


The Role of Intravenous Acetaminophen in Post-Operative Pain Control in Head and Neck Cancer Patients

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Objective: This study investigated the role of intravenous acetaminophen for alleviation of postoperative pain after surgical resection of head and neck cancers.

Methods: A single-center study was conducted, which investigated a prospective group of 48 participants who underwent surgery between April 2016 and May 2017 and postoperatively received scheduled IV acetaminophen (1 g every 6 hours for 4 doses) plus the standard opioid PCA and breakthrough narcotics. These were compared to a similar retrospective cohort of 51 patients who had surgery between January 2014 to March 2015 and only received an opioid patient controlled analgesia (PCA) pump and breakthrough narcotics. Outcome measures included averaged pain scores, total amount of narcotics received (in morphine equivalents), and number of PCA attempts measured in 8-hour intervals over the first 24 hours, as well as duration of PCA and length of stay. Statistical measures included descriptive analysis and gamma regression analysis.

Results: The acetaminophen group achieved equally low pain scores (0.8 ± 1.2 vs. 1.0 ± 1.3 , $P = .408$) with significantly less total narcotics in the first 8 hours after surgery (13.5 ± 13.3 vs. 22.5 ± 21.5 MEs, $P = .014$). This group had a significantly decreased length of stay (7.8 ± 4.6 vs. 10.6 ± 7.6 days, $P = .03$).

Conclusion: This study demonstrates that intravenous acetaminophen may play a role in reducing the total narcotic requirement in the first 8 hours after surgery and contribute to a decreased length of stay and potentially decrease cost to the patient and hospital overall. Future research should be aimed at comparing these groups in a randomized control study/setting.

Key Words: Postoperative pain, head and neck surgery, IV acetaminophen, postoperative opioids, multimodal analgesia, otolaryngology.

Level of Evidence: 3

INTRODUCTION

The role of opioid medications in pain management has become a contentious topic over the last two decades as the number of opioid prescriptions and associated prescription opioid deaths have been rapidly increasing.¹ There are over 55,000 cases of head and neck cancer in the United States annually,² and cancer pain is experienced in up to 80% to 100% of these patients.³⁻⁶ Surgical resection is

one of the most common treatment modalities, and postoperative pain management has traditionally consisted of intravenous and oral opiates. At our institution, the current standard of care is a postoperative morphine, fentanyl, or hydromorphone patient controlled analgesia (PCA) pump for patients undergoing large cancer resections. Opiates are known to have many adverse effects including nausea, emesis, constipation, urinary retention, and dysphoria, as well as more serious reactions such as respiratory depression, hypotension, and bradycardia.⁷

There have been few studies that investigate how to optimally manage postoperative pain in head and neck.³⁻⁶ IV acetaminophen was FDA approved in 2010 for the treatment of acute pain and fever in adults and children. IV acetaminophen does not cause an increased incidence of nausea, vomiting, constipation, or respiratory depression that is seen with opiates and has been shown to have a higher plasma maximum concentration than its oral or rectal counterpart. It has been well-studied in improving pain control and decreasing opiate requirements in orthopedic surgery patients.⁸ At this time, however, its role in improving pain control in head and neck surgery is limited to pediatric tonsillectomies, where it has been shown to give better pain control and be more cost-effective than opioids alone.⁹

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In this study we examine the role of acetaminophen in the pain management of postoperative patients undergoing surgery for resection of a head and neck cancer. We compare a prospective cohort of patients who received scheduled IV acetaminophen for the first 24 hours after surgery and the standard postoperative PCA pump and breakthrough narcotics to a retrospective cohort of patients who received a standard postoperative PCA pump and breakthrough narcotics. We hypothesize that the acetaminophen group will have decreased pain scores and PCA attempts and require decreased total amount of narcotics, measured in morphine equivalents, in the first 24 hours after surgery.

MATERIALS AND METHODS

Approval for this study was obtained from the University of Mississippi Medical Center Institutional Review Board. Participants in the prospective arm of the study signed an informed consent regarding the study's goals, rationale, risks, design, and voluntary nature.

Study Sample

Adults (≥ 18 years) with advanced stage or recurrent head and neck cancer requiring a major surgical resection were candidates for enrollment in this study. This included patients who underwent a surgery that required a narcotic PCA for the first 24 hours, including but not limited to, glossectomy with neck dissection, composite oral resection with a neck dissection, mandibulectomy, laryngectomy, and upper/lower extremity free flap reconstruction. Patients were excluded if they required sedation for the first 24 hours postoperatively, were unable to report a pain score, had known liver failure, or had an allergy to acetaminophen. The retrospective arm was obtained by performing a chart review over the study time period to enroll patients who underwent the aforementioned procedures and met the inclusion/exclusion criteria. The surgical procedures between these two groups were similar.

