Value of indomethacin suppository for preoperative analgesia and anti-inflammation in laparoscopic appendectomy: a protocol of prospective, double-blinded, single-centre, randomised controlled trial in China

Jinhong Gao, Shaolong Hao, Yong Liu, Wei Han, Yibing Weng, Xinyu Zhao

ABSTRACT

Introduction Postoperative pain has always been a problem for patients and surgeons. Local inflammation, surgical trauma and pain in the body can cause a systemic stress response and immune imbalance, which can affect the patient's rapid recovery. Currently, most of the perioperative pain management is focused on the postoperative phase. The non-steroidal anti-inflammatory drug indomethacin suppository has antipyretic and analgesic effects. This study will evaluate the value of indomethacin suppository for analgesia and anti-inflammation before laparoscopic appendectomy (LA).

Methods and analysis A single-centre, double-blinded (clinician, assessor, data entry), randomised controlled trial will be conducted in 128 adult patients undergoing LA under emergency general anaesthesia with a Visual Analogue Scale (VAS) >2. The trial was divided into two groups (n=64) using a randomised number table: group A will be given 100 mg of indomethacin suppository rectally and group B will be given 8 mg of intravenous lornoxicam. The postoperative analgesic effect, inflammatory response and incidence of postoperative adverse effects will be compared.

Ethics and dissemination The study is in accordance with the Declaration of Helsinki and will be conducted in accordance with the principles of Good Clinical Practice. This trial was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University (2021-LHKY-123-02). We will disseminate our study findings at national and international paediatric research conferences.

Trial registration number Chinese Clinical Trial Registry (ChiCTRZ200062004).

BACKGROUND

Acute appendicitis is a common condition in general surgery and laparoscopic appendectomy (LA) has become the treatment of choice, and perioperative pain management is very important for rapid recovery. The pain is not as severe and persistent as in open surgery but still requires good analgesia. Postoperative pain has always been a problem for patients and surgeons alike, which requires increased attention to the patient’s pain status, rational use of pain scoring and preventive analgesia. Traditional analgesic treatment is mainly based on opioid analgesics, but their application can lead to a range of adverse effects such as intestinal paralysis, abdominal distention, nausea, vomiting, respiratory depression, urinary retention, tolerance and physical dependence, muscle rigidity, myoclonus, convulsions, cognitive dysfunction, decreased body temperature and immune suppression. Several studies have shown that in adults or children, analgesia in the presence of abdominal pain does not delay the diagnosis of appendicitis, and that preemptive analgesia reduces postoperative pain in patients undergoing appendectomy, with good results in clinical practice. Opioids are often used for over-the-counter analgesia, and opioid use does not significantly increase or delay the risk of
unnecessary surgery. Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) should also be considered for pain management in patients with suspected acute appendicitis, particularly in those with contraindications to opioids. Pain control does not significantly increase the risk of delayed or unnecessary intervention and does not alter the Alvarado Score.12

Lornoxicam is a new ciclosporin NSAIDs, non-selective inhibition of cyclooxygenase (COX), can also activate the opioid neuropeptide system, exerting a central-type analgesic effect, with strong analgesic and anti-inflammatory effects, has been widely used in clinical practice for perioperative analgesia and has been applied before LA.13–16 COX inhibitors do not easily achieve effective plasma concentrations by slow intravenous infusion, and lornoxicam is mainly administered intramuscularly or intravenously with one-third renal and two-third hepatic clearance, and is not indicated for patients with severe hepatic or renal impairment.13 17 18

Indomethacin is a non-selective inhibitor of COX-1 and COX-2 and may modulate inflammatory mediators by inhibiting phospholipase A2, resulting in a reduced inflammatory response in the early stages of acute abdomen. Indomethacin suppositories are inhibitors in prostaglandin synthesis. After absorption in the rectum, the majority of the drug enters the circulation directly without the liver, accounting for up to 50%–75% of the total. It is also possible that it enters the enterohepatic circulation by excreting its glucuronide metabolites into the bile, which then absorbs indomethacin after hydrolysis. Indomethacin suppository reaches peak blood concentrations 30–90 min after rectal administration, with a bioavailability of approximately 80%–90%, and provides an effective clinical inhibition of inflammation as a means of blocking the sensation of pain. The use of suppository can significantly reduce the damage to the gastric mucosa and avoid adverse effects such as gastrointestinal bleeding.19 It can also reduce portal venous pressure, which is effective in the prevention and treatment of portal phlebitis. The effect of indomethacin suppository in analgesia and anti-inflammation has been shown to be significant,4 14 19–25 but the effect of indomethacin suppository before LA is currently unclear.

