Effectiveness of Local Wound Infiltration with Morphine, Ketorolac, and Bupivacaine Compared to Bupivacaine Alone Following Tibial Osteotomy in Pediatric Patients: A Randomized Controlled Trial

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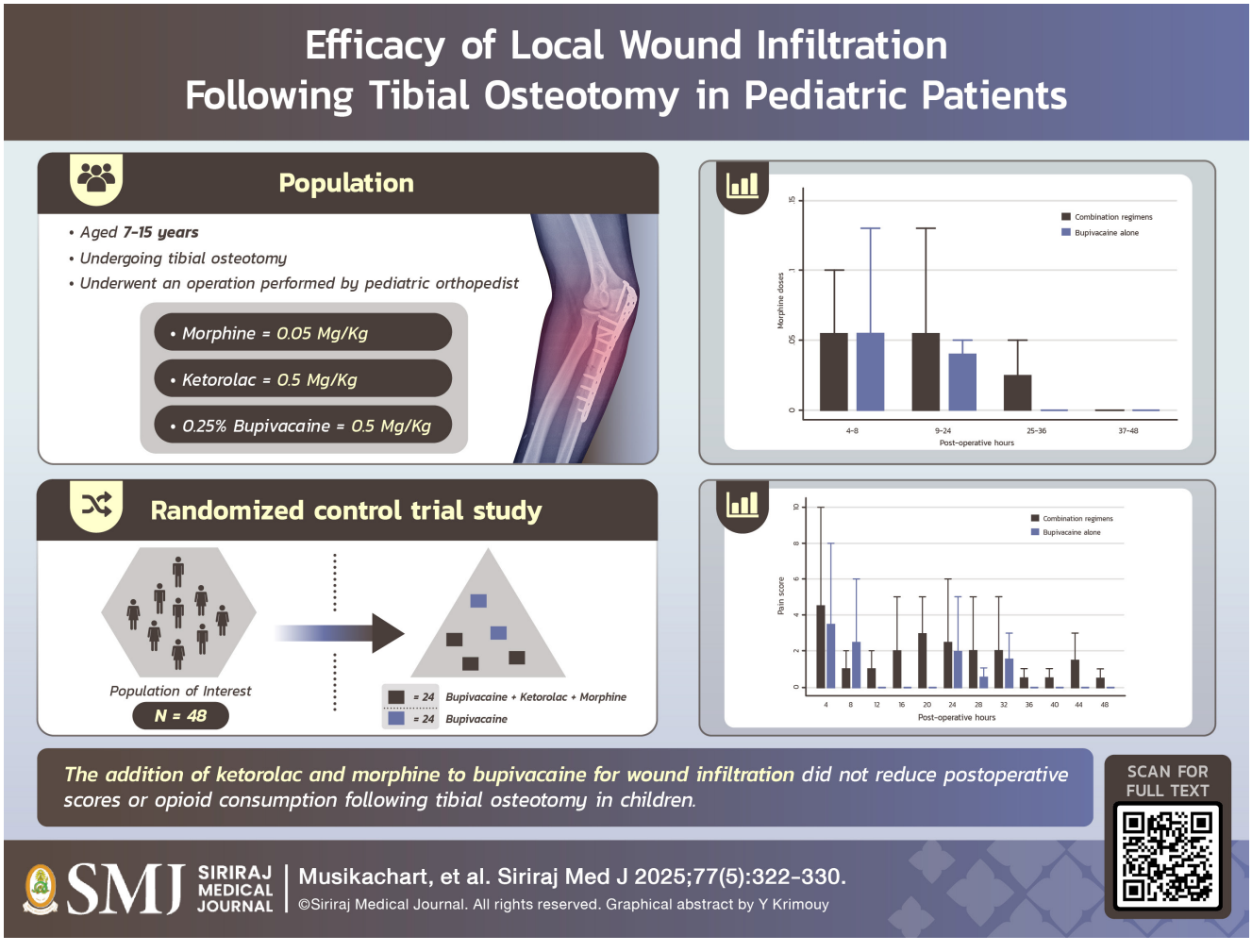

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ABSTRACT

Objective: To compare postoperative pain in children receiving ketorolac plus morphine local wound infiltration as adjunct analgesic agents with bupivacaine for local wound infiltration following tibial osteotomy

Materials and Methods: This randomized, double-blind, placebo-controlled trial included patients aged 7-15 years underwent tibial osteotomy. Participants were allocated into two groups. The combination group received wound infiltration with 0.5 ml/kg bupivacaine 0.25% and 0.5 mg/kg ketorolac and 0.05 mg/kg morphine, while the control group received bupivacaine alone before skin closure. Primary outcomes were Visual Analog Scale (VAS) pain scores measured every 4 hours during the first 48 hours after surgery. Secondary outcomes included morphine consumption and opioid-related complications.

