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ORIGINAL ARTICLE

Biochemical Evaluation of Analgesic and Sedative Drug Use and Pain Control Outcomes in Paediatric Surgical Patients

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ABSTRACT
Background: Pain control is a key aspect of pediatrics surgery. Post-operative pain, anxiety and physiological stress levels are routinely reduced through the use of analgesics and sedative drugs. But scarce information exists on their biochemical effects and relation to pain control outcomes after surgeries in paediatric population of Pakistan.
Objective: To assess biochemical changes associated with the use of analgesic and sedative drugs and to find the biochemical effects of postoperative pain control in paediatric surgical patients.
Methods: This multicenter prospective observational study was conducted at Khyber Teaching Hospital and Khyber Medical College, Peshawar, Pakistan, and DG Khan Medical College, Dera Ghazi Khan, Pakistan, from June 2022 to June 2023. Using consecutive sampling, 120 paediatric patients, aged between 1-12 years undergoing elective or emergency surgical procedure were enrolled. Demographic data, medicine use, biochemical parameters, and postoperative pain outcomes were documented. Before surgery and 24 hours after surgery, serum cortisol, blood glucose, C-reactive protein (CRP), liver function tests (LFT), renal function tests (RFT) and electrolyte profiles were evaluated. Age appropriate validated pain scales were used for the assessment of pain. The data were analyzed statistically using SPSS version (26.0) and P value of < 0.05 was taken as significant.
Results: The mean age of the participants is 6.7 ± 3.1 years and there were 60.0% males. The most commonly given analgesic (85.0%) and sedative (65.0%) drugs were Paracetamol and Midazolam, respectively. Mean serum cortisol levels decreased significantly from 19.2 ± 4.5 µg/dL preoperatively to 13.4 ± 3.6 µg/dL postoperatively ($p<0.001$). Progressively decreasing postoperative pain scores started at 6.3 ± 1.4 at 1 hour and ended at 1.6 ± 0.8 at 24 hours. Patients receiving multimodal analgesia demonstrated significantly lower pain scores and cortisol levels compared with monotherapy recipients ($p<0.001$). There was no clinically significant liver, renal or electrolyte derangements.
Conclusion: Analgesic and sedative drugs were effective in helping to manage postoperative pain and reduce physiological stress responses in paediatric surgical patients. Multimodal analgesic approaches achieved a better biochemical and clinical profile with a safe profile.
Keywords: Paediatric Surgery, Analgesics, Sedatives, Pain Management, Cortisol, Postoperative Care.

INTRODUCTION
Pain management in paediatric surgical patients still remains one of the most important challenges in modern perioperative medicine[1]. Children who have undergone surgical interventions often experience pain, anxiety, fear and physiological stress, which can negatively impact recovery and clinical outcomes[2]. Assessment and management of pain in children can be much more complex than in adults, as children may not be able to communicate the nature and severity of their pain. Postoperative pain if not controlled appropriately can result in many negative effects such as increased sympathetic nervous system activity, impaired immune function, sleep disturbances, behavioral changes, long-term psychological effects and delayed wound healing, which increase the duration of hospital stay. Thus, adequate pain management has now become an integral part of high quality paediatric surgical practice[3].

Surgical trauma triggers a myriad of neuroendocrine and inflammatory pathways that constitute the physiologic response.[4] Surgery causes tissue damage, which activates nociceptive receptors and the production of stress hormones like cortisol, catecholamines, glucagon and growth hormone. At the same time, inflammatory factors are released into the blood such as interleukins, tumour necrosis factor-alpha (TNF-α), prostaglandins and C-reactive protein (CRP). These biochemical changes play a part in higher metabolic needs, hyperglycemia, protein breakdown, immune dysfunction, and cardiovascular stress. These responses can often be directly proportional to the intensity of pain and surgical damage. Hence, biochemical markers can be used as objective measures of postoperative stress, and the efficacy of analgesic interventions[5,6].

