ERAS improves postoperative recovery in children

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Abstract

Objective: Enhanced recovery after surgery (ERAS) protocols are established in adults but not fully evaluated in children. This study investigated whether an ERAS protocol improved recovery and influenced postoperative inflammatory cytokine levels in children undergoing surgery for hydronephrosis.

Methods: This randomized controlled study included patients who underwent robot-assisted laparoscopic surgery for hydronephrosis at Bayi Children's Hospital (Beijing, China) between October 2018 and September 2019. Patients were randomized to an ERAS group (perioperative ERAS protocol) or control group (standard perioperative management). Outcomes related to postoperative recovery and inflammatory cytokine levels were evaluated.

Results: The final analysis included 18 patients in each group. Five patients (27.78%) in each group experienced postoperative complications (abdominal pain, nausea and vomiting, subcutaneous emphysema or fever). The ERAS group had a shorter time to first postoperative flatus than the control group (25 vs. 49 hours; P=0.009), although the time for abdominal drainage flow to reach ≤20 mL/day, time to urinary catheter removal and length of hospital stay did not differ significantly between groups. Preoperative plasma cytokine levels were comparable between groups. Compared with the control group, the ERAS group had a higher IL-6 level on postoperative day 2 (P<0.05) and a lower concentration of IL-1β on postoperative days 1 and 2 (P<0.05). Postoperative levels of CRP, TNFα and IL-10 did not differ significantly between groups.

Conclusions: ERAS may accelerate postoperative recovery and modulate the postoperative inflammatory response in pediatric patients undergoing robot-assisted laparoscopic pyeloplasty for hydronephrosis.

Keywords

Enhanced Recovery After Surgery; Pediatrics; Laparoscopic Surgery; Robot-Assisted Surgery; Cytokines

Introduction

Renal system abnormalities are among the most common congenital defects detected by prenatal ultrasound [1], and antenatal hydronephrosis (dilatation of the renal pelvis and calyces) is observed in 1–4.5% of pregnancies [2]. Hydronephrosis in children has various underlying causes but is most often due to uretero-pelvic junction stenosis or primary vesicoureteral reflux [3]. Many cases of pediatric hydronephrosis resolve spontaneously [4]. However, surgical treatment is required in cases where hydronephrosis persists to avoid the development of permanent renal damage. Surgical management of hydronephrosis in infants and children can be performed using open, endoscopic, laparoscopic or robot-assisted procedures [5, 6].

Robot-assisted laparoscopic surgery was first developed for use in adult patients but is now also applied in pediatric surgery. Robot-assisted laparoscopic surgery is well suited to operations that require fine dissection or suturing in small anatomic spaces [7] and has been used successfully in the management of pediatric

hydronephrosis [8, 9]. However, the operation requires extensive preparation of the gastrointestinal tract, use of the Trendelenburg position and a CO_2 pneumoperitoneum, and surgery is associated with non-negligible risks of perioperative pneumoperitoneum-related complications, hypothermia, pressure injury, and scald injury. In addition, perioperative management is more challenging for pediatric patients than for adults because of physiological immaturity, poorer cooperation during the perioperative period, more limited scope for preoperative education, lesser ability to express postoperative pain and discomfort, and limitations in the therapeutic drugs that can be administered.

Postoperative recovery is influenced by cytokines produced in response to surgical trauma. Inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6) and interleukin-10 (IL-10) have been implicated in the injury and dysfunction of the central nervous system, lungs, liver, cardiovascular system and kidneys after surgery, and the overproduction of inflammatory cytokines can induce systemic responses that result in tissue necrosis and death [10–13]. Inhibition of cytokines has the potential to decrease postoperative organ dysfunction [10, 11]. Therefore, there is considerable interest in identifying perioperative management strategies that can reduce cytokine levels and thereby the improve postoperative recovery in children undergoing surgery.

Enhanced recovery after surgery (ERAS) was first proposed more than 25 years ago as a multi-modal, perioperative approach to reducing organ dysfunction, the surgical stress response and postoperative morbidity [14, 15]. The objective of ERAS

is to optimize perioperative management strategies and thereby improve prognosis, shorten hospital stay and reduce complications, readmissions and treatment costs [15, 16]. ERAS protocols require a multidisciplinary team for their implementation and include shortening the perioperative fasting period, use of minimally-invasive surgical techniques, careful maintenance of fluid balance, early postoperative oral feeding and early mobilization [15, 16]. Increasing evidence indicates that ERAS can shorten the duration of intensive care unit (ICU) stay and hospitalization, reduce postoperative complications and influence postoperative inflammatory cytokine levels in adults [17–20]. However, the potential benefits of ERAS on robot-assisted laparoscopic surgery in pediatric patients remain to be evaluated.

