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SCHEDULED INTRAVENOUS ACETAMINOPHEN IMPROVES PATIENT SATISFACTION WITH POSTCRANIOTOMY PAIN MANAGEMENT: A PROSPECTIVE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY

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Abstract

Background—Postcraniotomy pain can be difficult to manage with opioids due to opioid-related side effects, including drowsiness, nausea/vomiting, confusion, and pupillary changes, potentially masking the signs of postoperative neurological deterioration. Intravenous (IV) acetaminophen, a non-opioid analgesic, has been reported to have opioid-sparing effects after abdominal and orthopedic surgeries. This study investigates whether IV acetaminophen has similar effects after craniotomy.

Methods—In this prospective, randomized, placebo-controlled, double-blind clinical trial, 100 adult patients scheduled to undergo supratentorial craniotomy for excision of a brain mass were randomized to receive either IV acetaminophen or placebo pre-incision and then every 6 hours for a total of 24 hours after surgery. Total 24-hour opioid consumption, pain scores, satisfaction with overall pain management, time to meet PACU discharge criteria, and incidence of opioid-related side effects were compared.

Results—There was no difference in the 24 hour postoperative opioid consumption in morphine equivalents between the IV acetaminophen group (median 11 mg, n = 45) and the placebo group (median 10.1 mg, n = 41). No statistically significant difference of VAS pain score was observed between two treatment groups. Patient satisfaction with overall postoperative pain management was significantly higher in the IV acetaminophen group than the placebo group on a 1–10 scale (8.1 ± 0.4 vs. 6.9 ± 0.4 , $p=0.03$). There was no significant difference in secondary outcomes, including the incidence of opioid-related side effects.

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Conclusion—IV acetaminophen, as adjunctive therapy for craniotomy procedures, did not show an opioid-sparing effect in patients for the 24 hours after craniotomy; however, it was associated with improved patient satisfaction regarding overall pain control.

Keywords

Acetaminophen; Pain; Craniotomy

INTRODUCTION

It was traditionally believed that pain following craniotomy was minimal and insignificant, and when present, challenging to treat due to the potential interference with postoperative neurological examination.^{1–3} This belief was challenged in the mid-1990's when several studies showed that with limited pain management strategies, almost 70% of patients reported moderate to severe pain on the first postoperative day, and nearly 50% of patients experienced the same level of pain on the second postoperative day. In addition, attending anesthesiologists surveyed during these studies believed that 50% of their postcraniotomy patients did not receive adequate pain control.^{1,4–6} Recently, studies show that despite improved awareness of the problem, the challenges of adequately managing postcraniotomy pain continues due to limited selection of pharmaceutical agents.^{7–9}

Currently, opioids are the first-line treatment for postoperative pain in craniotomy patients; however, opioid-related side effects are undesirable and potentially hazardous in this patient population. Opioid-induced respiratory depression can lead to hypercapnia, which can lead to elevated intracranial pressure.^{10, 11} Sedation, confusion, and agitation resulting from opioid therapy can mimic neurologic pathology, potentially masking signs of legitimate neurological catastrophe in the postcraniotomy patient. After craniotomy, patients are also at moderate to high risk for postoperative nausea and vomiting (PONV), which can be exacerbated by opioid administration.¹² Due to these potential risks of using opioids in postcraniotomy patients, several drugs have been studied as analgesic adjuvants in an attempt to limit opioid requirements, including non-steroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase-2 (COX-2) inhibitors, gabapentinoids, and acetaminophen. While NSAIDs have been shown to have analgesic and opioid-sparing effects,¹³ their platelet inhibition quality precludes their usage in patients after craniotomy.¹⁴ Selective COX-2 inhibitors are also a controversial drug group due to their association with an increased risk of adverse cardiovascular events,¹⁵ as well as being linked to salt and water retention and hypertension.¹⁶ Furthermore, no significant benefits have been demonstrated by adding parecoxib, a COX-2 inhibitor, to the analgesic regimen for postcraniotomy pain.¹⁷