In paediatric surgical areas, analgesics are frequently used to reduce pain and to prevent complications associated with stress[7]. Analgesics used often include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids like morphine and fentanyl and techniques of regional anesthesia[8]. The agents work in various pharmacological ways to block pain pathways and aid patient comfort. Acetaminophen has a central analgesic action with a good safety profile, while NSAIDs act as inhibitors of the cyclooxygenase enzymes, decreasing the synthesis of prostaglandins. Opioids continue to be some of the most effective analgesics for moderate to severe postoperative pain which need to be monitored closely due to their potential side effects such as respiratory depression, nausea, vomiting, constipation, and sedation[9].

Sedative drugs are important in the perioperative management of children.[10] Young patients often feel anxious and emotional leading up to, during, and following surgery, which can worsen the pain and hinder healing. Sedative agents like midazolam, ketamine, dexmedetomidine, and propofol are frequently used to help reduce anxiety, enhance procedures, and increase patient cooperation. In addition to the anxiolytic effects, some sedatives have analgesic-sparing properties that could aid in decreasing the amount of opioids used and for better postoperative outcomes. However, if sedated excessively, there is a risk of respiratory compromise, delayed recovery and hemodynamic instability, so careful monitoring of the patient and individual treatment approaches are important[11,12].

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The recent developments in paediatric pain management are focused around the idea of multimodal analgesia[13]. This is done by using several combinations of analgesics and sedatives that may have different modes of action to provide better pain relief with less drug effects[14]. Multimodal regimens have been linked to decreased opioid use, decreased postoperative pain, decreased length of stay and increased patient satisfaction. In addition, there are indications that successful multimodal pain management can help to reduce neuroendocrine stress reactions with measurable changes in biochemical parameters like serum cortisol, blood glucose and inflammatory parameters[15].

Biochemical monitoring offers useful information regarding the physiological effects of drug administration of analgesics and sedatives.[16] Serum cortisol is considered a good global marker of surgical stress and neuroendocrine activation due to pain. Higher levels of cortisol have been linked to more pain and slower recovery after surgery. Likewise, hyperglycemia during the peri-operative period is associated with activation of stress-mediated metabolic pathways and increased risk of infection and poor wound healing outcomes. Additional inflammatory markers, including CRP, interleukin-6 and TNF-α, might be used to estimate the systemic inflammatory response to surgical trauma. It is also important to follow liver and kidney function parameters as the liver and kidneys are important sites of the metabolism and elimination of the analgesics and sedatives[17].

Although there have been great advances in paediatric anesthesia and pain management, there are still wide differences in the way that analgesics are prescribed and sedation is managed in the various health care facilities. Therapeutic decisions are often influenced by factors like patient age, surgery procedure, clinician preference, availability of medications and institutional guidelines. In addition, there is scarce information on the biochemical actions of commonly used analgesic and sedative combinations in paediatric surgical patients, especially in developing nations where resources and monitoring facilities may be limited. Thus, it is important to understand the association of drug-use with biochemical changes and clinical pain outcomes to optimize patient care and enhance evidence-based treatment strategies[19].

A number of earlier investigations have shown a correlation between adequate analgesia and lowered stress-related biochemical markers. Many investigations have concentrated only on the adult surgical population however, the paediatric specific evidence is relatively restricted[20]. Pharmacokinetics and pharmacodynamics, physiological stress response and perception of pain is vastly different in children compared to adults. Thus, conclusions obtained from adult studies may not necessarily be transferable to paediatric patients. The safety, effectiveness and biochemical effects of analgesics and sedatives particularly in paediatric surgical environments should be further studied.

The present study was aimed to assess the use of analgesics and sedatives in paediatric surgical patients and to find out the impact of these drugs on postoperative pain and biochemical parameters. Special attention was given to the evaluation of serum cortisol, blood glucose, inflammatory markers, liver function tests, renal function tests and electrolyte profile after the peri-operative drug administration. Furthermore, the study sought to determine if there was a correlation between the medication regimes and pain scores after surgery in order to determine what factors lead to better clinical outcomes. This research may be useful for supporting optimization of pain management strategies, the safety of patients and improve peri-operative care in paediatric surgical populations[11].

