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Clinical Studies

Can oral caffeine decrease postoperative opioid consumption following posterior spinal fusion in adolescent idiopathic scoliosis? A randomized placebo-controlled trial

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ABSTRACT

Background: Current studies have examined the efficacy of opioid-sparing analgesics primarily in adult surgical populations, while fewer guide pediatric postoperative pain treatment. Caffeine exerts most of its biological effects by binding to adenosine receptors, which are important for modifying pain and inflammation. Caffeine's ability to modulate pain following posterior spinal fusion (PSF) for adolescent idiopathic scoliosis (AIS) has not been previously assessed.

Methods: The hospital investigational drug study (IDS) pharmacy provided either a treatment dose or placebo dose of caffeine to be given to the patient and was also in charge of randomization for the study.

Results: There were 24 patients in the caffeine group (mean 14.3±1.5 years, 91.7% female) and 27 in the control group (mean 14.8±1.4 years, 88.9% female). Postoperative opioid usage was lower in the caffeine cohort for POD 1 (18.6 MME vs. 21.6 MME; p=.19), but this difference was not statistically significant. Opioid usage decreased in the caffeine study group for POD 1 (caffeine: 0.35 MME/kg vs. 0.4 MME/kg; p=.19) and mean daily total opioid usage over the hospital stay (caffeine: 0.32 MME/kg vs. 0.37 MME/kg; p=1), but these differences were not statistically significant. The caffeine study group demonstrated a mean reduction in total opioid consumption over the hospital stay of 5 MME.

Conclusions: Oral caffeine use resulted in an average reduction of 5 MME opioid consumption, equivalent to 5 mg of hydrocodone. While this trial was underpowered to definitively assess the outcome, oral caffeine shows potential as an adjunct medication for opioid stewardship in AIS patients. This trial's reported mean total oral opioid consumption range of 0.83 to 0.92 MME/kg is lower than the amounts typically observed in clinical trials. This finding could indicate a successful strategy in reducing opioid use, which aligns with current medical efforts for opioid stewardship.

Background

Caffeine, the most highly consumed psychoactive drug on earth, belongs to the methylxanthine class of central nervous system stimulants. It is found in various products, from coffee and tea to yerba mate and pharmaceutical compounds for headaches. Caffeine historically has been used to increase focus and alertness but has also found its way into mainstream medical practices and is commonly employed in combination with over-the-counter (OTC) medications [1,5,13,21,23]. Caffeine also has documented benefits when paired with aerobic activity and resistance training [7].

Caffeine is an adenosine antagonist and attaches to all types of adenosine receptors [1,7]. Higher dose caffeine (≥100 mg) produces inherent antinociception from blocking A2ARs and A2BRs and inhibiting

FDA device/drug status: Not applicable.

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cyclooxygenase activity [15,16]. Adenosine regulates various functions in the central and peripheral nervous systems, and its receptors provide antinociception. Caffeine's structure mimics adenosine, and while competing with A2a receptors, may reduce perception of pain [8]. Blood caffeine levels peak 30–120 min after oral ingestion, with a typical half-life of 3–6 h [1]. Derry et al. [3] reported that the addition of caffeine (≥ 100 mg) to a standard dose of common OTC analgesics provided a small but clinically significant benefit to the participants who reported an improved level of pain relief. Data have been collected in children and adolescents using dose–response and placebo-controlled research methods. Outcomes such as cardiovascular function, mood, and cognitive performance have been evaluated at caffeine doses ranging from 50 to 300 mg. The data suggest that caffeine at these doses is not acutely harmful to children and adolescents [13].

Caffeine may also facilitate muscle recovery after exercise. Hurley et al. [7] reported that athletes who ingested caffeine showed a marked decrease in their perception of muscle soreness in the days following maximal resistance exercise. Caffeine also improves muscle performance by increasing the susceptibility of calcium release channels in the sarcoplasmic reticulum [7]. Orthopaedic surgery mimics resistance training in that it also results in progressive muscle soreness. Therefore, ingesting caffeine after spinal surgery could similarly decrease the patient's perception of muscle soreness. In addition to physiological impacts, caffeine affects both hormones and endorphins, moderating the patient's perception of muscle fatigue [7]. Zhu et al. [10] demonstrated that caffeine improves "alertness, contentment, motivation to work, talkativeness, and energy and decreases muscle twitches" in adolescents. We believe that these additional caffeine effects could aid our goal of improved opioid stewardship in the postoperative period for adolescent idiopathic scoliosis (AIS) patients.

