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Intravenous Acetaminophen Versus Placebo as an Adjuvant Therapy for Pain Management in Transsphenoidal Pituitary Surgery Patients: A Double-blinded Randomized Controlled Trial

Surunchana Lerdsirisopon[1], Vorrachai Sae-phua[2], Kornkamon Yuwapattanawong[2], Lawan Tuchinda[1], Tharinan Tangworanigoonkit[2], Chayanee Srira[2]

[1]*Department of Anesthesiology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

[2]*Department of Anesthesiology, King Chulalongkorn Memorial Hospital, Bangkok, Thailand*

Background: Transsphenoidal pituitary surgery (TSS) is a neurosurgical procedure with mild to moderate postoperative pain, which is usually controlled by opioid analgesics. However, concerns about side effects associated with opioids have been challenges among these patients. Thus, multimodal analgesics are often required to optimize pain control with less undesired effects.

Objective: Our study aimed to determine intravenous acetaminophen's efficacy as an adjuvant therapy for postoperative pain management in TSS patients.

Methods: We conducted a prospective, double-blinded, randomized controlled trial. Forty-six patients who had undergone elective TSS were recruited and randomly assigned to the acetaminophen or placebo group. The total fentanyl consumptions in the first 24 hours were recorded. Pain scores and adverse effects such as nausea, vomiting, and sedation were recorded. All statistical analyses were performed using STATA 14.

Results: Based on the average pain scores, both groups received optimal postoperative pain management. Postoperative fentanyl consumption was 284.1±152.8 mcg in the study group and 364.4±211.7 mcg in the placebo group, respectively. Adding acetaminophen to fentanyl was associated with an opioid-sparing effect of 22% (*P*-value = 0.15) in the first 24 hours postoperative period. The incidences of nausea, vomit, sedation and respiratory depression were not different in both groups.

Conclusion: In our study, acetaminophen administration was not associated with a reduction of postoperative fentanyl consumption. Acetaminophen had neither significant fentanyl-sparing effects nor side effects reduction for postoperative pain management in TSS patients.

Keywords: acetaminophen, pain, paracetamol, transsphenoidal pituitary surgery

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Pain management following intracranial surgery is still a challenging issue. It has been under-treated because of a belief that intracranial procedures have been considered to be less painful compared with other surgical procedures and the reluctant use of opioids concerning its side effects. In these recent years, studies reveal that pain after intracranial procedure is common and up to 75% of patients experienced moderate-to-severe pain.[1-3] Inadequate pain control in neurosurgical patients may cause complications such as agitation and high blood pressure, leading to intracranial hemorrhage, which severely prolongs hospital stay and increases mortality.[4-5]

Opioids, the mainstay analgesics for postoperative pain, need to be used with caution in neurosurgical

Correspondence to: Surunchana Lerdsirisopon, M.D., E-mail: surunchana.l@chulahospital.org

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patients. Significant opioids side effects, including sedation, respiratory depression, nausea, and vomiting, can obscure neurological conditions, cause hypercapnia, brain swelling and increase intracranial pressure.[2,6] Thus, the rationale of multimodal analgesia is widely used. Non-opioid analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs), local anesthetics, anticonvulsants (gabapentin and pregabalin) are combined with opioids to maximize pain control and minimize unfavorable side effects.[7] Nevertheless, the use of NSAIDs in neurosurgical patients is still controversial. NSAIDs may enhance analgesia with opioid-sparing effect, but there were reports of irreversible inhibitory effect on platelet aggregation and associated risk factor of a postoperative hematoma.[8,9] Then, it should be used in neurosurgical patients with cautions.[10-13]

