Oral Analgesics Utilization for Children With Musculoskeletal Injury (OUCH Trial): An RCT

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abstract

BACKGROUND: Musculoskeletal injuries (MSK-Is) are a common and painful condition among children that remains poorly treated in the emergency department (ED). We aimed to test the efficacy of a combination of an anti-inflammatory drug with an opioid for pain management of MSK-I in children presenting to the ED.

METHODS: In this randomized, double-blinded, placebo-controlled trial, we enrolled children between 6 and 17 years presenting to the ED with an MSK-I and a pain score >29 mm on the visual analog scale (VAS). Participants were randomly assigned to oral morphine (0.2 mg/kg) + ibuprofen (10 mg/kg) (morphine + ibuprofen) or morphine (0.2 mg/kg) + placebo of ibuprofen or ibuprofen (10 mg/kg) + placebo of morphine. Primary outcome was children with VAS pain score <30 mm at 60 minutes postmedication administration.

RESULTS: A total of 501 participants were enrolled and 456 were included in primary analyses (morphine + ibuprofen = 177; morphine = 188; ibuprofen = 91). Only 29.9% (morphine + ibuprofen), 29.3% (morphine), and 33.0% (ibuprofen) of participants achieved the primary outcome ($P = .81$). Mean VAS pain reduction at 60 minutes were −18.7 (95% confidence interval [CI]: −21.9 to −16.6) (morphine + ibuprofen), −17.0 (95% CI: −20.0 to −13.9) (morphine), −18.6 (95% CI: −22.9 to −14.2) (ibuprofen) ($P = .69$). Children in the morphine + ibuprofen group ($P < .001$) and in the morphine group ($P < .001$) experienced more side effects than those in the ibuprofen group. No serious adverse event was reported.

CONCLUSIONS: Combination of morphine with ibuprofen did not provide adequate pain relief for children with MSK-I in the ED. None of the study medication provided an optimal pain management because most of children did not reach a mild pain score (NCT02064894).

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WHAT'S KNOWN ON THIS SUBJECT: Pain related to musculoskeletal injury in children is poorly treated in the emergency department (ED). Oral ibuprofen is an analgesic that can be administered for pain treatment in the ED, but it does not provide optimal pain relief.

WHAT THIS STUDY ADDS: Neither a combination of morphine with ibuprofen, nor either drug alone, provided optimal analgesia for pain management of children presenting to the ED with a musculoskeletal injury. No serious adverse events were observed in children among all study groups.

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Musculoskeletal injuries (MSK-Is) are one of the most common cause of pain-related visits to the emergency department (ED) in children and typically generate moderate to severe levels of pain.[1] Pain management for MSK-Is varies widely in practice and remains suboptimal.[1–7] Previous research has revealed that only 35% of children presenting to Canadian pediatric EDs with a fracture or severe sprain were given an analgesic.[8] A systematic review conducted by our team highlighted that the undertreatment of children's pain may be associated, in part, with the fact that health care providers do not seem to have clear evidence to effectively manage pediatric pain related to this type of injury.[9] In addition, the fear of adverse events (AEs) may also explain reluctance of emergency physicians to prescribe an opioid to children.[10]

Researchers for recent studies suggest that nonsteroidal anti-inflammatory drugs (NSAIDs), alone or in combination with low- and midpotency oral opioids, are the most commonly used analgesics in the ED management of children's fracture pain.[7,9,11,12] Despite these findings, there is currently little evidence regarding their efficacy. A large trial led by Clark et al[13] found that ibuprofen (10 mg/kg) was significantly more effective than acetaminophen (15 mg/kg) or codeine (1 mg/kg) in decreasing pain intensity at 60 minutes postmedication administration. However, only 52% of children enrolled in the ibuprofen group achieved a pain score <30 mm on a visual analog scale (VAS) (0–100 mm). The authors of this seminal study and others suggest that although ibuprofen is currently the standard first-line therapy, using it alone might not adequately treat moderate to severe MSK-I pain.[9,11,13–16]

