OPTIMISATION OF ACUTE PAIN TREATMENT IN CHILDREN IN ABDOMINAL SURGERY AT THE STAGES OF THE PERIOPERATIVE PERIOD

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The aim of the study. To improve the quality of perioperative analgesia by combined multimodal use of paracetamol and ketorolac tromethamine in children after abdominal surgery.

Materials and methods. 48 children (6–17 years old) with choledochal, pancreatic cysts, hepatic echinococcosis, and abdominal trauma. The study period was from January 2021 to January 2022. Group 1 (main group, n=28): baseline analgesia - 15 min before surgery, intravenous paracetamol administration at 25–30 mg/kg. In order to prevent postoperative pain syndrome 15 minutes before the end of the surgery, we administered ketorolac and tromethamine in a dose of 0.5 mg/kg. Pain relief was repeated 6-8 h later with ketorolac at a dose of 0.5 mg/kg. Group 2 (comparison, n=20), who received 0.2 – 0.3 mg/kg promedol (trimeperidin) in the postoperative period. Both groups received standard endotracheal anaesthesia (propofol + fentanyl + arduan against the background of Low-flow anaesthesia with sevoflurane MAK=1). Systemic haemodynamics, C-reactive protein, and glucose were investigated, and a visual analogue scale was applied at the main stages of the study.

Results: Analysis of the parameters of central hemodynamics, parameters of the operational stress response and clinical data showed that in the postoperative period, sufficient analgesic effect was established only in children in group 1 with the preventive combined administration of paracetamol and ketorolac on the operating table, which allows recommending them in the practice of perioperative analgesia during abdominal surgical interventions.

Conclusions. Optimised method of preventive (preoperative) use of paracetamol in children at a dose of 25–30 mg/kg during abdominal surgery followed by administration of ketorolac tromethamine (15 minutes before the end of the surgery) increases the degree of nociceptive protection. It ensures high efficiency of postoperative pain relief, which allows to recommend it in the practice of perioperative analgesia for the above abdominal surgical interventions in children.

Keywords: perioperative analgesia, child on the operating table, surgical stress, multimodal anaesthesia, effectiveness of analgesia.

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1. Introduction

Children are a particular category of surgical patients in terms of the choice and control of the effectiveness of pain relief. In addition, many of them experience fear and anxiety about the upcoming operation and have a negative psycho-emotional background and discomfort due to separation from their parents and being in a medical ward. All these factors can contribute to increased pain after surgery [1, 2]. According to the literature, despite using a wide range of drugs and non-drug pain relief, 33–75 % of patients complain of moderate to severe pain in the early postoperative period [3, 4].

Uncontrolled postoperative pain syndrome (PPS) can cause cardiorespiratory and thromboembolic complications, accompanied by impaired gastrointestinal tract motility and chronic pain development [5]. For this reason, ensuring adequate postoperative pain relief (PPR) is an urgent issue in modern anesthesiology.

Specific skills and special training are required when providing surgical care to the pediatric population. Lack of verbal contact, especially with preschool children, shyness of the child, the need for simultaneous psychological preparation of parents, and many other factors determine the specificity of this problem in pediatrics. Parents expect medical workers to reduce their child's suffering to the greatest extent possible. Establishing an appropriate level of patient and parental expectation that can be safely achieved prior to surgery will help reduce anxiety and improve their understanding of modern pain management [6]. Apart from this, unreasonable fear of respiratory depression, the development of dependence when prescribing opioids, and the difficulty in assessing the degree of pain, especially in young children, partially explain the lack of pain relief in this category of patients [7]. Therefore, the attitude towards pediatric patients should be more personalised.

At the International Association for the Study of Pain (IASP) initiative, 2017 was declared Global Year Against Pain After Surgery [8]. This initiative pursued the following objectives: dissemination of information about the pain after surgery around the world, training of medical personnel, researchers, medical administrators
and the general public about the problems related the pain after surgery, moreover encouraging healthcare organisations and other entities which support policies that lead to improved pain management after surgery [9, 10]. An important direction in improving the quality of pain relief and reducing the severity of side effects is developing and optimising methods for combining analgesics with different mechanisms of action [11, 12]. Nowadays, interest in drugs that realise their analgesic effect bypassing opioid receptors, which include NSAIDs (ketorolac tromethamine) and paracetamol, has grown.

