

Comparison of Intraoperative Opioid Consumption in Elective Cranial Surgery Patients with and without Preemptive Oral Paracetamol: A Propensity Score Matching Analysis

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Abstract:

Objective: Cranial surgery is associated with significant postoperative pain. Opioids are commonly used to provide pain relief. However, their use can lead to unwanted consequences, including neurological deterioration and respiratory depression. This study aimed to assess the benefits of preemptive oral paracetamol on intraoperative opioid consumption in patients undergoing elective cranial surgery.

Material and Methods: This retrospective propensity score-matched cohort study analyzed data from 336 patients who underwent elective cranial surgery. Patients receiving preemptive oral paracetamol were matched with those not receiving preemptive oral paracetamol using propensity scoring (nearest neighbor matching without replacement) with a caliper distance of 0.2 in a ratio of 1:2. Regression models were used to analyze the association between preemptive oral paracetamol, intraoperative opioid consumption, and hemodynamic changes at intubation.

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Results: Among 336 patients, 193 were matched for analysis (78 with and 115 without preemptive oral paracetamol). For the primary outcome, patients receiving preemptive oral paracetamol required significantly less intraoperative fentanyl (-5.1 mcg/hours, 95% CI -0.8 to -9.3 ; p -value=0.02). There were no significant differences in hemodynamics during intubation between groups.

Conclusion: Preemptive oral paracetamol led to a statistically significant, but not clinically meaningful, reduction of intraoperative fentanyl consumption. These findings should be interpreted with caution regarding potential changes in practice.

Keywords: cranial surgery, opioid, paracetamol, preemptive analgesia, propensity score matching

Introduction

Cranial surgery can result in significant postoperative pain. Nearly 70% of patients undergoing craniotomy suffer from moderate to severe postoperative pain, which may reflect the high density of nociceptors and outsized representation of the head in the brain's cortical representation of the body, aka homunculus. Severe postoperative pain is an independent risk factor for persistent postsurgical pain, which in turn affects 30% of patients after craniotomy, and approaches 50% after acoustic neuroma surgery¹⁻³. Opioids are commonly used to provide pain relief following cranial surgery^{4,5}, but their use is associated with chronic pain and opioid therapy, respiratory depression, sedation, and nausea and vomiting, which may contribute to or mask neurological deterioration and prolong hospital discharge^{1,6-9}.

Procedure-specific (PROSPECT) postoperative pain management guidelines on perioperative pain management for craniotomy surgery have recommended perioperative use of paracetamol along with other analgesics.¹⁰ A meta-analysis demonstrated that scheduled intravenous paracetamol during craniotomy significantly decreased postoperative pain, analgesic requirements, and the need for rescue analgesics after craniotomy surgery¹¹. In one large, propensity-score matching analysis, the intraoperative use of intravenous paracetamol was associated with a 15% reduction in intraoperative opioid use during transsphenoidal pituitary resection¹².

Previous studies on craniotomy pain management have focused on intravenous paracetamol. One systematic review involving 14 studies ($n=1,695$) found that intravenous paracetamol did not differ from the oral formulation for postoperative pain control through 24 hours (hr)¹³. However, intravenous paracetamol is 10 times more expensive¹³, with a 12-fold higher life cycle of carbon emissions compared to oral paracetamol¹⁴. For the effect of oral paracetamol on intraoperative opioid requirements, there are no clinical trials available to inform practice. To address the gaps in the literature, we conducted a propensity-matched study in patients undergoing craniotomy whose main objectives were to: 1) assess the effects of a single dose of paracetamol on intraoperative opioid requirements; and 2) determine whether preemptive paracetamol affected hemodynamic status during intubation.