Results: Among the 48 patients included in the study, no significant differences were observed in postoperative VAS pain scores between the two groups at nearly all time points. The combination group showed a trend towards higher mean pain levels compared to the control group at almost every time point from 4-hour to 48-hours post-operation. The maximum mean postoperative pain level in both groups, at four hours, was higher in the combination group, with a maximum mean postoperative pain level of 2.1 vs. 1.9. Higher mean opioid use was noted in the combination group, with a mean of 0.04±0.08 mg/kg vs. 0.03±0.04, at 4-8 hours postoperatively. Also, the cumulative morphine dose was lower in the control group compared to the combination group.

Conclusion: The addition of ketorolac and morphine to bupivacaine for wound infiltration did not reduce postoperative VAS pain scores or opioid consumption following tibial osteotomy in children.

Keywords: Tibial osteotomy; postoperative pain; wound infiltration; morphine; ketorolac; bupivacaine (Siriraj Med J 2025; 77: 322-330)

INTRODUCTION

Operative treatments in pediatric patients, such as orthopedic surgery, often result in significant postoperative pain, placing burden on both children and their caregivers. Accordingly, adequate perioperative pain control is important in operative treatments in children. However, achieving optimal pain control in pediatric patients is challenging due to various factors, including children's limited ability to communicate and cooperate.[1] Consequently, children often experience residual postoperative pain due to insufficient analgesic prescription. Previous studies have emphasized that acute postoperative pain can cause short- and long-term effects on pediatric patients, with up to twenty-two percent of children experiencing moderate to severe chronic postsurgical pain.[2] Moreover, a magnetic resonance imaging (MRI) study demonstrated that nociceptive stimulation in the brains of school-aged children and adolescents who had undergone medical procedures during infancy in the neonatal intensive care unit (NICU) affects long-term pain perception.[3]

Evaluating pain in children is more difficult. Different tools have been developed to assess pain accurately, including self-report measures, questionnaires, and behavioral observational scales. One such tool is the Visual Analogue Scales (VAS), which is a reliable behavioral scale for rating postoperative pain in patients >=5 years.[4]

Local surgical site analgesia infiltration was a popular perioperative analgesic method known for effectively preventing postoperative pain. This analgesic method is cost-effective, demands minimal technical expertise, and has limited potential for adverse effects. The mechanism of local analgesics relies on the reduction of neural transmission and blocking axonal depolarization. This increases the threshold for action potential, decreases nociceptor sensitization, and reduces local inflammatory reactions.[5]

Several local surgical site infiltration regimens have been introduced. Theoretically, combining various analgesic substances could enhance the effectiveness of pain control properties while minimizing the dosage of each substance, resulting in fewer medication-related adverse events. Moreover, the use of combination local surgical site infiltration could reduce postoperative opioid consumption. Commonly used adjuvant analgesic agents were ketorolac, morphine, epinephrine, bupivacaine, dexamethasone and ketamine.[6-9] Although several studies have demonstrated the effectiveness of local surgical site infiltration for postoperative pain control, data on its use in pediatric orthopaedic procedures was limited. Some studies have reported efficacy of postoperative pain and opioid use with local wound infiltration following surgical hip dislocation for management of femoroacetabular impingement (FAI).[10] However, other studies found

that wound infiltration did not significantly reduce pain scores following abdominal surgery in children.[11-13]

The purpose of this study was to compare the efficacy of combined analgesic wound infiltration regimens (bupivacaine, ketorolac, and morphine) with a control group receiving bupivacaine alone for postoperative pain control following tibial osteotomy Moreover, we aimed to assess intravascular opioid consumption following the surgery between these treatment groups.

