



Research Report

Incisional infiltration versus transversus abdominis plane block of liposomal bupivacaine after midline vertical laparotomy for suspected gynecologic malignancy: a pilot study

Ashley S. Moon^{a,1,*}, Vaagn Andikyan^{a,2}, Rakhee Agarwal^b, Stephanie Stroever^b, David Misita^c, Anya Laibangyang^a, David Doo^a, Linus T. Chuang^a

^a Division of Gynecologic Oncology, Department of Obstetrics, Gynecology and Reproductive Biology, Danbury/Norwalk Hospitals, Nuvance Health, 24 Hospital Avenue, Danbury, CT 06810, United States

^b Department of Research and Innovation, Danbury/Norwalk Hospitals, Nuvance Health, 24 Hospital Avenue, Danbury, CT 06810, United States

^c Department of Anesthesiology, Danbury/Norwalk Hospitals, Nuvance Health, 24 Hospital Avenue, Danbury, CT 06810, United States

ARTICLE INFO

Keywords:

Liposomal bupivacaine
Opioid
Laparotomy
Incisional infiltration

ABSTRACT

Background: To evaluate whether incisional infiltration of liposomal bupivacaine would decrease opioid requirement and pain scores after midline vertical laparotomy for suspected or known gynecologic malignancy compared with transversus abdominis plane (TAP) block with liposomal bupivacaine.

Methods: A prospective, single blind randomized controlled trial compared incisional infiltration of liposomal bupivacaine plus 0.5% bupivacaine versus TAP block with liposomal bupivacaine plus 0.5% bupivacaine. In the incisional infiltration group, patients received 266 mg free base liposomal bupivacaine with 150 mg bupivacaine hydrochloride. In the TAP block group, 266 mg free base bupivacaine with 150 mg bupivacaine hydrochloride was administered bilaterally. The primary outcome was total opioid use during the first 48-hour postoperative period. Secondary outcomes included pain scores at rest and with exertion at 2, 6, 12, 24 and 48 h after surgery. **Results:** Forty three patients were evaluated. After interim analysis, a three-fold higher sample size than originally calculated was required to detect a statistically significant difference. There was no clinical difference between the two arms in mean opioid requirement (morphine milligram equivalents) for the first 48 h after surgery (59.9 vs. 80.8, $p = 0.13$). There were no differences in pain scores at rest or with exertion between the two groups at pre-specified time intervals.

Conclusion: In this pilot study, incisional infiltration of liposomal bupivacaine and TAP block with liposomal bupivacaine demonstrated clinically similar opioid requirement after gynecologic laparotomy for suspected or known gynecologic cancer. Given the underpowered study, these findings cannot support the superiority of either modality after open gynecologic surgery.

1. Introduction

Exploratory laparotomy by vertical incision is often performed for gynecologic procedures and can result in significant pain and discomfort. Enhanced recovery after surgery (ERAS) protocols that utilize a multimodal, opioid-sparing approach have demonstrated improved clinical outcomes for these surgical patients, including earlier return of oral intake, bowel function, mobility, and shorter hospital stays

(Chapman et al., 2016; Dickson et al., 2017; Lindemann et al., 2017; Mendivil et al., 2018; Miralpeix et al., 2016; Myriokefalitaki et al., 2016; Bisch et al., 2021).

According to the American College of Obstetricians and Gynecologists, transversus abdominis plane (TAP) blocks or wound infiltration may be considered for analgesia as a component of an ERAS program (ACOG Committee Opinion No, 2018). TAP blocks provide local anesthetics in the plane superficial to the transversus abdominal muscle

* Corresponding author at: Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Stanford University School of Medicine, 900 Welch Road, Palo Alto, CA 94304, United States.

E-mail address: ashmoon@stanford.edu (A.S. Moon).

¹ Present address: Stanford University School of Medicine, Stanford, CA, United States.

² Present address: Yale University School of Medicine, New Haven, CT, United States.

<https://doi.org/10.1016/j.gore.2023.101203>

Received 17 April 2023; Received in revised form 9 May 2023; Accepted 13 May 2023

Available online 17 May 2023

2352-5789/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

through which the abdominal sensory afferent nerves travel (Rafi, 2001). These blocks have shown efficacy in reducing postoperative pain in patients undergoing abdominal surgeries, including abdominal and laparoscopic hysterectomy, colorectal surgery, laparoscopic cholecystectomy, open and laparoscopic appendectomy and cesarean deliveries (McDonnell, 2007; Brogi et al., 2016; Abdallah et al., 2012; Atim et al., 2011; Carney et al., 2008; Joshi et al., 2012). Since a significant component of the postoperative pain may be attributed to the incision itself (Grantcharov and Rosenberg, 2001), TAP blocks may be useful in patients with a vertical laparotomy.

Recent studies have been conducted to clarify the role of liposomal bupivacaine as an adjunct to the ERAS protocol. Liposomal bupivacaine has a slower release and prolonged plasma concentration than plain bupivacaine, thereby theoretically providing longer analgesia (Davidson et al., 2010; Cummings, 2012). It can be administered as a component of the TAP block or directly into the surgical incision, with infiltration into the preperitoneal, subfascial and/or subcutaneous planes. Retrospective data indicate liposomal bupivacaine by incisional infiltration may decrease rescue opioid use after gynecologic cancer surgery (Kalogera et al., 2016). A recent randomized controlled trial comparing incisional injection of liposomal bupivacaine in addition to bupivacaine vs. bupivacaine alone demonstrated no significant differences in percentage of patients who were opioid free in the first 48 h after surgery (Meyer et al., 2021). In another randomized controlled trial studying abdominal hysterectomies by Pfannenstiel incision, liposomal bupivacaine by surgical site infiltration provided superior pain relief and reduced opioid consumption than TAP block (Gasanova et al., 2015). The heterogeneity of study designs does not provide clear guidance on the effectiveness of analgesic techniques in the gynecologic cancer surgical population. Specifically, there is a paucity of data directly comparing different modalities of administration of liposomal bupivacaine after midline vertical laparotomy (Charlton et al., 2010).