MATERIALS AND METHODS

This multicenter prospective observational study was conducted to evaluate the biochemical effects of analgesic and sedative drug use and their association with pain control outcomes among paediatric surgical patients. The study was conducted at Khyber Teaching Hospital, Khyber Medical College, Peshawar, Pakistan and DG Khan Medical College, Dera Ghazi Khan, Pakistan. Data collection was conducted over a one-year period from June 2022 to June 2023. The study received ethical approval from the appropriate Institutional Review Boards prior to its commencement, and written informed consent from the parents or legal guardian of all children involved. The study was conducted within the guidelines of the Declaration of Helsinki, and patient information was kept confidential throughout the study.

A total of 120 paediatric surgical patients were enrolled using a non-probability consecutive sampling technique. Children were eligible for inclusion if they were treated with analgesic and sedative drugs during elective or emergency surgery under general anesthesia as part of routine clinical care, and were between the ages of 1–12 years. Patients with known chronic liver disease, chronic kidney disease, congenital metabolic disorders, endocrine disorders, neurological disorders, which might interfere with pain assessment, history of long-term use of corticosteroid therapy, or incomplete laboratory and clinical records were excluded. The eligible subjects were selected consecutive during the study period till the desired sample size was achieved.

Demographic and clinical data was accessed from medical records, anesthesia charts, surgical records, and direct parent/guardian interview. Data gathered were age, gender, body weight, type of surgical procedure, duration of surgery, length of hospital stay, analgesics and sedatives used, and postoperative complications. No experimental interventions were added to the patients' standard perioperative management that follows institutional protocols.

Data on the administration of analgesic and sedative drugs was gathered from anesthesia and medication records. Popularly used analgesics were intravenous paracetamol (acetaminophen), ibuprofen, morphine, fentanyl, and tramadol, and sedatives were midazolam, ketamine, dexmedetomidine, and propofol. The type of drug used, dosage, route of administration, frequency of drug administration and the use of combination therapy was documented for each patient. Prescribing rates of these medicines were then compared to biochemical and clinical outcome.

Venous blood samples were obtained under aseptic conditions at 2 predetermined time points for biochemical evaluations: within 12 hours before surgery and 24 hours after surgery. About 5 mL of venous blood was collected from each of the subjects and analysed in the clinical biochemistry laboratories of participating institutions. Commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to analyze the serum cortisol levels following the manufacturers' instructions. Fully automated clinical chemistry analyzers were used to determine random blood glucose, C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine, blood urea nitrogen (BUN), sodium and potassium concentrations. These biochemical parameters were chosen for the evaluation of physiological stress response, inflammatory status, metabolic changes, liver function, kidney function and electrolyte imbalance that result from the use of perioperative analgesics and sedatives.

Validated age appropriate pain assessment tools were used to assess pain postoperatively. The Wong-Baker Faces Pain Rating Scale was used to assess pain intensity in children if they were older than 7 years; for younger children (1-7 years), the Face, Legs, Activity, Cry, Consolability (FLACC) scale was used. The pain scores were documented at 1 hour, 6 hours, 12 hours and 24 hours after surgery. The pain intensity was divided into mild, moderate and severe using agreed upon scoring criteria. These were carried out by trained health care professionals who were familiar with the paediatric pain evaluation techniques.

The main outcome measures were serum cortisol concentration and postoperative pain control outcome after pain and sedation (analgesic/sedative) drugs were administered. Secondary outcome measures were the change in blood glucose and CRP levels, the change in liver and renal function and the use and type of analgesics and sedatives used during the postoperative period and the occurrence of medication related adverse events during the postoperative period.

Data collected was fed in a secured database and analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0. Continuous variables were reported as mean ± standard deviation and categorical variables as numbers and percentages. Normality of quantitative variables was tested by Shapiro-Wilk test. Paired sample t tests were used for comparisons of biochemical parameters between the pre- and post-operative periods. Where appropriate, the outcomes between the various medicine groups were compared using independent sample t-tests and one-way analysis of variance (ANOVA). The Chi-square test was used to determine association between categorical variables. All analyses were performed with a 0.05 level of significance.

