Research Paper

The Effect of Perioperative Injection of Lidocaine and Nursing Intervention on the Immune Functions of Patients Receiving Radical Resection for Colorectal Cancer

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This study aimed to investigate the effect of perioperative injection of lidocaine and nursing intervention on the immune functions of patients receiving radical resection for colorectal cancer and to shed new light on the selection of anaesthetic regimens for perioperative patients. Fifty-eight patients receiving laparoscopic radical resection for colorectal cancer were recruited, and randomly divided into control group and experiment group, with 29 patients in each group. Patients in the control group received conventional perioperative nursing, and those in the experimental group accepted comprehensive perioperative nursing. For the experimental group, lidocaine was intravenously injected for about 10 min at 15 min before general anaesthesia. Orotracheal intubation was performed under the optical laryngoscope for general intravenous anaesthesia. Lidocaine was constantly pumped during the operation, until the skin suture was over. The control group received intravenous injection of an equal volume of normal saline instead of lidocaine. At 24 h before surgery, 0 h after surgery and 24 h after surgery, 10.0 ml of peripheral blood was collected from each subject, respectively, and added with ethylenediaminetetraacetic acid. The samples were sent for determination by flow cytometry within 24 h. Time-to-ambulation, time-to-eat, length of hospital stay and incidence of complications were recorded for the two groups. Compared with 24 h before surgery (T0), the percentages of lymphocytes per total peripheral white blood cells decreased at 0 h after surgery (T1) and at 24 h after surgery (T2) for the two groups ($p<0.05$). The ratios of T-lymphocytes to total lymphocytes, ratios of helper T cells to T-lymphocytes and CD4+/CD8+ ratios first increased and then decreased for the two groups ($p>0.05$). The percentages of NK cells to lymphocytes first decreased and then increased ($p>0.05$). The percentage of Treg cells to T-lymphocytes at T1 and T2 for the control group first decreased and then increased ($p>0.05$). Compared with the control group, percent lymphocytes in the experimental group decreased less dramatically. Percent helper T cells to T-lymphocytes and CD4+/CD8+ ratio increased more faster at T1 and decreased at a lower rate at T2. The percentage of cytotoxic lymphocytes (CTLs) to T-lymphocytes at T1 decreased faster and increased slowly at T2 ($p>0.05$). The percentage of Treg cells to T-lymphocytes decreased at both T1 ($p<0.05$) and T2 ($p>0.05$). The percentage of NK cells to lymphocytes decreased slowly at T1 and increased faster at T2 ($p>0.05$). Time-to-ambulation time-to-eat and length of hospital stay were all shorter in the experimental group than in the control group ($p<0.05$). The incidence of complications in the experimental group was significantly lower than that of the control group ($p<0.05$). In conclusion, lidocaine improved the inhibitory effect on the T-cell-mediated immune response during perioperative period, blocking the proliferation of Treg cells. However, it had no apparent impact on the proliferative ability of NK cells during the perioperative period. Nursing intervention facilitated patients' recovery and lowered the incidence of complications.

Key words: Lidocaine, nursing intervention, radical resection for colorectal cancer, immune cells

Solid tumor resection is preferred for colorectal cancer (CRC) at present[1,2]. Resection-related effects on neuroendocrinology, metabolism and inflammation will hinder the cell-mediated immunity (CMI)[3-5]. Tumor cell spread and damage to the immune system both contribute to postoperative tumor recurrence and

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metastasis[6]. In addition, anaesthetic technique, drugs and nursing in the perioperative period also affect the long-term prognosis of patients receiving radical tumor resection[7]. Lidocaine is a local anaesthetic which can be used for perioperative intravenous injection[8]. It can not only directly regulate molecular and cellular biology of tumours, but also has an indirect impact on the prognosis of tumor patients through modulating the immune system[9,10]. It has been shown that lidocaine at a clinically applied concentration offers protection for natural killer (NK) cells and enhances the killing effect on tumors[11]. Moreover, lidocaine has been found to reduce the secretion of pro-inflammatory factor interleukin-6 (IL-6) and interleukin 1 receptor antagonist (IL-1ra) in patients receiving uterectomy, thus attenuating the immune response to stress related to the surgery[12]. Whether lidocaine has a protective effect for CMI in patients receiving radical tumor resection has to be figured out through clinical observation and prospective trials. This study aimed to clarify the effect of perioperative lidocaine injection on the immune cells in patients receiving radical resection for CRC, including lymphocytes, NK cells and CD4 T cells.

