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Effectiveness and Safety of Opioid-Free Anaesthesia and Analgesia in pain control and postoperative recovery of patients undergoing gynaecologic oncologic surgery: a retrospective cohort study

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Abstract

Background Opioids have been essential for the anesthesiologic management of patients undergoing surgical procedures such as gynecologic oncology, but incorrect dosage can lead to unwanted hemodynamic effects. Opioid-free anesthesia (OFA) and multimodal postoperative analgesia techniques can solve this problem as they can restrict the excessive use of opioids.

Methodology A retrospective observational cohort study was conducted by reviewing the medical records of patients at the Hernando Moncaleano Perdomo University Hospital. Female patients who underwent gynecologic oncology surgery at the MPUHN and who received OFA, or opioid-based anesthesia (OBA) were identified. Two cohorts were created in which one have all patients (unadjusted cohort) and one with randomly selected patients (adjust cohort). Data on pain were collected using a visual analog pain scale (VAPS), along with hemodynamic variables and adverse events at 7 different times from admission to the operating room until discharge from the hospital. A bivariate analysis was performed between OFA and OBA, comparing frequencies of VAPS and adverse events with chi2, while mean difference for hemodynamic variables with t student. A multivariate analysis was performed with multiple logistic regression to evaluate differences in frequency of VAPS between OFA and OBA.

Results For unadjusted cohort, difference was identified for greater pain in OFA than in OBA ($p < 0.001$) for the times before surgery, recovery room, and 24 h after surgery, while differences were only identified at recovery room in the adjusted cohort. The heart rate has significant differences only at pre-surgery, 30 min of induction and admission to the recovery room. Respiratory rate has significant differences at admission to the operating room, 30 min of induction. Mean arterial pressure was significant only in the recovery room and for oxygen saturation at admission to the operating room and discharge from recovery. Higher frequency of requiring antiemetics was only identified in

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patients with OFA than OBA on the fifth day of surgery. Significance was identified in multivariate analysis between OBA and OFA for at discharge from recovery room.

Conclusions The OFA technique for gynecologic oncologic surgery patients has a similar impact on pain control compared to OBA.

Trial registration Does not apply.

Keywords Opioid free anaesthesia, Surgery, Cancer, Gynecologic oncology, Multimodal analgesia, Gynecological surgery, Opioids

Introduction

Balanced anesthesia involves the administration and combination of different pharmacological groups to achieve an optimal anesthetic state by achieving more adjusted doses, increasing the proportion of desired effects and reducing side effects [1]. In turn, general anesthesia could be defined as the result of the pharmacological combination that seeks to achieve its fundamental pillars, the loss of consciousness or hypnosis, amnesia, and immobility during the surgical procedure, together with adequate control of postoperative pain avoiding hemodynamic alterations; all dependent on specific therapeutic agents and sensitive to the body's response according to the dose used [2].

Multiple drugs meet those objectives, opioids are considered the second most used drug after inhaled agents and propofol. Their preference lies in the controlling effect of the central nervous system's responses to nociception, maintaining stable hemodynamics, in addition to their effects on postoperative pain control, decreased anesthetic requirements and control of the sympathetic response [2]. However, the administration of opioids in the perioperative period involves a risk due to the high incidence of minor adverse events in about 82% of cases and moderate events in 13.6%. Sedation, transient delirium, dizziness, nausea and vomiting, constipation, respiratory depression, and increased stay in the post-anesthesia care unit are frequent and unwanted side effects in early postoperative recovery techniques [3].

In addition, drug dependence and chronic abuse of patients using opioids in the intra- and postoperative period affects developed countries to the point of constituting a "crisis". For example, in the United States nearly 107,000 overdose deaths were reported in 2021, of which 75% were related to an opioid [4, 5]. In Colombia, the Ministry of Justice reported 30 deaths associated with fentanyl use between 2013 and 2023, distributed in the cities of Medellín, Cartagena, Bogotá, Pereira and Villavicencio, without finding reports of deaths due to fentanyl abuse in the department of Huila [6].

Thus, adverse events related to opioids, as well as the epidemic of excessive use of them, has motivated specialists to replace them and opt for the use of techniques based on complementary medications [7]. Opioid-free anesthesia (OFA) has demonstrated a decrease in hypotensive events, lower consumption of rescue analgesics and ondansetron in laparoscopic abdominal surgery [5]. In a meta-analysis evaluating 33 randomized controlled clinical trials, it was found that patients who received OFA had lower pain levels at 2 h postoperatively, required lower doses of morphine at 2 and 24 h after the surgical procedure, and additionally had a lower incidence of nausea, vomiting, sedation, and chills [8].

Although current evidence focuses the benefits of OFA mainly on the prevention of postoperative adverse events, the benefit and safety of these regimens in particular surgical procedures such as gynecologic oncologic surgeries remain to be elucidated, where studies comparing the use of intra- or postoperative opioids versus opioid-free techniques are limited. New studies are required to support the generation of universal anesthetic management recommendations and protocols to impact postoperative patient outcomes, satisfaction, and quality of life. Therefore, to offer an effective alternative that reduces opioid consumption and its unwanted effects [9–12], opioid-free techniques have been developed at the Hernando Moncaleano Perdomo University Hospital in Neiva, which allowed us to raise the question: What is the effectiveness and safety of opioid-free anesthesia and analgesia in pain control at postoperative recovery of adult patients undergoing gynecologic-oncologic surgery?

Methodology

Study design

This study answered the research question and objective set out through a retrospective observational cohort analytical design. The approval by the "COMITE DE ÉTICA, BIOETICA E INVETSIGACIÓN" (code GDI-INV-F-100 A) at Hernando Moncaleano Perdomo University Hospital was submitted on December 14, 2023, and approved by act No. 12 – 07. The consent to participate was waived due to a study in which only medical records were reviewed, and all

the necessary information was found in them. This study did not receive funding from any source.

Place and time

The population information was obtained from the medical records of adult patients undergoing gynecologic oncology surgery at the Hospital Universitario de Neiva between the period from January 2021 to December 2022.

Inclusion and Exclusion Criteria

All patients undergoing gynecologic oncology surgery at the Hernando Moncaleano Perdomo University Hospital between the period from January 2021 to December 2022 were included. Patients who were administered during the intra- and postoperative period (no opioid drugs administered by any intravenous, oral, rectal, intrathecal or epidural route) were included as OFA. Those who were administered opioids at intra- and postoperative period were included as Opioid-based Anesthesia (OBA). Exclusion criteria were patients who had underreporting or missing data in their clinical histories for sample collection, cases of mortality or data that did not meet the objectives proposed in the research work were not considered.

