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Comparison of the effects of thoracic epidural analgesia and i.v. infusion with lidocaine on cytokine response, postoperative pain and bowel function in patients undergoing colonic surgery

C. P. Kuo[1], S. W. Jao[2], K. M. Chen[3], C. S. Wong[1], C. C. Yeh[1], M. J. Sheen[1] and C.T. Wu[1]*

[1]Department of Anesthesiology and [2]Department of Colon and Rectum Surgery, Tri-Service General Hospital and National Defense Medical Center, Taipei, Taiwan. [3]Department of Statistics, Rutgers University, Piscataway, NJ, USA

**Corresponding author: Department of Anesthesiology, Tri-Service General Hospital and National Defense Medical Center, #325, Section 2, Chenggung Road, Neihu 114, Taipei, Taiwan. E-mail: wuchingtang@msn.com*

Background. Both thoracic epidural analgesia (TEA) and i.v. lidocaine were able to decrease postoperative pain and duration of ileus. We compared TEA and i.v. lidocaine (IV) regarding their effects on cytokines, pain and bowel function after colonic surgery.

Methods. Sixty patients were randomly allocated to one of the three groups. TEA group had lidocaine 2 mg kg^{-1} followed by 3 mg kg^{-1} h^{-1} epidurally and an equal volume of i.v. normal saline. The IV group received the same amount of lidocaine i.v. and normal saline epidurally. The control group received normal saline via both routes. These regimens were started 30 min before surgery and were continued throughout. Blood cytokines were measured at scheduled times within 72 h.

Results. Both TEA and IV groups had better pain relief. The total consumptions using patient-controlled epidural analgesia were 81.6 (6.5), 55.0 (5.3) and 45.6 (3.9) ml ($P<0.01$) and the times of flatus passage were 50.2 (4.9), 60.2 (5.8) and 71.7 (4.7) h ($P<0.01$) in the TEA, IV and control groups, respectively. The TEA group exhibited the best postoperative pain relief and the least cytokine surge. The IV group experienced better pain relief and less cytokine release than the control group.

Conclusions. The TEA lidocaine had better pain relief, lower opioid consumption, earlier return of bowel function and lesser production of cytokines than IV lidocaine during 72 h after colonic surgery; IV group was better than the control group.

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Cytokines such as interleukin (IL)-6 and IL-8, released during inflammatory responses, can also produce a long-lasting hyperalgesia.[1 2] These pro-inflammatory cytokines can modulate pain indirectly by altering pain signal transmission via cytokine-induced release of neuroactive substances such as nitric oxide, oxygen-free radicals and excitatory amino acids.[3] Meanwhile, the anti-inflammatory cytokines also increase during inflammation to maintain balance in responses. Therefore, IL-1 receptor antagonist (RA) acts as a 'functional antagonist' and reduces inflammation after injury.[3]

Colonic surgery is associated with increased levels of pro-inflammatory cytokines, and is associated with postoperative ileus.[4] In the previous studies,[5 6] we demonstrated that epidural or i.v. lidocaine could reduce postoperative pain and ileus through different mechanisms.[7 8] We also found that, with other additives, i.v. or epidural lidocaine had enhanced effects on postoperative pain and bowel function.[5 6 9 10] However, to the best of our knowledge, a comparison of the effects of lidocaine, given i.v. or epidurally, on postoperative pain, cytokine response and bowel function is lacking. Therefore, we compared the effect of

epidural and i.v. lidocaine on cytokine levels, pain and bowel function recovery after colonic surgery.

Methods

This study was approved by our Institutional Review Board and was performed between December 2003 and November 2004. After obtaining written informed consent, an anaesthesiologist nurse randomly allocated the patients to one of the three groups using a computer program. Preoperatively, on the day before surgery a thoracic epidural analgesia (TEA) catheter was placed in T6–T12 interspaces, and was advanced 3–4 cm in cephalad direction. The position of the epidural catheter was tested with 6 ml of lidocaine 1%. The study drugs (lidocaine and saline) were prepared by the hospital pharmacy in identical containers.

