Intravenous acetaminophen for acute pain control in neurocritical care subarachnoid hemorrhage patients

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ABSTRACT

Introduction: Limited data exists evaluating the effects of IV APAP for pain control in neurocritical care patients. This study evaluates differences in pain scores and the need for rescue medications in patients receiving IV APAP as compared to other analgesics in subarachnoid hemorrhage (SAH).

Methods: This retrospective study evaluated SAH patients who received analgesics within six hours after procedure. The pain score, the pain intensity difference (PID) within 0-3 hours, 3-6 hours, and within six hours of IV APAP (PID 0-6) versus other analgesics were compared. Additionally, the need for rescue medications within six hours was compared.

Results: We included 157 SAH patients. Mean (SD) pain scores for the IV APAP group (n=16) pre-dose, 0-3 hours post dose, and 3-6 hours post-dose were 2.31 (3.2), 1.25 (2.2), and 0.81 (1.2), respectively. The mean PID (0-3 hours) for patients receiving IV APAP was 1.06 compared to 0.75 for oral APAP (n=8); 0.14 for opioids (n=63); and 1.4 for butalbital/APAP/Caffeine combination products (BAC) and other analgesics (n=66) (p=0.1). The mean PID (0-6 hours) for patients receiving IV APAP was 1.5 compared to 0.88 for oral APAP; 0.76 for opioids; and 1.95 for butalbital/APAP/Caffeine combination products (BAC) and other analgesics (p=0.12). Rescue medications were needed in 50% of IV APAP patients as compared to 50% receiving oral APAP, 70% opioids and 75% BAC and others (p=0.08)

Conclusion: IV APAP for acute pain in neurocritical care SAH showed no statistical difference compared to other analgesics; however, there was a potential trend in better pain control up to 6 hours post dose as compared to oral APAP and opioids and less used of rescue medications as compared to opioids and BAC. Larger, prospective studies are needed to assess any proposed benefit.

Key Words: *Acetaminophen APAP; Subarachnoid hemorrhage; Aneurysm; Pain; Analgesia*

INTRODUCTION

The use of non-opioid analgesics for pain management in postoperative patient populations provides multiple benefits including reduction of opioid use, improvement of patient pain relief and satisfaction, support of earlier recovery, and reduction of adverse events and healthcare costs (1,2). The use of non-opioid pain medications in the postoperative neurocritical care setting is of significance as this patient population requires frequent neurological monitoring which may be limited by the sedative effects of narcotic pain medications. Patient with subarachnoid hemorrhage (SAH) frequently require intravenous medications for pain control, and typically experience severe headaches, further complicated by nausea and vomiting, which limits the use of oral medications. In SAH patients, the ideal analgesic would be one that has an option for intravenous (IV) administration, high central nervous system (CNS) concentrations (site of action) and a quick onset of action.

Multiple non-opioid analgesics are available and approved for the treatment of post-operative pain; however, intravenous options are limited. Acetaminophen (APAP) is one such non-opioid analgesic, with oral (PO) and rectal (PR) formulations widely used in the United States for many decades as an analgesic and antipyretic. The IV form of acetaminophen (OFIRMEV®) was approved for use in the United States in 2010 (3,4). Studies have demonstrated some efficacy of IV acetaminophen in other surgical populations, however the evidence in the neurocritical care population is limited, but promising for post-operative pain control (5,6).

Singla and colleagues demonstrated that the IV formulation of acetaminophen produces both earlier and higher plasma and cerebrospinal fluid (CSF) concentrations of acetaminophen when compared to the PO and PR formulations (4). The higher noted CSF concentration is likely secondary to the lack of first-pass metabolism in the IV formulation, and this increased CSF bioavailability suggests that the IV formulation of acetaminophen may be particularly efficacious in postoperative neurosurgical patients. Additionally, the onset of action in the CSF of IV APAP has been reported as soon as five minutes, which is potentially beneficial in patients whose pain may cause further neurological deficits such as delirium. These findings encourage the use of intravenous APAP in a neurocritical care population (6,7).

Since opioids decrease gastrointestinal motility, which in turn may reduce medication absorption in the small bowel, the use of oral medications may not be as effective and may lead to further use of IV opioids that continue the vicious cycle. Therefore, acute pain medications like IV APAP that may lead to less opioid rescue medication use is desirable to avoid further delays in normal GI motility and medication absorption post-operatively.

Our study evaluates the use of IV acetaminophen for post-operative pain control in patients with SAH who have undergone a neurosurgical procedure and compares clinical outcomes with the use of other analgesics, measured by pain control and need for rescue medications. We propose that the use of the IV formulation of APAP would increase pain relief in the post-operative neurocritical care population, thus minimizing the use of opioids or other rescue medications and thereby reducing adverse effects.

