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A Randomized Controlled Trial Comparing IV to Oral Acetaminophen for Postoperative Recovery After Ambulatory Spine Surgery

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Introduction

Lumbar spine surgery is associated with moderate to high levels of pain and early postoperative pain is associated with prolonged length of stay.1 Multimodal analgesia including acetaminophen has been recommended and endorsed by a consensus panel.2 Acetaminophen is most commonly given perioperatively in either oral or intravenous (IV) form but prospective studies in spine surgery are lacking. Some authors have reported clinical benefit from IV acetaminophen in spine surgery.3 Although IV acetaminophen became generic in 2020, a large cost difference remains (a range of $10.85-28.42 per dose for IV versus $0.03-0.07 for oral as of 12/4/2023) and the benefit of IV acetaminophen in spine surgery remains uncertain. We performed a randomized controlled trial comparing IV to oral acetaminophen in ambulatory lumbar spine patients and hypothesized that IV acetaminophen would reduce pain-related outcomes and improve quality of recovery.

Materials and Methods

Institutional review board approval was obtained and the study was registered on clinicaltrials.gov (NCT04574778) prior to patient enrollment on 10/5/2020. Written informed consent was obtained from all patients. From 3/2021 – 10/2023, adult patients undergoing ambulatory lumbar spine surgery (microdiscectomy or single-level decompression) were randomized 1:1 to receive either 1000 mg of oral acetaminophen preoperatively or oral placebo preoperative with 1000 mg IV acetaminophen intra-operatively 30 minutes prior to skin closure. An IV placebo was not administered because of difficulty obtaining suitably shaped vials needed for blinding. As a result, the intraoperative anesthesia team was not blinded. However, all investigators, patients, post-operative nurses, and data collection personnel were blinded. Exclusion criteria included weight < 50 kg, pregnancy, revision surgery, contraindication to acetaminophen, chronic pain other than back pain, and taking > 20 mg of oxycodone daily or the equivalent for a week during the past month. Data collected included preoperative questionnaire responses, intraoperative opioids, surgery duration, postoperative opioids, PACU arrival and discharge times, post-operative pain ratings, post-discharge opioids used, and QoR-15 responses at 24 hours post-operatively. The primary outcome was 24-hour post-operative opioid usage in IV morphine equivalents, beginning with arrival to the post-anesthesia care unit (PACU) and ending with the 24-hour phone call or visit on post-operative day (POD) 1. A standard opioid conversion chart was used. Secondary outcomes included 30-minute, 60-minute, and discharge numerical rating scale (NRS)

pain ratings (0-10), quality of recovery (QoR)-15 survey4 scores at 24 hours, PACU length of stay, and correlation analysis between pain catastrophizing scale (PCS) scores and pain outcomes.

Standard Study Procedures

Patients completed a QoR-15 survey and a PCS prior to surgery. Pre-operatively, the study oral drug (acetaminophen or placebo) was given no earlier than 30 minutes prior to arrival in the operating room. General anesthesia was induced and maintained at the discretion of the intra-operative team with parameters to administer fentanyl 25 mcg for increases in heart rate or blood pressure of 25% or greater. Anesthesia maintenance was provided with sevoflurane or a propofol infusion at the discretion of the team. The intra-operative protocol included dexamethasone 8 mg and ketorolac 15 mg for post-operative pain per local standards. For IV acetaminophen patients, the drug was given 30 minutes prior to skin closure. Surgical wound infiltration with bupivacaine prior to end of surgery was encouraged but not mandated. Standard PACU discharge criteria including an Aldrete score of ≥ 9 were used for discharge to home or, if a patient required overnight admission, the medical floor. Patients were called at 24 hours post-operatively and the QoR-15 responses and number of opioid pills taken after discharge were recorded.

Statistical Analyses and Sample Size

Based on unpublished institutional data the mean daily IV morphine equivalents used by spine patients who received PO acetaminophen equaled 29 ± 9 mg. Based on data from Hansen et al.,3 we assumed that a 7-mg IV morphine equivalent reduction with IV acetaminophen would be clinically relevant representing approximately a 25% reduction in opioid consumption. A sample size of 36 patients per group would be able to detect a statistically significant difference (effect size 0.389) with a power of 0.90 and 5% alpha level. An additional 10 subjects were added for dropouts.

Continuous data were analyzed using student t test or the Mann-Whitney U test as appropriate. Pain scores were analyzed using ANOVA with repeated measures. Categorical data were analyzed using Pearson chi-square test. Correlation analysis used Pearson correlation. Data are reported as mean ± SD or median [IQR]. The p value was set to 0.05 for statistical significance. Analyses were performed using SPSS, version 29.0.1 and GraphPad Prism, version 10.1.1.