Morphine is a widely used, potent opioid for children with moderate to severe pain and has been studied for the management of different diseases, states, and injuries in the ED.[17–23] Early studies have revealed its safety[17,22,23] and efficacy[22,23] for pain management of MSK-I and other conditions in the ED.[17,20–23]

The combination of an opioid with an NSAID would theoretically offer better pain management by targeting different pain pathways simultaneously.[24–26] To date, no study has previously assessed the efficacy of a combination of morphine and ibuprofen for MSK-I in children. Our primary hypothesis was that the addition of morphine to ibuprofen would provide better pain management than either of the 2 drugs, alone, for the treatment of MSK-I pain in children presenting to the ED.

METHODS

Study Design

This study was a 3-arm, double-blinded, randomized, placebo-controlled trial. It was conducted in the ED of 3 pediatric hospitals who are members of the Pediatric Emergency Research Canada network: CHU Sainte-Justine (Montreal, Quebec), Stollery Children's Hospital (Edmonton, Alberta), and Children's Hospital of Eastern Ontario (Ottawa, Ontario). The study was approved by each institutional review board.

Participants and Recruitment

Children were eligible for this study at any time after their initial assessment by the triage nurse in the ED. They were eligible if they: (1) were aged 6 to 17 years, (2) presented to the ED with an MSK-I to either an upper or lower limb that was neither obviously deformed nor neurovascularly compromised, (3) had a self-reported pain score >29 mm on the VAS, and (4) could communicate in either French or English. Exclusion criteria were: (1) known allergy to morphine, ibuprofen, or artificial coloring; (2) suspected child abuse; (3) inability to self-report pain; (4) chronic pain requiring daily analgesics; (5) NSAIDs or opioid use within 3 hours before triage; (6) injury to >1 limb; (7) known hepatic or renal disease and/or dysfunction; (8) known bleeding disorder; (9) neurocognitive disability precluding assent and participation in the study; and (10) a known history of sleep apnea or loud snoring in the past 5 days.

Participants were recruited consecutively by a research nurse in the ED who was present for ~30 hours per week during the study period. Triage nurses notified the research nurse whenever a child presented with an MSK-I. After verifying that the child met all inclusion criteria, the research nurse approached the child and parents or legal guardian to obtain written informed consent and assent for enrollment in the study.

Study Arms

Immediately after enrollment and before examination by the treating physician, the research nurse administered the medication(s) to the participant according to 1 of the 3 study arms the child was randomly assigned to: (1) oral morphine (0.2 mg/kg, maximum 15 mg[27]) + oral ibuprofen (10 mg/kg, maximum 600 mg), or (2) oral morphine (0.2 mg/kg, maximum 15 mg) + oral placebo of ibuprofen, or (3) oral ibuprofen (10 mg/kg, maximum 600 mg) + oral placebo of morphine.

Randomization

The randomization sequence was generated by an independent biostatistician by use of a computer-generated random listing of the arms using a prespecified seed. Recruited participants were randomly assigned by following a 2:2:1 ratio with a stratified permuted block design to receive either of the

3 arms treatments. This unequal allocation ratio was used to increase study power for evaluation of the safety profile of the arms by using morphine. Randomization was stratified by center and by VAS score at baseline (30–69 vs ≥70 mm). Stratification by pain severity was done to evaluate if 1 of the 3 treatments demonstrated more efficacy in children presenting with moderate pain (30–69 mm) compared with severe pain (≥70 mm).