Study Design

A single-center prospective study was conducted between April 2016 and May 2017. The treatment group included 48 participants who underwent surgical resection of head and neck cancer and postoperatively received intravenous acetaminophen (1 g every 6 hours for 4 doses), in conjunction with the standard opioid PCA and other breakthrough narcotics. These patients were compared to a similar historical group of 51 patients who underwent surgery from January 2014 to March 2015 and received the standard opioid PCA and breakthrough narcotics. The standard opioid PCA was a morphine, hydromorphone, or fentanyl PCA, which was ordered for all patients in the study postoperatively. The PCA dose and any additional breakthrough narcotics administered were collected from the medication administration record. These dosages were converted to morphine equivalents for comparison.¹⁰ Pain scores were collected by the nurses using either the Critical Care Pain Observation Tool (CPOT) or 11-point numeric scales, which have been validated in previous literature. The 11-point numeric scale ranges from 0 (no pain) to 10 (worst possible pain).¹¹ The CPOT scale uses objective measures of pain, including facial expression, body movement, ventilator compliance, vocalizations, and muscle tension, and is used to assess pain in patients who are unable to report it themselves.¹²

Outcome Measures

The primary outcome measures included the 1) total number of PCA attempts in 8-hour intervals over the first 24 hours after surgery, 2) averaged and highest 8-hour pain scores over the first 24 hours after surgery, and 3) total amount of narcotics, measured in morphine equivalents (MEs), in 8-hour intervals over the first 24 hours after surgery. A secondary outcome measure was length of hospital stay. The total IV morphine equivalents was derived from adding the amount of narcotic administered through the PCA to any additional breakthrough narcotic medication the patient required. For each patient, the total IV morphine equivalents received in the first 24 hours was calculated.

Statistical Analyses

The targeted sample size of 53 patients in the treatment arm was determined to be sufficient to provide 80% power. Five of the 53 prospective patients were excluded from the final analyses due to these patients not receiving the full 24 hours of

TABLE I.
Comparison of Demographic Characteristics, Pain Scores, and IV Morphine Equivalents Between Non-Acetaminophen and Acetaminophen Groups.

Characteristic	Acetaminophen	Non-Acetaminophen	P-value	
	N = 48	N = 51		
Age	63.7 (10.7)	59.9 (8.3)	.055	
Male	34 (71%)	38 (75%)	.681	
Race	African American	20 (42%)	21 (41%)	.380
	Caucasian	28 (58%)	28 (55%)	
	Other	0 (0%)	2 (4%)	
LOS in Hours	188.4 (110.6)	254.1 (181.4)	.033	
LOS in Days	7.8 (4.6)	10.6 (7.6)	.033	
PCA Duration	55.7 (28.7)	73.6 (57)	.054	
PCA Type	Morphine	31 (65%)	27 (53%)	.009
	Fentanyl	0 (0%)	9 (18%)	
	Hydromorphone	17 (35%)	15 (29%)	
PCA Attempts	1st 8 hours	44.3 (68.5)	33.9 (45.8)	.421
	2nd 8 hours	33.1 (47)	50.6 (83)	.231
	3rd 8 hours	41.0 (63.5)	37.0 (53)	.762
Average Pain Score	1st 8 hours	0.8 (1.2)	1.0 (1.3)	.408
	2nd 8 hours	1.3 (2)	0.9 (1.4)	.178
	3rd 8 hours	0.9 (1.5)	0.9 (1.5)	.837
Highest Pain Score	1st 8 hours	2.2 (3.1)	2.8 (3)	.387
	2nd 8 hours	3.0 (3.6)	2.1 (3.1)	.204
	3rd 8 hours	2.2 (3)	1.9 (2.7)	.673
PCA IV ME	1st 8 hours	13.0 (13.1)	18.5 (19.2)	.099
	2nd 8 hours	15.1 (13.9)	18.9 (22.2)	.314
	3rd 8 hours	14.9 (14.2)	17.6 (21.6)	.473
Total IV ME	1st 8 hours	13.5 (13.3)	22.5 (21.5)	.014
	2nd 8 hours	15.5 (14.2)	21.7 (23)	.108
	3rd 8 hours	15.9 (15.2)	20.5 (22.5)	.237
Total IV ME in 24 h	44.8 (38.6)	64.7 (60.2)	.055	

Continuous variables are reported using means/standard deviations. Categorical data is reported using percentiles. Statistical significance (bolded) was set at the 95% level of confidence ($\alpha = 0.05$).