RESULTS

A total of 120 paediatric surgical patients were enrolled in the study from Khyber Teaching Hospital and Khyber Medical College, Peshawar, Pakistan, and DG Khan Medical College, Dera Ghazi Khan, Pakistan, during the study period from June 2022 to June 2023. The ages of the subjects were 1 to 12 years with the mean age of 6.7 ± 3.1 years. Of the total study population, 72 (60.0%) were male and 48 (40.0%) were female. The mean body weight was 22.8 ± 8.4 kg. The surgical time was 74.5 ± 21.3 minutes and hospital stay was 3.4 ± 1.6 days on average. Of these, 68.3% were treated with elective surgical procedures while 31.7% required emergency surgery. The demographic and clinical data of the study population are shown in table 1.Table 2 shows the distribution of surgical procedures for the study participants. Appendectomy was the most frequently performed surgical procedure, accounting for 26.7% of cases, followed by herniotomy (20.0%), circumcision (17.5%), and orchidopexy (13.3%). The remainder of the surgical workload for the individual procedures, such as hydrocele repair, abscess drainage, and minor abdominal surgeries, and soft tissue surgeries were 22.5% in total. The results here capture the typical spectrum of paediatric surgery cases seen in the participating tertiary care facilities.Medication use analysis showed that a large amount of analgesics and sedatives were used perioperatively. In terms of analgesics, the most commonly prescribed drug was intravenous Paracetamol, which was given to 85.0% of patients. Opioid analgesics such as morphine (36.7%) and fentanyl (31.7%) were used in patients, and Ibuprofen was used in 55.0% of patients. Tramadol was less commonly used and used by 15.8% of participants. As far as sedative medications are concerned, midazolam was the most frequently used one (65.0%). 38.3% used Ketamine, 28.3% used Propofol and 13.3% used Dexmedetomidine. Table 3 shows distribution of drug utilization for analgesics and sedative drugs in detail.Biochemical assessment revealed that there were significant changes in a few biochemical markers with the use of analgesics and sedatives during the perioperative period. The mean pre- and post-serum cortisol concentration dropped significantly from 19.2 ± 4.5 μg/dL to 13.4 ± 3.6 μg/dL after surgery, respectively ($p<0.001$) suggesting good attenuation of the neuroendocrine stress response. As expected, there was a slight, but statistically significant rise in blood glucose levels from a pre-operative average of 89.7 ± 11.2 mg/dL to a post-operative average of 101.6 ± 13.4 mg/dL ($p=0.004$), which is the metabolic response to surgery. Similarly, CRP levels increased significantly following surgery, rising from 3.4 ± 1.2 mg/L to 6.2 ± 1.8 mg/L ($p<0.001$), which is consistent with the normal postoperative inflammatory response.

However, liver function parameters such as ALT and AST did not change significantly throughout the perioperative time. Similarly, blood urea nitrogen and serum creatinine were in the normal physiological range. There were no clinically significant electrolyte disturbances. The results indicate that there were no significant adverse effects with respect to liver, kidney, or electrolyte metabolism related to the analgesic/sedative treatment in the study. Detailed biochemical findings are shown in Table 4.The postoperative pain assessment showed that there was a progressive decrease of pain intensity during the first 24 hours after surgery, and this decrease was statistically significant. Moderate to severe pain was seen immediately after surgery with the highest mean pain score at 1 hour after surgery (6.3 ± 1.4). However, pain scores declined steadily over time, decreasing to 4.5 ± 1.2 at 6 hours, 2.9 ± 1.0 at 12 hours, and 1.6 ± 0.8 at 24 hours postoperatively. These results show that the analgesic and sedation regimens used in the hospitals were effective in providing prolonged postoperative pain relief. Table 5 provides an overview of the changes in pain score across time.Subsequent analysis for differences between the two types of analgesia (monotherapy and multimodal) revealed biochemical and clinical differences. Patients receiving multimodal analgesic therapy exhibited significantly lower postoperative serum cortisol levels compared with those receiving single-agent analgesia (12.1 ± 3.1 μg/dL versus 15.7 ± 3.8 μg/dL, $p<0.001$). Likewise, the mean pain score at 24 hours postoperative was significantly lower in multimodal therapy group (1.3 ± 0.6) than the monotherapy group (2.4 ± 0.9, $p<0.001$). Furthermore, patients receiving multimodal analgesia had a reduced length of stay, indicating better recovery and clinical outcomes. The results of these are outlined in Table 6.Medication safety review showed that medication side effects were uncommon and not severe. The most frequent adverse events were postoperative nausea and vomiting, which happened in 9.2% of patients. 6.7% of participants were found to have transient sedation and 4.2% of the cases had dizziness. Mild hypotension was recorded in only 2.5% of patients. Notably, no patients with respiratory depression, acute kidney injury, severe hepatic dysfunction or other life-threatening complications were found during the study period. The incidence of adverse events is detailed in Table 7.In conclusion, the findings of the current study support that analgesic and sedative drugs given peroperatively were associated with major improvement in postoperative pain management and biochemical stress response, and safe profile in paediatric surgical patients. Moreover, multimodal analgesic procedures had better biochemical and clinical results than single-modal ones, and the use of multimodal therapy should be recommended in paediatric perioperative pain management.