Material and Methods

Patients and methods

This retrospective propensity score-matched study recruited patients aged ≥ 18 years with an ASA classification of I-III who underwent elective cranial surgery at a tertiary care medical school in Hat Yai, Thailand, from January 2018 to June 2022. Inclusion criteria included individuals who underwent an elective craniotomy, who received intravenous fentanyl as the sole opioid analgesic, and received between 500 and 1,000 mg of paracetamol within 8 hr of the surgical start time. Individuals who underwent emergency surgery,

awake craniotomy, received preoperative analgesics, such as membrane stabilizers and opioids, intraoperative intravenous paracetamol, infusions of lidocaine or opioids, and who were pregnant were excluded. The study was approved by the Human Research Ethics Committee of the Faculty of Medicine, Prince of Songkla University (REC 65–262–8–4) prior to data collection. This retrospective study involved no more than minimal risk to subjects, and thus patient written informed consent to review their medical records was waived by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University. This manuscript adheres to the applicable Equator Guidelines.

Data collection

Outcome measures

The primary outcome measure was the fentanyl dose per hour, calculated as the total intraoperative dose divided by the duration of surgery, which was determined by the difference in time between room entry and exit. The secondary outcome measures were the maximum changes from baseline in hemodynamic parameters within 5 minutes of intubation, including heart rate, systolic and diastolic blood pressure, as recorded using a pulse oximeter and a non-invasive blood pressure monitoring before induction of anesthesia and a zeroed arterial line after induction.

To minimize selection bias, we compared patients receiving and not receiving preemptive oral paracetamol using propensity score matching (PSM). Propensity scores were estimated using a logistic regression model based on potential covariates, including: demographic data (age, sex), clinical data (body mass index [BMI], Glasgow Coma Score [GCS], presence of co-morbidities), surgical data (tumor diagnosis, anatomical location and size of lesion, surgery type and duration, midline shift, preoperative glucocorticoids), and anesthetic data (anesthesia type, anesthesia time, intraoperative corticosteroids, midazolam, propofol infusion, muscle relaxant choice, lidocaine skin infiltration, scalp block). Matching was performed using a

nearest neighbor matching algorithm without replacement in a 1:2 ratio, with a caliper width set at 0.2 of the standard deviation of the logit of the propensity score. After matching, covariate balance was assessed by calculating the standardized mean difference (SMD) for all variables; an SMD <0.1 was considered indicative of adequate matching/balance between the groups.

Sample size calculation

The sample size was calculated based on a pilot study performed in 52 patients who underwent cranial surgery, of which 13 received preemptive oral paracetamol. The mean intraoperative fentanyl consumption was 35.29 ± 18.11 mcg/hr in those patients who received preemptive oral paracetamol vs. 43.45 ± 19.45 mcg/hr in those who did not. Considering a potential effect size of 0.43, with a S.D. of 18.80, we estimated that a total of 216 patients were required to detect a difference between the two groups with 80% power and a significance level set at 0.05.

Statistical analysis

Categorical variables are presented as frequency and percentage. Continuous variables with a normal distribution are presented as mean (S.D.) and median (IQR) for those that are non-normally distributed. After matching, univariate and multivariate linear regression analyses, controlling for potential covariates, were performed for the primary and secondary outcome measures. Factors with a p -value < 0.2 in univariate regression were incorporated into the multivariate regression model. The final model for multivariate analysis was based on stepwise backward regression. Subgroup analyses comparing the dosage and timing of preemptive oral paracetamol, as well as preemptive oral paracetamol with or without intraoperative intravenous paracetamol, were performed using linear regression. Data analysis was performed using RStudio 2022.12.0. p -value < 0.05 was considered statistically significant.

Results

Demographic and clinical data

A total of 1,014 patients who underwent cranial surgery were screened. Six hundred and seventy-eight subjects were excluded, with the most common reason being emergency surgery (n=375). From the 336 eligible patients, 193 were analyzed after propensity score matching, including 78 who received preemptive oral paracetamol and 115 who did not. For those receiving preemptive oral paracetamol, 65 (83.3%) received 500 mg and 13 (16.7%) received 1,000 mg. Most patients (n=54, 65%) received the drug within 4 hrs of surgical start time. Demographic,

clinical, surgical, and anesthetic characteristics before and after propensity score matching are shown in Table 1.