Acetaminophen is a cyclo-oxygenase (COX) inhibitor, acting on a serotonergic pathway, has analgesic effects with few side effects. There was no opioid-like drowsiness effect and no coagulation effect like NSAIDs. Many studies in postoperative pain relief found that acetaminophen has an opioid-sparing effect[14-16] and reduces complications from opioid use, such as nausea, vomiting, drowsy and helps to recover faster.[17-19] Kemppainen *et al*. reported a randomized controlled trial showing that acetaminophen was more effective than placebo in pain management after endoscopic sinus surgery and it decreases doses of rescue drug during the first 4 hours.[20] A systematic review and meta-analysis indicated that preoperative intravenous acetaminophen associated with lower postoperative pain scores, decreased needs of rescue analgesics, dosages of analgesics and ICU length of stay in elective craniotomy patients.[21]

It is seen that acetaminophen is useful as an adjunct to opioids in a wide range of postoperative pain relief. However, the data on using acetaminophen in pain management after TSS is limited. We conducted a randomized controlled trial to compare intravenous acetaminophen with placebo as an adjuvant to our standard pain treatment protocol. Our hypotheses were 1) patients receiving intravenous acetaminophen would require less opioid consumption in the first 24 hours, and 2) these patients would experience less opioid side effects.

Methods

We conducted a prospective randomized, double-blinded, placebo-controlled study. The study protocol was approved by the Institutional Review Board of Faculty of Medicine, Chulalongkorn University.

Study Design and Data Collection

Patients scheduled for elective TSS at King Chulalongkorn Memorial Hospital (KCMH), Bangkok, were approached for enrollment in the study between December 2019 to October 2020. Included patients were older than 20 years and able to use patient-controlled analgesia (PCA) device and rate their pain by the numerical verbal rating scales (NRS). Patients were excluded if they were undergoing emergency TSS, alteration of consciousness with Glasgow Coma Score (GCS) below 15 before and after surgery, documented allergy to protocol drugs, taking any pain medications continuously before surgery, history of alcohol dependence or substance use, abnormal liver function test, and pregnancy. Written informed consent was obtained from each participant.

Patients were classified into microscopic or endoscopic groups according to the surgical approach, then were randomly assigned to the intervention or placebo group by a block-of-four randomization scheme. Patients in the intervention group received 1,000 mg of acetaminophen intravenously after induction of anesthesia prior incision. Repeated doses were given every 6 hours for a total of 24 hours after surgery. Patients in the placebo group were given the same volume (100 mL) of 0.9% sodium chloride at similar schedules. On the morning of surgery day, the investigators prepared acetaminophen or placebo in the pre-filled 100-mL plastic bag. Both solutions were similar in color (clear) and equal volume. The anesthesiologists, nurses in post-anesthetic care unit (PACU) and intensive care unit (ICU) were to administer

the study drug and assess the NRS score without knowing the patient's group.

In the operating room, general anesthesia was induced using propofol (1.5-2 mg/kg) and fentanyl (1-2 mcg/kg). Cis-atracurium (0.15 -0.2 mg/kg) was used to facilitate tracheal intubation. Anesthesia was maintained with desflurane (MAC 0.8-1.5) in an oxygen-nitrous mixture (FiO_2 0.5) with a total flow of 1 L/min. Lidocaine 1% with epinephrine (1:100,000) up to 10 mL was routinely infiltrated along the incision by neurosurgeons. Anesthetic depth was titrated, and additional fentanyl was given to maintain hemodynamic parameters (blood pressure and heart rate within 20% of baseline). Boluses of cis-atracurium were based on train-of-four monitoring. Anesthesiologists considered giving fluids, blood components, vasopressor drugs or anti-hypertensive drugs as appropriate. Upon completing surgery, 4 mg ondansetron was given to all patients. The anesthesiologist administered neostigmine 0.05 mg/kg with glycopyrrolate 0.01 mg/kg and patients were extubated in operating room.