This study aimed to explore the safety, efficacy and clinical outcomes of an ERAS protocol in children undergoing urological surgery for hydronephrosis. In addition, we assessed the influence of ERAS on the levels of several inflammatory cytokines (CRP, TNF-α, IL-1β, IL-6 and IL-10).

Materials and Methods

Study design

This prospective, randomized controlled study included patients who underwent robot-assisted laparoscopic surgery at Bayi Children's Hospital affiliated to the Seventh Medical Center of Chinese PLA General Hospital (Beijing, People's Republic of China) between October 2018 and September 2019. The study was approved by our institutional ethics committee (registered at China Clinical Trials

Registry: ChiCTR1900020682), and the legal guardians of all the children included in this study provided informed written consent.

The inclusion criteria were as follows: (1) aged 3–12 years at the time of surgery; (2) the diagnosis of hydronephrosis was confirmed by abdominal ultrasound and computed tomography [2]; and (3) scheduled for robot-assisted laparoscopic pyeloplasty without any additional medical treatment. The exclusion criteria were a history of abdominal surgery, perforation, obstruction, severe infection, moderate-to-severe dehydration, toxic shock, high abdominal distension, severe malnutrition, high fever, or malignant lesions of any organ. In addition, the patient was withdrawn from the study if requested by the legal guardian of the patient or the investigator.

Patients who met the inclusion criteria and agreed to participate in the study were divided into an ERAS group (to receive perioperative care using an ERAS protocol) and a control group (to receive standard perioperative care) in a 1:1 ratio according to a random number table method. All patients/guardians and data collectors were blinded to the grouping. The following measures were taken to reduce the potential for bias: (1) the investigators involved in the allocation of patients to the study groups did not participate in the administration of anesthesia or perioperative management of the patients and were only involved in the statistical analysis of the final dataset; (2) evaluation of postoperative recovery was performed by a specially trained nurse who was blinded to the grouping and not involved in any other aspects of the experiment, and the anesthesiologist, supervising physician and investigators responsible for the

grouping protocol did not participate in the measurement of outcomes; and (3) the patients and their families were blinded to the grouping.

Perioperative management

Patients in the control group were treated conservatively, while patients in the ERAS groups were managed using an ERAS protocol (**Table 1**). The nurses, anesthesiologists and surgeons who administered the ERAS protocol had received specialized training and education in the principles of ERAS.

Intraoperative management

Intraoperative management of patients in the control and ERAS groups was performed according to the procedures described in **Table 1**. All operations were performed by the same group of pediatric urological surgeons. Peripheral venous access was obtained on the ward early in the morning on the day of surgery. The electrocardiogram (ECG), oxygen saturation (SpO_2), non-invasive blood pressure (NIBP) and bispectral index (BIS) were monitored. Anesthesia was induced by intravenous injection of propofol 2.5 mg/kg, fentanyl 3 μg/kg, midazolam 2 mg and methylprednisolone 1 mg/kg. Tracheal intubation was performed following the administration of rocuronium 0.6 mg/kg, and the patient was mechanically ventilated to maintain the end-tidal partial pressure of CO_2 ($P_{ET}CO_2$) at 30–45 mmHg. Puncture catheterization of the radial artery was performed to allow invasive arterial pressure (IBP) monitoring, and central venous catheterization was carried out to measure

central venous pressure (CVP), which was used as the basis for goal-directed fluid therapy (GDFT). During the operation, the BIS was maintained at 40–70, and the patient was kept warm using a warm blanket and injections of pre-warmed fluid. The da Vinci SI robotic surgical system was used as described previously [21]. Briefly, the patient was placed in the flank position, and retrograde ureterography and cystoscopy were performed. Ports were placed in a midline or triangulated orientation, and anastomosis through the umbilicus with endoscopy. When used, an indwelling ureteral stent was placed percutaneously through an angiocatheter during the anastomosis. The depth of anesthesia was adjusted according to the monitored parameters. Careful observations were made for any cardiovascular adverse events (hypertension, hypotension, tachycardia or bradycardia) lasting more than 10 minutes. Ephedrine 3–15 mg was administered intravenously if the blood pressure fell by more than 20% of the baseline value during surgery despite a sufficient circulating blood volume and the drop in blood pressure could not be reversed by adjustment of the depth of anesthesia. Atropine 0.1–0.5 mg was administered intravenously for bradycardia (heart rate < 80 beats/min in children aged 3–6 years old or < 60 beats/min in children aged 6–12 years old). The depth of anesthesia was increased if blood pressure increased by more than 30% of the baseline value or tachycardia occurred (heart rate > 120 beats/min in children aged 3–6 years old or > 60 beats/min in children aged 6–12 years).