MATERIALS AND METHODS

Patient population

The study was approved by the Institutional Review Board (IRB) of Siriraj Hospital; COA Si590/2021. Patients aged 7-15 years who underwent unilateral tibial osteotomy were included. Tibial osteotomy was indicated for pediatric patients with tibial malalignment due to various causes, including Blount's disease, physeal arrest, or tibial hemimelia. The operations were performed by a pediatric orthopedist. The exclusion criteria included pre-existing pain (e.g from fractures or infections), loss of sensation, and history of allergies to NSAIDs, morphine, bupivacaine, or paracetamol. All patients that had renal dysfunction (eGFR< 90 mL/min/1.73 m^2) or language barriers were excluded. Informed consent was obtained from all patients and relevant persons (such as parents or legal guardians).

Randomization

Patients were randomized into two groups using a computer-generated block randomization table managed by research assistants. Forty-eight patients were allocated to either the combination group (n=24), which received wound infiltration with bupivacaine, ketorolac, and morphine, or the control group (n=24), which received bupivacaine alone. All patients were blinded to grouping. The envelope containing the group allocation was opened by the surgeon before the operation. Electrical operative notes were entered into a secure computer system accessible only by password to maintain blinding for the nursing staff.

Outcome measurements

The primary outcome was pain at rest scores collected at 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48 hours postoperatively using the VAS. The score consisted of a 100 mm straight horizontal line with endpoints representing no pain (left end) and worst pain (right end). A nurse blinded to the two groups evaluated the pain scores. Secondary outcomes included (1) cumulative breakthrough morphine consumption at 8, 24, 36 and 48 hours after surgery; (2) opioid-related side effects (i.e., respiratory depression, urinary retention, nausea/vomiting, skin irritation, hypotension); and (3) hospital length of stay from admission to discharge.

Treatment

All patients were managed under general anesthesia without regional nerve block or epidural block. Antibiotic prophylaxis consisted of a single 25 mg/kg/dose IV bolus dose of cefazolin (or clindamycin 25 mg/kg/dose in cases of allergy). Only our regimen of local wound anesthesia was administered with normal saline dilution to 10 ml. Patients received either a subcutaneous wound injection with a combination of 0.5 ml/kg bupivacaine 0.25% and 0.5 mg/kg ketorolac and 0.05 mg/kg morphine or with 0.5 ml/kg bupivacaine 0.25% alone, allocated at random.

Postoperative Protocol

Postoperative analgesic drugs were prescribed based on the patients' ideal body weight. Both study groups received 0.5 mg/kg/dose of intravenous ketorolac every 8 hours for the first 24 hours, and 10-15 mg/kg/dose of oral paracetamol every 6 hours. Oral ibuprofen 10-15 mg/kg/dose was administered every 8 hours following the last dose of intravenous ketorolac. This regimen continued for 48 hours after surgery. Patients were asked to rate their pain at rest level, starting at 4-hour after surgery, using a 100-mm VAS measurement printed on full A4 paper. The left side of scale represents least pain (pain score = 0) and the right side represented worst pain (pain score = 10). The rating scale was explained to the patients. Data on complications, such as nausea and vomiting, were also collected. If a VAS score ≥ 5 was reported, it was treated with an intravenous morphine bolus 0.03-0.05 mg/kg every 4 hours. Total medication requirements and side effects were recorded over a 48-hour period. Patients were encouraged to limit weight bearing after the surgery. Most patients were discharged on postoperative day 2 or 3, assuming no complications had arisen.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 18.0) software, Chicago, IL, USA. Continuous data between groups were compared using the independent *t*-test and ANOVA. Nominal data were analyzed with Chi-square tests and the Mann-Whitney U test for ordinal data. The graph in this study was generated using STATA version 16 (StataCorp LLC, College Station, TX, USA).

Sample size calculation was based on a previous

study,[8] which reported a mean VAS score of 4.5 (standard deviation, 1.9) for patients receiving local wound infiltration with bupivacaine plus epinephrine, and a mean VAS score of 3.2 (standard deviation, 1.8) for those receiving bupivacaine plus epinephrine and morphine plus ketorolac after spinal surgery. According to this, a sample size of 54 patients was needed to detect a difference of 2 (effect size, 0.4) with 90% power and alpha of 0.05.

