# FAILURE OF PROPHYLACTIC INTRAVENOUS NALOXONE TO PREVENT POST-OPERATIVE OPIOID SIDE EFFECTS FOLLOWING ABDOMINAL AND THORACIC SURGERY: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Zahra Pilehvari[1], George M Mckelvey[2], Adib Moussa[1], Karim Rashid[1], Hassan Amhaz[1] and Samir F Fuleihan[1]

## Abstract

**Background:** Administration of opioids after surgery may result in post-operative side effects including pruritis, nausea and vomiting (PONV). There are many options for treatment of opioid side effects including naloxone. The aim of this study was to observe if a prophylactic bolus of Naloxone could prevent post-operative pruritus and PONV.

**Methods:** Patients (n = 77) scheduled for abdominal or thoracic surgery were randomly allocated into two study groups. The Naloxone intervention group (n = 40) received a single intravascular dose of naloxone (40μg) 30 minutes prior to initiation of continuous epidural hydromorphone with the control group (n = 37) not receiving any naloxone prior to continuous epidural analgesia.

The post-operative incidence of pruritis, PONV, and visual analogue scale pain scores were analyzed in the 48 hours postoperative time period and compared between the two study groups.

**Results**: Unexpectedly, in the 24 hour post-operative period the naloxone treatment group had significantly higher incidences of pruritus ($p < 0.05$), nausea ($p < 0.005$), and vomiting ($p < 0.05$) compared to the control group. These significant differences did not persist by at the 48 hour post-operative mark. There were no significant differences in postoperative VAS pain scores between the two groups in the 24 h or 48 h post-operative period operation.

**Conclusion:** Prophylactic administration of 40μg naloxone prior to the initiation of epidural hydromorphone to abdominal and thoracic surgery patients significantly increased the post-operative incidence of pruritus and PONV. To avoid similar outcomes, we recommended using continuous post-operative infusion of naloxone or long-acting opioid antagonists for prevention of post-operative opioid induced pruritus and PONV.

**Keywords:** naloxone, pruritus, postoperative nausea and vomiting, hydromorphone.

1 MD.
2 PhD.
**Institution:** Department of Anesthesiology, Harper University Hospital, Detroit Medical Center.
**Corresponding Author:** Samir F Fuleihan, Medical Director, University Pain Clinic, Clinical Professor, Wayne State University, 4160 John R Street, Suite 522 Detroit, MI 48201. Cell: 248-931-8090, Fax: 313-833-8477. E-Mail: sfuleiha@dmc.org

## Introduction

Up to 80% of patients experience acute pain after surgical procedures with 75% of these patients reporting the severity of postoperative pain as moderate or severe[1-2]. Opioid analgesics have been the cornerstone of the treatment of moderate-to-severe pain. Hydromorphone (Dilaudid), a synthetic opioid is extensively used in the management of postoperative pain and commonly used via epidural for postoperative analgesia after various major abdominal or thoracic surgeries[3].

As with most opioids, hydromorphone is associated with a high incidence of side effects including pruritis, nausea, vomiting, and constipation. Approximately 40% of patients can experience nausea and 15-25% of patients may experience vomiting after opioid administration[4]. Opioid-induced pruritus (OIP) affects 10-50% of patients receiving intravenous (i.v.) opioids and 20-100% of patients who receive epidural or intrathecal opioid therapy[5-7]. There are several options available to treat opioid-induced side effect such as pentazocine (κ-opioid receptor agonist and partial μ-opioid receptors agonist), ondansetron (5-HT receptor antagonist), diphenhydramine or hydroxyzine (first-generation histamine 1 receptor antagonists), Mirtazapine (a newer antidepressant that selectively blocks 5-HT2 and 5-HT3 receptors) and naloxone[8-12].

Naloxone is a mixed opioid agonist-antagonist[13-14], deriving its analgesic and sedative effects through kappa-opioid receptors with attenuation of mu-opioid-receptor-related side effects[15]. Low dose continuous naloxone infusion can reduce of opioid-induced side effects, such as vomiting, nausea, pruritus, and respiratory depression[16-19].