Results/Case Report

Initially 82 patients were enrolled but an additional 8 were added to account for missing data collection forms that were discovered (Figure 1). Demographics are shown in Table 1. For the primary outcome, there was no significant difference in 24-hour median post-operative opioid consumption (13 [4, 27] mg versus 12 [4, 30] mg, p=0.893 for IV and PO groups, respectively; Table 2). There were no differences in NRS pain ratings at 30 minutes, 60 minutes, and PACU discharge. QoR-15 scores at 24 hours did not differ between groups at baseline or 24 hours postoperatively but did change from pre- to post-operative assessment (Figure 2). However, these differences have minimal clinical significance assuming a QoR-15 score between 90 and 121 represents “moderate” recovery. There were no differences in intra-operative opioid administration or any other analgesics.

For the PCS analysis, the mean PCS scores are shown in Table 1 and mean post-operative pain ratings are shown in Table 2. The Pearson correlation coefficient between mean PCS score and the mean pain score was R=0.571 (p<0.001) for IV and R=0.164 (p=0.346) for oral.

Discussion

Our study found no clinically meaningful differences between IV and oral acetaminophen in ambulatory spine surgery. Unlike previous studies, we included QoR, a patient-centered outcome, and we administered the IV drug close to end of surgery to maximize the chance of superiority. Our results contrast those of Hansen et al.,3 who reported superior outcomes for IV acetaminophen, but agreed

with a recent meta-analysis that concluded that IV acetaminophen offers no advantages over PO acetaminophen.5

References

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Disclosures

No

Tables / Images

CONSORT
TRANSPARENT REPORTING of TRIALS

Figure 1. CONSORT flow diagram

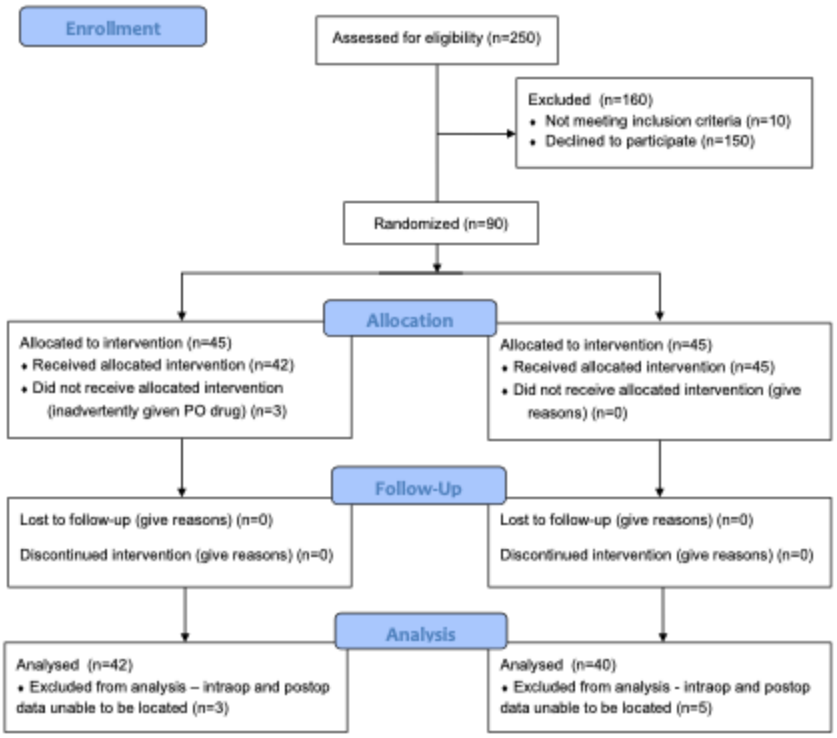

Figure 2. Quality of Recovery-15 scores at baseline (pre-operative) and 24 hours (post-operative)

