Research Report

One shot to control Pain: Decreasing postoperative opioid use in gynecologic oncology patients with intrathecal opioid injection

Yevgeniya Ioffe, Ruofan Yao, Eileen Hou, Michelle Wheeler, Mohamed Nour, Wei Yun Wang, Linda Hong

Abstract

Objectives: To determine whether regional anesthesia with single-shot intrathecal opioid injections (ITO) reduce postoperative pain and intravenous (IV) opioid use after exploratory laparotomy in major gynecologic surgeries.

Methods: A retrospective chart review of 315 consecutive cases of patients who underwent an exploratory laparotomy on the gynecologic oncology service from July 2015 to January 2018 was conducted. Single-shot ITO was offered to all patients undergoing open abdominal surgery. The primary outcomes of interest were IV opioid use in morphine equivalents during the first 48 hours after surgery. Univariate analyses were performed to estimate the effect of ITO on IV opioid use at 0, 6, 12, 24 and 48 hours after surgery. Longitudinal regression analyses were performed to estimate the effect of ITO on changes in outcomes of interest over time, adjusting for potential confounders.

Results: 35% (110/315) received ITO preoperatively. There were no differences in patient age, BMI, previous number of abdominal surgeries, history of opioid dependence, type of gynecologic surgery, or total EBL between the ITO and control groups. Preoperative ITO was associated with a significantly lower IV opioid requirement between 0 and 6 hours after surgery (9.7 ± 8.1 vs 14.3 ± 11.5, p < 0.0001) and between 6 and 12 hours after surgery (2.7 ± 3.8 vs 5.4 ± 9.5, p = 0.0054). There was no statistically significant difference in total hospital stay opioid requirement but median length of stay was increased by 1 day.

Conclusions: Preoperative administration of ITO reduced IV opioid requirement in the first 12 hours postoperatively but was associated with median 1 day increase in hospital stay.

Introduction

Opioids were involved in approximately 70% of drug overdose deaths in the US in 2018 – a total of 46,802 deaths (Wilson et al., 2020). The CDC estimates that 35% of current opioid overdose deaths are related to prescription opioid abuse (Prescription, 2020). Patients who receive postsurgical opioid prescription are 44% more likely to become chronic opioid users (Alam et al., 2012), with 3–10% of those having been previously opioid naïve (Hill et al., 2019).

In a more acute clinical realm, there are deleterious side effects associated with significant opioid use, such as postoperative nausea and vomiting, postoperative ileus, sedation, postoperative hyperalgesia, and immunosuppression (Fletcher and Martinez, 2014). Pain after abdominal procedures in gynecologic surgery can be severe (Massicotte et al., 2009) with pain itself having many deleterious effects on recovery and be a risk factor for chronic pain (Macrae, 2008).

There has been an increasing focus on implementation of multimodal medication strategy to spare the use of intravenous opioids as part of enhanced recovery after surgery (ERAS®) pathway (Feldheiser et al., 2016; Nelson, 2016; Nelson et al., 2019). Epidural anesthesia has been studied for over 20 years and is effective in achieving pain control, but the appropriateness of its use is still debated (Nelson, 2016; Kjolhede, 2019).

Preoperative administration of intrathecal opioids via spinal block,
either as the sole operative anesthetic or combined with general anesthesia, has been shown to reduce postoperative opioid consumption in abdominal hysterectomies (Moller et al., 2001) and pelvic organ prolapse surgeries (Bauchat and Habib, 2015; Ottesen et al., 2002). The use of intrathecal opioids along with spinal anesthesia (SA) was studied in patients undergoing hysterectomies for benign reasons by the GASPI study group led by Wodlin and colleagues. The patients in this cohort who received SA with intrathecal opiates had decreased overall post-operative inpatient opioid use. Furthermore, the pain intensity, as rated by patients, was higher in the general anesthesia (GA) group when compared to SA group during the first 2 days postoperatively (Wodlin et al., 2011). The pain intensity and opioid use equalized after post-operative day 1. A recent randomized trial by Kjolhede et al. (Kjolhede, 2019) indicated that ITO + GA was just as effective as epidural anesthesia + GA in achieving pain control but the ITO + GA combination had shorter length of stay.

