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Research Article

PCEA Reduced the Expression of Regulatory T Cells in Elderly Patients Undergoing Open Colectomy

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ABSTRACT

Background and aim: Open colectomy is associated with postsurgical pain. Regulatory T cells (Tregs) are crucial in the recovery and metastasis of tumor cells, infection and immune response. To compare the expression of Tregs on Patient-Controlled Epidural Analgesia (PCEA) and Patient-Controlled Intravenous Analgesia (PCIA) in elderly patients undergoing open colectomy.

Methods: From September 2015 to October 2017, 100 elderly patients were scheduled for elective open colectomy with general anesthesia. Patients were randomly divided into the PCEA and PCIA group. Detected CD4, CD25 and CD27 by flow cytometry and calculated the proportion of $CD4^+$ $CD25^+$ $CD127^-$ Tregs in $CD4^+$ T lymphocytes. Recorded Visual Analog Pain Score (VAS) on the first and second days postoperatively. Also, recorded adverse drug events, such as dizzy, respiratory suppression, nausea and vomit, itchy skin, sensory or motor block.

Results: Compared with the baseline before the surgery, the proportion of Tregs showed increased significantly in both groups on the first day after the surgery ($P<0.05$). On the first day after surgery, the proportion in the PCEA group (2.86% ± 0.73%) was significantly lower than that in the PCIA group (3.78% ± 0.87%) ($P<0.05$). VAS in the PCEA group was considerably lower than that in the PCIA group during 48 hours after the surgery ($P<0.05$). There was no significant difference in adverse drug events between groups ($P>0.05$).

Conclusion: Compared with PCIA, PCEA can reduce Tregs expression in elderly patients undergoing open colectomy on the first day after surgery, decreased postoperative pain during 48 hours and without significant adverse events.

Keywords: Regulatory T cells; Patient-controlled intravenous analgesia; Patient-controlled epidural analgesia; Elderly; Colectomy

INTRODUCTION

For elderly patients, surgical interventions activate a cascade of reactions that result in an inflammatory aseptic response and pain. Especially during operations in the colon region, which is an extensive residence of bacteria flora, every manipulation can destroy the integrity of the intestinal barrier for bacteria and initiate the organism's innate immunity [1].

The inflammatory reaction is associated with immune depression and is involved in the occurrence of various postoperative adverse outcomes, which may contribute to tissue injury and delayed postoperative rehabilitation.

Postoperative pain is also widely accepted as a contributing factor to immune disorder because of known interactions between the central nervous system and the immune system. Excellent analgesia can modulate the inflammatory response consecutive to tissue injury by various mechanisms at different levels. Although it has been studied in animals, little evidence is available that shows the influence of postoperative pain on the immune system and whether epidural anesthesia affects postoperative immune functions is less well known. As a subtype of T cells, Regulatory T cells (Tregs) can actively engage in the maintenance of immunological self-tolerance and homeostasis and play an essential role in the immunity system.

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Therefore, it is believed as the pattern recognition receptors in the innate immune defense system [2]. Compared with Patient-Controlled Intravenous Analgesia (PCIA), we studied whether Patient-Controlled Epidural Analgesia (PCEA) would improve immune function by suppressing Tregs responses. Therefore, we conducted this randomized, controlled, double-blind prospective trial. The subjects were elderly patients who underwent open colectomy with general anesthesia.

MATERIALS AND METHODS

Study participants

The study was approved by the human research ethics committee of the affiliated hospital of inner Mongolia medical university. Between September 2015 and October 2017, 100 patients diagnosed with colon tumor, ASA I-III, aged older than 65 years were recruited after obtaining written informed consent. All patients were scheduled for open colectomy (anticipated surgical incision 10 cm-15 cm). Exclusion criteria were drug or alcohol addiction, cardiopulmonary and cerebrovascular disease, renal or hepatic insufficiency, epidural contraindications, surgical incision more than 15 cm, preoperative signs of infection (such as White Blood Cell (WBC) count>12000/L, body temperature >38°C and C-Reactive Protein (CRP)>5 mg/dl). Rejection criteria also included noncompliance with perioperative follow-up, surgery canceled and epidural analgesia failure [3].

