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ORIGINAL ARTICLE

Determination of ED_{50} of hydromorphone for postoperative analgesia following cesarean delivery

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ABSTRACT

Background: Morphine is the most common opioid injected into the intrathecal space for postoperative analgesia following cesarean delivery, but ongoing medication shortages have resulted in limited availability. One proposed morphine alternative is hydromorphone. Studies investigating its use in post-cesarean analgesia are limited. This study was conducted to determine the median effective dose of intrathecal hydromorphone 12 h postpartum.

Methods: Twenty healthy women undergoing elective cesarean delivery were recruited into this study. Hydromorphone doses were determined using the up-down sequential method. The study dose of hydromorphone started at 6 μg and was raised or lowered by 2 μg depending on the 12-h efficacy of the preceding participant's dose. Pain scores of <3/10 were considered successful and the subsequent patient received a lower dose. Participants received 0.5% bupivacaine 12.5 mg, fentanyl 25 μg, and the study dose of hydromorphone as a single intrathecal injection.

Results: Ten of 20 participants reported an effective hydromorphone dosage 12 h post-injection. The median effective hydromorphone dosage was 4.6 μg (95% CI 3.72 to 5.48 μg) based on participants' reported visual analog pain scores of <3/10. No significant side effects or adverse outcomes were observed.

Conclusion: Intrathecal hydromorphone may be an effective alternative to morphine for post-cesarean pain management. The amount of intrathecal hydromorphone necessary to provide analgesia at 12 h postoperatively may be significantly lower than doses currently in use. Further research should be performed to identify the optimal dose of intrathecal hydromorphone for post-surgical pain relief.

Keywords: Cesarean delivery; Hydromorphone; Analgesia; Injections; Spinal

Introduction

Opioid analgesics have long been utilized for chronic and acute pain management, and the intrathecal use of morphine was shown effective for spinally-mediated analgesia more than four decades ago.[1] Morphine has historically been the most common opioid injected into the spinal canal for postsurgical pain relief, but anesthesiologists have been seeking alternatives due to ongoing medication shortages. Opioids are only one of three classes of medications approved for spinal administration by the US Food and Drug Administration, and the most frequently used spinal opioids for post-cesarean pain relief are morphine and fentanyl.[2,3]

Hydromorphone is a proposed alternative to intrathecal morphine for postoperative pain management. It provides similar analgesia and has similar side effects, with some moderate reduction in duration of action.[4] To date, intrathecal hydromorphone administration has been primarily described in the treatment of chronic pain with a wide range of dosages (0.71–5.5 mg per day).[5,6] While systematic investigations comparing the efficacy and side effects of intrathecal hydromorphone with morphine are ongoing, some studies suggest it as an adequate alternative, highlighting its effectiveness and safety for postoperative pain management.[7,8] However, what remains to be determined is the appropriate dose. While several studies have determined the optimal dose for intrathecal morphine after cesarean delivery, no similar studies exist for hydromorphone.

This study was designed to determine the median effective dose (ED_{50}) for postoperative pain relief at 12 h and to identify what side effects, if any, are present at that dose. Understanding the ED_{50} of a medication is important because it is located in the most sensitive portion of the dose–response curve and small, incremental, adjustments are expected to have significant increases in therapeutic response. Additionally, studying the ED_{50}

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can potentially limit the total number of patients enrolled in a clinical trial, which is important when there is limited published information related to side effect profile of a medication. This study utilized the up-down sequential allocation method to determine the effective dose which, when the starting dose is appropriately chosen close to the therapeutic range for the medication, results in identification of the ED_{50} using a limited number of patients.[9–12]

Methods

Institutional review board approval and a US Food and Drug Administration investigational new drug application (115523) were obtained and the study was registered in Clinicaltrials.gov (NCT01598545). Written informed consent was obtained from all women enrolled in the study. From January 2013 to June 2014, 20 women presenting for elective cesarean delivery were recruited. Exclusion criteria included difficulty understanding English, American Society of Anesthesiologists physical status score $\geqslant 3$, category 2 or 3 fetal heart tracing, known fetal anomaly, prior laparotomy, greater than two prior cesarean deliveries, contraindication to neuraxial analgesia, allergy or hypersensitivity to hydromorphone, severe liver or kidney impairment, or severe respiratory disease.