Objectives

The opioid epidemic has devastating effects on individuals, families, and children. Clinicians in surgical specialties have unintentionally been a primary cause of this national tragedy. Thus, we are tasked with researching alternative nonopioid pain medications that can provide therapeutic alternatives to the use of opioids. Current studies have examined the efficacy of opioid-sparing analgesics in adult surgical populations, while fewer studies are available to guide postoperative pain treatment in pediatric patients [10]. Little or no data exist from which to draw conclusions about the perioperative use of caffeine in pediatric surgical patients. We hypothesized that caffeine could decrease postoperative pain and opioid consumption in pediatric patients with AIS undergoing surgical management.

Methods

Trial design

This clinical trial titled *Oral Caffeine Use for Pain Management in AIS Patients After Spinal Fusion* was registered on ClinicalTrials.gov, Protocol ID STUDY00000775, ClinicalTrials.gov ID NCT04950660. The full trial protocol can be accessed at https://clinicaltrials.gov/study/NCT04950660. The investigational hospital's Institutional Review Board approved this prospective, randomized, placebo-controlled, and double-blinded clinical trial, which was funded internally through the Department of Orthopaedics.

Participants

All eligible AIS patients undergoing posterior spinal fusion (PSF) by 2 attending spine surgeons from December 2019 through December 2023 were approached, with an enrollment goal of 68 total subjects. Due to the extended time involved, and evolution of multimodal pain medications, the study was concluded with 51 completed subjects. Inclusion criteria were patients aged 12 through 17 years who presented to CMH for surgical treatment of AIS with either of the 2 treating surgeons. Additional inclusion criteria were the ability to swallow pills, English as the primary language, mental capacity sufficient to understand the purpose of the clinical trial, surgery performed via a posterior approach, patient assent, and at least 1 biological parent or guardian consenting for the patient to participate. Exclusion criteria included a history of obesity (defined by a body mass index at or above the 95th percentile), weight below 40 kg, any spine diagnosis other than AIS, revision spine surgery, anterior or combined approach, admission to the pediatric intensive care unit, postoperative oxycodone use, specific medication allergies (to ibuprofen, caffeine, codeine, and/or diazepam), history of renal disease, history of a coagulation disorder, history of cardiac dysrhythmia or open heart surgery, history of chronic pain syndrome or complex regional pain syndrome, current use of oral central nervous system stimulant (e.g., methylphenidate), age greater than 18 years, children or parents unable to consent, individuals with cognitive delays, pregnant females, and prisoners. Caffeine is reported to be toxic when consumed in high doses combined with other oral stimulants [2]. Therefore, it was decided to exclude patients who had been previously prescribed psychostimulants. The clinical trial was discussed, and informed consent obtained, during the preoperative visit.

Interventions

The interventional drug (caffeine) used in this clinical trial was prescribed as approved by the United States Food and Drug Administration for the treatment of postoperative pain in children. We extensively reviewed research focused on safe caffeine consumption in pediatrics and followed published guidelines for the administration of caffeine as an adjuvant to standard oral pain medications after surgery. This literature review showed that caffeine administered at the current doses in this clinical trial would not be harmful to children or adolescents. Data have been collected in children and adolescents using dose–response and placebo-controlled research methods regarding caffeine use. Outcomes, such as cardiovascular function, mood, and cognitive performance, have all been measured at caffeine doses ranging from 50 to 300 mg [3,4,13]. High caffeine intakes, defined as >5 mg/kg of body weight per day, correlated with risk of anxiety and withdrawal symptoms. Lower doses did not demonstrate these effects and had positive results with improved cognitive function, antidepressant action, and sports performance [6–8]. The goal caffeine consumption for children and adolescents should be less than 2.5 mg/kg of body weight per day [1].

The hospital investigational drug study (IDS) pharmacy provided either a treatment dose or placebo dose of caffeine to be given to the patient and was also in charge of randomization for the study. The experimental group received a 100 mg dose of caffeine (one half of a 200 mg capsule) twice daily. The control group received a placebo dose that was compounded to look identical to the caffeine capsule, also taken twice daily. Both the active and placebo doses were given at the time of transition off the patient-controlled analgesia (PCA) at 0900 on postoperative day (POD) 1.