Paracetamol has a central action mechanism and has almost no effect on the periphery. Ketorolac tromethamine and paracetamol have analgesic efficacy comparable to opioids, quick onset of action, and their combined use according to the multimodal principle reduces undesirable effects and prolongs postoperative pain relief [12, 13].

In the specialised literature, insufficient attention is paid to the study of the after-surgery problem. Thus, the works of foreign scientists confirm the unresolved nature of this issue and the further need for large-scale studies on the use of NSAIDs in children [14, 15].

The conducted literature analysis shows insufficient coverage of issues related to using the intravenous form of Paracetamol and Ketorolac and its effectiveness in the concept of proactive and multimodal analgesia in children after abdominal surgery [16, 17]. Primarily there is little information on this issue in the domestic literature [18, 19]. Lack of investigation of this issue and lack of consensus regarding the treatment methods of PPS in children make this issue relevant in pediatric anaesthesiology.

In this regard, our study is devoted to developing and implementing a pathogenetically substantiated method aimed at preventing the development of PPS or a significant reduction in its intensity through the combined multimodal use of Paracetamol and Ketorolac tromethamine in the perioperative period in children in abdominal surgery.

**The aim of the study.** Improving the quality of perioperative analgesia through the combined multimodal use of paracetamol and ketorolac tromethamine in children after abdominal surgery.

**2. Material and methods**

We observed 48 pediatric patients (6–17 years old - pupils) treated in the Children's National Medical Center elective surgery department in Tashkent. The observation period is January 2021 – January 2022. Of them, 25 girls (52.1 %), 23 boys (47.9 %). This study included patients (normotrophics) without premorbid pathology. Anaesthesia risk according to ASA I – II. As presented in Tab. 1, groups did not differ significantly in age, body weight, and duration of surgery. The operations were planned, and standard preoperative preparation and examination were carried out.

**Criteria for exclusion from the study:**
1. Individual intolerance to the drugs used in the study;
2. Patients at risk of ASA III-IV anaesthesia;
3. Conversion during the operation.
4. Non-consent of the patient or his relatives to participate in the study.
5. Refusal to sign informed consent.

Abdominal surgical pathology was represented by the following nosology: cysts of the choledochus, pancreas, spleen, liver echinococcosis, hernias and injuries of the abdominal organs. According to the approval of the ethics committee of the National Children's Medical Center No. 1-08/491 from 22/08/2022 – the study was approved, and informed consent was obtained from all participants (or their relatives) to participate in the study. In addition, written consent was obtained from the patient to publish relevant medical information and all accompanying images within the manuscript.

The patients were divided into two groups:

The first group (main) – 28 patients who received combined perioperative analgesia according to the following scheme: basic analgesia – before the surgery (15 minutes before surgery), prophylactic intravenous administration of paracetamol at a dose of 25–30 mg/kg. In order to prevent early postoperative pain syndrome, 15 minutes before the end of the operation, an intravenous injection of ketorolac tromethamine at a dose of 0.5 mg/kg. After 6-8 hours, ketorolac was reanaesthetised at a 0.5 mg/kg dose. On days 2 and 3, 0.5 mg/kg ketorolac was administered 2 and 1 times, respectively. The following cases were contraindications to the appointment of Paracetamol and NSAIDs: hypersensitivity and allergic reactions to Paracetamol and NSAIDs, hemorrhagic diathesis, a disorder of the blood coagulation system (coagulopathy), an active stomach or duodenal ulcer, abnormal liver, kidney function, haemophilia.

The second group (comparison) – 20 patients who received 0.2–0.3 mg/kg of Promedol in the postoperative period. Promedol was administered 3 times on the first day, on the 2nd and 3rd days – 2 times a day (Table 1).

**Table 1**

| Indicators                  | The first group main, n=28 | The second group comparison, n=20 | P       |
|----------------------------|-----------------------------|-----------------------------------|---------|
| Perioperative analgesia     | Paracetamol + Ketorolac     | Promedol                          |         |
| Age (years)                | 9.5±2.54                    | 10.1±3.02                         | >0.05   |
| Body weight (kg)           | 26.7±7.11                   | 31.0±8.41                         | >0.05   |
| Surgery time (min)         | 112.8±29.06                 | 99.3±21.76                        | >0.05   |

In both groups, standard endotracheal anaesthesia was performed.