MATERIALS AND METHODS

Lidocaine hydrochloride injection, cisatracurium besylate for injection, sufentanil citrate injection, midazolam injection, propofol injection, remifentanil hydrochloride for injection, atropine sulphate injection, neostigmine methyl sulphate injection, dopamine hydrochloride injection, nitroglycerin injection, sodium lactate Ringer's injection, hydroxyethyl starch 130/0.4 and sodium chloride injection were employed. Anaesthetic machine, multi-function health monitor and anaesthesia pump were the equipment used.

Subjects:

From July 2017 to August 2018, 58 patients with confirmed CRC and receiving elective laparoscopic radical resection at our hospital were recruited. They were randomly divided into control group and experimental group, with 29 patients in each group. Inclusion criteria: American Society of Anesthesiologists class I~II; normal blood pressure, excluding those with bradycardia arrhythmia and other heart diseases; no history of diabetes; normal results of routine blood test, routine urine test and routine faecal test before surgery, liver and kidney function tests, electrolyte or biochemical tests, without abnormalities of major organs; no preoperative use of anti-inflammatory drugs, analgesics or hormones; having received no preoperative chemotherapy, radiotherapy or blood transfusion; voluntary participation in the present study. Exclusion criteria: (1) termination of nursing intervention is required due to bradycardia or other types of arrhythmia in the perioperative period; (2) requiring emergency treatment for poisoning and allergic to local anaesthetics in the perioperative period; (3) requiring blood transfusion in the perioperative period; (4) poor compliance.

Nursing intervention:

Conventional preoperative nursing intervention was adopted for the control group, and comprehensive preoperative nursing intervention was performed for the experimental group. The details were as follows, for preoperative nursing patients were given psychological guidance, prescribed with oral laxatives at one day before surgery and enema the night before surgery and on the morning of surgery. Intralipid or amino acids were prescribed for those weak in constitution or lean, in addition to glucose supplementation. During intraoperative nursing, the operation room was kept comfortable. The patients were placed at an appropriate position and the venous access was established. Changes in blood pressure, heart rate and other vital signs were observed. During postoperative nursing, the patients were returned to the ward after awakening from anesthesia. The head was elevated by 30°, and the patients were assisted in turning and movement of the four limbs every 2 h. Changes in vital signs were closely monitored. The surgical incision was checked for any signs of blood oozing or infection and treated immediately in case of abnormalities. Postoperative pain assessment and timely intervention were performed to ensure sufficient rest and early ambulation of the patients. The patients and their relatives were told to forbid diet before restoring anal exsufflation. The patients were given intravenous fluid replacement or parenteral nutrition or advised to chew gum to promote appetite and bowel function recovery. After the anal exsufflation was restored, the patients were allowed to eat a small amount of liquid diet, then semi-liquid diet. Eating more frequent but smaller meals and high-protein high-vitamin food was recommended for the patients, and irritating food was forbidden. Early ambulation and some exercise were encouraged if possible to facilitate recovery. When indwelling gastric tube and urinary catheter, it was ensured that all the drainage tubes were properly

immobilized, and all pipelines were kept unobstructed. The nursing staff was responsible for observing the color, amount and nature of the drainage on a regular basis. The urinary catheter was closed regularly, the urethral office was cleaned and disinfected, and the urine drainage bag was timely replaced. After normal urination was restored, the urinary catheter was removed and automatic micturition was required. The gastric tube was removed after anal exsufflation was restored. Time-to-ambulation, time-to-eat, length of hospital stay and incidence of postoperative complications were recorded for each group.

Preparation before anaesthesia:

Venous access and access for lidocaine injection were opened before surgery. The access was kept unobstructed by intravenous drip of lactated Ringer's solution. Electrocardiogram (ECG) was connected, and pulse oxygen saturation (SpO_2), automated non-invasive blood pressure (NIBP) and end-tidal carbon dioxide ($PetCO_2$) were monitored conventionally. Radial artery puncture and catheterization were performed to monitor intraoperative blood pressure dynamically.

