Systemic Acute-phase Response in Laparoscopic and Open Ileal Pouch Anal Anastomosis in Patients With Ulcerative Colitis: A Case-matched Comparative Study

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Aim: The current trial was designed to study and compare the postoperative outcomes and systemic acute responses between patients undergoing laparoscopic-ileal pouch anal anastomosis (LAP-IPAA) and open IPAA for ulcerative colitis.

Methods: The clinical records of patients who underwent 89 restorative proctocolectomy procedures with IPAA were reviewed. After determining which patients underwent LAP-IPAA versus open IPAA, an equivalent number of controls matched for age and ulcerative colitis severity were selected.

Results: Twenty of 22 patients who underwent laparoscopic surgery met the inclusion criteria. Patients who underwent LAP-IPAA had significantly shorter times to first walking ($P = 0.021$) and food intake ($P = 0.0003$). The LAP-IPAA group had significantly lower interleukin-6 and interleukin-1ra levels soon after surgery ($P = 0.011$ and $P = 0.0076$). The LAP-IPAA group had significantly lower C-reactive protein levels on postoperative day 1 ($P = 0.0027$).

Conclusions: LAP-IPAA is a less-invasive operative procedure than open IPAA with respect to the postoperative systemic inflammatory response and postoperative recovery.

Key Words: ulcerative colitis, laparoscopy, cytokine, ileal pouch

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Restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) has become the surgical procedure of choice for definitive management of ulcerative colitis (UC) and familial adenomatous polyposis.[1] Many studies have shown that laparoscopic IPAA (LAP-IPAA) may be performed with the same safety as that in the conventional approach; however, because the short-term advantages of laparoscopy seemed to be limited, the clinical significance of this procedure is reportedly arguable.[2–5] LAP-IPAA is increasingly being considered a viable option for patients undergoing IPAA.

Surgical trauma is followed by a biological period of repair that triggers metabolic, hormonal, and hemodynamic reactions that collectively constitute the so-called systemic acute-phase response that restores homeostasis.[6] It has been hypothesized that postoperative outcomes in laparoscopic surgery are related to less severe tissue damage, which results in less metabolic stress and a lower immune response than in open surgery.[7,8] Cytokines such as interleukin-6 (IL-6) and interleukin-1ra (IL-1ra) are thought to play a pivotal role in the pathogenesis of surgical trauma.[9,10] C-reactive protein (CRP) provides an overall marker of the systemic acute-phase response and indicates the severity of surgical trauma.[9–11] The postoperative levels of these markers have been found to correlate with the magnitude of surgery and earlier recovery.[10,12]

However, to the best of our knowledge, no studies have evaluated the systemic acute-phase response in patients who underwent LAP-IPAA for UC. The current trial was designed to study and compare the postoperative outcomes and systemic acute-phase responses between LAP-IPAA and open IPAA for UC.

MATERIALS AND METHODS

Study Population

The clinical records of 89 patients who underwent IPAA for UC from January 2009 to December 2013 in our unit at Mie University Hospital were reviewed for this analysis. The investigations were performed in accordance with the Declaration of Helsinki and were approved by the institutional review board. Informed consent was obtained from all patients who agreed to have their personal data used for research purposes. Patients with UC undergoing LAP-IPAA were included. The indication for LAP-IPAA in our department was mild to moderate UC. The surgical approach was chosen based on a combination of the patient's and surgeon's preferences. The exclusion criteria were as follows: below 17 years of age, performance of procedures other than restorative proctocolectomy with IPAA, concomitant presence of advanced cancer, concomitant presence of comorbidities (cardiovascular disease, diabetes mellitus, deep venous thrombosis, renal disease, or pulmonary disease), the performance of concomitant procedures, and history of a

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previous gastrointestinal operation. After identifying the patients who underwent LAP-IPAA, those who underwent open IPAA were reviewed with respect to the inclusion and exclusion criteria. Equivalent numbers of patients who underwent open IPAA and controls were selected (matched for age within 5 y and UC severity). Data collected for both groups included demographics, operation details, and postoperative course. Use of immunomodulation and infliximab was defined as that within 4 and 8 weeks before surgery, respectively. Evaluation of the severity of UC was based on modification of Truelove and Witts' criteria[13,14]: (i) >6 stools/day, (ii) bloody diarrhea, (iii) fever of >37.5°C, (iv) heart rate of >90 bpm, (v) hemoglobin of >10 g/dL, and (vi) erythrocyte sedimentation rate of >30 mm/h. When criteria (i), (ii), and either (iii) or (iv) are satisfied, and at least 4 of the 6 criteria are satisfied, UC is diagnosed as severe. UC is diagnosed as mild when all of the 6 criteria are satisfied and as moderate in case of intermediate between severe and mild.