Upon admission to the PACU, the patients were immediately assessed NRS, postoperative nausea and vomiting (PONV) score, Richmond Agitation Sedation Scale (RASS) score and set at time zero. Patients with RASS score < -2 were recorded as an adverse event. An episode of respiratory depression denoted respiratory rate < 10 breath/minute. They were repeated at 15, 30, 45, 60 and every 15 minutes until the patients were discharged from PACU. All of the patients were eligible to receive PCA fentanyl for rescue pain. The PCA device contained 100 mL of fentanyl 10 mcg/mL, with the setting of basal infusion of 10 mcg/hour, fentanyl bolus dose 1 mL, lockout interval 5 minutes and 4 hour-limit 300 mcg. Shivering (at least grade 3 of Bedside Shivering Assessment Scales) was treated with 15 mg pethidine intravenously. Patients with complain of nausea, vomiting or retching were treated with an additional 4 mg ondansetron as rescue antiemetic.

Pain, PONV, sedation scores and episode of respiratory depression were assessed in the ICU at 6, 12 and 24 hours after surgery. All parameters were obtained by blinded nursing staff when patients were in PACU or ICU. The total amount of fentanyl consumption was the primary endpoint of the study. Secondary endpoints included pain, PONV, sedation scores and event of respiratory depression.

Sample Size Calculation and Statistical Analysis

There was no published data of scheduled intravenous acetaminophen in TSS patients at the time of study design. Thus, we reviewed the medical record of 15 patients who underwent TSS at KCMH in 2018. All of the patients received continuous intravenous fentanyl infusion for postoperative pain relief. During the first postoperative day, the total dose of fentanyl was 365.8 ± 126.3 mcg. One study had shown that the multimodal analgesia technique could reduce opioid use by approximately 30%.[22] Then we established a minimal clinically important difference (MCID) at 30% of fentanyl consumption between the intervention and placebo group.[23] Base on a two-sample t-test with 80% power at significance level of 5%, an enrollment of 23 patients in each group was needed (the calculated sample size was 22 with estimated number of drop out was 5% in each group).

The primary outcome was the amount of fentanyl use in the first 24 hours reported with mean and standard deviation (SD). Comparison between two groups was conducted by the Student's t-test in case of normal distribution and the non-parametric test was used to test in non-normal distributed data. The secondary outcome, which was the pain score at different time points, was reported with mean and SD, and the differences were compared using Repeated measures ANOVA. The incidence of side effects (nausea, vomiting, drowsiness, respiratory depression) and the number of patients requiring treatment were reported in number and percentage. Comparison of the other secondary outcomes was conducted using Chi-square or Fisher's exact test and Bonferroni correction. *P*-values less than 0.05 were considered significant. All statistical analyses were performed using STATA 14 (College Station, Texas, USA).

Results

The trial flow diagram is presented in Figure 1. Complete primary outcome data were collected on 46 of 47 patients. One was excluded for changing of operative technique from TSS to craniotomy for tumor removal. Both groups were similar in regard to patient characteristics and hormonal tests. (Table 1) There were no significant differences between groups in durations of anesthesia and surgery. There were also no differences in doses of local anesthetics or intraoperative anesthetics including intraoperative fentanyl.

