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ORIGINAL RESEARCH

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Intravenous vs oral acetaminophen in sinus surgery: A randomized clinical trial

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Abstract

Background: Multimodal perioperative analgesia including acetaminophen is recommended by current guidelines. The comparative efficacy of intravenous vs oral acetaminophen in sinus surgery is unknown. We aimed to determine whether intravenous or oral acetaminophen results in superior postoperative analgesia following sinus surgery.

Methods: This was a prospective randomized trial with blinded endpoint assessments conducted at a single large academic medical center. Subjects undergoing functional endoscopic sinus surgery were randomized to intravenous vs oral acetaminophen in addition to standard anesthetic and surgical care. The primary outcome was visual analogue scale pain score at 1 hour postoperatively.

Results: One hundred and ten adult patients were randomized; 9 were excluded from the data analysis. Fifty patients were assigned to intravenous acetaminophen and 51 to oral acetaminophen. Postoperative pain scores at 1 hour (primary endpoint) were not significantly different between the intravenous and oral acetaminophen groups. Similarly, there was no significant difference in pain scores at 24 hours postoperatively. Finally, there was no significant difference in postoperative opioid usage in the postanesthesia care unit or over the first 24 hours postoperatively.

Conclusions: This is the first comparative efficacy trial of oral vs intravenous acetaminophen in sinus surgery. There was no significant difference in pain scores at 1 or 24 hours postoperatively, and no difference in postoperative opioid use. Intravenous acetaminophen offers no apparent advantage over oral acetaminophen in patients undergoing sinus surgery.

Level of Evidence: 1b

KEYWORDS

acetaminophen, analgesia, functional endoscopic sinus surgery, intravenous, oral, postoperative pain, sinus surgery

Trial Registration: NCT02643394
ClinicalTrials.gov—https://clinicaltrials.gov/ct2/show/NCT02643394.

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1 | INTRODUCTION

Acetaminophen is recommended as a part of a balanced perioperative multimodal analgesic approach in current guidelines.[1] Opioids, which have traditionally been the mainstay of analgesic therapy for perioperative patients, are troubled by a host of adverse effects. Acetaminophen is used as an adjunct analgesic in the setting of ambulatory surgery to more effectively control pain while reducing opioid related side effects and expediting discharge to home.[2]

The availability of an intravenous acetaminophen preparation raises the question of the comparative efficacy of the oral vs intravenous formulations. Intravenous acetaminophen offers a favorable pharmacokinetic profile because of higher bioavailability, avoidance of first-pass hepatic metabolism, and generation of higher serum and cerebrospinal fluid levels than oral acetaminophen.[3-5] Intravenous acetaminophen also confers the advantage of intraoperative dosing which can offer a more prolonged effect into the postrecovery period since it can be given toward the end of surgery.

Intravenous acetaminophen has been demonstrated to be an effective analgesic in sinus surgery patients when compared to placebo.[6] The comparative clinical efficacy of preoperative oral vs intraoperative intravenous acetaminophen remains an open question in functional endoscopic sinus surgery (FESS). We designed this study to compare the efficacy of the two formulations. Based on published pharmacokinetic data, our primary hypothesis was that intravenous acetaminophen would be a superior analgesic when compared to oral acetaminophen.

2 | MATERIALS AND METHODS

This was a prospective randomized clinical trial conducted at a single large academic medical center with blinded endpoint assessments between August 2015 and September 2016. This study was approved by the Institutional Review Board of The University of Texas Southwestern Medical Center (IRB #STU052015-068) and funded by the Department of Anesthesiology and Pain Management. It is registered at clinicaltrials.gov (#NCT02643394). Eligible subjects were adult patients scheduled for elective FESS at Zale Lipshy University Hospital (UT Southwestern Medical Center). Individuals were enrolled on the day of surgery following written informed consent. After signing informed consent, patients were randomized 1:1 to intravenous vs oral acetaminophen by a computer-generated algorithm. Exclusion criteria included an inability to communicate, comprehend, and follow directions in either English or Spanish, patients with any contraindication to one of the study drugs, pre-existing liver disorders, chronic pain (baseline pain score > 4 out of 10), consumption of any analgesics on the morning of surgery, chronic opioid therapy, or a body weight < 50 kg.