Postoperatively, assessments were made to confirm that eye opening and the cough and swallowing reflexes had been restored following the withdrawal of

anesthesia. The tracheal tube was removed when the SpO_2 under spontaneous breathing was ≥ 95%, and the patient was then moved to the anesthesia recovery room.

Postoperative follow-up

Postoperative follow-up was performed by anesthesiologists. Complications and rehabilitation indexes (time to first postoperative flatus, abdominal drainage flow and time to urinary catheter removal) were followed up daily after surgery until the patient was discharged from hospital. Pain scores were recorded using the Faces Pain Scale-Revised (FPS-R) scale [22]. Fentanyl 0.25 μg/kg was administered by intravenous injection to relieve pain when the FPS-R scale score was ≥ 4.

Measurement of inflammatory cytokine levels

The levels of CRP, TNF-α, IL-1β, IL-6 and IL-10 proteins were detected on preoperative day (D0) and postoperative days 1, 2 and 5 (D1, D2 and D5). Blood specimens were drawn by nurses into EDTA-containing tubes, immediately transferred to the biomedical laboratory, and centrifuged for 10 min at 3000-*g*. Plasma was obtained and stored at −80°C until analysis. The plasma concentrations of CRP, TNF-α, IL-1β, IL-6 and IL-10 were measured using ELISA kits (Abcon Trading Co., Ltd, Shanghai, China).

Criteria for patient discharge

Patients were discharged if the following criteria were met: (1) the patient was able to take food and drink by mouth; (2) all intravenous infusions had been stopped; (3) the patient was pain-free; (4) the drainage tube and urinary catheter had been removed; and (5) the patient was able to get out of bed and walk freely.

Study endpoints

The primary endpoints were postoperative complications such as nausea and vomiting, abdominal pain, subcutaneous emphysema and postoperative fever. The definitions of the complications were established before study commencement, and the incidence of complications was recorded following the Clavien-Dindo classification [23]. Secondary endpoints included the time taken for the postoperative abdominal drainage flow to fall to ≤ 20 mL, time to first passage of flatus, time to removal of the urinary catheter, and postoperative hospital stay and inflammation cytokines (CRP, TNF-α, IL-1β, IL-6 and IL-10).

Statistical analysis

The analysis was performed on an intention-to-treat basis using SPSS 22 (IBM Corp., Armonk, NY, USA). Normally-distributed continuous data are presented as the mean ± standard deviation and were compared between groups using the t-test for independent samples. Non-normally-distributed continuous data are described as the median (interquartile range), except where noted, and were compared between groups

using the Mann–Whitney U test. Discrete variables were compared between groups using the chi-squared test. $P < 0.05$ was taken to indicate a statistically significant difference.

Results

Clinical characteristics of the patients

Among 218 children undergoing pyeloplasty, 78 met the inclusion criteria. A further 14 children were excluded because their family refused participation in the study. Therefore, 64 children were randomly allocated to the control and ERAS groups. Six patients in the ERAS group did not receive the allocated intervention and were excluded from the analysis. Additionally, 12 patients in the control group and 10 patients in the ERAS group were excluded because of inadequate blood samples for determination of cytokine levels or loss to follow-up. Therefore, a total of 36 children, including 18 patients in the ERAS group and 18 patients in the control group, were included in this analysis (**Figure 1**). As shown in **Table 2**, there were no significant differences in age, sex ratio, body mass index (BMI), surgical side (left or right), ASA score, duration of surgery or amount of intraoperative blood loss between groups ($P > 0.05$). There were no intraoperative adverse cardiovascular events or requirement for blood transfusion in any of the patients. Postoperatively, all vital signs (including breathing, swallowing function and blood gases) returned to normal in all patients. There were no instances of death, anastomotic fistula or bowel obstruction during the study period.