Data collection

Information was collected through Microsoft Excel®, which was completed solely by the principal researcher (JAPG) based on the information recorded in the institution's official legal document (medical records). Variables such as the age in years, BMI, history of heart disease, respiratory disease, anemia, kidney disease, liver disease, vascular disease, chronic pain, smoking, drug use, alcoholism, American Society of Anesthesiologist classification (ASA), clinical origin and premedication were collected for clinical descriptions. Other variables such as surgical approach (Laparoscopic, Laparotomic, vulvectomies or vaginal surgery), kind of anesthesia (General or Regional) kind of surgical wound (Contaminated surgical wound, Clean contaminated surgical wound or Clean surgical wound) time of surgery, blood loss, medications for induction of anesthesia (Bupivacaine, Lidocaine, propofol, Ketamine, Fentanyl or Rocuronium) and medications for anesthesia (Sevoflurane (MAC), Dexmedetomidine, Ketamine, Lidocaine, Fentanyl or Remifentanil) maintenance were collected for surgery description. Postoperative pain management was collected as the need of epidural catheter, kind of analgesic used and number of analgesic rescues at admission to recovery room and discharge from recovery room.

The primary outcome was the Visual Analogue Pain Scale (VAPS) from 0 to 10 and was classified as equal or below to 3 ($<=3$), between 4 and 7 [4–7] and greater or equal to 8 ($>=8$). The secondary's outcomes were hemodynamics variables such as Heart rate (HR), Mean arterial pressure (MAP), Respiratory rate (RR), Blood Oxygen Saturation (SaO2). Postoperative complications variables such as vomiting, urinary retention, nausea, hypotension, respiratory depression and delirium were collected to evaluate safety were also secondary outcomes. VAPS data were collected in 7 different times which were pre surgery, admission to recovery room, discharge from recovery room, 24 h, 48 h, 5 days and upon discharge from the hospital. Meanwhile, hemodynamics variables were only collected in 4 different timer which were pre surgery, 30 min after anesthesia induction, admission to recovery room and discharge from recovery room. Finally, Postoperative complications variables were only collected in 4 different times which were at admission to recovery room, discharge from recovery room., 24 h and 48 h.

Sample size calculation for adjusted cohort

Sample size was calculated by difference of proportions of VAPS $<=3$ or 4–7; to determine a 95% confidence level and a 90% power if the 90% proportion for patients exposed to OFA has VAPS $<=3$ and OBA has 70% proportion VAPS $<=3$. The final calculation was a minimum of 60 patients for each group for a total of 120. An excess of patients for both groups to randomly select a cohort that can be controlled for VAPS, HR, MAP, RR and SaO2 at pre surgery time and can have minimum patients calculated.

Statistical analysis

Data was analyzed using the statistical software Rstudio® version 3.6.1. A descriptive analysis of the information was performed between anesthetic techniques, using means and standard deviations for continuous quantitative variables with normal distribution, medians with interquartile ranges for continuous quantitative variables with non-parametric distributions. Categorical variables were described in absolute and relative frequencies. The association between VAPS, hemodynamics variables and postoperative complications between anesthetic techniques, in the 7 or 4 times periods were explored by bivariate analysis. Student's t-tests for continuous variables or the Mann-Whitney test when they did not meet normality assumptions were used. Contingency tables were constructed for categorical variables and the Chi-square test or Fisher's exact test was calculated when they did not meet the Chi-square assumptions. Significance was established at $p < 0.05$ and all previously statical analysis applied for both unadjusted cohort (complete data set of patients) and adjusted cohort (controlled randomly selected patients) .

For the association analysis, multivariable logistic regression models were built, where the outcome

was VAPS at times when differences between OFA and OBA was obtained, that difference was present in both unadjusted cohort and adjusted cohort and was after pre-surgery. The explanatory variables were the sociodemographic and clinical/surgical practice data collected. The model was interpreted from the exponential coefficients obtained by the final model (Odds Ratio-OR) in which greater than 1 is better pain control (VAPS < = 3) and lower than 1 in worst pain control (VAPS > = 4). The variables were adjusted and the model that best explained the response variable with the lowest Akaike information criterion (AIC) was selected.

Results

Clinical characteristics of patients

A total of 387 patients who underwent gynecologic oncologic surgery were collected, of which 335 patients were eligible for the present study and 52 patients were excluded because their medical history was incomplete, or they had died during their hospital stay (Fig. 1). Of the patients who met the proposed criteria for the unadjusted cohort, 196 received OBA regimen and 139 received OFA regimen. Of those patients, 123 were selected for the adjusted cohort from which 60 where for OBA and 63 for OFA. Clinical characteristics of the included patients are described in Table 1.

Surgical characteristics of patients and Postoperative pain management

For the unadjusted cohort, the types of surgeries were mostly laparotomy and laparoscopy, with less frequency of vulvectomies or vaginal surgery, with no significant differences between OBA and OFA. For the kind of anesthesia used, there were no statistically significant differences between the OBA and OFA groups. There were no differences between the groups in terms of surgical wound kind and same goes to time in minutes for the duration of. The duration of anesthesia in minutes was significant in which OFA has a greater time than OBA. Similar results were obtained for the adjusted cohort except for the time in minutes for anesthesia in which there were no differences between OFA and OBA. All surgical characteristics are described in Table 2.

It was found that at discharge from the recovery room there are statically significant differences in the use of epidural catheter and the need of analgesic rescue, in both cases greater for OFA than OBA for the unadjusted cohort. At discharge from recovery room, a great use of bupivacaine Infusion for OFA was identified but not for dipyrone in the unadjusted cohort. Similar results were obtained for the adjusted cohort except for dipyrone in which OFA has a greater use of them than OBA. All postoperative pain management are summarized in Table 3.