Acetaminophen, a non-opioid analgesic, has an established safety profile and has proven to be well tolerated in clinical trials.²¹ Perioperative administration of intravenous (IV) acetaminophen has been found to better control postoperative pain and reduce opioids consumption, especially in abdominal, pelvic, and orthopedic surgeries.^{20, 21} However, there is minimal research with regards to its efficacy or benefit in patients after craniotomy. In this study we hypothesize that the administration of IV acetaminophen would reduce

opioid requirements and opioid-related side effects and provide greater patient satisfaction and superior pain control than opioid therapy alone.

MATERIALS and METHODS

This study (HSC-MS-12-0055) was approved by the Institutional Review Board of McGovern Medical School at the University of Texas Health Sciences Center at Houston prior to initiation. Consecutive adult patients scheduled for supratentorial craniotomy for mass resection at Memorial Hermann Hospital at the Texas Medical Center in Houston, Texas were approached for enrollment in the study between 2013 to 2016. Patients were excluded if they were receiving chronic opioid therapy, were known to have hepatic or renal dysfunction, received any pain medication in the 12-hour period prior to surgery, did not weigh between 50 and 120 kg, were allergic to any medications in the study, or if neurological conditions rendered them unable to be evaluated reliably after surgery. Written consent was obtained from each participant included in the study.

Study Design and Data Collection

Once enrolled into the study, patients were randomized to either the IV acetaminophen group or placebo group. Randomization was performed by the hospital investigational pharmacy based on computer-based random list generator (<http://www.random.org>). Patients and all study personnel including research assistants, anesthesiologists, neurosurgeons and intensivists were blinded to group allocation, and this blind remained closed until after collection of data and analysis by the biostatistician.

Patients randomized to the intervention group were scheduled to receive 1,000 mg of IV acetaminophen (OFIRMEV®, Mallinckrodt Pharmaceuticals, St Louis, MO, USA) in the operating room following induction of general anesthesia but prior to skin incision. This dose was to be repeated every 6 hours for a total of 24 hours after the conclusion of surgery. Patients randomized to the placebo group were scheduled to receive the same volume (100 mL) of 0.9% saline instead at similar times. Study drug and placebo were formulated in identical bags to maintain blinding. Prior to surgery, all study participants were instructed on the use of the pain and nausea scales. Once this training had been completed, patients were eligible to receive 1–2 mg IV midazolam preinduction for anxiolysis at the discretion of the attending anesthesiologist. Once in the operating room, general anesthesia was induced using lidocaine (1 mg/kg), propofol (1.5 – 2.5 mg/kg) and fentanyl (2 – 3 mcg/kg). Rocuronium (0.6 mg/kg) was used to obtain muscle relaxation. Following endotracheal intubation, anesthesia was maintained with desflurane (3 – 3.5% end-tidal concentration), propofol and remifentanyl infusion, and boluses of rocuronium titrated based on train-of-four monitoring. Patients additionally received 8 – 12mg dexamethasone prior to skin incision as standard care for treatment of edema and as PONV prophylaxis. The scalp was routinely infiltrated along the incision with bupivacaine 0.5% with epinephrine (1:200,000) by neurosurgeons. Anesthetic depth was titrated intraoperatively based on the patient's hemodynamics as measured by EKG and invasive blood pressure monitoring. At the end of the procedure, IV anesthetic agents were discontinued approximately 20–30 minutes prior to skin closure, 4mg ondansetron was administered, and neuromuscular blockade was reversed

with neostigmine and glycopyrrolate according to TOF monitoring. Patients were extubated in the operating room or in the postanesthesia care unit (PACU). Any patient that did not meet extubation criteria within two hours of completion of surgery was withdrawn from the study.