Primary and secondary outcomes

Before propensity matching, the median intraoperative dose of fentanyl was 32 mcg/hr [23–45] in subjects who received preemptive oral paracetamol vs. 47 mcg/hr [32–65] in those who did not (p-value<0.001). After propensity matching, the median fentanyl dose was 33 mcg/hr [23–47] in patients who received paracetamol, which was not significantly different from those who did not (38 mcg/hr [27–57]; p-value=0.053). Given that the p-value is close

Table 1 Comparison of baseline, surgical, and intraoperative data before and after preemptive paracetamol matching

Variables	Before matching			After matching		
	Preemptive paracetamol N=85	No preemptive paracetamol N=251	SMD	Preemptive paracetamol N=78	No preemptive paracetamol N=115	SMD
<i>Demographic data</i>						
Age (years)	51 [43–57]	51 [44–60]	0.17	51 [42–56]	48 [41–55]	–0.02
Sex			0.09			–0.03
Male	27 (31.8)	69 (27.5)		23 (29.5)	35 (30.8)	
Female	58 (68.2)	182 (72.5)		55 (70.5)	80 (69.2)	
<i>Clinical data</i>						
ASA			0.20			0.04
I	0 (0)	0 (0)		0 (0)	0 (0)	
II	22 (25.9)	44 (17.5)		22 (28.2)	30 (26.3)	
III	63 (74.1)	207 (82.5)		56 (71.8)	85 (73.7)	
BMI (kg/m ²)			0.41			0.02
<18.5	0 (0)	16 (6.4)		0 (0)	0 (0)	
18.5–24.9	50 (58.8)	126 (50.2)		46 (59.0)	67 (58.3)	
25–29.9	28 (32.9)	77 (30.7)		25 (32.1)	36 (32.1)	
≥30	7 (8.2)	32 (12.7)		7 (9.0)	11 (9.6)	
GCS			0.16			0.00
3–8	0 (0)	0 (0)		0 (0)	0 (0)	
9–12	0 (0)	2 (0.8)		0 (0)	0 (0)	
13–14	1 (1.2)	6 (2.4)		1 (1.3)	1 (1.3)	
15	84 (98.8)	243 (96.8)		77 (98.7)	114 (98.7)	
Comorbidities			0.03			0.05
No	41 (48.2)	117 (46.6)		37 (47.4)	58 (50.0)	
Yes	44 (51.8)	134 (53.4)		41 (52.6)	58 (50.0)	
<i>Preoperative medications</i>						
Dexamethasone			0.37			0.07
No	30 (35.3)	48 (19.1)		27 (34.6)	36 (31.4)	
Yes	55 (64.7)	203 (80.9)		51 (65.4)	79 (68.6)	
Hydrocortisone			0.01			0.03
No	80 (94.1)	237 (94.4)		73 (93.6)	107 (92.9)	
Yes	5 (5.9)	14 (5.6)		5 (6.4)	8 (7.1)	

Table 1 (continued)