Randomization

The clinical trial subjects, clinicians, and researchers were all blinded to the group assignments. The IDS pharmacy used an internet randomization generator to create the code. The code used numbers 1-4 to create groups, and odd numbers were assigned to the experimental/caffeine group. Subjects were randomized the day prior to dosing. If a subject was randomized but did not become a study participant (i.e., did not receive a dose of medication), the IDS pharmacy did not reuse the randomization code; the next line on the randomization table was used. The doses were concealed in teal, opaque capsules. Empty capsules were

Table 1
Analgesia pathway for caffeine study

Preoperative analgesia
gabapentin 10 mg/kg up to 800 mg PO (given at least 30 min prior to OR, but ideally 45–60 min), rounded to the nearest 100 mg
if indicated, midazolam 0.5 mg/kg up to 20 mg PO or 0.1 mg/kg up to 4 mg IV
Intraoperative analgesia
remifentanil or sufentanil gtt
ketamine gtt 2.5–10 mcg/kg/min
acetaminophen 12.5 mg/kg
dexamethasone 0.1–0.25 mg/kg up to 8 mg prior to incision
intrathecal (IT) preservative-free morphine 5–8 mcg/kg (ideal body weight)
when IT morphine contra-indicated, then methadone 0.1–0.2 mg/kg up to 10 mg IV (unless methadone contra-indicated)
long-acting narcotic (morphine or hydromorphone) prior to wake-up, titrated to effect
ketorolac 0.5 mg/kg (up to 15 mg) IV prior to wake-up
Postoperative analgesia (POD 0)
hydromorphone (4 mcg/kg with 8 min lock-out) or morphine (10–20 mcg/kg with 8 min lock-out) PCA (patient controlled analgesia)
gabapentin 5 mg/kg PO (rounded to the nearest 100 mg) TID
acetaminophen 12.5 mg/kg IV (up to 1000 mg) and ketorolac 0.5 mg/kg IV (up to 15 mg) alternating q 3 h
clonidine patch 0.1 or 0.2 mg/24 h (0.1 mg patch for up to 75 kg, 0.2 mg patch for greater than 75 kg) - to be started in Recovery Room
Diazepam 0.05–0.1 mg/kg IV q 4–6 h PRN muscle spasms
Transition to PO analgesics/1st dose of caffeine at 0900 on POD 1-discharge
PO analgesics:
IDS caffeine 100 mg po BID
Hydrocodone/Acetaminophen (2 doses ordered)
Dosed 0.15 mg/kg (rounded down) to the nearest pill size (5 mg or max of 7.5 mg) for moderate pain: pain score of 0–5
Dosed 0.2 mg/kg (rounded down) to the nearest pill size (7.5 mg or max of 10 mg) for severe pain: pain score 6–10
Valium
Dosed 0.05 mg/kg rounded to the nearest whole number (Max of 5 mg)
Ibuprofen
10 mg/kg rounded down to the nearest pill size scheduled q6hrs
Gabapentin
5mg/kg (same as anesthesia dose) TID ×3 d total post-op
Clonidine patch
0.1 mg patch for up to 75 kg
0.2 mg patch for greater than 75 kg

used for placebo doses. Capsules were sent to the inpatient floor in 24-hour batches. The IDS pharmacy staff did not enter the randomization assignment into REDCap until after the patient was discharged and chart recordings were finalized.

Postoperative pain management protocol

The standard postoperative spinal fusion medications for patients with AIS at the clinical trial's initiation became the control pain pathway for the clinical trial with the addition of the placebo versus active caffeine dosages. To reduce bias, the Anesthesia Pain Service standardized their intraoperative and postoperative analgesia. During surgery, intrathecal preservative-free morphine was given after spine exposure. After surgery, a PCA was then used until POD 1. The medication in the PCA was standardized to hydromorphone on demand only. An oral dose of gabapentin was used preoperatively and was continued 3 times daily until POD 3. In the recovery room, a clonidine patch was placed and continued until discharge. Scheduled intravenous ketorolac and acetaminophen was used until transition off the PCA on POD 1. Patients were routinely transitioned off the PCA to oral pain medications the morning of POD 1 (defined as 0900–2359). IDS caffeine dosed at 100 mg twice daily (at 0900 and 1700) was ordered and provided as either a treatment or placebo dose based on their randomization. The drug was cut to fit into empty capsules in a dark color to mask the contents by the IDS pharmacist. The placebo capsules were empty.

Postoperative oral transition medications were also standardized (Table 1). The POD 1 transition opioid was hydrocodone/acetaminophen offered at 2 dose ranges (lower and higher). The lower dose was 0.15 mg/kg (rounded down) to the nearest pill size (5 mg or max of 7.5 mg) given for moderate pain (visual analog scale [VAS] score of 0–5). A higher dose measured at 0.2 mg/kg (rounded down) to the nearest pill size (7.5 mg or max of 10 mg) for severe pain was ordered for severe pain (VAS score of 6–10).