Patients undergoing FESS who were randomized to the oral acetaminophen group received 1000 mg oral acetaminophen within 1 hour prior to anesthetic induction. Patients in the intravenous acetaminophen group received 1000 mg intravenous acetaminophen intraoperatively 1 hour prior to emergence from anesthesia. All patients received preoperative oral celecoxib 400 mg within 1 hour prior to anesthetic induction.[7,8] The study patients underwent a standardized general anesthetic protocol. Induction consisted of remifentanil, lidocaine, propofol, rocuronium, and dexamethasone boluses. Maintenance anesthesia consisted of desflurane (end tidal 3%-6%) and continuous remifentanil infusion. Phenylephrine, ephedrine, additional neuromuscular blockade, and reversal with neostigmine and glycopyrrolate were given as needed at the discretion of the attending anesthesiologist. Pre-emergence medications included ondansetron and bolus fentanyl (1 mcg/kg intravenous). Orogastric tubes were not used to avoid aspiration of the study drug. All sinus surgeries were performed with an endonasal technique and endoscopic visualization, for a variety of indications and pathologies. Some subjects also underwent endonasal septoplasty. Nasal packing was not used.

3 | OUTCOMES

The primary endpoint was the pain score assessed 1-hour postoperatively using the visual analogue scale (VAS) in the postanesthesia care unit (PACU) by a blinded reviewer. Secondary outcome measures included 24-hour pain scores and postoperative opioid usage (converted to morphine equivalents). Additional assessments included time to first analgesic request and the incidence of nausea and vomiting. The 24-hour (± 12 hours) pain score (0-10) and analgesic use were collected by telephone by blinded personnel (or in person interview for inpatients).

4 | STATISTICAL ANALYSES

Continuous outcomes were summarized as median and interquartile range, while categorical data were summarized as frequency and percentages. Normality of continuous outcomes was assessed using normal quantile plots. The intravenous and oral acetaminophen groups were compared using the Wilcoxon-Mann-Whitney test since the normality assumption was not viable for continuous outcomes. Chi-square test or Fisher's exact test was used to compare the groups in terms of categorical variables. Statistical significance was set as $P < .05$. All analyses were done using SAS version 9.3 (SAS, Inc., Cary, North Carolina) conducted by a statistician (Author A.M.). No multiple comparison corrections were utilized since the study is powered for a single primary outcome.

Based on prior literature, the study was powered to detect a 1.5-point change in the VAS pain score at 1 hour postoperatively.[9] Following Koteswara and Sheetal's study,[9] we assumed a SD of 2.5 points resulting in an effect size of 0.6. Sample size calculations indicated that 45 patients per group (90 total) would provide 80% power (two-side $\alpha = .05$) to detect this difference. To allow for up to 20% loss to follow-up in this ambulatory patient population, 110 patients were enrolled.

5 | RESULTS

The two study groups were well matched for age, gender, body mass index, and type of surgical procedure (Tables 1 and 2). One hundred

TABLE 1 Baseline patient characteristics by treatment group

Variable	Total (n = 101)	Intravenous acetaminophen (n = 50)	Oral acetaminophen (n = 51)	95% Confidence interval for the difference
Age in years, mean (SD)	52.7 (16.0)	54.0 (15.7)	51.5 (16.3)	−3.80, 8.86
Female gender, n (%)	33 (32.7)	16 (32.0)	17 (33.3)	−17.0, 19.6
Weight (kg), mean (SD)	93.6 (25.3)	93.7 (26.2)	93.5 (24.7)	−9.82, 10.26
Height (cm), mean (SD)	173.9 (10.8)	173.6 (11.1)	174.3 (10.6)	−4.90, 3.67
BMI (kg/m^2), mean (SD)	30.3 (6.9)	30.1 (6.3)	30.5 (7.5)	−3.13, 2.33

Abbreviation: BMI, body mass index.