Blinding and Allocation Concealment

Allocation concealment was pharmacy-controlled with a sequentially numbered system. As such, only the research pharmacist at each site (not a team member) received the randomization list directly from the biostatistician and kept it concealed. The research pharmacist prepared 4 different solutions (morphine, ibuprofen, placebo of morphine, placebo of ibuprofen) presented in a concentration by milliliter per kilogram. The respective bottles of morphine and placebo of morphine solutions were identical in appearance (color), viscosity, and volume, each in separate, identical, unidentified bottles. The respective bottles of ibuprofen and placebo of ibuprofen were identical in appearance (color), viscosity, and volume, each in separate, identical, unidentified bottles. The pharmacist prepared 2 sets of kits in line with the 2 VAS strata (VAS 30–69 mm and VAS ≥70 mm). Each kit consisted of 2 bottles: the first bottle contained either a solution of morphine or a placebo of morphine, and the second bottle contained either a solution of ibuprofen or placebo of ibuprofen. The pharmacist placed the kits in a sequenced numbered order in a locked cupboard in the ED. After obtaining consent, the research nurse selected the next available numbered kit according to the participant's baseline pain severity strata. The research nurse then prepared the dosage required from each bottle according to the patient's weight. Participants and their parents, research nurses, and treating physicians were all blinded to the treatment received.

Rescue Analgesia

Enrolled participants were eligible to receive rescue analgesia at any time. If the treating physician wished to prescribe opioid analgesia and wanted to know what the child had received, the study blind could be broken for patient safety. To maintain blinding of the research nurse, participants, and participants' families, the research nurse provided a sealed envelope to the treating physician with the participant's study group allocation information. Only the treating physician and bedside nurse were, in such cases, aware of the allocation and selected further medication at their own discretion.

Study Outcomes and Measurements

Data were collected at recruitment after triage (time of recruitment [T-R]), at the time of study medication administration (T-0, baseline), and at 30 minutes (T-30), 60 minutes (T-60), 90 minutes (T-90), and 120 minutes (T-120) following study medication administration.

Our primary outcome was the proportion of participants in each group achieving pain intensity scores <30 mm at T-60. Pain was measured by using the VAS because it is the pain scale currently recommended for our study age group.[28–31] The choice of measuring the proportion of children with pain <30 mm as opposed to relative changes in VAS scores reflected our team's consideration for patients to achieve a mild level of pain to have reasonable functioning and satisfaction.[32] In addition, the T-60 primary efficacy outcome point also reflects the peak action of both oral morphine and ibuprofen.[33,34]

The secondary efficacy outcomes were: (1) the mean reduction in pain scores between groups from baseline to all study times and (2) the proportion of children administered rescue analgesia at T-60.

The safety outcomes were: (1) the proportion of children with serious adverse events (SAEs), and (2) the proportion of children with AEs. SAEs were defined as: clinical sedation (score >3 on the Ramsay Sedation Scale[35]), a respiratory rate under the standardized normal minimal value for age, or an oxygen saturation level <92% while breathing ambient (room) air, observed during the study period.

Sample Size

On the basis of previous studies,[9,13] we calculated the sample size by using Fleiss formulas 3.18 and 3.19,[36] according to the primary efficacy analysis. The assumption was that between 25% and 52% of children would achieve a pain intensity score <30 mm on the VAS at T-60. To be conservative, we set this proportion to 50%. We determined that an enrollment of 500 participants would provide at least 80% power to detect a 20% absolute difference in proportion with a 2-tailed test and an α level of 5%. For the pairwise comparison involving the groups using morphine (morphine + ibuprofen and morphine + placebo of ibuprofen), the absolute detectable difference was estimated at 14% (ie, 84% in the morphine + ibuprofen group vs 70% in the morphine + placebo of ibuprofen group). By using a 2:2:1 allocation scheme, children were respectively randomly assigned to the morphine + ibuprofen (200), morphine + placebo of ibuprofen (200), and ibuprofen + placebo of morphine (100) groups. The unbalanced 2:2:1 allocation allowed for greater power for pairwise

comparisons between the morphine + placebo and morphine + ibuprofen groups. We anticipated that the difference between those 2 arms would be less than the differences involving the ibuprofen + placebo of morphine group.

Statistical Analyses

We initially planned to conduct all analyses under the intention-to-treat principle. However, because of the loss to follow-up, the analyses were conducted per protocol. All analyses were performed by using SAS software, version 9.3 (SAS Institute, Cary, NC). We considered *P* value <.05 for statistical significance. Descriptive statistics were used for demographic and baseline characteristics.