RESULTS

Between January 2021 and April 2022, 48 patients, aged 7 to 15 years, who underwent elective tibial osteotomy were allocated into two groups. Six patients were excluded for not meeting the study's inclusion criteria. Thus, a total of 48 patients were enrolled (24 in the combination group, and 24 in the control group) in the study. None were excluded from their allocated group, and all patients completed the 48-hour assessment. There were no statistically significant differences in baseline patient characteristic between the groups in term of gender, age, BMI, side, duration of surgery, and length of hospital stay (Table 1). The majority of participants were male in both groups, with 54.2% in the control group and 62.5% in the combination group. The age range was 7 to 15 years in both groups, with mean ages of 10.7±3.1 years in the control group and 11.8±3.1 years in the combination group, respectively. The control group had a mean surgery duration of 68.4±35.8 minutes, compared to 78.9±50.6 in the combination group. The baseline characteristics were illustrated in Table 1.

Table 2 presents the postoperative VAS scores. Although not statistically significant, patients in the combination group tended to report higher mean pain levels compared to the control group at almost every time point from 4 to 48 hours post-operation, except at 8 hours (1.3 vs.1.2 for the control and combination groups, respectively). The maximum mean postoperative pain level in both groups, at four hours, was higher in combination group (2.1) compared to the control group (1.9). Pain levels decreased continuously after four hours. However, patients in the two groups experienced pain differently. The trends in mean VAS scores over time are shown in Fig 1.

In control group, patients reported experiencing intense pain after 24 hours of surgery, with a mean pain VAS score level of 1.3. In contrast, patients in the combination group experienced a continuous increase in pain starting from 16 hours, with the highest pain level recorded at 20 hours, reaching 1.7. Pain levels in the combination group slightly decreased after 28 hours and nearly disappeared by 36 hours post-surgery. In the control group, the results showed a progressive decline in pain and plateau with a mean pain level ranging from 0 to 1. Morphine consumption ranged from 0-1 mg/kg. There was no significant difference between the two groups in postoperative VAS scores at most time points, as shown in Table 2. The trends in VAS scores over time after surgery are illustrated in Fig 1.

TABLE 1. Demographic data.

	Combination Regimens (n=24)		Bupivacaine alone (n=24)		p-value
	Mean	±SD or percent	Mean	±SD or percent	
Gender (n, %)					0.77
Male	15	62.5	13	54.2	
Female	9	37.5	11	45.8	
Age (years)	11.8	3.1	10.7	3.1	0.25
BMI (kg/m^2)	23.8	7.7	22.4	8.2	0.47
Side (n, %)					>0.99
Right	14	58.3	13	54.2	
Left	10	41.7	11	45.8	
Duration of surgery (minutes)	78.9	50.6	68.4	35.8	0.84
Length of stay (day)	5.5	5.3	8.4	14.2	0.63

TABLE 2. Postoperative pain score.

	Combination Regimens (n=24)					Bupivacaine alone (n=24)					p-value
VAS at	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	
4 hours	2.1	2.9	0.0	0.0	4.8	1.9	2.9	0.0	0.0	3.8	0.66
8 hours	1.2	2.2	0.0	0.0	1.5	1.3	2.3	0.0	0.0	2.8	0.80
12 hours	1.1	2.2	0.0	0.0	1.5	0.4	1.2	0.0	0.0	0.0	0.24
16 hours	1.3	2.4	0.0	0.0	2.0	0.2	1.0	0.0	0.0	0.0	0.02
20 hours	1.7	2.3	0.0	0.0	3.0	0.9	2.1	0.0	0.0	0.0	0.10
24 hours	1.3	2.0	0.0	0.0	2.8	1.3	2.0	0.0	0.0	2.0	0.89
28 hours	1.1	1.8	0.0	0.0	2.0	0.9	2.0	0.0	0.0	0.8	0.54
32 hours	1.3	2.3	0.0	0.0	2.0	1.0	1.9	0.0	0.0	1.8	0.86
36 hours	1.2	2.5	0.0	0.0	0.8	0.4	1.3	0.0	0.0	0.0	0.12
40 hours	1.1	2.4	0.0	0.0	0.8	0.7	1.6	0.0	0.0	0.0	0.67
44 hours	1.0	1.9	0.0	0.0	1.8	0.4	1.2	0.0	0.0	0.0	0.15
48 hours	0.7	1.4	0.0	0.0	0.8	0.4	1.2	0.0	0.0	0.0	0.28