Induction of anaesthesia:

Intravenous injection of 2 % lidocaine was given at a dose of 1.5 mg/kg 15 min before anaesthetic induction, and the injection lasted for about 10 min. After that, the patients were given facemask ventilation for denitrogenation. Anaesthesia induction was performed using midazolam 0.05~0.1 mg/kg, remifentanil 0.5 μg/kg, propofol 2 mg/kg and cisatracurium besylate 0.2 mg/kg. This was followed by orotracheal intubation under the optical laryngoscope. Artificial mechanical ventilation was given in the volume control mode, with an oxygen flow rate of 2 l/min, respiratory rate of 12 breaths/min, and tidal volume of 8-10 ml/kg. After anaesthetic induction, the above drugs were continuously pumped using micro injection pump at a rate of 1.5 mg/kg/h until the skin suture was over. For the control group, an equal volume of normal saline was injected instead of lidocaine, while the other procedures remained the same.

Anaesthesia maintenance:

Propofol and remifentanil were pumped for the two groups during the operation, and cisatracurium besylate was used for maintaining muscle relaxation. $PetCO_2$ was controlled at 35~45 mmHg during surgery, and the blood pressure and heart rate were kept stable. The dose of maintenance anaesthetics was adjusted to control blood pressure and heart rate. If fluctuation of blood pressure and heart rate was to large, vasoactive drugs such as atropine, dopamine, trinitroglycerin and epinephrine were prescribed.

Resuscitation of anaesthesia:

After surgery, the patients were sent to the postoperative recovery room. Intravenous administration of neostigmine and atropine was performed if necessary to counteract the effect of muscle relaxants. Cough and swallowing reflexes were observed in all patients. Tracheal tubes were removed when patients restored spontaneous breathing and gained consciousness.

Sample collection and detection:

At 24 h before surgery, 0 h after surgery and 24 h after surgery, 10.0 ml of peripheral blood was collected from each subject, respectively, and added with ethylenediaminetetraacetic acid. The samples were sent for determination by flow cytometry within 24 h. CD3+, CD4+CD8-, CD8+CD4-, CD4+/CD8+, CD4+DC25+CD127- and CD3-CD16+CD56+ ratios were determined as the observation indicators.

Statistics:

All statistical analyses were performed using SPSS 22.0 software. Measurements were reported as mean±standard deviation. Values obeying normal distribution and homogeneity of variance were subjected to independent two-sample t-test for paired comparison, or one-way ANOVA for multiple comparison. Otherwise, the rank sum test was used. $P<0.05$ indicated significant difference.

RESULTS AND DISCUSSION

As shown in Table 1, both the groups of patients had no significant differences in age, BMI, TNM staging, anaesthesia time and surgery time, total intraoperative amount of remifentanil, propofol and fluid replacement ($p>0.05$).

As shown in Table 2, percent lymphocytes per total peripheral white blood cells at T1 and T2 decreased significantly than those at T0 for the two groups ($p<0.05$). There was a significant reduction in percent lymphocytes per total peripheral white blood cells at T2 than at T1 ($p<0.05$). Compared to the control group, the lymphocytes percentage per total peripheral white blood cells at T0 in the experimental group was not

TABLE 1: BASELINE INFORMATION OF THE TWO GROUPS

Group		Experimental group	Control group	P value
Age (y)		62.33±7.34	64.15±8.27	0.413
BMI		22.93±2.44	21.63±2.37	0.434
Operation time (min)		218.92±43.19	207.63±42.03	0.667
Anesthesia time (min)		231.03±31.04	245.91±38.82	0.203
Remifentanil (mg)		1.83±0.31	1.92±0.35	0.419
Propofol (mg)		1006.96±137.28	987.47±161.94	0.526
Fluid replacement (ml)		2003.19±171.22	1947.22±270.81	0.379
TNM (TxN0M0)	T1	14	15	0.284
	T2	10	8	
	T3	5	6	