TABLE 2 Distribution of sinonasal surgical procedures across treatment groups; number (percentage)

	Intravenous acetaminophen (n = 50)	Oral acetaminophen (n = 51)	*P* value	95% Confidence interval for the difference
Endoscopic sinus surgery with or without endoscopic septoplasty	30 (60.0)	34 (66.7)	.54	−25.4, 12.1
Extended sinus procedure (endoscopic modified Lothrop procedure, etc)	7 (14.0)	7 (13.7)	.99	−13.2, 13.8
Tumor resection, skull base procedure (eg, CSF leak)	3 (6.0)	6 (11.8)	.49	−16.8, 5.3
Septoplasty with/without nasal valve repair, turbinate reduction	7 (14.0)	3 (5.9)	.20	−3.5, 19.7
Nasal endoscopy with biopsy	3 (6.0)	1 (2.0)	.36	−3.5, 11.6

Abbreviation: CSF, cerebrospinal fluid.

TABLE 3 Visual analogue scale pain scores in the postanesthesia care unit (1 hour postoperative, primary outcome) and at home (24 hours, secondary outcome)

Variable	Total (n = 101)	Intravenous acetaminophen (n = 50)	Oral acetaminophen (n = 51)	*P* value[a]	95% Confidence interval for the difference
Visual analogue scale in postanesthesia care unit, median (IQR)	2.0 (0.0, 4.0)	2.0 (0.0, 5.0)	2.0 (0.0, 3.0)	.252	0.00, 16.00
Visual analogue scale in postanesthesia care unit, mean (SD)	2.48 (2.28)	2.83 (2.55)	2.13 (1.93)		
24 h Visual analogue scale at home, median (IQR)	1.0 (0.0, 3.0)	1.0 (0.0, 4.0)	1.0 (0.0, 3.0)	.142	0.00, 1.00
24 h Visual analogue scale at home, mean (SD)	1.81 (2.10)	2.24 (2.50)	1.39 (1.54)		

Abbreviation: IQR, interquartile range.
[a]Wilcoxon-Mann–Whitney test.

and ten patients were randomized; 55 to intravenous acetaminophen and 55 to oral acetaminophen. Nine patients were subsequently excluded from the final data analysis. In the intravenous acetaminophen group, 3 did not receive acetaminophen and 2 did not receive celecoxib, leaving 50 patients analyzed. In the oral acetaminophen group, 1 did not receive acetaminophen, 2 did not receive celecoxib, and 1 was lost to follow-up, leaving 51 patients analyzed. The trial was stopped at the target enrollment. There was no crossover between treatment groups; all patients in the analysis received the study treatment.

VAS pain score median and interquartile ranges were determined for the oral and intravenous groups at 1 hour (in PACU) and 24 hour postoperative time points. The median VAS scores obtained at 1 hour and at 24 hours postoperatively were not significantly different (1 hour postoperatively [Wilcoxon-Mann-Whitney test, P = .252; median difference = 0.0, 95% confidence interval = 0.0-16.0]; 24 hours [Wilcoxon-Mann-Whitney test, P = .142; median difference = 0.0, 95% confidence interval = 0.0-1.0]) between the intravenous and oral acetaminophen groups (Table 3). Figure 1 shows that the intravenous acetaminophen group had