Sixty patients, ASA I or II, aged 40–80 yr, and undergoing elective surgery for colon cancer were recruited. The patients who had other systemic diseases, such as diabetes mellitus, or hypertension, or received opioids or non-steroidal anti-inflammatory drugs within 1 week of surgery, were excluded. All the procedures were performed by the same team of anaesthetists and surgeons. Patients were familiarized with the visual analogue scale (VAS) and instructed in the use of the patient-controlled epidural analgesia (PCEA) pump (Pain Management Provider; Abbott, Chicago, IL). Patients of Group TEA (n=20) received lidocaine 2 mg kg^{-1} for 10 min and then 3 mg kg^{-1} h^{-1} via the epidural catheter and an equal volume of normal saline through i.v. Patients of Group IV (n=20) received the same dosage of lidocaine and normal saline via the peripheral i.v. line and the epidural catheter, respectively. Patients of the control group (Group C, n=20) received normal saline via both the peripheral i.v. line and the epidural catheter. The drugs were started 30 min before surgery and the infusions maintained throughout the surgical procedure.

General anaesthesia was induced with fentanyl 2 μg kg^{-1} and thiopental 3–5 mg kg^{-1}, given i.v., and tracheal intubation was facilitated with succinylcholine 1.5 mg kg^{-1}. Anaesthesia was maintained with desflurane in oxygen, and the concentration of desflurane was adjusted to maintain the systolic arterial pressure within the range of 20% of the baseline and to keep the auditory evoked potential index (AAI) within 15–25. Fentanyl 1 μg kg^{-1} or ephedrine 5 mg would be given if the AAI was in the set range, but the arterial pressure either increased or decreased by >20% of baseline. Atropine 0.5 mg would be given if the heart rate decreased to <60 beats min^{-1} along with hypotension. Respiratory frequency and tidal volume were adjusted to maintain the end-tidal carbon dioxide at approximately 4.5 kPa. Oesophageal temperature was maintained at 35–37°C. All patients received balanced salt solution at a rate of 6 m kg^{-1} h^{-1} during surgery and 2 ml kg^{-1} h^{-1} after operation. Patients likely to have received blood transfusion during the perioperative period were excluded. At the end of surgery, residual neuromuscular block was antagonized with edrophonium (0.8 mg kg^{-1}) and atropine (0.01 mg kg^{-1}), and the tracheal tube was removed when the patient breathed spontaneously and smoothly.

On arrival at the postanaesthesia care unit, all patients were connected with the PCEA pump with morphine (0.1 mg ml^{-1}) in 100 ml of ropivacaine 0.2%. They received PCEA solution 10 ml at the first trigger and then 4 ml per delivery (lockout time was 15 min without a 4 h limitation or continuous background infusion). A 10 cm VAS (with end points labelled 'no pain' and 'worst possible pain') was used to assess pain intensity at rest and during coughing at 1, 2, 4, 12, 24, 48 and 72 h after completion of surgery.

We recorded the end-tidal desflurane concentration 1 h after skin incision, the number of patients who received fentanyl, ephedrine and atropine, the first PCEA trigger time, total PCEA delivery time and consumption, the first time of flatus passage and side-effects related to morphine (drowsiness, dizziness, nausea and vomiting) for 72 h after the operation. All observations were double-blinded and made by a study nurse. Side-effects were treated if necessary.

