Observational Study

Medicine®

OPEN

Effects of oxycodone on immune function in patients undergoing radical resection of rectal cancer under general anesthesia

Jia-Hua Cui, Resident Physician, Wan-Wei Jiang, Chief Physician*, Ya-Jing Liao, Resident Physician, Qing-Hui Wang, Physician-in-Charge, Min Xu, Associate Chief Physician, Yu Li, Physician-in-Charge

Abstract

This study aims to explore the effect of oxycodone hydrochloride injection on the immune function of patients who underwent radical resection of rectal cancer under general anesthesia.

Eighty patients were enrolled and randomly divided into group A and B (n = 40, each). All patients underwent general intravenous anesthesia. At the end of surgery, each patient in group A was injected with 5 mg (5 mL) of oxycodone hydrochloride, while 5 mg (5 mL) of morphine hydrochloride in group B. Venous blood was withdrawn in both groups at different time points. Changes in the numbers of T lymphocyte subsets and natural killer (NK) cells were determined by flow cytometry.

First the numbers of T lymphocyte subsets and NK cells at T1, T2, T3, and T4 decreased in both groups, compared with those at T0, and the differences were statistically significant. Furthermore, the numbers reduced to a minimum at T2 and began to recover at T3. Second the differences between group A and B at T1, T2, T3, and T4 were statistically significant; and the numbers of T lymphocytes and NK cells were higher in group A than in group B at corresponding time points.

Oxycodone hydrochloride and morphine hydrochloride both have inhibitory effects on immune function in patients undergoing radical resection of rectal cancer after surgery. However, oxycodone hydrochloride has a smaller effect compared to morphine hydrochloride.

Abbreviations: BP = blood pressure, HR = heart rate, NK = natural killer, PCEA = patient-controlled epidural analgesia, PCIA = patient-controlled intravenous analgesia.

Keywords: analgesia, anesthesia, immune function, morphine hydrochloride, oxycodone hydrochloride

1. Introduction

The incidence of rectal cancer has continuously increased recently. Surgery has become the first choice for the radical treatment of early rectal cancer. However, surgical stimulation and anesthesia can affect the immune function of patients. An impaired immune function after surgery will bring harm to the patient such as increased survival rate of the tumor cell microembolus, high rates of recurrence and metastasis, high rates of systemic and wound infections and sepsis, slow healing of wounds, and the waste of medical resources. Furthermore, a good postoperative analgesia is also necessary, which can reduce and prevent a series of stress reactions caused by surgical trauma, and reduce the incidence of postoperative complications.[1] A strong stress reaction can inhibit the immune function of patients. Hence, a good postoperative analgesia is conducive to the rehabilitation of patients, and in shortening the length of hospital stay and reducing cost. This would provide more comfortable humanistic care, reflecting the new concept of comfortable medical treatment. At present, oxycodone is often used for postoperative analgesia. It has a lasting analgesic effect and can effectively reduce analgesic gaps. All commonly used traditional opioid analgesic drugs have effects on immunity to a different extent.[2] Morphine, fentanyl, and other strong opioid drugs have immunosuppressive effects that can reduce T cells and inhibit the secretions of the hypothalamic-pituitary-adrenal/gonadal axes. The equivalent analgesic dose of oxycodone is two-thirds of morphine.[3] At present, it is believed that the excitation of the kappa receptor can produce an analgesic effect and relieve visceral pain. However, it does not cause euphoria, gastrointestinal motility inhibition, and respiratory inhibition, and does not lead to addiction. Oxycodone does not induce histamine release, does not inhibit the parasympathetic nerve, and does not induce bradyrhythmia.[4] At present, oxycodone is the only clinically used U-K dual receptor agonist.[5,6] An ideal drug should have a good postoperative analgesic effect and little influence on immune function. Few studies on the influence of oxycodone on immunity have been reported, at present. After being absorbed, oxycodone distributes in the whole body, and approximately 45% of it binds with plasma protein, and is converted into oxymorphone, noroxycodone, and its glucuronic acid-bound form via the metabolism of the liver.[7]

Editor: Ashham Mansur.

The authors have no funding and conflicts of interest to disclose.

Second Department of Anesthesia, Zhongshan Hospital Affiliated Dalian University, Dalian, Liaoning Province, China.