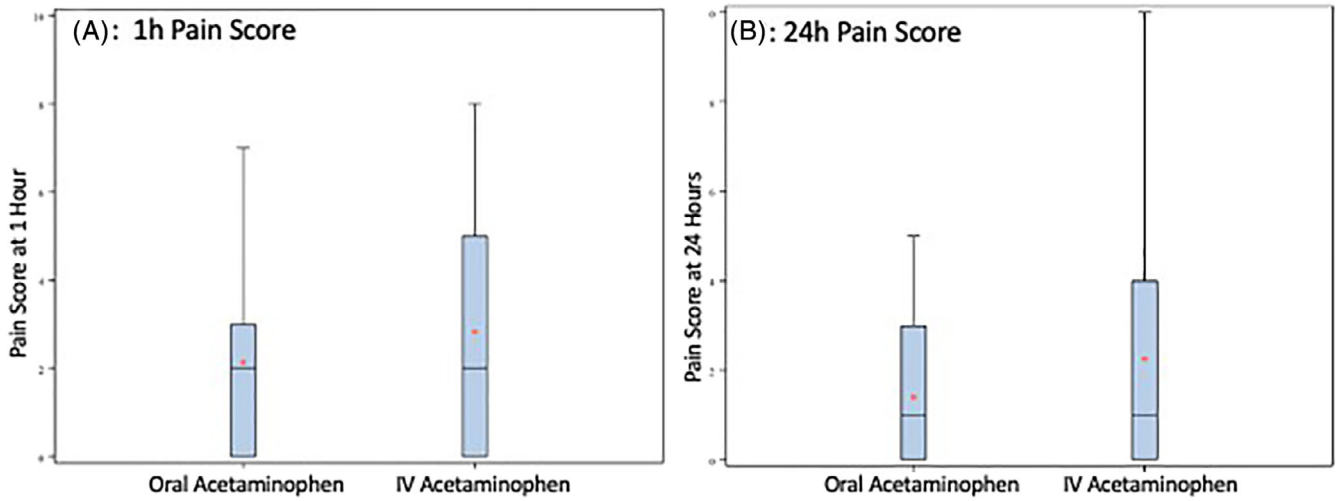

FIGURE 1 A, Visual analogue scale scores in the postanesthesia care unit 1 hour postoperatively. Orange dot represents the mean values, horizontal line represents median values; length of the box represents the 25th and 75th percent interquartile ranges. B, Visual analogue scale scores at home 24-hours postoperatively. Orange dot represents the mean values, horizontal line represents median values; length of the box represents the 25th and 75th percent interquartile ranges

a higher variability in pain scores. There were no significant differences between intravenous and oral groups in regard to total opioid usage in the PACU (Wilcoxon-Mann-Whitney test, P = .402, median difference = 0.0, 95% confidence interval = 0.0-4.2) or time to first analgesic request in the PACU (Wilcoxon-Mann-Whitney test, P = .237, median difference = −7.0 minutes, 95% confidence interval = −18.0 to 5.0 minutes) (Table 4). No significant differences in opioid requirements or use of other analgesics were found at 24 hours postoperatively for home analgesic use, which was completely at the discretion of the patient and surgeon (Wilcoxon-Mann-Whitney test, P = .184 for total opioid use, P = .698 for total acetaminophen use, and P = .609 for frequency of analgesic use at home; Table 5). No differences in nausea or vomiting were observed between groups (Tables 4 and 5).

6 | DISCUSSION

The use of intravenous acetaminophen has previously been studied in sinus surgery patients. A double blind placebo-controlled clinical trial in 74 sinus surgery patients demonstrated the superiority of intravenous acetaminophen over placebo in patients undergoing endoscopic sinus surgery.[6] However, another prospective, randomized clinical trial examining the effects of intravenous acetaminophen compared to placebo in 62 sinus surgery patients did not find significant differences in postoperative analgesia between groups, and was deemed "inconclusive" by the authors.[10]

Our trial is the first published comparison of oral vs intravenous acetaminophen in sinus surgery patients to date. In this prospective randomized study of intravenous vs oral acetaminophen in adults

TABLE 4 Postoperative opioid analgesic requirements (morphine equivalents)