Data collection

Data from the electronic medical record consisted of patient demographic variables as well as surgical variables (duration of operative time, estimate of intraoperative blood loss, and spinal segments fused). The primary outcome variable was postoperative oral opioid consumption, with secondary outcomes including postoperative pain scores, number of requests for diazepam, average heart rate, average systolic blood pressure, and length of hospital stay (LOS). Opioid consumption was standardized to milligram of morphine equivalents (MME). To control variability of MME, based on patient weight, a point system was derived and was measured daily until discharge. The lower dose of opioid counted as one point, and the higher dose was counted as 2 points. Total MME/kg/day was also calculated and recorded daily. Patients were on scheduled ibuprofen (~10 mg/kg) from transition off PCA until discharge. All patients had diazepam (equal to or less than 0.05 mg/kg) ordered as needed for muscle spasms. Standardization of postoperative analgesia also included oral gabapentin (5 mg/kg) 3 times daily continued through POD 3. An outline of the anesthesia pain standardization pathway and postoperative pain medication pathway for this clinical trial are detailed in Table 1. Pain scores were obtained per nursing standard using the VAS. The primary outcomes were the number of demands (total points) for oral opioids from transition off PCA until discharge and total MME/kg/day.

Early study evaluation revealed multiple study participants being disqualified because the research team was missing details on inclusion and exclusion criteria. Subsequently, a member of the research team was assigned solely to review each patient candidate's chart to ensure study compatibility before approaching patients for the study. Clinician error in following the research protocol was also noted; therefore, the caffeine study participant label was added to the operating room (OR) time out, and an email was sent to OR scheduling, anesthesia staff, and inpatient floor charge nurses within 2 days of the scheduled surgery. On the day of surgery, a standard study email outlining the nursing pain manage-

Table 2
Demographic, clinical, and surgical characteristics of the caffeine and control groups

Demographics	n	Caffeine mean (sd)	n	Control mean (sd)	p-value	95% CI
Female, n (%)	24	22(91.7)	27	24 (88.9)	1.00	
Race, n (%)	24		26		.24	
White		20 (83.3)		19 (73.1)		
Black		0 (0)		3 (11.5)		
Hispanic		1 (4.2)		3 (11.5)		
Other		3 (12.5)		1 (3.9)		
Age	24	14.25 (1.5)	27	14.81 (1.4)	.16	−0.23 to 1.36
Weight	24	53.80 (8.2)	27	54.72 (7.1)	.67	−3.38 to 5.21
Any complications	24	0 (0)	26	0 (0)		
Operative time (min)	24	230.92 (49.6)	27	246.15 (43.4)	.25	−10.93 to 41.40
Number of segments fused	24	9.92 (2.1)	27	10.52 (1.9)	.28	−0.51 to 1.71

Patient data were segmented into subgroups to enable a detailed analysis. These demographic subgroups were the following defined metrics: sex, race, age, complications, duration of operative time, weight, and spinal segments fused.

Table 3
Summary of primary outcomes variables, subdivided by study group

	Caffeine (mean) N=24	Control (mean) N=27	*p*-value
Length of stay (days±SD)	2.53±0.6	2.47±0.5	.68
VAS pain (±SD)			
POD1	3.2±1.6	3.27±1.6	.54
POD2	3.38±1.7	3.5±1.5	.74
POD3	3.8±1.2	3.8±1.2	.92
Mean daily VAS (±SD)	3.33±1.65	3.51±1.48	.69
Total opioid usage (MME)			
POD1	18.6	21.6	.19
POD2	20.3	22.5	.48
POD3	13.75	13.9	.89
Total opioid usage (MME) for hospital stay	45.0	50.6	.38
Total MME/kg for hospital Stay	0.83	0.92	.40

SD, standard deviation; MME, morphine milliequivalent; VAS, visual analog pain score.

ment protocol was sent out to all nursing staff involved with caring for the patient in an attempt to avoid breaches in protocol.

Statistical methods and sample size

A retrospective review with analogous criteria was conducted of the 2 senior surgeons' postsurgical patients who were managed from February 2018 through January 2019. The data collected from this review determined a sample size of 34 in each group, yielding 80% power to detect a difference in group means of 3. This calculation assumed a common standard deviation of 4.3 and was based on a 2-group t-test with a significance level of 0.05. Because of the protracted study time and change in pain management practice to the benefit of the patients, we concluded this clinical trial at 51 patients (CONSORT Flow Diagram).

A biostatistician performed statistical analysis on this trial. Descriptive statistics were generated, including 95% confidence intervals (CI). The caffeine/experimental and control groups were compared using independent samples t-tests for continuous variables and Fisher's Exact tests for categorical variables. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC), with a significance level set at 0.05.

