

# Association between intravenous acetaminophen and reduction in intraoperative opioid consumption during transsphenoidal surgery for pituitary tumors

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## Abstract

**Background and Aims:** Pain during and after transsphenoidal surgeries originates from stimulation of branches of the trigeminal cranial nerve that supply the inner aspect of the nose cavity and dura mater. Thereby, patients undergoing transsphenoidal surgery may require moderate-to-large amounts of analgesics including opioids. Intravenous acetaminophen provides analgesia and reduces opioid consumption for a wide variety of surgeries. We hypothesized that the use of intravenous acetaminophen is associated with a reduction in intraoperative opioid consumption and provides significant analgesia during and after transsphenoidal surgery.

**Material and Methods:** This retrospective study included 413 patients who underwent transsphenoidal surgery for pituitary adenomas. The primary outcome of this study was intraoperative opioid consumption. Secondary outcomes included pain intensity, Richmond Agitation Sedation Scale scores, and nausea and vomiting upon arrival to postoperative anesthesia care unit. Patients were divided into two groups based on the intraoperative acetaminophen use. A propensity score matching analysis was used to balance for important variables between the two groups of treatment. Regression models were fitted after matching the covariates. A  $P < 0.05$  was considered statistically significant.

**Results:** After matching, 126 patients were included in each group of treatment. Patients in the acetaminophen group required significantly less amount (a decrease by 14.9%) of opioids during surgery than those in the non-acetaminophen group. Postoperative pain, postoperative nausea and vomiting, and sedation scores were not significantly different between patients who received intravenous acetaminophen and those who did not.

**Conclusion:** Intravenous acetaminophen is associated with a reduction in intraoperative opioids during transsphenoidal pituitary surgery.

**Keywords:** Acetaminophen, opioids, pituitary adenoma, transsphenoidal surgery

## Introduction

Pituitary adenomas are intracranial neoplasms arising from the anterior lobe of the pituitary gland.<sup>[1,2]</sup> Treatments for

pituitary adenoma include transsphenoidal resection along with medical treatment and/or radiotherapy.<sup>[3]</sup> As is true for many other neurosurgical procedures, one of the important aspects of successful transsphenoidal surgery includes adequate analgesia. Insufficient analgesia can be associated with agitation, hypertension, and vomiting, which increase the risk of postoperative hemorrhage and return to the operating

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**How to cite this article:** Banerjee U, Hagan K, Bhavsar S, Grasu R, Dang A, McCutcheon IE, et al. Association between intravenous acetaminophen and reduction in intraoperative opioid consumption during transsphenoidal surgery for pituitary tumors. *J Anaesthesiol Clin Pharmacol* 2018;34:465-71.

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10.4103/joacp.JOACP\_276\_17

room.<sup>[4]</sup> Postoperative pain after transsphenoidal procedures is usually controlled by opioid analgesics or nonsteroidal anti-inflammatory drugs (NSAIDs) which have several adverse effects including opioid-related sedation and respiratory depression, and bleeding.<sup>[5]</sup> Therefore, a safer and more effective alternative such as intravenous acetaminophen may be considered for pain control after transsphenoidal surgery.

Acetaminophen is a cyclooxygenase inhibitor that is used worldwide as a centrally acting analgesic.<sup>[6]</sup> It also modulates serotonergic pathways.<sup>[6]</sup> Acetaminophen produces effective analgesia without severe side effects, unlike opioids or NSAIDs.<sup>[7]</sup> Intravenous acetaminophen has a faster action, attains a greater peak plasma concentration, and takes effect sooner than oral acetaminophen.<sup>[8,9]</sup> Studies have shown that intravenous acetaminophen has opioid-sparing effects and allows rapid emergence from general anesthesia.<sup>[10]</sup> Hong *et al.* demonstrated the fentanyl-sparing effects of intravenous acetaminophen along with reduction in opioid side effects such as nausea, vomiting, and sedation.<sup>[11]</sup> A retrospective cohort study of patients who underwent ear, nose, and throat procedures demonstrated a significant reduction in early postoperative pain when intravenous acetaminophen was given, although there was no difference in morphine consumption.<sup>[12]</sup> Similarly, a randomized controlled trial has shown that acetaminophen is more effective than placebo in providing analgesia and that it decreases the need for rescue treatments with oxycodone during the first 4 h after sinus surgery.<sup>[13]</sup>