On arrival to the postanesthesia care unit (PACU), a visual analog scale (VAS) pain score and nausea score were obtained from each patient and used as time 0. Patients were eligible to receive either IV morphine 2 mg or hydromorphone 0.3 mg upon request or upon assessment of pain scale $\geq 4/10$. At the end of the 24-hour period, the total amount of opioid consumed was calculated in morphine equivalents (MEs); this was the primary endpoint of the study.

Secondary endpoints included pain and nausea scores assessed 1, 2, 4, 8, 12, 16, 20, and 24 hours following surgery. Pain measurement was obtained by blinded research personnel when patients were in PACU or intensive care unit (ICU) nursing staff once patients were transferred to ICU. Time to extubation at emergence and time to meet PACU discharge criteria were recorded. Each patient was also provided a one-page survey with questions pertaining to their postoperative pain and analgesic regimen (Appendix 1), including the incidence of emesis, itching, dizziness, and drowsiness.

Statistical Analysis

Because no published studies of IV acetaminophen in craniotomy patients was found at the time of study design, 6-hour morphine consumption from a study on orthopedic patients by Sinatra et al.²¹ was used to estimate the 24-hour morphine consumption in craniotomy patients to determine the required sample size. The power analysis was conducted using the primary endpoint of total 24-hour postoperative opioid consumption in MEs. Control group mean (standard deviation, SD) was assumed to be: 17.8 (16.7), with treatment group mean (SD): 9.7 (10). Based a two-sample t-test with 80% power at significance level 5%, the needed sample size was calculated to be 47 per group. Allowing for patient withdrawals, a total 50 patients were recruited per group.

In reporting results, mean \pm SD were reported for continuous variables with normal distribution, and median and interquartile range were reported for skewed data. Frequency and percentage were reported for categorical variables. The comparison of total opioid consumption between two groups was conducted using Wilcoxon rank sum test. The treatment effect on VAS collected at different postoperative time points were evaluated after controlling for the VAS score collected at time 0 by performing a longitudinal analysis of VAS pain scores over time. Generalized estimating equations method was used to account for the correlation within patients. A time-weighted total VAS pain score was calculated and compared between the two groups using a two sample t-test. The incidence of moderate (VAS ≥ 4) and severe pain (VAS ≥ 7) was compared between the two groups using the Chi-squared test. The comparison of additional secondary outcomes was conducted using two sample t-test or Wilcoxon rank sum test as appropriate for continuous variables, and Chi-squared test or Fisher's exact test as appropriate for categorical variables. P-values less than 0.05 were considered significant. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC).

RESULTS

A total of 394 patients underwent craniotomy for resection of supratentorial brain mass with general anesthesia at our institution during the years 2013 and 2016. After exclusion criteria were applied, 181 patients were approached to participate in the study. A total of 100 patients agreed to enroll in the study, with 50 patients randomized to the IV acetaminophen group and 50 patients randomized to the placebo group. A total of 14 patients (5 from the IV acetaminophen group and 9 from the placebo group) were withdrawn from the study prior to collection of the primary outcome data secondary to postoperative complications, voluntary withdrawal, or procedure change (Figure 1). The principle of intent-to-treat was used to analyze the data.

