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Original Contribution

Dose-ranging effect of systemic diphenhydramine on postoperative quality of recovery after ambulatory laparoscopic surgery: a randomized, placebo-controlled, double-blinded, clinical trial☆,☆☆

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Abstract

Study objective: Diphenhydramine is an antihistamine with previously demonstrated analgesic and antiemetic properties. However, it is unknown if the beneficial perioperative properties of diphenhydramine can translate to a better quality of postsurgical recovery. The main objective of the current investigation was to investigate dose-ranging effects of diphenhydramine on quality of recovery after surgery.

Setting: Tertiary hospital in the United States.

Design: A prospective, randomized, double-blind trial.

Intervention: Saline, diphenhydramine 25 >mg, or diphenhydramine 50 mg given intravenously before induction.

Measurements: The primary outcome was global Quality of Recovery–40 at 24 hours. Postoperative pain, nausea, opioid consumption, and discharge time were also evaluated.

Main results: Ninety subjects were randomized, and 75 completed the study. The median (interquartile range) Quality of Recovery–40 scores were not different among study groups: 164 (151-189), 169 (159-181), and 172 (157-185) for the saline, 25-mg diphenhydramine, and 50-mg diphenhydramine groups, respectively ($P = .74$). Postoperative nausea was decreased in the 50-mg group, 3 of 24 (12.5%), compared with the saline group, 12 of 27 (44%), $P = .01$. There was an inverse linear association between postoperative opioid consumption and quality of recovery ($R^2 = 0.37$, $P < .001$).

Conclusions: Diphenhydramine does not provide dose-ranging improvements on postoperative quality of recovery after ambulatory laparoscopic gynecologic surgery. Our results support a recent concept that not all postoperative nausea and vomiting symptoms are clinically important. Future studies evaluating postoperative nausea and vomiting should include patient-centered outcomes to validate the clinical importance of the examined interventions.

1. Introduction

Recent advances in surgical techniques and anesthetic drugs have resulted in a very large proportion of surgical

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procedures that are currently performed in an ambulatory setting [1–3]. The ambulatory setting can pose challenges to patients' recovery because patients do not have access to potent intravenous (IV) medications and the support of a structured hospital facility after hospital discharge [4,5]. Female patients are particularly vulnerable to poor quality of surgical recovery due to a greater sensitivity to pain and greater propensity to develop postoperative nausea and vomiting when compared with male patients [6–8]. Strategies to improve quality of surgical recovery in female patients undergoing ambulatory procedures are, therefore, largely needed.

Diphenhydramine is an antihistamine drug commonly used perioperatively to minimize postoperative nausea and vomiting [9]. In addition, histamine blocking agents can reduce pain, improve sleep, and reduce anxiety, leading to an improvement in other dimensions of postsurgical recovery [10,11]. However, it remains to be determined if diphenhydramine can improve global postoperative quality of recovery after ambulatory surgery. Because diphenhydramine also has sedative properties, it is conceivable that the drug may prolong hospital discharge, which is undesirable in ambulatory surgical patients [12,13].

The main objective of the current investigation was to evaluate the dose-ranging effects of diphenhydramine on postoperative quality of recovery when used in combination with ondansetron after outpatient laparoscopic gynecologic surgery. We hypothesized that subjects receiving diphenhydramine would have a better quality of recovery that the ones receiving saline. In addition, we also sought to determine if diphenhydramine prolongs time to hospital discharge compared with saline after ambulatory surgery.

2. Methods

This study was a prospective, randomized, double-blind, placebo-controlled trial. Clinical trial registration for this study can be found at ClinicalTrials.gov (NCT01451762). Study approval was obtained from the Northwestern University Institutional Review Board, and written informed consent was obtained from all the study participants. Eligible subjects were healthy women undergoing outpatient gynecologic laparoscopy. Patients with a history of allergy to diphenhydramine, those with long-term use of an opioid analgesic or corticosteroid, and/or pregnant subjects were not enrolled. The reason for exclusion from the study after study drug administration was conversion from a laparoscopic to an open incision. Subjects were randomized using a computer-generated table of random numbers into 3 groups to receive 50 mg IV diphenhydramine, 25 mg IV diphenhydramine, or saline. Group assignments were sealed in sequentially numbered, opaque envelopes that were opened by a research nurse not involved with patient care or data collection after the subject provided written informed consent. The same nurse prepared syringes labeled with study drug to blind the anesthesia personnel and the investigators collecting the data.

All subjects were premedicated with 0.04 mg/kg IV midazolam. Propofol 1 to 2 mg/kg was administered for anesthesia induction, a remifentanil 0.1-μg/(kg min) IV infusion was begun, and rocuronium 0.6 mg/kg IV was administered to induce muscle paralysis. Tracheal intubation was initially attempted by an anesthesia resident physician or a certified registered nurse anesthetist under supervision of an attending anesthesiologist. The study drug was administered after anesthesia induction. Anesthesia maintenance was achieved using remifentanil, titrated to maintain the mean arterial blood pressure within 20% of baseline; sevoflurane, titrated to a Bispectral Index (Aspect Medical Systems, Inc, Norwood, MA) between 40 and 60; and rocuronium.

At the end of the procedure upon removal of the laparoscopic instruments, the remifentanil infusion was discontinued, and the subjects received IV ketorolac 30 mg and ondansetron 4 mg.

In the postanesthesia care unit (PACU), subjects were asked to rate their pain at rest upon arrival and at regular intervals on a 0 to 10 numeric rating scale (NRS), where 0 means no pain and 10 is the worst pain imaginable. The area under the NRS pain score vs time curve was calculated using the trapezoidal method as an indicator of pain burden during early recovery (GraphPad Prism version 5.03; GraphPad Software, Inc, La Jolla, CA). Hydromorphone 0.2-0.4 mg IV was administered every 5 minutes to maintain an NRS pain score <4 of 10. In cases of postoperative nausea or vomiting, subjects received 10 mg IV metoclopramide, followed by 5 mg IV prochlorperazine if necessary [15]. Discharge readiness was assessed using the modified Post-Anesthetic Discharge Scoring System [14] every 15 minutes until subjects met discharge criteria. The Post-Anesthetic Discharge Scoring System assesses 5 criteria: vital signs, activity and mental status, pain nausea and/or vomiting, surgical bleeding, and intake and output. Each criterion is scored on a 0 to 2 scale, with higher scores representing a more acceptable condition. A score of ≥ 9 is considered ready for discharge. At discharge, subjects were instructed to take ibuprofen 400 mg orally every 6 hours and a combination of hydrocodone 10 mg plus acetaminophen 325 mg for pain >4 of 10. Postoperative opioid consumption (24 hours) was converted to an equivalent dose of oral morphine [16].

Subjects were contacted by telephone 24 hours after the procedure by an investigator unaware of group allocation and were questioned regarding analgesic consumption and pain score, and the Quality of Recovery (QoR)–40 questionnaire was administered [17]. The questionnaire consists of 40 questions that examine 5 domains of patients' recovery using a 5-point Likert scale: none of the time, some of the time, usually, most of the time, and all of the time. The 5 domains include physical comfort, pain, physical independence, psychological support, and emotional state. The individual components of the instrument have been previously presented by our group [18]. Perioperative data collected included subjects' age, height, weight, +American Society of