TABLE 2: PERCENT LYMPHOCYTES PER TOTAL PERIPHERAL WHITE BLOOD CELLS

Groups	T0	T1	T2
Control	30.96±9.72	15.68±8.11*	7.49±3.91*#
Experimental	30.32±9.86	20.22±9.89*ἀ	13.23±7.24*#ἀ

*p<0.05, compared with T0 for each group; #p<0.05, compared with T1 for each group; and p<0.05, compared with the control group

TABLE 3: PERCENT T-LYMPHOCYTES TO TOTAL LYMPHOCYTES

Groups	T0	T1	T2
Control	65.14±11.42	69.77±14.68	61.49±10.52
Experimental	62.63±9.52	69.88±11.72*	67.48±7.66#

*p<0.05, intergroup comparison; #p<0.05, compared with the control group

significantly different (p>0.05). But there was a marked increase at T1 and T2 (p<0.05).

In Table 3, percent T-lymphocytes to total lymphocytes was not changed significantly within the control group at different time points (p>0.05). There was a marked increase at T1 than at T0 for the control group (p<0.05), but the change was not significant at T2 (p>0.05). As to intergroup comparison, percent T-lymphocytes to total lymphocytes increased dramatically at T2 in the experimental group (p<0.05), but there were no significant changes at other time points (p>0.05).

As shown in Table 4, percent Th cells to T-lymphocytes, percent CTL to T-lymphocytes and CD4+/CD8+ ratios were not changed significantly over time within the control group (p>0.05). In the experimental group, the percentage of Th cells to T-lymphocytes and percentage of CTL to T-lymphocytes increased considerably at T1 than at T0 (p<0.05), but without significant changes at T2 (p>0.05). The experimental group had no significant changes in the CD4+/CD8+ ratio across the time points (p>0.05). As to intergroup comparison, the percentage of Th cells to T-lymphocytes and percentage of CTL to T-lymphocytes increased significantly at T2 compared with the control group (p<0.05). However, the CD4+/CD8+ ratio decreased dramatically at T2 in the experimental group compared with the control group (p<0.05). There were no significant changes between the two groups at other time points (p>0.05).

According to Table 5, the control group had no significant changes in the percentage of CD127+ Treg cells to T-lymphocytes at each time point compared with the control group (p>0.05). For the experimental group, the percentage of CD127+ Treg cells to T-lymphocytes decreased significantly at T2 than at T0 (p<0.05), but there was no significant change at T1 than at T0 (p>0.05). Compared with the control group, the percentage of CD127+ Treg cells to T-lymphocytes decreased significantly at T2 in the experimental group (p>0.05), but there were no significant changes between the two groups at other time points (p<0.05).

In Table 5, the percentage of NK cells to T-lymphocytes decreased at T1 than at T0 within the control group (p<0.05). Such a decrease continued at T2, but no significantly compared with T0 (p>0.05). Although this indicator decreased from T0, through T1 to T2 in the experimental group, the change was not significant across the time points (p>0.05). Compared with the control group, the percentage of NK cells to T-lymphocytes was not changed significantly across the time points in the experimental group (p>0.05).

As shown in Table 6, time-to-ambulation, time-to-eat and length of hospital stay were significantly shorter in the experimental group than in the control group. Moreover, the incidence of postoperative complications was also significantly lower in the experimental group than in the control group (p<0.05).

Laparoscopic radical tumor resection is preferred for CRC, though it may not necessarily improve the prognosis. Surgical procedures in the perioperative period may increase the number of circulatory tumor cells (CTCs) and hence the risk of metastasis[13]. In addition, changes in the immune functions caused by

TABLE 4: CHANGES IN PERCENT TH CELLS TO T-LYMPHOCYTES, PERCENT CTL TO T-LYMPHOCYTES AND CD4+/CD8+ RATIOS

Parameter	Groups	T0	T1	T2
Percent Th cells to T-lymphocytes	Control	48.22±10.81	55.68±12.52	47.31±12.09
	Experimental	51.04±11.12	59.68±12.45*	56.76±12.45#
Percent CTL to T-lymphocytes	Control	42.43±10.22	39.08±12.13	46.11±10.43
	Experimental	41.46±11.19	32.83±9.52*	40.17±12.42#
CD4+/CD8+ ratio	Control	1.25±0.51	1.69±0.70	1.13±0.41
	Experimental	1.49±0.81	2.03±1.03	1.83±0.90#