Our goal was to investigate the impact of the use of intravenous acetaminophen on opioid consumption, sedation, and postoperative nausea and vomiting (PONV) following transsphenoidal surgery. The primary hypothesis is that intravenous acetaminophen is associated with a reduction in opioid consumption and improved analgesia compared with no acetaminophen after transsphenoidal surgery for pituitary adenoma. Our secondary hypothesis is that intravenous acetaminophen is associated with a decrease in opioid-related adverse events such as nausea, vomiting, and sedation.

## Material and Methods

After approval from the MD Anderson Cancer Center Institutional Review Board (PA12-0447), a retrospective cohort study was conducted that included data from adult ( $\geq 18$  years old) patients who underwent scheduled transsphenoidal procedures for pituitary tumor performed between June 2008 and February 2016. Patients who had emergency surgery (for pituitary apoplexy) and those who

underwent surgery for craniopharyngiomas, metastasis to the pituitary, or Rathke's cleft cysts were excluded from the study. Preoperative demographic data included age, gender, body mass index, history of previous pituitary surgery, type of pituitary tumor (macroadenoma versus microadenoma), history of chronic pain, chronic opioid use, and history of headaches. The following intraoperative variables were collected: intravenous acetaminophen administration, intravenous opioids and midazolam use, intravenous corticosteroid administration, surgical approach (endonasal versus sublabial), spinal drain placement, and duration of anesthesia. One surgeon who performs only microscopic surgery operated most patients. Postoperative data included Richmond Agitation Sedation Scale (RASS) score upon arrival to the postoperative anesthesia care unit (PACU), average and maximum pain score (verbal numeric rating scale: 0, no pain and 10, worst pain ever), and average and maximum nausea score (verbal numeric rating scale: 0, no nausea and 10, worst nausea ever) and vomiting.

The anesthesia technique consisted of general balanced anesthesia. Typically, induction of general anesthesia was obtained with propofol and fentanyl followed by intravenous administration of rocuronium or succinylcholine. Maintenance of general anesthesia consisted of the coadministration of a volatile anesthetic agent (desflurane, sevoflurane, or isoflurane), intravenous opioids (sufentanil, fentanyl, remifentanil, or hydromorphone), either as a bolus dose or continuous intravenous infusion, and propofol infusion according to clinical judgment. Intravenous acetaminophen (1,000 mg) was typically given before surgical incision and was repeated only in cases extending beyond 6 h according to the anesthesiologist's clinical judgment. Sublabial infiltration with 1%–2% lidocaine and endonasal topical administration of cocaine was performed before incision in all cases. Postoperative analgesia consisted of administration of intravenous opioids (morphine, fentanyl, or hydromorphone) according to the anesthesiologist's or surgical team's clinical judgment. All intravenous opioids administered intraoperatively during surgery and in PACU were converted to fentanyl equivalents.<sup>[14,15]</sup>

## Statistical analysis

Patients were divided into two groups according to the intraoperative administration of intravenous acetaminophen (yes versus no). The primary outcome of this study was intraoperative opioid consumption. Secondary outcomes included pain intensity, RASS scores, and nausea and vomiting upon arrival to PACU. Descriptive statistics were used to analyze continuous and categorical variables. Comparison of continuous and categorical variables between the treatment groups was done using Wilcoxon's rank-sum test and Chi-square test, respectively. Hodges–Lehmann