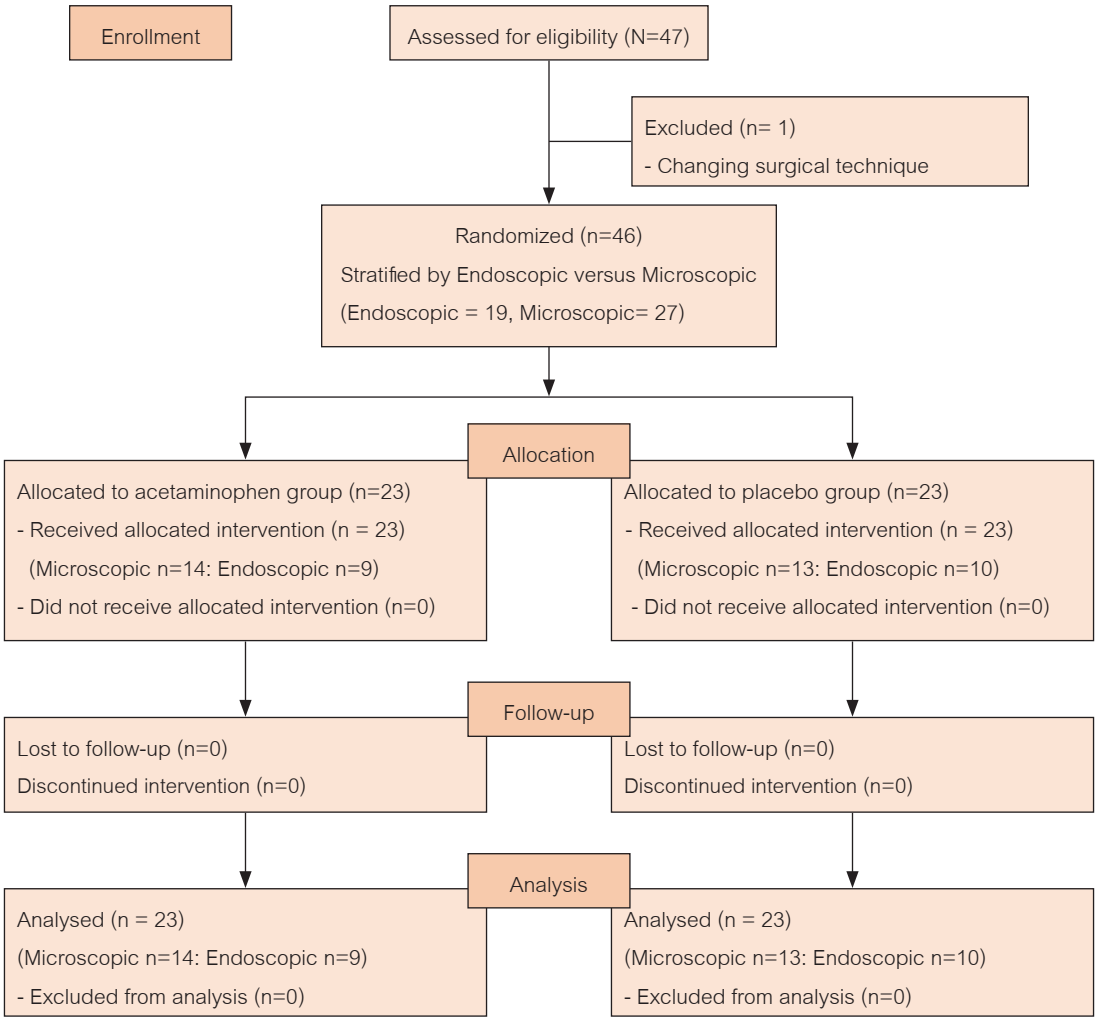


Figure 1 The Consolidated Standards of Reporting Trials (CONSORT) diagram

Table 1 Patient demographics, preoperative and intraoperative data

Parameter	Acetaminophen group (n=23)	Placebo group (n=23)	*P*-value
Age (year)	51.6 ± 13.4	45.6 ± 13.9	0.14
Gender			0.35
Male	11 (47.8)	10 (43.5)	
Female	12 (52.2)	10 (43.5)	
Weight (kg)	72.1 ± 19.2	67.0 ± 10.5	0.50
BMI (kg/m^2)	27.3 ± 7.0	26.3 ± 3.8	0.52
Underlying disease			
Hypertension	5 (21.7)	10 (43.5)	0.12
Diabetes mellitus	5 (21.7)	1 (4.4)	0.08
Dyslipidemia	6 (26.1)	5 (21.7)	0.73
Asthma/COPD	1 (4.4)	0 (0)	0.31
Others	8 (34.8)	6 (26.1)	0.52
ASA physical status			0.54
I	5 (21.7)	6 (26.1)	
II	17 (73.9)	15 (65.2)	
III	1 (4.4)	2 (8.7)	
Diameter of tumor (mm)	26.6 ± 15.3	22.2 ± 10.8	0.27
Type of tumor			0.34
- Functioning	11 (47.8)	13 (56.5)	
- Non-functioning	12 (52.2)	10 (43.5)	
Surgical techniques			0.77
- Microscopic	14 (60.9)	13 (56.5)	
- Endoscopic	9 (39.1)	10 (43.5)	
Patients with endocrine abnormalities			
Growth hormone	14 (60.9)	11 (47.8)	0.38
Prolactin	10 (43.5)	10 (43.5)	1.00
Cortisol	10 (43.5)	9 (39.1)	0.77
FSH, LH	11 (47.8)	16 (69.6)	0.13
Thyroid stimulating hormone	9 (39.1)	6 (26.1)	0.35