Surgical Procedure

All operations in this study involved mucosal restorative proctocolectomy with hand-sewn IPAA using a J-shaped ileal pouch. Patients were placed in the lithotomy position. Laparoscopic operations were started with the use of 5 or 6 ports, and pneumoperitoneum of 8 mm Hg was maintained during the intra-abdominal approach. Standard open IPAA was performed through the smallest feasible lower midline abdominal incision (7 cm), and the incision was expanded if the operation was too difficult to be continued through mini-laparotomy. In both laparoscopic and open surgery, colectomy began with mobilization of the ascending colon mesentery; the sigmoid, descending, and transverse colon mesentery were then mobilized. In both groups, dissection of the mesentery began with the terminal ileum and was performed in a medial to lateral direction with high vessel ligation. The circumferential mucosectomy began at the lower margin of the dentate line. The mucosa was stripped to approximately 3 to 4 cm from the dentate line above the levator ani muscle. In laparoscopic surgery, the umbilical site was enlarged to exteriorize the bowel and construct an ileal J pouch with a 3 to 4 cm incision. An approximately 18 cm ileal J pouch was constructed. After pneumoperitoneum had been established, the ileal pouch was delivered to the anus under laparoscopic vision, and a hand-sewn IPAA was created. The anastomosis was performed in the same manner in both the laparoscopic and open groups under direct vision. Finally, a temporal loop ileostomy was created. A diverting loop ileostomy was routinely created in all patients.

Perioperative Management

The premedication and anesthetic procedures were standardized by the same team. Epidural analgesia was applied during surgery for all patients. There were no changes in the postoperative care of any patients. All patients in both groups received similar parenteral therapy during the first 24 hours of the postoperative period. The indication for perioperative steroid coverage was the administration of steroid therapy within 12 months of surgery. All patients were encouraged to ambulate on postoperative day 1. Pain management included epidural and/or intravenous patient-controlled analgesia and early conversion to oral medication. Water intake was usually started on postoperative day 1, and food intake was initiated after bowel movements had begun.

Surgical Outcomes

The incisional length was defined as the length of the midline abdominal incision created to exteriorize the ileum and construct the ileal J pouch. The time until first walking was defined as the number of days until the first day of walking in the room without any help. To assess bowel movement, we measured fecal output at postoperative day 2. Postoperative complications and postoperative mortality were defined as those occurring within 30 days after the operation, and the severity of each postoperative complication was evaluated using the Clavien-Dindo classification.[15] Patients with postoperative complications of Clavien grade I or higher were considered to have complications. Complications classified as grade I and II were considered to be minor complications, whereas those classified as grade III or higher were considered to be major complications. No patients died within 30 days after the operation.

Serum Antitumor Necrosis Factor-α (TNF-α) Antibody Levels

To assess the impact of preoperative administration of infliximab on the acute-phase response after surgery, the qualitative level of free therapeutic TNF-α antibodies (infliximab) was measured as follows. Peripheral blood samples were taken just before surgery. The samples were centrifuged and the serum was stored in aliquots at −80°C until tested. Enzyme-linked immunosorbent assay (ELISA) (TNF-α blocker monitoring, infliximab drug level; Immundiagnostik Inc., Bensheim, Germany) was performed to determine the quantitative level of free therapeutic TNF-α antibodies (infliximab) in the serum samples according to the manufacturer's instructions. The detection limit of free therapeutic TNF-α antibodies (infliximab) was 1.0 μg/dL; levels below this limit were considered to be undetectable.