Despite many reported studies using naloxone for the prevention of opioid related side effects, the overall effectiveness, most efficacious route of administration and the required amount of naloxone necessary to prevent opioid-induced pruritis and post-operative nausea and vomiting (PONV) are unclear.

The primary aim of this study is to determine whether a single intravascular dose of naloxone (40μg) given within 30 minutes prior to initiating continuous epidural analgesia using hydromorphone is effective in the prevention of pruritus, PONV, and constipation in patients compared with epidural hydromorphone alone (control) in the first 24 to 48 postoperative hours after abdominal or thoracic surgery without affecting the efficacy of pain control.

## Methods

This study was approved by Wayne State University Internal Review Board. This was a double-blinded, prospective randomized study comparing the incidence of opioid (hydromorphone) related pruritis, nausea, vomiting and constipation and the efficacy of pain control in the first 48 hours of postoperative compared between patients who received a single dose of naloxone and patients who did not receive any naloxone.

## Patients

Patients who were undergoing abdominal or thoracic surgery (unilateral or bilateral) at Harper University Hospital that presented for surgery and scheduled for general anesthesia with continuous epidural analgesia for postoperative pain control and who provided written informed consents were considered for the study.

### *Inclusion criteria included:*

1. Patients with the ability to provide written informed consent,
2. Adult male or non-pregnant female patients aged 18-65 years,
3. ASA physical status I, II, or III,
4. Patients undergoing major abdominal or thoracic surgical procedures at Harper University Hospital operating rooms.

Exclusion criteria were as followed:

1. ASA physical status IV,
2. Patients with absolute or relative contraindications for epidural anesthesia such as patients on anticoagulant treatment (blood thinners) including coumadin or plavix, with coagulopathy (a tendency to bleed), neuromuscular disease, sepsis,

severe hypovolemia (low blood volume), increased intracranial (brain) pressure, severe aortic stenosis (narrow heart valve), severe mitral stenosis (narrow heart valve), or infection at the site of injection

3. Immobile patients,
4. Patients who could not provide written informed consent,
5. Patients with known history of allergic reactions to hydromorphone or naloxone.

Patients were randomly allocated into two groups using a computer-generated randomized number table. The intervention group received a single intravascular dose of naloxone 40µg within 30 minutes prior to initiation of continuous epidural analgesia. The control group received a placebo within the 30 minutes prior to initiation of continuous epidural analgesia.

*Table 1*
*Demographic and Clinical Characteristics of the Intervention Group and Control Group*

| Variables | Control group n = 37 | Naloxone group n = 40 | p-value |
|---|---|---|---|
| **Age (mean ± SD)** | 54 ± 12.2 | 48 ± (12.9) | 0.030 |
| **Sex** | | | |
| **Male (%)** | 40.5 | 27.5 | |
| **Female (%)** | 59.4 | 72.5 | 0.24 |
| **ASA I, n (%)** | 0 (0) | 3 (7.5%) | 0.24 |
| **ASA II, n (%)** | 11 (30%) | 19 (47.5%) | 0.16 |
| **ASA III, n (%)** | 26 (70%) | 26 (58%) | 0.63 |

SD: Standard deviation. ASA: American Society of Anesthesiologists.

## Procedure

An epidural catheter was inserted using a Tuohy needle in an aseptic manner thirty to sixty minutes before the induction of general anesthesia. A test dose using 3 cc of 1.5% Lidocaine with epinephrine (1:200,000) was injected in the epidural catheter to rule out intravascular or intrathecal placement, as per standard procedure. The correct placement of the catheter in the epidural space was assessed by injecting 4cc of a local anesthetic (0.5% bupivacaine) through the epidural catheter and checking for dermatomal analgesia (loss of painful sensation) at the projected surgical site.