Results

There were 24 patients in the caffeine group (mean 14.3±1.5 years, 91.7% female) and 27 in the control group (mean 14.8±1.4 years, 88.9% female). Patient demographic variables are shown in Table 2. There were no differences in patient demographic variables between groups. The mean number of levels fused was similar between groups (caffeine: 9.9 vs. 10.5; p=.28) with comparable operative times (caffeine: 231 min vs. 246 min; p=.25). The total cohort had an average hospital LOS of 2.5 days. There were no documented complications, adverse events, or adverse drug reactions related to caffeine usage in this study. Only 1 patient developed a complication following surgery, a superficial wound dehiscence that was successfully treated without surgical intervention. There were no unplanned reoperations in either study group.

Comparison of primary outcome measures

The mean LOS was comparable between study groups with discharge after 2.53 surgical days (N=24) for caffeine patients and 2.47 surgical days (N=27) for the control group (Table 3). Mean daily VAS pain scores were statistically similar between study groups as well as the mean daily VAS score, with slightly lower pain scores in the caffeine cohort. Postoperative mean total oral opioid usage (measured in MME) was lower in the caffeine cohort for POD 1, but there were no significant differences between study groups (caffeine 18.6 vs. control 21.6, p=.19). After standardizing opioid usage for patient weight (MME/kg), there was decreased mean oral opioid usage in the caffeine study group for POD 1 (caffeine 0.35 vs. control 0.40, p=.19) and mean daily total oral opioid usage over the hospital stay (caffeine 0.32 vs. control 0.37, p=.1), but these differences were not statistically significant (Fig. 1). The mean total oral MME/kg for the hospital stay was 0.83 for the caffeine group and 0.92 in the control group, p=.40. Using the Mann-Whitney test, median oral MME/kg for the hospital stay was 0.74 in the caffeine group and 0.90 in the control group (difference 0.16). In assessing the mean total oral MME usage of the hospital stay, the caffeine cohort had 5 MME less total opioid consumption (caffeine 45.0 vs. control 50.6, p=.38, Table 3).

Secondary outcome variables

Caffeine usage was not associated with an elevation in heart rate or blood pressure, but there was a decrease in mean heart rate for POD 2