Primary Efficacy Analyses

Proportion of participants with VAS pain scores <30 mm at T-60 was compared by using the Cochran-Mantel-Haenszel test with stratification by baseline VAS scores. To ensure an overall α level of 5%, a Bonferroni correction was applied to account for the 3 pairwise comparisons. Additional analyses compared reduction in mean pain scores from baseline to all study times and the proportion of participants who received rescue analgesia.

Subgroup Analyses

A priori planned subgroups analyses included comparison of the outcomes by age group (6–11 vs 12–17 years) and type of injury (fracture versus soft tissue injury) per study group.

Primary Safety Analyses

The Cochran-Mantel-Haenszel test was performed to compare the proportion of patients in each group experiencing AEs and SAEs. No Bonferroni correction was applied for analyses on safety outcomes because we were primarily concerned with false-negative results.

RESULTS

Study Population

Between July 2013 and June 2015, a total of 5127 pediatric patients presented to the study EDs with MSK-Is during the research nurses' coverage hours. Of these, 501 were enrolled and randomly assigned to receive morphine + ibuprofen (*n* = 201), morphine + placebo of ibuprofen (*n* = 201), or ibuprofen + placebo of morphine (*n* = 99) (Fig 1). Among them, 6 participants were excluded from the analysis because of withdrawn consent (*n* = 4) or having been randomly assigned twice (*n* = 2). Of the 495 who received the intervention, primary efficacy outcome at T-60 was available for 456 (92.1%) participants, and 241 (48.7%) completed the trial up to T-120.

Mean age of participants was 11.9 ± 2.7 years, with a majority being boys (55.3%). Participants reported a mean VAS pain score of 60.9 ± 16.2 mm at baseline. Approximately 60% of the injuries were soft tissue injuries (*n* = 277), and 38% (*n* = 175) were fractures. Confirmation of diagnosis was performed by a certified radiologist after the study period. The ankle (21.1%, *n* = 96), wrist (16.9%, *n* = 77), and knees (14.7%, *n* = 67) were the sites most commonly injured. Detailed results are presented in Table 1.

Primary Outcome and Efficacy Analyses

At T-60, 30.0% of the morphine + ibuprofen group, 29.0% of the morphine + placebo of ibuprofen group, and 33.0% of the ibuprofen + placebo of morphine group achieved a VAS pain score <30 mm, indicating mild pain (Table 2). There was no significant difference among the 3 groups (*P* = .81). Comparisons at T-60 between baseline VAS strata (30–69 mm; ≥70 mm), by each treatment group, showed no significant difference for both strata (*P* = .56; *P* = .41), respectively.

Secondary Outcomes

All groups showed a reduction in mean VAS pain scores from baseline at T-0, to T-60, T-90, and T-120, but it was only significant at T-120 (*P* = .02) (Table 3). Post hoc analysis revealed that the difference at T-120 was statistically significant between the morphine + placebo of ibuprofen group (−16.5; 95% confidence interval [CI]: −21.1 to −12.0) and the ibuprofen + placebo of morphine group (−27.1; 95% CI: −33.1 to −21.1). Finally, 2 participants (1.0%) in the morphine + ibuprofen group, 1 (0.5%) in the morphine + placebo of ibuprofen group, and 2 (2.0%) in the ibuprofen + placebo of morphine group required rescue analgesia at T-60.

Subgroup Analyses

No subgroup analyses were performed for age groups and type of injuries by treatment groups, considering that the analysis conducted on the primary outcome showed no statistically significant differences.

Safety Outcomes

None of the trial participants experienced any SAEs. Regarding the occurrence of AEs, a significant difference was observed between groups (*P* < .001). Post hoc analysis revealed that more children in the morphine + ibuprofen group (*P* < .001) and the morphine + placebo of ibuprofen group (*P* < .001) experienced AEs when compared with the ibuprofen + placebo of morphine group. Although fatigue and headaches were common to all groups (~2% of participants), nausea, abdominal pain, and drowsiness were reported only in the morphine + ibuprofen and morphine + placebo of ibuprofen groups, ranging from 2% to 6% of participants (Table 4).