Variables	Before matching			After matching		
	Preemptive paracetamol N=85	No preemptive paracetamol N=251	SMD	Preemptive paracetamol N=78	No preemptive paracetamol N=115	SMD
<i>Surgical parameters</i>						
Type of surgery			0.28			0.04
Craniotomy	77 (90.6)	203 (80.9)		70 (89.7)	102 (88.5)	
Craniectomy	8 (9.4)	48 (19.1)		8 (10.3)	13 (11.5)	
Surgery duration (min)	300 [225–415]	285 [212–418]	-0.05	300 [235–412]	295 [235–420]	0.04
Brain Tumor			0.00			0.07
No	1 (1.2)	3 (1.2)		1 (1.3)	1 (0.6)	
Yes	84 (98.8)	248 (98.8)		77 (98.7)	114 (99.4)	
Location			0.15			0.06
Supratentorium	82 (96.5)	234 (93.2)		75 (96.2)	109 (94.9)	
Infratentorium	3 (3.5)	17 (6.8)		3 (3.8)	6 (5.1)	
Size of lesion (mm)	47 [36–59]	44 [33–60]	-0.15	46 [32–58]	47 [35–62]	0.09
Midline shift (mm)	0 [0–5]	0 [0–7]	0.19	0 [0–6]	0 [0–7]	0.08
<i>Anesthesia parameters</i>						
Anesthesia			0.09			0.05
Balanced	78 (91.8)	236 (94.0)		73 (93.6)	106 (92.3)	
TIVA	7 (8.2)	15 (6.0)		5 (6.4)	8 (7.7)	
Duration of anesthesia (min)	375 [315–510]	360 [280–490]	-0.07	380 [312–508]	385 [305–490]	0.04
Dexamethasone			0.38			0.08
No	43 (50.6)	81 (32.3)		38 (48.7)	52 (44.9)	
Yes	42 (49.4)	170 (67.7)		40 (51.3)	63 (55.1)	
Hydrocortisone			0.09			0.03
No	80 (94.1)	241 (96.0)		73 (93.6)	107 (92.9)	
Yes	5 (5.9)	10 (4.0)		5 (6.4)	8 (7.1)	
Wound infiltration			0.05			0.00
No	2 (2.4)	8 (3.2)		2 (2.6)	2 (2.6)	
Yes	83 (97.6)	243 (96.8)		76 (97.4)	112 (97.4)	
Scalp block			0.8			0.04
No	21 (24.7)	154 (61.4)		20 (25.6)	32 (27.6)	
Yes	64 (75.3)	97 (38.6)		58 (74.4)	83 (72.4)	
Propofol infusion			0.01			0.00
No	75 (88.2)	222 (88.4)		70 (89.7)	103 (89.7)	
Yes	10 (11.8)	29 (11.6)		8 (10.3)	12 (10.3)	
Muscle relaxant			0.15			0.00
None	6 (7.1)	12 (4.8)		5 (6.4)	7 (6.4)	
Rocuronium	76 (89.4)	224 (89.2)		70 (89.7)	103 (89.7)	
Cisatracurium	3 (3.5)	15 (6.0)		3 (3.8)	4 (3.8)	
Midazolam			0.13			0.07
No	82 (96.5)	235 (93.6)		75 (96.2)	112 (97.4)	
Yes	3 (3.5)	16 (6.4)		3 (3.8)	3 (2.6)	
Fentanyl (mcg/hr)	32 [23–45]	47 [32–65]	0.75	33 [23–47]	35 [27–53]	0.28
<i>Baseline hemodynamics</i>						
Pulse	73 [66–80]	72 [66–82]	0.03	72 [65–80]	73 [68–82]	0.12
Systolic blood pressure	122 [113–133]	122 [114–132]	0.12	121 [112–133]	123 [111–130]	0.06
Diastolic blood pressure	73 [68–80]	76 [70–81]	0.19	73 [68–80]	76 [69–81]	0.15

Data presented as median (IQR), n (%)

ASA=American Society of Anesthesiologists, BMI=body mass index, GCS=Glasgow Coma score, mcg=micrograms, SMD=standardized mean difference, TIVA=total intravenous anesthesia

to the conventional significance threshold, this result should be interpreted with caution. For hemodynamic parameters during intubation, there were no significant differences in any variable stratified by paracetamol administration after propensity matching (Table 2).

Multivariate analysis

The results of multivariate analysis are shown in Table 3. The use of preemptive oral paracetamol and scalp

block was associated with significantly less intraoperative fentanyl consumption: 5.1 mcg/hr (p-value=0.02, 95% CI -9.4 to -0.8) for paracetamol and 25.2 mcg/hr (p-value<0.001, 95% CI -29.9 to -20.6) for scalp block. Adjusting for the log-transformed duration of anesthesia, paracetamol was associated with a 12.0 mcg/hr decrease in intraoperative fentanyl usage (p-value<0.001, 95% CI -17.6 to -6.4).