Cytokine and CRP Serum Levels

The IL-6, IL-1ra, and CRP serum levels were measured to assess the impact of the 2 operative techniques on the acute-phase response. Peripheral blood samples were taken just before surgery, and postoperative samples were collected on postoperative days 1, 3, and 7. For cytokine analysis, samples were centrifuged and serum was stored in aliquots at −80°C until tested. IL-6 and IL1ra were measured using ELISA (Human IL-6, Human IL-1ra/IL-1F3 DuoSet ELISA kit; R&D Systems Inc., Minneapolis, MN) according to the manufacturer's instructions. The detection limits of IL-6 and IL1ra were 9.38 and 39.1 pg/mL, respectively; levels below these limits were considered to be undetectable. The serum CRP levels were determined with an institutional chemistry analyzer (TBA-c16000; Toshiba Medical Systems, Tokyo, Japan).

Statistical Analysis

Quantitative data were expressed as mean ± SD. The Wilcoxon, Kruskal-Wallis, and Fisher exact tests were used as appropriate (JMP version 5; SAS Institute Inc., Cary, NC). A P-value of <0.05 was considered statistically significant.

RESULTS

Demographics

Figure 1 shows the patient selection for the matched-pair study. Of the 89 patients with UC who underwent

restorative proctocolectomy and IPAA with ileostomy, 22 who underwent laparoscopic surgery were initially identified by the database search. Of this group, 2 patients with UC associated with advanced cancer who underwent IPAA were excluded.

Of the 67 patients with UC who underwent open IPAA, 24 were excluded because of an age of below 17 years (n = 4), the presence of concomitant UC-associated cancer (n = 6), comorbidities (n = 10), concomitant procedures (n = 2), or a history of a previous gastrointestinal operation (n = 2). Of the 43 patients who met the inclusion criteria, we selected the 20 patients who underwent open IPAA who best matched the laparoscopic controls by age and UC severity. A summary of the demographic data of patients who underwent LAP-IPAA and open IPAA is presented in Table 1. There were significant differences in the preoperative use of infliximab between the LAP-IPAA and open IPAA groups, but there was no difference in the proportion of blood samples in which infliximab could be detected according to the serum anti-TNF-α antibody level. No patients took adalimumab. There were no differences in any other preoperative demographic data between the LAP-IPAA and open IPAA groups.

TABLE 1. Patient Characteristics and Disease-related Variables

Preoperative Factors	LAP-IPAA Group (N = 20)	Open IPAA Group (N = 20)	*P*
Sex (male/female)	8/12	14/6	0.056
Age at surgery (y)	39.4 ± 13.4	39.9 ± 13.9	0.81
Age at UC onset (y)	32.3 ± 12.7	32.3 ± 14.2	0.84
Body mass index (kg/m^2)	19.5 ± 3.70	20.9 ± 3.56	0.25
Disease duration (y)	7.1 ± 6.3	7.9 ± 5.2	0.47
Extent of colitis (total colitis/left-sided colitis)	15/5	16/4	0.70
Matts classification (1/2/3/4)	2/11/5/2	2/12/6/0	0.54
Severity of colitis (moderate/mild)	14/6	14/6	1.00
Dosage of steroid per month just before colectomy (mg)	191 ± 197	312 ± 297	0.25
Dosage of steroid per day just before colectomy (mg)	6.0 ± 6.0	11.2 ± 10.9	0.18
Immunomodulator (yes/no)	7/13	4/16	0.28
Anti-TNF-α antibody therapy (yes/no)	11/9	3/17	0.0080
Detection of anti-TNF-α antibody (yes/no)	4/16	2/18	0.37
Perioperative steroid cover (yes/no)	19/1	18/2	0.54

LAP-IPAA indicates laparoscopic restorative proctocolectomy with ileal pouch anal anastomosis; open IPAA, open restorative proctocolectomy with ileal pouch anal anastomosis; UC, ulcerative colitis.