Anesthesia regimens

Before the surgery, patients were randomized to PCEA or PCIA group by a computerized list. On arriving at the operation, all patients received vital signs monitor, including electrocardiograms, heart rate, non-invasive blood pressure and oxygen saturation. In PCEA group, the lumbar epidural catheter was inserted at L1-2 interspace and cephalic advanced 3 cm-4 cm for PCEA. In PCIA group, the peripheral vein catheter was placed for PCIA. Then all patients underwent standard general anesthesia. Anesthesia was induced with sufentanil 0.4 μg/kg, etomidate 0.3 mg/kg and rocuronium 0.6 mg/kg, followed by a continuous infusion of propofol and remifentanil, added sufentanil and rocuronium as required. All patients were ventilated with an oxygen/air mixture. Before incision, all patients were inserted central venous line, a peripheral artery catheter and a urinary catheter and received perioperative antibiotic prophylaxis [4].

Postoperative analgesic therapy

Approximately 30 min prior to the end of the operation, postoperative analgesic therapy was initiated with a bolus (2 ml) and the patient-controlled system was used with a lockout time of 15 min.

In PCEA group, ropivacaine 0.125% plus sufentanil 0.12 μg/ml was used with a background infusion of 5 ml/h, while in PCIA group, sufentanil was used in a concentration of 1.0 μg/ml with a background infusion of 3 ml/h. The analgesia catheter was removed on the morning of the third postoperative day and the analgesic therapy was converted to systemic oral analgesia as required. Except for postoperative analgesic controlled treatment (PCEA or PCIA), if patients required other rescue medication during 48 hours postoperatively, the patients were excluded [5].

Study outcomes

The primary outcome was the proportion of $CD4^+$ $CD25^+$ $CD127^-$ Tregs in $CD4^+$ T lymphocytes. Blood samples were collected one day before the surgery and on the first postoperative morning. Serum and plasma of these samples were immediately stored at -80°C for later analysis. The cluster of differentiation (CD4, CD25 and CD27) were measured by using labeled monoclonal antibodies, FACSCanto II and Lysys II® software (all from Becton Dickinson, Heidelberg, Germany) as previously described. Calculated the proportion of $CD4^+$ $CD25^+$ $CD127^-$ Tregs in $CD4^+$ T lymphocytes [6].

The secondary outcome included pain scores, which were evaluated to compare the postoperative analgesic efficacy of the analgesic regimens described previously. The Visual Analog Pain Score (VAS) was used with a scale between 0 (no pain) and 10 (unbearable pain). VAS was estimated on the first and second day after the surgery. In addition, adverse drug events, such as dizzy, nausea and vomit, itchy skin, sensory or motor block and respiratory depression, were recorded [7].

Statistical analysis and sample size

The data was analyzed by SPSS software (SPSS Inc., Chicago, IL). Patient demographic data were presented as mean ± standard deviation and analyzed with t-tests for continuous data. Count data were expressed by the number of cases or proportion and analyzed with x^2 test. A nonparametric analysis of variance was performed to compare group differences. The criterion for statistical significance was P value<0.05. This analysis indicated that a sample size of at least 45 patients per group was necessary, with a power of 90% and type I error 0.05. Allowing for 5 with additional participants recruited to allow for loss due to protocol violations. Therefore, 50 patients were required in each group for a total of 100 patients [8].

RESULTS

Epidural puncture failed in 1 patient and PCEA failed in 2 patients, a total of 3 patients were excluded in PCEA group. Finally, 97 patients completed the trial. Demographic variables did not differ significantly between the groups (Table 1) [9].

Table 1: Basic patient characteristics.

Variables	Group		P
	PCEA (n=47)	PCIA (n=50)	
Sex (M/F)	24/23	29/21	0.493

Age (yr)	70.41 ± 2.98	70.72 ± 3.61	0.641
BMI (kg/m^2)	22.60 ± 0.64	22.36 ± 0.84	0.111
ASA (I/II/III)	0/38/9	0/40/10	0.984
Surgery time (min)	187.66 ± 4.54	188.64 ± 5.37	0.335
Anesthesia time (min)	202.17 ± 11.36	210.58 ± 15.68	0.335

Collected the blood samples, added $CD4^+$, $CD25^+$ and $CD127^-$ fluorescent markers to the specimen and detected them by flow cytometry and integrated them on the computer. The proportion of $CD4^+$ $CD25^+$ $CD127^-$ Tregs in $CD4^+$ T lymphocytes in venous blood was analyzed and compared. Compared between groups on one day before the surgery, the proportion had no significant difference ($P>0.05$). Compared with one day before the surgery, the proportion showed increased significantly in both groups on the first day after the surgery ($P<0.05$). On the first day after the surgery, the proportion in PCEA group was significantly lower than that in PCIA group and the difference was statistically significant ($P<0.05$) (Table 2) [10].

