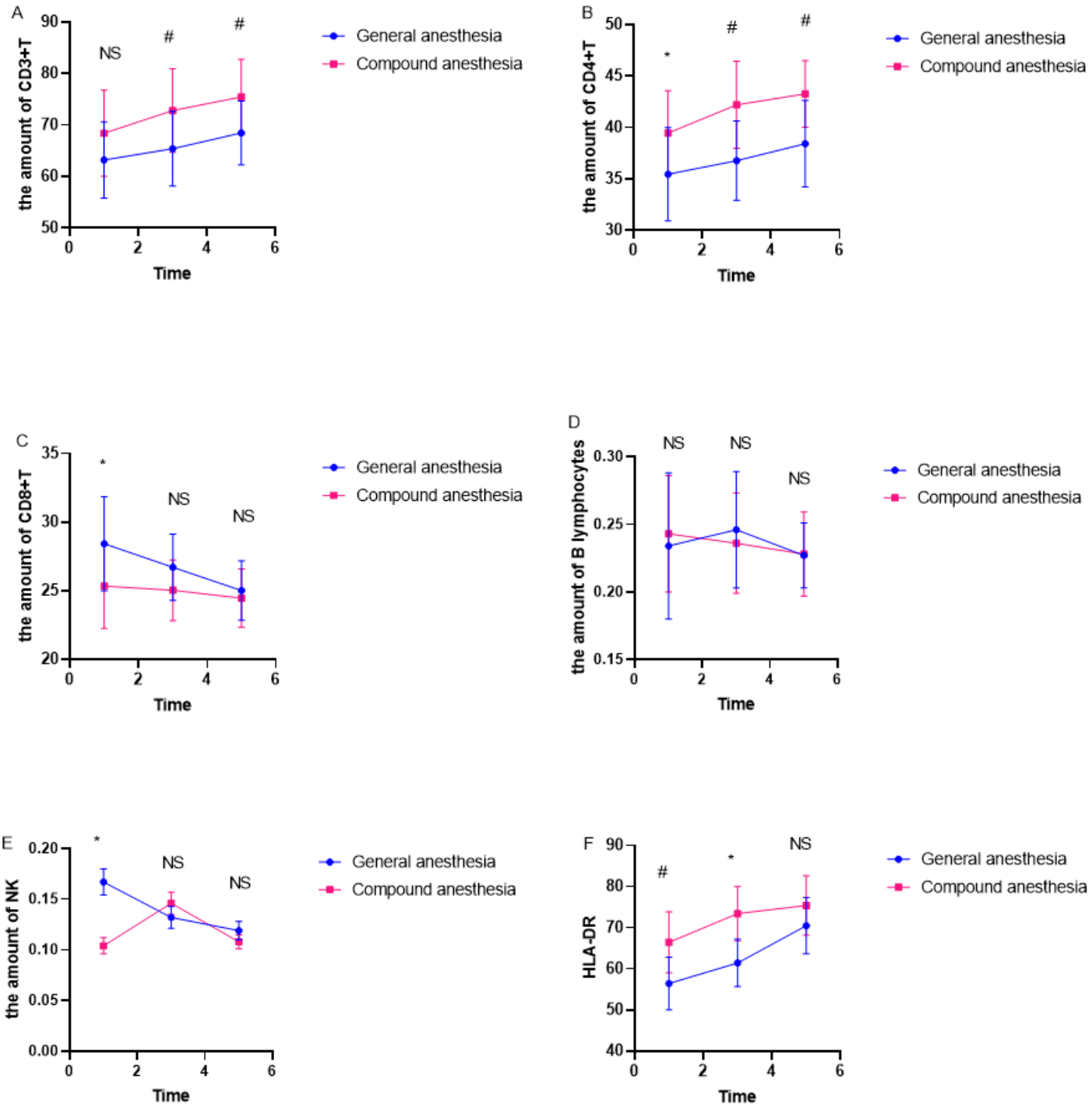

Figure 2

Dynamic changes in lymphocyte subsets and HLA-DR during hospitalization

A: The dynamic change in CD3+ T lymphocytes; B: The dynamic change in CD4+ T lymphocytes; C: The dynamic change in CD8+ T lymphocytes; D: The dynamic change in B lymphocytes; E: The dynamic change in NK cells; F: The dynamic change in HLA-DR.