Table 2 Outcome data before and after preemptive paracetamol matching

Outcome measures	Before matching				After matching			
	Preemptive paracetamol N=85	No preemptive paracetamol N=251	SMD	p-value	Preemptive paracetamol N=78	No preemptive paracetamol N=115	SMD	p-value
Intraoperative fentanyl use (mcg/hr)	32 [23–45]	47 [32–65]	0.75	<0.001	33 [23–47]	38 [27–57]	0.37	0.053
<i>Hemodynamics during intubation</i>								
Pulse rate (bpm)	85 [80–95]	90 [75–100]	0.17	0.9	85 [78–95]	90 [75–100]	0.24	0.6
Systolic blood pressure (mmHg)	155 [135–180]	150 [135–175]	-0.08	0.6	155 [135–178]	150 [140–175]	-0.04	0.8
Diastolic blood pressure (mmHg)	85 [70–95]	85 [75–100]	0.04	0.2	85 [70–98]	85 [75–100]	0.07	0.2

Data presented as median (IQR)
bpm=beats per minute, mcg=micrograms, SMD=standardized mean difference

Table 3 Multivariate linear regression analysis of the factors associated with intraoperative fentanyl consumption

Variables	Beta (95% CI)	p-value
Preemptive oral paracetamol		0.02
No (ref)	-	
Yes	-5.1 (-9.4 to -0.8)	
Scalp block		<0.001
No (ref)	-	
Yes	-25.2 (-29.9 to -20.6)	
Type of surgery		0.39
Craniectomy (ref)	-	
Craniotomy	-2.9 (-9.6 to 3.8)	
Duration of anesthesia (log value)	-12.0 (-17.6 to -6.4)	<0.001
Anatomical location		0.34
Infratentorium (ref)	-	
Supratentorium	4.6 (-4.9 to 14.1)	
Midline shift (mm)	-0.4 (-0.8 to 0.1)	0.13

CI=confidence interval, ref=reference

Subgroup analyses

After subgroup analysis, we found no significant difference in intraoperative fentanyl consumption stratified by dose (500 mg vs. 1000 mg) of preemptive oral paracetamol (p-value=0.19, 95% CI -16.2 to 3.2), add-on intraoperative intravenous paracetamol (p-value=0.31, 95% CI -11.1 to 3.5) or based on the timing of preemptive oral paracetamol (p-value=0.31) (Table 4). Additionally, there was no significant difference in pulse rate, systolic blood pressure,

and diastolic blood pressure during intubation between the two main study groups (Table 5).

Discussion

Our study found that preemptive oral paracetamol (either 500 mg or 1,000 mg) statistically reduced intraoperative fentanyl consumption by 5.1 mcg/hr, or 3.9%. Nonetheless, this difference is considered clinically insignificant. Although there is no consensus on what constitutes a meaningful

Table 4 Subgroup analysis of dosage, timing of preemptive oral paracetamol, and preemptive oral paracetamol with or without intraoperative intravenous paracetamol

Variables	Number of patients	Beta (95% CI)	p-value
Dose of preemptive oral paracetamol			0.19
500 mg (ref)	65	-	
1,000 mg	13	-6.5 (-16.2 to 3.2)	
Timing of preemptive oral paracetamol			0.31
<120 min (ref)	3	-	
120-240 min	51	-9.3 (-28.6 to 9.9)	
240-360 min	18	-5.5 (-25.7 to 14.7)	
>360 min	6	-7.0 (-29.9 to 15.9)	
Preemptive oral paracetamol with intraoperative intravenous paracetamol			0.31
No (ref)	37	-	
Yes	41	-3.8 (-11.1 to 3.5)	