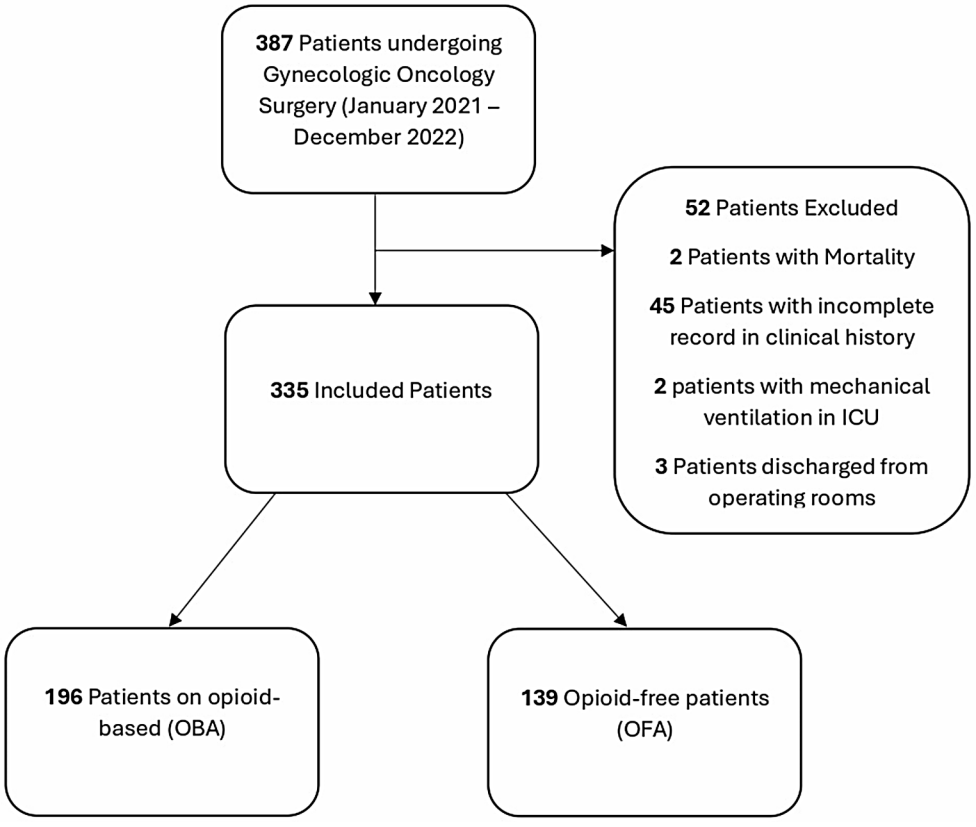

Fig. 1 Flowchart for patient selection

Table 1 Clinical characteristics by anesthesia regimen: OBA vs. OFA

Clinical features	Unadjusted Cohort				adjusted Cohort			
	OBA	**OFA**	**Total**	***p***	**OBA**	**OFA**	**Total**	***p***
Patients (%)	196 (58.5%)	139 (41.5%)	335 (100%)	-	60 (48%)	63 (51.2%)	123 (100%)	-
Age Median-IQR	48.5 [40–60]	47 [36–61]	47 [38–61]	0.43 Ψ	46 [38–58]	48 [37–58]	47 [37–58]	0.61 Ψ
IMC (Kg/m2) Median-IQR	25.9 [23.7–30.8]	26.4 [22.6–30.1]	26.0 [23.4–30.3]	0.43 Ψ	26.6 [23.8–33.2]	26 [23.8–30.1]	26.2 [23.8–30.8]	0.21 Ψ
Cardiovascular disease (%)	14 (7.1%)	13 (9.4%)	27 (8.1%)	0.46 †	9 (14.3%)	2 (3.3%)	11 (8.9%)	0.07 †
Respiratory disease n (%)	11 (5.6%)	2 (1.4%)	13 (3.8%)	0,13 ‡	1 (1.6%)	3 (5%)	4 (3.3%)	0.57 ‡
Anemia (%)	9 (4.6%)	21 (15.1%)	30 (9.0%)	0,001* †	8 (12.7%)	3 (5%)	11 (8.9%)	0.23 †
Diabetes (%)	8 (4.1%)	10 (7.2%)	18 (5.4%)	0.21 †	4 (6.3%)	2 (3.3%)	6 (4.9%)	0.72 †
Renal disease (%)	2 (1.0%)	3 (2.2%)	5 (1.5%)	0.65 ‡	1 (1.6%)	0 (0%)	1 (0.8%)	1 ‡
Hepatic disease (%)	5 (2.6%)	3 (2.2%)	8 (2.4%)	0.82 ‡	2 (3.2%)	1 (1.7%)	3 (2.4%)	1 ‡
Chronic pain (%)	20 (10.3%)	36 (25.9%)	56 (16.8)	< 0.0001* †	16 (25.4%)	4 (6.8%)	20 (16.4%)	0.011* †
vulvar cancer (%)	5 (2.6%)	2 (1.4%)	7 (2.1%)	0.38 ‡	0 (0%)	3 (5%)	3 (2.4%)	0.1
Cervical cancer (%)	31 (15.8%)	17 (12.2%)	48 (14.3%)		**6 (9.5%)**	**6 (10%)**	**12 (9.8%)**	
Endometrial cancer (%)	33 (16.8%)	30 (21.6%)	63 (18.8%)		**19 (30.2%)**	**7 (11.7%)**	**26 (21.1%)**	
Ovarian cancer (%)	98 (50%)	76 (54.7%)	174 (51.9%)		**27 (42.9%)**	**30 (50%)**	**57 (46.3%)**	
Body of uterus cancer (%)	12 (6.1%)	3 (2.2%)	15 (4.5%)		**3 (4.8%)**	**5 (8.3%)**	**8 (6.5%)**	
Other gynecologic cancers (%)	17 (8.7%)	11 (7.9%)	28 (8.4%)		**8 (12.7)**	**9 (15%)**	**17 (13.8)**	
Smoking (%)	8 (4.1%)	6 (4.3%)	14 (4.2%)	1.0 †	0 (0%)	2 (3.3%	2 (1.6%)	0.45 †
History of IV analgesics (%)	1 (0.5%)	0 (0%)	1 (0.3%)	0.39 ‡	0 (0%)	0 (0%)	0 (0%)	-
Previous use of painkillers (%)	100 (51%)	99 (71.2%)	199 (59.4%)	< 0.0001* †	48 (76.2%)	33 (55%)	81 (65.9%	0.02* †
ASA 1 (%)	10 (5.1%)	0 (0%)	10 (3.0%)	0,002* ‡	0 (0%)	1 (1.7%)	1 (0.8%)	0.45 ‡
ASA 2 (%)	76 (38.8%)	78 (56.1%)	154 (46%)		**29 (46%)**	**23 (38.3%)**	**52 (42.3%)**	
ASA 3 (%)	109 (55.6%)	61 (43.9%)	170 (50.7%)		**34 (54%)**	**35 (58.3%)**	**69 (56.1%)**	
ASA 4 (%)	1 (0.5%)	0 (0%)	1 (0.3%)		0 (0%)	**1 (1.7%)**	**1 (0.8%)**	
Outpatient origin (%)	111 (56.6%)	53 (38.1%)	164 (49%)	0,001* ‡	24 (38.1%)	20 (33.3%)	44 (35.8%)	0.55 ‡
Hospitalization origin (%)	84 (42.9%)	83 (59.7%)	167 (49.8%)		**30 (47.6%)**	**27 (45%)**	**57 (46.3%)**	
Urgency origin n (%)	1 (0.5%)	3 (2.2%)	4 (1.2%)		**9 (14.3%)**	**13 (21.7%)**	**22 (17.8%)**	
Premedication Acetaminophen (1 gram) + Pregabalin (150 mg)	153 (78.1%)	117 (84.2%)	270 (80.6%)	0,16†	56 (88.9%)	52 (86.7%)	108 (87.8%)	0.91 †