Blood samples were obtained 10 min before the lidocaine infusion, at the end of surgery, and after operation at 12 and 24 h. Blood was collected into EDTA tubes and centrifuged at 3000 g for 10 min at 4°C immediately after sampling. Thereafter, plasma was stored at −70°C until all the samples were collected. Plasma concentrations of IL-6, IL-8 and IL-1RA were measured with commercially quantitative sandwich ELISA kits (Quantikine, R&D Systems, Minneapolis, MN, USA). The sensitivity of the assay for IL-6, IL-8 and IL-1RA was 0.7, 4.4 and 22 pg ml^{-1}, respectively. Standards were prepared, and the appropriate volume of sample or standard was added to a 96-well polystyrene microtitre plate, precoated with monoclonal antibody to the appropriate cytokine, or RA. All samples and standards were run in duplicate. The plate was incubated for the manufacturer's recommended period of time. Each well was then aspirated and the plates washed with the buffered surfactant provided. An enzyme-linked polyclonal antibody against the cytokine, or RA was then added, and again the plates were incubated and washed. Substrate solution was added to each well and the optical density was read at the appropriate wavelength for each assay period. All values are reported in pg ml^{-1}. The intra-assay and interassay coefficients of variation of the immunoassay kits ranged between 5 and 10%. Cross-reactivity with other factors was negligible in all cytokine assays.

Based on retrospective data from our institution in the same surgical population, a power analysis was performed using PCEA consumption as the primary variable. We calculated a sample size so that a between-group difference in PCEA solution consumption of 25 ml would permit a one-tailed type I error rate of α=0.05 with a power of 80%. This analysis indicated that a sample size of at least 18 patients per group was necessary. Patient characteristics such as gender, age, weight and height, and operation time

Table 1 Patient characteristics in different study groups. C, control; IV, intravenous; TEA, thoracic epidural analgesia. Data are expressed as mean (SD) or [range] or numbers. *$P<0.01$ as compared with Group C; †$P<0.01$ as compared with Groups C and IV; ‡$P<0.01$ as compared with Groups TEA and IV; §$P<0.01$ as compared with Groups TEA and C

	Group C (n=20)	Group IV (n=20)	Group TEA (n=20)
Gender (male/female)	12/8	10/10	11/9
Age (yr)	62 (46–85)	63 (50–75)	63 (47–75)
Weight (kg)	61.6 (8.5)	61.5 (6.9)	60.1 (5.4)
Height (cm)	163.5 (4.9)	161.7 (4.6)	163.2 (6.0)
Operation time (min)	150.8 (11.5)	157.8 (13.4)	153.5 (17.9)
End-tidal desflurane (%)	4.9 (0.3)	4.0 (0.2)*	3.0 (0.2)†
Fentanyl (n)	17‡	1	1
Fentanyl dosage (μg kg^{-1})	3.3 (0.7)‡	2.0 (0.3)	2.0 (0.2)
Ephedrine (n)	2	2	2
Atropine (n)	1	2	1
Bradycardia (n)	0	3§	0

and concentration of end-tidal desflurane were evaluated using ANOVA with repeated measures. Other physical characteristics, ratio of male:female and rate of additional fentanyl use among groups, were analysed by proportion test without continuity correction. We used the Kruskal–Wallis rank sum test to compare VAS pain scores among groups. The effects of time (from observations 10 min before lidocaine infusion, at the end of surgery, and after operation at 12 and 24 h) and group on the levels of IL-1RA, IL-6 and IL-8 were constructed by two-way repeated measures ANOVA. P-values less than 0.05 were considered statistically significant. Continuous data are expressed as mean (SD).