The objective of this study is to compare surgeon administered incisional infiltration versus ultrasound guided anesthesiologist administered TAP block with liposomal bupivacaine for acute postoperative pain control after vertical laparotomy for gynecologic malignancy. We hypothesize that total opioid requirement in the first 48 h of the postoperative period will be less in patients who receive incisional infiltration of liposomal bupivacaine compared to those who receive TAP block with liposomal bupivacaine.

2. Materials and Methods

This was a single blind, randomized controlled trial of incisional infiltration of liposomal bupivacaine (experimental arm) versus transversus abdominis plane (TAP) block with liposomal bupivacaine (control arm) in patients undergoing exploratory laparotomy for suspected or known gynecologic malignancy. The study was approved by the Institutional Review Board at the institute where it was conducted. The trial is registered on the United States National Clinical Trials Registry ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier # NCT03870685). The trial was conducted at two community teaching hospitals from July 2018 to March 2021. The primary outcome was total morphine milligram equivalents (MME) required by participants during the first 48 h after surgery. The secondary outcomes were pain scores at rest and upon exertion (Valsalva maneuver) at 2, 6, 12, 24 and 48 h postoperatively.

Participants were required to be 18 years or older, speak English or Spanish, and undergo an exploratory laparotomy via vertical midline incision with known or suspected gynecologic malignancy. Patients with history of acute or chronic pain disorder, or a history of opioid, drug, or alcohol dependence were excluded. Full inclusion and exclusion criteria are listed in the [Supplementary Data](#). Research personnel screened and consented interested candidates. Participants were randomized to one of two groups in blocks of ten using a computer-generated randomization scheme. Group assignments were concealed in sealed envelopes until all documentation was verified. Study personnel opened the assigned

envelope 1–3 days prior to the scheduled surgery and communicated group assignment to the physician team. The surgeons and anesthesiologist involved in the case were not blinded to the study group. All participants and study personnel that collected pain scores were blinded to the assignment.

In the incisional infiltration arm, the surgeon performed injections using a moving needle technique, injecting 2–3 ml every 1–2 cm as the needle was withdrawn through the subcutaneous tissue. Infiltrations occurred below and above the fascia and into the subcutaneous space along the length of the incision. Patients with an infraumbilical incision received 20 ml liposomal bupivacaine (266 mg free base bupivacaine) admixed with 60 ml 0.5% bupivacaine HCl (150 mg) and 20 ml normal saline for an expanded solution. Patients with a supraumbilical incision received 20 ml liposomal bupivacaine (266 mg free base bupivacaine) admixed with 60 ml 0.5% bupivacaine HCl (150 mg) and 120 ml normal saline for an expanded solution. In the TAP block arm, the anesthesiologist administered 20 ml liposomal bupivacaine (266 mg free base bupivacaine) admixed with 60 ml 0.5% bupivacaine HCl (150 mg) and 20 ml normal saline for a 100 ml expanded solution. The 100 ml was divided into two 50 ml syringes, which were administered bilaterally (one syringe on each side) under direct ultrasound guidance. All participants received a standard regimen of analgesia during all phases of surgery and recovery ([Supplementary Figure](#)). In brief, preoperatively, PO acetaminophen 1000 mg and gabapentin 300 mg were given. Intraoperatively, IV fentanyl up to 350 mcg, IV ketorolac 15–30 mg, IV ondansetron 4 mg, IV dexamethasone 4 mg and a propofol infusion of 25 mcg/kg/min up to 100 mcg/kg/min were given. Postoperatively, for the first 24 h, IV ketorolac 15–30 mg every 6 h and IV acetaminophen 1 g every 8 h were given, with PO oxycodone 5–10 mg or PO hydro-morphone 2–4 mg every 4 h as needed. For 24–48 h postoperatively, NSAIDs were transitioned to oral formulations.

Total morphine milligram equivalents (MME) was calculated according to an opioid conversion calculator ([OPIOID CONVERSION CALCULATOR MORPHINE EQUIVALENTS -ADVANCED \[Internet\], 2021](#)). Pain scores were collected according to a numeric rating scale 0–10, with 0 being “no hurt” and 10 being “hurts worst” by blinded study personnel either in person or by phone if the patient discharged prior to the 48-hour time interval. Demographic and baseline clinical characteristics were collected including age, race/ethnicity, body mass index (BMI), American Society of Anesthesia (ASA) physical classification score, medical co-morbidities, surgery specifics (date, duration, incision length, pathology). Surgery duration was measured as from skin incision to skin closure for both groups. The time for placement of postoperative TAP block after skin closure was not included in time duration for surgery.

3. Statistical methods

We considered a 25% reduction in 48-hour morphine consumption to be clinically significant in patients undergoing incisional infiltration of liposomal bupivacaine compared to TAP block with liposomal bupivacaine. We estimated the average morphine usage over 48 h to be between 60 and 80 mg with a standard deviation of between 15 and 20 mg. For a two-sample pooled *t* test of a normal mean difference with a two-sided significance level of 0.05, assuming a common standard deviation of 17 mg, we estimated a required sample size of 28 per group to obtain a power of at least 0.9 to detect a mean difference of 15 mg. To account for patient dropout and loss to follow-up, we increased the sample size to 60 (30 in each arm).

We conducted all analyses with StataSE version 16 (StataCorps, LLC, College Station, Texas), and we calculated descriptive statistics for demographic and clinical variables using mean/standard deviation for continuous and number/percentage for categorical variables. We assessed study group differences using a two-sided independent student's *t*-test, chi-square, or Fisher's exact test as appropriate. We defined a *p*-value < 0.05 as statistically significant *a priori*. Missing data, while

rare, were accounted for using listwise deletion.

Upon preliminary analyses, we discovered the distribution of total MMEs heavily skewed to the right and mirrored a count distribution. The mean and variance were not equal between the two groups. Therefore, negative binomial regression was utilized to estimate the crude and adjusted differences in MME across treatment groups. The classical definition of confounding was used to select variables for our multivariable model and included age, BMI, and history of hypertension.