Surgical Outcomes

Table 2 shows the surgical outcome in the 2 groups. The incision length (3.6 ± 0.4 vs. 8.1 ± 1.8 cm, $P < 0.0001$), amount of blood loss (442 ± 74 vs. 303 ± 46 g, $P = 0.0009$), and rate of intraoperative blood transfusion (0 vs. 4 patients, $P = 0.0035$) were significantly lower in the LAP-IPAA than in the open IPAA group. The LAP-IPAA had shorter times to first walking (2.4 ± 0.7 vs. 2.9 ± 0.6 d, $P = 0.021$) and food intake (1.9 ± 0.6 vs. 3.1 ± 1.4 d, $P = 0.0003$). The LAP-IPAA group had greater fecal output on postoperative day 2 (1272 ± 931 vs. 737 ± 541 mL, $P = 0.0022$) and a longer operation time (442 ± 74 vs. 303 ± 46 min, $P < 0.0001$). There were no differences in the frequencies of major or minor postoperative complications between the 2 groups (major postoperative complications, 2 vs. 1 patient, $P = 0.54$; minor postoperative complications, 4 vs. 9 patients, $P = 0.091$).

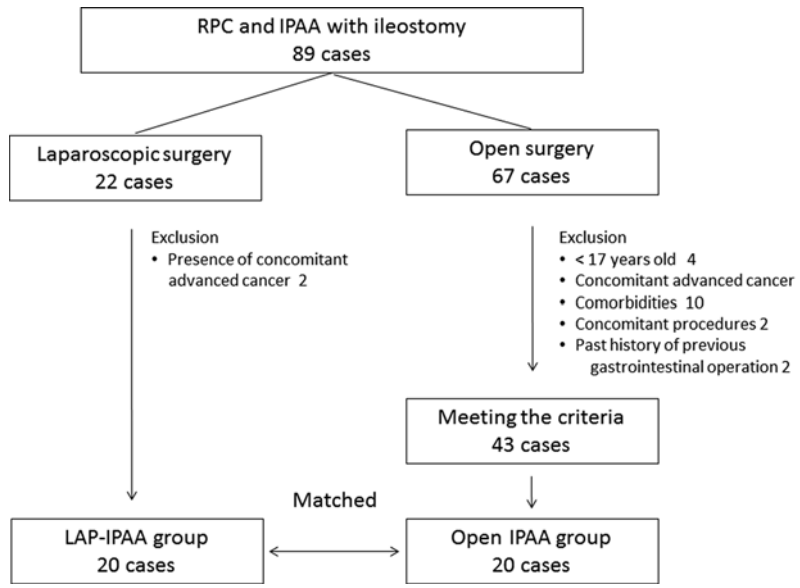

FIGURE 1. Patient selection for the matched-pair study. LAP-IPAA indicates laparoscopic restorative proctocolectomy with ileal pouch anal anastomosis; open IPAA, open restorative proctocolectomy with ileal pouch anal anastomosis.

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TABLE 2. Surgical Outcomes

Preoperative Factors	LAP-IPAA Group (N = 20)	Open IPAA Group (N = 20)	*P*
Incisional length (cm)	3.6 ± 0.4	8.1 ± 1.8	< 0.0001
Operative time (min)	442 ± 74	303 ± 46	< 0.0001
Operative blood loss (g)	181 ± 162	550 ± 400	0.0009
Intraoperative blood transfusion (yes/no)	0/20	4/16	0.035
Days until first walking (d)	2.4 ± 0.7	2.9 ± 0.6	0.021
Days until first food intake (d)	1.9 ± 0.6	3.1 ± 1.4	0.0003
Fecal output on postoperative day 2 (mL)	1272 ± 931	737 ± 541	0.0022
Major postoperative complication (yes/no) [n (%)]	2 (10)	1 (5)	0.54
Postoperative intra-abdominal abscess (yes/no)	2	1	
Anastomotic leakage (yes/no)	1	1	
Minor postoperative complication (yes/no) [n (%)]	4 (20)	9 (45)	0.091
Acute enteritis (yes/no)	0	1	
Small bowel obstruction (yes/no)	4	6	
Wound infection (yes/no)	0	2	

LAP-IPAA indicates laparoscopic restorative proctocolectomy with ileal pouch anal anastomosis; open IPAA, open restorative proctocolectomy with ileal pouch anal anastomosis.