*: Statistically significant ($p < 0.05$),

†: Calculated by χ2 test

‡: Calculated by Fisher's exact test

Ψ: Calculated by Mann-Whitney U test

IQR: interquartile range

IMC: index of mass corporal

ASA: American Society of Anesthesiologists score

VASP by anesthesia regimen and time

Regarding the pain assessment for the unadjusted cohort, the VAPS pre surgery was found to have significant differences between the groups ($p = 0.001$), VAPS category < = 3 pre surgery was 280 patients (84.4%) for all patients, 176 (90.2%) for OBA and 106 (76.3%) for OFA. VAPS category 4–7 for OBA was 19 (9.7%) and OFA 23 (16.5%) for a total of 42 patients (12.6%) and VAPS category > = 8 for a total of 10 (7.2%) for OFA. At admission to the recovery room, differences were detected between groups in the VAPS category's ($p = 0.42$). For the OBA group in the VAPS category < = 3 there were 179 patients (91.8%), between 4 and 7 were 10 patients (5.1%) and VAPS category > = 8 were 6 patients (3.1%), while for the OFA group in the VAPS category < = 3 there were 119 patients (87.5%), between VAPS category 4–7 were 10 patients (7.4%) and > 7 were 7 (5.1%) patients. In the discharge from recovery room time, there were differences between groups ($p < 0.001$), but at 24 h there were differences in pain assessment between groups ($p = 0.02$). No differences were observed at 48 h, 5 days and

Table 2 Surgical characteristics by anesthesia regimen: OBA vs. OFA

Surgical features	Unadjusted Cohort				adjusted Cohort			
	OBA	OFA	Total	*p*	OBA	OFA	Total	*p*
Laparoscopic approach (%)	71 (36.2%)	49 (35.3%)	120 (35.8%)	0.8 ‡	23 (38.4%)	23 (36.5%)	26 (21.1%)	0.92 ‡
Laparotomic approach (%)	120 (61.2%)	88 (63.3%)	208 (62.1%)		36 (60%)	39 (61.9%)	75 (60.9%)	
vulvectomies or vaginal surgery (%)	5 (2.6%)	2 (1.4%)	7 (2.1%)		1 (1.6%)	1 (1.5%)	2 (1.6%)	
General anesthesia (%)	186 (94.9%)	134 (98.5%)	320 (96.4%)	0.13 * ‡	57 (95%)	61 (96.8%)	118 (95.9%)	0.45 ‡
Regional anesthesia (%)	10 (5.1%)	2 (1.5%)	12 (3.6%)		3 (5%)	2 (3.2%)	5 (4.1%)	
Contaminated surgical wound (%)	2 (1.0%)	0 (0%)	2 (0.6%)	0.10 ‡	0 (0%)	0 (0%)	0 (0%)	1 ‡
Clean contaminated surgical wound (%)	144 (73.5%)	96 (69.1%)	240 (71.6%)		45 (71.4%)	42 (70%)	87 (70.7%)	
Clean surgical wound (%)	50 (25.5%)	43 (30.9%)	93 (27.8%)		18 (28.6%)	18 (30%)	36 (29.3%)	
Surgical time (min) Median-IQR	135.5 [95–195]	148 [112–195)]	141 [105–195]	0.12 Ψ	150 [120–185]	150 [120–190]	150 [120–185]	0.07 Ψ
Anesthesia time (min) Median-IQR	180 [125–235]	190 [150–245]	185 [135–240]	0.02* Ψ	215 [160–235]	160 [160–258]	170 [160–238]	0.86 Ψ
Blood loss (ml) Median-IQR	300 [200–600]	350 [200–400]	350 [200–600]	0.62 Ψ	375 [200–625]	380 [250–400]	380 [200–600]	0.98 Ψ
Anesthesia induction								
Bupivacaine 0.5% Median-IQR	15 [0]	-	15 [0]	-	-	-	-	-
Lidocaine (mg) Median-IQR	80 [60–80]	80 [60–80]	80 [60–80]	0.76 Ψ	80 [60–80]	80 [60–80]	80 [60–80]	0.78 Ψ
propofol (mg) Median-IQR	100 [80–100]	100 [80–100]	100 [80–100]	0.34 Ψ	90 [80–100]	100 [80–100]	100 [80–100]	0.055 Ψ
Ketamine (mg) Median-IQR	20 [15–30]	20 [15–25]	20 [15–25]	0.16 Ψ	20 [15-27.5]	20 [15–25]	20 [15–25]	0.13 Ψ
Fentanyl (mg) Median-IQR	200 [150–200]	-	200 [150–200]	-	150 [150–200]	-	150 [150–200]	-
Rocuronium (mg) Median-IQR	50 [45–70]	50 [50–70]	50 [50–70]	< 0.0001* Ψ	50 [50–70]	60 [50–70]	50 [50–70]	0.051 Ψ
Anesthesia maintenance								
Sevoflurane (MAC) Median-IQR	0.6 [0.5-0. 7]	0.6 [0.5-1]	0.6 [0.5–0.8]	0.58 Ψ	0.6 [0.5-1]	0.6 [0.5–1.15]	0.6 [0.5–1.12]	0.15 Ψ
Dexmedetomidine (mcg/kg/hour) Median-IQR	0.5 [0.4–0.7]	0.4 [0.3–0.55]	0.4 [0.3–0.55]	0.16Ψ	0.4 [0.3–0.4]	0.4 [0.3–0.6]	0.4 [0.3–0.6]	0.86 Ψ
Ketamine (mg/kg/hour) Median-IQR	0.3 [0]	0.2 [0.15–0.36]	0.2 [0.15–0.36]	0.44 Ψ	0.3 [0.3–0.3]	0.2 [0.15–0.35]	0.2 [0.15–0.35]	0.43 Ψ
Lidocaine (mg/kg/hour) Median-IQR	1 [1–2]	1 [0]	1 [0]	< 0,0001* Ψ	1 [1–2]	1 [0]	1 [0]	< 0,0001* Ψ
Fentanyl (mcg/kg/hour) Median-IQR	2 [2–3]	-	2 [2–3]	-	5 [2–5]	-	5 [2–5]	-
Remifentanil (mcg/kg/min) Median-IQR	0.2 [0]	-	0.2 [0]	-	0.2 [0]	-	0.2 [0]	-

* Statistically significant ($p < 0.05$)

† Calculated by $\chi 2$ test

‡ Calculated by Fisher's exact test

Ψ Calculated by Mann-Whitney U test

IQR: interquartile range

upon discharge from the hospital ($p > 0.05$). For the adjusted cohort, different results were obtained. Only at discharge from recovery room time differences were detected ($p < 0.001$), as VAPS category < = 3 for OFA was 45 (71%) and VAPS category 4–7 was 18 (29%). Meanwhile VAPS category < = 3 for OBA was 60 (95%) and VAPS category 4–7 was 3 (5%). No other time presented statical significant differences for VAPS category between OFA and OBA in the adjusted cohort. Results for both the unadjusted and adjusted cohort analyses are illustrated in Fig. 2.

