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RESEARCH ARTICLE

Efficacy of Intravenous Acetaminophen after Coronary Artery Bypass Graft Surgery

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ABSTRACT

In recent years, a multimodal approach to post-operative pain control consisting of opioid and non-opioid agents administered simultaneously has been used to provide synergistic effects and reduce opioid-related adverse effects. This is a retrospective, cohort study involving coronary artery bypass graft surgery patients who received scheduled intravenous IV acetaminophen 1gm every 6 hours for 4 doses starting at surgery end time with opioids administered as needed versus opioids as monotherapy for postoperative pain control. The primary endpoint assessed was total morphine equivalents administered post-operatively in each group with a secondary focus on degree of pain control, total length of stay, ICU length of stay, and time to first bowel movement. The study concludes that the addition of IV acetaminophen to opioids for postoperative pain relief did not produce an opioid sparing effect and paradoxically led to an increase in opioid use. Clinical outcomes including pain control, total length of stay, and ICU length of stay were unaffected by the addition of IV acetaminophen.

KEYWORDS

Intravenous Acetaminophen, Post-Operative Pain, Adult, Ventilator Time, Length of Stay

INTRODUCTION

Acetaminophen (APAP) has long been recognized as a safe and effective agent for pain management and fever reduction. It has been widely utilized in diverse patient populations and disease states. Until 2010, acetaminophen was only available in oral and rectal formulations in the United States. In November 2010, the Food and Drug Administration (FDA) approved a parenteral formulation of acetaminophen for the treatment of pain and fever. The intravenous (IV) formulation has a quicker pharmacokinetic onset and higher peak concentration than the oral form.

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FDA-approved indications for this parenteral formulation include management of mild to moderate pain, management of moderate to severe pain with adjunctive opioid analgesics, and the reduction of fever in adults and children beginning at two years of age[1].

Early studies have shown a reduction in morphine doses administered when used in combination with IV acetaminophen,[2,3] hence the IV formulation was touted as opioid sparing. Since then, several studies have shown no difference in morphine consumption[4-6] or pain scores[5,6] when used in combination with IV acetaminophen. Despite the discrepancy in data, The American Society of Anesthesiologists Guidelines for Acute Pain Management in the Perioperative Setting recommends multimodal postoperative pain management whenever

possible[7]. Multimodal therapy consists of non-opioid agents, such as acetaminophen, used in combination with opioid analgesics to provide synergistic pain control[8] while reducing opioid-related adverse effects, including nausea, vomiting, constipation, sedation, and respiratory depression.

Independent to its analgesic effects, IV acetaminophen has been shown to alter additional outcomes post-operatively, including decreased ventilator times[9], decreased time in the post anesthesia care unit, and shortened length of hospital stay.[10-13] These studies were primarily conducted in patients undergoing abdominal surgery in countries other than the United States, so they may not be directly generalizable in the United States. One study conducted in cardiac surgery patients correlated IV acetaminophen with a reduced ICU length of stay, total length of stay, and shortened ventilator times[14]. A similar study showed reduced pain scores but no change in morphine consumption or postoperative nausea and vomiting with the addition of IV acetaminophen[4]. When the IV formulation of acetaminophen was compared to orally or rectally administered acetaminophen in cardiac surgery patients, no significant difference was shown in pain levels or rate of postoperative nausea and vomiting, although the IV formulation was associated with a lower opioid consumption than oral acetaminophen[5]. The cost of a typical dosing regimen of 1 gm IV acetaminophen administered every 6 hours is approximately $130, which is significantly more expensive than the daily cost of oral acetaminophen at around $1 per day.

Due to lack of consistent data regarding the opioid-sparing effects of IV acetaminophen, the goal of this study was to determine if such an effect would be seen in post coronary artery bypass graft (CABG) patients. Secondarily, if an opioid-sparing effect was identified, it would be determined if this correlated with a reduction in adverse effects and improved clinical outcomes through analysis of secondary clinical endpoints. A secondary analysis was also conducted to analyze the effects of IV acetaminophen on ventilator time in a subset of patients.