Comparison of clinical endpoints between groups

Five patients (27.78%) in each group experienced complications after surgery, including 2 cases of abdominal pain, 1 case of nausea and vomiting, 1 case of subcutaneous emphysema and 1 case of postoperative fever in the ERAS group, and 3 cases of abdominal pain and 2 cases of nausea and vomiting in the control group. As shown in **Table 3**, the time to first postoperative flatus was significantly shorter in the ERAS group than in the control group (25 vs. 49 hours; $P = 0.009$). Although the time to achieve an abdominal drainage flow ≤ 20 mL/day, time to urinary catheter removal and length of hospital stay appeared to be shorter in the ERAS group than in the control group, the apparent differences were not statistically significant (see **Table 3**).

Comparison of inflammatory cytokine levels between groups

Since inflammatory cytokines serve as biomarkers for postoperative organ injury and dysfunction, we compared the protein levels of CRP, TNF-α, IL-1β, IL-6 and IL-10 between the ERAS and control groups. As shown in **Figure 2**, there were no significant differences between groups in the plasma concentrations of these inflammatory cytokines before surgery. However, the plasma concentration of IL-6 was significantly higher in the ERAS group than in the control group on postoperative day 2 (**Figure 2a**, $P < 0.05$), and the plasma concentration of IL-1β was significantly lower in the ERAS group than in the control group on postoperative days 1 and 2 **(Figure 2c**, $P < 0.05$). There were no significant differences in the postoperative

levels of CRP, TNFα or IL-10 between groups.

Discussion

A notable finding of the present study was that the ERAS group had a shorter time to first postoperative flatus than the control group. Furthermore, when compared with the control group, the ERAS group had a higher IL-6 level on postoperative day 2 and a lower concentration of IL-1β on postoperative days 1 and 2. Our results indicate that ERAS may accelerate recovery after surgery and modulate the postoperative inflammatory response in pediatric patients undergoing robot-assisted laparoscopic pyeloplasty for hydronephrosis.

The current observational study found that the application of ERAS to children with hydronephrosis undergoing robotic-assisted laparoscopic pyeloplasty is safe and effective, which is consistent with the results of prior research evaluating ERAS in pediatrics [24, 25]. Previous studies of adult patients undergoing cardiac or non-cardiac surgery demonstrated that ERAS shortened the time to recovery of bowel function, time to drainage tube removal, duration of vasoactive drug support, duration of mechanical ventilation, length of stay in the ICU or hospital, and total medical cost [18, 20, 26]. Assessments of ERAS in pediatric patients undergoing surgery have also shown benefits such as reductions in perioperative opioid use, time to recovery of bowel function, time to oral intake, length of hospital stay and treatment costs [24, 25, 27–30]. The present analysis revealed that ERAS significantly shortened the time to the first postoperative flatus, consistent with the faster recovery of bowel function

reported by the previous investigations described above. Although our study did not find any significant differences between groups in the time for abdominal drainage flow to fall to ≤20 mL/day, time to urinary catheter removal and length of hospital stay, it was notable that the values for all these parameters were lower in the ERAS group than in the control group. It is possible that our study was underpowered to detect real differences between groups in these parameters due to the small sample size, hence additional research will be needed to investigate this further. Nevertheless, our data are consistent with those of other studies showing benefits of ERAS in pediatric patients undergoing surgery.

The ERAS measures used in this study had three innovative features that merit mention. First, the maintenance of anesthesia was optimized for patients in the ERAS group. This optimization was based on previous studies demonstrating that a propofol/remifentanil mixture is safe and effective for anesthesia in pediatric surgery [31] and that total intravenous anesthesia may have a favorable effect on surgery-associated stress [32]. Second, since surface anesthesia was reported to reduce the incidence and severity of catheter-related bladder discomfort [33], we used dyclonine gel for local anesthesia during catheterization to prevent postoperative urethral pain. Third, ropivacaine was injected locally into the surgical incision for prophylactic analgesia with the aim of reducing postoperative sensory nerve fiber and pain center sensitization and inhibiting nerve plasticity changes [34] so as to achieve effective pain relief and a reduction in the dosage of intravenous analgesics. Reasonable ERAS measures should run throughout the entire perioperative period and

include good postoperative analgesia, resumption of oral feeding as soon as possible and avoidance of intravenous infusion so as to facilitate early mobilization. The results of our evaluation of ERAS in pediatric patients undergoing robotic-assisted laparoscopic pyeloplasty indicated that ERAS did not elevate the incidence of intraoperative adverse cardiovascular events or total postoperative complications when compared to a conventional perioperative management protocol, and no patients reached the criteria for remedial analgesia after surgery.