In the control group, a syringe containing 5 cc of normal saline was given by pharmacy to the investigator performing the procedure. In the intervention group, a syringe containing 5cc of normal saline mixed with 40 µg of naloxone was given instead. The syringe was labeled with the patient's name, medical record number, and the assigned 3digit number that was recorded by the investigators on separate data sheets that subsequently was used to record the occurrence of symptoms, and other participant data.

The continuous epidural solution consisted of a combination of a local anesthetic (Bupivicaine 0.075%) and an opioid hydromorphone (30µg/cc) and was delivered at a rate of 4 to 12 cc/hour. The 5cc control treatment dose obtained from the pharmacy was injected intravascularly to the patient within 30 minutes prior to initiation of the continuous epidural solution.

All patients underwent general anesthesia that did not differ from their regularly conducted standard general anesthesia technique. In both groups propofol and volatile anesthetics were administered for induction and maintenance of anesthesia in patients undergoing abdominal and thoracic surgery.

## Patient Data

Patients were assessed at 24 and 48 hours post operatively for the occurrence of pruritis, nausea, and constipation, and for the adequacy of pain control. Pruritis and nausea were assessed by talking to the patient and by checking for any requests for anti-pruritis or anti-emetic medicine. This patient assessment was per standard of care and was recorded in the progress notes/patient's medical chart. Constipation was assessed by ausculting the abdomen for bowel sounds and asking the patient about passing flatus or having a bowel movement (also per standard of care). Pain control was assessed by reviewing the patient chart records for the 10point Visual Analogue Scale (VAS) score recorded every 6 hours in the first 48 hours postoperatively. The exact rate at which the epidural

solution was running (4 to12 cc/hour) as well as the number of requests for break through pain medicine were also recorded.

## Statistical Analysis

A power analysis showed that 70 patients per group would provide 80% power to detect a decrease in the incidence of pruritus from 35% in the placebo group to 15% in the Naloxone group. Comparisons of continuous data will use ANOVA tests (unpaired t-test two tailed). Comparisons between study groups on categorical data were examined using a non-parametric Fisher's Exact Chi-square test, when applied to 2 × 2 tables. Statistical significance was set at a p-value ≤0.05. Assumptions of normality and/or homogeny of variance were checked and verified. All continuous data were expressed as the mean, mean ± standard deviation.

## Results

Initially the study aim was to recruit 200 patients. However, upon interim analysis of patient data after 100 patients were recruited it was observed that the Naloxone treatment group had significantly higher pruritis and PONV rates. Following consultation between the study authors, concerns of patient discomfort led to recruitment being discontinued.

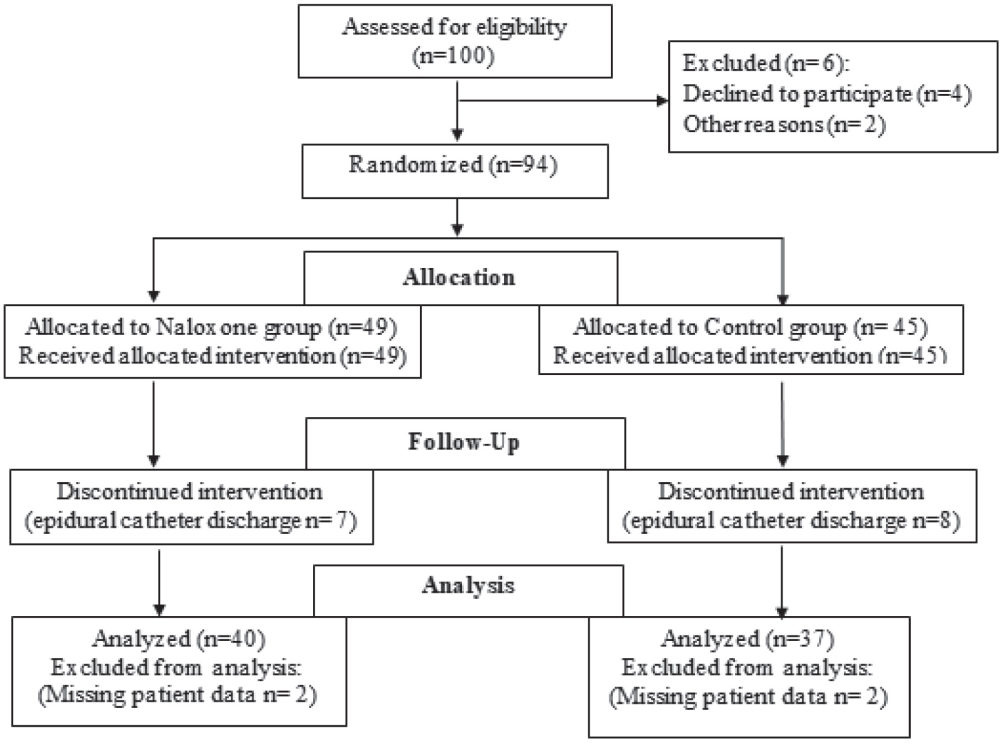
In our study, 100 patients were consented, with a total of 77 patients completing the study. The final analysis compared 37 patients in the control group, and 40 patients in the naloxone intervention group (Figure 1).

