2024

Can Oral Caffeine Decrease Postoperative Opioid Consumption following Posterior Spinal Fusion in Adolescent Idiopathic Scoliosis? A Randomized Placebo-Controlled Trial

NCT04950660

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Trial Design

This clinical trial titled "*Can Oral Caffeine Decrease Postoperative Opioid Consumption following Posterior Spinal Fusion in Adolescent Idiopathic Scoliosis? A Randomized Placebo-Controlled Trial"* 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 Institutional Review Board (IRB) approved this prospective, randomized, placebo-controlled, and double-blinded clinical trial.

Participants

All eligible adolescent idiopathic scoliosis patients undergoing posterior spinal fusion by two attending spine surgeons from December 2019-December 2023 were approached, with an enrollment goal of 68 total subjects. Due to the extended time involved, the study was concluded with 51 completed subjects. Inclusion criteria were patients aged 12 through 17 years of age who presented for surgical treatment of AIS with either of the two treating surgeons. Additional inclusion criteria were the ability to swallow pills (blinded clinical trial using a blank pill capsule), 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 of one of their biological parents or guardian(s) consenting for the patient to participate Exclusion criteria was a history of obesity (defined by a BMI 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 PICU (Pediatric Intensive Care Unit), postoperative oxycodone use, specific medication allergies (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 when combined with other oral stimulants[1] Therefore, it was decided to exclude patients 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 FDA (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 in the administration of caffeine as an adjuvant to standard oral pain medications after surgery. This literature review showed that caffeine being administered at the current doses in this clinical trial would not be harmful to children or adolescents. Data has 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 [2-4]. 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 [5-7]. The goal caffeine consumption for children and adolescents should be less than 2.5 mg/kg of body weight per day [8].

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 (1/2 of a 200mg tablet) 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 POD 1.

Randomization

The clinical trial subjects, clinician, and researcher were all blinded to the group assignments. IDS pharmacy utilized 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), IDS pharmacy did not reuse the randomization code; the next line on the randomization table was utilized. The doses were concealed in teal, opaque capsules. Empty capsules were used for placebo doses. Capsules were sent to the inpatient floor in 24-hour batches. 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 intra-operative and post-operative analgesia. During surgery, intrathecal (IT) preservative-free morphine was given after spine exposure. After surgery, a PCA was then utilized until post-operative day (POD) 1. The medication in the PCA was standardized to hydromorphone on demand only. An oral dose of gabapentin was used pre-operatively and was continued three times daily until POD 3. In the recovery room, a clonidine patch was placed and continued until discharge. Intravenous (IV) ketorolac and acetaminophen scheduled 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.

Post-operative 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 0.15mg/kg (rounded down) to the nearest pill size (5mg or max of 7.5mg) given for moderate pain (VAS score of 0-5). A higher dose measured at 0.2mg/kg (rounded down) to the nearest pill size (7.5mg or max of 10mg) for severe pain was ordered for severe pain (VAS score of 6-10).

Data Collection

Data from the EMR (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 two points. Total MME/kg/day was also calculated and recorded daily. Patients were on scheduled ibuprofen (~10mg/kg) from transition off PCA until discharge. All patients had diazepam (equal to or less than 0.05mg/kg) ordered as needed for muscle spasms. Standardization of post-operative analgesia also included oral gabapentin (5mg/kg) TID 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 Visual Analog Scale (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.

Table 1: Analgesia Pathway for Caffeine Study

Pre-operative 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

Intra-operative 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

Post-operative 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 hrs
- clonidine patch 0.1 or 0.2 mg/24 hrs (0.1mg patch for up to 75kg, 0.2mg patch for greater than 75kg) - to be started in Recovery Room
- diazepam 0.05-0.1 mg/kg IV q 4-6 hrs PRN muscle spasms