** Correspondence: Wan-Wei Jiang, Second Department of Anesthesia, Zhongshan Hospital Affiliated Dalian University, No.6, Liberation Street, Zhongshan District, Dalian, 116001 Liaoning Province, China (e-mail: jiangww0405@163.com).*

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Medicine (2017) 96:31(e7519)

Received: 9 November 2016 / Received in final form: 28 April 2017 / Accepted: 26 June 2017

http://dx.doi.org/10.1097/MD.0000000000007519

2. Information and methods

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of our hospital. Written informed consent was obtained from all participants.

2.1. General information

A total of 80 patients who underwent radical resection of rectal cancer under general anesthesia in Zhongshan Hospital Affiliated to Dalian University, China were enrolled into this study. The age of these patients ranged within 40 to 60 years old. Among these patients, 40 patients were male and 40 patients were female. The included patients had anesthesia ASA grade I or II, and Dukes stage A or B. These patients were randomly divided into 2 groups: groups A and B. At the end of the surgery, each patient in group A was injected with 5 mg (5 mL) of oxycodone hydrochloride, while each patient in group B was injected with 5 mg (5 mL) of morphine hydrochloride. All patients had normal liver and kidney functions, had no endocrine, immune, and circulatory system diseases, did not receive blood transfusion during the perioperative period, and did not take steroid hormones and opioids. Differences in body weight, age, ASA grade, gender, and operation time between these 2 groups were not statistically significant (Table 1).

2.2. Anesthesia protocol

Thirty minutes before entering the operation room, 3 mg of midazolam was intramuscularly injected. Patients in both groups underwent total intravenous anesthesia. Induction: 0.1 to 0.2 mg/kg of midazolam, 0.5 to 1 μg/kg of sufentanil, 0.2 to 0.3 mg/kg of etomidate, and 0.2 to 0.3 mg/kg of cisatracurium besilate. Maintenance: 4 to 6 mg/(kg h) of propofol, 0.2 to 0.8 μg/(kg min) of remifentanil, and 0.15 to 0.3 mg/(kg h) of cisatracurium besilate. After 5 minutes of assisted ventilation, which began at the onset of the muscle relaxation effect of cisatracurium besilate, tracheal intubation was conducted using a steel-reinforced tracheal tube. Different types of tracheal tubes were chosen according to the situation of the patients. Tidal volume was set at 8 to 10 mL/kg, respiratory rate was set at 13 to 15 times/min, and inspiratory-to-expiratory ratio was set at 1:2. Respiration was controlled using a breathing machine. In the operation, the depth of anesthesia was adjusted according to the surgical stimulation, and the circulatory system was kept stable. At the end of the surgery, each patient in group A was injected with 5 mg (5 mL) of oxycodone hydrochloride, while each patient in group B was injected with 5 mg (5 mL) of morphine hydrochloride.

2.3. Observation indexes

Five time points were set for each group: before injection (T0), 0.5 hours after injection (T1), 6 hours after injection (T2), 12 hours after injection (T3), and 24 hours after injection (T4). Vital signs, heart rate (HR), blood pressure (BP), respiration (R), body temperature (T), and blood oxygen saturation (SpO_2) at each time point were observed. At each time point, 2 mL of peripheral venous blood was collected using a vacuum tube with heparin (for anticoagulation), and the percentages of CD4, CD8 positive cells, and natural killer (NK) cells were detected by flow cytometry.

2.4. Statistics processing

All measurement data were statistically analyzed using SPSS 19.0 statistical software. Changes in T lymphocyte subsets and NK cells, as well as other measurement data, were expressed as mean ± standard deviation. Data were evaluated using independent sample t test and analysis of variance. $P < .05$ was considered statistically significant.

3. Results

Vital signs of patients in the 2 groups: mean blood loss during the operation was 301 ± 40 mL in group A and 296 ± 38 mL in group B, and the difference between these 2 groups was not statistically significant ($P > .05$). The results of the observations revealed that the BP, HR, R, T, and SpO_2 in the 2 groups did not undergo significant changes during the process of anesthesia and perioperative period ($P > .05$).