## Demographics

In the control group, 22 (59.4%) patients were female and 15 (40.5%) patients were male; in the Naloxone treatment group, 29 (72.5%) patients were female and 11 (27.5%) patients were male (p = 0.24). There was a statistically significant difference in age between the two groups (p = 0.030). However, this difference was not unexpected given the surgery performed**.**

There were no statistically significantly differences in postoperative VAS between the naloxone or control groups at 24 h and 48 h. The

*Fig. 1*
*CONSORT Flow Diagram*



incidence of nausea was significantly lower in the control group (13.5%) than the intervention group after 24 h of operation (45%; p <0.05) and there were no significant differences in nausea after 48 hours of operation between 2 groups (Table 2). The incidence of vomiting was significantly lower in the control group than the naloxone intervention group after 24 h of operation (p <0.05). The incidence of vomiting did not differ significantly between the two groups after 48 h of operation. The incidence of pruritus differed significantly between the two groups after 24 h of operation (p <0.05) however, there was no difference in pruritus between the two groups 48 h after operation. There were no significant differences in ausculting bowel sounds between the two groups after 24 h and 48 h operation.

## Discussion

The major outcome of this study was that a single 40μg intravenous dose of naloxone administered within 30 minutes prior to initiation of continuous epidural analgesia with hydromorphone significantly increased the incidence of pruritus, nausea and vomiting in the first 24 to 48 postoperative hours after abdominal or thoracic surgery while not affecting post-operative pain control when compared to a control group of patients who did not receive any naloxone. This was an unexpected finding and opposite to our initial hypothesis that a single bolus of naloxone would decrease pruritus and PONV.

As reported earlier, interim data review before patient recruitment had ended revealed that naloxone treatment resulted in significantly higher rates of pruritus and PONV compared to the control arm of the study. Upon discussion between the study authors, concerns of patient discomfort led to recruitment being discontinued and the trial stopped for the overall consideration of patient benefit. Prospective studies with unexpected results observed during interim analysis should be stopped if participants are being put at risk of adverse effects[20].

Currently there is a publication bias in anesthesiology studies that excludes a high proportion of studies which do not publish their proceedings due to null or unexpected results[21]. As authors of this study, we wanted to publish our results so as to prevent similar studies being conducted using ineffective interventions that could put patients under unnecessary discomfit.

The failure or success of an opioid antagonist preventing opioid-induced side effects whilst maintaining analgesia may be related to how the opioid antagonist is administered. In our study, we administered a single bolus of naloxone for the treatment patients. Other studies have had mixed outcomes using single bolus doses of opioid antagonists. Administration of the opioid antagonist nalmefene observed that a single