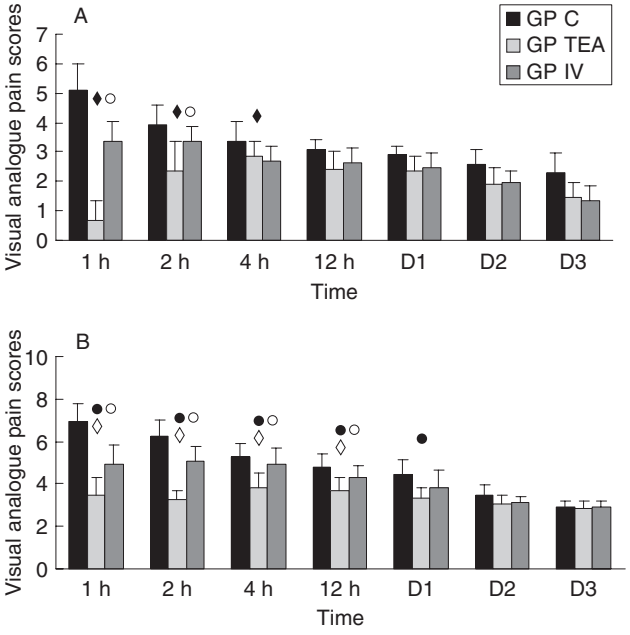

Fig 1 VAS pain scores at rest (A) and during coughing (B). Resting VAS pain scores were significantly lower at 2 and 4 h after surgery in the IV (i.v. lidocaine) and TEA (thoracic epidural analgesia with lidocaine) groups compared with the control group. Coughing VAS pain scores were significantly lower at 12 h and at day 2 (D2) after surgery in the IV and TEA groups compared with the control group. Resting and coughing VAS pain scores were significantly higher at 4 and 12 h after surgery in the IV group compared with the TEA group. Values are mean (SD). ♦$P<0.001$ compared with IV and control groups, ○$P<0.001$ compared with the control group, •$P<0.001$ compared with the control group, ◇$P<0.001$ compared with the IV group. GP, Group.

Results

There were no significant differences in the patient characteristics and duration of surgery (Table 1). Patients with i.v. lidocaine infusion all finished their full course of infusion. No patient experienced an identifiable adverse event related to i.v. lidocaine infusion; three patients had occasional bradycardia with stable other vital signs (Table 1). Average end-tidal desflurane concentration was 3.0 (0.2), 4.0 (0.2) and 4.9 (0.3)% in Groups TEA, IV, and C, respectively ($P<0.001$, Table 1). Fentanyl supplement was needed in 85% of patients in Group C compared with only 5% in both Group TEA and Group IV ($P<0.001$, Table 1). Total dosage of fentanyl was higher in Group C (3.3 μg kg^{-1}) compared with both Group TEA and Group IV (2.0 μg kg^{-1}) ($P<0.01$) (Table 1). There were no differences in ephedrine and atropine use between groups (Table 1). In addition, neither awareness nor recall before the patient returned to the common ward was noted in the postanaesthesia care unit.

VAS pain scores at rest at 2 and 4 h after surgery, and during coughing at 12 h after surgery, were significantly lower in Groups IV and TEA compared with Group C ($P<0.001$, Fig. 1). Resting and coughing VAS pain scores were significantly higher at 4 h and at 12 h after surgery in Group IV compared with Group TEA ($P<0.001$, Fig. 1). The first PCEA trigger times were 99.8 (17.7), 40.3 (10.2) and 15.8 (5.7) min in Groups TEA, IV and C, respectively ($P<0.01$, Table 2). During the 3 day observation after surgery, PCEA delivery were 10.0 (1.1), 13.8 (1.8) and 20.3 (3.7) times in Groups TEA, IV and C, respectively ($P<0.01$, Table 2). The total consumption of PCEA was 81.6 (6.5), 55.0 (5.3) and 45.6 (3.9) ml in Groups TEA, IV and C, respectively ($P<0.01$, Table 2). There were also significant differences among groups in the PCEA delivery times on the first 3 days after surgery ($P<0.01$, Fig. 2). Nausea or vomiting associated with morphine were observed in four, five and nine patients in Groups TEA, IV and C, respectively ($P<0.01$, Table 2). In addition, the time of the first flatus passage was 50.2 (4.9), 60.2 (5.8) and 71.7 (4.7) h in Groups TEA, IV and C, respectively ($P<0.01$, Table 2). However, there was no significant difference among groups regarding hospital stay (Table 2).