Local inflammation, surgical trauma and pain in the organism cause a systemic stress response, which leads to the release of inflammatory mediators, thus affecting the patient’s perioperative immune function. Interleukin (IL)-10 maintains immune dynamic balance and suppresses pro-inflammatory immune responses.26 IL-6 reflects stress levels and its elevated levels correlate with the degree of tissue damage. IL-8 promotes a massive release of inflammatory factors and triggers a cascade of inflammatory responses in the organism. Bacterial endotoxins stimulate the body to produce excess Tumour Necrosis Factor-α (TNF-α), which can stimulate endothelial cells and lead to inflammation, tissue damage and coagulation, causing fever. IL-10 affects T-cell function at all stages of inflammation, and the main T-cell subpopulation that senses IL-10 during dynamic homeostasis is Foxp3+ regulatory T cells (Foxp3+Treg). IL-10 produced by Foxp3+Treg promoted its own activity through a positive feedback loop and inhibits the pro-inflammatory function of Antigen Presenting Tell and T helper cell 17.27

Most of the LA surgeries last from half an hour to 1 hour. Applying indomethacin bolus 30 min before surgery, its serum concentration just reaches the peak at the end of surgery, which can effectively reduce the early postoperative pain, as it is not easy to reach the effective blood concentration by slow intravenous drip of COX inhibitors, indomethacin bolus can play a local slow-release role through rectal administration, which can play a better analgesic effect than intravenous administration, avoiding the pain caused by intravenous puncture. It avoids the pain associated with intravenous puncture or intramuscular injection and facilitates the patient’s rapid recovery. Indomethacin suppository reduces neutrophil chemotaxis, thereby inhibiting neutrophil activation and reducing the inflammatory response.27 Indomethacin reduces the synthesis and release of prostaglandin E2 by inhibiting COX, which regulates autoimmunity by altering the IL-23 axis and the development of regulatory T cells.28 This trial hopes to explore the effect of indomethacin suppository and lornoxicam on immune function by comparing their analgesic and anti-inflammatory functions when applied preoperatively in LA, with a view to informing the optimisation of the LA perioperative pain management process and facilitating the development of a daytime LA model.

Main purpose
To compare the analgesic and anti-inflammatory function of indomethacin suppository and lornoxicam applied before LA.

METHODOLOGY AND STUDY DESIGN
This is a single-centre, double-blind, parallel design, randomised controlled study.

Recruitment period
The participants will be recruited from the Beijing Luhe Hospital, Capital Medical University. Recruitment is expected to span from 20 July 2022 to 31 December 2023.

Inclusion criteria
(1) Patients aged 18–75 years with a diagnosis of acute appendicitis; (2) receiving LA and (3) preoperative Visual Analogue Scale (VAS) >2.

Exclusion criteria
(1) Those with contraindications to LA; (2) those who refuse or cannot cooperate to complete this study; (3) those using other analgesic regimens preoperatively; (4) patients with a history of allergy to any NSAIDs such as indomethacin or lornoxicam; (5) patients with acute or chronic renal insufficiency, bronchial asthma,
coagulation disorders, peptic ulcer disease and liver failure; (6) patients taking NSAIDs within 48 hours or corticosteroids (due to chronic inflammatory diseases) within 48 hours; (7) patients with opioid or substance abuse; (8) pregnancy; (9) patients receiving antidepressants 24 hours prior to the procedure; (10) patients with rectal or anal disorders unsuitable for rectal administration and (11) patients with missing clinical data.

**Case grouping and treatment modalities**

**Grouping**

Grouping patients who met the nadir criteria will be divided into group A (indomethacin suppository) and group B (lornoxicam) using the random number table method.

**Randomisation method and blindness**

A statistician will use Excel to generate a set of random integers 1–128, numbered 1–128 (ie, the order of patients), if the random number ≤64, it is group A, and if >64 is group B. When subjects meet the inclusion criteria, the attending physician will be included in the treatment group according to the random number corresponding to the patient's serial number. Pain scoring will be performed by a dedicated nurse, with the nurse, operator and data entry person not knowing which group the patient belonged to and unblinding for the final statistical analysis.