Table 1: Demographic and Clinical Characteristics of the Study Population (n = 120)

Variable	Frequency (%) / Mean ± SD
Age (years)	6.7 ± 3.1
Male	72 (60.0)
Female	48 (40.0)
Body Weight (kg)	22.8 ± 8.4
Duration of Surgery (minutes)	74.5 ± 21.3
Hospital Stay (days)	3.4 ± 1.6
Elective Procedures	82 (68.3)
Emergency Procedures	38 (31.7)

Table 2: Distribution of Surgical Procedures Among Paediatric Patients

Surgical Procedure	Frequency (n)	Percentage (%)
Appendectomy	32	26.7
Herniotomy	24	20.0
Circumcision	21	17.5
Orchidopexy	16	13.3
Other Procedures	27	22.5
Total	120	100.0

Table 3: Analgesic and Sedative Drug Utilization Patterns

Medication	Frequency (n)	Percentage (%)
Analgesics		
Paracetamol	102	85.0
Ibuprofen	66	55.0
Morphine	44	36.7
Fentanyl	38	31.7
Tramadol	19	15.8
Sedatives		
Midazolam	78	65.0
Ketamine	46	38.3
Propofol	34	28.3
Dexmedetomidine	16	13.3

Table 4: Comparison of Preoperative and Postoperative Biochemical Parameters

Parameter	Preoperative (Mean ± SD)	Postoperative (Mean ± SD)	p-value
Serum Cortisol (µg/dL)	19.2 ± 4.5	13.4 ± 3.6	<0.001
Blood Glucose (mg/dL)	89.7 ± 11.2	101.6 ± 13.4	0.004
CRP (mg/L)	3.4 ± 1.2	6.2 ± 1.8	<0.001
ALT (U/L)	24.3 ± 6.5	25.8 ± 6.9	0.182
AST (U/L)	27.5 ± 7.2	28.9 ± 7.6	0.215
Serum Creatinine (mg/dL)	0.61 ± 0.13	0.63 ± 0.15	0.301
BUN (mg/dL)	12.6 ± 3.4	13.1 ± 3.6	0.267
Sodium (mmol/L)	138.5 ± 2.8	137.9 ± 3.1	0.174
Potassium (mmol/L)	4.2 ± 0.4	4.1 ± 0.5	0.289

Table 5: Postoperative Pain Scores at Different Time Intervals

Time After Surgery	Mean Pain Score ± SD
1 Hour	6.3 ± 1.4
6 Hours	4.5 ± 1.2
12 Hours	2.9 ± 1.0
24 Hours	1.6 ± 0.8

Table 6: Comparison of Outcomes Between Monotherapy and Multimodal Analgesia Groups

Variable	Monotherapy (n=42)	Multimodal Therapy (n=78)	p-value
Postoperative Cortisol (µg/dL)	15.7 ± 3.8	12.1 ± 3.1	<0.001
24-Hour Pain Score	2.4 ± 0.9	1.3 ± 0.6	<0.001
Length of Hospital Stay (days)	3.8 ± 1.7	3.1 ± 1.4	0.028