Changes in the percentages of CD4, CD8 positive cells, and NK cells. First the number of T lymphocyte subsets and NK cells at T1, T2, T3, and T4 decreased in both groups, compared with those at T0; and the differences were statistically significant. Furthermore, these numbers reduced to a minimum at T2, and began to recover at T3. In both groups, the differences between T1 and T2 were statistically significant ($P < .05$), the differences between T1 and T3 were statistically significant ($P < .05$), the differences between T1 and T4 were statistically significant ($P < .05$), the differences between T2 and T3 were statistically significant ($P < .05$), the differences between T2 and T4 were statistically significant ($P < .05$), and the differences between T3 and T4 were statistically significant ($P < .05$). Second the differences between group A and B at T1 ($P < .05$), T2 ($P < .05$), T3 ($P < .05$), and T4 ($P < .05$) were all statistically significant; and the number of T lymphocytes and NK cells were higher in group A than those in group B at corresponding time points. However, the differences in various indices between groups A and B at T0 were not statistically significant ($P > .05$, details are shown in Table 2).

4. Discussion

According to the activation stage, T cells can be divided into initial T cells, effector T cells, and memory T cells.[8] Furthermore, according to the expression of CD4 or CD8 molecules,[9] T cells can be generally divided into $CD4^+$ T cells and $CD8^+$ T cells. Th0 cells can further differentiate into different subsets such as Th1 cells, Th2 cells, Th3 cells, and Th17 cells, etc.[10] The effect of Th1 cells is mainly to enhance the

Table 1

General information in body weight, age, ASA grade, gender, and operation time between these 2 groups (x ± s).

Groups	Cases	Age, y	Gender (male/female)	Body weight, kg	ASA grade (I/II)	Operation time, min
Group A	40	57.72 ± 4.63	18/22	66.45 ± 6.62	17/23	160.58 ± 22.12
Group B	40	58.63 ± 5.56	22/18	63.51 ± 5.67	19/21	153.57 ± 30.47

Table 2

Changes in the percentages of CD4, CD8 positive cells, and NK cells (x±s).

Index	Groups	n	T0	T1	T2	T3	T4
CD4+%	Group A	40	43.1±5.2	38.6±4.9	30.1±3.4	40.1±4.2	42.1±4.1
	Group B	40	42.5±5.1	34.6±3.6	25.7±3.1	32.6±3.5	40.9±4.3
CD8+%	Group A	40	26.3±2.8	25.2±2.1	22.1±2.4	25.6±2.7	26.1±2.2
	Group B	40	26.4±2.7	22.4±2.2	18.4±1.9	22.5±2.5	25.6±2.8
NK%	Group A	40	30.6±3.8	28.6±3.1	23.4±2.8	25.6±2.2	29.3±2.3
	Group B	40	31.6±3.5	26.4±3.2	20.2±2.8	23.6±3.2	26.4±2.7

A total of 100% means the total number of lymphocytes in the body. CD4+% means CD4+T cells account for the total number of lymphocytes in proportion. CD8+% means CD8+T cells account for the total number of lymphocytes in proportion. NK% means NK cells account for the total number of lymphocytes in proportion. T0 means before injection. T1 means 0.5 hours after injection. T2 means 6 hours after injection. T3 means 12 hours after injection. T4 means 24 hours after injection. CD = cluster of differentiation, NK = natural killer.

antiinfection immunity mediated by phagocytes, in particular, the resistance to intracellular pathogen infections.[11] The effect of Th2 cells is mainly to promote and induce humoral immune response mediated by B cells, and the cytokines secreted by these cells can promote the proliferation and differentiation of B cells and antibody production. $CD8^+$ T cells are mainly killer T cells, and their main function is to specifically and directly kill target cells.[12] NK cells are the primary immune cells for antitumor defense in the body.[13] This kind of cells can directly kill virus-infected cells and some tumor cells without antigen sensitization. Therefore, it plays an important role in the immune response of antitumor, antiintracellular parasite infection, and antivirus in the body. Thus, it has a broad spectrum function of killing tumor cells. Kondo et al revealed that the number of NK or T cells and the function of NK or T cells before operation with important significance for predicting the proliferation and metastasis about tumor cells at postoperative intestinal cancer. Therefore, the number of CD4, CD8 positive cells, and NK cells can reflect the immune function level of the body. Oxycodone belongs to the U-K dual receptor agonist.[14]