Univariate linear regression of pain scores by treatment group was performed for each time interval at rest and upon exertion to determine crude differences in pain scores. We also used multivariable linear regression at each time interval to control for age and prior MME use (i.e. we controlled for MMEs used between 2 and 6 h after surgery in the 6-hour regression). All analyses were verified to have met the assumptions of the selected regression models prior to finalizing our results.

4. Results

A total of 76 individuals were screened for eligibility between July 2018 and March 2021 (Fig. 1). We randomized 62 participants with 32 allocated to the TAP block group and 30 to the incisional infiltration group. Following allocation, eight patients in the TAP block group and five patients in the incisional infiltration group had surgeries that remained laparoscopic and were withdrawn. Additionally, two patients from the TAP block group and one patient from the incisional infiltration group withdrew from the study, and one in each group declined to participate at the time of surgery. No patients were lost to follow-up.

Our final analysis included 43 participants. Upon interim analysis in February 2021, we calculated the mean difference in MME was 20 with a standard deviation in both groups > 50. *Post hoc* power analyses given these parameters resulted in new sample size estimates of 85 per group – three-fold higher than the original estimate. The research committee recommended ending the study at this time given the miniscule difference demonstrated between groups and the challenges associated with

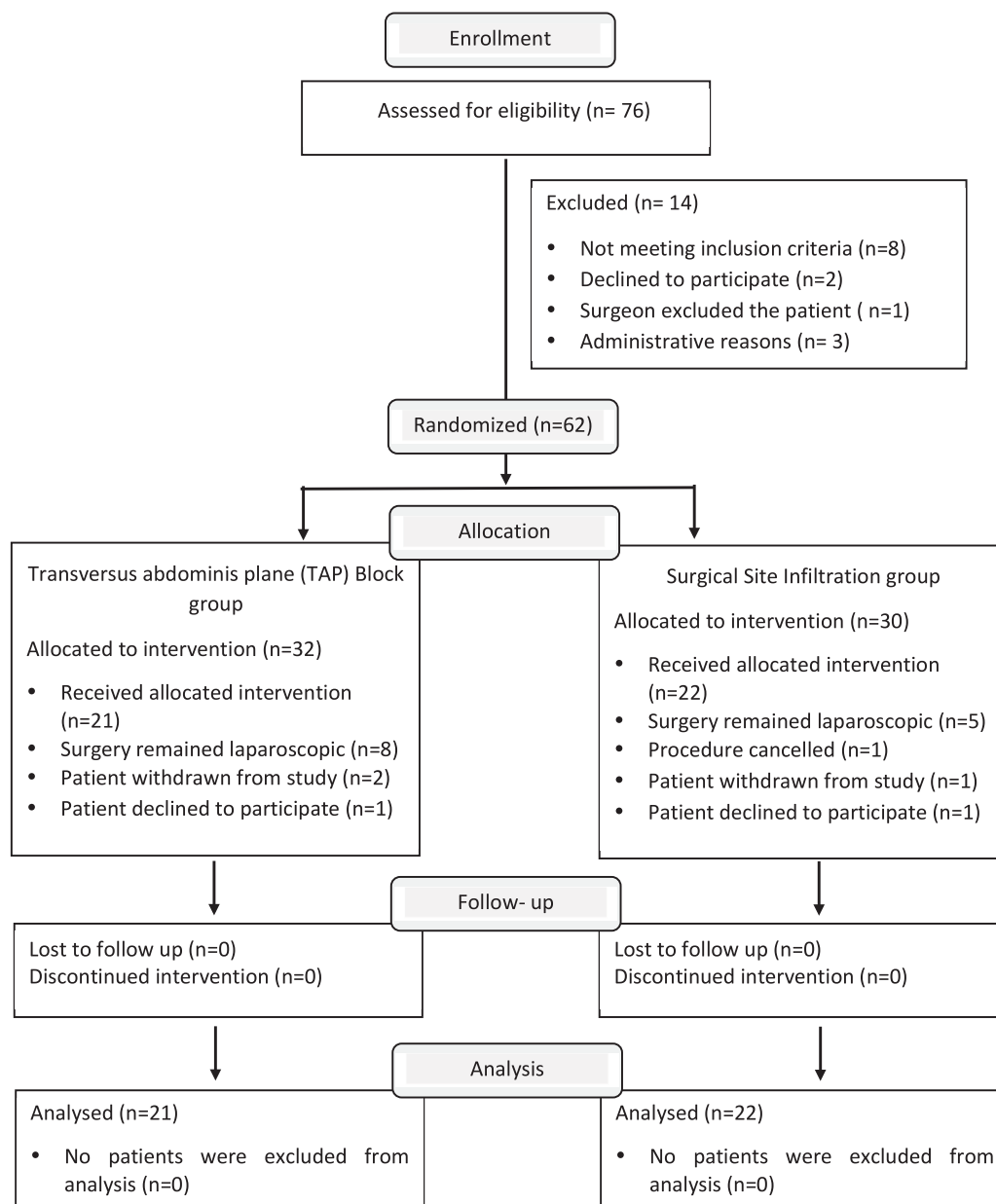


Fig. 1. CONSORT diagram.

recruitment during the COVID-19 pandemic.

The mean age of study participants was 57.8 [standard deviation (SD) 11.5]. More than half of the sample was obese or overweight with an average BMI of 30.1 (SD = 6.7), and the majority of patients had ASA scores of either II (48.8%) or III (41.8%). Table 1 displays additional descriptive statistics by treatment group. There were no significant differences in demographic or clinical variables across groups, including age, race/ethnicity, history of diabetes or hypertension, tumor pathology, or surgery duration. Incision type (supraumbilical vs. infraumbilical) and length were not significantly different between the groups with mean length of 19.3 cm in TAP block and 20.3 cm in incisional infiltration. No patients had patient controlled analgesia devices or epidurals.

5. Differences in MME use

Upon crude negative binomial regression, there was no difference in MME utilization among patients in the TAP block and incisional infiltration groups (Table 2). Though the point estimate suggests patients in the incisional infiltration group used fewer total MME, the confidence interval crosses 0 and p-value is > 0.05. Upon multivariable negative

Table 1 Participant demographics and clinical information.