ANOVA with repeated measures for IL-6 and IL-8 levels revealed significant differences between groups and times ($P<0.0001$), and a significant interaction of group on time ($P<0.0001$, Fig. 3A and B). The ANOVA test of IL-1RA also revealed significant main effects of groups and times ($P<0.0001$), and a significant interaction of group on time ($P<0.0001$, Fig. 3C). These results indicate that both

Table 2 Postoperative analgesia, incidence of side-effects, morphine requirements and hospital stay. C, control; IV, intravenous; TEA, thoracic epidural analgesia; PCEA, patient-controlled epidural analgesia. Data are expressed as mean (SD) or numbers. **P*<0.01 as compared with Group C; †*P*<0.01 as compared with Groups C and IV

	Group C (*n*=20)	Group IV (*n*=20)	Group TEA (*n*=20)
Time to first trigger of PCEA (min)	15.8 (5.7)	40.3 (10.2)*	99.8 (17.7)†
Total PCEA delivery time	20.3 (3.7)	13.8 (1.8)*	10.0 (1.1)†
Total PCEA consumption (ml)	81.6 (6.5)	55.0 (5.3)*	45.6 (3.9)†
Time to first pass of flatus (h)	71.7 (4.7)	60.2 (5.8)*	50.2 (4.9)†
Morphine-associated nausea/vomiting	9	5*	4*
Hospital stay (days)	7.1 (0.8)	6.9 (0.8)	6.8 (0.8)

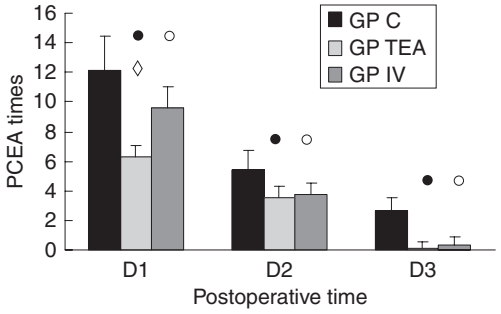

Fig 2 Total patient-controlled epidural analgesia (PCEA) delivery times more than 3 days (D) after surgery. Total delivery times in TEA (thoracic epidural analgesia with lidocaine) or IV (i.v. lidocaine) group were less than those in the control group. °*P*<0.01 compared with the control group, •*P*<0.01 compared with the control group, ◇*P*<0.01 compared with IV group. GP, Group.

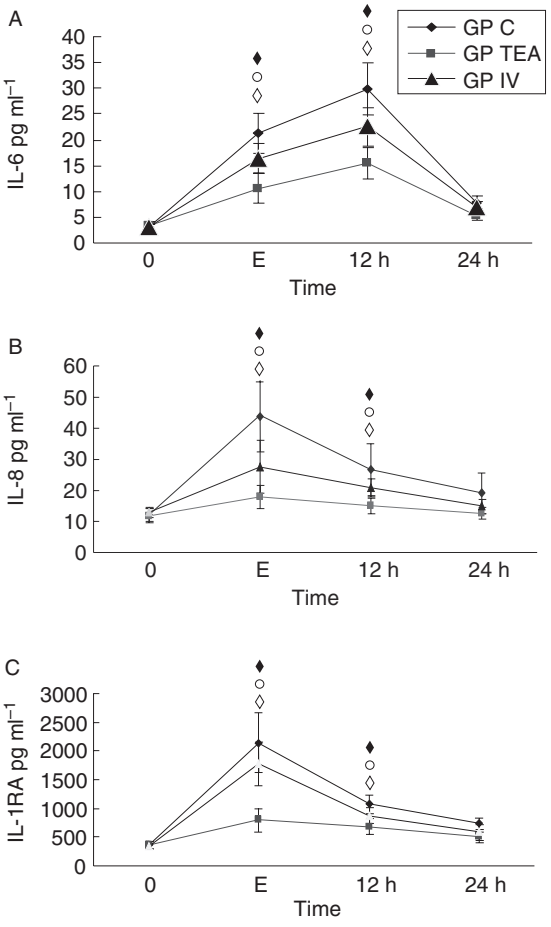

Fig 3 Mean plasma concentrations of interleukin (IL)-6 (A), IL-8 (B) and IL-1 receptor antagonist (IL-1RA) (C) concentrations, mean (SD). ♦*P*<0.01 in TEA (thoracic epidural analgesia with lidocaine) group compared with IV (i.v. lidocaine) and control groups, °*P*<0.01 in IV group compared with control group; ◇*P*<0.01 in TEA compared with IV group. GP, Group.

pro-inflammatory and anti-inflammatory cytokine production increased in the perioperative period and that such increase was least in Group TEA and intermediate Group IV.