estimation was done to calculate the differences in medians with confidence intervals. The distribution of continuous variables was assessed using Q–Q plot and histograms. The balance between the treatment groups was evaluated using standardized differences after propensity score matching (PSM) in a 1:1 ratio to control for confounders. A standardized difference of  $<0.15$  was considered to be an adequate matching. Regression models were fitted after matching the covariates. To assess the association of intravenous acetaminophen use on pain, RASS score, and PONV, we used multivariable logistic regression. We normalized the cumulative opioid consumption with log transformation and estimated the effects of intravenous acetaminophen on opioid consumption using a repeated-measures linear regression model. Based on a previous study indicating that the average morphine equivalent consumption in PACU after pituitary surgery was 6.3 mg and assuming a standard deviation of 4 mg, we estimated that 104 patients in each group would be needed to demonstrate a 30% reduction in opioids.<sup>[16]</sup>

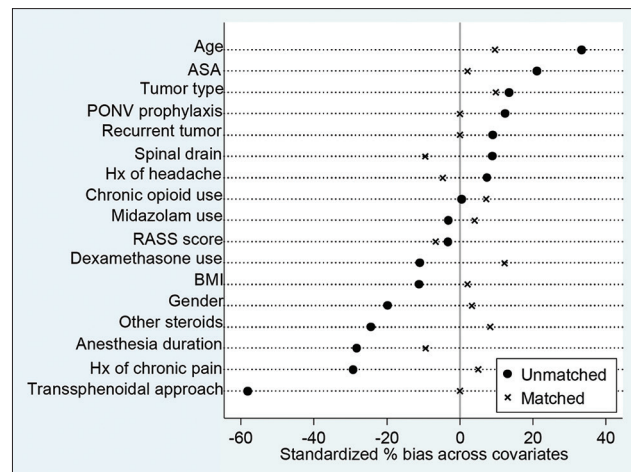
All data were expressed as mean (standard deviation), median (Q1, Q3), or the number (%) of patients. Statistical significance was set at  $\alpha = 0.05$  with a desired power ( $\beta$ ) of 0.9. Statistical analysis was performed using STATA v14 (StataCorp, College Station, TX, USA).

## Results

A total of 413 patients were included in this study. The baseline, intraoperative, and postoperative characteristics of the patients are given in Table 1. In all, 185 patients were in the acetaminophen group and 228 patients were in the group that did not receive acetaminophen. Before matching, patients in the acetaminophen group were significantly older, included fewer women, and presented a lower rate of chronic pain than those who did not receive acetaminophen [Table 1]. The duration of anesthesia and non-dexamethasone steroid use was slightly but significantly shorter and higher, respectively, in the acetaminophen group than in the non-acetaminophen group. After matching, there were no statistically significant differences in other demographic, intraoperative, and postoperative variables between the treatment groups [Table 1 and Figure 1].

### Opioid consumption

Both before and after matching, the intraoperative consumption of fentanyl equivalents was significantly lower in the acetaminophen group than in the non-acetaminophen group [Table 2]. In addition, the post-matching analysis showed that patients in the acetaminophen group required 23% less fentanyl equivalents than those in the non-acetaminophen



**Figure 1:** Standardized differences between surgical patients who received IV acetaminophen and those who did not. The standardized differences  $<15\%$  show adequate matching. BMI=Body mass index, ASA=American Society of Anesthesiologists, Hx=History, RASS=Richmond Agitation Sedation Scale

group [Table 2]. After PSM, the analysis demonstrated a significant negative association between the administration of acetaminophen and opioid consumption. For each 1,000 mg use in acetaminophen dose, we found a 14.87% decrease in opioid dose [95% confidence interval (CI): 0.742–0.976;  $P = 0.021$ ] (coeff:  $-0.161$ ; 95% CI:  $-0.298$  to  $-0.024$ ;  $P = 0.021$ ). For PACU fentanyl equivalents consumption, there were not statistically significant differences between the two groups [Table 2].

