Journal of Anesthesia & Clinical Research

Hoefnagel et al., J Anesth Clin Res 2015, 6:9
DOI: 10.4172/2155-6148.1000568

Research Article Open Access

Intravenous Acetaminophen Administration in Patients Undergoing Craniotomy - A Retrospective Institutional Study

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Received date: August 22, 2015, **Accepted date:** September 21, 2015, **Published date:** September 25, 2015

Abstract

Introduction: Patients undergoing craniotomy for tumor resection often experience moderate to severe postoperative pain. Intravenous acetaminophen has been proposed as an analgesic adjunct to potentially decrease opioid requirements and incidence of nausea in these patients allowing for prompt postoperative neurological evaluations. At this time, however, there is no evidence to show that acetaminophen reduces patient pain or opioid consumption after craniotomy.

Methods: A retrospective analysis of 81 patients undergoing craniotomy was done to evaluate the effect of IV acetaminophen (APAP) administration on reported pain scores, opioid usage, time in the post-anesthesia care unit (PACU), and incidence of nausea within the first 24 hours.

Results: No significant differences in patient reported pain scores, opioid consumption within the first 24 hours, anti-emetic use, or time in PACU were found in patients who received intravenous acetaminophen compared to those who received opioids alone.

Discussion: Our investigation represents the first evidence looking for an effect of acetaminophen on post-craniotomy pain and nausea. There are randomized and blinded trials currently in progress that will add to our knowledge on this topic. Acetaminophen is a relatively safe intervention. However, until those randomized trials are completed and reported, we cannot uniformly recommend the intraoperative administration of intravenous acetaminophen to patients undergoing craniotomy.

Keywords: Acetaminophen; Intravenous; Craniotomy; Pain; Opioid; Nausea

Introduction

Patients undergoing elective craniotomy often experience moderate to severe post-operative pain; the management of which is believed suboptimal and continually evolving [1-5]. Historically, post-craniotomy pain has been undertreated for fear of opioid interference with prompt postoperative neurologic examinations [6,7]. Opioids have several well-established, dose-dependent side effects: sedation, hypoventilation, hypercarbia, and impaired cognition [8,9]. These adverse effects can result in increased cerebral blood flow and concomitant rise in intracranial pressure, possibly leading to additional poor outcomes [9,10]. Opioids may also exacerbate post-operative nausea and vomiting (PONV), a common complication of intracranial surgery [11-13], and treatment with anti-emetics can further depress mental status and perpetuate a negative cycle [14]. Opioid selection during craniotomy (and the subsequent effects on postoperative recovery) has been reviewed in detail [15]. Still, it is essential to maintain adequate analgesia in neurosurgical patients. Insufficient treatment of pain can result in decreased patient satisfaction [16]. More alarmingly, uncontrolled pain may lead to increased agitation, shivering, hypertension, and vomiting, which may increase intracranial pressure and risk of bleeding [17].

The ideal anesthetic in craniotomies remains one that provides a fast offset to aid in post-operative neurological examinations as well as providing adequate analgesia. This had led physicians to pursue other modalities to reduce opioid requirements in the perioperative period. Scalp infiltrations with local anesthetics have demonstrated mixed results with little effect on intraoperative opioid administration [18-20]. Recent work has shown that dexmedetomidine can reduce pain after craniotomy [21], but dexmedetomidine also has sedative and hemodynamic effects that may not be desirable. More promisingly, non-steroidal anti-inflammatory drugs (NSAIDs) can also be used as adjuncts in the multi-modal approach to pain management [22,23]. NSAIDs are shown to reduce post-operative analgesic requirements and limit narcotic-related side effects, particularly PONV, but may negatively impact surgical hemostasis, and thus cannot be used universally [22]. Acetaminophen has a well-established safety profile, relatively few side effects or contraindications, and intravenous administration can provide fast and predictable analgesia along with a significant opioid sparing effect [24,25]. Acetaminophen alone is not likely to provide adequate pain relief after supratentorial craniotomy: oral acetaminophen has been shown to provide adequate relief postoperatively in only 27% of patients [26], and another study that included a paracetamol arm stopped enrollment in that arm due to inadequate pain control [27]. But while it also compares unfavorably with opioids when administered post-operatively for craniotomy pain [28], it may make for a suitable adjunct.