Hemodynamic variables and postoperative complications by anesthesia regimen and time

In the unadjusted cohort, the hemodynamic variables pre surgery there were significant differences for HR, RR and SaO2. For 30 min after anesthetic induction, only HR and RR were statically significant, but not for the rest of the hemodynamic variables. At admission to the recovery room, only Sa02 presented statically significant differences, Finally, at discharge from the recovery room, HR and MAP were statically significant. Different results were obtained for the adjusted cohort as HR was statically different between OFA and OBA for 30 min after

Table 3 Postoperative pain management by anesthesia regimen: OBA vs. OFA

Analgesic features								
	OBA	**OFA**	**Total**	***p***	**OBA**	**OFA**	**Total**	***p***
Admission to recovery room								
Epidural Catheter (%)	152 (77.6%)	137 (98.6%)	289 (86.2%)	< 0.001* †	53 (88.3%)	63 (100%)	116 (94.3%)	< 0.001* †
no analgesic rescue (%)	193 (98.5%)	116 (83.5%)	309 (92.2%)	< 0.001* †	60 (100%)	53 (84.1%)	113 (91.9%)	< 0.001* †
one analgesic rescue (%)	3 (1.5%)	15 (10.8%)	18 (5.4%)		0 (0%)	6 (9.5%)	6 (4.9%)	
Two analgesic rescue (%)	0 (0%)	6 (4.3%)	6 (1.8%)		0 (0%)	3 (4.8%)	3 (2.4%)	
three analgesic rescue (%)	0 (0%)	2 (1.4%)	2 (0.6)		0 (0%)	1 (1.6%)	1 (0.8%)	
Epidural Morphine (mg) Median-IQR	2 [0]	-	2 [0]	-	2 [0]	-	2 [0]	-
Ketamine infusion (mg/kg/hour) Median-IQR	-	2 [0]	2 [0]	-	-	2 [0]	2 [0]	-
Discharge from recovery room								
Bupivacaine Infusion (ml/hour) Median-IQR	4 [4–6]	6 [0]	6 [0]	0.0006* Ψ	6 [5–6]	-	6 [5–6]	-
Dipyrone (gr) Median-IQR	2 [1–2]	2 [0]	2 [0]	0.8 Ψ	2 [1.75-2]	2 [0]	2 [0]	< 0.001* Ψ
Morphine (mg) Median-IQR	2 [0]	2 [2–3]	2 [2–3]	0.54 Ψ	-	2.5 [0]	2.5 [0]	-
Ketamine infusion (mg/kg/hour) Median-IQR	-	0.2 [0]	0.2 [0]	-	-	0.2 [0]	0.2 [0]	-

* Statistically significant ($p < 0.05$)

† Calculated by χ2 test

‡ Calculated by Fisher's exact test

Ψ Calculated by Mann-Whitney U test

IQR: interquartile range

anesthetic induction, at admission to recovery room and at discharge fro gynecologic oncologic surgery gynecologic oncologic surgery m recovery room. Only MAP at discharge from recovery room and SaO2 at admission to the recovery room have difference between OFA and OBA in the adjusted cohort. Results for both the unadjusted and adjusted cohort analysis are illustrated in Fig. 3.

In the unadjusted cohort, except for antiemetic requirement all postoperative complications present percentages below 10% between anesthesia regimen in all 4 times evaluated and no patient present delirium at any time. In many cases, due to the absence of any complication, it was not possible to evaluate possible differences. Only antiemetic requirement at 5 days post-surgery evidenced significantly higher prevalence for OFA, and hypotension with greater prevalence for OBA at 24-hour post-surgery. Similar percentages for postoperative complications in the adjusted cohort were obtained and the antiemetic requirement at discharge from recovery room was the only statically significant difference observed. Results for both the unadjusted and adjusted cohort for post-operative complications are presented in Fig. 4.

Multivariable VAPS model

Due to only observing statistical significance at discharge from recovery room in both adjusted and unadjusted cohort, no other time was evaluated in a logistic multivariate model for VAPS and anesthetic regime. OFA generates an incurrence odds of having VAPS category of > = 4 than OBA, the same goes to not having epidural catheter and prolonged times of anesthesia. No other variable selected has statical significance and results can be seen in Table 4. AIC for the model described was 281 which was the one with the lowest value.

Discussion

It was found in the present study that OFA has less pain control in gynecological surgery for cancer management that OBA in the unadjusted cohort. But, this results are not present in the adjusted cohort which controls for VAPS category's at pre-surgery times as for HR, MAP, RR and SaO2. These findings suggest that preoperative pain perception may influence the efficacy of the OFA regimen on the efficacy of the OFA regimen. This only applied in 6 of the seven times studies as in the moment of discharge from the recovery room, VAPS was greater in OFA than OBA. This can be corroborated given the multivariate analysis in which OFA has greater VAPS than OBA and only other variables such as epidural catheter and anesthesia time impact on the VAPS. Even so, Interpretation of the multivariate model should be cautious due to the limited sample size necessary for the recommended use of the AIC. It is then evident that the selection of OFA versus OBA should be based on the patient's perception of pain and is not necessarily a strategy that should be used in all patients. The same can be said for the results obtained in the hemodynamic variables, in which the unadjusted cohort presented lower values for the hemodynamic variables in OFA than OBA but in the adjusted cohort these differences disappeared except for MAP. This again indicates the little impact of OFA on hemodynamic variables over time. Finally, in both the adjusted and unadjusted cohorts there were no differences for most adverse events at