### Postoperative anesthesia care unit pain scores

Before and after PSM, the median PACU average and highest pain scores were nearly identical in both groups of patients [Table 2]. Before matching, the proportion of patients reporting severe pain was smaller in the acetaminophen group than in the non-acetaminophen group, with more patients in the former group reporting no pain ( $P = 0.052$ ). Post-matching, the proportion of patients having pain was similar in acetaminophen and non-acetaminophen groups. [Table 2]. After adjusting for intraoperative and postoperative fentanyl equivalents, the post-matching ordinal logistic regression analysis showed no association between acetaminophen and postoperative pain in PACU [odds ratio (OR): 0.551; 95% CI: 0.231–1.318;  $P = 0.181$ ].

### Postoperative nausea and vomiting

Before and after PSM, the median highest and median average nausea scores were not different between patients treated with and without intravenous acetaminophen [Table 2]. Similarly, the administration of acetaminophen was not associated with a change in the proportion of patients with mild to moderate and severe nausea in comparison to the non-acetaminophen group [Table 2]. The rate of postoperative vomiting did not differ in the two study groups before and after PSM.

**Table 1: Demographic, perioperative, intraoperative, and postoperative variables in pituitary tumor patients undergoing transsphenoidal hypophysectomy**

	Acetaminophen						
	Before matching			After matching			
	Yes (n=185)	No (n=228)	P	Yes (n=126)	No (n=126)	Standardized difference (%)	P
Age (years), mean (SD)	49.8 (15.4)	44.7 (15.4)	0.001	47.2 (15.3)	45.7 (15.8)	9.6	0.430
Gender, n (%)							
Female	103 (55.7)	149 (65.4)	0.045	80 (63.5)	78 (61.9)	3.3	0.794
Male	82 (44.3)	79 (34.7)		46 (36.5)	48 (38.1)		
BMI, mean (SD)	33.1 (8.9)	34.0 (9.0)	0.211	33.8 (9.1)	33.6 (7.9)	2.1	0.847
ASA, n (%)							
1-2	27 (14.6)	52 (22.8)	0.035	23 (18.3)	24 (19.1)	2.0	0.872
3-4	158 (85.4)	176 (77.2)		103 (81.8)	102 (81.0)		
Tumor type, n (%)							
Macroadenoma	120 (64.9)	133 (58.3)	0.175	76 (60.3)	70 (55.6)	9.8	0.444
Microadenoma	65 (35.1)	95 (41.7)		50 (39.7)	56 (44.4)		
Headache, n (%)							
No	88 (47.6)	117 (51.3)	0.449	62 (49.2)	59 (46.9)	-4.8	0.705
Yes	97 (52.4)	111 (48.7)		64 (50.8)	67 (53.2)		
Chronic pain, n (%)							
No	132 (71.6)	131 (57.5)	0.004	80 (63.5)	83 (65.9)	5.0	0.693
Yes	53 (28.7)	97 (42.5)		46 (36.5)	43 (34.1)		
Chronic opioid, n (%)							
No	162 (87.6)	200 (87.8)	0.963	107 (85.0)	110 (87.3)	7.2	0.585
Yes	23 (12.4)	28 (12.3)		19 (15.1)	16 (12.7)		
Anesthesia duration (min), mean (SD)	259.4 (58.5)	277.4 (68.7)	0.004	263.3 (61.9)	269.4 (63.7)	-9.5	0.336
Recurrent tumor, n (%)							
No	146 (78.9)	188 (82.5)	0.363	99 (78.6)	99 (78.6)	0.0	1.000
Yes	39 (21.1)	40 (17.5)		27 (21.4)	27 (21.4)		
Approach, n (%)							
Endonasal	178 (96.2)	176 (77.2)	<0.001	119 (94.4)	119 (94.4)	0.0	1.000
Sublabial	7 (3.8)	52 (22.81)		7 (5.6)	7 (5.6)		
Spinal drain, n (%)							
No	140 (75.7)	181 (79.4)	0.368	100 (79.4)	95 (75.4)	-9.5	0.452
Yes	45 (24.3)	47 (20.6)		26 (20.6)	31 (24.6)		
Dexamethasone (intraoperative), n (%)							
No	154 (83.2)	180 (79.0)	0.270	99 (78.6)	105 (83.3)	12.2	0.336
Yes	31 (16.8)	48 (21.1)		27 (21.4)	21 (16.7)		
Other steroids (intraoperative), n (%)							
No	128 (69.2)	131 (57.5)	0.037	78 (61.9)	83 (65.9)	8.3	0.512
Yes	57 (30.8)	97 (42.1)		48 (38.1)	43 (34.1)		
Midazolam, n (%)							
No	38 (20.5)	44 (19.3)	0.753	27 (21.4)	29 (23.0)	4.0	0.762
Yes	147 (79.5)	184 (80.7)		99 (78.6)	97 (77.0)		