METHODS

This is a retrospective study of neurocritical care patients admitted to the Virginia Commonwealth University Health System Neuroscience ICU between 2011 and 2013. All aspects of the study were approved by the institutional review board (IRB).

The study evaluated patients with SAH who received analgesics within 6 hours after a neurosurgical procedure. Criteria for inclusion into the study were age between 18 and 88 years, neurosurgical procedure for management of acute SAH, and first analgesic dosing within 6 hours post-operatively. Neurosurgical procedure included any procedure related to the SAH,

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such as diagnostic angiography, aneurysm coiling, aneurysm clipping, or ventriculoperitoneal shunt placement.

Exclusion criteria included ICU stay less than 24 hours, inmate status, pregnancy, sedative infusion concurrent with analgesic administration, and inability to evaluate pain by visual analog scale (VAS). Pain was reported on a 0-10 visual analog scale (VAS) by patient and recorded by nursing staff into the health system's electronic medical record. Analgesic dosing times were also recorded into the electronic medical record by nursing staff.

Pain scores were recorded at 0 (baseline), 3, and 6 hours from initial analgesic dosing. Patients were divided into groups based on initial analgesic: IV acetaminophen 1000 mg, oral acetaminophen 650 mg, any opioid analgesic (including oral and intravenous formulations), and butalbital/APAP/caffeine combination products (BAC) with other analgesics (including any analgesic not included in the previous categories (oral NSAIDS, ketorolac, or tramadol). The difference in dosing of IV and PO reflects the commonly prescribed doses for both oral and IV APAP at our institution. The pain intensity difference (PID) is the difference in pain score between two-time points. We studied the PID in the first 3 hours, 3 to 6 hours, and the first 6 hours of receiving the initial analgesic. We compared different time points PIDs between groups, in a similar manner to prior studies (8). Additionally, the need for use of rescue medications, defined as narcotic rescue medications within 6 hours of administration of IV acetaminophen versus other groups, was compared. Categorical data are presented as a percentage and normally distributed continuous data are reported as means (SD). PID scores between groups were compared by the Kruskal-Wallis one-way analysis of variance test. Difference in the proportion of patients receiving a rescue drug was assessed using Fisher's exact test. P-values of <0.05 were considered statistically significant. All statistical analyses were performed using JMP 10.0.0 (SAS Institute, Cary, NC, USA).

RESULTS

Overall, 157 neurocritical care SAH patients were included in this study. Females were slightly more (54% vs. 46%). Mean age was 50.6 (SD 12.6) years. Median Hunt & Hess score was 2 (IQR 1-5), and median Glasgow Coma Score (GCS) was 11(IQR 8-15) (Table 1).

Mean pain scores for patients receiving intravenous (IV) APAP (n=16), oral APAP (n=8), opioid (n=63), and BAC (n=58) plus other pain medications (n=8) for a total of 66 patients in this treatment group) at baseline (i.e. pre-dose) were 2.31 (SD 3.24), 2.5 (SD 2.83), 2.25 (SD 2.88), and 4.2 (SD 3.14), respectively. Mean pain scores for patients receiving intravenous (IV) APAP, oral APAP, opioid, and BAC plus other pain medications at 0-3 hours post dose were 1.25(SD 2.18), 1.75(SD 2.43), 2.11(SD 2.7), and 2.8(SD 2.18) respectively. Mean pain scores for patients receiving intravenous (IV) APAP, oral APAP, opioid, and BAC plus other pain medications at 3-6 hours post dose were 0.81(SD 1.17), 1.63(SD 1.77), 1.49(SD 2.46), and 2.25(SD 2.45) respectively.

The mean pain intensity difference in the first 3 hours (PID 0-3) for patients receiving IV APAP, oral APAP, opioids, and BAC plus others were 1.06 (SD 3.51), 0.75 (SD 1.16), 0.14 (SD 3.45), and 1.4 (SD 2.7) respectively (p=0.1). Similarly, the mean pain intensity difference in the first 6 hours (PID 0-6) for patients receiving IV APAP, oral APAP, opioids, and BAC plus others were 1.5 (SD 2.8), 0.88 (SD 3.1), 0.76 (SD 2.91), and 1.95 (SD 3.5), respectively (Table 2). There was no statistically significant difference between PID scores at any duration between IV APAP and other analgesics (p=0.12).