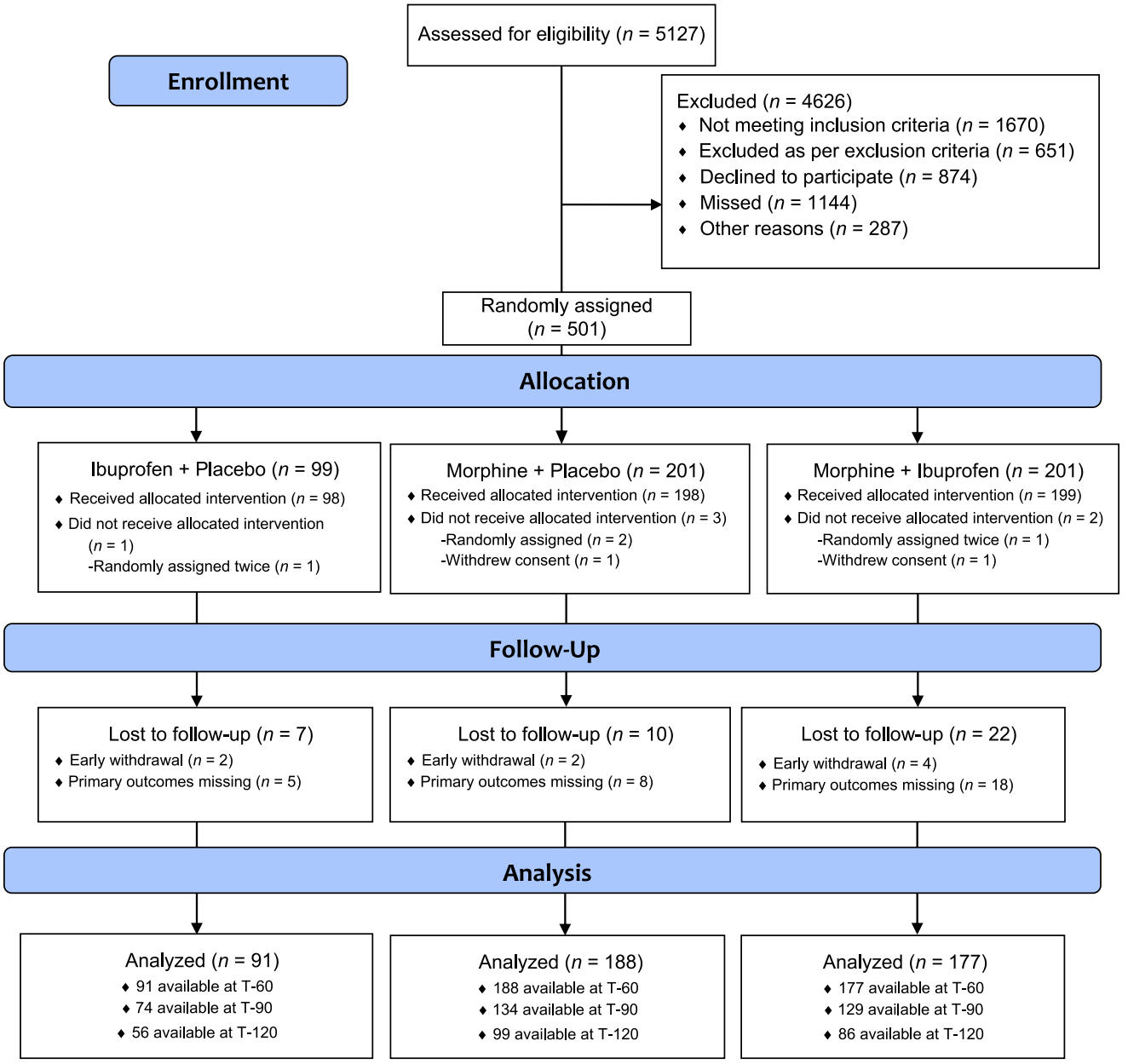

FIGURE 1
Consolidated Standards of Reporting Trials flowchart of subjects' enrollment and/or allocation and study proceedings.