CI=confidence interval, ref=reference

Table 5 Univariate linear regression analysis examining the relationship between preemptive oral paracetamol and hemodynamic changes during intubation

Variables	Beta (95% CI)	p-value
Change of pulse rate		0.22
Without preemptive paracetamol (ref)	-	
With preemptive paracetamol	-2.5 (-5.9 to 1.4)	
Change of systolic blood pressure		0.47
Without preemptive paracetamol (ref)	-	
With preemptive paracetamol	2.5 (-4.4 to 9.5)	
Change of diastolic blood pressure		0.77
Without preemptive paracetamol (ref)	-	
With preemptive paracetamol	0.6 (-3.8 to 5.0)	

CI=confidence interval, ref=reference

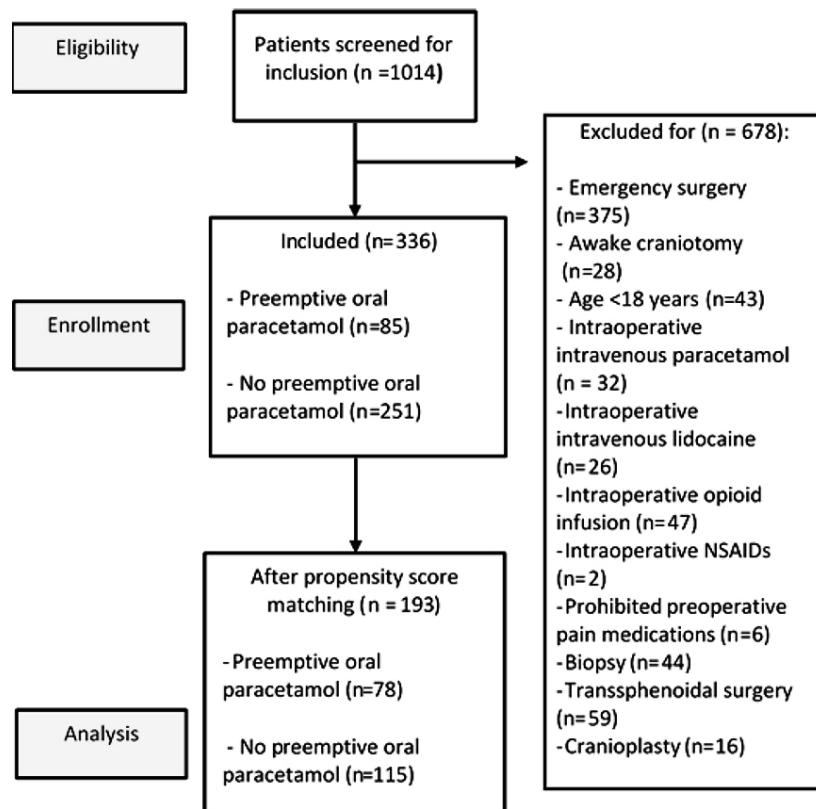


Figure 1 Study flowchart

increase or decrease in intraoperative opioid requirements, one highly publicized study calculated predictions on mean expected differences in postoperative pain outcomes for each additional administration of 100 mcg of fentanyl over the course of non-cardiac surgery¹⁵. Based on this, the small decrease in intraoperative opioid use in the paracetamol group falls shy of being clinically meaningful in a relatively young population.

Comparison to other studies

There are no randomized studies that have evaluated the effect of preemptive oral paracetamol on intraoperative opioid consumption; studies assessing the effect of intravenous paracetamol have yielded mixed results. One large (n=413) retrospective analysis found a statistically

significant difference in the intraoperative opioid consumption of 40 mcg/hr (or 14.9% reduction) in patients undergoing transsphenoidal cranial surgery who received intraoperative intravenous paracetamol¹². Conversely, a subsequent, very small (n=46) industry-sponsored, placebo-controlled trial did not find a reduction in intraoperative opioid use, though it did report a 22% reduction in 24-hr postoperative opioid consumption¹⁶.