Anaesthesia was induced by administering Propofol – 3 mg/kg, Fentanyl – 1–2 μg/kg, Arduan – 0.06–0.08 mg/kg, followed by tracheal intubation and transfer to artificial ventilation (AV). Respiratory support was performed at the anaesthesia station (GE Healthcare, USA) using the forced ventilation mode by volume with
an oxygen-air mixture with EtO2 – 30 % in the normoventilation mode (EtCO2 at the level of 34–44 mm Hg). Anaesthesia was maintained with Sevoflurane 1.0–1.2 MAC according to the low-flow anaesthesia technique (LFA, flow <1 liter). Analgesia was maintained by fractional administration of Fentanyl at a dose of 0.5–1 μg/kg every 30 minutes.

Infusion therapy was similar in both groups and was represented by crystalloids: isotonic NaCl and/or Ringer’s solution, on average 4–6 ml/kg/h. In the case of significant blood loss and long-term operations, compensation for current losses was carried out individually (in 6.2 % of cases).

The study of systemic hemodynamics was performed by transesophageal echocardiography (Transeosophageal echocardiography, LOGIQ P7, 9T-RS probe, D-7.2 mm, length 80 cm), invasive blood pressure measurement method (radial artery). In transesophageal echocardiography, the transducer was removed before the patient was extubated on the operating table. Monitoring the depth of anaesthesia BIS + entropy (RE and SE) and determining the pain index SPI (Surgical Plethysmographic Index) with registration at the following stages of the study: 1 – before surgery, 2 – traumatic stage of the surgery, 3 – end of the surgery.

Intergroup comparison of hemodynamic parameters at the following three stages of the study: 1 – before surgery, 2 – traumatic stage of surgery, 3 – 24 hours after the end of the surgery (Analyzer ABL 800 FLEX, Radiometer Medical Russia). Determination of C-reactive protein levels was carried out in the following two stages: 1 – before surgery (preoperative examination), 2–24 hours after the end of the surgery (immunoturbidimetric test for the quantitative determination of C-reactive protein (CRP) in blood serum using COBAS C systems, Roche Diagnostics GmbH).

The severity of postoperative pain syndrome was analysed in study groups 2, 5, 24, 48 and 72 hours after the end of the surgical intervention. For the assessment of pain in the postoperative period, the Wong-Baker pain rating scale was used (Fig. 1). Assessment of pain: extreme pain (10 and 9 points), strong (8, 7, 6 points), medium (5, 4, 3 points), weak (2, 1 point), no pain (0 points). A survey on patient satisfaction with postoperative pain relief was conducted 24 hours after surgery in two response options: negative and positive. The presence of nausea, vomiting, headache, as well as medication load in the early postoperative period, were taken into account (Fig. 1).

![Wong-Baker pain rating scale](image)

The received data was processed using the StatSoft© STATISTICA ® 10 and Microsoft® Office Excel 2016 application package. To compare groups, non-parametric criteria were used: the significance of differences was assessed using the Mann-Whitney test (U-test). In addition, the Pearson test (χ²) was used to compare the qualitative characteristics. Differences were considered significant at p<0.05.

3. Results

Initial hemodynamic parameters in patients in the studied groups were comparable and were within the physiological norm. The intraoperative period in both groups proceeded against the background of relatively stable systemic hemodynamics, which can be explained by using one type of anaesthesia in the study groups.

However, the following trends were noted: in patients of the leading group at the 2nd and 3rd stages of the study, there was an unreliable decrease in the average values of average arterial pressure by 4.5 % and 5 % (Fig. 2). On the contrary, in the comparison group, an increase in average arterial pressure and heart rate was noted at the 2nd stage of the study concerning the initial data by 7 % (p>0.05) and 10.9 % (p<0.05), respectively (Fig. 3). At 3rd stage, there was a further increase in average arterial pressure and an increase in heart rate by 9.6 % (p>0.05) and 13.1 % (p<0.05) concerning the outcome.

At the same time, at all stages of the study, the indicators were within the reference values and age norms. Intergroup comparison of hemodynamic parameters at the stages of the study did not reveal statistically significant differences.