Variable	Total (n = 101)	Intravenous acetaminophen (n = 50)	Oral acetaminophen (n = 51)	Difference (95% confidence interval)
Postanesthesia care unit				
Total opioids, median (IQR)	5.0 (0.0, 11.6)	5.0 (0.0, 14.8)	5.0 (0.0, 10.0)	0.0 (0.0, 4.2)
Total fentanyl, median (IQR)	5.0 (0.0, 10.0)	5.0 (0.0, 10.0)	5.0 (0.0, 10.0)	0.0 (0.0, 2.5)
Total hydromorphone, median (IQR)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Number of antiemetics, median (IQR)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)
Minutes to first analgesic request, median (IQR)	29.0 (18.0, 48.5)	26.0 (12.0, 48.0)	39.0 (21.0, 52.0)	−7.0 (−18.0, 5.0)
At home				
Total opioids, median (IQR)	0.0 (0.0, 3.3)	0.0 (0.0, 1.7)	0.0 (0.0, 3.3)	0.0 (0.0, 0.0)
Analgesic frequency, median (IQR)	1.0 (0.0, 2.0)	1.0 (0.0, 1.7)	1.0 (0.0, 2.0)	0.0 (−1.0, 0.0)
Total tylenol, median (IQR)	0.0 (0.0, 650.0)	0.0 (0.0, 600.0)	0.0 (0.0, 900.0)	0.0 (0.0, 0.0)

Abbreviation: IQR, interquartile range.

TABLE 5 Postoperative analgesic use; number (percentage)

Variable	Total (n = 101)	Intravenous acetaminophen (n = 50)	Oral acetaminophen (n = 51)	*P* value	95% Confidence interval for the difference
Postanesthesia care unit					
Any analgesic, n (%)	62 (61.4)	31 (62.0)	31 (60.8)	.900[a]	1.2 (−17.8, 20.2)
Any morphine, n (%)	1 (1.0)	0 (0.0)	1 (2.0)	.999[b]	−2.0 (−5.8, 1.8)
Any fentanyl, n (%)	53 (52.5)	27 (54.0)	26 (51.0)	.761[a]	3.0 (−16.5, 22.5)
Any hydromorphone, n (%)	18 (17.8)	9 (18.0)	9 (17.7)	.963[a]	0.3 (−14.6, 15.3)
Any hydrocodone, n (%)	16 (15.8)	10 (20.0)	6 (11.8)	.257[a]	8.2 (−6.0, 22.4)
Any tramadol, n (%)	2 (2.0)	1 (2.0)	1 (2.0)	.999[b]	0.0 (−5.4, 5.5)
Nausea, n (%)	32 (31.7)	17 (34.0)	15 (29.4)	.620[a]	4.6 (−13.5, 22.7)
Vomiting, n (%)	2 (2.0)	0 (0.0)	2 (3.9)	.495[b]	−3.9 (−9.3, 1.4)
At home					
Any oral analgesic, n (%)	70 (69.3)	33 (66.0)	37 (72.6)	.476[a]	−6.6 (−24.5, 11.4)
Tylenol, n (%); oral acetaminophen	20 (19.8)	8 (16.0)	12 (22.5)	.342[a]	−7.5 (−23.0, 7.9)
Tylenol 3, n (%); oral acetaminophen with codeine	28 (27.7)	13 (26.0)	15 (29.4)	.702[a]	−3.4 (−20.9, 14.0)
Tramadol, n (%)	15 (14.9)	9 (18.0)	6 (11.8)	.378[a]	6.2 (−7.6, 20.1)
Hydrocodone, n (%)	9 (8.9)	4 (8.0)	5 (9.8)	.754[a]	−1.8 (−12.9, 9.3)
Oxycodone, n (%)	3 (3.0)	1 (2.0)	2 (3.9)	.999[b]	−1.9 (−8.5, 4.7)
Nausea, n (%)	9 (8.9)	6 (12.0)	3 (5.9)	.281[a]	6.1 (−5.0, 17.2)
Vomiting, n (%)	1 (1.0)	1 (2.0)	0 (0.0)	.495[b]	2.0 (−1.9, 5.9)

[a]Chi-square test.
[b]Fisher's exact test.