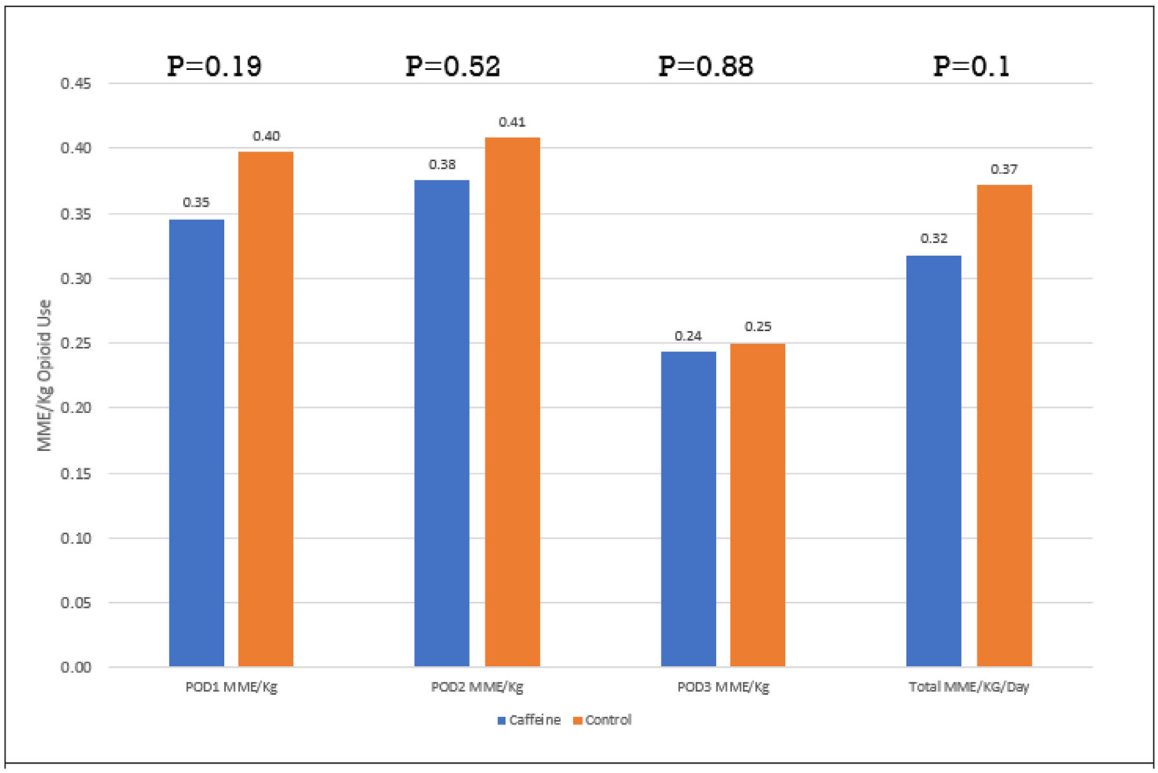


Fig. 1. Graphic summary of narcotic usage, measured in morphine milliequivalents/kilogram (mme/kg), subdivided by study group over various in-hospital time-points.
*MME, morphine milligram equivalents. Mean MME/kg in each group for postoperative days 1, 2, and 3. The last column is the total MME/KG/Day for each group. The caffeine group had 5 MME less opioid use, the equivalent of 5 mg of hydrocodone.

Table 4
Summary of mean blood pressure and heart rate between study groups in the acute postoperative period

	POD 1	POD2	POD3	Mean for Hospital Stay
Heart rate (bpm±SD)				
Caffeine	83.0 (14.6)	77.5 (10.4)	76.0(8.7)	78.8 (10.3)
Control	85.1 (12.8)	84.6 (13.9)	79.3 (13.8)	83.8 (12.4)
p-value	.59	**.04**	.48	.12
Systolic blood pressure (mmHg±SD)				
Caffeine	98.2 (7.6)	97.2 (6.2)	101.7 (11.6)	98.3 (6.5)
Control	103.1 (8.7)	98.8 (13.9)	101.3 (5.7)	101.4 (6.6)
p-value	.04	.44	.92	.09

*=legend for abbreviations; POD, postoperative day; bpm, beats per minute; SD, standard deviation.
Bold value demonstrating the decrease in mean heart rate for POD 2 as mentioned in above text.

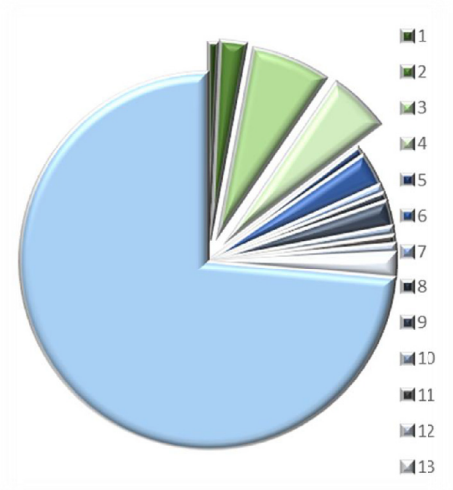
(caffeine:77.5±10.4 vs. control 84.6±13.9; p=.04) (Table 4). Additionally, there were no differences in the mean number of diazepam requests between study groups (caffeine: 1.15±0.7 vs. control:1.13±0.7; p=.9)

Discussion

The 2017 National Survey of Drug Use and Health estimates the cost related to opioid use disorder and fatal overdose to be $1.02 trillion [9], including the costs of healthcare, lost productivity, reduced quality of life, and criminal justice participation. Further, the study reported that 2.1 million people aged 12 years and older have an opioid use disorder, with a staggering 47,600 fatal opioid overdoses [9]. As such, clinicians who prescribe opioids must continuously focus on adjuvant medications that can provide therapeutic alternatives to the use of opioids. While many adult studies have examined the efficacy of opioid-sparing analgesics, fewer multimodal pain studies are available to guide postoperative pain treatment in children [10].

The impetus of this clinical trial was based on clinical observation. Caffeine was ordered postoperatively for patients who had a cerebral spinal fluid leak during spine surgery or a suspected leak after surgery. Comparable to the results found in the Temple et al. [12] questionnaire, we observed patients who were prescribed caffeine to be more alert, verbose, and content when compared to other postsurgical AIS patients. A review of literature demonstrated the role of caffeine as an adjuvant pain therapy [11–13]. In the current study, although we did not find a statistically significant difference in opioid consumption, the caffeine group demonstrated a mean 5 MME decrease in total opioid consumption in comparison to the control group, a reduction equivalent to 5 mg of hydrocodone. Furthermore, the caffeine group had a lower heart rate on POD 2 that was statistically significant. Perhaps, this finding reflected better pain control after the effects of intrathecal duramorph had waned.