The standardized differences <15% show adequate matching. BMI=Body mass index, ASA=American Society of Anesthesiologists, SD=Standard deviation

After adjusting for the intraoperative and postoperative fentanyl equivalents, logistic regression after PSM showed no association between acetaminophen and postoperative vomiting (OR: 0.410; 95% CI: 0.077–2.193;  $P = 0.297$ ).

### Richmond Agitation Sedation Scale score

RASS scores were not different between the two groups of patients [Table 2]. The median RASS score was also similar between groups before and after PSM [Table 2].

Before matching, the proportion of patients showing mild to moderate and deep sedation was slightly smaller in patients who were treated with acetaminophen compared with those who did not receive it. After PSM, almost the same proportion of patients in both groups had mild to moderate, or deep sedation. Post-matching ordinal logistic regression analysis showed no association between acetaminophen use and postoperative RASS score (OR: 0.855; 95% CI: 0.508–1.437;  $P = 0.553$ ).

**Table 2: Effect of acetaminophen versus no acetaminophen on opioid dose, pain, postoperative nausea and vomiting, and Richmond Agitation Sedation Scale in pituitary tumor patients undergoing transsphenoidal hypophysectomy**

Variable	Acetaminophen					
	Before matching			After matching		
	Yes (n=185)	No (n=228)	P	Yes (n=124)	No (n=124)	P
Intraoperative fentanyl equivalent, median (Q1, Q3)	550.00 (315.6, 925.0)	845.23 (639.1, 1193.1)	<0.001	626.9 (394.2, 988.8)	809.4 (541.1, 1151.2)	0.003
Postoperative fentanyl equivalent, median (Q1, Q3)	100 (25, 200)	100 (50, 200)	0.682	125 (31.25, 200)	100 (50, 193.6)	0.480
Highest pain, median (Q1, Q3)	7 (5, 8)	6 (5, 8)	0.594	6 (5, 8)	6 (5, 8)	0.192
Average pain, median (Q1, Q3)	3 (1.6, 4.3)	3 (1.85, 4.2)	0.287	3.1 (1.8, 4.5)	2.8 (1.6, 4)	0.164
Pain, n (%)						
No	18 (9.8)	12 (5.3)	0.052	12 (9.7)	6 (4.8)	0.276
Mild to moderate	163 (88.1)	203 (89.0)		109 (87.9)	113 (91.1)	
Severe	4 (2.2)	13 (5.7)		3 (2.4)	5 (4.0)	
Highest nausea, median (Q1, Q3)	0 (0, 1)	0 (0, 0)	0.684	0 (0, 2)	0 (0, 0)	0.150
Average nausea, median (Q1, Q3)	0 (0, 0.3)	0 (0, 0)	0.929	0 (0, 0.2)	0 (0, 0)	0.165
Nausea, n (%)						
No	137 (74.1)	174 (76.3)	0.490	90 (72.6)	99 (79.8)	0.180
Mild to moderate	47 (25.4)	54 (23.7)		34 (27.4)	25 (20.2)	
Severe	1 (0.5)	0 (0)		0 (0)	0 (0)	
Vomiting, n (%)	5 (2.7)	10 (4.4)	0.363	2 (1.7)	5 (4.03)	0.25
Time to first RASS (min), median (Q1, Q3)	237 (195, 272)	241 (215, 298)	0.007	240 (208, 277.5)	240 (204.5, 283.5)	0.812
RASS score, median (Q1, Q3)	-1 (-1, 0)	-1 (-1, 0)	0.348	-1 (-1, 0)	-1 (-1, 0)	0.559
RASS, n (%)						
Restless - agitated	10 (5.4)	5 (2.2)	0.139	8 (6.4)	2 (1.6)	0.124
Alert-calm	60 (32.4)	72 (31.6)		36 (29.0)	38 (30.6)	
Mild to moderate sedation	110 (59.5)	149 (65.4)		76 (61.3)	83 (66.9)	
Deep sedation - unarousable	5 (2.7)	2 (0.9)		4 (3.2)	1 (0.8)	