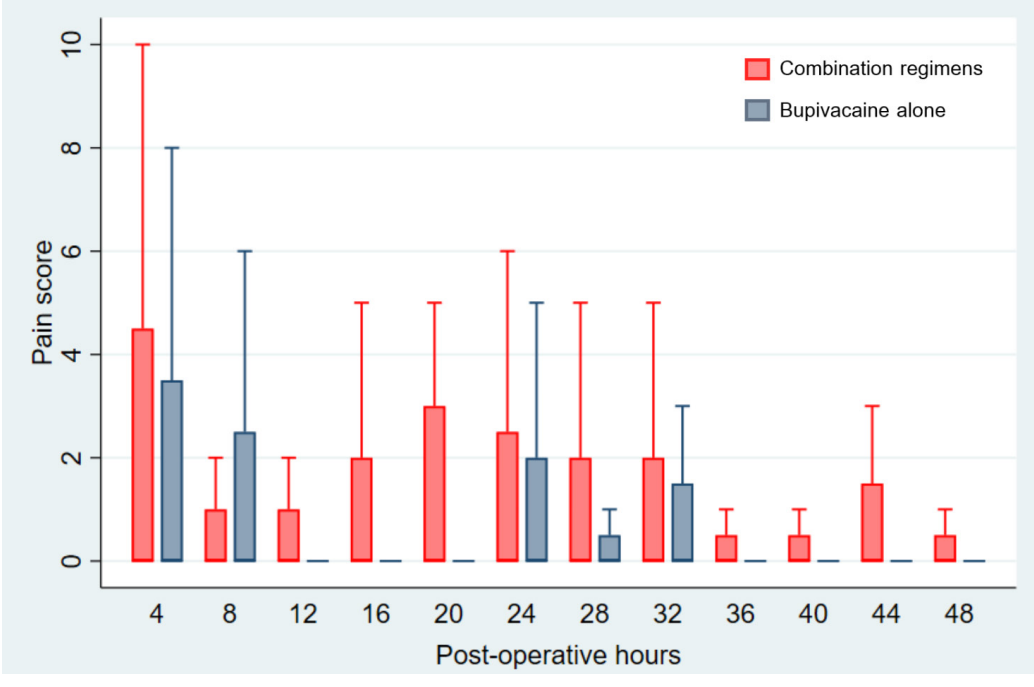

Fig 1. Postoperative pain score.

Opioid consumption after surgery is detailed in Table 3. The combination group had a higher mean morphine usage of 0.04±0.08 mg/kg compared to 0.03±0.04 in the control group at 4-8 hours postoperatively. Similarly, mean morphine consumption in the combination group was higher at 9-24 hours postoperatively (0.11±0.42 vs. 0.03±0.05). After 25 hours, the results aligned with the VAS pain score. Overall, the cumulative morphine dose was lower in the control group compared to the combination group, as shown in Fig 2.

TABLE 3. Postoperative morphine.

	Combination Regimens (n=24)					Bupivacaine alone (n=24)					p-value
Postop time at	Mean	SD	Median	Q1	Q3	Mean	SD	Median	Q1	Q3	
4 – 8 hours	0.04	0.08	0.00	0.00	0.06	0.03	0.04	0.00	0.00	0.06	0.90
9 – 24 hours	0.03	0.05	0.00	0.00	0.06	0.11	0.42	0.00	0.00	0.04	0.74
25 – 36 hours	0.10	0.41	0.00	0.00	0.04	0.01	0.02	0.00	0.00	0.00	0.60
37 – 48 hours	0.01	0.03	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.27