Anesthetic time (min)	174.1 ± 52.5	193.8 ± 40.7	0.16
Surgical time (min)	116.3 ± 52.5	137.4 ± 53.0	0.18
Volume of local infiltration (mL)	6.7 ± 3.5	6.6 ±4.6	0.97
Intraoperative anesthetic drugs			
Propofol (mg)	147.0 ± 39.5	159.1± 32.3	0.26
Cis-atracurium (mg)	15.7 ± 5.0	17.1 ± 3.7	0.28
Fentanyl (mcg)	94.4 ± 39.6	92.8 ± 37.9	0.89
LOS in ICU (hours)	20.3 ± 6.1	21.1 ±5.8	0.63

Values are expressed as mean±standard deviation (SD) or number of patients (%). ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; FSH, follicle-stimulating hormone; ICU, intensive care unit; LH, Luteinizing hormone; LOS, length of stay.

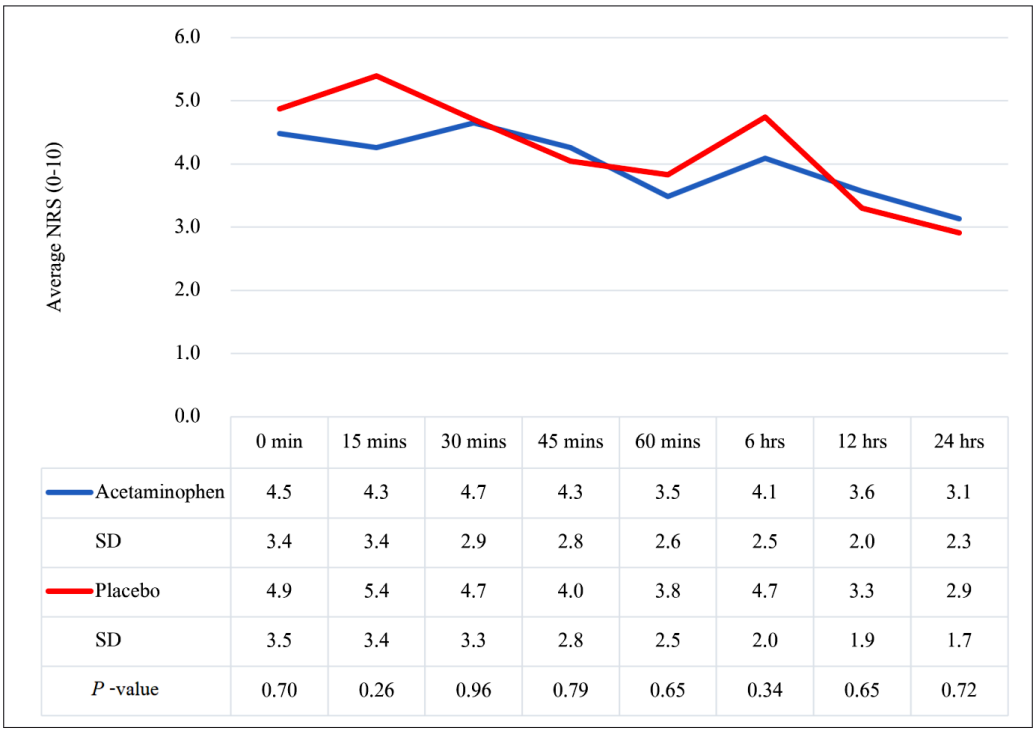
The primary outcomes are presented in Table 2. Although patients in the acetaminophen group required less fentanyl than the placebo group in PACU and there was a trend toward lower fentanyl requirement within the first 24 hours postoperatively, these differences were not statistically significant (245.7±148.4 mcg [95% CI 181.5 to 309.8] vs 314.8±185.0 mcg [95% CI 234.8 to 394.8], *P*-value = 0.17). Adding scheduled acetaminophen to fentanyl was associated with an opioid-sparing effect of 22% (mean -80.3 mcg; 95%CI -29.5 to 190.0; p= 0.15) in the first 24 hours postoperative period.