	TAP block (n = 21)	Incisional infiltration (n = 22)	p- value
	Mean (SD)	Mean (SD)	
Age	54.6 (10.6)	60.9 (11.8)	0.08
Body mass index	29.8 (6.7)	30.5 (6.7)	0.76
Surgery duration (minutes)	151.7 (52.5)	155.8 (47.1)	0.79
PACU duration (minutes)	151.0 (53.3)	156.6 (44.9)	0.71
Incision length (centimeters)	19.3 (5.2)	20.3 (5.1)	0.54
Hospital stay (days)	4.0 (1.5)	3.6 (1.1)	0.38
	N (%)	N (%)	p- value
Race/Ethnicity			0.53
White	15 (71.4)	17 (77.3)	
Black/African American	1 (4.8)	0 (0.0)	
Asian	0 (0.0)	2 (9.1)	
Hispanic	4 (19.1)	3 (13.6)	
Does not identify	1 (4.7)	0 (0.0)	
Smoking history			0.73
Never	11 (52.4)	12 (54.5)	
Former	4 (19.1)	5 (18.2)	
Current	4 (19.1)	2 (9.1)	
Unknown	2 (9.4)	4 (18.2)	
ASA score			0.09
I	0 (0.0)	2 (9.1)	
II	12 (57.1)	9 (40.9)	
III	7 (33.3)	11 (50.0)	
IV	2 (9.5)	0 (0.0)	
Diabetes (yes)	2 (9.5)	4 (18.2)	0.67
Hypertension (yes)	1 (4.8)	5 (22.7)	0.19
Depression (yes)	0 (0.0)	1 (4.5)	1.00
Anxiety (yes)	2 (9.5)	1 (4.6)	0.60
Incision type			0.27
Infraumbilical	7 (33.3)	11 (50.0)	
Supraumbilical	14 (66.7)	11 (50.0)	
Lymph node dissected (yes)	5 (23.8)	11 (50.0)	0.08
Tumor debulking performed (yes)	8 (38.1)	5 (22.7)	0.27
Malignant tumor (yes)	10 (47.6)	14 (63.6)	0.29
Readmission (yes)	1 (4.8)	4 (18.2)	0.35
Post-operative complication (yes) ^a	3 (14.3)	5 (22.7)	0.70

Note: SD = standard deviation; TAP = transversus abdominis plane.

^a Post-operative complications included severe nausea and vomiting, wound opening or dehiscence, ileus, severe constipation, severe abdominal pain requiring re-admission, and transfusion.

Table 2

Negative binomial regression of morphine milligram equivalents (MME) across treatment groups (N = 43).

	β	95% Confidence Interval	p-value
Crude model	-0.30	-0.97, 0.38	0.38
Multivariable model ^a	-0.17	-0.77, 0.43	0.59

Note: β = regression coefficient.

^a Final model included treatment group, age, body mass index, and history of hypertension.

binomial regression, there was not a significant difference in MME use by treatment group, with the point estimate closer to the null and the confidence interval continuing to cross 0 (p = 0.59). There were minimal differences in opioid use at pre-specified intervals, including pre-operatively on day of surgery, intraoperatively, 0–24 h after surgery, 24–48 h after surgery and cumulatively up to 48 h after surgery (Table 3).

6. Differences in pain scores

Upon univariate analysis, there were minimal differences in pain scores at each time interval at rest or upon exertion between the two treatment groups (Figs. 2A-B). Additionally, multivariable linear regression demonstrated minimal difference in pain scores at each interval at rest or upon exertion when adjusting for age and prior pain medication use (Table 4). At 2, 12, and 24 h postoperatively, the regression coefficients are negative although the confidence intervals cross 0. The point estimates at 6 and 48 h (upon exertion) were in the opposite direction with positive values along with confidence intervals that also crossed 0.

7. Discussion

In this cohort of patients undergoing midline vertical laparotomy for suspected or known gynecologic malignancy, opioid consumption was similar after incisional infiltration of liposomal bupivacaine compared to TAP block with liposomal bupivacaine for the first 48 h after surgery. Although our study was discontinued before statistical significance was reached, there are clinical implications from our results.

The negative point estimates at 2, 12, and 24 h suggest incisional infiltration may result in less pain; however, the positive point estimates at 6 and 48 h suggest participants with incisional infiltration had greater pain. The contradiction across time points makes the results challenging to interpret. Since all the confidence intervals cross 0, it cannot be definitively concluded that incisional infiltration is superior in reducing postoperative pain. At the same time, this study was not designed as a non-inferiority study and should be considered for future research.

Table 3

Unadjusted differences in mean opioid requirements [morphine milligram equivalents (MME)] at a priori specified intervals.

	TAP block (n = 21)	Incisional infiltration (n = 22)	Test statistic	P- value
Preoperative	16.0 (6.5)	16.5 (8.3)	0.20	0.84
Intraoperative	15.1 (9.0)	15.7 (8.2)	-0.42	0.67
Post-surgery 0–24 h	49.6 (34.0)	46.7 (49.7)	0.72	0.47
Post-surgery 24–48 h	31.1 (33.7)	16.5 (23.6)	1.41	0.16
Cumulative 0–48 h	80.8 (61.8)	59.9 (67.9)	1.51	0.13

Data are mean (standard deviation); test statistic is the z-score from Wilcoxon rank-sum test, 2-sided null hypothesis; TAP = transversus abdominis plane.

