Gynecologic Oncology Reports 38 (2021) 100858

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Research Report

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

Yevgeniya Ioffe [a], Ruofan Yao [a], Eileen Hou [b], Michelle Wheeler [a], Mohamed Nour [c], Wei Yun Wang [d], Linda Hong [a,*]

[a] Loma Linda University Medical Center, 11234 Anderson Street, Loma Linda, CA, 92354
[b] Advocate Outpatient Center, 9555 S. 52nd Ave, 2nd floor, Oak Lawn, IL, 60453
[c] Kaiser Permanente West Los Angeles Medical Center, 6041 Cadillac Avenue, Los Angeles, CA 90034
[d] University of Washington, 1959 NE Pacific Street, BB-1469, Seattle, WA, 98195

ARTICLE INFO

Keywords:
Intrathecal opioid
Postoperative pain
Gynecologic oncology
Exploratory laparotomy

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.

1. 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., 2018).

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,

* Corresponding author at: 11234 Anderson St, Loma Linda, CA, 92354.
E-mail addresses: YIoffe@llu.edu (Y. Ioffe), RYao@llu.edu (R. Yao), eileen.hou@gmail.com (E. Hou), Mewheeler2@gmail.com (M. Wheeler), MOHAMED.B.NOUR@kp.org (M. Nour), dorothy.wy.wang@gmail.com (W.Y. Wang), lihong@llu.edu (L. Hong).

https://doi.org/10.1016/j.gore.2021.100858
Received 29 June 2021; Received in revised form 29 August 2021; Accepted 1 September 2021
Available online 6 September 2021

either as the sole operative anesthetic or combined with general anesthesia, has been shown to reduce postoperative opioid consumption in abdominal hysterectomies (Møller 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 postoperative 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 postoperative 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 *peri*-operative complications such as 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 postoperatively. 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 was consulted and administered the intrathecal opioid injection utilizing a combination of morphine and fentanyl. Patients received 200–350 mcg of intrathecal in addition to 20 mg of fentanyl. 3 out of 110 patients did not receive fentanyl due to allergies. Nursing assessment of postoperative pain scores, based on the Wong-Baker Pain Scale, was performed per the medical/surgical unit protocol. The recorded pain score at around 0, 12, 24 and 48 hours after surgery were abstracted for analysis. Postoperative opioid requirement for pain control was calculated based on the total dose of intravenous (IV) opioid administration as well as the type of opioid medication given. Given the different options of opioid medication available, we simplified the analysis by converting each type of opioid medication to its morphine equivalent in strength, based on the American Pain Society Guidelines using an equianalgesic dosage conversion calculator. The total opioid equivalent administered between 0 and 6, 6–12, 12–24 and 24–48 hours were then calculated for analysis.

The primary intervention of interest was preoperative intrathecal analgesia. Basic demographic information was compared between the intervention group and control group, using the appropriate univariate statistical methods. The primary outcomes of interest were postoperative pain and postoperative IV opioid requirement. Univariate analysis was performed to compare the median pain score and opioid requirement for each time point assessed, using Kruskal-Wallis test; p-value < 0.05 was considered statistically significant. Longitudinal regression analysis was then performed to assess the differences in pain and IV opioid requirement over the entire 48 hour postoperative period between the intervention and control group. All statistical analysis was performed using Stata 12 (College Station, TX).

3. Results

A total of 342 records were identified and reviewed. Of these, 27 patients were excluded as they were identified as having underwent 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)	p-value
Age (years)	57 [45,67]	59 [46,67]	54.5 [45,65]	0.11
BMI (kg/m^2)	29.3 [24.5, 36.6]	29.2 [24.6, 37.1]	29.2 [23.6, 35.3]	0.42
Number of prior surgeries[a]	1 [0,2]	1 [0,2]	1 [0,2]	0.83
Opioid dependence	96 (30.6)	63 (30.7)	33 (30.3)	0.93
Cancer staging case	81 (25.7)	47 (22.9)	34 (30.9)	0.12
Cancer debulking case	141 (44.8)	86 (42)	55 (50)	0.39
Bowel resection	49 (15.6)	30 (14.5)	19 (17.8)	0.51