DISCUSSION

In this study, we compared the efficacy of a combination of oral morphine and oral ibuprofen to both drugs, alone, for pain management of MSK-Is in children. Previous studies have examined the effect of NSAIDs (ibuprofen) alone or in combination with other opioids (codeine, oxycodone) and nonopioid analgesics (acetaminophen).[13,14,16,37–39] Of those, only 1 study[39] has compared ibuprofen to morphine but not a combination of both.

In the current trial, results revealed that the proportion of children achieving a VAS score <30 mm at T-60 was not statistically significant among all study groups. A possible explanation for these results might be related to the dosage of morphine used. Although our study dose of oral morphine (0.2 mg/kg) was within the recommended range for pediatric pain management (0.2–0.5 mg/kg), higher doses have been used in other clinical trials for pain management of MSK-Is in children (0.5 mg/kg).[23,39] Conflicting results have been reported for higher doses. Kelly et al[40] (in a trial of children with post-tonsillectomy pain) favored oral morphine (0.2–0.5 mg/kg) over ibuprofen (10 mg/kg), whereas the Poonai et al[39] trial of MSK-Is found no difference. However, this latter

trial measured pain intensity at 30 minutes after drug administration, which is 30 minutes earlier than the required time for peak effect of both drugs.[41] This might explain why no significant differences were observed between the morphine and ibuprofen groups.

TABLE 1 Participants Characteristics

Parameters	Trial Groups		
	Ibuprofen + Placebo (*n* = 91)	Morphine + Placebo (*n* = 188)	Morphine + Ibuprofen (*n* = 177)
Age			
Mean (SD), y	12.2 (2.6)	11.7 (2.7)	12.0 (2.7)
Median (range), y	12.0 (6.0, 17.0)	12.0 (6.0, 17.0)	12.0 (6.0, 17.0)
Distribution, *n* (%)			
6–11 y	39 (42.9)	85 (45.2)	74 (41.8)
12–17 y	52 (57.1)	103 (54.8)	103 (58.2)
Male sex *n* (%)	53 (58.2)	106 (56.4)	93 (52.5)
VAS[a] score at baseline, mm			
Overall: mean (SD)	60.9 (15.5)	60.8 (15.8)	61.0 (17.1)
Distribution: mean (SD)			
30–69 mm	64 (70.3)	128 (68.1)	121 (68.4)
≥70 mm	27 (29.7)	60 (31.9)	56 (31.6)
Injury type, *n* (%)			
Fracture	43 (47.3)	67 (35.6)	65 (36.7)
Soft tissue injury	48 (52.7)	117 (62.2)	112 (63.3)
Missing	0 (0.0)	4 (2.1)	0 (0.0)
Injury location, *n* (%)			
Ankle	21 (23.1)	38 (20.2)	37 (20.9)
Wrist	24 (26.4)	28 (14.9)	25 (14.1)
Knee	15 (16.5)	25 (13.3)	27 (15.3)
Foot	6 (6.6)	21 (11.2)	12 (6.8)
Single finger	3 (3.3)	14 (7.4)	18 (10.2)
Elbow	6 (6.6)	14 (7.4)	10 (5.6)
Forearm	6 (6.6)	11 (5.9)	12 (6.8)
Shoulder	2 (2.2)	5 (2.7)	8 (4.5)
Collarbone	5 (5.5)	2 (1.1)	4 (2.3)
Lower leg	1 (1.1)	5 (2.7)	5 (2.8)
Hand	1 (1.1)	4 (2.1)	6 (3.4)
Upper arm	0 (0.0)	7 (3.7)	1 (0.6)
Single toe	0 (0.0)	3 (1.6)	4 (2.3)
Multiple fingers	0 (0.0)	3 (1.6)	3 (1.7)
Single toe or multiples toes + foot	0 (0.0)	2 (1.1)	2 (1.1)
Hip	1 (1.1)	0 (0.0)	2 (1.1)
Single or multiples fingers + wrist	0 (0.0)	2 (1.1)	1 (0.6)
Thigh	0 (0.0)	2 (1.1)	0 (0.0)
Single toe or multiples toes + legs	0 (0.0)	1 (0.5)	0 (0.0)
Missing	0 (0.0)	1 (0.5)	0 (0.0)