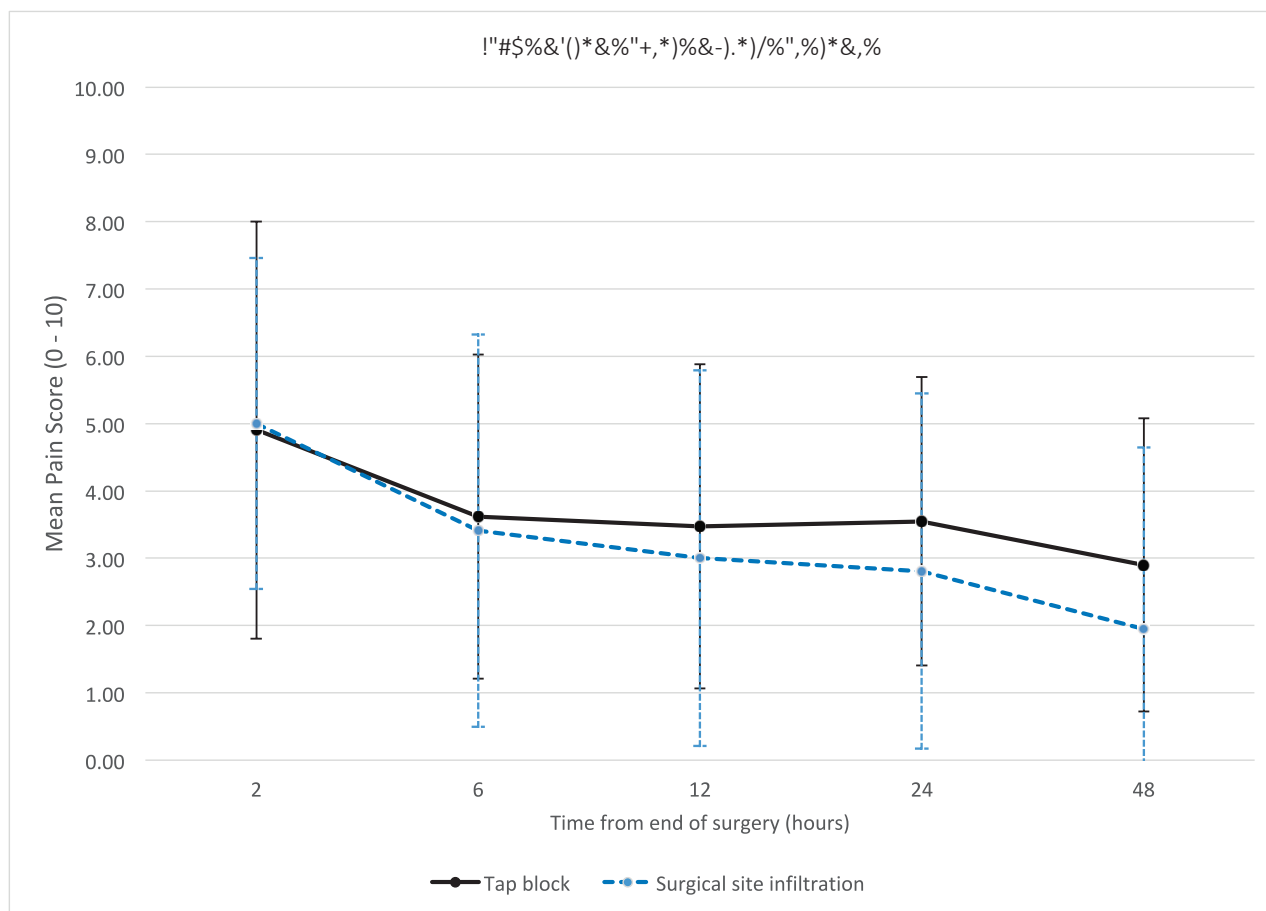


Fig. 2A. Pain scores after surgery at rest Assessment of pain scores at rest (mean and standard deviation) at prespecified time intervals after surgery.

Given a successful TAP block requires not only skill level but also ultrasound equipment and additional resources, incisional infiltration may be a reasonable alternative option.

Although this study evaluated patients with suspected or known gynecologic malignancy, up to two-thirds of patients had a confirmed malignant tumor. The mean duration of surgery from incision to closure for both study arms was 150 min, which is relatively short for a tumor debulking procedure. Therefore, these study's results may not be applicable for longer and more complex surgeries.

Meyer and colleagues studied wound infiltration of liposomal bupivacaine in addition to bupivacaine vs. bupivacaine HCl after exploratory laparotomy for a gynecologic indication (Meyer et al., 2021). Given the trial was conducted at a major referral cancer center, over 70% of participants in each arm had presumed malignancy and therefore likely underwent extensive surgical staging. There was no observed difference in patients receiving opioids during the first 48-hour postoperative period as well as no difference in the time to first opioid use and percentage of patients who were opioid free up to three days after surgery. Interestingly, there were also no improvements in patient reported outcomes such as mobility issues or pain up to eight weeks postoperatively. Prabhu et al studied liposomal bupivacaine vs. placebo in incisional infiltration after scheduled cesarean birth by Pfannenstiel incision in a randomized controlled trial. There was no reported difference in median pain score or opioid use during the first 48 h postoperatively (Prabhu et al., 2018). In a similar patient cohort, a randomized controlled trial evaluated TAP block with liposomal bupivacaine and bupivacaine HCl vs. bupivacaine HCl in women undergoing elective cesarean birth. The liposomal bupivacaine arm was reported to have a 51.6% reduction in total opioid consumption through 72 h postoperatively compared to the bupivacaine only arm (Nedeljkovic

et al., 2020). The reported decreased pain scores with liposomal bupivacaine were supported by a prespecified noninferiority margin, indicating liposomal bupivacaine in TAP block may be an important part of multimodal regimens after open abdominal surgery.

In a randomized controlled trial comparing two different techniques, Gasanova and colleagues evaluated women undergoing total abdominal hysterectomy by Pfannenstiel incision who received either surgical site infiltration with liposomal bupivacaine or TAP block with bupivacaine HCl. They had hypothesized the TAP block arm would provide improved pain scores at 6 h after surgery; however, it was observed that pain scores at rest and upon coughing were significantly lower in the surgical site infiltration group across time. The secondary outcome of opioid requirements was not statistically different between the two arms intraoperatively and postoperatively in the PACU but was significantly higher in the TAP block group for the first 24 h after surgery. Of note, Gasanova and colleagues evaluated two different anesthetics and two different administration techniques. It is therefore unclear as to whether it was the liposomal bupivacaine or surgical site infiltration that resulted in reduced pain and opioid use in their study. Given the theoretically extended duration of analgesia with liposome technology, their observations could be attributed to the anesthetic rather than the modality. As mentioned, other studies have since compared liposomal bupivacaine with either bupivacaine alone or placebo while using a single modality during laparotomy in obstetrics and gynecology, and have reported minimal difference in outcomes. In turn, we strived to answer the question of whether the analgesic technique may be associated with the improved pain score and opioid use reported in the study by Gasanova and colleagues. Expanding on previous preliminary data (Kindig et al., 2020), we compared two different techniques using the reported prolonged effects of liposomal bupivacaine but with a vertical surgical