Rescue opioid medications were necessary for further pain control within 6 hours after the IV APAP dose, oral APAP, oral opioids, and BAC/others as follow: 50%, 50%, 70%, and 75%, respectively. There was also no statistically significant difference in the need for rescue medication between groups (p=0.08) (Table 2).

TABLE 1

Patient demographics

Demographic	
Mean Age (SD)	50.58 (12.64)
Female	54%
Median Hunt & Hess Score (IQR)	2 (1-5)
Median ASA physical status (IQR)	2 (1-3)
Median GCS (IQR)	11 (8-15)
Opioid naïve	88%

ASA American society of anesthesiologists; GCS: Glasgow coma score

TABLE 2

Mean pain scores and pain intensity differences over time

Medication (n)	Pre-dose mean pain score (SD)	0-3 hours post-dose mean pain score (SD)	3-6 hours post-dose mean pain score (SD)	PID 0-3 hours (SD)	PID 3-6 hours (SD)	PID 0-6 hours (SD)	% requiring rescue medication
IV APAP (16)	2.31 (3.24)	1.25 (2.18)	0.81 (1.17)	1.06 (3.51)	0.44 (1.63)	1.5 (2.8)	50
PO APAP (8)	2.5 (2.83)	1.75 (2.43)	1.63 (1.77)	0.75 (1.16)	0.13 (2.47)	0.88 (3.1)	50
Opioid (63)	2.25 (2.88)	2.11 (2.70)	1.49 (2.46)	0.14 (3.45)	0.62 (2.81)	0.76 (2.91)	70
BAC/others (66)	4.2 (3.14)	2.8 (2.8)	2.25 (2.67)	1.4 (2.7)	0.55 (2.8)	1.95 (3.5)	75
Total (157)	3.03 (3.18)	2.24 (2.72)	1.71 (2.45)	0.79 (3.17)	0.54 (2.62)	1.32 (3.2)	

PID Pain intensity difference; BAC: Butalbital/APAP/caffeine combination products

DISCUSSION

SAH patients frequently present with severe headaches, nausea, and vomiting which often limits the use of oral medications for pain relief. This leads to unwanted opioid use to treat acute pain in this population, which can interfere with neurological assessment and possibly lead to unnecessary and costly neuro imaging. Therefore, it is imperative to optimize acute pain control with a drug that allows for IV administration, high CSF penetration but minimal CNS impairment, and a quick onset of action. Additionally, the risk of continued headaches is high in the SAH patient population which necessitates avoidance of compounds such as BAC or opioids which are known to contribute to development of rebound headache (6-9).

In this study, SAH patients undergoing a neurosurgical procedure and who received IV APAP as the initial post-operative analgesic, were compared to those treated with other options. There were no statistically significant differences between IV APAP patient mean pain scores and PID as compared to patients receiving other pain medications. A beneficial trend was observed for IV APAP over oral APAP and opioids in decreasing the pain score in the first 3 and in the first 6 hours after procedure, possibly due to IV APAP's pharmacokinetic profile. This is very important in the SAH patient population as their initial complaint is the "worst headache of their life" which is the main source of pain in these patients post aneurysmal rupture. Having a medication that can be quickly administered, attain therapeutic concentrations in the central nervous system and provide symptomatic relief is a true benefit in this patient population. Although this was only a 1 dose, post procedural study, the fact that there was a beneficial change in PID and a trend towards quicker onset than oral options is promising.

The need for rescue medication also did not statistically differ among the groups, regardless of the initial drug type. However, there was also a trend in lower use of rescue meds in the APAP treated patients as compared to those receiving opioids or BAC/other as their initial medication. Determining the correct balance between non-opioid and opioid medications in the post-operative period is key to helping decrease the use of opioids administered. Studies where pre- and post-operative doses are routinely administered for a short period of time, with options for rescue are crucial to the management of the SAH patient population.

This study was limited by factors inherent to retrospective study designs and a small sample size of SAH patients receiving IV or oral APAP in the immediate post-operative period. The comparison of oral 650 mg *vs.* IV 1000 mg of acetaminophen might not be balanced not only because of the dosage difference, but also because oral acetaminophen undergoes first pass metabolism in the liver and exposure will be lower, plus the body mass index

for the patients may affect the dosing. This difference in dosing reflects the common prescribed doses for both oral and IV APAP in our practice. In addition, we were only able to analyze pain scores documented in the intensive care unit medical record, and may have missed the peak times for pain control.

CONCLUSION

As similar trends were noted in the pain medication groups studied, IV APAP may be considered as an option in treating acute post-operative pain in SAH patients without oral access for medication administration.

Prospective studies are needed to address the findings of the current study and to optimize patient satisfaction with pain control following surgical management of SAH.

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