Opioids are undoubtedly the most commonly used and most effective drugs for the treatment of intraoperative and postoperative acute pains. The pharmacologies of opioid agonists mainly include analgesia, antitussive effect, respiratory depression, constipation induction, antianxiety, euphoria, etc.[15] Compared with nonsteroidal antiinflammatory drugs, opioid agonists have no risk of gastrointestinal bleeding, and its analgesic effect does not have the "ceiling effect." However, a number of studies have revealed that the effects of many opioid analgesic drugs on immune function are inhibitory[16] such as fentanyl, sufentanil, and morphine. These drugs often impair the immune function of patients,[17] and people often ignore these due to the absence of obvious clinical symptoms. However, many scholars have also observed that opioid drugs increase the susceptibility of the body, and promote and accelerate the spread of cancer cells.[18] Furthermore, the application of its receptor antagonist, nalmefene, can improve the survival rate of bacteria. For postoperative patients, poor control of pains can also lead to the inhibition of immune function. Therefore, the balance between opioid drug dosage and pain control should be considered when patients undergo analgesia using opioid drugs after surgery.[19] In addition, many studies have explored the effects of opioid drugs in different administration routes on immune function. Beilin et al revealed that the following 3 methods of analgesia had an effect on immune function in patients after abdominal surgery: patient-controlled intravenous analgesia (PCIA) with morphine, intermittent opiate regimen with morphine, and patient-controlled epidural analgesia (PCEA) with local anesthetics and opioid drugs. At 24 hours after surgery, lymphocyte mitogen responses were inhibited in patients in all 3 groups. At 72 hours after surgery, lymphocyte mitogen responses were still in an inhibited state in patients in the PCIA group, and recovered to preoperative level in the PCEA group. Furthermore, IL-1 and IL-6 levels significantly increased in the intermittent opiate regimen and PCIA groups, but these did not change in the PCEA group.[20] In addition, Volk et al reported that the effects of morphine PCIA and sufentanil plus ropivacaine PCEA on immune function were observed in patients after spinal surgery. Compared with PCIA, PCEA maintained a good lymphocyte function, thus, protecting specific immune function. In addition, Yokota et al reported that the effect of 0.5 and 0.1 mg of morphine (subarachnoid space administration), anesthetics (inhalation), and 10 mg of morphine (intravenous injection) were observed on NK cell function in 40 patients. These results revealed that the function of NK cells was significantly lower in patients with a subarachnoid space administration of 0.5 mg of morphine at 24 hours after surgery, compared that before surgery; and this did not significantly change in patients in other 3 groups. However, at 2 and 24 hours after surgery, the visual analogue scale was the lowest in patients who had taken 0.5 mg of morphine.[21] Sacerdote et al reported that the effects of morphine and tramadol on immune function in 30 patients who underwent abdominal uterine tumor surgery were observed. Before and after surgery, as well as at 2 hours after intramuscular injection of tramadol or morphine, the activity of NK cells and lymphocyte proliferation stimulated by phytohemagglutinin were observed. Results revealed that the surgery significantly inhibited phytohemagglutinin-stimulated lymphocyte proliferation in all patients, and at 2 hours after treatment. This proliferation recovered to the preoperative basic value in patients who receiving tramadol treatment, and the proliferation remained lower than that in the preoperative basic value in patients who receiving morphine treatment. Surgery and morphine did not affect NK cell activity, but tramadol could enhance NK cell activity.[22] The improvement degree of postoperative analgesics was evaluated by the numerical rating scale. Different degrees of pain were represented by 0 to 10 numbers. We should ask patients about the degrees of pain, make a marker, or let the patient himself write a number that would mostly be able to represent the degree of pain.[23] This method has been commonly used in clinic, at present.[24] Points are defined as follows: 0 point represents painless, 1 to 3 points represent mild pain (that does not affect sleep), 4 to 6 points represent moderate pain, 7 to 9 points represent severe pain (in which patients cannot sleep or wake up in sleep), and 10 points represents sharp pain. The ideal postoperative analgesic effect should be that the score is controlled at $\leq$3 points. Oxycodone is commonly used in postoperative analgesia, at present; and its side effects have been a research hotspot for many scholars.[25] Postoperative acute pain