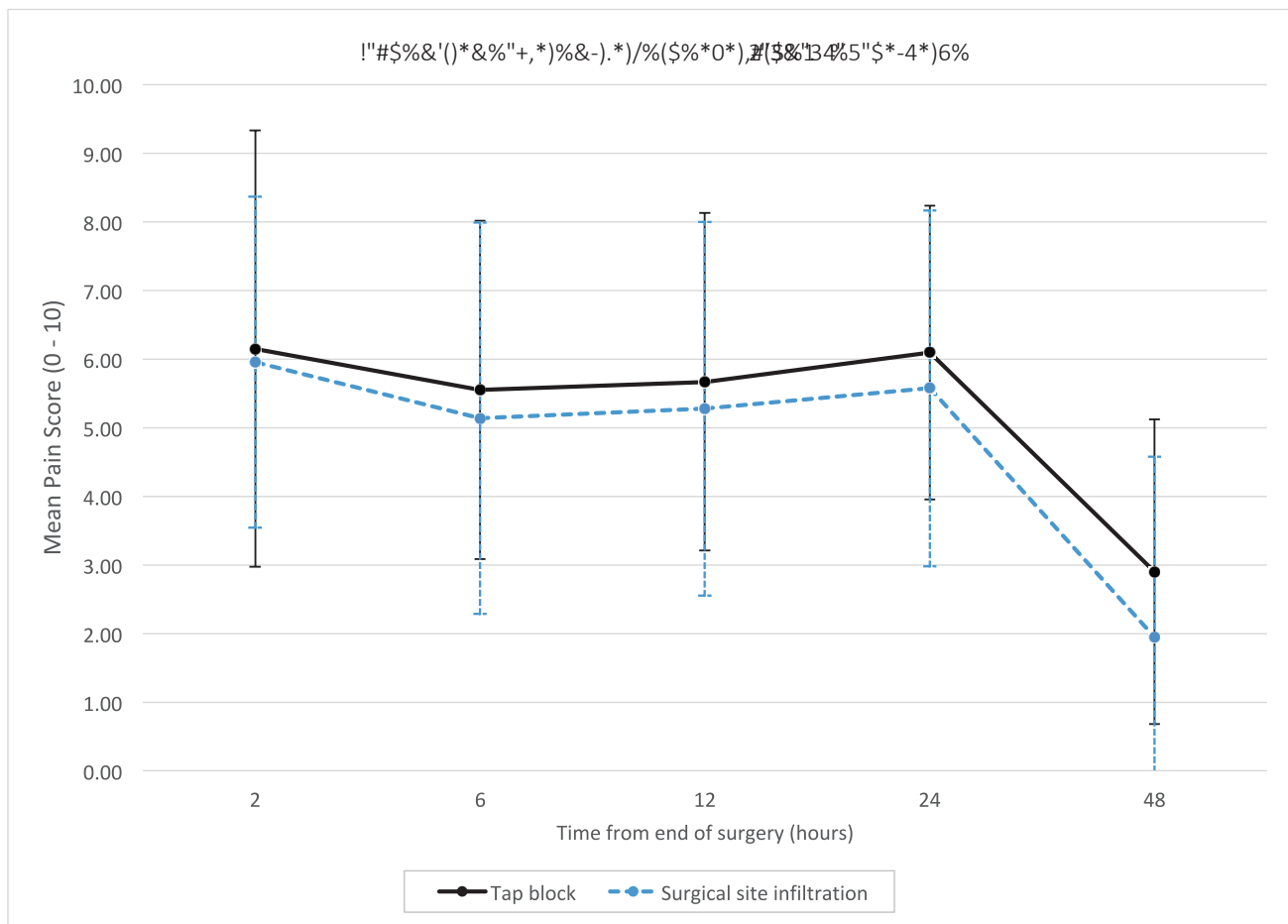


Fig. 2B. Pain scores after surgery on exertion (Valsalva maneuver) Assessment of pain scores on exertion (mean and standard deviation) at prespecified time intervals after surgery.

Table 4
Linear regression of pain scores at time intervals across treatment groups.

	β	95% Confidence Interval	p-value
<i>At rest</i>			
2 h	-0.23	-1.94, 1.48	0.76
6 h	0.25	-1.11, 1.63	0.70
12 h	-0.36	-1.40, 0.69	0.49
24 h	-0.45	-1.76, 0.86	0.49
48 h	-0.22	-1.30, 0.87	0.69
<i>Upon exertion^a</i>			
2 h	-0.41	-2.23, 1.40	0.65
6 h	0.30	-1.32, 1.91	0.71
12 h	-0.09	-1.62, 1.43	0.90
24 h	-0.18	-1.65, 1.29	0.80
48 h	0.48	-0.92, 1.88	0.49

Note: Regression performed after controlling for age and MME; β = regression coefficient; sample size at 2, 6 and 12 h = 43, sample size at 24, 48 h = 4.

^a Exertion defined as the Valsalva maneuver.

incision. Specifically, we evaluated whether a surgeon-administered modality of analgesia by direct incisional infiltration could be another viable option to offer to patients in addition to ultrasound-guided anesthesiologist administered TAP block.

Bernard et al recently published a randomized controlled trial evaluating surgeon-administered TAP block with bupivacaine versus placebo in a similar patient population as this cohort of suspected or known gynecologic malignancy (Bernard et al., 2023). Their data showed that surgeon-administered TAP block was not superior to placebo in reducing

postoperative opioid requirement or improving postoperative outcomes. The authors concluded that surgeon-administered TAP block should not be considered standard of care in perioperative multimodal analgesia after midline laparotomy. This study highlights the need for more research in alternative anesthetic modalities, including administered by the surgeon, which we strived to achieve in our current study.