Perioperative Cytokine and CRP Serum Levels

We evaluated the postoperative changes in IL-6, IL-1ra, and CRP (Fig. 2). There were no differences in the preoperative values of IL-6, IL-1ra, or CRP between the 2 groups. The LAP-IPAA group had significantly lower IL-6 and IL-1ra levels soon after surgery (IL-6, 101 ± 73 vs. 228 ± 193 pg/mL, $P = 0.011$; IL-1ra, 173 ± 390 vs. 565 ± 875 pg/mL, $P = 0.0076$), although there were no differences in the IL-6 or IL-1ra levels between the 2 groups on postoperative days 1, 3, and 7. The LAP-IPAA group had significantly lower CRP levels on postoperative day 1 (7.4 ± 3.6 vs. 11.1 ± 3.8 pg/mL, $P = 0.0027$), although there were no differences in the CRP levels between the 2 groups soon after surgery or on postoperative days 3 and 7.

DISCUSSION

Our data show that LAP-IPAA is associated with reduced incision length, operative blood loss, intraoperative blood transfusion, days until first walking, and days until first food intake and an increased operative time compared with open IPAA. No differences were demonstrated between the open and laparoscopic approaches with respect to the major and minor postoperative complication rates. Both this study and previous reports have shown that LAP-IPAA for UC is a feasible and safe procedure for select patients compared with open surgery.

In a meta-analysis performed by the Cochrane Foundation, the short-term postoperative results of the laparoscopic and open approaches to IPAA were compared.[2] The review demonstrated no significant differences in mortality or postoperative complications. LAP-IPAA was associated with a significantly longer operative time by an average of about 90 minutes, and the hospital stay in this group was shorter with a weighted mean difference of −2.66 days. The total incision length was significantly shorter and the cosmetic scores were significantly higher in the laparoscopic group. No reliable conclusions could be made regarding the benefit of LAP-IPAA for times to postoperative return of bowel movements and a regular diet.

A systematic review and meta-analysis reported by Singh et al[5] demonstrated that the time to resumption of a solid diet was significantly shorter among patients undergoing laparoscopic surgery. They stated that previous trial findings suggest that the laparoscopic approach may improve postoperative recovery, but that the importance of these advantages seems limited.

It has been hypothesized that 1 reason for the better results of minimally invasive surgery might be associated with modified immunologic and metabolic responses to laparoscopic surgery.[7,8]

This study showed that LAP-IPAA for UC results in significantly lower IL-6 and IL-1ra levels soon after surgery and significantly lower CRP levels on postoperative day 1.

Dunker et al[16] analyzed the effect of surgical trauma as part of a randomized trial comparing laparoscopically assisted versus open bowel resection for Crohn disease, UC, and familial adenomatous polyps. Surgical procedures in that study included IPAA. They concluded that the surgical approach did not significantly affect the immune status. Our study is the first to analyze the systemic acute-phase response only among patients who underwent IPAA for UC.

Similar results concerning the systemic acute-phase response have been shown in some studies that compared laparoscopic and open surgery among patients with colorectal cancer. Harmon et al[17] were the first to describe lower postoperative IL-6 levels with laparoscopic colectomy than with the open approach. Several randomized control studies have demonstrated significantly lower concentrations of systemic IL-6 and CRP after laparoscopic colon or rectal surgery than those associated with the conventional approach.[7,18,19] Veenhof et al[8] evaluated the effect of laparoscopic or open colectomy with either fast track or standard perioperative care on the patient's stress response after surgery. This randomized trial showed that laparoscopic colectomy was associated with higher presentation of the human leukocyte antigen-DR on monocytes and lower peak concentrations of serum IL-6 and CRP. They concluded that the differences in the immune function and systemic acute-phase response seem to be correlated with the type of surgery and not with aftercare.

The results obtained in the present study suggest that LAP-IPAA for the treatment of UC may be associated with a lower systemic acute-phase response, which may affect the postoperative recovery parameters. This may be because of the smaller incision, lower intraoperative blood loss, and less intestinal manipulation associated with laparoscopic surgery.

The limitations of the present study relate to its retrospective nature and small sample size. Another limitation was the decision regarding the surgical approach, which was based on a combination of the patient's and surgeon's preferences. We did our best to avoid bias with respect to preoperative systemic inflammation by matching the 2 groups for age and UC severity.