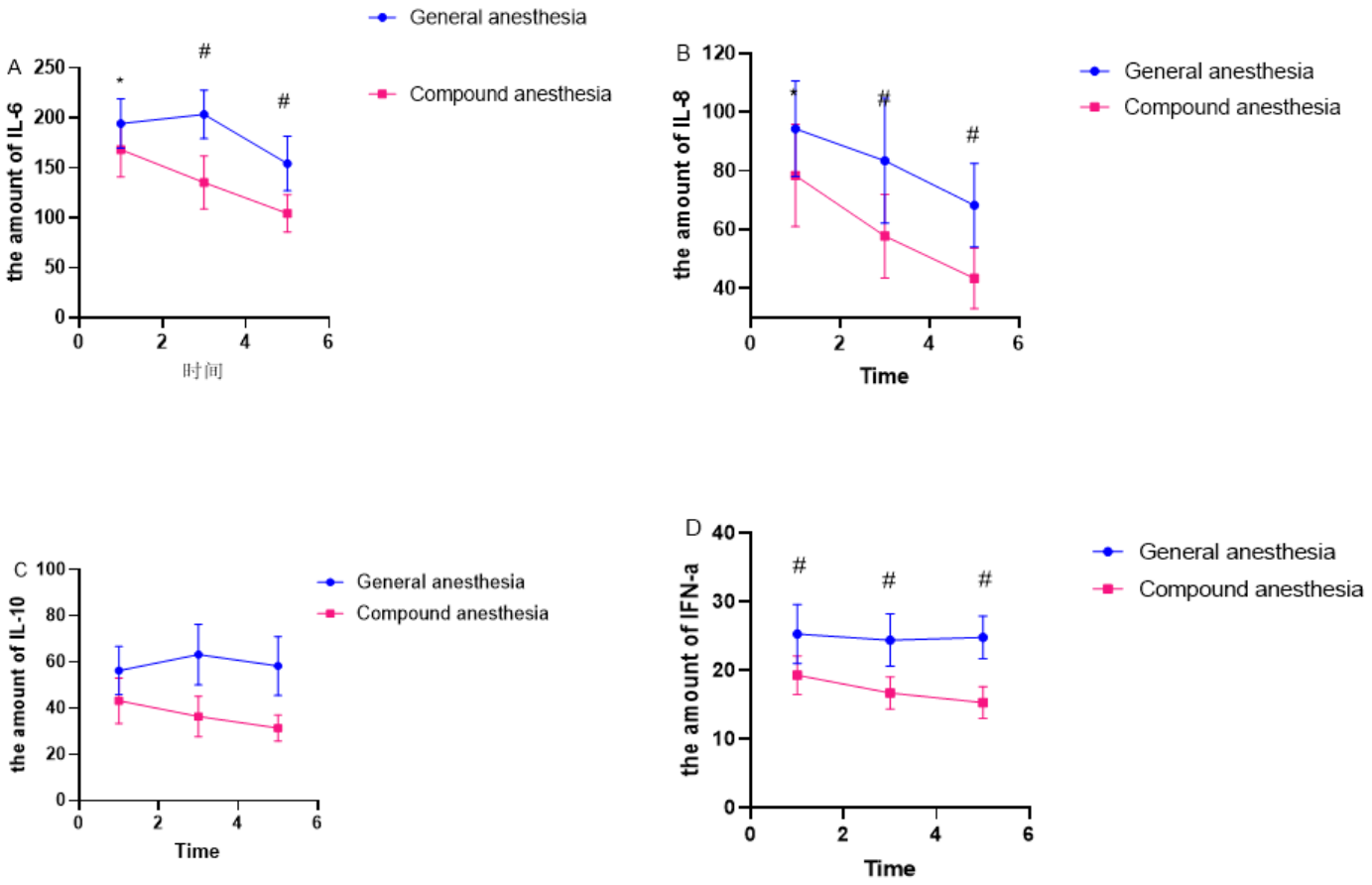

Figure 3

Dynamic comparison of inflammatory cytokine levels

A: The dynamic change in IL-6; B: The dynamic change in IL-8; C: The dynamic change in IL-10; D: The dynamic change in IFN-a. *p <0.05, #p <0.001.