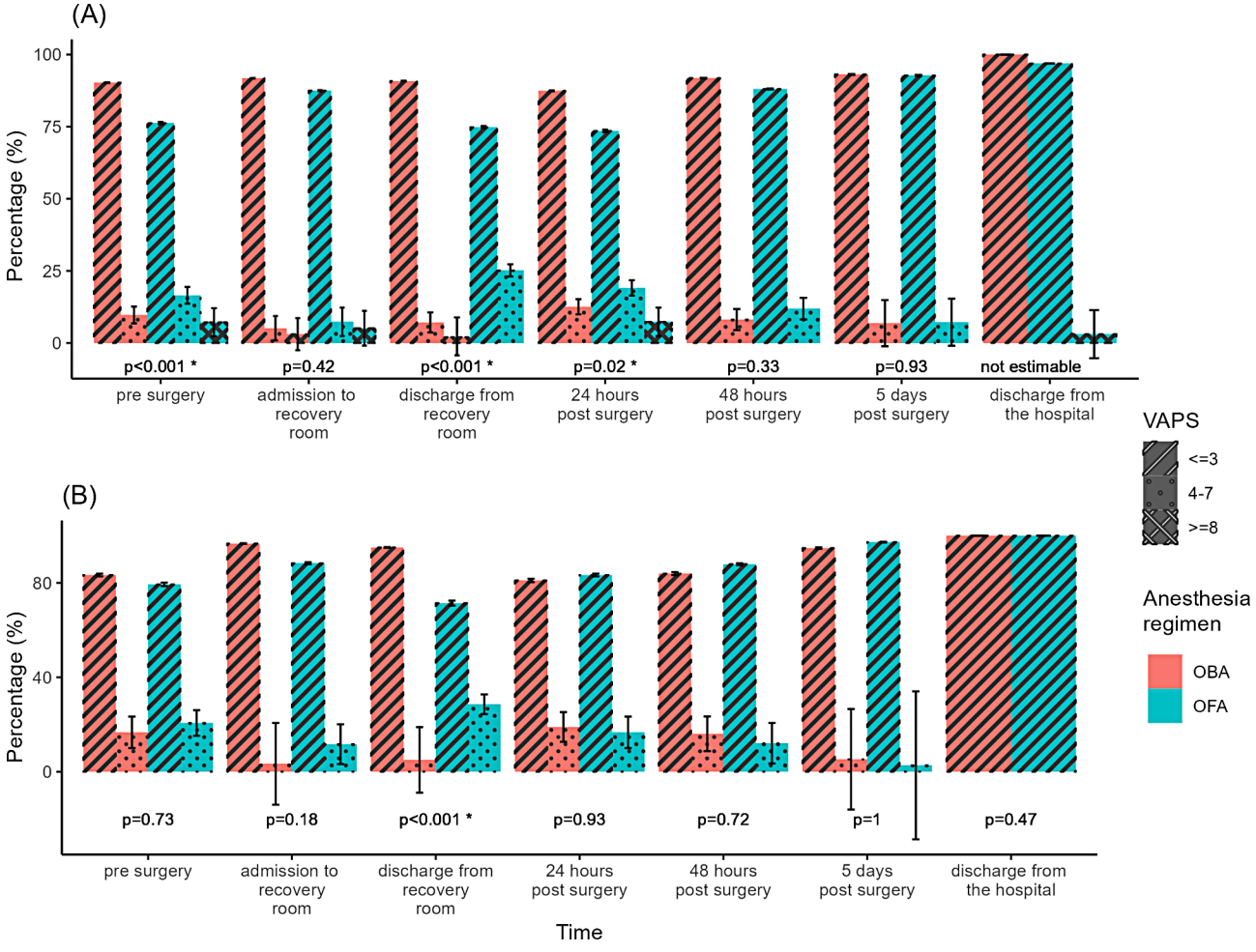

Fig. 2 Pain control over time by anesthesia regimen. X axes have 7 different times, while Y axes have percentage for the frequency of Visual Analogue Pain Score (VAPS) in which the score were categorized in <=3 points (stripe pattern), 4-7 points (circle pattern) and >=8 point (cross pattern). In the unadjusted cohort (**A**) it shows that only two times (pre surgery and discharge from recovery room) present statistically significant differences between OBA (Pink) vs OFA (Blue) in their frequency of stablished VAPS categories. OFA has greater frequency of VAPS between 4-7 than OBA at pre surgery and at discharge from recovery room. No other time presents statistically significant differences. In the adjusted cohort (**B**) only at discharge from recovery room OFA has greater 4-7 VAPS percentage than OBA and no other time has differences between OBA and OFA

most times, again demonstrating the lack of difference between OFA and OBA.

Since the introduction of intravenous synthetic opioids around the 1960s, the paradigm of balanced anesthesia with opioids has been established [13]. The OFA technique is a multimodal approach that avoids the use of systemic opioids by any route of administration. Instead, drugs with diverse mechanisms of action are used that act synergistically or additively to provide analgesia at different levels of the nociceptive process. Although current evidence on this technique is limited, since approximately 2005 both benefits and disadvantages have been documented in its application, especially in obese patients undergoing bariatric surgery and plastic surgery [14]. Its main advantage lies in the reduction of common adverse events associated with opioids, such as nausea, vomiting, respiratory depression, constipation, tolerance, secondary hyperalgesia, immunomodulation mediated by μ receptors, neurotoxicity, neuronal hypermetabolism and even dependence [15–17]. Currently, there is no specific protocol for the perioperative management of cancer patients, although the available evidence suggests that this technique may be beneficial in pathologies such as breast and colorectal cancer. In gynecologic oncologic surgery, the evidence is scarce, and some data suggests its application in laparoscopic gynecologic surgery. Although current oncologic treatments have improved survival, multiple side effects have been documented that affect the quality of life of patients, the prevalence of which varies according to the type of pharmacological treatment [18–20].

There are controversies regarding pain management in cancer patients using opioid-free techniques. Some