refers to a series of physiological and pathological reactions caused by the stimulation of the disease and the surgical trauma in the body. It manifests as a series of reactions and an unpleasant emotional experience in the mind and behavior. Furthermore, pain has become the 5th vital sign following HR, BP, R, and T.[26] Pain is extremely unfavorable to the postoperative recovery of patients. Pain control is one of the key factors that influence the postoperative recovery speed of patients. With the continuous deepening of the reform for the national health system, and the continuous increase in the public health needs, the requirements of improvement on medical quality, and the reduction of medical costs are increasingly urgent.[27] A number of hospitals are actively advocated a painless medicine and comfortable care. The idea of enhanced recovery after surgery, which was derived from Europe more than 10 years ago and currently has been popularized and applied in the world, is in accordance with historical trends. It is a new idea for clinical surgery,[28] which is based on the evidence of evidence-based medicine, adopts multimode strategy, optimizes perioperative treatment measures, decreases perioperative stress of surgical patients, and finally accelerates and improves the postoperative recovery speed of surgical patients.[29] The enhanced recovery after surgery idea refers to stress responses and complications before, during, and after the operation, causing the operation and other treatment measures to be reduced by the application of various effective methods; hence, accelerating the postoperative rehabilitation of patients. Effective postoperative analgesia can improve the anxiety of patients and decrease the occurrence of complications in respiratory circulation and coagulation system.[30] This is also a necessary precondition for early out-of-bed activity and oral nutrition, which can be used as an important measure to reduce surgical stress response, and can accelerate the postoperative rehabilitation of patients. A drug that can exert a good analgesic effect with a small or even no effect on immune function is urgently required. Oxycodone hydrochloride can fully meet this requirement. However, the effects of oxycodone on immune function have not been fully understood at home and abroad.[31]

5. Conclusion

Oxycodone hydrochloride injection and morphine hydrochloride injection both have inhibitory effects on immune function in patients undergoing radical resection of rectal cancer after surgery. However, oxycodone hydrochloride has a lower effect compared to morphine hydrochloride. This has the greatest inhibitory effect on the immune function in patients at 6 hours after the injection, and the immune function begins to recover 6 hours after injection. Therefore, oxycodone is a relative ideal postoperative analgesic drug in clinic, which has small side effects.

References

[1] Sun YT, Hou M, Zou T, et al. Effect of ketamine anesthesia on cognitive function and immune function in young rats. Cell Mol Biol (Noisy-le-grand) 2016;62:63–6.

[2] Ji M, Tao J, Wang QL, et al. Influence of target controlled infusion with propofol combined with remifentanil on immune and stress reaction. Med J Natl Defend Forces Southwest China 2013;23:499–502.

[3] Zhao J, Mo H. The impact of different anesthesia methods on stress reaction and immune function of the patients with gastric cancer during peri-operative period. J Med Assoc Thai 2015;98:568–73.

[4] Tanatarov SZ, Neimark MI, Zhakupov RK. Influence of various types of anesthesia in oncosurgical practice on immune parameters. Vestn Ross Akad Med Nauk 2012;12:18–21.

[5] Gu CY, Zhang J, Qian YN, et al. Effects of epidural anesthesia and postoperative epidural analgesia on immune function in esophageal carcinoma patients undergoing thoracic surgery. Mol Clin Oncol 2015;3:190–6.

[6] Ezhevskaia AA, Prusakova ZhB, Maksimova LP, et al. Effects of epidural anesthesia on stress-induced immune supression during major corrective spine surgery. Anesteziol Reanimatol 2014;59:4–9.

[7] Konstantatos AH, Kavnoudias H, Stegeman JR, et al. A randomized, double-blind, placebo-controlled study of preemptive oral oxycodone with morphine patient-controlled anesthesia for postoperative pain management in patients undergoing uterine artery embolization for symptomatic uterine fibroids. Cardiovasc Intervent Radiol 2014;37: 1191–7.

[8] Scardino M, Grappiolo G, Gurgone A, et al. Single-shot epidural-spinal anesthesia followed by oral oxycodone/naloxone and ketoprofen combination in patients undergoing total hip replacement: analgesic efficacy and tolerability. Minerva Anestesiol 2015;81:19–27.

[9] Wagner F, Radermacher P, Stahl W. Anesthesia and the immune response: evidence for an "isoflurane paradox"? Shock 2010;34:437–8.

[10] Gao XC, Yang Y, Yan XQ. Comparing the differences between target controlled intravenous anesthesia and traditional intravenous compound anesthesia by taking propofol combined with fentanyl or remifentanil. Guide China Med 2013;11:353–4.

[11] Wang J, Pang L, Han W, et al. Effect of preemptive intravenous oxycodone on low-dose bupivacaine spinal anesthesia with intrathecal sufentanil. Saudi Med J 2015;36:437–41.