Spinal anesthesia was performed at either the L2–3 or L3–4 interspace. Intrathecal injection contained bupivacaine 12.5 mg, fentanyl 25 μg and the study dose of preservative-free hydromorphone. Each dose of hydromorphone was determined using the up-down sequential allocation method in which dosages administered to subsequent patients are dependent on the reported effects of the dose in the previous patient: ergo, if the initial study patient reports adequate pain relief, the second patient receives a decreased dose (of fixed interval) of hydromorphone. If the initial patient does not report effective pain relief, the second patient receives an increased dose (again, of fixed interval) of hydromorphone.

As a result of previous unpublished experience with intrathecal hydromorphone, the starting hydromorphone dose was 6 μg. The interval sequential dose was varied by 2 μg based on the previous patient's response 12 h post-injection. Patients reported pain at rest based on a 0–10 visual analog pain score (VAPS), where 0=no pain and 10=worst pain imaginable. If the patient's VAPS rating at rest $\geqslant 3/10$ 12 h post-injection, intravenous patient-controlled morphine was initiated and the hydromorphone dose was determined to be "ineffective" (a negative result). The dose was then increased in the next participant. A pain score $<3/10$ 12 h post-injection was counted as a positive ("effective") result. All patients were given intravenous acetaminophen 1 g and ketorolac 30 mg every six hours beginning with closure of the surgical incision.

Patients were evaluated and data collected every six hours by anesthesiology residents trained in the study protocol. These residents were blinded to the hydromorphone dose. Pain was assessed at 6, 12, 18, and 24 h post-injection via VAPS rating. During these assessments patients were examined for side effects. Patients were asked if they were experiencing nausea, vomiting, and pruritus. Additionally, patient requests for antiemetic and antipruritic administration were recorded.

Intraoperative and postoperative blood pressure, heart rate, arterial oxygen saturation, 1- and 5-min Apgar scores, and maternal side effects were also assessed. Hypotension was defined as a systolic blood pressure <90 mmHg, or 20% below baseline, whichever was higher. Sedation was assessed using the Ramsay sedation scale and was defined as a patient who demonstrated a score >2.[13]

Statistical analysis

Data are presented as mean [range]. The median effective dose of hydromorphone was estimated from the up-down sequential allocation technique described by Dixon.[9–12] Analysis for group comparisons were made with Students t-test, Mann-Whitney U test and Fisher's exact test for parametric, non-parametric and categorical data as appropriate. Data were analyzed using JMP® (Version 10. SAS Institute Inc., Cary, NC, 1989–2007).

Results

From January 2013 to June 2014, 20 women completed the study. The mean age of participants was 28 years [range 19–40] and mean body weight was 89.2 kg [range 63–122]. Seventeen of 20 participants were of Black/African-American ancestry; the remaining were White/Caucasian. Additional participant demographic information is listed in Table 1. All 20 women who were recruited completed the study. No patient received supplemental intravenous medication during surgery.

Ten participants reported the dosage of hydromorphone to be effective (VAPS <3/10), and 10 reported their dosage to be ineffective (VAPS $\geqslant 3/10$) 12 h post-injection. Fig. 1 displays each dose, result, and subsequent dosing. Based on the VAPS scores, the median effective dose of hydromorphone 12 h post-injection was determined to be 4.6 μg (95% confidence interval 3.72 to 5.48 μg). No patient had postoperative hypotension, nausea, vomiting or sedation. Three patients reported pruritus; however, there was no correlation with either hydromorphone dose or with effectiveness of the medication. None of these three

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