Intravenous acetaminophen (Ofrimev®) has been available for use in the United States for quite a while. However, its increased cost in recent months prompts further investigation into its utility. Here we aim to investigate whether a single dose of Ofrimev®, given at the time of dural closure, impacts patient reported pain score, overall usage of opioid medications within 24 hours, post-operative nausea and vomiting, or anti-emetic usage. It is our hypothesis that patients who received intraoperative intravenous acetaminophen will have less post-operative pain and nausea than those patients who did not.

Materials and Methods

After obtaining IRB approval, records of 225 patients, aged 18 and older, undergoing craniotomy at a single tertiary care hospital, during an 8-month period in 2014 were reviewed. Patients were excluded from analysis if they were on chronic opioids or anti-emetics defined as daily medication intake for a period of greater than 2 weeks prior to date of surgery. Patients were also excluded from analysis if they could not participate in an assessment of their pain scores, which involved a comparative number scale. Forty-two patients received IV APAP intra-operatively in addition to traditional anesthetic management during this time period. Thirty-nine age-matched controls were selected from this same time period.

All patients received 10 mg of dexamethasone and 4 mg of ondansetron intravenously for PONV prophylaxis. Patients with a history of PONV and those undergoing posterior fossa surgery also had a scopolamine patch placed prior to being transferred to the operating room.

General anesthesia with an endotracheal tube in place was used in 79 patients; while an asleep-awake-asleep [19] technique was used for 3 patients (2 in the APAP group, 1 in the standard group). Anesthetic management was accomplished with infusions of propofol, dexmedetomidine, and/or remifentanil as needed to facilitate neurophysiologic monitoring [22]. Location of tumor and surgical approach also determine pain severity, which is why patients were matched for procedure location [14] (Table 1).

		APAP	Standard	p value
Gender	Male	19	17	0.88
	Female	23	22	
Mean		53.4 ± 16.5	52.9 ± 17.9	0.91
BMI		29 ± 6.9	29.5 ± 7.2	0.76
ASA Status	2	27	7	0.06
	3	23	25	
	3E	1	1	
	4	1	5	
	4E	1	1	
Craniotomy Type	S	30	30	0.09
	O	6	4	

Table 1: Patient characteristic; SD: Standard Deviation; in craniotomy type S: Supratentorial; O: Suboccipital; P: Posterior fossa; APAP: Acetaminophen.

Following extubation, patients were transferred to the PACU for recovery from general anesthesia and monitoring of hemodynamic and neurologic status. Patient pain scores using a verbal 10-point scale or visual analog scale (VAS) were recorded every 15 minutes by the PACU nurse. Uncontrolled pain (>5/10) or discomfort visualized by the PACU RN were treated with intravenous opioids. Presence of nausea requiring anti-emetic medications was also documented during PACU stay. Total amounts of medications administered in PACU were noted. Following transfer from PACU to the neurosurgical inpatient unit, pain scores were recorded by floor RNs every 2 hours. Total amounts of opioid and anti-emetic medications received on the floor were reviewed in the electronic medical record and 24-hour totals were obtained.

Results

A total of 81 patients were included in the data analysis. Primary outcomes were highest pain score in PACU and in the first 24 hours, length of stay in PACU, opioid use in PACU and within the first 24 hours, and use of anti-emetics in PACU and within 24 hours. The mean and standard deviation of pain score in each treatment group was calculated and the two-sample t-test used to compare the mean pain scores between two groups. Linear regression analysis was utilized to compare treatment effect controlling for patient factors (age, gender, ASA physical status), and the surgical procedure.