Surgical injury initiates an inflammatory cascade involving numerous cytokines (including IL-1β, IL-6, CRP, TNFα and IL-10) that is associated with the postoperative dysfunction of various organs, and the cytokines might be useful biomarkers of surgical recovery [13, 18, 26, 35, 36]. Previous investigations of multiple types of surgery showed that the blood levels of these inflammatory cytokines were influenced by ERAS [18, 26, 36]. We found that the plasma concentration of IL-6 on postoperative day 2 was significantly higher in the ERAS group than in the control group. Moreover, we observed that the IL-6 level increased rapidly from baseline to reach a peak at postoperative day 2 before subsequently declining, which is similar to previous studies reporting that IL-6 peaked on postoperative day 2 or 3 and then declined after postoperative day 3 in patients undergoing cardiac or non-cardiac surgery [37, 38]. IL-6 is typically regarded as a pro-inflammatory cytokine, although there is increasing evidence that is can exert an anti-inflammatory role that benefits tissue homeostasis [39, 40]. The elevation of IL-6 in the ERAS group at postoperative day 2 suggests that the immune response was

primed to respond more powerfully to injury and target cells more effectively, as proposed by others [41]. IL-6 can induce lipolysis, enhance the release of energy sources into the bloodstream, and increase insulin secretion and sensitivity, thereby promoting a metabolic shift from catabolic, glucagon-dependent pathways to anabolic, insulin-dependent pathways that facilitate glucose absorption by muscle and body recovery [40]. In addition, regenerative processes in epithelial tissue also seem to depend on IL-6 signaling [42], which is particularly relevant to this study because the postoperative recovery period involved ureteral epithelial regeneration. IL-1β is an important pro-inflammatory regulator of the inflammatory response and participates in various cellular activities such as proliferation, differentiation and apoptosis [43]. In this study, the plasma levels of IL-1β on postoperative days 1 and 2 were significantly lower in the ERAS group than in the control group, in agreement with previous observations in patients who underwent radical resection for colorectal cancer [36]. These findings imply that ERAS may influence the postoperative inflammatory response by decreasing the IL-1β level or elevating the IL-6 level. However, we did not find any significant differences in CRP, TNFα or IL-10 levels between groups. Since our sample size was small, additional research will be needed to definitively establish whether ERAS affects the levels of CRP, TNFα or IL-10 in pediatric patients undergoing surgery.

This study has some limitations. First, this was a single-center study, so it remains to be established whether the results are generalizable. Second, the sample size was small, so our analysis may have been underpowered to detect some real

differences between groups. Third, only patients with hydronephrosis undergoing robot-assisted laparoscopic surgery were included in the analysis, so it remains unknown whether ERAS would have benefits in pediatric patients with other diseases undergoing different types of surgical procedure. Fourth, since this randomized controlled trial had strict inclusion and exclusion criteria, further research will be needed to assess the real-world effectiveness of ERAS. Fifth, the follow-up was short, hence the effects of ERAS on longer-term outcomes were not evaluated.

Conclusion

ERAS was safe and effective in pediatric patients with hydronephrosis undergoing robot-assisted laparoscopic pyeloplasty. Notably, ERAS accelerated the postoperative recovery of intestinal function and modulated the postoperative inflammatory response by decreasing the IL-1β level and increasing IL-6 level. These findings may help improve our understanding of the mechanisms by which ERAS enhances the recovery of children after urological surgery. However, further studies are needed to clarify the effects of ERAS on cytokines during the postoperative recovery period.

Availability of data and materials

All survey data is available from the corresponding author on reasonable request.

Abbreviations

ERAS：Enhanced Recovery after Surgery

CRP：C-reactive Protein

TNF-α：Tumor Necrosis Factor-α

IL-1β：Interleukin-1β

IL-6：Interleukin-6

IL-10：Interleukin-10

ICU：Intensive care unit

ECG：Electrocardiogram

SpO2：Oxygen Saturation

NIBP：Non-Invasive Blood Pressure

BIS：Bispectral Index

$P_{ET}CO2$：End-tidal Partial Pressure of CO2

IBP：Invasive Arterial Pressure

CVP：Central Venous Pressure

GDFT：Goal-Directed Fluid Therapy

FPS-R：Faces Pain Scale-Revised (FPS-R) Scale

BMI：Body Mass Index

ASA：American Society of Anesthesiologists

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Army General Hospital (Committee's reference number 2018-30). All patients gave consent for inclusion in

this study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the Capital Clinical Specialty Applied Research Program (Z181100001718002).