Discussion

In the present study, epidural or i.v. lidocaine before the start of surgical procedure provided significant pain relief with reduced pain intensity, diminished volatile agent and opioid consumption, accelerated return of the bowel function, and attenuated production of IL-6, IL-8 and IL-1RA. The benefit of lidocaine was more obvious in Group TEA.

In Group TEA, the first PCEA trigger time after surgery was prolonged and morphine use was reduced with less postoperative pain, which is consistent with our previous studies.[6 9 11] Incisional pain produces ongoing afferent inputs generated from the wound, and preincisional and continuous intraoperative infusion of lidocaine contribute to suppression of spinal sensitization.[1] Hodgson and Liu[12] found that the effect of epidural lidocaine was not a result of systemic lidocaine absorption. Therefore, the spinal cord remains the preferential site for analgesic action for local anaesthetics and the major analgesic effect seems to be mediated at the spinal level rather than as a supraspinal effect.[13]

In a previous study, we have demonstrated that i.v. lidocaine could reduce postoperative pain in patients undergoing laparoscopic cholecystectomy.[5 10] In the current study, we show that the VAS pain scores at rest and coughing were significantly lower in Group IV than in Group C in the first 2 and 12 h after surgery, respectively. This might have been as a result of the analgesic and anti-inflammatory effect of lidocaine, which may persist after serum levels have decreased[14] as a result of block or inhibition of nerve conduction.[8] In addition, the same dosage of i.v. lidocaine was found to decrease the heat-1 capsaicin-induced secondary hyperalgesia via its central effect,[15] which also suppressed secondary hyperalgesia in experimental incision-induced pain by inhibiting centralization.[16]

The most commonly accepted pathophysiological feature of postoperative ileus is surgically induced abdominal pain, which activates a spinal reflex arc and sympathetic hyperactivity that inhibits intestinal motility and propulsive

activity. In addition, paravertebral reflex relayed through the prevertebral ganglia might play an important role in postoperative ileus.[7] There are many anaesthetic techniques to improve bowel function after colonic surgery, but there are insufficient data to recommend an optimal anaesthetic technique.[17] Clinical evidence suggests that epidural anaesthesia can speed the return of normal bowel function after surgery.[7 11 18 19] The mechanisms might be as a result of a decrease in postoperative pain and opioid use, systemic absorption of lidocaine, and block of sympathetic innervation of the bowel.[7 18 19] Our study showed that TEA is better than i.v. lidocaine in bowel function recovery; therefore, the role of sympathetic activity is more important than paravertebral reflexes.

Lidocaine has significant anti-inflammatory properties[20] and was shown to decrease cytokine release both *in vitro* and *in vivo* by inhibiting neutrophil activation.[21–23] In a clinical study, Kato and colleagues[24 25] found pro-inflammatory cytokines increased during major abdominal surgery in patients undergoing combined general and epidural anaesthesia. We also have found that TEA anaesthesia combined with epidural clonidine or preincisional i.v. pentoxifylline attenuated perioperative cytokine response and improved recovery of bowel function after colorectal cancer surgery.[10 11] In the present study, we further demonstrate that lidocaine administered both epidurally and by i.v. infusion can attenuate IL-6, IL-8 and IL-1RA production and accelerate recovery of bowel function. The lowest cytokine response was associated with the best bowel function; as the present study shows, the least cytokine increase was observed in the TEA group, followed by the IV group and the control group. The result was consistent with that of Kalff and colleagues[26] who demonstrated that upregulation and release of pro-inflammatory cytokines after surgery contribute to postoperative ileus.