<sup>†</sup>Hodges-Lehmann median differences. RASS=Richmond Agitation Sedation Scale, CI=Confidence interval, Q1=First quartile, Q3=Third quartile



## Discussion

This is the first study to investigate the impact of intravenous acetaminophen on opioid consumption, postoperative pain scores, and opioid-related side effects after transsphenoidal surgery for pituitary microadenoma and macroadenoma. Our analysis demonstrates that the intraoperative administration of intravenous acetaminophen is associated with a reduction in intraoperative opioid consumption. Consistent with our findings, Kempainen *et al.* demonstrated in a randomized placebo-controlled study that intravenous acetaminophen had an opioid-sparing effect in patients undergoing endoscopic sinus surgery.<sup>[13]</sup> Our results are supported by a meta-analysis conducted by McNicol *et al.* who reported that intravenous acetaminophen has significant opioid-sparing effects.<sup>[17]</sup> In that meta-analysis, the average reduction in opioids was 26%, which is similar to the 23% decrease in fentanyl equivalents observed in our study.<sup>[17]</sup>

Our work indicates that the effect of intraoperative intravenous acetaminophen is limited to the duration of surgery since we were unable to show an association with improvements in postoperative pain scores or postoperative opioid consumption in PACU. This finding is not surprising since the analgesic effect of intravenous acetaminophen only lasts 4–6 h, and the mean duration of anesthesia of our group of patients was 4.3 h. Furthermore, patients included in our study were not routinely re-dosed intraoperatively. A recent study by Hoefnagel *et al.* supports our findings.<sup>[18]</sup> In that study, the intraoperative administration of acetaminophen had no impact on the average PACU pain scores and the average opioid use in PACU after craniotomy.

Avoidance of nausea and vomiting in patients undergoing pituitary surgery is desired to reduce the risk of postoperative bleeding and cerebrospinal fluid leak.<sup>[19]</sup> No study has investigated the impact of acetaminophen on PONV after transsphenoidal surgery. Our study shows that a single dose of intravenous acetaminophen had no significant effect on PONV. This contradicts the findings of studies conducted in different surgical settings in which acetaminophen is superior to placebo in reducing the severity and incidence of PONV.<sup>[20-23]</sup> One possible explanation for our finding is that despite a reduction in opioids and the use of prophylactic therapy, PONV in patients undergoing transsphenoidal surgery has a complex mechanism that may involve dural irritation or trigeminal nerve stimulation as well as the gastric irritation by swallowed blood.<sup>[16]</sup> It is worth mentioning that the overall rate of PONV in our study is higher (24.4%) than that reported for transsphenoidal surgery.<sup>[16,24,25]</sup> This can be explained by the fact that only a third of the patients

received dexamethasone for PONV prophylaxis despite the fact that 97.09% had intravenous ondansetron.