7.1. Strengths and weaknesses

This study differs from published data in that this is a randomized single-blind designed trial comparing two different modalities of liposomal bupivacaine administration in open gynecologic surgery: incisional infiltration administered by the surgeon and TAP block administered by the anesthesiologist. The strength of studying a single analgesic is that the varying pharmacokinetics of different drugs among a heterogeneous group of patients is minimized. In turn, differences in outcomes can be cleanly evaluated based on type of administration. Furthermore, this study was conducted within an enhanced recovery after surgery (ERAS) program where standard non-opioid medications were given preoperatively, intraoperatively and postoperatively.

We acknowledge that our study has limitations in addition to what has been discussed thus far. Although our study is underpowered to show a statistically significant difference between the two approaches, there are clinical implications from our findings. For instance, pain scores in the surgical infiltration group were decreased at all time intervals upon exertion compared to the TAP block group. Our data indicate that TAP block and surgical infiltration provide clinically similar acute postoperative opioid use and pain scores. Another

limitation is the lack of a placebo group; however, it was considered unethical to include sham incisional infiltration and TAP block arms with normal saline solution when bupivacaine HCl may be considered a standard option. Another possible placebo group would be incisional infiltration and TAP block arms with bupivacaine HCl alone. But a four-arm clinical trial for laparotomy would not be economically or logistically feasible given the increasing rate of minimally invasive gynecologic surgery. Interestingly, a recent study evaluated laparoscopic guided TAP block of liposomal bupivacaine versus ultrasound guided TAP block of liposomal bupivacaine after robotic gynecologic oncology surgery (McDonald et al., 2022). Total opioid use and pain scores over the first 72 h were not statistically different between the two groups.

Finally, this current study did not analyze the cost of liposomal bupivacaine but a cost-effective analysis should be considered for not only the drug itself but also potentially on hospital admissions, time in the operating room and other associated healthcare expenses, which has been performed previously after TAP block of liposomal bupivacaine for laparoscopic hysterectomy (Seagle et al., 2017).

8. Conclusions

Incisional infiltration of liposomal bupivacaine and TAP block with liposomal bupivacaine have clinically similar opioid requirement after open gynecologic surgery. These findings may support the selective use of either incisional infiltration or TAP block of liposomal bupivacaine after gynecologic laparotomy.

9. Declarations

The Biomedical Research Alliance of New York Institutional Review Board approved the study on May 9, 2018. Reference number: 18-08-132.

10. Consent for publication

Not applicable.

11. Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to proprietary information but are available from the corresponding author on reasonable request.

Funding

Funding was provided by Nuvance Health.

CRedit authorship contribution statement

Ashley S. Moon: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Vaagn Andikyan:** Conceptualization, Methodology, Validation, Investigation, Resources, Writing – review & editing, Supervision. **Rakhee Agarwal:** Software, Formal analysis, Investigation, Data curation, Writing – original draft, Visualization. **Stephanie Stroever:** Validation, Formal analysis, Data curation, Writing – original draft, Visualization. **David Misita:** Conceptualization, Investigation, Resources, Writing – review & editing. **Anya Laibangyang:** Formal analysis, Writing – review & editing. **David Doo:** Investigation, Resources, Writing – review & editing. **Linus T. Chuang:** Investigation, Resources, Writing – review & editing, Supervision.

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.

Acknowledgements

We would like to acknowledge the resident physicians in the Department of Obstetrics and Gynecology at Danbury Hospital as well as Joann Petrini, PhD and Jonathan Serino in the Department of Research and Innovation at Nuvance Health.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.gore.2023.101203>.

