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Brief Report

USE OF PROPHYLACTIC ONDANSETRON WITH INTRAVENOUS OPIOIDS IN EMERGENCY DEPARTMENT PATIENTS: A PROSPECTIVE OBSERVATIONAL PILOT STUDY

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□ **Abstract—Background: The current literature suggests that the prophylactic use of antiemetics is ineffective at preventing nausea or vomiting caused by opioids in the emergency department (ED). While there is no data evaluating ondansetron's efficacy for preventing opioid-induced nausea and vomiting, this practice remains common despite a lack of supporting evidence. Objectives: This study aimed to identify if prophylactic ondansetron administered with intravenous (IV) opioids prevents opioid-induced nausea or vomiting. Methods: This prospective observational study was conducted in the ED at two academic medical institutions. Patients were eligible for enrollment if they were prescribed an IV opioid with or without IV ondansetron and absence of baseline nausea. Patients' level of nausea was evaluated at baseline, 5 min, and 30 min after an IV opioid was administered and then observed for 2 hours. Results: One hundred thirty-three patients were enrolled, with 90% of patients presenting with a chief complaint of pain. Sixty-four (48.1%) patients received an IV opioid alone and 69 (51.9%) patients received both IV ondansetron and an IV opioid. Twenty-three (17.3%) patients developed nausea caused by opioid administration. One (0.75%) patient had an emetic event and 3 (2.3%) patients required rescue antiemetics during their observation period. Rate of nausea was similar between treatment groups 5 min after the opioid was administered (p = 0.153). There was no statistical difference in emesis, rescue medication requirements, or nausea severity between treatment groups. Conclusion: Our trial found that ondansetron did not appear to be effective at preventing opioid-induced nausea or vomiting. These findings and previous literature suggest prophylactic ondansetron should not be given to ED patients who are receiving IV opioids.** © **2017 Elsevier Inc. All rights reserved.**

□ **Keywords—emesis; nausea; ondansetron; opioids; pain**

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INTRODUCTION

In 2011, the Centers for Disease Control and Prevention (CDC) estimated that 11 million people presented to emergency departments (EDs) in the United States (US) with a chief complaint of uncontrolled pain. According to the CDC report, approximately 54 million doses of analgesia were administered to ED patients, and 25 million were opioids. In addition, an estimated 27 million antiemetics were administered, of which 17 million (63%) were ondansetron (Zofran; GlaxoSmithKline, Brentford, London) (1). All opioids approved by the US Food and Drug Administration carry a warning that nausea and vomiting may occur, with evidence varying in degree of prevalence.

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Opioids bind directly to the chemoreceptor trigger zone and activate the central nervous system vomiting center, inducing nausea or emesis (2). Previous studies have shown a low incidence of opioid-induced nausea and vomiting in ED patients, ranging from 2% to 20.2% (3–8).

Given the potential for opioids to induce nausea and vomiting, it is not uncommon for prophylactic antiemetics to be administered concurrently with opioid analgesics in the ED, despite limited evidence to support this practice. In a randomized, double-blind, placebo-controlled trial performed in a New Zealand ED, patients received either placebo or metoclopramide with IV morphine administration (5). While not statistically significant, the authors found a clear trend toward an increase in vomiting when patients received metoclopramide compared with placebo (5.4% vs. 1.9%, $p = 0.17$). A similar study performed in a United Kingdom ED determined that metoclopramide did not prevent nausea and vomiting associated with IV morphine use (6). Both groups of researchers concluded that nausea and vomiting is not a common adverse event from IV opioids and did not warrant pretreatment with antiemetic therapy. A 2014 trial from India evaluated the efficacy of promethazine, metoclopramide, ramosetron (a 5HT-3 antagonist), or placebo to prevent opioid-induced nausea or vomiting (7). The trial concluded that there was no difference in preventing nausea or vomiting between ramosetron, metoclopramide, or promethazine vs. placebo. In fact, patients treated with placebo had a trend toward less nausea compared to all treatment groups.

A multicenter trial conducted in nine countries assessed the safety and efficacy of ondansetron for the treatment of nausea and vomiting induced by opioid exposure (8). A total of 2574 patients who received an IV opioid in the ED were included, of which 520 patients (20.2%) developed nausea or emesis caused by the opioid. The 520 patients with nausea or emesis were enrolled to receive either placebo, 8 mg of ondansetron, or 16 mg of ondansetron. The trial found that one dose of either 8 mg or 16 mg of ondansetron controlled emesis in 62% and 69% of the patients, respectively. The authors concluded that ondansetron was effective at treating opioid-induced nausea and vomiting, but should be preserved for patients complaining of nausea or vomiting. For ED patients presenting with nausea, a 2011 randomized, placebo-controlled, double-blind superiority trial was unable to detect statistical differences between ondansetron, promethazine, metoclopramide, or placebo in nausea reduction (9).

To our knowledge, published research assessing the efficacy of prophylactic antiemetic therapy has only been evaluated outside of the United States, and none of these studies included ondansetron (4–7). Prophylactic ondansetron has been studied in the postoperative setting and in settings involving patient-controlled analgesia with mixed results, but has never been studied for antiemetic prophylaxis caused by opioid-induced nausea and vomiting in the ED (10–13). Despite a lack of supporting evidence, it remains common practice to pretreat patients with antiemetic therapy before they receive IV opioids. While ondansetron is generally well tolerated, it does have some concerning adverse effects, including QTc prolongation (14). The primary purpose of this study is to determine if prophylactic ondansetron reduces opioid-induced nausea and vomiting.

METHODS

This prospective, observational study was approved by the Institutional Review Boards at Banner University Medical Center Phoenix and Banner University Medical Center Tucson. Patients were eligible for enrollment if they were ≥18 years of age, had a medication order for an IV opioid (fentanyl, morphine, or hydromorphone), spoke English, and did not have nausea at baseline. Patients were excluded if they received any antiemetic therapy other than IV ondansetron, reported an allergy to ondansetron, presented with altered mental status, were breastfeeding or pregnant, received an opioid or antiemetic within 24 hours before presentation to the ED, or were unable to consent. Convenience sampling was used based on study team availability in the ED. Enrollment began in November 2015 and continued until January 2016. Trained ED study nurses acted as collaborators and helped to identify eligible patients. The decision to use an opioid analgesic, the type of opioid used, and the use of prophylactic ondansetron use were all done solely at the discretion of the treatment team before screening or enrollment in the study. Pharmacists used an electronic ED patient tracking board (Cerner or Epic) to identify patients with orders for an IV opioid with or without IV ondansetron. Patients were consented either before the IV opioid was administered or immediately after (within 5 min) to ensure that no delay in therapy occurred because of study enrollment. The investigators assessed nausea or presence of emesis at baseline, 5 min after opioid administration, and again at 30 min after opioid administration. Nausea was assessed using a verbally administered 11-point numeric rating scale (NRS) (Figure 1). The data collection tool and example NRS are available in the Figure 2. Patients were

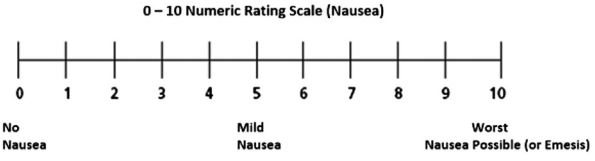

Figure 1. Numeric rating scale for severity of nausea.