The mean high pain score in PACU was 3.8 in the acetaminophen group, and 4.6 in the opioid only group (p=0.29). The mean 24-hour pain score was 3.4 vs. 3.9 (p=0.21) in the respective groups, and 24-hour administration of opioids in morphine equivalents was not significantly different in the patients who had received APAP intra-operatively (23.1 mg/18.9 mg, p=0.47). No difference in the amount of time in PACU was observed between the groups (p=0.21). Similarly there was no difference in anti-emetic use in the PACU or in the first 24 hours post-operatively between the two groups (p=0.19, 0.17) (Table 2).

	APAP	Standard	p value
PACU high pain score	3.7 ± 3.4	4.6 ± 3.8	0.29
Opioid PACU (mg)	7.9 ± 6	7.2 ± 5	0.67
24hr pain mean	3.4 ± 1.9	3.9 ± 2.4	0.21
Opioids 24hr (mg)	20.1 ± 18.6	22.9 ± 15.6	0.57
Mean time in PACU (min)	167 ± 117	138 ± 87	0.21
Antiemetic PACU %	38	55	0.19
24hr antiemetic %	42	56	0.17

Table 2: Primary outcomes; Opioid dose are reported in milligrams (mg) of morphine equivalents. APAP: Acetaminophen; PACU: Post-Anesthesia Care Unit.

Dexmedetomidine has been shown to provide analgesic effect [28-32]. This was identified as a potential confounding variable. There was significantly more dexmedetomidine use in the group that also received IV APAP (p=0.002).

Discussion

Decreasing post-operative pain and nausea are goals in the management of any anesthetic, but it is especially important for patients undergoing craniotomy. This report suggests that administration of a single dose of intravenous acetaminophen during anesthesia does not reduce pain or nausea following craniotomy.

Given the cost of intravenous acetaminophen, it is important to demonstrate that a reduction in pain score is not just statistically significant, but also clinically relevant. This study had a 0.8 power of detecting a 30% decrease in our primary outcome of peak PACU pain scores. It is possible that acetaminophen did alleviate pain to a smaller degree than our study was powered to detect. For the most common measure of pain intensity; the 11-point pain intensity numerical rating scale (as used in this study); a reduction of approximately 30% represents a clinically important difference [33]. A larger study would have been more likely to return a significantly different result, but that result may not have been clinically relevant.

This study has several limitations. First, we cannot rule out the possibility that there may have been a sizable percentage of individual patients or subgroups that experienced a clinically important pain reduction despite the lack of a mean difference between our groups at the population level. For example, infratentorial procedures are associated with more pain than supratentorial craniotomies [34], and so perhaps that subgroup would benefit more from the addition of adjunctive pain medications. Likewise, age, gender and the presence of preoperative opioid requirements affect post-craniotomy pain [4,7,34], and these groups might have difference responses to the addition of acetaminophen. Second, our investigation only examined the effect of a single dose of intravenous acetaminophen administered intra-operatively. Third, some patients received a combination of oral medications that included acetaminophen with an opioid within the first 24 hours post-operatively. This may have lowered the pain scores, opioid requirements, and anti-emetic usage in both groups, making any difference more difficult to detect. Fourth, there are limitations inherent in any retrospective study, including selection bias on the part of practitioners who may have based their administration of acetaminophen on patient or surgical factors not captured by our review or recall bias that may exist in the capture of data from medical record [35].

In 2014 the cost of a dose of intravenous acetaminophen increased by 140% [36]. This has prompted a much closer look into value-added and case-by-case results for intravenous acetaminophen versus alternative therapies. Our investigation represents the first evidence looking for an effect of acetaminophen on post-craniotomy pain and nausea. We had hypothesized that patients who received intraoperative intravenous acetaminophen would have had less pain and nausea than those who did not, but this was not the case. Using our chosen metrics, there was no difference between the group that received intraoperative acetaminophen and the group that did not.

There are randomized and blinded trials currently in progress that will add to our knowledge on this topic. Acetaminophen is a relatively safe intervention; however, until those randomized trials are completed and reported, we cannot uniformly recommend the intraoperative administration of intravenous acetaminophen to patients undergoing craniotomy.

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