Patients were similar in regards to demographic data and surgical factors (Table 1). Total opioid consumption was calculated based on MEs, where 1 mg of IV morphine was equivalent to 1 ME, and 1 mg IV hydromorphone was calculated as 7 MEs. There was no significant difference in MEs between the two groups. Median opioid consumption in the IV acetaminophen group was 11.0 MEs, while opioid consumption in the control group was 10.1 MEs ($p = 0.61$). The distribution of VAS pain scores at each time point is shown in Figure 1. After controlling for VAS pain score collected at time 0, no statistically significant difference of VAS pain score was observed between two treatment groups, but we observed a statistically significant reduction in pain score over time ($p < 0.0001$). A time-weighted sum of pain scores over the 24 hour study period showed lower total pain scores in the IV acetaminophen group, though this was not statistically significant (2.6 ± 1.9 versus 3.2 ± 2.1 , $p = .14$). Meanwhile, the least amount of pain reported was lower in the IV acetaminophen group (1.4 ± 1.8 versus 2.6 ± 2.7 , $p = 0.03$). Mean worst pain was similar between the two groups, (6.3 ± 2.5 , 6.4 ± 3.2 , $p = 0.98$). 74% of patients in the IV acetaminophen group reported moderate pain (VAS = 4) at some point in the first 24 hours, and 26% of patients reported severe pain (VAS = 7); in the placebo group, 76% of patients reported moderate pain, and 50% reported severe pain. A lower incidence of severe pain (VAS = 7) was observed in the IV acetaminophen group ($p = 0.01$). The incidence of moderate and severe pain in the control group appears higher than reported in other recent literature.²³ The post-operative questionnaire was completed by 42 patients in the IV acetaminophen group and 37 patients in the placebo group. When asked regarding percentage of time spent in severe pain, the response was similar between the two groups (23.3 ± 24.1 , 26.2 ± 24.1 , $p = 0.60$). Patients were also asked about their overall satisfaction with their pain control, as assessed on a 10 point Likert scale. Patients in the IV acetaminophen group were more satisfied with their pain regimen, with mean satisfaction scores of 8.1 ± 2.3 , compared to mean satisfaction scores of 6.9 ± 2.6 ($p = 0.03$) in the placebo group.

No significant difference was found between the two groups in terms of secondary outcomes with regards to time to extubation, time for patient to meet PACU discharge criteria, and opioid-related side effects, such as nausea, vomiting, drowsiness or pruritus (Table 2).

DISCUSSION

This study did not find a reduction in opioid requirement in patients receiving scheduled IV acetaminophen in the first 24 hours after supratentorial craniotomy. However, patients receiving IV acetaminophen were more satisfied with their overall pain regimen. While several analyses of pain scores did not show any statistically significant differences, pain scores were lower in the IV acetaminophen group, and there was a statistically significant lower incidence of VAS pain scores ≥ 7 in the treatment group.

In a 2013 review article, Macario et al. analyzed 16 previous prospective, randomized studies investigating the effects of perioperative IV acetaminophen use.² These studies generally demonstrated improved analgesia with IV acetaminophen but with variable impacts in opioid consumption and VAS pain scores. This theme has appeared to remain consistent with other two similarly designed studies investigating perioperative use of IV acetaminophen following sternotomy, in which one study demonstrated association of less consumption of opioid with adjunctive IV acetaminophen use whereas the other did not.^{24, 25} Interestingly, even in studies that a reduction in opioid requirement was not observed, other markers often pointed to improved analgesia, such as lower pain scores, improved satisfaction, or decreased opioid-related side effects such as sedation. This trend appears in line with the results of our study, where opioid consumption was similar but other markers pointed towards improved pain control.

The improved pain satisfaction scores in the IV acetaminophen group in this study are possibly due to a general trend towards lower pain scores. Good pain control after surgery can lead to improved recovery and less development of chronic postoperative pain.²⁶ Pain satisfaction ratings have also been found to have a strong positive correlation with overall patient satisfaction scores.²⁷ As patient satisfaction scores are now factored in by Medicare to hospital reimbursements, improved pain satisfaction scores are of increasing significance to hospital systems as well as patients.

In this study, patients in the IV acetaminophen group demonstrated no prolongation in terms of time to extubation or PACU discharge, and no additional adverse events were noted. Although liver function tests were not monitored, there were no incidences of clinically significant hepatic dysfunction in patients receiving IV acetaminophen. There was no difference in the rate of surgical complications such as rebleeding in the two groups. This is in expectation with the known safety profile of acetaminophen.