A number of pelvic surgery guidelines have recommended use of regional anesthesia during the surgery and post-operatively (Feldheiser et al., 2016; Nygren, 2012). Reducing peri-operative complications and hospital length of stay can lower the cost of hospitalizations significantly (Gerardi et al., 2008; Kalogera, 2013). Improved pain control and decrease in opioid requirements may benefit in decreasing postoperative ileus and thus lead to shorter, safer hospitalizations. A recent study by Kay et al. showed that implementation of ERAS® pathways with multi-modal pain management protocol decreases the number of opioid prescriptions filled postoperatively (Kay et al., 2020). However, the protocol implemented by Kay and colleagues did not utilize patient controlled anesthesia or spinal anesthesia, leaving a potential void for pain control in patients with extensive intestinal/upper abdominal debulking, as they may not be able to tolerate per os (PO) analgesics.

There is a paucity of literature addressing the addition of single-shot intrathecal opioid injections (ITO) to general anesthesia to reduce postoperative pain and improve patient outcomes in the gynecologic oncology population. The aim of the current study was to determine whether regional anesthesia with ITO reduced postoperative pain and intravenous (IV) opioid use after exploratory laparotomy surgeries performed by the members of the gynecologic oncology division; secondary aim was to evaluate the effect of ITO on LOS.

2. Methods

This was a retrospective cohort analysis of patients who underwent open abdominal surgery on the gynecologic oncology service at a tertiary care teaching hospital in San Bernardino, California. Data were abstracted from surgical patients from July 2015 to January 2018. Patients were excluded from the study if multiple surgeries were required within the same admission or if the patient remained intubated post-operatively. This study was approved by the institutional review board (IRB# 5180366).

Basic demographic information and past medical history were abstracted from review of medical records. During the time period of interest, all patients who were undergoing an exploratory laparotomy were offered a preoperative intrathecal analgesia by the gynecologic oncologist. If the patient was agreeable and did not have any contraindications, an anesthesiologist on the Acute Pain Management service performed by the members of the gynecologic oncology division; secondary aim was to evaluate the effect of ITO on LOS.

3. Results

A total of 342 records were identified and reviewed. Of these, 27 patients were excluded as they were identified as having undergone a laparoscopic procedure, had an unplanned return to the operating room, or were duplicate records. After completion of record review, 315 patients were included in this study. 110 of 315 patients (35%) received intrathecal opioid injections preoperatively. There were no differences in patient age, BMI, previous number of abdominal surgeries, history of opioid dependence, cancer staging and debulking cases between the ITO and control groups (Table 1). Perioperative outcomes including postoperative VTE, wound complications, and infections were not statistically different between the ITO and control groups (Table 2).

Preoperative ITO administration was associated with significantly lower IV opioid requirement between 0 and 6 hours after surgery (9.7 ± 8.1 vs 14.3 ± 11.5, p < 0.0001) and between 6 and 12 hours after surgery (2.7 ± 3.8 vs 5.4 ± 9.5, p = 0.0054). IV opioid use 12–48 hours postoperatively did not differ significantly between the two groups (Fig. 1). While the morphine equivalent use was lower in the ITO group 0–12 hours after surgery, the pain scores did not differ between the two groups (Fig. 2). The pain scores did not differ between the ITO and non-ITO groups over the entire period of 48 hours, i.e., the length of pain score abstraction for this study (Table 3). There was no difference in total morphine equivalent administration between the ITO and non-ITO groups (p = 0.29). The ITO group was associated with a 17% increase (6 vs. 5 days, p = 0.02) in the length of hospital stay.