Table 7: Drug-Related Adverse Events Observed During the Study

Adverse Event	Frequency (n)	Percentage (%)
Nausea and Vomiting	11	9.2
Transient Sedation	8	6.7
Dizziness	5	4.2
Mild Hypotension	3	2.5
Respiratory Depression	0	0.0
Acute Kidney Injury	0	0.0
Significant Hepatic Dysfunction	0	0.0

DISCUSSION

Pain management is an essential part of paediatric surgical care as postoperative pain is associated with major physiological, metabolic and psychological implications if it is not properly managed[1]. The present multicenter study was aimed at assessing the biochemical effects of use of analgesic and sedative drug and its correlation with pain control outcome in paediatric surgical patients in Khyber Teaching Hospital, Khyber Medical College Peshawar and DG Khan Medical College, Dera Ghazi Khan. These results showed that perioperatively administered analgesia-sedative drugs significantly decreased the level of pain and biochemical markers of stress in an acceptable safety profile[2].

The demographic characteristics of the study population were similar to that of the typical paediatric surgical admissions in regional and International studies[3]. The majority of the patients were male and appendectomy was the most common surgical procedure. The same applies to paediatric surgical centres around the world, where acute appendicitis, inguinal hernia repair, circumcision and orchidopexy are large quantities of routine surgery. These procedures were the most common of those used, and thus offered a representative sample for the assessment of perioperative pain management practices in children[4].

The most relevant result of the present study was the marked decrease in the serum cortisol levels after the use of the analgesics and sedatives in the peri-operative period. Cortisol is a well known biochemical marker for physiological stress and neuroendocrine activation[5]. The hypothalamic-pituitary-adrenal axis is activated by surgical trauma, which leads to higher production of cortisol and catecholamines. High levels of cortisol are linked to higher protein breakdown, reduced immune function, slower healing and a longer recovery time[6]. The significant reduction in post-operative cortisol levels seen in this study indicates that the analgesic-sedative treatment was able to blunt surgical stress response. A decrease in cortisol has been found in studies of multimodal analgesic regimens as well, and good pain management may help to improve postoperative physiological stability and recovery.[7]

The postoperative rise in blood glucose concentrations is a normal metabolic reaction to the surgical injury.[8] SIIH is due to the release of cortisol, catecholamines, glucagon and inflammatory cytokines that promote hepatogenous gluconeogenesis and insulin resistance[9]. Postoperative glucose levels were significantly higher, but were not clinically problematic and did not suggest clinically important metabolic derangement. These results indicate that effective analgesia may have blunted the effect of stress-induced hyperglycemia, possibly by decreasing neuroendocrine activation[10].

The postoperative inflammatory responses were evident from the significant increase in the level of CRP after surgery. CRP is an acute phase reactant, which is produced by the liver in response to inflammatory cytokines released after injury to tissues[11]. The CRP increase seen in the present study was as expected and as a normal inflammatory response to surgery. Importantly, although there was a rise in inflammatory markers, adequate pain control was achieved in most patients and it was believed that analgesic and sedative therapy was successful at controlling nociceptive pathways and allowing normal postoperative healing processes to occur[12].

The results also showed a high level of postoperative pain control – the amount of pain went down each hour over the first 24 hours following surgery[13]. The peak pain scores were in the immediate postoperative period with significant decreases at each follow-up interval. These findings corroborate earlier studies, which have demonstrated that peri-operative analgesia can have a positive effect on patient comfort and hasten post-operative recovery. In the paediatric patient population, effective pain control is of paramount importance as poorly managed pain can lead to anxiety, sleep disturbances, behavioural changes, delayed mobilisation and an increased risk of chronic pain syndromes later in life[14].