[12] Wang N, Zhang S, Fu Y, et al. Effect of preoperative intravenous oxycodone on low-dose ropivacaine spinal anesthesia combined with intrathecal fentanyl. Middle East J Anaesthesiol 2016;23:437–42.

[13] Wei L, Meng QG, Bi ZG. Result of a randomized clinical trial comparing different types of anesthesia on the immune function of patients with osteosarcoma undergoing radical resection. Panminerva Med 2013;55: 211–6.

[14] Cata JP, Bauer M, Sokari T, et al. Effects of surgery, general anesthesia, and perioperative epidural analgesia on the immune function of patients with non-small cell lung cancer. J Clin Anesth 2013;25:255–62.

[15] Cheng YC, Cheng XB, Li XJ, et al. Combined general and regional anesthesia and effects on immune function in patients with benign ovarian tumors treated by laparoscopic therapy. Int J Clin Exp Med 2013;6:716–9.

[16] Fan WC, Ma W, Zhao C, et al. Influence of acupuncture-drug compound anesthesia with different frequency electroacupuncture on immune function in patients undergoing pneumonectomy. Zhongguo Zhen Jiu 2012;32:715–9.

[17] Zhang WL, Liu MY, Zhang ZC, et al. Effect of different anesthesia methods on erythrocyte immune function in mice. Asian Pac J Trop Med 2013;6:995–8.

[18] Griffis CA, Page G, Kremer M, et al. Implications of immune function to anesthesia care. AANA J 2008;76:449–54.

[19] Gu CY, Shen LR, Ding YH, et al. Effect of different anesthesia methods on immune function in patients of laparoscopic cholecystectomy in peri-operational period. Zhongguo Zhen Jiu 2011;31:236–40.

[20] Kasachenko VM, Briskin BS, Evstifeeva OV, et al. The impact of the type of anesthesia on stress-realizing and stress-limiting mechanisms of the immune system in gerontological patients at abdominal surgeries. Eksp Klin Gastroenterol 2004;3:58–61. 105.

[21] Kosachenko VM, Briskin BS, Evstifeeva OV, et al. Effect of the anesthesia method on the immune status of gerontological patients during abdominal operations. Eksp Klin Gastroenterol 2004;4:67–72. 110.

[22] Liu S, Wang B, Li S, et al. Immune cell populations decrease during craniotomy under general anesthesia. Anesth Analg 2011;113:572–7.

[23] Li HL, She SZ, Yan Y, et al. Effect of dexmedetomidine on bispectral index and auditory evoked potential index during anesthesia with target controlled infusion of propofol and remifentanyl. Zhejiang University Medicine 2010;39:84.

[24] Ji M, Tao J, Wang QL, et al. The influence of different anesthesia methods for the immune function of the patients with radical resection of rectal carcinoma. Chongqing Med 2013;42:385–7.

[25] Neuman Y. What does pain signify? A hypothesis concerning pain, the immune system and unconscious pain experience under general anesthesia. Med Hypotheses 2004;63:1051–3.

[26] Rizzo A, Campanile D, Spedicato M, et al. Update on anesthesia and the immune response in newborns delivered by cesarian section. Immuno-pharmacol Immunotoxicol 2011;33:581–5.

[27] Sepbaeva AD, Mikhel'son VA, Degtiareva MV, et al. Immune reaction to anesthesia and surgical injury in neonatal infants. Anesteziol Reanimatol 2010;1:37–40.

[28] Yan B, Wei J, Chen J, et al. Study on T lymphocyte subsets and the cellular immune functions in peripheral blood from the patients with multiple myeloma. Chongqing Med 2013;42: 1210–2.
[29] Siebert JN, Posfay-Barbe KM, Habre W, et al. Influence of anesthesia on immune responses and its effect on vaccination in children: review of evidence. Paediatr Anaesth 2007;17:410–20.
[30] Takahashi T, Kinoshita M, Shono S, et al. The effect of ketamine anesthesia on the immune function of mice with postoperative septicemia. Anesth Analg 2010;111:1051–8.
[31] Zou JF, Li JY, Wu XW, et al. Effects of different anesthesia and analgesia on erythrocyte immune function of patients with ovarian benign tumor treated by laparoscopic therapeutic. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi 2010;26:1252–4.