After injury, IL-6 levels in the circulation are detectable at 60 min, peak at between 4 and 6 h, and can persist for as long as 10 days.[27] Therefore, we believe that the actual peak level was underestimated in the present study. In our study, IL-6 returned to baseline 24 h after operation in all groups, so circulating IL-6 appears to be proportionate to the extent of tissue injury during the operation.[27] Moreover, IL-6 can induce peripheral and central nervous system sensitization, leading to hyperalgesia.[28] It was reported that the sympathetic nervous system could produce IL-6 and responded to it in an autocrine or paracrine manner.[29] Our results are consistent with this report; the level of IL-6 was lowest in the TEA group; the IV group had lower levels of IL-6 than the control group, a finding which also supports the anti-inflammatory effect of lidocaine.

Chemokine IL-8 potentially recruits neutrophils and monocytes into the inflammatory site, accelerating inflammation.[30] Its expression and activity is temporally associated with IL-6 after injury,[27] and identified as the first endogenous mediator for evoking hyperalgesia involving the sympathetic nervous system.[2] As IL-8 released by activated macrophages and endothelial cells may be a humoral link between tissue injury and sympathetic hyperalgesia, IL-8-induced persistent mechanical nociceptor hypersensitivity might be via sympathetic amines.[31] Lahav and colleagues[32] demonstrated that lidocaine could inhibit secretion of IL-8 by using cultured epithelial cells. Our results are consistent with these reports, showing that both routes of lidocaine suppressed the perioperative levels of IL-8 and provided more effective pain relief. However, we believe that the true peak concentration is underestimated in this study.

IL-1RA is a competitive inhibitor of IL-1β, which competes for binding of its cell surface receptors on effector cells. Therefore, IL-1RA has been commonly assumed to provide a marker for the presence of the IL-1β.[33 34] IL-1RA is released with IL-1β, signalling the acute phase response and correlating well with the grade of inflammation.[35] Josephs and colleagues[34] showed that endogenously produced IL-1RA plays a central role in mitigating the magnitude of the IL-1-mediated inflammatory response. In previous studies, we found patients with less increased level of IL-1RA experienced less postoperative pain.[10 11] In this study, the levels of IL-1RA were least increased in the TEA group, resulting in least postoperative pain. The IV group had lower levels of IL-1RA than the control group probably because of the anti-inflammatory effect of lidocaine. In contrast, cultured epithelial cells have been used to demonstrate that lidocaine could stimulate secretion of IL-1RA.[32] However, Cunha and colleagues[36] demonstrated that IL-1RA is released at sites of inflammation and limits inflammatory hyperalgesia. It acts as a 'functional antagonist' by inhibiting the production of pro-inflammatory cytokines, reducing the inflammatory response, antagonizing substance P release and providing an analgesic effect.[3] To achieve immune homeostasis, the IL-1RA levels were lower in our lidocaine-treated groups.

There are some limitations to our study. First, the opioid (fentanyl) used during surgery might have confounding effects on bowel function after operation. The short-acting opioid, remifentanil, might be the best choice for this study. However, it is not available in our hospital or country. Nevertheless, patients in the control group had highest fentanyl use, but the dosage was still low [3.3 (0.7) $\mu g\ kg^{-1}$]. In addition, patients in the control group exhibited shortest first delivery time of analgesia, highest VAS at first hour after operation, and largest total PCEA consumption, which could present the confounding effect of fentanyl. Second, the designed interspaces (T6–12) ranged too wide, which might block hormonal responses to surgery differentially. Third, the ropivacaine used in our PCEA regimen might also have anti-inflammatory effect, which might also confound the study. As the aim of this study was to evaluate the effects of lidocaine on pain relief, bowel movement and cytokine response via different routes, we could not use ropivacaine during operation. In addition, lidocaine was not suitable for postoperative pain control

because of its short duration of action. However, the regimen of the PCEA was the same in all three groups, which should have had similar effects of modulation of the inflammatory response. Therefore, the confounding effects of ropivacain would be minimal.

We demonstrate that lidocaine via both epidural and i.v. routes, before and during the surgical procedure provides significant pain relief, diminished opioid consumption, faster return of bowel function and reduced production of pro-inflammatory cytokines. Finally, we suggest that in patients with contraindications or presenting difficulty for epidural insertion, i.v. lidocaine may be an alternative for improving postoperative pain.

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