**Treatment protocol**

Group A will be given indomethacin suppository (Beijing Shuangji Pharmaceutical, size: 100 mg) 100 mg rectally 30 min before surgery and group B will be given lornoxicam (Zhejiang Zhenyuan Pharmaceutical, size: 8 mg) 8 mg intravenously 30 min before surgery. All patients will be operated by the same group of surgeons and had good compliance. All patients will be given general anaesthesia and the same type of anaesthetic drugs. VAS will be performed at 0, 3, 6, 12 and 18 hours postoperatively and before discharge (T1 to T6), respectively, and if patients are asleep they were not awakened for assessment. When the VAS is >4 and analgesia is ineffective, then flurbiprofen ester 50 mg should be administered intravenously for remedial analgesia and postoperative pain, inflammation, immune-related indicators and adverse effects will be recorded and all patients will be assessed for complications caused by indomethacin or lornoxicam (ie, haematoma, liver and renal failure and stress ulcers).

**Observed indicators**

**Baseline indicators**

A case report form will be created to collect and record baseline indicators of the study population. These included the following: age, gender, Body Mass Index (BMI), preoperative VAS, Appendicitis Inflammatory Response (AIR) Score (table 1), inflammatory indicators and immunological indicators.

**Observed indicators during hospitalisation**

**Main evaluation indicator**

Pain score: VAS Score at 0, 3, 6, 12 and 18 hours postoperatively and before discharge (T1–T6).

**Secondary evaluation indicators**

Analgesic effect: time to first remedial analgesia, 24-hour analgesic drug use, time to postoperative VAS <2. Incidence of nausea and vomiting, time to recovery of gastrointestinal function (time to deflation), preoperative and postoperative inflammatory markers (WBC (white blood cell) count), N (centrophil percentage), N% (centrophil percentage), L (lymphocyte count), L% (lymphocyte percentage), N/L, CRP (C reactive protein), PCT (calcitoninogen), TNF-α, IL-6, IL-8, IL-10, IL-23), immune indicators (T lymphocytes, B lymphocytes, CD4+ T cells, CD8+ T cell percentage, CD4+/CD25+ T cells, CD4+ Foxp3+ T cells, CD25+ Foxp3+ T cells, Th17 cells, CD4+/CD8+), AIR Score, gastrointestinal recovery time (exhaust time), length of hospital stay, hospitalisation costs and unplanned readmission rates.

**Sample size calculation**

The pain score was main evaluation indicator, so we calculated based on the efficiency of pain score reduction at discharge (analgesic efficacy). As there are no valid data on the analgesic efficacy of indomethacin suppository used preoperatively in LA, referring to the statistical parameters of previous studies and the results of the pretest, we expected the effective rate to be 75% in the

### Table 1: Appendicitis Inflammation Response Score

<table>
<thead>
<tr>
<th>Diagnostic criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or pressure in the right lower abdomen</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Pressure pain, rebound pain</td>
<td>Mild: 1; Moderate: 2; Severe: 3</td>
</tr>
<tr>
<td>WBC count</td>
<td>10–14.9×10⁹/L: 1; ≥15.0×10⁹/L: 2</td>
</tr>
<tr>
<td>Percentage of neutrophils</td>
<td>70%–84%: 1; ≥85%: 2</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>10–49: 1; ≥50: 2</td>
</tr>
<tr>
<td>Body temperature (°C)</td>
<td>≥38.5°C: 1</td>
</tr>
</tbody>
</table>

Note: A score of 0–4 indicates a low likelihood of acute appendicitis (AA); a score of 5–8 suggests active observation by rescoring/imaging or diagnostic laparoscopic techniques based on local experience; a score of 9–12 indicates a high likelihood of AA. CRP, C reactive protein; WBC, white blood cell.
indomethacin group and 45% in the lornoxicam group, respectively; with \( P_1=0.75 \) and \( P_2=0.45 \), setting a two-sided test level of 0.05 and a test efficacy (power) of 90%. Using a parallel design, the required sample size is estimated to be 51 cases in each group, and taking into account a 20% case dropout rate, the number of cases required is 64 cases in each group, making a total of 128 cases in both groups.

The author’s unit is the largest comprehensive medical institution in Tongzhou District, absorbing a large number of patients with acute appendicitis from the district and Sanhe, Dafang and Yanjiao, etc. The source of patients is sufficient, with an average of about 100 cases of acute appendicitis admitted each month and a strong follow-up, which can provide sufficient clinical cases for this study.

**Statistical processing**

**Data management**

1. **Collection of data:** The investigator must ensure that the data are true, complete and accurate; all items in the study record must be completed and no empty items or omissions are allowed; laboratory tests are complete; and the study record and other information is submitted to the project leader for review within 3 days after the study case is completed.

2. **Data entry and verification:** Epidata software will be used to create the entry database. Data will be entered in pairs, that is, one postgraduate student is responsible for data entry and the other for secondary entry, followed by double entry consistency checks.