*p<0.05, intragroup comparison; #p<0.05, compared with the control group

TABLE 5: PERCENTAGE OF TREG CELLS AND NK CELLS TO T-LYMPHOCYTES

Percent TREG cells (CD4+CD25+CD127-) to T-lymphocytes			
Groups	T0	T1	T2
Control	2.66±2.62	3.79±4.11	3.15±2.02
Experimental	2.48±1.83	2.23±1.10	1.49±0.82*#
Percent NK cells (CD3-CD16+CD56+) to T-lymphocytes			
Control	22.41±10.32	14.52±11.14*	19.71±7.75
Experimental	21.82±7.32	17.57±10.13	23.61±10.29

*p<0.05, intragroup comparison; #p<0.05, compared with the control group

TABLE 6: TIME-TO-RECOVERY AND INCIDENCE OF POSTOPERATIVE COMPLICATIONS

Groups	Time-to-ambulation (days)	Time-to-eat (days)	Length of hospital stay (days)	Incidence of postoperative complications (%)
Control	6.22±2.03	4.87±0.71	11.26±3.35	6.90
Experimental	3.57±1.25*	2.04±0.39*	7.48±2.11*	20.69*

*p<0.05, compared with the control group

surgery and anesthesia may result in imbalance between the immune system and tumor cells, which further leads to immune escape of CTCs[14,15]. This process has an important impact on recurrence, metastasis and prognosis of tumor patients. The influence of anaesthesia on the prognosis of tumor patients is two-fold: regulating the number and activity of tumor cells and immune cells[16]. The present study discussed the relationship between anaesthesia and immunity against tumor cells.

Lymphocytes have a major impact on postoperative recovery of patients receiving radical tumor resection[17]. It has been shown that surgery-related stress inhibits the proliferation and accelerates the apoptosis of lymphocytes, which further leads to a decrease in the number of circulatory lymphocytes than before surgery[18]. A group researcher believed that lidocaine regulates the HPA axis through its antiinflammatory effect, inducing the changes of immune-related inflammatory factors[19]. This would further influence lymphocyte proliferation and apoptosis and attenuate postoperative immunosuppressive status. In the present study, the percentages of lymphocytes per total peripheral while blood cells decreased at T1 and T2 in both two groups compared with T0 ($p<0.05$). This decrease was milder in the experimental group than in the control group, with $p<0.05$ at T2. From the above findings it was inferred that intravenous injection of lidocaine attenuated the inhibitory effect of surgery on lymphocytes during the perioperative period. However, the molecular mechanism of lidocaine acting on lymphocytes is not fully known, and *in vitro* mechanism researches are needed to clarify.

Generally, surgery can lessen the immunosuppressive effect of Treg cells in tumor patients[20,21]. There is usually a reduction in the postoperative number of Treg cells than before. Danna *et al*. reported a reduction in the number of Treg cells after solid cancer resection, with attenuation or even disappearance of immunosuppressive effects from the cancer cells, which was conducive to the prognosis[22]. In the present study, the percentages of CD127-Treg cells to T-lymphocytes decreased at 0 h after surgery for the two groups, which was probably attributed to the limited sample size. Many researches have been conducted on the immune evaluation of Treg cells, but few are concerned with the effect of perioperative anaesthesia-related factors on Treg cells. We performed intravenous injection of lidocaine with nursing intervention, and it was found that the percentage of CD127-Treg cells to T-lymphocytes decreased faster in the experimental group after surgery than in the control group ($p<0.05$).

From this finding, it was inferred that lidocaine further inhibited the proliferation of CD127-Treg cells, thereby relieving the immunosuppressive effect of Treg cells.

Koltun *et al*. showed that intraspinal anaesthesia using local anaesthetics could lower the levels of epinephrine and cortisol in patients receiving resection for CRC, thus protecting the activity of NK cells[23]. In the present study, the percentage of NK cells to lymphocytes decreased slowly in the experimental group at 0h after surgery, but it increased faster at 24 h. These results indicated that lidocaine lessened the inhibitory effect of surgery on NK cells and accelerated the immune function recovery of NK cells after surgery.

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