We also investigated whether the intraoperative use of acetaminophen was associated with less sedation at the time of arrival to PACU. Our analysis indicates that despite a reduction in intraoperative opioids, the RASS scores were similar in both groups of patients (median RASS = -1) and approximately 90% of the patients had scores between 0 and -1. Although the impact of intravenous acetaminophen on postoperative sedation scores has not been investigated in the context of pituitary surgery, other studies have demonstrated mixed results.<sup>[22,23,26-28]</sup> It is possible that our study is underpowered to show a statistically significant difference between groups of patients with extreme RASS scores, or that a true association does not exist.

Our study has several limitations. First, there is always a chance of confounders since it is a retrospective study. Selection and recall bias are major limitations of studies like ours. We tried to address this by PSM to balance the covariates. Provider bias could have confounded the findings of this study. It is possible to speculate that providers who favor the use of acetaminophen also try to use opioids in a lower amount. Second, all patients in our study received preoperative prophylactic antiemetics such as ondansetron (97.09%). Previous research has shown that acetaminophen modulates the serotonin pathway as well; therefore, serotonin inhibitors such as ondansetron may interact with the analgesic action of acetaminophen.<sup>[6]</sup> Third, patients in the treatment group received only a single dose of intravenous acetaminophen. Our results have no data regarding the effect of repeated doses of acetaminophen in the PACU.

## Conclusion

The intraoperative administration of acetaminophen is associated with opioid-sparing effects. Our results should not be generalized since our study was retrospective and conducted in pituitary tumor patients who underwent transsphenoidal surgery in a single hospital. A randomized controlled trial should be conducted to confirm these findings.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## References