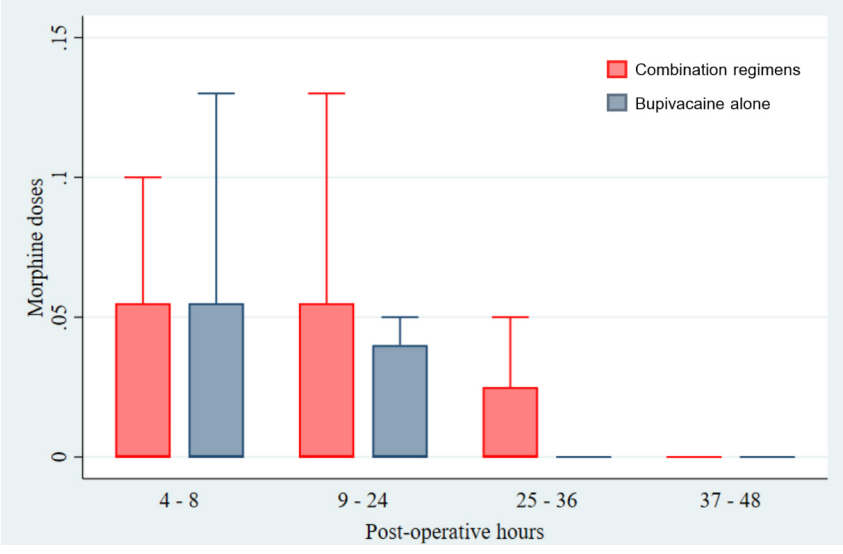

Fig 2. Postoperative morphine.

DISCUSSION

This clinical trial attempted to compare the anesthetic effects of wound infiltration using a combination of bupivacaine, ketorolac, and morphine, versus bupivacaine alone in children undergoing tibial osteotomy. The dosage of bupivacaine was based on European Society for Paediatric Anaesthesiology (ESPA) guidelines. Since there were no reported studies on the use of ketorolac or morphine for local infiltration in children, the dosage regimens for intravenous ketorolac and morphine were applied.[14] An ideal body weight was used to adjust drug dosing to mitigate concerns about adverse effects, especially in children.[15]

The mechanisms of action to reduce pain of the three drugs are different. Morphine exerts its effects by interacting with mu-opioid receptors located in both the central and peripheral nervous systems.[16] Bupivacaine, like other local anesthetics, works by preventing the initiation of action potentials in nerve cells, achieved by raising the threshold for electrical stimulation.[17] Ketorolac works by inhibiting cyclooxygenase (COX) enzymes, which play a key role in transforming arachidonic acid into prostaglandins, thromboxane, and prostacyclin. This action effectively alleviates pain and inflammation.[18]

There was no significant difference in postoperative VAS pain scores or morphine consumption between the two groups. Our findings indicated that bupivacaine alone resulted in lower pain scores compared to the combination group, though the difference was not statistically significant.

Local wound filtration was commonly used to optimize postoperative pain due to its simplicity, low cost, and low risk of side effects. Bupivacaine has a long history of use as a primary agent for local wound infiltration, acting by inhibiting sodium channels and NMDA receptors.[19] The 2018 guidance from the Pain Committee of ESPA emphasizes the use of bupivacaine for managing limb fractures in patients aged> 1 month.[17]

Based on different mechanisms for blocking nerve conduction, combining various infiltration drugs with

anesthetic agents has garnered interest for improving pain managements and reducing opioid consumption after surgery.[20,21] Clinical trials following lumbar discectomy have shown that the use of combination drug infiltration significantly reduces the need for postoperative analgesics.[22,23] Recent studies also indicate that patients receiving a combination of local drug infiltration required less IV-PCA compared to those in the control group.[24,25] However, *Singhatanadgige et al.* observed no significant difference in pain management between patients treated with a combination of bupivacaine and epinephine, with or without ketorolac and morphine.[8] Although many studies have demonstrated the efficacy of combination drug infiltration in adults, evidence supporting its effectiveness in pediatric orthopaedic patients remains limited.

Previous studies have shown that the onset of bupivacaine injection occurs within 10±5 minutes,[26] with a duration of action of up to 12 hours.[27] However, research involving pediatric patients after spinal surgery indicated that bupivacaine wound infiltration only reduces pain for the first 4 hours after surgery.[28] In our study, pain scores were first evaluated at four hours post-operation to ensure that all patients had been fully transferred from the recovery room to the ward. As shown in Fig 1, pain decreased after 4 hours post-operation in both groups. This reduction in pain may be attributed to the administration of oral paracetamol and intravenous ketorolac injection. The efficacy of NSAIDs in reducing pain after surgery in children was evaluated by *Raslan N et al.* In a randomized clinical trial study involving 66 pediatric patients aged 6-8 years who underwent tooth extraction, pain scores significantly decreased in patients who received preoperative ibuprofen compared to those who received a placebo, immediately after injection, after extraction, and 5 hours after extraction ($P<0.05$).[29]