Caffeine is a legal, noncontrolled central nervous system stimulant that is safe for most healthy individuals when used in moderation. Caffeine has been extensively documented to prevent apnea in vulnerable premature infants and improve their neurodevelopmental outcome, re-



1. Surgeon unable to administer IT Duramorph (n=1)
2. Protocol breach by Anesthesia (n=2)
3. Did not meet inclusion/exclusion criteria (n=7)
4. Protocol breach by Nursing (n=3)
5. PICU post op (n=1)
6. Declined participating (n=3)
7. Positive suicide screening (n=1)
8. Parent request to remove from study (n=1)
9. Uncontrolled pain, switch to Oxycodone (n=2)
10. Abnormal clotting labs, risk with IT meds (n=1)
11. Hypotension, removal of clonidine patch (n=1)
12. Patient self-removed clonidine patch (n=1)
13. Human research suspended due to COVID (n=1)

Nonadherence to establish protocols and guidelines resulted in the disqualification of 13 patients, accounting for 17% of the participants. Furthermore, 12 additional patients (representing 16% of the total) were excluded due to various other factors. Consequently, this led to a significant exclusion of 25 patients from the study.

Fig. 2. Disqualification details.
Nonadherence to establish protocols and guidelines resulted in the disqualification of 13 patients, accounting for 17% of the participants. Furthermore, 12 additional patients (representing 16% of the total) were xcluded due to various other factors. Consequently, this led to a significant exclusion of 25 patients from the study.

sulting in a lower incidence of cerebral palsy and cognitive delay, suggesting a neuroprotectant quality [14]. Caffeine is also a popular stimulant used by athletes to boost their performance that improves perceived muscle pain, effort, and performance after maximal resistance exercise. Mechanisms to explain this increase in performance include increased lipid oxidation, decreased muscle glycogen consumption, and release of cortisol and beta endorphins, which may affect the perception of fatigue [7]. Caffeine also affects adenosine receptors. These receptors are part of the nociception pathway and affect the subjective pain experience [15,16]. These combined research variables validated our drug trial's hypothesis that caffeine may reduce opioid consumption and pain scores post pediatric spinal surgery.

Grgic et al. assessed the effects of caffeine on muscle strength and power. This placebo-controlled, double-blinded cross-over study supported the hypothesis that caffeine ingestion both decreased the rate of perceived exertion and enhanced lower body strength [8]. Increased muscle activity increases adenosine concentrations. Caffeine affects the activity of central nervous system by blocking adenosine receptors as an antagonist of adenosine, resulting in decreased levels of soreness and reduced feelings of pain and fatigue [1,7,15]. Spinal surgery causes profound acute muscle injury and pain that should correlate with patient pain scores. Caffeine combined with OTC adjunct pain medications such as paracetamol and ibuprofen is safe and effective for treatment of acute pain [3,4,17]. A 2012 Cochrane review concluded that ≥ 100 mg of caffeine, adjunct to standard OTC analgesics, provided a minor increase in pain relief. This review pooled double-blinded study data on a cumulative 4262 participants, comparing a single dose of oral analgesic with caffeine with the same dose of the oral analgesic alone [3]. Another

randomized placebo-controlled trial with 20 participants demonstrated a reduction in pain after 4 mg/kg caffeine was administered [18]. Our clinical trial used a standardized 100 mg of caffeine given twice daily. This dosage resulted in a slightly lower pain score average than the experimental group (3.3) vs. the control group (3.5) on the VAS. One study looking at total joint arthroplasty and VAS scores emphasized that statistically significant changes in VAS scores do not necessarily imply clinically important changes when evaluating interventions. Instead, VAS scores correlated with the trend in a patient's subjective pain rating [19]. Pain scores for both groups in our study demonstrated an adequate pain protocol with an overall average VAS score of 3.4.

In comparison to recent research, our trial total median MME/kg oral opioid consumption was 0.74 in the caffeine group and 0.90 in the control group, with an actual difference of 0.16. These data compare favorably with previous reported opioid consumption [20], [21]. Fletcher et al. [21] reported a total median MME/kg consumption of 0.91 in patients treated with a standard enhanced recovery after surgery (ERAS) pathway and 24 h of dexamethasone following PSF for AIS in comparison to 1.29 MME/kg in patients treated with only an ERAS pathway. Benes et al. [20] reported daily mean MME/kg consumptions for AIS patients following PSF (POD 1: 0.63, POD 2: 0.74, POD 3: 0.40). Anderson et al. [22] also graphed their mean MME/kg results per postoperative day on AIS patients with documented ranges from greater than 0.5 to 1.0. Our trial demonstrated lower mean oral MME/kg consumptions in both groups when stratified by day (POD 1: 0.35–0.40, POD 2: 0.38–0.40, POD 3: 0.32–0.37). The observation of consistent MME/kg consumption across studies highlights a potential benchmark for postoperative pain management in AIS. While the trial in question did not yield statistically significant results, the potential for reduced MME consumption is clinically relevant. This clinical relevance is particularly important considering the opioid crisis and the need to minimize opioid prescriptions while managing pain effectively.