IV ME = intravenous morphine equivalents; LOS = length of stay; PCA = patient controlled analgesia.

TABLE II.
Associations Between IV Acetaminophen and PCA Attempts, Pain Scores, and IV Morphine Equivalents.

Characteristic		Model 1	Model 2
PCA attempts	1st 8 hours	1.307 (0.701, 2.437) <i>P</i> = .400	1.137 (0.661, 1.956) <i>P</i> = .641
	2nd 8 hours	0.654 (0.341, 1.255) <i>P</i> = .202	0.664 (0.321, 1.374) <i>P</i> = .269
	3rd 8 hours	1.109 (0.573, 2.145) <i>P</i> = .759	1.520 (0.862, 2.679) <i>P</i> = .148
Average pain score	1st 8 hours	0.781 (0.436, 1.399) <i>P</i> = .406	0.745 (0.349, 1.591) <i>P</i> = .448
	2nd 8 hours	1.548 (0.835, 2.869) <i>P</i> = .165	2.171 (1.046, 4.507) <i>P</i> = .037
	3rd 8 hours	1.072 (0.555, 2.07) <i>P</i> = .837	1.304 (0.647, 2.627) <i>P</i> = .458
Highest pain score	1st 8 hours	0.806 (0.492, 1.32) <i>P</i> = .392	0.708 (0.377, 1.331) <i>P</i> = .284
	2nd 8 hours	1.404 (0.828, 2.38) <i>P</i> = .208	1.908 (0.983, 3.705) <i>P</i> = .056
	3rd 8 hours	1.128 (0.645, 1.973) <i>P</i> = .672	1.253 (0.676, 2.321) <i>P</i> = .473
PCA IV ME	1st 8 hours	0.701 (0.468, 1.05) <i>P</i> = .085	0.697 (0.486, 0.999) <i>P</i> = .049
	2nd 8 hours	0.799 (0.526, 1.214) <i>P</i> = .293	0.847 (0.548, 1.309) <i>P</i> = .456
	3rd 8 hours	0.849 (0.550, 1.311) <i>P</i> = .460	0.955 (0.600, 1.521) <i>P</i> = .848
Total IV ME	1st 8 hours	0.599 (0.408, 0.878) <i>P</i> = .009	0.610 (0.432, 0.86) <i>P</i> = .005
	2nd 8 hours	0.712 (0.482, 1.052) <i>P</i> = .088	0.756 (0.506, 1.13) <i>P</i> = .173
	3rd 8 hours	0.775 (0.516, 1.163) <i>P</i> = .218	0.872 (0.574, 1.325) <i>P</i> = .521
Total IV ME in 24 h		0.692 (0.486, 0.987) <i>P</i> = .042	0.739 (0.523, 1.045) <i>P</i> = .087

Values are reported in odds ratios using gamma regression. Statistical significance (bolded) was set at the 95% level of confidence ($\alpha = 0.05$). Model 1: unadjusted; Model 2: adjusted for age, sex, and race.

IV ME = intravenous morphine equivalents; PCA = patient controlled analgesia.

scheduled acetaminophen. Two of the 53 retrospective patients were omitted because of insufficient PCA data. Descriptive analyses were used to compare the differences in participants' demographic characteristics, length of stay, PCA type, PCA number of attempts, IV morphine equivalents, average pain score, and highest pain score, stratified by treatment group. Continuous data are described using mean (standard deviation) and categorical data are described using n (%). Gamma regression was used to perform covariant adjustment for age at time of surgery, sex, and race to examine the associations between acetaminophen and amount of IV morphine equivalents given, number of PCA attempts, average pain score and highest pain score. All analyses were performed using SAS software, Version 9.4 (SAS Institute, Inc., Cary, NC). Statistical significance was set as $P < .05$.

RESULTS

Patient demographic characteristics (age, sex, race), length of stay, PCA type, PCA number of attempts, IV morphine equivalents, average pain score, and highest pain score, stratified by treatment group (acetaminophen vs. non-acetaminophen) are reported in Table I. Patients in the acetaminophen group received significantly less total narcotics in the first 8 hours after surgery compared to non-acetaminophen group (13.5 ± 13.3 vs. 22.5 ± 21.5 MEs, $P = .014$). There was no significant difference in the total narcotics received in the second and third 8-hour intervals; however, the total IV MEs received over 24 hours approached significance (44.8 ± 38.6 MEs in acetaminophen group vs. 64.7 ± 60.2 MEs in the non-acetaminophen group, $P = .055$). The acetaminophen group had their PCA pump for an average of 18 hours less than the non-acetaminophen group (55.7 ± 28.7 vs. 73.6 ± 57 hours, $P = .054$), which approached statistical significance. In addition, the acetaminophen group had a significantly decreased length of

stay (188.4 ± 110.6 vs. 254.1 ± 181.4 hours, $P = .033$). Most patients (59%) had a morphine PCA. When analyzing the averaged and highest 8 hour pain scores and averaged number of PCA attempts over the first 24 hours, there was no difference between the two groups. The average age of the group was 61.7 ± 9.7 years. The majority of the patients (73%) were male, with 57% being Caucasian. There was no difference in demographic characteristics between the acetaminophen group and non-acetaminophen group.