In the present study, the combination analgesia group exhibited higher VAS scores compared to the control group. One plausible explanation for this observation is the lower concentration of local anesthetic agents resulting from the dilution in normal saline that occurs when they are combined with adjunct medications. Both study groups also experienced a decrease in pain during the first 20 hours postoperatively, followed by a rapid increase at 24 hours. The initial pain relief may be attributed to the effect of intravenous ketorolac, which was routinely administered every 8 hours for first 24 hours after surgery. The increase in pain scores at 24 hours could be due to the decrease in serum NSAID levels when switching from IV to oral medication. Few studies have reported on the efficacy of intravenous ketorolac in pediatric orthopaedic surgery. *CP Eberson et al.* conducted a study with 27 patients aged between 6 months and 18 years who underwent long-bone osteotomies or foot procedures. They compared ketorolac 0.5 mg/kg every 6 hours postoperatively versus placebo. Patients receiving ketorolac required significantly lower doses of morphine and had a shorter length of stay.[30] Similarly, intravenous ketorolac was associated with lower pain scores and reduced morphine consumption after spinal fusion at 24 and 48 hours postoperatively.[33] However, the conclusions could not be fully supported due to lack of a control group without kelotorac IV injection data.

The secondary objectives of the study were to compare opioid consumption and complications between the two groups. No statistically significant differences in opioid use was observed, which was consistent with the postoperative pain scores noted in primary outcomes. Additionally, complications such as nausea, vomiting, skin irritation, and hypotension were not detected in either group.

Most patients reported higher pain levels on the first day after surgery. This finding aligns with previous studies on postoperative pain in children aged ≤ 18 years undergoing various types of surgery. The results indicate that the type of operation was a significant factor influencing pain levels in patients aged ≥ 4 years. In the orthopedic surgery group, pain scores were highest on the first day after surgery, averaging approximately 2 points on the pain scale.[32] *Kart et al.* also observed increased pain and analgesic requirements following tibial osteotomy maximum on first day as well.[21]

No previous studies have documented the effects of local wound infiltration on post-osteotomy pain control in pediatric patients. Our findings suggest that neither ketorolac nor morphine, when added to bupivacaine, significantly reduced VAS scores or opioid use after tibial osteotomy. This is consistent with other surgical fields involving children. For instance, a recent study on postoperative pain management in pediatric patients (30 patients, aged 8-17, randomized into two groups) undergoing spinal deformity correction found no significant difference in opioid use between the control group and those receiving 0.25% bupivacaine wound infiltration group four hours post-operation ($p= 0.54$). Additionally, bleeding was more frequently observed in the bupivacaine group compared to the control group. The authors did not recommend using bupivacaine wound infiltration as a standard management protocol following spinal surgery in children.[25] However, no studies have yet examined the use of morphine or ketorolac for local wound infiltration in pediatric patients.

CONCLUSION

Multidrugs for local wound infiltration drug regimens involving bupivacaine, morphine, and ketorolac do not reduce postoperative VAS pain scores or opioid consumption following tibial osteotomy in children compared to bupivacaine alone. Future research should focus on conducting studies to explore alternative combination modalities for postoperative pain control following tibial osteotomy in pediatric patients. Given that surgical procedures involving bone procedure can result in significant pain, relying on local wound infiltration may be insufficient to adequately manage postoperative discomfort.

Limitations

There were several limitations to this study. Firstly, assessing pain levels in children can be particularly challenging due to their developmental stage and ability to communicate effectively. Secondly, our study showed only a modest decrease in pain scores, which may not be clinically relevant. Thirdly, since most pain scores recorded were below 5 on the VAS, the study may have been underpowered to detect statistical significance, especially when using a minimal clinically important difference (MCID) of 2.

Data Availability Statement

The data supporting this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

None

Registration Number of Clinical Trial

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design: PE; data collection: PM; analysis and interpretation of results: SC and PM; draft manuscript preparation and critical revision: PE. All authors reviewed the results and approved the final version of the manuscript.

Use of Artificial Intelligence

None

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