Of the 110 patients who received ITO, all of patients received subcutaneous administration of preoperative heparin prophylaxis. The Table 1

| Demographics and surgical details of patients undergoing an exploratory laparotomy with or without intrathecal opioid administration. |
|-------------------------------|----------------|----------------|----------------|
|                              | Total (n = 315) | No ITO (n = 205) | With ITO (n = 110) |
| Age (years)                  | 57 [45,67]     | 59 [46,67]     | 54.5 [45,65]    |
| BMI (kg/m²)                  | 29.3 [24.5, 36.6] | 29.2 [24.6, 37.1] | 29.2 [23.6, 35.3] |
| Number of prior surgeries¹   | 1 [0,2]        | 1 [0,2]        | 1 [0,2]         |
| Opioid dependence            | 96 [30.6]      | 63 [30.7]      | 33 [30.3]       |
| Cancer staging case          | 81 [25.7]      | 47 [22.9]      | 34 [30.9]       |
| Cancer debulking case        | 141 [44.8]     | 86 [42]        | 55 [50]         |
| Bowel resection              | 49 [15.6]      | 30 [14.5]      | 19 [17.8]       |

ITP, intrathecal opioids
Data are n(%) or median[IQR] unless otherwise specified
¹ Previous intra-abdominal or pelvic surgery
Table 2
Perioperative outcomes of patients undergoing an exploratory laparotomy with or without intrathecal opioid administration.

|               | Total (n = 315) | No ITO (n = 205) | With ITO (n = 110) | p-value |
|---------------|----------------|------------------|--------------------|---------|
| EBL (in mL)   | 200 [100, 400] | 200 [100, 400]   | 212.5 [150, 500]   | 0.18    |
| Wound infection/disruption | 32 (10.2) | 21 (10.1) | 11 (10.3) | 1 |
| PE            | 3 (1.0)        | 1 (0.5)          | 2 (1.9)            | 0.27    |
| DVT           | 7 (2.2)        | 3 (1.5)          | 4 (3.7)            | 0.24    |
| Ileus/SBO     | 24 (7.6)       | 15 (7.3)         | 9 (8.4)            | 0.82    |
| Abscess/other infections* | 16.5 (3.1) | 11 (5.3) | 5 (4.7) | 1 |
| LOS (days)    | 5 [4, 7]       | 5 [4, 7]         | 6 [4, 8]           | 0.02    |
| Total ME during | 111.3 | 108.5 | 119.5 | 0.29 |
| LOS (mg)      | 66.2,197.7     | 66.175.8         | 64.7,241.8         |         |

ITO, intrathecal opioids; EBL, estimated blood loss; PE, pulmonary embolism; DVT, deep venous thrombosis; SBO, small bowel obstruction; LOS, length of stay; ME, morphine equivalent Data are n(%) or median [IQR] unless otherwise specified.

* Infections including sepsis, C. difficile colitis, and acute cystitis.

Fig. 1. Postoperative IV opioid requirements in IV morphine equivalents over time (hours).

Fig. 2. Postoperative pain scores over time (hours).

Timing of heparin administration after the placement of ITO was available for review for 91 patients. The timing varied with a range of 1 min to 2 hours and 43 min post administration of ITO. 78 patients (86%) received heparin within one hour from ITO placement. No complications were observed from the placement of ITO with 0% rate of spinal hematoma or injection area cellulitis/deep tissue infections.

4. Discussion

Our retrospective cohort study aimed to look at the effect of ITO on postoperative pain control and IV opioid use, specifically after major gynecologic oncology surgeries. Our results demonstrated decreased IV opioid requirements in the first 12 hours postoperatively. While the IV opioid use was decreased in the ITO group, the pain scores were not higher than that of control group. However, beyond 12 hours postoperatively, the addition of a preoperative ITO did not significantly decrease IV opioid use. Pain scores remained similar for the two groups throughout the entire 48 hour study period. There were no spinal hematomas or infections in the group receiving ITO.