Table II shows associations in odds ratios between administration of IV acetaminophen and number of PCA attempts, averaged and highest pain scores, total PCA morphine equivalents, and overall total of IV morphine equivalents. Model 1 is unadjusted, while Model 2 is adjusted for age, sex, and race. In Model 1, in the first 8-hour interval after surgery, there was an association between acetaminophen and the overall total of morphine equivalents given, with the patients who received acetaminophen receiving over 40% less morphine equivalents compared to the non-acetaminophen group (RR = 0.599, 95% CI 0.408–0.878). A similar finding was noted in Model 1 for the acetaminophen group for the overall total morphine equivalents received in the 24 hours following surgery, with the acetaminophen group receiving 30% less overall (RR = 0.692, 95% CI 0.486–0.987). In Model 2, after adjustments were made for age, sex, and race, similar findings were noted, with the acetaminophen group receiving 30% less PCA IV morphine equivalents (RR = 0.697, 95% CI 0.486–0.999) and almost 40% less total IV morphine equivalents (RR = 0.610, 95% CI 0.432–0.860) in the first 8 hours after surgery. Unlike Model 1, in Model 2 there was no significant association between acetaminophen and the total amount of IV morphine equivalents the patients received in 24 hours. One

unexpected finding in the adjusted model was that the acetaminophen group had a twice as high of average pain score in the second 8-hour interval after surgery (RR = 2.171, 95% CI 1.046–4.507). There was no relation between acetaminophen administration and number of PCA attempts or highest pain score in either model at any of the postop 8-hour increments.

DISCUSSION

In this study we examined the role of IV acetaminophen in the treatment of postoperative pain in head and neck cancer patients, which was measured by patient pain scores, number of PCA attempts, and total narcotic pain medication requirements in the first 24 hours after surgery. There was a significant decrease in the total narcotics administered in the first 8 hours after surgery for patients receiving scheduled IV acetaminophen, and the total amount received in the first 24 hours approached significance. Patients in the acetaminophen group also had their PCA pump for less time and had a significantly decreased length of stay compared to the non-acetaminophen group. The patient pain scores and PCA attempts did not differ between the treatment group who received acetaminophen and the non-treatment group who received the standard narcotic PCA regimen,

Overall the patients who received scheduled acetaminophen received about 40% less total IV morphine equivalents in the first 8 hours after surgery in both the adjusted and unadjusted models. When looking at the total amount of IV morphine equivalents received over the first 24 hours, patients in the acetaminophen group received 30% less in the unadjusted model and the adjusted model approached significance. This suggests that similar pain relief can be achieved with lower doses of IV narcotics by administering adjuvant IV acetaminophen. This supports the recent pain literature which promotes opioid-sparing multimodal analgesia for postoperative pain, utilizing acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and cyclooxygenase (COX) inhibitors for patients undergoing head and neck cancer surgery, with PCA use being reserved for cases when these modalities are insufficient.^{13,14}

Another important finding was that the acetaminophen group had a significantly decreased length of stay by almost 2 days. This group also had their PCA pump for an average of 18 hours less than the non-acetaminophen group, which approached significance. We hypothesize that the acetaminophen group had equal pain control with less narcotics, and therefore were at less risk of the side effects from opioids such as respiratory depression and constipation. Decreased side effects leads to earlier mobilization, return of bowel function, and fulfillment of discharge criteria.

There was no difference in pain scores between the two groups in the unadjusted model, which is likely due to several factors. The majority of patients were admitted to the intensive care unit (ICU) postoperatively where there is a low ratio of nurses to patients, allowing the patient's pain to be closely monitored and treated. Due to this fact, aside from a few outliers, most patients' pain scores averaged to be 1 or

less. In addition, the pain scores are entered by the nurses, who could be biased to enter lower scores to show they were properly attending to the patient's pain. One unexpected finding in the adjusted models was that the acetaminophen group had a twice as high of average pain score in the second 8-hour interval after surgery. The most likely reason for this is that overall most people were reporting low pain scores of 1 or less but there was one patient in the acetaminophen group who reported a pain score of 10 during the second 8-hour interval, which skewed the results.