[a] The VAS is a 100 mm line with 0 representing no pain and 100 representing the worst pain imaginable.

TABLE 2 Proportion of Participants Achieving a VAS Pain Score <30 mm

Study Times, min	Trial Groups (%, 95% CI)			*P*[a]
	Ibuprofen + Placebo (*n* = 91)	Morphine + Placebo (*n* = 188)	Morphine + Ibuprofen (*n* = 177)	
30	19.8 (12.9 to 29.1)	21.0 (15.7 to 27.4)	15.9 (11.2 to 22.0)	.45
60	33.0 (24.2 to 43.1)	29.3 (23.2 to 36.1)	29.9 (23.7 to 37.1)	.81
90	39.2 (28.9 to 50.6)	29.9 (22.8 to 38.1)	37.2 (29.4 to 45.8)	.30
120	42.9 (30.8 to 55.9)	28.3 (20.4 to 37.8)	32.6 (23.6 to 43.0)	.18

The VAS is a 100 mm line with 0 representing no pain and 100 representing the worst pain imaginable.
[a] $P < .05$ is considered statistically significant.

Furthermore, although our results did not reveal superiority of morphine over ibuprofen, it is not possible to conclude that both analgesics have equivalent analgesic properties considering that our study was not a noninferiority or equivalence trial but rather a superiority trial.

At T-60, only 30% of children in each study group had achieved the targeted mild pain score. This result challenges the decision to select a 30 mm VAS cutoff as the primary outcome. A significant decrease in mean pain scores could provide a more accurate outcome on the efficacy of treatment, because a comfortable level of pain may not be necessarily equivalent to a level of mild pain or no pain at all. Yet, the difference in mean pain scores reduction from baseline (T-0) was similar in all 3 groups at all study times except for T-120 in which there was a statistically significant difference between both the morphine + placebo of ibuprofen and the ibuprofen + placebo of morphine groups, in favor of ibuprofen. However, this result should be interpreted with caution given the high attrition rate (>50%) between the time of recruitment and T-120. The notable loss of participants may be explained by the fact that patients were discharged after clinical care was completed and did not stay in the ED long enough to complete the study protocol, although the research nurse requested that they remain for the full study period (2 hours). Participants still available for the study at T-120 might have been more likely to remain in the ED if their pain was inadequately relieved.

Regarding safety outcomes, no SAEs were reported during the study period. This result contributes to the important discussion on the safety of

TABLE 3 Mean VAS Pain Score Reduction From Baseline (T-0)

Study Times, min	Trial Groups (95% CI)			*P*[a]
	Ibuprofen + Placebo (*n* = 91)	Morphine + Placebo (*n* = 188)	Morphine + Ibuprofen (*n* = 177)	
30	−12.9 (−16.5 to −9.2)	−12.0 (−14.5 to −9.4)	−12.8 (−15.4 to −10.2)	.87
60	−18.6 (−22.9 to −14.2)	−17.0 (−20.0 to −13.9)	−18.7 (−21.9 to −16.6)	.69
90	−23.1 (−28.3 to −18.0)	−18.1 (−21.9 to −14.3)	−23.6 (−27.5 to −19.7)	.10
120	−27.1 (−33.1 to −21.1)	−16.5 (−21.1 to −12.0)	−20.9 (−25.7 to −16.0)	.02[b]

The VAS is a 100 mm line with 0 representing no pain and 100 representing the worst pain imaginable.