Undesirable side effects have limited the use of other non-opioid analgesics for postcraniotomy pain. For example, in a 2009 study patients receiving gabapentin prior to craniotomy demonstrated significant delay in time to extubation as well as increased postoperative sedation.²⁸ These side effects could limit the role of gabapentin in the management of postcraniotomy pain. Tramadol has also been used as part of a postcraniotomy pain regimen in order to limit opioid use and side-effects. However, some concerns exist about the possibility of increased risk of seizures even at therapeutic levels of tramadol, as well as side effects such as dizziness and drowsiness, which may discourage widespread use in postcraniotomy pain regimens. Non-steroidal anti-inflammatory drugs

(NSAIDs) may increase the risk for bleeding and, as such, are not commonly used after craniotomy. Dexmedetomidine has shown to provide short-term analgesic benefits after craniotomy, but prolonged emergence and sedation are concerns.²⁹

In this study, remifentanyl was used as the intraoperative opioid because of its short half-life, minimizing the impact of intraoperative opioid administration on outcome parameters, such as time to first rescue analgesic and cumulative consumption of MEs. The limitation of this approach, however, is the possibility of remifentanyl-induced hyperalgesia and/or acute opioid tolerance, which could potentially influence the study outcomes.^{30,31} In the perioperative period, clinically significant remifentanyl-induced hyperalgesia is seen with doses of remifentanyl > 0.2 mcg/kg/min and/or cumulative doses > 50 mcg/kg.^{30,31} Patients in this study did not receive doses of remifentanyl > 0.15 mcg/kg/min and only rarely exceeded the cumulative threshold of 50 mcg/kg, thereby limiting this potentially confounding effect on the results.

As with most trials, this study has limitations. Attributable to standard practice at our institution and a reluctance to deviate from that for the purposes of this study, patients were not given a patient-controlled analgesia (PCA) device; rather, administration of morphine was dependent on nurse administration. This may have affected the amount of morphine administered and may have increased the chance that there was no difference seen in MEs administered during the study period. Also, this study was not powered to detect differences in pain score. While the total time-weighted average pain score during the study period was lower in the IV acetaminophen group, 350 total patients would have been needed to establish statistical significance considering the difference in total pain score seen in this study.

Overall, this study suggests that IV acetaminophen is a safe and effective drug to use in the management of postcraniotomy pain. Further studies may center around the effectiveness of IV dosing versus oral dosing of acetaminophen, and also longer-term consequences such as time to hospital discharge and differences in the incidence of chronic postcraniotomy pain.