Table 2: The proportion of $CD4^+$ $CD25^+$ $CD127^-$ Tregs in $CD4^+$ T lymphocytes in patients' venous blood (%).

Time	Group		P
	PCEA	PCIA	
1 day before the surgery	2.42 ± 0.56	2.49 ± 0.69	0.557
1 day after the surgery	2.86 ± 0.73	3.78 ± 0.87	0

Patients in PCEA group experienced significantly less pain; VAS was lower than that in PCIA group during 48 hours after surgery (Table 3). During the postoperative self-controlled analgesia period, the rescue medication was not applied. 2 patients felt dizzy in PCIA group, 1 patient complained motor block in PCEA group; 5 patients had symptoms of nausea and vomit in PCIA group, while 4 patients in PCEA group. No patient occurred respiratory depression and itchy skin. There was no significant difference in adverse drug events [11].

Table 3: Comparisons of postoperative VAS.

Variables	Group		P
	PCEA	PCIA	
VAS at rest on the 1st day postoperatively	0.03 ± 0.14	0.15 ± 0.30	0.048
VAS at movement on the 1st day postoperatively	1.97 ± 0.18	2.08 ± 0.26	0.013
VAS at rest on the 2nd day postoperatively	0.07 ± 0.26	0.71 ± 0.39	0.043
VAS at movement on the 2nd day postoperatively	2.92 ± 0.23	3.03 ± 0.19	0.025

DISCUSSION

Colorectal cancer is the third most frequent type of cancer in the world; recently, some trials have already proven the oncological equivalency of laparoscopic and open colectomy. However, surgery is well known to result in the suppression of some immune functions. A systematic review supported the view that innate immune response was activated to a higher degree in

open colectomy, which may be related to the more extensive trauma and surgical stress [12].

Cytokines have already been used as markers of innate immune responses after colectomy. Some studies further supported that, compared with laparoscopic colectomy, open colectomy increased the stimulation of the innate immune system. They used IL, α-defensins, Toll-Like Receptors (TLRs) and CRP as early markers of innate immune stimulation. Researches demonstrated that α-defensins, IL-6, CRP and TLRs were mostly significantly higher at 24 hours after surgery. Therefore, 1 day after the surgery, we detected the postoperative immune function.

Tregs, as a special type of T cell subset, can suppress the immune response and regulate various diseases caused by immune imbalance. The main phenotypes of Tregs, $CD4^+$, $CD25^+$, $CD127^-$, can reflect the immune function typically. In this study, the proportion of $CD4^+$ $CD25^+$ $CD127^-$ Tregs in $CD4^+$ T lymphocytes in both groups on the first postoperative day was significantly higher than that on one day before the surgery, showed that the increased expression of Tregs was related to the inflammatory response caused by surgical trauma. Although both of the postoperative analgesia methods provided satisfied analgesia effect, Tregs in PCEA group was significantly lower than that in PCIA group on the first day after the surgery. The possible reason is that PCEA reduced the stress response; the result was consistent with the previous study. The related mechanism deserved further study [13].

Pain is the critical factor, which related to immune function. Pain-relieving anesthesia techniques and perioperative analgesia provide some protection against surgery-induced immune suppression and infectious surgical sequelae, PCEA could relieve postoperative pain. There is a strong evidence that pain-relieving interventions significantly enhanced recovery from surgery. Because of the anesthesia protocol, perioperative pain management becomes an essential strategy for reducing postoperative sequelae.

Our results showed that PCEA significantly reduced immune suppression on the first day after open colectomy, reduced pain during 48 hours postoperatively and did not significantly increase the incidence of adverse events. The strengths of this study were as follows. First, we recruited elderly patients as the subjects, who were the high-risk populations of immune suppression. Second, we chose effective PCEA or PCIA to inhibit stress and inflammation after the operation, improved postoperative analgesia effect to the greatest. Third, we used Tregs to assess immune function, including quantitative analysis and ratio calculation. However, our study also had some limitations. First, it was a single-center study. Second, because the budget limited, we just assessed Tregs on the first day after the surgery, when was the most frequent day of immune suppression cited by the previous citation. Third, there was no other cytokine detection.

CONCLUSION

In conclusion, for elderly patients undergoing open colectomy, compared with PCIA, PCEA can reduce Tregs expression on the first day after the surgery, effectively decreased postoperative pain and without significant adverse events.

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CONFLICTS OF INTEREST

There are no conflicts of interest.

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