ITO, intrathecal opioids
Data are n(%) or median[IQR] unless otherwise specified
[a] 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[a]	16.(5.1)	11 (5.3)	5 (4.7)	1
LOS (days)	5 [4,7]	5 [4,7]	6 [4,8]	0.02
Total ME during LOS (mg)	111.3 [66.2,197.7]	108.5 [68,175.8]	119.5 [64.7,241.8]	0.29

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

[a] Infections including sepsis, C. difficile colitis, and acute cystitis

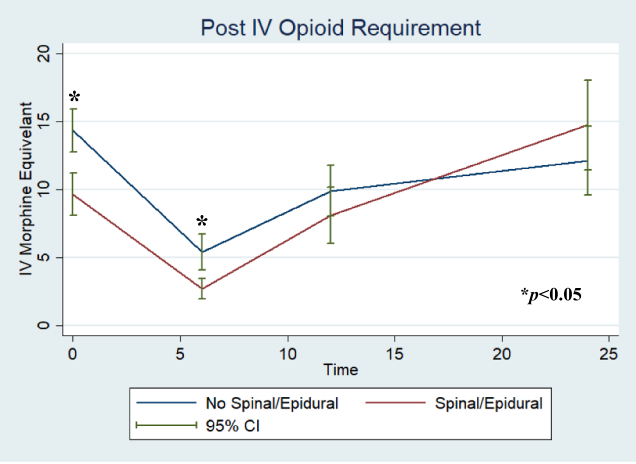

Fig. 1. Postoperative IV opioid requirements in IV morphine equivalents over time (hours).

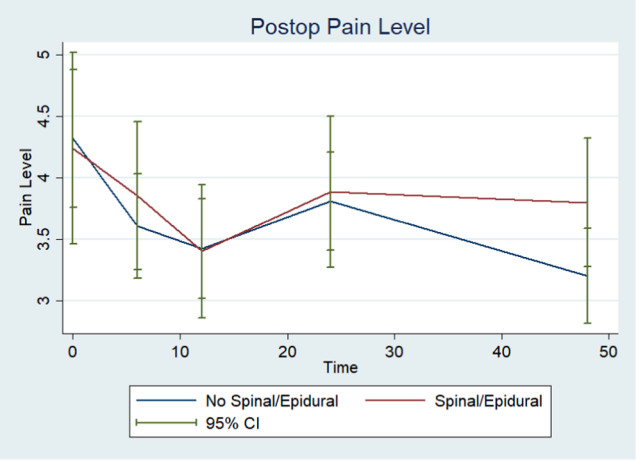

Fig. 2. Postoperative pain scores over time (hours).

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 hematomas or injection area cellulitis/deep tissue infections.

Table 3
Pain score and IV opioid use in the first 48 h following surgery.

	Pain Score*			IV Morphine Equivalent (mg)		
Time (hours)	No ITO	With ITO	*p*-value	No ITO	With ITO	*p*-value
0–6	5 [0,8]	4 [0,8]	0.93	14.3 ± 11.5	9.7 ± 8.1	<0.0001
6–12	3 [0,6]	4 [1,6]	0.51	5.4 ± 9.5	2.7 ± 3.8	0.0054
12–24	3 [0,6]	4 [0,5]	0.97	9.9 ± 13.3	8.1 ± 10.8	0.23
24–48	4 [1,6]	4 [0,6]	0.93	12.1 ± 18.1	14.7 ± 17.3	0.22

ITO, intrathecal opioids
Data are median[IQR] or mean ± SD unless otherwise specified
* Pain score reported based on the Wong-Baker Scale with a range of 0–10

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, this 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 ileus 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.

References

Wilson, N., Kariisa, M., Seth, P., Smith, H., Davis, N.L., 2020. Drug and Opioid-Involved Overdose Deaths - United States, 2017–2018. MMWR Morb Mortal Wkly Rep 69 (11), 290–297.