undergoing elective sinus surgery, we found no difference in pain scores at 1 or 24 hours postoperatively. Similarly, there was no difference between groups in opioid usage in the PACU or over the first 24 hours postoperatively. As compared to oral acetaminophen, intravenous acetaminophen does offer favorable pharmacokinetics and can be dosed intraoperatively closer to the postoperative course. However, the clinical analgesic effect might not be accurately predicted by the serum drug level, and/or the magnitude of clinical benefit may be too small to be clinically significant.[3] Moreover, there may be benefit to "preemptive" or "preventive" administration of an analgesic such as acetaminophen prior to the surgical intervention that might supersede the benefit of the same drug at the end of surgery.[9]

There are limitations to this study. Patients and anesthesia providers were not blinded to the acetaminophen formulation. However, pain assessments were conducted by blinded observers. Celecoxib was used in all study patients as that is standard practice in our hospital (based on previously published data from our institution).[8] Similarly, we chose to dose the intravenous acetaminophen at the end of surgery in order to be consistent with our standard practice. In choosing this dosing strategy for acetaminophen, our study design favored the intravenous formulation. Published pharmacokinetic data indicate that serum and cerebrospinal fluid acetaminophen levels should be higher in the intravenous group at the time of our clinical analgesic assessment, 1 hour postoperatively (the primary endpoint). Finally, the use of celecoxib and fentanyl, in addition to acetaminophen, as part of a multimodal analgesic approach makes it impossible to analyze the analgesic effect of acetaminophen alone. We chose this approach on clinical grounds due to concerns that acetaminophen monotherapy would not provide sufficient postoperative analgesia.

Another consideration is the substantial cost difference between intravenous and oral formulations of acetaminophen. At our Institution, the pharmacy acquisition cost for a single dose of intravenous acetaminophen exceeds $30.00 USD, whereas a dose of oral acetaminophen costs $0.01 USD. Based on the data from this study, substantial cost savings could be achieved by substituting oral for intravenous acetaminophen in patients able to receive either formulation.

From our study data, we conclude that intravenous acetaminophen offers no significant advantage over oral acetaminophen in sinus surgery patients. The superior pharmacokinetic profile of intravenous acetaminophen did not translate into superior clinical benefit, and the cost difference argues against the routine use of intravenous acetaminophen in this patient population.

Similar findings have recently been obtained in other surgical populations. Westrich et al randomized 154 total hip arthroplasty patients to intravenous vs oral acetaminophen as part of a multimodal analgesic regimen and found no difference in pain scores or opioid use.[11] Similarly, Patel et al randomized 100 laparoscopic inguinal hernia repair patients to intravenous vs oral acetaminophen and found no difference in postoperative pain scores, opioid use, or patient satisfaction.[12] It is important to note that acetaminophen is not sufficient as a lone analgesic agent in sinus surgery. An evidence-based review by

Nguyen and colleagues determined that nonsteroidal anti-inflammatory drugs, gabapentin, local anesthetics, and alpha-agonists are all effective perioperative analgesics and provide the opportunity to reduce or eliminate opioid analgesic therapy.[13] Finally, Wu et al studied the introduction of ibuprofen into a prospective cohort of endoscopic sinus and nasal surgery patients.[14] They found a significant reduction in pain and opioid usage, with no bleeding complications, in 101 patients treated with ibuprofen as compared to 65 controls.

7 | CONCLUSION

This is the first comparative efficacy trial of oral vs intravenous acetaminophen in sinus surgery. We found no difference in pain scores at 1 or 24 hours postoperatively, and no difference in postoperative opioid use. Intravenous acetaminophen offers no apparent advantage over oral acetaminophen in patients undergoing FESS.

CONFLICT OF INTEREST

Dr McDonagh receives research funding from Lungpacer Medical, Inc. (No relation to this study/manuscript).

AUTHOR CONTRIBUTIONS

R.B.: manuscript writing and data analysis; M.W.R.: manuscript writing and patient recruitment; K.K. and B.F.M.: patient recruitment and manuscript review; A.M.: statistical analysis; E.M. and M.H.: patient enrollment and data collection; D.L.M.: study design, oversight, and manuscript preparation.

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