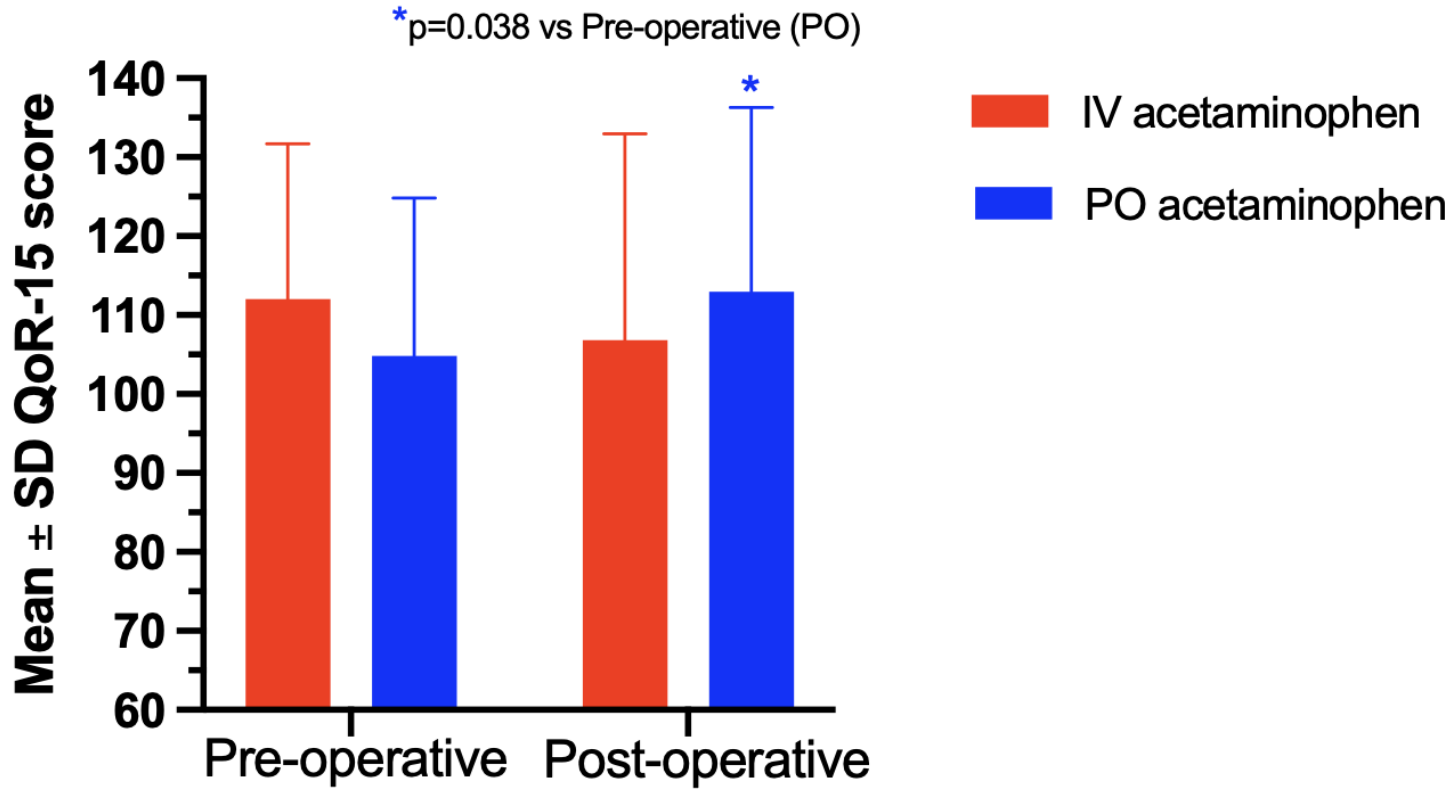

Table 1. Baseline Characteristics

Baseline Characteristics	IV acetaminophen (n = 42)^	Oral acetaminophen (n = 40)
Mean Age (SD) in years	50 (14)	52 (14)
Sex, n (%)		
Female	15 (35.7)	8 (20.0)
Male	27 (64.3)	32 (80.0)
Race, n (%)		
White	38 (90.5)	38 (95.0)
Black	2 (4.8)	1 (2.5)
Asian	2 (4.8)	0
Other	0	1 (2.5)
Mean BMI (SD) in kg/m^2	28.9 (4.6)	29.3 (4.8)
ASA physical status, n (%)		
1	12 (28.6)	5 (12.5)
2	25 (59.5)	23 (57.5)
3	5 (11.9)	12 (30.0)
Location, N (%)		
Ambulatory Surgery Center	30 (71.4)	31 (77.5)
Academic Medical Center	12 (28.6)	9 (22.5)
Mean (SD) PCS score	19 (13)	24 (12)

^Three patients assigned to IV acetaminophen were inadvertently given oral acetaminophen and were analyzed based on the intent-to-treat principle.
PCS=pain catastrophizing scale

Table 2. Intra- and Post-Operative Outcomes

Outcome	IV acetaminophen^ (n = 42)	Oral acetaminophen (n = 40)	P value
Intra-operative ketorolac, n (%)	28/42 (66.7)	25/40 (62.5)	0.693
Intra-operative local anesthetic wound infiltration, n (%)	18/42 (42.9)	16/40 (40.0)	0.793
Median [IQR] opioid consumption at 24 h in mg#	13 [4, 27]	12 [4,30]	0.893
Median [IQR] intra-operative opioid consumption in mg#	16 [11, 18]	18 [10, 23]	0.251
Mean (SD) NRS pain rating at 30 min (0-10)	4.6 (3.3)	3.6 (3.4)	0.368
Mean (SD) NRS pain rating at 60 min (0-10)	4.2 (2.7)	4.3 (2.8)	
Mean (SD) NRS pain rating at PACU discharge (0-10)	3.7 (2.3)	3.4 (2.3)	
Mean (SD) overall post-operative NRS pain rating (0-10)	4.2 (2.4)	3.7 (2.5)	0.368
Mean (SD) QoR-15 score at 24 h	107 (26)	113 (23)	0.272
Mean (SD) PACU LOS in minutes	127 (49)	143 (64)	0.203

#Opioids were converted to IV morphine equivalents using a table from Sinatra RS, de Leon-Casasola OA, Viscusi ER, Ginsberg B, eds. Acute Pain Management. New York, NY: Cambridge University Press, 2009.

^Three patients assigned to IV acetaminophen were inadvertently given oral acetaminophen and were analyzed based on the intent-to-treat principle.

IV=intravenous; IQR=interquartile range; NRS=numerical rating scale; PACU=post-anesthesia care unit; QoR=quality of recovery; SD=standard deviation