Table 2 Total doses of fentanyl requirement in PACU and during the first 24 hours postoperative period

Doses of fentanyl consumption (mcg)	Acetaminophen group (n=23)	Placebo group (n=23)	*P*-value
Doses of fentanyl in PACU	38.4 ± 21.8	49.6 ± 36.4	0.21
Doses of fentanyl in ICU	245.7 ± 148.4	314.8 ± 185.0	0.17
Doses of fentanyl in 24 hours	284.1 ± 152.8	364.4 ± 211.7	0.15

Values are expressed as mean±standard deviation (SD). ICU, intensive care unit; PACU, postanesthetic care unit.

At each of the five time points in PACU (0, 15, 30, 45 and 60 minutes), there were differences in NRS scores between acetaminophen and placebo group at 0, 15 and 60 minutes favoring the acetaminophen group. However, none of these differences were large enough to be clinically meaningful. Pain scores in both groups tended to improve over time, but the acetaminophen group was characterized by a slightly decreased mean NRS score. While the placebo group was associated with significant drops at 12 and 24 hours after surgery. (Figure 2)



	0 min	15 mins	30 mins	45 mins	60 mins	6 hrs	12 hrs	24 hrs
Acetaminophen	4.5	4.3	4.7	4.3	3.5	4.1	3.6	3.1
SD	3.4	3.4	2.9	2.8	2.6	2.5	2.0	2.3
Placebo	4.9	5.4	4.7	4.0	3.8	4.7	3.3	2.9
SD	3.5	3.4	3.3	2.8	2.5	2.0	1.9	1.7
P -value	0.70	0.26	0.96	0.79	0.65	0.34	0.65	0.72

Figure 2 Postoperative pain scores based on NRS score (0-10). Pain scores recorded at 0, 15, 30, 45, 60 minutes, 6, 12, and 24 hours after surgery. Standard deviation, SD.

For the additional endpoints that were evaluated, the incidences of both groups' side effects, including PONV, sedation, and respiratory depression at immediate postoperative and at 24 hours postoperative, did not show significant intergroup differences (Table 3). Most patients (73.9% of the acetaminophen group and 56.5% of the placebo group) were satisfied with pain management modalities by satisfaction scores of 9 to 10. According to the Chi-square test, the patients in the acetaminophen group were slightly more satisfied with PCA than those in the placebo group (*P*-value = 0.60).

Table 3 Comparison of adverse events between acetaminophen and placebo groups

Outcomes	Acetaminophen Group (n=23)	Placebo group (n=23)	*P*-value
PONV (nausea/vomiting/retching)			
PACU	3 (13.0)	4 (17.4)	0.68
ICU	3 (13.0)	3 (13.0)	1
Sedation (RASS score < -2)			
PACU	6 (26.1)	5 (21.7)	0.73
ICU	0 (0)	1 (4.4)	0.31
Respiratory depression			
PACU	0 (0)	0 (0)	N/A
ICU	0 (0)	0 (0)	N/A

Values are expressed as number of patients (%). ICU, intensive care unit; PACU, post anesthetic care unit.