These changes in hemodynamic parameters indicated a sufficient degree of anaesthetic protection of the above abdominal surgery in children.
BIS+entropy (RE+SE), SPI data were registered continuously; values in the range of 40–60 conventional units were taken as adequate BIS+entropy (RE+SE) values, which corresponds to the level of general anaesthesia on the sedation scale. SPI values ≤ 50 correspond to clinically significant anaesthesia with a low probability of response to painful stimulus [20].

When studying the BIS dynamics + entropy (RE + SE), SPI in patients of both groups at the first stage, the initial indicators corresponded to clear consciousness and were within 98; at the second stage – the traumatic stage of the operation – there was a significant unidirectional decrease in both groups of values (RE+SE), SPI by 54.1 %, 59.2 %, 61.3 % (57.2 %, 54.1 %, 61.3 %), respectively, which indicated the achievement of a sufficient depth of sedation against the background of combined general anaesthesia (Fig. 3, 4). Furthermore, these BIS+entropy (RE+SE) SPI values persisted throughout the entire period of anaesthesia and corresponded to a sufficient depth of consciousness depression. However, in the main group, there was a significant difference in the BIS+entropy (RE+SE) and SPI values at the fifth stage from baseline by 18.4 %, 23.5 %, and 39.8 %, indicating persistent sedation and incomplete recovery of the level of consciousness after general anaesthesia.
The values of BIS+entropy (RE+SE) and SPI did not have statistically significant differences in the intergroup comparison but were statistically significantly different from the outcome in the study groups.

Comparative analysis of blood glucose levels as a marker of stress response at the stages of abdominal interventions in the studied groups of patients demonstrated unidirectional changes in glycemia characteristic of the intraoperative period. However, their severity was different (Fig. 5). There was a significant increase in average blood glucose levels at the second stage of the study in the comparison group by 47.8 % (p<0.05), which was due to insufficient intraoperative anti-stress protection.

![Fig. 5. Bis+entropy(RE+SE), SPI indicators in patients of the second group](image)

In the main group of patients, blood glucose dynamics at the study's second stage were within the acceptable operating stress norm. However, there was only an upward trend of 10.8 % (Fig. 6). At the third stage of the study, in the comparison group, the glucose index remained elevated by 43.4 %. In the main group of patients, the increase in glucose was 6.5 %. The dynamics of blood glucose levels showed the effectiveness of ketorolac tromethamine and paracetamol in the perioperative period in preventing hormonal stress reactions during abdominal surgeries in children.

Comparative analysis of the C-reactive protein level (immunoturbidimetric test) in order to assess the degree of activity of the proinflammatory cytokine cascade and the adequacy of postoperative analgesia in patients in selected groups at the first stage demonstrated that the initial indicators in all groups corresponded to the physiological norm, this fact shows the absence of acute inflammation signs in the preoperative period. However, after 24 hours, a significant increase (p<0.05) of C-reactive protein in the blood was registered in all the studied groups, which is associated with perioperative tissue damage, activation of pathological inflammatory reactions, and the release of mediators of pain sensitivity. In a comparative assessment, the CRP increase in the comparison group was 413.04 %, confirming the well-known fact of the absence of suppressing proinflammatory reactions by narcotic analgesics. In the main group of patients, changes in the CRP index were significantly lower (p<0.05) than in the comparison group (250 % of the initial level), so this confirmed the effectiveness of PA and postoperative analgesia based on the combined use of Paracetamol and Ketorolac tromethamine, due to the synergism of effects, the impact on different levels of pain impulses, and the inflammatory response to surgical trauma.

In the early postoperative period, differences were found in the onset time of pain syndrome and its intensity...
in patients of the studied groups. In both groups, postoperative pain was usually moderate or severe, accompanied by weakness, headache, malaise, anxiety, crying, and apathy.

On the first day in patients of the first group, 2 hours after the operation, the pain was absent in 85.7 % of patients. On average, 5 hours after surgery in patients of the first group, severe pain (6–8 points) was detected in 39.2 % and moderate pain (5 points) – in 60.8 % of the subjects (Table 2). On average, 5 hours after surgery in patients of the first group, severe pain (6–8 points) was detected in 39.2 % and moderate pain (5 points) – in 60.8 % of the examined patients (Table 2). Re-administration of ketorolac after 6 hours led to a significant decrease in the intensity of these pains and relative stabilization of hemodynamic and respiratory parameters (blood pressure, heart rate, respiratory rate). On the second day after surgery, severe pain was detected in 21.4 % of patients, and moderate pain (5–4 points) – in 78.6 %. On the 3rd day, postoperative pain in this group of patients was moderate (4.3 points) – in 17.8 %, weak (2.1 points) – in 71.4 %, and no pain in 10.7 % of patients. Side effects (sleepiness, sweating, anxiety) were observed in two patients (7.1 %).