Acute caffeine administration increases alertness, contentment, motivation to work, verbosity, and overall energy [13]. Our trial did not document caffeine's effect on mood, although clinical observation during the 4-year trial supports caffeine's effects as a stimulant and mood elevator, which should benefit the patient. Caffeine typically raises blood pressure slightly and can either slow down or speed up the heart rate depending on the amount consumed [13]. This trial demonstrated that caffeine administration did not increase heart rate or blood pressure. Conversely, lower heart rates were noted on POD 2.

This complex multidisciplinary, pediatric surgical care clinical trial had a number of limitations. To reduce bias, every clinician caring for a child needed to abide by the strict structure of the intraoperative and postoperative pain algorithms and charting guidelines. Seventy-six children were assessed for eligibility and 61 children were approached and randomized. Failure to comply with study protocols and guidelines from research staff, orthopaedic staff, and nursing staff led to 13 patients (17%) being disqualified from the study (Fig. 2). An additional 12 patients (16%) were excluded for other reasons, for a total of 25 patients being disqualified. The results of these exclusions are that the current study was under-powered to identify significant differences. Cohen's d effect size was also measured and estimated a small to moderate reduction in weight-based opioid usage (Cohen's d=0.42). Pain medication dosing and delivery were inherently inconsistent given their dependence on patient activity, nurse/patient load, and the frequency with which the nurse recorded pain scores. The variability in how often nurses assessed, documented, and treated pain scores may have affected the overall MME average. Time of discharge was also incongruous and often delayed by the availability of physical therapy and patient transportation needs. Extension in LOS unsurprisingly equates to a higher total MME consumed, thus producing bias. The inaugural patient enrolled in this study was surgically treated in January 2020. In March of 2020, all institutional active human research studies were halted related to the COVID-19 pandemic, and the operating rooms were closed to all elective cases. These closures delayed enrollment and caused a significant backlog of high-risk surgical spine cases. Once the OR reopened, capacity for elective surgery remained limited, with priority given to cases of higher medical necessity. The volume of AIS surgical cases was restricted, which impacted study enrollment. Surgeon turnover further compounded the surgical load of complex patients on the remaining surgeons, decreasing study enrollment. In December of 2023, new innovations in global pain management for postsurgical AIS had been determined superior to the study standards, and it was therefore decided to complete the trial prior to goal enrollment, which caused this trial to be underpowered. Non–English-speaking participants were excluded, which limited health equity and diversity.

Conclusion

Opioid usage entails significant side effects and morbidity that warrant pharmacodynamic trials with opioid-sparing analgesics in the pediatric population. Opioid stewardship is a vital component in postoperative pain management following PSF for AIS. In this prospective, placebo-controlled randomized trial, oral caffeine use was found to produce a mean reduction in total opioid consumption of 5 MME, the equivalent of 5 mg of hydrocodone. Although this trial was underpowered to adequately assess the primary outcome measure, oral caffeine may be a promising adjunct medication for opioid stewardship in AIS patients. The trial's findings on reduced oral opioid MME/kg consumption are indeed promising, reflecting a positive trend in opioid stewardship when compared to similar clinical trials. These results align with the global efforts to optimize opioid use and support ongoing development of national benchmarks. Our study clearly demonstrates the practical challenges a research team faces when attempting to do a clinical trial in surgical patients, particularly in a pediatric setting.

In the realm of evidence-based medicine, continuous evaluation and comparison of treatment methodologies are crucial for maintaining the highest standards of patient care. Hospitals that actively engage in clinical trials, even when the hypothesis may not be groundbreaking, contribute significantly to collective medical knowledge. This process not only helps in minimizing bias but also ensures that the care provided aligns with and sets national benchmarks. Such trials are instrumental in validating the effectiveness of treatment plans and fostering a culture of transparency and accountability in healthcare practices. By comparing outcomes with peer institutions, hospitals can identify areas for improvement, adopt best practices, and ultimately enhance the quality of care for patients nationwide. Further multimodal opioid-sparing drug trials to investigate both the clinical benefit and efficacy of nonopioid analgesia in pediatric populations are warranted.

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Declaration of competing interest

One or more of the authors declare financial or professional relationships on ICMJE-NASSJ disclosure forms." Please include a request on the AQF for the author to approve.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.xnsj.2025.100582.

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Further Reading

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