Discussion

There are very few studies that examined postoperative pain control following TSS. Shepherd *et al*. designed a randomized double-blinded study of 136 patients undergoing TSS. This study found that intravenous ibuprofen significantly improved pain score and decreased opioid use compare with placebo.[24] Banerjee *et al*. conducted a retrospective study to investigate the impact of single-dose intravenous acetaminophen on opioid consumption, pain scores and side effects. These authors reported that acetaminophen before surgical incision was associated with a reduction in intraoperative opioids, but there were no significant differences in postoperative pain scores, nausea, vomiting, and sedation scores.[25] For our study, we present the result of a prospective, double-blinded, randomized controlled trial that aimed at evaluating the efficacy of scheduled intravenous acetaminophen as an adjuvant in pain management in TSS patients. The intervention group regimen, in which patients received 1,000 mg intravenous acetaminophen before incision and repeated doses, was given every 6 hours for 24 hours after surgery, were not reported in any previous study.

Our first aim was to determine the efficacy of scheduled intravenous acetaminophen on reducing intraoperative and postoperative fentanyl use. We found that the patients in the acetaminophen group required less fentanyl than the placebo group in PACU and there was a trend toward lower fentanyl requirement within the first 24 hours postoperatively. The 24-hour postoperative accumulative dose of fentanyl in the placebo group was 364.4 ± 211.7 mcg, similar to the total dose of fentanyl obtained from the clinical review of the medical records. Adding scheduled acetaminophen to fentanyl was associated with an opioid-sparing effect of 22%, comparable to a 23% decrease in fentanyl equivalents observed in a previous study.[25] These data suggest that scheduled intravenous acetaminophen may reduce postoperative opioid requirement

compared with placebo. However, our imprecision estimated MCID at 30% fentanyl reduction, thus we are unable to show a statistically significant difference between the study and placebo group.

We found that pain scores following TSS were mild to moderate. The mean NSR score in PACU and ICU in the acetaminophen group were 4.2 ± 2.9 and 3.6 ± 2.1 respectively, while 4.4 ± 3.3 and 3.7 ± 1.7 in the placebo group. Most patients reported good pain control with a high satisfaction score (9-10) in both groups.

The second aim of our study was to investigate the impact of acetaminophen on opioid side effects. We examined several outcomes such as PONV, sedation and respiratory depression. Our study shows that scheduled intravenous acetaminophen had no significant effects on PONV. This finding is not correlated with other previous studies in different surgical procedures in which acetaminophen is superior to placebo in reducing the incidence and severity of PONV.[17,26] Causes of PONV in TSS patients are complex, including dural irritation, trigeminal nerve stimulation, and gastric distension by swallowed blood. Severe PONV may lead to surgical wound bleeding and cerebrospinal fluid leak.[27] The overall incidence of immediate PONV in our study was 15.2% higher than previous reports for transsphenoidal surgery.[27-28] Thus, PONV is still considerably problematic among TSS patients and should be aggressively managed as our protocol was designed that ondansetron was given in every patient.

We also examined additional outcomes such as sedation and respiratory depression but did not find a significant difference between the study and placebo group.

Study Limitation

Limitations of this study include the impact of study size and low precision. A further larger randomized controlled trial should be conducted to confirm these findings. The variability demonstrated by the wide CIs, associated with the primary outcomes measure a total dose of fentanyl consumption and the secondary outcome measures, undermines the ability to make a definitive conclusion from the sample data.

Conclusion

The results of this study are inconclusive. The data suggest that the scheduled intravenous acetaminophen can reduce a total 24-hour postoperative fentanyl consumption by 22% compared with placebo. However, this difference was not statistically significant. Significant differences were also not identified in secondary outcome parameters, including nausea and vomiting, sedation, and respiratory depression.

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