3. **Data storage:** Data entry using a predesigned online standardised CRF. Only the person in charge of the project and the research coordinator can access the online form and enter the data through the username and password. All data obtained through the online CRF will be stored in a password-protected computer. The data are deleted after 10 years of storage.

**Treatment of missing values**

The effect that any missing data might have on results will be assessed via sensitivity analysis of augmented data sets. Dropouts (essentially, participants who withdraw consent for continued follow-up) will be included in the analysis by modern imputation methods for missing data. This will be accomplished using a set of repeated imputations created by predictive models based on the majority of participants with complete data.

**Statistical analysis**

Before performing statistical analysis, patients with negative appendectomies (no inflammation shown in the histopathological specimen) will be secondarily excluded. (Considering that pathological results are not available at the time of recruitment, this secondarily exclusion criterion is more appropriate to write in the statistical analysis than in the exclusion criteria, so we didn’t include this in the exclusion criteria in the registry). All statistical
analyses were completed using SPSS 26.0 software. The methodology was as follows.

VAS Score, Analgesic Efficacy Index, time to first remedial analgesia, amount of postoperative analgesic medication used, time to postoperative VAS <2, time to recovery of gastrointestinal function (time to venting), inflammatory markers (WBC, N%, CRP, PCT, TNF-α, IL-6, IL-8, IL-10, IL-23), immune markers (T lymphocytes, B lymphocytes, CD4+ T cells, CD8+ T cell ratio, CD4+/CD25+ T cells, CD4+ Foxp3+ T cells, CD25+ Foxp3+ T cells, Th17 cells, CD4+/CD8+), AIR Score (preoperative, postoperative), length of stay and hospital costs are quantitative variables. The incidence of nausea and vomiting and the incidence of postoperative adverse reactions are qualitative data and will be tested by Pearson’s χ² test or Fisher’s exact probability method. P value <0.05 is considered a statistically significant difference. The flow chart of this study is shown in figure 1.

Data and safety monitoring
To ensure the quality of the data is in accordance with the predetermined protocol, regular monitoring will be carried out. Monitors will be blinded to the allocation and will examine whether the recruitment procedures and data recording followed the protocol in the CRFs. In case modifications in the study methods are necessary, such as changes to the eligibility criteria, treatment regimens or duration of follow-up, the principal investigator may discuss the issue with independent researchers and statisticians.

Management of adverse events
If adverse events occur during hospitalisation, the following procedures are followed: After the adverse events are found in the subjects, the tube bed doctor or the doctor on duty should inform the investigator in time, if necessary, the symptomatic treatment can be carried out first, and the research physician will initially assess the degree of adverse events and the relevance to the experimental drug, and give further treatment advice. If serious adverse events or critical issues arise, the principal investigator will decide whether these events are acceptable or whether it is necessary to alter or terminate the trial.

Expected results
The preoperative use of indomethacin suppositories compared with lornoxicam in LA reduces postoperative pain scores, prolongs the duration of postoperative remedial analgesia in patients, reduces 24-hour analgesic use, reduces postoperative inflammatory response, reduces postoperative fever, facilitates the maintenance of stable immune function and promotes rapid recovery.

Patient and public involvement
During the early stages of study question conceptualisation and design, we have engaged the local hospital ethics committee, nurses and a subset of patients. A formal presentation was done on all aspects of the study including the research question, design, recruitment strategy and outcome measures. It was decided that an analgesic regimen that effectively reduces postoperative pain and has fewer side effects should be a major priority. Before the start of the clinical trial, a pretrial was conducted, where potential participants were interviewed about the feasibility and acceptability of the experimental procedure during the trial. The completed feasibility trial publication will be shared with study participant. The burden of intervention is not assessed by the patients themselves.

ETHICS AND DISSEMINATION
The study is in accordance with the Declaration of Helsinki and will be conducted in accordance with the principles of Good Clinical Practice. This trial was approved by the Ethics Committee of Beijing Luhe Hospital, Capital Medical University (2021-LHKY-123-02). The participants will be informed on the potential benefits, risks, alternatives and responsibilities of the study by the researchers during the consent process. The findings will be disseminated in peer-reviewed journals and conference presentations.

Acknowledgements The authors thank Professors Yong Liu and Wei Han for encouraging suggestions and helpful comments.

Contributors YW, JG and SH planned the overall study protocol. JG drafted the manuscript. SH, YL, WH and XZ participated in critical revision of the manuscript. YW had the final responsibility for the decision to submit for publication. All of the authors have read and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Jinhong Gao http://orcid.org/0000-0001-6735-2674

REFERENCES