In conclusion, LAP-IPAA is a less-invasive operative procedure than open IPAA with respect to the

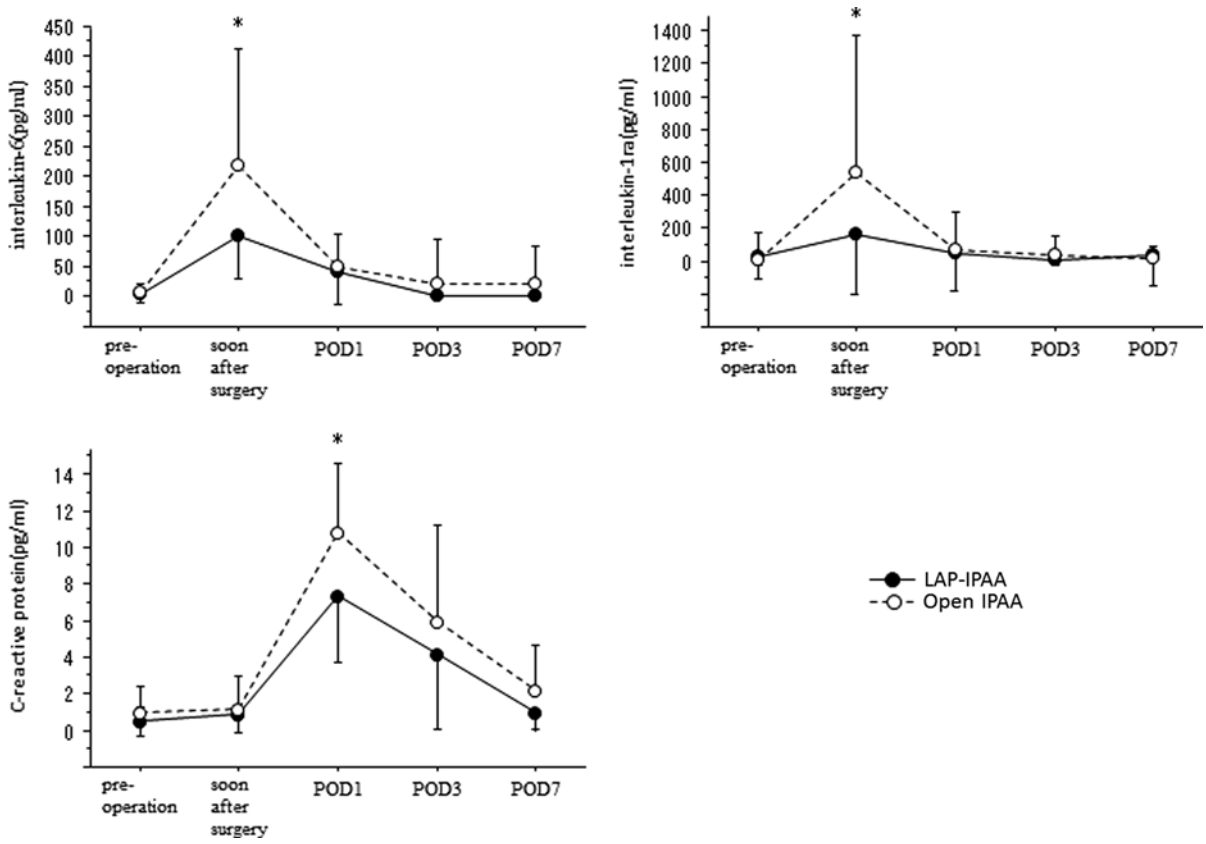

FIGURE 2. Evaluation of the postoperative changes in the interleukin (IL)-6, IL-1ra, and C-reactive protein (CRP) levels. There were no differences in the preoperative IL-6, IL-1ra, and CRP levels between the 2 groups. The LAP-IPAA group had significantly lower IL-6 and IL-1ra levels soon after surgery and a lower CRP level on postoperative day 1. $*P < 0.05$. LAP-IPAA indicates laparoscopic restorative proctocolectomy with ileal pouch anal anastomosis; open IPAA, open restorative proctocolectomy with ileal pouch anal anastomosis; POD, postoperative day.

postoperative systemic inflammatory response and postoperative recovery. Because we performed this study in a nonrandomized manner and used historic controls, a prospective randomized study is necessary to define the role of minimally invasive restorative proctocolectomy for UC.

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