Table 2

| Days after surgery | YOUR (points) |
|-------------------|---------------|
|                   | 8             | 7             | 6             | 5             | 4             | 3             | 2             | 1             | 0             |
| 1                 | 17.8 % (5)    | 14.2 % (4)    | 7.1 % (2)     | 60.7 % (17)   |               |               |               |               |               |
| 2                 | 21.4 % (6)    | 50 % (14)     | 28.5 % (8)    |               |               |               |               |               |               |
| 3                 | 10.7 % (3)    | 7.1 % (2)     | 46.4 % (13)   | 25 % (7)      | 10.7 % (3)    |               |               |               |               |

On the first day, in patients of the second group, PPS resumed on average 2.5–3 hours after the surgery: extreme and severe pain (9–6 points) was detected in 75 %, moderate (5 points) pain – in 25 % of patients (Table 3). Approximately 30–40 minutes after the intra-muscular injection of Promedol, there was a moderate decrease in the intensity of these pains, and the alignment of hemodynamic and respiratory parameters (BP, heart rate, respiratory rate). On the 2nd day after the surgery, severe pain was detected in 45 % of patients and moderate pain (5.4 points) in 55 % of patients. On the 3rd day, severe pain (7.6 points) was detected in 20 % of the subjects, and moderate (5.4 points) in 80 %. Side effects (excessive sleepiness, nausea, vomiting, urinary retention, intestinal paresis) were observed in three patients (15 %). Side effects disappeared on their own after the abolition of Promedol.

Analysis of the results of assessing satisfaction with pain relief in the early postoperative period of abdominal operations (Table 4) showed that in the first and second groups, the number of patients satisfied with the level of pain relief was 78.5 % and 55 %, respectively. The above statistics proved the high efficiency of multimodal PA in preventing PBS. The above statistics proved the high efficiency of multimodal PA in PPS prevention.

Table 3

| Days after surgery | YOUR (points) |
|-------------------|---------------|
|                   | 9             | 8             | 7             | 6             | 5             | 4             | 3             | 2             | 1             | 0             |
| 1                 | 35 % (7)      | 20 % (4)      | 15 % (3)      | 5 % (1)       | 25 % (5)      |               |               |               |               |               |
| 2                 | 20 % (3)      | 15 % (3)      | 10 % (2)      | 50 % (10)     | 5 % (1)       |               |               |               |               |               |
| 3                 | 5 % (1)       | 15 % (3)      | 35 % (7)      | 25 % (5)      | 20 % (4)      |               |               |               |               |               |

Table 4

| Comparative assessment of patient satisfaction with postoperative pain relief (%/abs) |
| Study groups               | Satisfaction score | Main, n=28 | Comparison, n=20 | \( \chi^2 \) |
|----------------------------|--------------------|------------|------------------|----------|
| Positive                   |                    | 78.5 % (22)| 55.0 % (11)      | P<0.01   |
| Negative                   |                    | 21.4 % (6) | 45.0 % (9)       | P<0.01   |

4. Discussion

Nowadays, postoperative opioid analgesia is characterized by a high frequency of use (up to 60 % of patients in the ICU) and high efficiency, mainly if it is carried out according to the Western method of patient-controlled intravenous bolus administration of morphine (patient-controlled analgesia). However, during the last 15–20 years, enough negative information has accumulated about an increase in the frequency of postoperative complications related to the appointment of opioids and even an increase in mortality [21, 22]. According to a study performed on orthopaedic patients, the frequency of complications of opioid analgesia reached 54.2 % [23]. At the same time, 25.6 % of patients had two or
more side effects, and 7.2 % had three or more. Side effects of opioid analgesia increased the length of stay of patients in the clinic by 18–80 % (depending on their number and severity) and treatment costs by 7.4 % [24]. Furthermore, the concept of accelerated postoperative rehabilitation of patients «Enhanced Recovery After Surgery (ERAS)» recommends using short-term drugs and techniques in anaesthesia schemes, with rapid postoperative rehabilitation and the absence of complications such as uncontrolled PBS, nausea, vomiting and excessive sedation.