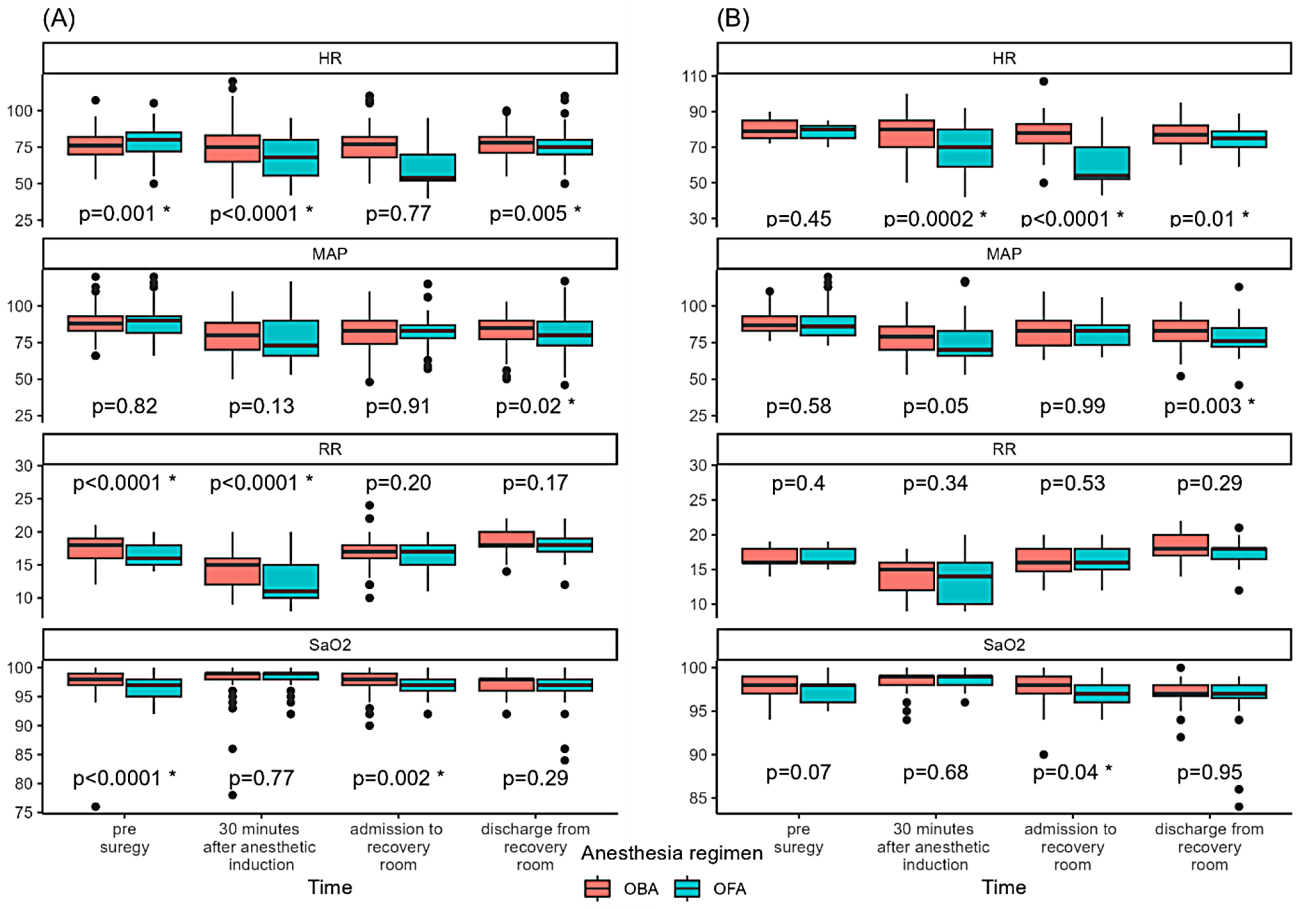

Fig. 3 Anesthesia regimen and hemodynamic variables. In the unadjusted cohort (**A**) Hear Rate (HR) was statically different between anesthesia regimen at pre surgery, 30 min after anesthesia induction and discharge from recovery room. The mean Arterial Pressure (MAP) has only differences at discharge from recovery room between OFA (Blue) and OBA (Pink). Respiratory Rate (RR) have differences in pre surgery and 30 min between OFA and OBA. Oxygen Saturation (SaO2) only have two important differences in pre surgery and at admission to recovery room between OFA and OBA. In the adjusted cohort (**B**) HR was always greater in OBA than OFA after pre surgery, while MAP only at discharge from recovery room and SaO2 at admission to recovery room where greater for OBA than OFA. * = statistically significant differences ($p < 0.05$)

studies question its efficacy, suggesting that it does not provide additional benefits [21]. Although no specific studies have been conducted in gynecologic oncologic surgery with opioid-free anesthesia, Lian Chen et al. evaluated the OFA technique versus OBA in patients undergoing laparoscopic gynecologic surgery under an ERAS protocol. They found that, although OFA was not inferior to the traditional technique in terms of reducing pain measured with VAPS, it cannot be considered an inferior technique [22].

The OFA technique has been shown to allow for a more satisfactory postoperative recovery. In a systematic review by Salomé et al., which included randomized controlled clinical trials comparing OFA with OBA, a reduction in the incidence of postoperative nausea and vomiting was observed, with high certainty in the evidence [23]. The same authors found no significant differences in the incidence of intraoperative tachycardia, bradycardia, hypertension and hypotension [23], different from those reported in the present study. Feenstra et al. confirmed that, although there were no differences in postoperative pain scores, the quality of recovery was better in the OFA group. Additional benefits of OFA have been reported, such as the reduction in the incidence of postoperative pain [24].

On the other hand, Beloeil et al. conducted a multicenter randomized clinical trial to evaluate the outcomes in the first 48 postoperative hours with a regimen of OFA with dexmedetomidine versus OBA with remifentanil. The results obtained showed the appearance of the composite primary outcome (postoperative hypoxemia, postoperative ileus and postoperative cognitive dysfunction) for the dexmedetomidine group in 122 of 156 (78%) patients and in 105 of 156 (67%) patients in the remifentanil group, concluding that there is a greater risk of adverse effects