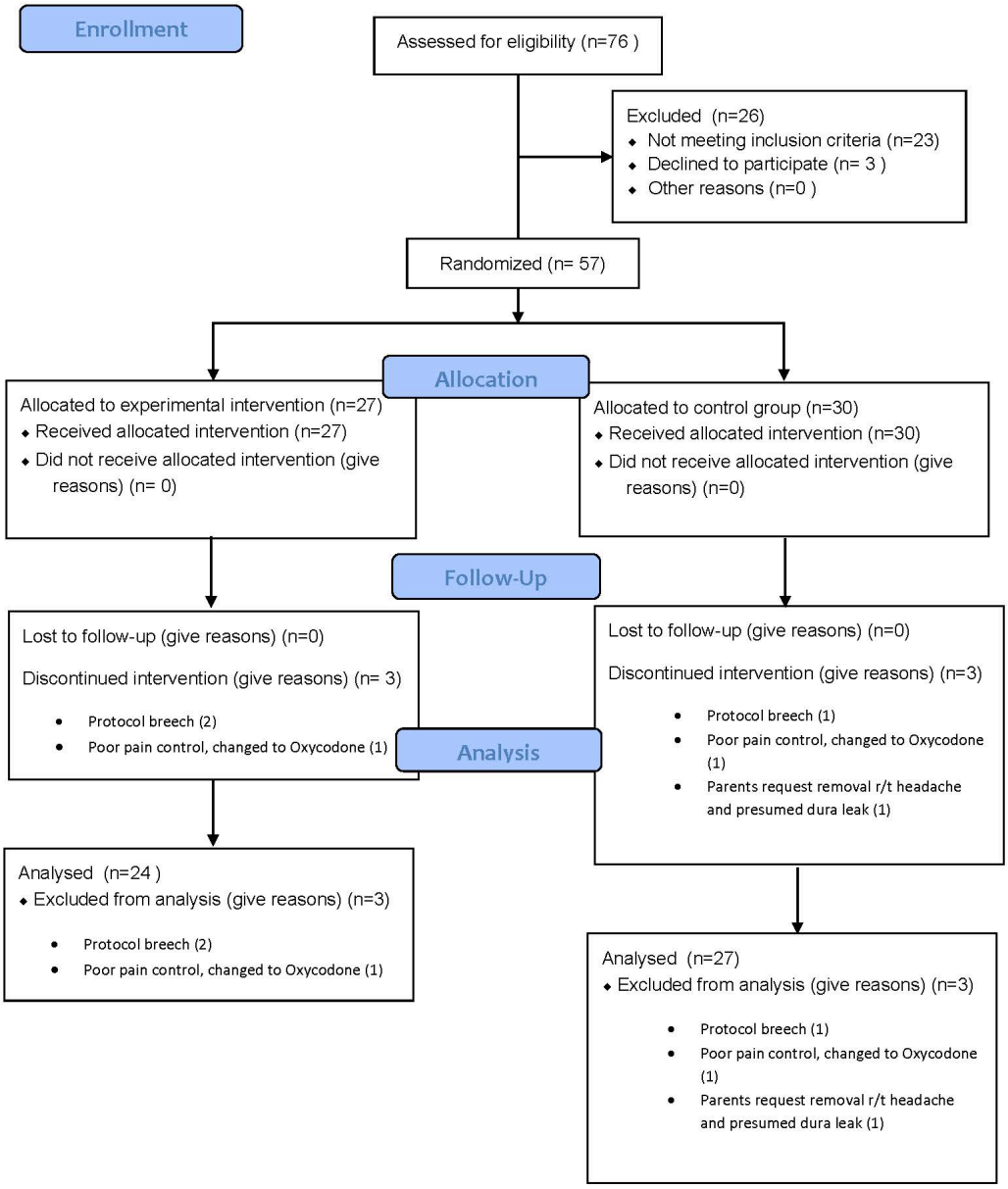
Transition to PO Analgesics/1st Dose of Caffeine at 0900 on POD 1-Discharge

PO Analgesics:

- IDS Caffeine 100mg po BID
- Hydrocodone/Acetaminophen (2 doses ordered)
  - Dosed 0.15mg/kg (rounded down) to the nearest pill size (5mg or max of 7.5mg) for moderate pain: pain score of 0-5
  - Dosed 0.2mg/kg (rounded down) to the nearest pill size (7.5mg or max of 10mg) for severe pain: pain score 6-10
- Valium
  - Dosed 0.05mg/kg rounded to the nearest whole number (Max of 5mg)
- Ibuprofen
  - 10mg/kg rounded down to the nearest pill size scheduled q6hrs
- Gabapentin
  - 5mg/kg (same as anesthesia dose) TID x3 days total post-op
- Clonidine patch
  - 0.1mg patch for up to 75kg
  - 0.2mg patch for greater than 75kg

Early study evaluation revealed multiple study participants being disqualified related to the research team 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 being approached 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 before the scheduled surgery. On the day of surgery, a standard study email outlining the nursing pain management protocol was sent out to all nursing staff involved with caring for the patient in attempts to avoid breeches in protocol.

CONSORT 2010 Flow Diagram



Statistical Methods and Sample Size

A review of post-surgical patients of the 2 senior surgeons that were managed from February 2018-January 2019 was conducted. Similar inclusion/exclusion criteria recorded daily opioid demand via the point system and whether caffeine had been prescribed was analyzed. This data determined a sample size of 34 in each group, yielding 80% power to detect a difference in group means of 3. This assumed a common standard deviation of 4.3 and was based on a two-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 v 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 were similar between groups (caffeine: 9.9 vs 10.5; P=0.28) with comparable operative times (caffeine: 231 minutes vs 246 minutes; P=0.25). 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 one 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.