MATERIAL AND METHODS

This was a retrospective, single center, cohort study conducted at 432 bed tertiary care center. The study protocol was approved by the Western International Review Board through exemption status prior to data collection. Data was compiled for patients undergoing CABG procedures between July 2011 and October 2013 by accessing electronic medical records and through manual chart review. This time period was chosen as it was preceding the addition of IV acetaminophen to formulary and succeeding it. The primary endpoint evaluated was total oral morphine equivalents administered in the opioid monotherapy group versus the opioid and IV acetaminophen group. Secondary endpoints consisted of maximum pain scores at 24 and 48 hours, time to first bowel movement, length of stay (LOS) in the intensive care unit (ICU), and total hospital LOS. Opioid medications included in the analysis were oxycodone, hydrocodone, morphine, fentanyl, and hydromorphone administered either orally or parenterally.

Patients were eligible for inclusion if they were 18 years of age or older, had undergone CABG surgery on or off pump, and had received either post-operative opioids with IV acetaminophen or opioid monotherapy. Patients were excluded if they had been admitted to the ICU for greater than 30 days, had a documented allergy or intolerance to either study drug, had severe hepatic impairment defined as liver function tests (LFTs) greater than three times the upper limit of normal, or had received either an analgesic patch or patient-controlled analgesia (PCA) pump.

Data was analyzed electronically using Microsoft Excel and Origin Lab statistical software. The Shipiro-Wilk test was used to test for normality. After normality was determined, the F-test was used to test for equal or unequal variance between groups continuous in nature. Normally distributed continuous data was analyzed using a one-sided T test. Nominal data was analyzed using the Fisher's exact test. A p value of <0.05 was set a priori for statistical significance and all tests used a 95% confidence interval. Log^{10} transformation was utilized if data sets were not

normally distributed due to large standards of deviation seen with biological data. In the event the $\log^{10}$ transformation was determined to be not normal by the Shipiro-Wilk test, the data was considered non-parametric. Non-parametric data was analyzed utilizing the Mann-Whitney U test to test for statistical significance. In order to meet 80% power, it was determined that the opioid only group needed to have 90 patients and the IV acetaminophen plus opioid group needed to have 94 patients for a total group size of 184 patients.

RESULTS AND DISCUSSION

Of the patients who underwent CABG surgery between July 2011 and October 2013, 204 patients were analyzed. Ten patients were excluded from the analysis, resulting in a cohort of 193 patients. Of these patients, 98 had received IV acetaminophen and opioids, and 95 had received opioid monotherapy. The baseline characteristics of the two groups had no statistically significant differences as seen in Table 1 below. The population was mostly Caucasian males in their 70's.

Table 1: Baseline Characteristics

Characteristic	Opioids only (n=95)	IV APAP + Opioids (n=98)
Age - yrs (SD)	73.0 (± 0.8)	71.5 (± 1.0)
Height - cm (SD)	171.9 (± 1.1)	171.1 (± 1.4)
Weight - kg (SD)	92.87 (± 2.1)	88.0 (± 1.9)
SCr - mg/dL(SD)	1.25 (± 0.16)	1.30 (± 0.12)
Male gender – no. (%)	67 (70)	64 (65)
Caucasian – no. (%)	93 (97)	95 (97)

With regards to the primary endpoint, total oral morphine equivalents administered to patients receiving IV acetaminophen was significantly increased when compared to the opioid monotherapy group as shown in Table 2.

Table 2: Primary Outcomes

Characteristic	Opioids only (n=95)	IV APAP + Opioids (n=98)	p-value
Total oral morphine equivalents used in mg (SD)	124.2 (± 7.8)	167.3 (± 12.8)	0.002

There were no statistically significant differences found between secondary endpoints with the exception of time to first bowel movement. Maximum pain scores 24 and 48 hours following surgery were similar between groups (p= 0.34, p=0.31), as was length of stay in the ICU (p=0.77) and total length of stay (p=0.45) Time to first bowel movement was found statistically significant (p = 0.04) between the two groups, with an increase seen in the IV acetaminophen combination group. These results are found in Table 3.