Contributions

Tingmei Wu、Haiwen Li、Hang Guo and Yaqun Ma conceived the study. Tingmei Wu、Haiwen Li、Huixia Zhou、Xuemei Hao、Xiaojun Wang、Lifei Ma、Tian Tao、Xiaoguang Zhou、Hang Guo and Yaqun Ma contributed to the study design. Tingmei Wu、Haiwen Li、Yan Lu、Wenchao Ge、Xiangpeng Li、Dongming Li and Wei Li undertook data collection.Tingmei Wu and Haiwen Li drafted the manuscript, which underwent revision by all other authors. All authors read and approved the final manuscript.

Acknowledgments

We thank all the patients and their families for agreeing to participate in this study. We thank the Bayi Children's Hospital for providing the experimental platform and the pediatric urologists for their assistanceThanks to for providing the experimental platform.

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Table and Figures

Table 1 Comparison of perioperative measures between the control and ERAS groups

Measure	ERAS group (n = 18)	Control group (n = 18)
Preoperative education	Concept of ERAS program	Concept of standard protocol
Preoperative diet	Fasting for 6 h, 2 ml/kg of 10% glucose taken orally 2 h before surgery	Fasting all night
Measures to improve preoperative comfort	Yes	None
Indwelling catheter after general anesthesia	Yes, local anesthesia with dacronine gel	Yes
Intraoperative warming	Yes	Yes
Anesthesia maintenance	Intravenous propofol 9–13 $mg \cdot kg^{-1} \cdot h^{-1}$, remifentanil 0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and dexmedetomidine 0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$	1%–3% sevoflurane driven by 2 L/min oxygen flow for inhalation, intermittent intravenous injection of fentanyl 1 $\mu g \cdot kg^{-1}$ (total amount during surgery not exceeding 10 $\mu g \cdot kg^{-1}$)
Ventilator mode	Protective pulmonary ventilation mode dominated by pressure control	Volume control ventilation
Intraoperative intravenous rehydration	Infusion volume controlled by target-directed fluid therapy	4-2-1 Principle of rehydration
Incision local anesthesia	Yes, 8 mL of 0.25% ropivacaine used as local anesthesia for 3 incisions (before skin incision and suture)	None

Intraoperative preventive antiemetic	Intravenous injection of ondansetron 0.05 mg·kg^{-1} and dexamethasone 0.015 mg·kg^{-1} before surgery	None
Postoperative analgesia	Patient-controlled intravenous analgesia, oral use of nonsteroidal analgesic painkillers according to instructions; pharmaceutical formulation: 10 μg·kg^{-1} fentanyl + 0.05 mg·kg^{-1} ondansetron + 50 mL saline	Patient-controlled intravenous analgesia; pharmaceutical formulation: 20 μg·kg^{-1} fentanyl + 0.1 mg·kg^{-1} ondansetron + 100 mL saline
	Single dose of pump, 0.5 mL; locking interval, 15 min; background rate, 2 mL·h; capacity, 100 mL	
Early exercise	Bed exercises for the lower limbs	According to patient willingness
Diet postoperatively	Children allowed to drink a small amount of water according to their wishes 2 h after surgery; oral 10% glucose in water 2 mL·kg^{-1} 4 h after surgery; then able to try liquid food if abdominal pain and bloating are absent	Wait for bowel flatus before starting
Measures to promote bowel movements	Sucking lollipop	None

Table 2 Clinical characteristics of the patients in the control and ERAS groups

Group	ERAS (n = 18)	Control (n = 18)	*P* value
Age (years), mean (SD)	7.17 (2.73)	6.16 (1.93)	0.208[a]
Sex, *n*			0.109[b]
Male	16	12	
Female	2	6	
ASA score			0.317[c]
ASA I	18	17	
ASA II	0	1	
BMI (kg/m^2), median (IQR)	16.52 (2.75)	16.08 (2.37)	0.125[c]
Operation side			0.298[b]
Left	10	13	
Right	8	5	
Duration of surgery (h), median (IQR)	4.55 (0.80)	4.50 (1.21)	0.657[c]
Intraoperative blood loss (mL), median (IQR)	15.00 (12.50)	22.50 (32.50)	0.318[c]

Note: [a] *t*-test; [b] chi-squared test; [c] Mann-Whitney U test; ASA: American Society of Anesthesiologists; BMI: body mass index; IQR: interquartile range; SD: standard deviation.