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		0.24	
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)	0.16	-0.23 - 1.36
Weight	24	53.80 (8.2)	27	54.72 (7.1)	0.67	-3.38 - 5.21
Any Complications	24	0 (0)	26	0 (0)		
Operative Time (minutes)	24	230.92 (49.6)	27	246.15 (43.4)	0.25	-10.93 - 41.40
Number of Segments Fused	24	9.92 (2.1)	27	10.52 (1.9)	0.28	-0.51 - 1.71

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

Comparison of Primary Outcome Measures

The mean length of stay was comparable between study groups with 50% (N=12) of caffeine patients and 55.6% (N=15) being discharged home on postoperative day (POD) 2 (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

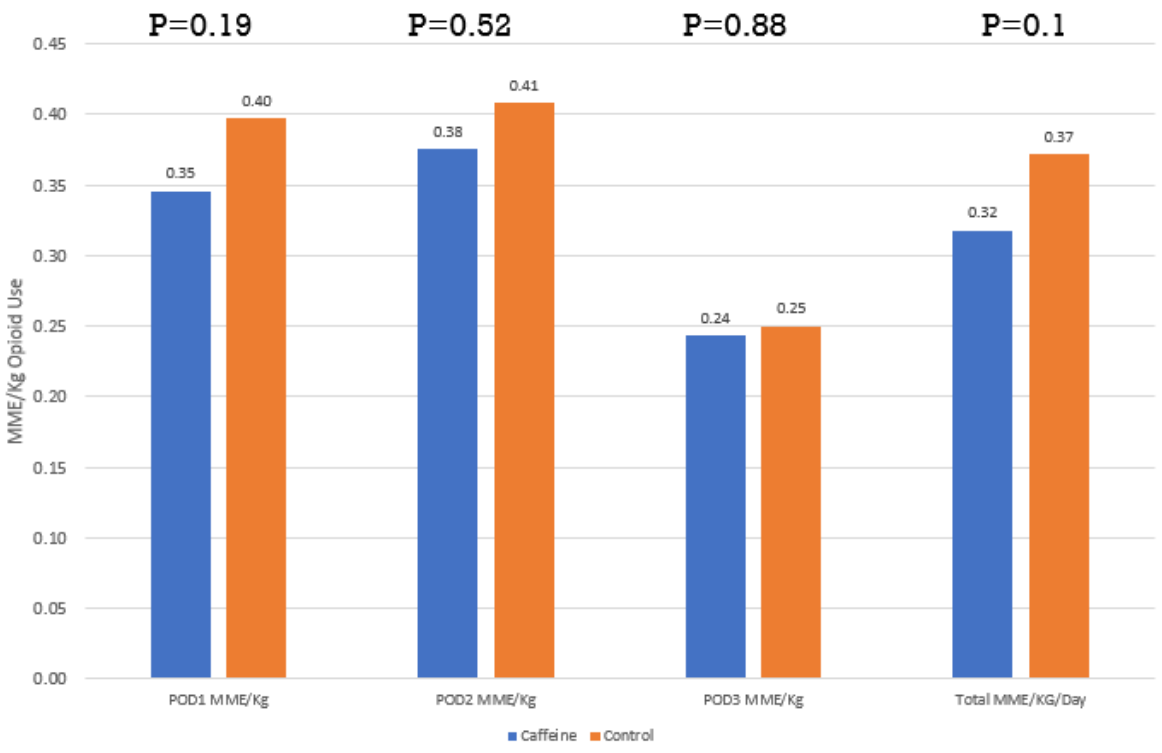
MME) had lower usage in the caffeine cohort for POD1 but there were no significant differences between study groups (caffeine 18.6 vs control 21.6, *P* = 0.19). After standardizing opioid usage for patient weight (MME/kg), there was decreased mean oral opioid usage in the caffeine study group for POD1 (caffeine 0.35 vs control 0.40, *P* = 0.19) and mean daily total oral opioid usage over the hospital stay (caffeine 0.32 vs control 0.37, *P* = 0.1), but these differences were not statistically significant (Figure 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*=0.40. Utilizing 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* = 0.38, Table 3).

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	0.68
***VAS Pain (*±SD)**			
POD1	3.2±1.6	3.27±1.6	0.54
POD2	3.38±1.7	3.5±1.5	0.74
POD3	3.8±1.2	3.8±1.2	0.92
***Mean Daily VAS (*±SD)**	3.33±1.65	3.51±1.48	0.69
Total Opioid Usage (MME)			
POD1	18.6	21.6	0.19
POD2	20.3	22.5	0.48
POD3	13.75	13.9	0.89
Total Opioid Usage (MME) for Hospital Stay	45.0	50.6	0.38
Total MME/kg for Hospital Stay	0.83	0.92	0.40

- SD- standard deviation; MME=morphine milliequivalent; VAS=visual analog pain score

Figure 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.

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 POD2 (caffeine:77.5±10.4 vs control 84.6±13.9; *P*=0.04) (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*=0.9)

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	0.59	**0.04**	0.48	0.12

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	**0.04**	0.44	0.92	0.09
* POD=Postoperative day; bpm=beats per minute; SD=standard deviation				