When looking at the number PCA attempts of the patients, the data was highly variable, with some patients rarely pushing their button and reporting higher pain scores, and other patients pushing their button over thirty times in an hour and reporting very low pain scores. The most likely reason for this is poor patient understanding of how the PCA works. In future studies, it would be important to provide more preoperative patient education on the mechanism of a PCA pump and its role in pain relief.

A limitation of the study is that a prospective treatment group was compared to a retrospective cohort. The pain score entry and pain medication administration record was performed by the nurses who were aware the patients were in a pain study and therefore were subject to a reporting bias. All efforts were taken to overcome this bias by meeting with the nurses at the beginning of the prospective component to educate them on the purpose of the pain score reporting and to reassure them that the patients could have as much additional narcotics as needed to control their pain.

In future studies it would be beneficial to undergo a double-blinded prospective clinical trial in which the nurses and physicians were unaware of which patients are in each group to minimize any study bias. It would also be useful to look at the effect of administration of scheduled acetaminophen over a longer postoperative time period to see if the narcotic requirements could be decreased over a patient's hospital course and even after discharge. This would also allow for us to study if specific opioid-related side effects such as constipation and respiratory depression could be minimized by giving non-opioid adjuvant medications such as acetaminophen and contribute to a decreased length of hospital stay.

CONCLUSION

In summary, the current findings suggest that administration of IV acetaminophen after surgery can decrease the postoperative narcotic requirements and lead to a decreased length of hospital stay. These are important findings as there is a now a push for non-opioid multimodal analgesia in the literature and in the news. Additional studies looking at this relationship in a randomized control trial are needed to further elucidate these findings.

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AUTHOR CONTRIBUTIONS

Dr. Erin Smith assisted with patient enrollment and data collection and analysis and wrote the manuscript. Dr. Jessica Lange designed the study, assisted with patient enrollment, and reviewed the manuscript. Dr. Cindy Moore collected and analyzed the data and contributed to writing the manuscript. Dr. Isaam Eid and Dr. Lana Jackson helped design the study, enroll patients, and reviewed the manuscript. Dr. Jesus Monico was the principal investigator, designed the study, and reviewed the manuscript.

BIBLIOGRAPHY

1. Renthal W. Seeking balance between pain relief and safety: CDC issues new opioid-prescribing guidelines. *JAMA Neurol* 2016;73(5):513–514.
2. American Cancer Society. *Cancer Facts and Figures*. New York: American Cancer Society, 2002.
3. Olsen KD, Creagan ET. Pain management in advanced carcinoma of the head and neck. *Am J Otolaryngol* 1991;12:154–160.
4. Grond S, Detlev Z, Diefenbach C, Radbruch L. Assessment of cancer pain: a prospective evaluation in 2266 cancer patients referred to a pain service. *Pain* 1996;64:107–124.
5. Trotter, et al. pharmacological and other interventions for head and neck cancer pain: a systemic review. *J Oral Maxillofac Res* 2012;3(4):1–12.
6. Talmi YP, Waller A, Bercovici M, Horowitz Z. Pain experienced by patients with terminal head and neck carcinoma. *Cancer* 1997;80:1117–1123.
7. Schug SA, Zech D, Grond S. Adverse effects of systemic opioid analgesics. *Drug Saf* 1992;7(3):200–213.
8. Sinatra RS, Jahr JS, Reynolds L, et al. Intravenous acetaminophen for pain after major orthopedic surgery: an expanded analysis. *Pain Pract* 2012;12:357–365.
9. Subramanyam R, Varughese A, Kurth CD, Eckman MH. Cost-effectiveness of intravenous acetaminophen for pediatric tonsillectomy. *Pediatr Anesth* 2014;24:467–475.
10. McAuley David. Opioids – Equianalgesic Dosages. [Online] Available at: <http://www.globalrph.com/narcotic.htm>. Accessed September 25, 2017.
11. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005;14(7):798–804.
12. Keane KM. Validity and reliability of the critical care pain observation tool: a replication study. *Pain Manag Nurs* 2013;14(4):e216–e225.
13. Dort JC, Farwell DG, Findlay M, et al. Optimal perioperative care in major head and neck cancer surgery with free flap reconstruction: a consensus review and recommendations from the enhanced recovery after surgery society. *JAMA Otolaryngol Head Neck Surg* 2017;143(3):292–303.
14. Apfelbaum JL, Ashburn MA, Connis RT. American Society of Anesthesiologists Task Force on Acute Pain M. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology* 2012;116:248–273.