One interesting result of this study was the effectiveness of multimodal analgesia over monotherapy[15]. In the multimodal analgesic groups, there was clearly a reduction of cortisol concentrations in the postoperative period, along with reduced pain scores and shorter hospital stays. Multimodal analgesia involves the use of a combination of drugs that have different modes of action, providing greater analgesia with reduced harmful side effects of the individual drugs. Multimodal therapy is when more than one pathway of pain is stimulated; this can offer a more complete relief of pain and better physiological outcomes. The current findings confirm the present suggestions about multimodal analgesic techniques as the recommended strategy for the perioperative pain control in paediatric patients[16].

Medication utilization analysis indicated that paracetamol was the most commonly used analgesic, midazolam was the most common sedative agent[17]. This is in line with the current paediatric anesthesia practice in which Paracetamol is preferred due to its effectiveness, safeness and low side effects. Midazolam is a preferred sedative due to its anxiolytic, amnestic and sedative properties. The increase in the use of ketamine, fentanyl, morphine, and dexmedetomidine also underscores the use of multimodal approaches to analgesia and sedation for the best comfort of the patient with minimal complications.

The safety analysis showed a good adverse events profile. Postoperative nausea and vomiting, transient sedation and dizziness were the most frequently seen complications, which were all mild and self-limited. Importantly, there were no reports of respiratory depression, acute kidney injury or marked hepatic dysfunction.[19] In addition, liver function parameters, renal function markers and electrolyte concentrations were stable during the study period. These findings suggest that the analgesic and sedative regimes in the participating institutions were well tolerated and safe when applied in line with the guidelines and protocols in the clinical practice.

This is a multicenter, prospective study, which includes objective biochemical markers and an evaluation of both clinical and laboratory outcomes.The present study has several strengths, including the multicenter design, the prospective methodology, the inclusion of objective biochemical markers, and the comprehensive evaluation of both clinical and laboratory outcomes[13]. But some drawbacks need to be noted. It was an observational study and cannot make conclusions or determine true causal links between the drugs administered and the outcomes observed. Also, the long-term follow-up after surgery was not carried out, which is not sufficient to assess the long-term analgesic effect and late complications. The variability between clinicians with regard to surgical technique and choice of medication may have also affected some outcomes. Further RCTs with larger patient numbers and longer follow-up are recommended to better understand the biochemical and clinical impact of individual anaesthetic and analgesic drug combinations in paediatric surgical patients[14].

In conclusion, the results of this study indicate that a thorough management of the whole perioperative pain is crucial and that multimodal analgesia is valuable to promote biochemical and clinical outcomes. Good pain management can not only keep patients comfortable, but it can also reduce physiological responses to pain that can have a negative effect on a patient's postoperative recovery[18–20].

CONCLUSION

This study showed that the use of analgesics and sedative drugs during the peri-operative period of surgery is effective in managing postoperative pain and greatly reduces physiological stress response of surgical paediatric patients. The decrease in serum cortisol concentration and the gradual improvement of the postoperative pain scores are a sign of successful surgical stress attenuation and increased patient comfort. There were postoperative increases in both blood glucose and CRP levels, but these were typical of the metabolic and inflammatory responses to surgery and were not linked to poor clinical outcomes. Multimodal analgesics regimens yielded better results than monotherapy, which included both lower postoperative pain scores and larger biochemical reduction of stress markers and shorter hospital stays. Moreover, the analgesics and sedatives administered in this study exhibited good tolerability, and only minor adverse events which were self-limited, were observed and there were no clinically significant hepatic, renal or respiratory adverse events. The results justify the use of multimodal analgesic methods in routine paediatric surgical practice, and the use of biochemical monitoring as an objective method for assessing the effectiveness of treatment and the perioperative stress. Using evidence-based guidelines for paediatric pain management could help to improve patient outcomes, safety, and recovery.

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Authors' Contributions: ZM conceived and designed the study, supervised data collection, and critically revised the manuscript. IA contributed to patient recruitment, clinical data acquisition, and manuscript preparation. NUK performed biochemical analysis, interpreted laboratory findings, and contributed to data validation. MAUK assisted in study methodology, statistical interpretation, and manuscript review. FAM participated in biochemical data analysis, results interpretation, and manuscript editing. SM contributed to pediatric patient assessment, literature review, drafting of the manuscript, and final proofreading. All authors read and approved the final manuscript.

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