[a] $P < .05$ is considered statistically significant.

[b] Pairwise comparisons for change in VAS from baseline, at T-120: ibuprofen + placebo versus morphine + placebo: $P = .02$, ibuprofen + placebo versus morphine + ibuprofen: $P = .34$, and morphine + placebo versus morphine + ibuprofen: $P = .60$.

TABLE 4 Proportion of Children Experiencing AEs and SAEs

AEs and SAEs	Trial Group			*P*
	Ibuprofen + Placebo (*n* = 91)	Morphine + Placebo (*n* = 188)	Morphine + Ibuprofen (*n* = 177)	
AEs; *n* (%)	6 (6.6)	39 (20.7)	38 (21.5)	<.001
Nausea	0 (0.0)	11 (5.9)	7 (4.0)	—
Abdominal pain	0 (0.0)	7 (3.7)	7 (4.0)	—
Drowsiness	0 (0.0)	5 (2.7)	4 (2.3)	—
Fatigue	2 (2.2)	4 (2.1)	4 (2.3)	—
Headache	2 (2.2)	4 (2.1)	4 (2.3)	—
SAEs; *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	—

—, not applicable.

prescribing opioids to children presenting with moderate to severe acute pain. On the other hand, children receiving ibuprofen alone experienced significantly fewer AEs than children receiving morphine + ibuprofen or morphine + placebo of ibuprofen. This result does not, however, affect the safety of opioid administration.

Finally, to address delay in time to effective analgesia and also undertreatment, future researchers should consider the combination of rapid-acting and long-acting analgesics. For instance, intranasal fentanyl has recently gained popularity for the time-sensitive treatment of pain related to MSK-Is.[42–46] It has an onset of action of 10 minutes[47,48] and few AEs related to its administration in children.[45] Because its effect lasts ∼30 to 40 minutes,[47,48] this fast-acting opioid could be combined to an NSAID or another opioid for sustained analgesia to children with an MSK-I to provide proper pain management.

Limitations

The high attrition rate at T-120 presents a limit to the interpretation of the data. Nevertheless, considering that the primary outcome was set at T-60 and that the attrition rate at this study time was <8%, it does not present a threat to the internal validity of the study.[49] It did, however, influence the way the analysis was conducted. As such, we initially planned to analyze the results according to the intention-to-treat principle, but we had to defer to per protocol analysis because of the important loss to follow-up.

CONCLUSIONS

Debate regarding ideal pain management for MSK-Is in children continues. Our multisite, 500-patient, randomized controlled trial suggests that the combination of 2 medications, oral morphine and oral ibuprofen, did not provide better pain relief than either drug alone. Overall, no child participating in this trial experienced an SAE. Future researchers should explore combination therapies that could provide effective, timely, and sustained analgesia for pain management of MSK-Is in children during their ED stay.

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ABBREVIATIONS

AE: adverse event
CI: confidence interval
ED: emergency department
MSK-I: musculoskeletal injuries
NSAID: nonsteroidal anti-inflammatory drug
SAE: serious adverse event
T-60: 60 minutes
T-90: 90 minutes
T-120: 120 minutes
VAS: visual analog scale
T-0: baseline

analysis, and critically reviewed and revised the manuscript; Dr Neto supervised data collection at 1 of the 3 sites and critically reviewed the manuscript; Mrs Auclair supervised data collection and cleansing from the 3 sites, and critically reviewed and revised the manuscript; Ms Ballard and Mrs Khadra participated in the literature review and data interpretation, drafted the initial manuscript, and critically reviewed the manuscript; Drs Villeneuve, Parent, McGrath, and Drendel contributed as content experts, critically reviewed the manuscript and revised the final manuscript; Dr Leclair was in charge of all pharmacological issues related to this study including preparation of placebo solutions and communications with research pharmacies at all sites and reviewed the initial draft; Dr Gouin reviewed and approved the protocol, supervised data collection at 1 of the 3 sites, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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