A 2019 update to perioperative care guidelines for gynecologic oncology patients specifically highlights that regional anesthesia including SA is a major component of multi-modal pain control and a mode to reduce opioid requirement and peri-operative stress (Nelson et al., 2019). Our study further delineates the mechanism and specifics of opioid requirement reduction in the acute postoperative setting. Patients in this study were given intrathecal morphine and fentanyl. The CSF concentration of intrathecal morphine starts to decrease after twelve hours. It may be deduced that this is the reason that IV opioid requirements decreased in the first 12 h postoperatively, with IV opioid requirements returning to baseline and match that of the non ITO group as the effects of ITO wear off. This matches the finding of our study that the total opioid use (IV and PO), as measured by total morphine equivalents, was not different between the two groups. Previous study by Wodlin et al. that utilized SA as anesthesia for hysterectomy procedures vs GA, demonstrated that IV opioid requirements equalize between the SA and GA groups by postoperative day 2 (Wodlin et al., 2011). This is in line with the findings of the current study. There could have been a self-selection bias where patients with lower pain threshold were more likely to agree to the preoperative ITO. This may be due to prior surgeries or prior experience with pain. The patients electing to proceed with ITO may be more likely to anticipate pain and lasting discomfort from surgery and elect to stay longer. We do believe this needs further investigation.

The interesting finding of our study was that LOS was increased by 1 day in preoperative ITO + GA group, as compared with GA only group. A randomized study of the GASPI group where patients undergoing hysterectomy were assigned to GA vs. SA and fast track postoperative protocol did not show a difference in length of hospitalization, i.e. 46 vs. 50 hours (Wodlin et al., 2011). This finding suggests that SA intrinsically is not associated with increased LOS for gynecologic patients. While our study was retrospective, and thus confounding factors more likely, the 1 day increase length of stay may not have been confirmed in...
a randomized prospective trial.

The strengths of the study include its sample size, which allowed for statistically meaningful analysis. As the surgeries performed in this study were carried out by the same cohort of 5 physicians within the department at the institution, there was consistency of physician practices as well as protocols, leading to decreased variation in practice and patient management. Another strength of the study is that the ITO vs. non-ITO cohorts were comparable with regards to extent and type of surgical intervention performed: procedure performed for cancer vs. benign pathology, cancer staging performed or bowel resections performed. Finally, the ease of performing preoperative ITO makes it a straightforward intervention to enact, without any observed complications, such as spinal hematoma or increased risk of VTE.

This study had several limitations as a retrospective cohort study. Patients were counseled extensively regarding the benefits of preoperative ITO, but the intervention was ultimately decided based on patient preference, increasing the risk for self-selection bias. However, despite this risk of self-selection bias, there was no significant difference in results based on history of prior opioid use. In addition, the current chart review did not stratify results by the primary cancer, nor the extent of the surgery performed. Overall, studying pain is challenging, as it is difficult to tangibly quantify pain in the postoperative period. Pain is subjective to the individual, which can lead to discrepancy in the results. However objective methods were used to quantify the patient’s pain level including the Wong-Baker scale, as well as the amounts of opioids used.

Despite limitations of the study, the results indicate the potential of preoperative ITO to decrease opioid use during the immediate postoperative period. This has several clinical implications moving forward. The results of this study can aid in the counseling of patients that are interested in preoperative ITO to supplement pain control. The results can also impact how physician opioid orders are written in the immediate postoperative period and may aid in dropping the patient-controlled anesthesia from use. Future studies on the effects of ITO on postoperative pain could examine whether use of preoperative ITO decreases opioid use in postoperative patients in the outpatient setting as well to determine the long-term impact of preoperative ITO use on opioid use overall. Future studies could also look into randomizing patients with a specific type of gynecologic malignancy, such as ovarian cancer, to receive ITO or not.

While overall pain scores were similar between the GA vs. GA + preoperative ITO group, IV opioid requirements were decreased in the first 12 hours postoperatively in the GA + preoperative ITO group. We did however find a 1 day increase in LOS in the GA + ITO group.

In conclusion, ITO did not account for clinically meaningful change in clinical practice of pain management. However, we do wish to highlight that decrease in opioid total use at 6 and 12 hour mark is statistically significant. Most opioids are used in the first one to two days postop and this small, yet significant decrease in use may have lasting benefits translating into decrease in iules and decrease in potential opioid long term use and addiction potential and needs to be further investigated.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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