CDC. Prescription Opioid Data. 2020; Available from: https://www.cdc.gov/drugoverdose/data/prescribing.html.

Alam, A., Gomes, T., Bell, C.M., 2012. Long-term Analgesic Use: Sometimes Less Is Not More-Reply. Arch Intern Med 172 (15), 1189–1190.

Hill, M.V., et al., An Educational Intervention Decreases Opioid Prescribing After General Surgical Operations. Ann Surg, 2018. 267(3): p. 468-472.

Fletcher, D., Martinez, V., 2014. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth 112 (6), 991–1004.

Massicotte, L., et al., 2009. *Comparison of spinal anesthesia with general anesthesia on morphine requirement after abdominal hysterectomy*. Acta Anaesthesiol Scand 53 (5), 641–647.

Macrae, W.A., 2008. Chronic post-surgical pain: 10 years on. Br J Anaesth 101 (1), 77–86.

Feldheiser, A., Aziz, O., Baldini, G., Cox, B.P.B.W., Fearon, K.C.H., Feldman, L.S., Gan, T. J., Kennedy, R.H., Ljungqvist, O., Lobo, D.N., Miller, T., Radtke, F.F., Ruiz Garces, T., Schricker, T., Scott, M.J., Thacker, J.K., Ytrebø, L.M., Carli, F., 2016. Enhanced Recovery After Surgery (ERAS) for gastrointestinal surgery, part 2: consensus statement for anaesthesia practice. Acta Anaesthesiol Scand 60 (3), 289–334.

Nelson, G., et al., 2016. Guidelines for postoperative care in gynecologic/oncology surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations–Part II. Gynecol Oncol 140 (2), 323–332.

Nelson, G., Bakkum-Gamez, J., Kalogera, E., Glaser, G., Altman, A., Meyer, L.A., Taylor, J.S., Iniesta, M., Lasala, J., Mena, G., Scott, M., Gillis, C., Elias, K., Wijk, L., Huang, J., Nygren, J., Ljungqvist, O., Ramirez, P.T., Dowdy, S.C., 2019. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. Int J Gynecol Cancer 29 (4), 651–668.

Kjolhede, P., et al., 2019. Effect of intrathecal morphine and epidural analgesia on postoperative recovery after abdominal surgery for gynecologic malignancy: an open-label randomised trial. BMJ Open 9 (3), e024484.

Møller, C., Kehlet, H., Friland, S.G., Schouenborg, L.O., Lund, C., Ottesen, B., 2001. Fast track hysterectomy. Eur J Obstet Gynecol Reprod Biol 98 (1), 18–22.

Bauchat, J.R., Habib, A.S., 2015. Evidence-based anesthesia for major gynecologic surgery. Anesthesiol Clin 33 (1), 173–207.

Ottesen, M., et al., Fast track vaginal surgery. Acta Obstet Gynecol Scand, 2002. 81(2): p. 138-46.

Wodlin, N.B., et al., Mode of anesthesia and postoperative symptoms following abdominal hysterectomy in a fast-track setting. Acta Obstet Gynecol Scand, 2011. 90 (4): p. 369-79.

Nygren, J., et al., Guidelines for perioperative care in elective rectal/pelvic surgery: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. Clin Nutr, 2012. 31(6): p. 801-16.

Gerardi, M.A., Santillan, A., Meisner, B., Zahurak, M.L., Diaz Montes, T.P., Giuntoli, R.L., Bristow, R.E., 2008. A clinical pathway for patients undergoing primary cytoreductive surgery with rectosigmoid colectomy for advanced ovarian and primary peritoneal cancers. Gynecol Oncol 108 (2), 282–286.

Kalogera, E., et al., 2013. Enhanced recovery in gynecologic surgery. Obstet Gynecol 122 (2 Pt 1), 319–328.

Kay, A.H., Venn, M., Urban, R., Gray, H.J., Goff, B., 2020. Postoperative narcotic use in patients with ovarian cancer on an Enhanced Recovery After Surgery (ERAS) pathway. Gynecol Oncol 156 (3), 624–628.