*Table 2*
*Post-operative outcomes of Control and Naloxone treatments*

| Variables | Post-operative timepoint | Control group n = 37 | Naloxone group n = 40 | p-value |
|---|---|---|---|---|
| **VAS (mean±SD)** | 24 h | 3.27 ± 2.54 | 3.57 ± 2.35 | 0.58 |
| | 48 h | 2.60 ± 2.12 | 2.64 ± 1.78 | 0.96 |
| **Pruritus (%)** | 24 h | 35 | 57.5 | 0.048 |
| | 48 h | 16.6 | 35.7 | 0.182 |
| **Nausea (%)** | 24 h | 13.5 | 45 | 0.002 |
| | 48 h | 12.5 | 7.1 | 0.603 |
| **Vomiting (%)** | 24 h | 2.5 | 17.5 | 0.033 |
| | 48 h | 4.1 | 7.1 | 0.691 |
| **Bowel sound (%)** | 24 h | 35.2 | 34.2 | 0.923 |
| | 48 h | 36.3 | 14.2 | 0.149 |

VAS-Visual Analog Pain Score, SD-Standard Deviation

intravenous bolus of 15-25 µg, decreased both pruritus and PONV in patients who received intravenous PCA morphine[22]. A single bolus of subcutaneous methylnaltrexone bromide (12mg) did not reduce the overall severity or incidence of intrathecal morphine-induced pruritus[23]. The incidence of pruritus and PONV after a subcutaneous dose of 400ug naloxone following intrathecal morphine administration in elective Cesarean delivery showed no significantly differences of pruritus and nausea and vomiting compared to controls[24].

The lack of benefit observed in our study may be due to the pharmokinetics of naloxone. Naloxone IV has a half-life of approximately 55 min. If administered as a single bolus intravenously its effects may not persist for prolonged periods[5,25]. A continuous infusion produces less fluctuation of naloxone concentrations than bolus injections and compensates for naloxone's relatively short half-life. Repeated doses or continual infusion of naloxone have resulted in a reduction of pruritus, PONV after administration of epidural hydromorphone[16-17, 19]. The subcutaneous route of naloxone has a duration of action between 2-48 hours[24]. Intravenous administration of a single bolus of nalmefene 15 or 25 µg has an elimination half-life of 8.5 hrs[26] and showed a decrease in opioid side effects in patients using PCA morphine[22]. A continuous naloxone i.v, infusion (0.25 µg/kg/h) significantly reduces morphine-induced pruritus, nausea and vomiting via PCA[17]. Continuous infusions of naloxone (0.20-0.27 µg/kg/h) via PCA[16] or epidural[19] significantly decreases the incidence of pruritus and vomiting.

Another factor that may have influenced our study is dose by weight of naloxone administered to the patients. The naloxone dose administered in our study was at a fixed dose (40µg) rather than a weight adjusted dose and in retrospect, dosing on a µg/kg basis, instead of an empirical 40µg, may have been more appropriate. Naloxone infusion rates >0.25 µg/kg/h, achieved reductions in pruritus and PONV, which increased higher infusion rates[27]. An optimal dose of naloxone infusion rate of ≥1µg/kg/h was identified to be most effective in reducing opioid induced pruritus[27].

The most commonly identified risk factors for PONV include female gender, non-smoking status, history of PONV or motion sickness, postoperative opioid use, and age[28]. A potential confounding factor in this study that may have resulted in increased PONV in naloxone treated group is the age of patients which was statistically higher than the control patient group. PONV incidence is known to be higher for adults under the age of 50 years and in our study, patients are younger in the intervention group in comparison to control group[2,29-31]. Even a small age gap can have a significant effect as patients aged <53 yrs experienced a higher rate of PONV than older patients >56 yrs[30].

In our study, pain wasn't affected by naloxone administration. Previous studies observed similar results with analgesia unaffected by naloxone administered via epidural and intravenously[16,19,32-33]. Higher doses of naloxone can affect analgesia with doses above 2µg/kg/h more likely to lead to reversal of analgesia[12].

In summary, an intraoperative single intravenous 40µg bolus of naloxone administered prior to initiating epidural hydromorphone significantly increased pruritus, nausea and vomiting. To avoid similar outcomes, we recommended using a continuous infusion of naloxone or long-acting opioid antagonists for prevention of opioid induced pruritus and PONV.

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