As a result of the research, we have established the features of shifts in systemic hemodynamics, BIS+ entropy data (RE and SE), SPI, stress response reactions of the body and the intensity of postoperative pain syndrome in patients of the main group in abdominal surgery. The use of multimodal preventive analgesia with Paracetamol and Ketorolac tromethamine avoids excessive stress response of the body and reduces the intensity of postoperative pain in patients after abdominal surgery. While in patients of the comparison group at the 2nd and 3rd stages of anesthesia, there was an increase in the average heart rate (10.9 % and 13.1 %) and blood glucose (47.8 % and 43.4 %), which indicated insufficient intraoperative anti-stress protection. C-reactive protein (stage 2) remained significantly elevated (41.3 %) in the early postoperative period, confirming the absence of suppression of the inflammatory response to surgical trauma in patients of the comparison group. C-reactive protein (stage 2) remained significantly elevated (41.3 %) in the early postoperative period, confirming the absence of suppression of the inflammatory response to surgical trauma in patients of the main group.

Our results align with the works of various authors, in which the effect of opioids is considered to a greater extent symptomatic, and non-steroidal anti-inflammatory drugs are classified as pathogenetic drugs. Their use does not lead to impaired consciousness and breathing or cognitive dysfunctions. The safety of using NSAIDs is determined by an adequate assessment of the patient's condition, taking into account the existing contraindications and the short duration of the appointment [25].

Thus, the advantages of the combined multimodal method with the preventive administration of Paracetamol and Ketorolac tromethamine at the recommended doses in patients of the first group are apparent: the intensity of postoperative pain syndrome decreases almost 2 times, and the time of PPS development lengthens 2 times. Ketorolac administration frequency decreases in the next 2 and 3 days and improves patients' quality of life in the early postoperative period without serious side effects.

Study limitations

The results of this study should be viewed in light of some limitations. First, given the insufficient sample size (48 patients), we pooled children from all age groups for statistical analysis. As a result, anatomical and physiological parameters and laboratory indicators have slight age-related deviations. However, it should be noted that the study was prospective; both groups were homogeneous in terms of age, body weight, duration of surgery, and inclusion and exclusion criteria from the study. In the future, we will conduct a study in different age groups: younger, middle and older to obtain guaranteed reasonable conclusions.

In order to assess the degree of activity of the pro-inflammatory cytokine cascade, the adequacy of postoperative pain relief in patients, interleukin 6 or tumour necrosis factor as early markers are most often studied in world studies. However, for us the possibility of studying cytokines in the blood became another limitation due to the lack of reagents in the clinic at the time of the study. Therefore, we limited ourselves to studying C-reactive protein, which rises later than the early markers of cytokines and studied it at 2 stages of outcome and 24 hours after surgery.

Prospects for further research. We plan to conduct similar studies to assess the quality of postoperative pain relief in pediatric cardiac surgery.

5. Conclusion

1. Optimised method of preventive (preoperative) use of paracetamol in children at a dose of 25–30 mg/kg during abdominal surgery followed by administration of ketorolac tromethamine (15 minutes before the end of the surgery) increases the degree of nociceptive protection. It ensures high efficiency of postoperative pain relief, which allows to recommend it in the practice of periparative analgesia for the above abdominal surgical interventions in children.

2. The use of multimodal preventive analgesia with paracetamol and ketorolac tromethamine significantly reduces the severity of stress response reactions in the perioperative period. Reliable dynamics of C-reactive protein levels reflect a clinically significant anti-inflammatory effect and an expressed decrease in pain impulses in patients of the main group.

3. The transition from the intraoperative to the postoperative stage proceeded smoothly in 60.9 % of patients in the main group. On average, 5 hours after surgery, 39.1 % of patients had moderate-severe pain (8–6 points). In the comparison group, very severe and severe pain (9–6 points) resumed 2.5 hours after surgery in 75 % of patients.

4. Applying the Wong-Baker pain rating scale makes it possible to evaluate the effectiveness of postoperative analgesia with the possibility of correcting analgesic therapy for PPS in children after the above abdominal surgical interventions.

Conflict of interests

The authors declare that they have no conflict of interest concerning this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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