- Kontogeorgos G, Kovacs K, Horvath E, Scheithauer BW. Multiple adenomas of the human pituitary. A retrospective autopsy study with clinical implications. *J Neurosurg* 1991;74:243-7.
- Molitch ME, Russell EJ. The pituitary "incidentaloma." *Ann Intern Med* 1990;112:925-31.
- Molitch ME. Diagnosis and treatment of pituitary adenomas: A review. *JAMA* 2017;317:516-24.
- Magni G, La Rosa I, Melillo G, Abeni D, Hernandez H, Rosa G, *et al.* Intracranial hemorrhage requiring surgery in neurosurgical patients given ketorolac: A case-control study within a cohort (2001-2010). *Anesth Analg* 2013;116:443-7.
- Cazacu I, Mogosan C, Loghin F. Safety issues of current analgesics: An update. *Clujul Med* 2015;88:128-36.
- Pickering G, Loriot MA, Libert F, Eschaliere A, Beaune P, Dubray C, *et al.* Analgesic effect of acetaminophen in humans: First evidence of a central serotonergic mechanism. *Clin Pharmacol Ther* 2006;79:371-8.
- Bannwarth B, Péhourcq F. Pharmacologic basis for using paracetamol: Pharmacokinetic and pharmacodynamic issues. *Drugs* 2003;63:5-13.
- Moller PL, Sindet-Pedersen S, Petersen CT, Juhl GI, Dillenschneider A, Skoglund LA, *et al.* Onset of acetaminophen analgesia: Comparison of oral and intravenous routes after third molar surgery. *Br J Anaesth* 2005;94:642-8.
- Brett CN, Barnett SG, Pearson J. Postoperative plasma paracetamol levels following oral or intravenous paracetamol administration: A double-blind randomised controlled trial. *Anaesth Intensive Care* 2012;40:166-71.
- Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: Meta-analysis of randomized controlled trials. *Br J Anaesth* 2005;94:505-13.
- Hong JY, Kim WO, Koo BN, Cho JS, Suk EH, Kil HK, *et al.* Fentanyl-sparing effect of acetaminophen as a mixture of fentanyl in intravenous parent-/nurse-controlled analgesia after pediatric ureteroneocystostomy. *Anesthesiology* 2010;113:672-7.
- Khobrani MA, Camamo JM, Patanwala AE. Effect of intravenous acetaminophen on post-anesthesia care unit length of stay, opioid consumption, pain, and analgesic drug costs after ambulatory surgery. *P T* 2017;42:125-39.
- Kemppainen T, Kokki H, Tuomilehto H, Seppä J, Nuutinen J. Acetaminophen is highly effective in pain treatment after endoscopic sinus surgery. *Laryngoscope* 2006;116:2125-8.
- Cata JP, Zafereo M, Villarreal J, Unruh BD, Truong A, Truong DT, *et al.* Intraoperative opioids use for laryngeal squamous cell carcinoma surgery and recurrence: A retrospective study. *J Clin Anesth* 2015;27:672-9.
- Cata JP, Keerty V, Keerty D, Feng L, Norman PH, Gottumukkala V, *et al.* A retrospective analysis of the effect of intraoperative opioid dose on cancer recurrence after non-small cell lung cancer resection. *Cancer Med* 2014;3:900-8.
- Flynn BC, Nemergut EC. Postoperative nausea and vomiting and pain after transsphenoidal surgery: A review of 877 patients. *Anesth Analg* 2006;103:162-7.
- McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database Syst Rev* 2016;5:CD007126.
- Hoefnagel AL, Lopez M, Mitchell K, Smith DI, Feng C, Nadler JW. Intravenous acetaminophen administration in patients undergoing craniotomy – A retrospective institutional study. *J Anesth Clin Res* 2015;6:658.
- Habib AS, Keifer JC, Borel CO, White WD, Gan TJ. A comparison of the combination of aprepitant and dexamethasone versus the combination of ondansetron and dexamethasone for the prevention of postoperative nausea and vomiting in patients undergoing craniotomy. *Anesth Analg* 2011;112:813-8.
- Arici S, Gurbet A, Türker G, Yavaşcaoglu B, Sahin S. Preemptive analgesic effects of intravenous paracetamol in total abdominal hysterectomy. *Agri* 2009;21:54-61.
- Cakan T, Inan N, Culhaoglu S, Bakkal K, Başar H. Intravenous paracetamol improves the quality of postoperative analgesia but does not decrease narcotic requirements. *J Neurosurg Anesthesiol* 2008;20:169-73.
- Hong JY, Kim WO, Chung WY, Yun JS, Kil HK. Paracetamol reduces postoperative pain and rescue analgesic demand after robot-assisted endoscopic thyroidectomy by the transaxillary approach. *World J Surg* 2010;34:521-6.
- Moon YE, Lee YK, Lee J, Moon DE. The effects of preoperative intravenous acetaminophen in patients undergoing abdominal hysterectomy. *Arch Gynecol Obstet* 2011;284:1455-60.
- Burkhardt T, Rotermond R, Schmidt NO, Kiefmann R, Flitsch J. Dexamethasone PONV prophylaxis alters the hypothalamic-pituitary-adrenal axis after transsphenoidal pituitary surgery. *J Neurosurg Anesthesiol* 2014;26:216-9.
- Chowdhury T, Prabhakar H, Bithal PK, Schaller B, Dash HH. Immediate postoperative complications in transsphenoidal pituitary surgery: A prospective study. *Saudi J Anaesth* 2014;8:335-41.
- Hashemi SM, Esmaelajah A, Golzari S, Keyhani S, Maserrat A, Mohseni G, *et al.* Intravenous paracetamol versus patient-controlled analgesia with morphine for the pain management following diagnostic knee arthroscopy in trauma patients: A randomized clinical trial. *Arch Trauma Res* 2015;4:e30788.
- Faiz HR, Rahimzadeh P, Visnjevac O, Behzadi B, Ghodrati MR, Nader ND, *et al.* Intravenous acetaminophen is superior to ketamine for postoperative pain after abdominal hysterectomy: Results of a prospective, randomized, double-blind, multicenter clinical trial. *J Pain Res* 2014;7:65-70.
- Memis D, Inal MT, Kavalci G, Sezer A, Sut N. Intravenous paracetamol reduced the use of opioids, extubation time, and opioid-related adverse effects after major surgery in Intensive Care Unit. *J Crit Care* 2010;25:458-62.