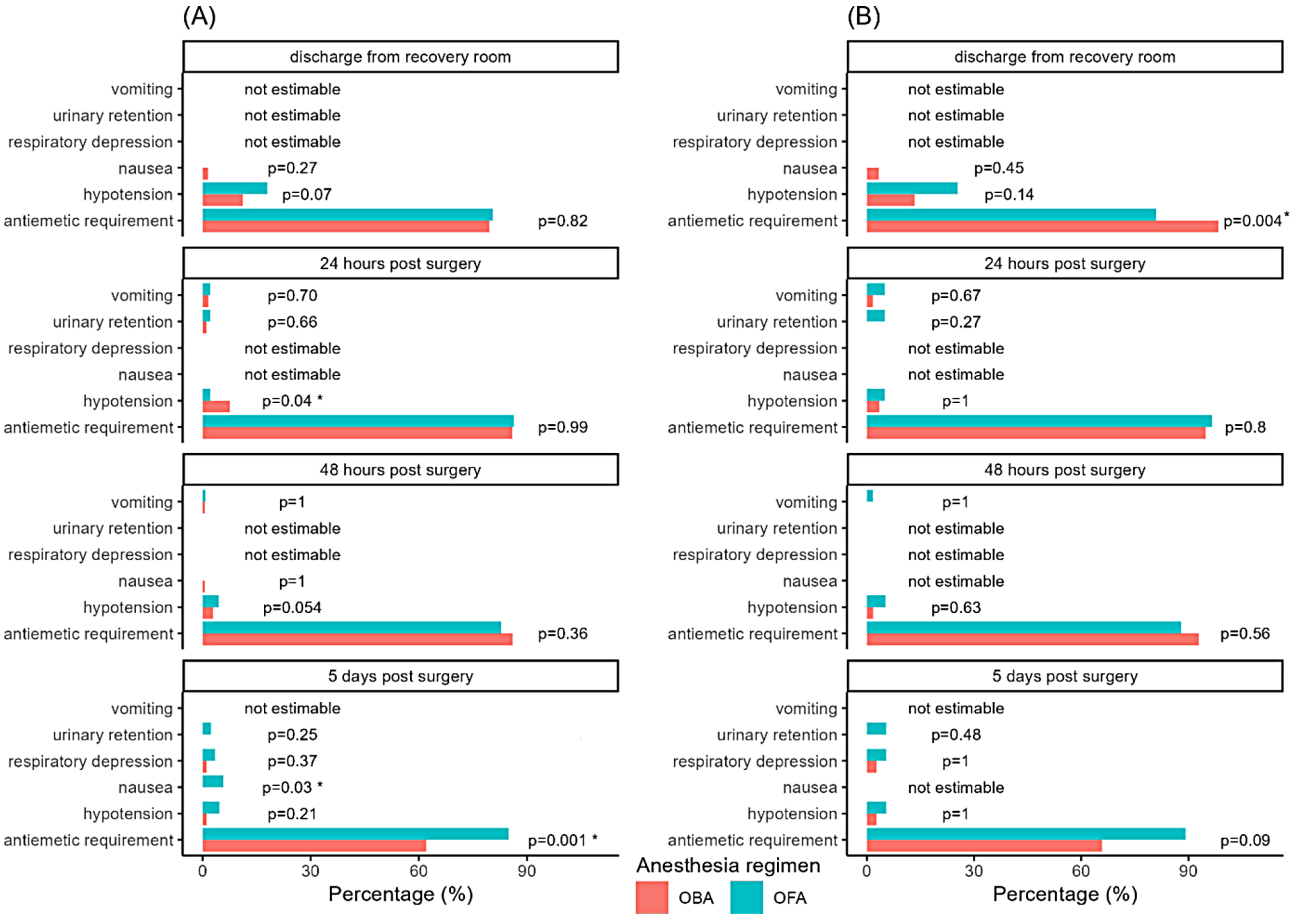

Fig. 4 Anesthesia regimen and Postoperative complications. In the unadjusted cohort (**A**) vomiting, urinary retention and respiratory depression frequency weren't different between anesthesia regimens. OFA (Blue) presents more nausea frequency than OBA (Pink) at 5 days post-surgery, while hypotension was more frequent on OBA than OFA at 24 h post-surgery. Differences for antiemetics requirements use frequency was detected only at 5 days post-surgery, with a greater use for OFA than OBA. In the adjusted cohort (**B**) OFA also has antiemetics requirements frequency at discharge from recovery room and at 5 days post-surgery and no other complications were different between OFA and OBA. * = statistically significant differences ($p < 0.05$)

when exposed to an OFA regimen with dexmedetomidine versus the opioid-based regimen with remifentanil [25].

Regarding complications and safety, our study confirms some problems related to hemodynamic compromise and anesthetic complications. Hypotension was identified as a main complication; Although not statistically significant, 64.8% of patients exposed to opioid-free anesthesia required vasopressor support during their stay in recovery rooms. Bradycardia was also observed with a lower mean in the OFA group, and being different from OBA when leaving the recovery rooms. In addition, antiemetics were noted to be required, which were administered prophylactically in both OBA and OFA patients. However, it was not possible to achieve adequate convergence in the regression models for the main outcomes related to complications (respiratory depression, urinary retention, hypotension, nausea/vomiting and delirium) at the evaluated times (admission to recovery room, 24 h, 48 hours and fifth day) due to the low frequency of these events.

Finally, opting for opioid-free anesthesia presents several challenges. One of the main ones is the appearance of unforeseen adverse effects that can arise from the analgesics used and from the possible interactions between anesthetics. Furthermore, the lack of studies conducted in more homogeneous populations, especially in oncological subgroups, and the lack of research with high methodological quality that evaluates chronic pain after opioid-free anesthesia and the quality of recovery are important limitations. Also, future studies comparing OFA versus OBA should include postoperative quality (Aldrete's scoring system).

Conclusion

The OFA technique for gynecologic oncologic surgery patients has a similar impact on pain control to OBA, with partial control upon discharge to recovery areas,

Table 4 Adjusted multivariable regression model for pain control at discharge from recovery room ($n=297$)

Variables	OR	IC 95%	*p*
Constant	0.047	0–1,540,387	0.79
anesthesia regimen	6.28	2.81–15.38	< 0.0001 *
Epidural Catheter	0.22	0.66–0.74	0.01 *
IMC	1.04	0.98–1.09	0.11
Surgery time (min)	1.01	0.99–1.02	0.24
Anesthesia time (min)	0.98	0.97–0.99	0.049 *
Previous use of analgesic	0.88	0.37–2.12	0.78
Mean Arterial Pressure at pre-surgery	0.98	0.94–1.02	0.23
Hear Rate pressure at pre-surgery	1.02	0.98–1.05	0.18
Respiratory Rate at pre-surgery	0.82	0.64–1.05	0.12
SaO2 pre-surgery	1.05	0.87–1.35	0.67
ASA	0.88	0.47–1.64	0.69
Pre surgery VAPS			
<= 3	1	-	-
4–7	0.56	0.21–1.33	0.21
Kind of gynecological cancer			
Endometrial	1	-	-
Cervical	1.96	0.52–7.25	0.30
Vulvar	0.01	0.01–8.033440	0.98
Ovarian	1.95	0.76–5.31	0.18
Body of uterus	1.52	0.26–7.26	0.61
Others	2.98	0.47–1.06	0.08

* Statistically significant ($p < 0.05$)

IC: Intervale of confidence

IMC: index of mass corporal

ASA: American Society of Anesthesiologists score

at 24 and 48 h; often requiring rescue interventions with potent opioids, therefore it is a partially effective technique in terms of pain control for this group of patients. Regarding complications, hemodynamic compromise such as hypotension and bradycardia presented in this type of patients must be evaluated given their clinical condition and some of them under comorbid conditions, in addition to the evaluation of length of stay in recovery rooms and hospital stays to provide patient-focused care with application to ERAS® protocols. These outcomes are confirmed in other populations that undergo OFA. More studies are required with adequate methodologies and statistical weight that allow reaching a definitive conclusion.

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Design: Jose Alexander Puentes Garcia, Daniel Rivera Tocancipa, Eugenio Medina. Performed the literature review: Alexander Puentes Garcia, Daniel Rivera Tocancipa, Eugenio Medina. Acquisition of data: Jose Alexander Puentes Garcia, Julián Jovel Díaz, Francisco Javier Quinayas Pisso, Vincent Jean Carlo García Gil. Interpretation of data: Jose Alexander Puentes Garcia, Fredy Leonardo Carreño Hernandez. Writing the manuscript: Jose Alexander Puentes Garcia, Fredy Leonardo Carreño Hernandez.

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Data availability
Data is provided within the Related files as "Base de datos de anestesia y opioides en cirugia Gineco-Oncologica_final".

Declarations

Human ethics and consent to participate declarations
The approval by the medical ethics committee of the Hernando Moncaleano Perdomo University Hospital, which was our Institutional Review Board (IRB) was submitted on December 14, 2023, which was approved by approval act No. 12 – 07. Our study consists of reviewing medical records for data collection and statistical analysis. The IRB did not consider the need for new consent for the data used from these patients and was deemed unnecessary according to national regulations (resolucion 8430 de 1993 del congreso de la nacion). Instead, consent for medical record management that is requested from all those who enter the institution is sufficient. Therefore, an informed consent waiver was used, and the data used in this study were anonymized before use.

Consent for publication
Does not apply.

Clinical trial number
Does not apply.

Competing interests
The authors declare no competing interests.

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