Table 3: Secondary Outcomes

Characteristic	Opioids only (n=95)	IV APAP + Opioids (n=98)	p-value
Hospital LOS – days (SD)	7.9 (± 0.45)	7.97 (± 0.46)	0.45
Time to 1st BM – days (SD)	3.76 (± 0.16)	3.36 (± 0.15)	0.04
ICU LOS – days (SD)	4.3 (± 0.38)	3.9 (± 0.26)	0.77
Pain score (24 hour max) Scale 1-10 (SD)	6.5(± 0.24)	6.3(± 0.26)	0.34
Pain score (48 hour max) Scale 1-10 (SD)	6.9 (± 0.24)	6.7 (± 0.23)	0.21

Of note, AST and ALT levels in patients who had these labs drawn were slightly higher in the IV acetaminophen combination group, but this was not a statistically significant difference.

Table 4: Liver Enzymes

Liver Enzymes	Opioids only (n=65)	IV APAP + Opioids (n=59)	p-value
AST	26.1 (± 1.9)	39.1 (± 6.3)	0.34
ALT	28.1 (± 2.3)	30.1 (± 2.7)	0.57

Results of this study indicate that the addition of IV acetaminophen to opioid therapy did not reduce the amount of oral morphine equivalents administered post-CABG surgery. Additionally, the length of stay and degree of pain control were unaffected by the addition of IV acetaminophen in this subset of patients. The cardiothoracic surgeons at our facility implemented the addition of IV acetaminophen to formulary in 2011 with the expectation of improved post-operative outcomes, including time on the ventilator, ICU length of stay, and time to first bowel movement. Data was analyzed after implementation to determine if improved outcomes would be seen with the addition of the costly medication. There may still be a potential to decrease opioid use in postoperative patients while utilizing IV acetaminophen, but it would require significant education of the nursing staff to only use opioids for uncontrolled pain.

There were several potential limitations identified for this study. Patients with significant opioid tolerance may require higher doses of opioid medications to achieve adequate pain relief. This dose-dependent effect can be difficult to quantify in patients on long term opioid therapy. Patients exhibiting tolerance to opioid medications were not taken into consideration during the study. Due to the inherently subjective nature of pain scores, bias may have occurred from significant variability in patients' detected levels of pain. PCA pumps and medications administered in transdermal formulations were not taken into consideration due to the inability to accurately quantify the amount of drug administered prior to implementation of electronic medication administration records. Additionally, several inconsistencies with pain score recording were identified, further increasing risk of bias with regards to pain control data.

It is difficult to explain why higher opioid exposure was seen in patients administered IV acetaminophen in combination with opioid medications than patients receiving opioid monotherapy. It is possible that physicians at our institution may be over-estimating their ability to achieve adequate basal pain control in certain patients. If this were the case for patients in the acetaminophen group during the study period, inadequately controlled baseline pain may account for the increased need for opioid pain medications in this group. However, no difference was observed in pain scores at 24 and 48 hours, total length of stay, or ICU length of stay between groups. It did, however, lead to a statistically significant increase in time to first post-operative bowel movement in the IV acetaminophen group, which would logically occur in patients receiving more opioids. However, an increase of 0.4 days is likely not clinically relevant.

CONCLUSION

The data available regarding the use of IV acetaminophen is divisive. This study adds to the available literature postulating that IV acetaminophen does not affect clinical outcomes adequately enough to justify its cost. The study concludes that the addition of IV acetaminophen to opioids for postoperative pain relief had no opioid sparing effects and paradoxically led to an increase in opioid use. Clinical outcomes including pain control, total length of stay, and ICU length of stay were unaffected by the addition of IV acetaminophen. However, time to first bowel movement was longer with combination therapy. More robust studies with other surgical and nonsurgical populations would be helpful in the future given the inconsistencies in the current literature.

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