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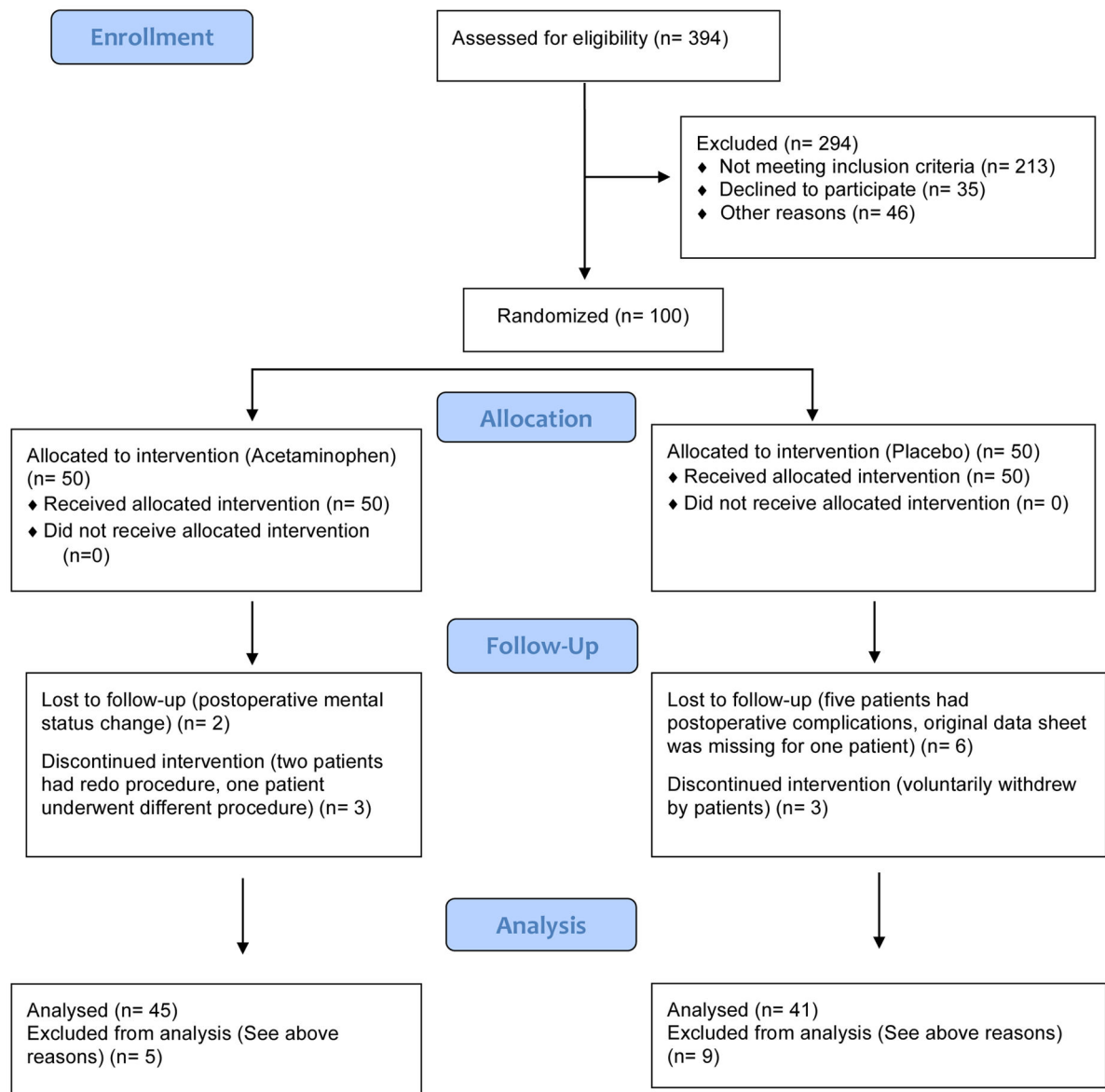


Figure 1.
CONSORT Flow Diagram.