Not surprisingly, considering the primary findings, we also found no association between either the dose of preemptive oral paracetamol or the timing of the administration on intraoperative fentanyl consumption. The bioavailability of paracetamol increased from 0.63 to 0.89 mg, and the peak plasma concentration increased from 15.6 to 44 mcg/ml when the dosage was increased from

500 mg to 1,000 mg; the approximately 2.75–24-hr half-life remained unchanged¹⁷. Current evidence suggests a lack of increased analgesic effect beyond 1,000 mg¹⁸.

We also found that a preincision scalp block significantly reduced intraoperative fentanyl consumption. This aligns with previous evidence showing that both scalp nerve blocks and non-nervous tissue injections provide a notable opioid-sparing effect in the postoperative period^{19,20}. Although preincision local anesthetic use may exert opioid-sparing effects by anesthetizing the nociceptors stimulated during surgery, it would not be expected to alter the hemodynamic response associated with intubation, which stimulates pharyngeal and laryngeal nociceptors²¹.

Explanation of findings

Paracetamol is a weak analgesic devoid of anti-inflammatory effects, so its lack of a significant effect on the acute inflammatory pain associated with surgery might be expected. For chronic pain conditions, paracetamol has not been shown to provide meaningful benefit for the two most common nociceptive pain conditions, back pain and osteoarthritis, based on systematic reviews of placebo-controlled trials^{22,23}.

So why has intravenous paracetamol been shown in some studies to provide benefit? Whereas oral paracetamol has high bioavailability (>60%), the peak blood levels are lower after oral administration. Anesthesia and surgery also adversely affect gastrointestinal motility and absorption, which may be particularly relevant for medications, such as paracetamol, which are mainly absorbed in the small intestine^{24,25}. The difference may also be related to the industry sponsorship of intravenous paracetamol studies, as systematic reviews have found that industry-sponsored studies are more likely to yield positive results than federally funded or unfunded studies²⁶. A final contributing reason may be the different operations studied, as transsphenoidal pituitary resection is considered an especially stimulating surgery²⁷.

Limitations

Our study has a number of limitations that should be considered when interpreting the results. First, the retrospective nature may lead to imbalances in demographic and clinical characteristics, which can be further amplified in a relatively small sample. Although propensity score matching followed by multivariate analysis was performed to reduce selection bias and balance covariates, unmeasured covariates, such as psychiatric comorbidities, could confound the treatment effects. Second, we did not classify tumors as malignant or non-malignant, nor did we stage cancerous tumors. Whereas this might be hypothesized to have a stronger effect on subjective postoperative pain scores that are heavily influenced by psychosocial variables²⁸, resection of more advanced malignancies might be inherently more stimulating. Third, we limited our study to measuring intraoperative fentanyl administration. This approach removes the subjective basis of pain reporting and opioid requirement, which are often used to treat non-pain-related symptoms, such as anxiety and insomnia; however, it does not account for anesthesia provider differences in intraoperative opioid administration, which can be profound²⁹. However, detecting a difference in postoperative opioid consumption for a short-acting analgesic, when none was found for intraoperative opioid use, seems unlikely. Last, because this single-center study followed a specific anesthetic protocol, caution is needed when generalizing these findings to other settings or populations.

Conclusion

We found small and clinically insignificant effects for the preemptive use of oral paracetamol. Given the risks associated with intraoperative non-steroidal anti-inflammatory drug use and the cost of intravenous paracetamol, further research, ideally free from industry sponsorship, is needed to determine whether intravenous paracetamol is truly effective as a preemptive analgesic. Large-scale clinical trials are also required to clarify whether

oral paracetamol is truly ineffective or non-inferior to intravenous paracetamol as a safe, effective agent suitable for inclusion in multimodal anesthetic plans.

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Conflict of interest

The authors declare no conflict of interest.

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