Table 3 Comparison of clinical endpoints between the ERAS and control groups

Endpoint	ERAS (n = 18)	Control (n = 18)	*P* value [a]
Complications, *n*	5	5	0.919
Grade I, *n*	5	4	
Grade II, *n*	0	0	
Grade III, *n*	0	1	
Abdominal pain, *n*	2	3	
Nausea and vomiting, *n*	1	2	
Subcutaneous emphysema, *n*	1	0	
Postoperative fever, *n*	1	0	
Time to abdominal drainage flow < 20 mL/day, median (IQR)	7.00 (13.5)	7.50 (4.25)	0.811
Time to first postoperative flatus (h), median (IQR)	25.00 (28.50)	49.00 (44.00)	**0.009**[*]
Time to urinary catheter removal (days), median (IQR)	6.00 (8.50)	8.00 (5.00)	0.337
Length of hospital stay (days), median (IQR)	9.50 (16.00)	12.00 (8.75)	0.622

Note: [a] Mann-Whitney U-test; [*] $P < 0.05$; IQR: interquartile range.

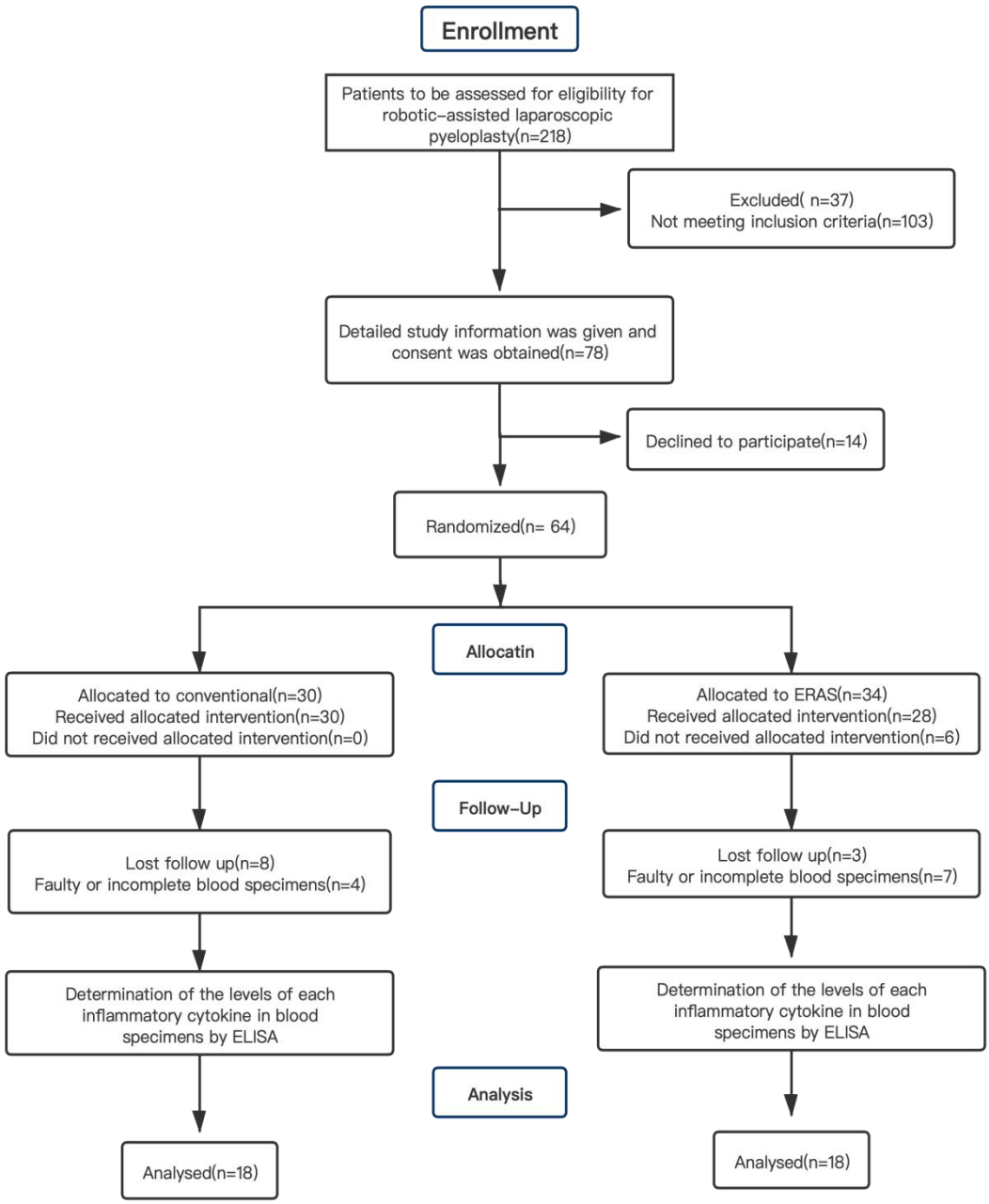

Figure 1 Flow diagram showing patient enrolment

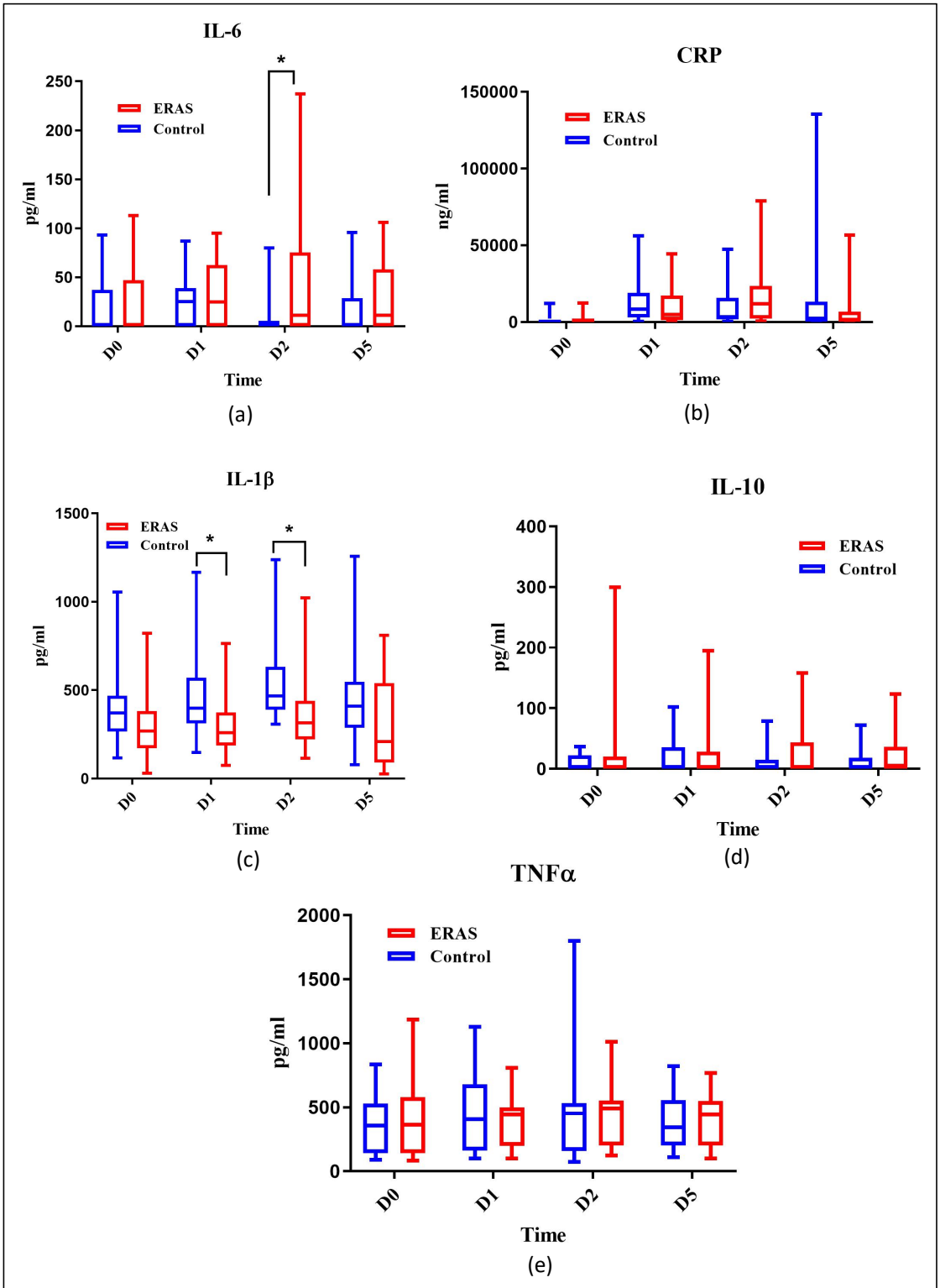

Figure 2 The plasma concentration of IL-6, CRP, IL-1β, IL-10, and TNFα. D0: morning of surgery, D1, D2, D5: Day 1, Day 2, Day 5 postoperatively. (a) (b) (c) (d) (e): Lines were expressed as median and range P-values with respect to Mann-Whitney U test. $^{*}p < 0.05$