References

- Abdallah, F.W., Halpern, S.H., Margarido, C.B., 2012. Transversus abdominis plane block for postoperative analgesia after Caesarean delivery performed under spinal anaesthesia? A systematic review and meta-analysis. *Br. J. Anaesth.* 109 (5), 679–687.
- ACOG Committee Opinion No. 750: Perioperative Pathways: Enhanced Recovery After Surgery. *Obstet. Gynecol.* 2018 Sep; 132(3): e120–30.
- Atim, A., Bilgin, F., Kilickaya, O., Purtuloglu, T., Alanbay, I., Orhan, M.E., et al., 2011. The Efficacy of Ultrasound-Guided Transversus Abdominis Plane Block in Patients Undergoing Hysterectomy. *Anaesth. Intensive Care.* 39 (4), 630–634.
- Bernard, L., Lavecchia, M., Trepanier, G., Mah, S., Pokoradi, A., McGinnis, J.M., et al., 2023. A double-blinded, randomized trial comparing surgeon-administered transversus abdominis plane block with placebo after midline laparotomy in gynecologic oncology surgery. Feb 14 [cited 2023 Apr 12]; Available from: *Am. J. Obstet. Gynecol.* [Internet]. <https://www.sciencedirect.com/science/article/pii/S0002937823001102>.
- Bisch, S.P., Jago, C.A., Kalogera, E., Ganshorn, H., Meyer, L.A., Ramirez, P.T., et al., 2021. Outcomes of enhanced recovery after surgery (ERAS) in gynecologic oncology – A systematic review and meta-analysis. *Gynecol. Oncol.* 161 (1), 46–55.
- Broggi, E., Kazan, R., Cyr, S., Giunta, F., Hemmerling, T.M., 2016. Transversus abdominal plane block for postoperative analgesia: a systematic review and meta-analysis of randomized-controlled trials. *Can. J. Anesth. Can Anesth.* 63 (10), 1184–1196.
- Carney, J., McDonnell, J.G., Ochana, A., Bhinder, R., Laffey, J.G., 2008. The Transversus Abdominis Plane Block Provides Effective Postoperative Analgesia in Patients Undergoing Total Abdominal Hysterectomy: *Anesth. Analg.* 107(6), 2056–2060.
- Chapman, J.S., Roddy, E., Ueda, S., Brooks, R., Chen, L., Lynn, Chen L may, 2016 Jul. Enhanced Recovery Pathways for Improving Outcomes After Minimally Invasive Gynecologic Oncology Surgery. *Obstet. Gynecol.* 128 (1), 138–144.
- Charlton, S., Cyna, A.M., Middleton, P., Griffiths, J.D., 2010. Perioperative transversus abdominis plane (TAP) blocks for analgesia after abdominal surgery [cited 2021 Apr 1];(12). Available from: Cochrane Database Syst. Rev. [Internet]. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD007705.pub2/full>.
- Cummings, III K., Chahar. Liposomal bupivacaine: a review of a new bupivacaine formulation. *J. Pain Res.* 2012; 257.
- Davidson, E.M., Barenholz, Y., Cohen, R., Haroutiunian, S., Kagan, L., Ginosar, Y., 2010. High-dose bupivacaine remotely loaded into multivesicular liposomes demonstrates slow drug release without systemic toxic plasma concentrations after subcutaneous administration in humans. *Anesth Analg.* 110 (4), 1018–1023.
- Dickson, E.L., Stockwell, E., Geller, M.A., Vogel, R.L., Mullany, S.A., Ghebre, R., et al., 2017. Enhanced Recovery Program and Length of Stay After Laparotomy on a Gynecologic Oncology Service: A Randomized Controlled Trial. *Obstet. Gynecol.* 129 (2), 355–362.
- Gasanova, I., Alexander, J., Ogunnaike, B., Hamid, C., Rogers, D., Minhajuddin, A., et al., 2015. Transversus Abdominis Plane Block Versus Surgical Site Infiltration for Pain Management After Open Total Abdominal Hysterectomy. *Anesth. Analg.* 121 (5), 1383–1388.
- Grantcharov, T.P., Rosenberg, J., 2001. Vertical compared with transverse incisions in abdominal surgery. *Eur. J. Surg. Acta Chir.* 167 (4), 260–267.
- Joshi, G.P., Rawal, N., Kehlet, H., 2012. Evidence-based management of postoperative pain in adults undergoing open inguinal hernia surgery. *Br. J. Surg.* 99 (2), 168–185.
- Kalogera, E., Bakkum-Gamez, J.N., Weaver, A.L., Moriarty, J.P., Borah, B.J., Langstraat, C.L., et al., 2016. Abdominal Incision Injection of Liposomal Bupivacaine and Opioid Use After Laparotomy for Gynecologic Malignancies. *Obstet. Gynecol.* 128 (5), 1009–1017.
- Kindig, M., Mouch, A., Adams, D., Maxwell, R., Yaklic, J., 2020. Liposomal Bupivacaine Decreases Pain Scores and Narcotic Use After Cesarean Delivery [19E]. *Obstet. Gynecol.* 135, 54S.
- Lindemann, K., Kok, P.S., Stockler, M., Jaaback, K., Brand, A., 2017. Enhanced Recovery After Surgery for Advanced Ovarian Cancer: A Systematic Review of Interventions Trialed. *Int. J. Gynecol. Cancer.* 27 (6), 1274–1282.
- McDonald, V., Wang, Y., Patel, A., Betcher, R., Fontenot, A.C., Scoggin, S., et al., 2022. Laparoscopic guided liposomal bupivacaine injection compared to transversus abdominis plane block for postoperative pain after robotic gynecologic oncology surgery. *Gynecol. Oncol.* 166 (3), 432–437.
- McDonnell, J.G., O’Donnell, B., Curley, G., Heffernan, A., Power, C., Laffey, J.G., 2007. The Analgesic Efficacy of Transversus Abdominis Plane Block After Abdominal

- Surgery: A Prospective Randomized Controlled Trial: *Anesth. Analg.* 104(1), 193–197.
- Mendivil, A.A., Busch, J.R., Richards, D.C., Vittori, H., Goldstein, B.H., 2018. The Impact of an Enhanced Recovery After Surgery Program on Patients Treated for Gynecologic Cancer in the Community Hospital Setting. *Int. J. Gynecol. Cancer Off. J. Int. Gynecol. Cancer Soc.* 28 (3), 581–585.
- Meyer, L.A., Corzo, C., Iniesta, M.D., Munsell, M., Shi, Q., Pitcher, B., et al., 2021. A prospective randomized trial comparing liposomal bupivacaine vs standard bupivacaine wound infiltration in open gynecologic surgery on an enhanced recovery pathway. *Am. J. Obstet. Gynecol.* 224 (1), 70.e1–70.e11.
- Miralpeix, E., Nick, A.M., Meyer, L.A., Cata, J., Lasala, J., Mena, G.E., et al., 2016. A call for new standard of care in perioperative gynecologic oncology practice: Impact of enhanced recovery after surgery (ERAS) programs. *Gynecol. Oncol.* 141 (2), 371–378.
- Myriokefalitaki, E., Smith, M., Ahmed, A.S., 2016. Implementation of enhanced recovery after surgery (ERAS) in gynaecological oncology. *Arch. Gynecol. Obstet.* 294 (1), 137–143.
- Nedeljkovic, S.S., Kett, A., Vallejo, M.C., Horn, J.L., Carvalho, B., Bao, X., et al., 2020. Transversus Abdominis Plane Block With Liposomal Bupivacaine for Pain After Cesarean Delivery in a Multicenter, Randomized, Double-Blind, Controlled Trial. *Anesth. Analg.* 131 (6), 1830–1839.
- OPIOID CONVERSION CALCULATOR MORPHINE EQUIVALENTS -ADVANCED [Internet]. [cited 2021 Mar 1]. Available from: <https://globalrph.com/medcalcs/opioid-pain-management-converter-advanced/>.
- Prabhu, M., Clapp, M.A., McQuaid-Hanson, E., Ona, S., O'Donnell, T., James, K., et al., 2018. Liposomal Bupivacaine Block at the Time of Cesarean Delivery to Decrease Postoperative Pain: A Randomized Controlled Trial. *Obstet. Gynecol.* 132 (1), 70–78.
- Rafi, A.N., 2001. Abdominal field block: a new approach via the lumbar triangle. *Anaesthesia.* 56 (10), 1024–1026.
- Seagle, B.L.L., Miller, E.S., Strohl, A.E., Hoekstra, A., Shahabi, S., 2017. Transversus abdominis plane block with liposomal bupivacaine compared to oral opioids alone for acute postoperative pain after laparoscopic hysterectomy for early endometrial cancer: a cost-effectiveness analysis. *Gynecol. Oncol. Res. Pract.* 4 (1), 12.