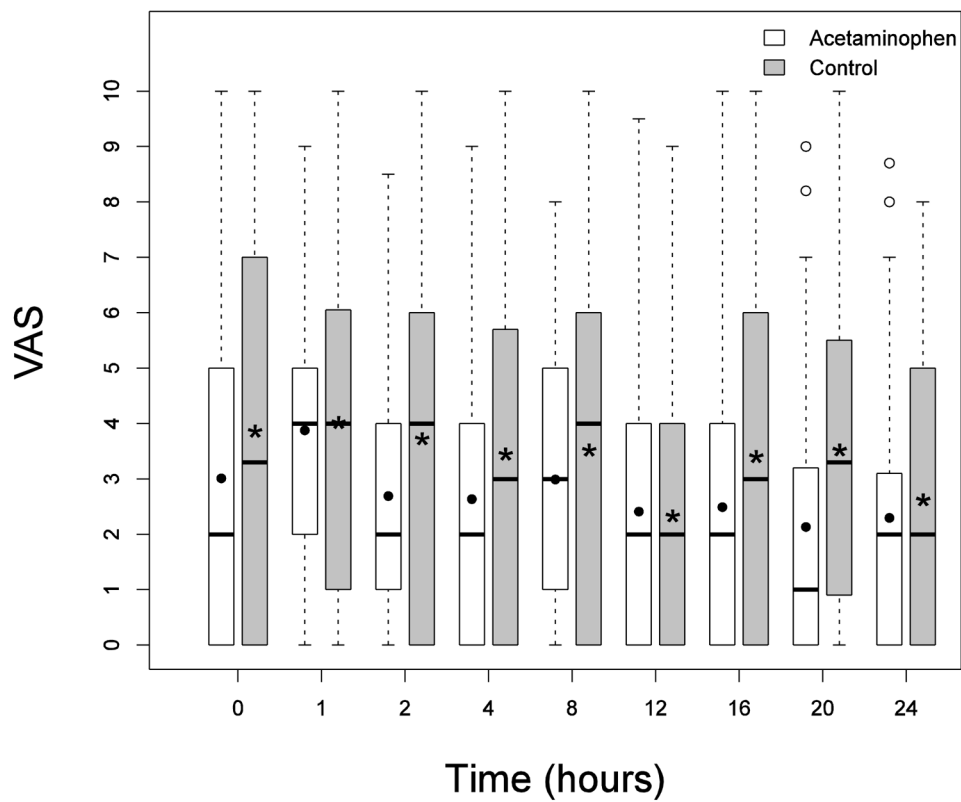


Figure 2.

VAS Pain Scores.

Box-and-whisker plot displaying the distribution of visual analog scale (VAS) pain score at baseline and follow-up time points. The bottom and top margins of the box indicate 1st and 3rd quartiles, and the band inside the box is the median. The bottom and top of whiskers indicate the maximum and minimum values of all data except outliers. Empty circles represent outliers. “Solid circle” indicates the mean of VAS in the Acetaminophen group and “*” indicates the mean of VAS in the control group.

Table 1

Baseline Demographic Data.

| Variables | Acetaminophen (n=50) | | Control (n=50) | |
|--|----------------------|--------------------|----------------|--------------------|
| | n | Summary Statistics | n | Summary Statistics |
| Age (year), mean \pm SD | 50 | 50.0 \pm 16.3 | 50 | 51.5 \pm 14.4 |
| Gender, n(%) | 50 | | 50 | |
| Female | | 24 (48.0%) | | 31 (62.0%) |
| Male | | 26 (52.0%) | | 19 (38.0%) |
| BMI, mean \pm SD | 49 | 30.0 \pm 5.9 | 49 | 27.3 \pm 7.3 |
| ASA Classification, n(%) | 50 | | 50 | |
| 1 | | 0 (0%) | | 2 (4.0%) |
| 2 | | 18 (36.0%) | | 13 (26.0%) |
| 3 | | 32 (64.0%) | | 35 (70.0%) |
| Length of Surgery (minutes), mean \pm SD | 50 | 211 \pm 89 | 50 | 222 \pm 108 |

SD, standard deviation

Table 2

Secondary Outcomes including Opioid Related Side Effects

| Variables | Acetaminophen | | Control | | <i>p</i> |
|---|---------------|--------------------|----------|--------------------|-------------------|
| | <i>n</i> | Summary statistics | <i>n</i> | Summary statistics | |
| Emesis, <i>n</i> (%) [*] | 45 | 23 (51.1%) | 40 | 20 (50.0%) | 0.92 ^c |
| Itching, <i>n</i> (%) ^{**} | 42 | 8 (19.0%) | 37 | 5 (13.5%) | 0.56 ^f |
| Dizziness, <i>n</i> (%) ^{**} | 42 | 14 (33.3%) | 37 | 14 (37.8%) | 0.68 ^c |
| Drowsiness, <i>n</i> (%) ^{**} | 42 | 24 (57.1%) | 37 | 19 (51.4%) | 0.61 ^c |
| Time to PACU Discharge (minutes), mean ± SD | 46 | 11.4 ± 7.2 | 43 | 13.5 ± 8.4 | 0.22 ^t |
| Extubation time (minutes), median (IQR) | 48 | 6 (3 – 13) | 45 | 8 (5 – 12) | 0.21 ^w |

^c denotes p-values obtained by Chi-square test;

^f denotes p-values obtained by extended Fisher's exact test;

^t denotes p-values obtained by two sample t-test;

^w denotes p-values obtained by Wilcoxon rank sum test;

IQR: interquartile range; SD: standard deviation.

^{*} As reported by research / nursing staff;

^{**} The percentage of patients who reported this side effect on the end of study questionnaire