Randomized Controlled Trial

Effects of Intravenous Dexmedetomidine Versus Lidocaine on Postoperative Pain, Analgesic Consumption and Functional Recovery After Abdominal Gynecological Surgery: A Randomized Placebo-controlled Double Blind Study

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Background: The management of acute postoperative pain remains challenging, and the search for adjuvants to reduce opioid use continues.

Objectives: We studied the effect of intravenous dexmedetomidine and lidocaine on postoperative pain, opioid consumption, and functional recovery.

Study Design: A randomized controlled trial was performed.

Setting: The trial was conducted at Aretaieio University Hospital, Athens, Greece.

Methods: In this double-blind study, 91 women, 30–70 years old, with an American Society of Anesthesiologists Physical Status of I or II, scheduled for abdominal hysterectomy or myomectomy, were randomized to receive either dexmedetomidine (DEX group), lidocaine (LIDO group), or placebo (CONTROL group). Before anesthesia induction, a loading intravenous dose of one of the aforementioned drugs was given to all patients (0.9mL/kg/h for 10 minutes), followed by 0.15mL/kg/h infusion until the last suture. Identical 50 mL syringes containing dexmedetomidine 4 mg/mL (bolus: 0.6 μg/kg, infusion: 0.6 μg/kg/h), or lidocaine 10 mg/mL (bolus: 1.5 mg/kg, infusion: 1.5 mg/kg/ h), or NaCl 0.9% were used. The main outcomes were cumulative morphine consumption and postoperative pain at rest and cough (Numeric Rating Scale, [NRS]: 0-10). Other measurements included anesthetic (sevoflurane) consumption, nausea/vomiting, postoperative sedation, time to first passage of flatus/stool, mobilization, sleep quality, satisfaction, discharge time, and drug side effects. Measurements were performed at Post-anesthesia Care Unit (PACU), 2 hours, 4 hours, 8 hours, 24 hours, and 48 hours.

Results: Data from 81 patients were analyzed (DEX group:26, LIDO group:29, CONTROL group:26). Cumulative morphine consumption (mg) was significantly lower in the LIDO group versus the CONTROL group in the PACU (LIDO group: 8.41 ± 1.45, CONTROL group: 10.4 ± 3.29, $P = 0.017$); at 24 hours (LIDO group: 16.86 ± 5.85, CONTROL group: 23.4 ± 9.54, $P = 0.036$); and 48 hours (LIDO group: 20.45 ± 6.58, CONTROL group: 28.87 ± 12.55, $P = 0.022$). The DEX group experienced significantly less nausea compared to the CONTROL group in the PACU ($P = 0.041$). Finally, the use of vasoconstrictors was higher in the treatment groups, especially in the DEX group compared to the CONTROL group ($P = 0.012$). The rest of the measurements regarding NRS scores, sevoflurane consumption, bowel function, and other recovery characteristics, satisfaction, discharge time, and drug side effects did not differ significantly among the groups.

Limitations: Different doses of the studied medications were not assessed, drugs were administered only pre- and intraoperatively, and pain was not managed according to the World Health Organization (WHO) pain relief ladder. However, all patients were adequately covered with patient-controlled anesthesia morphine and acetaminophen; parecoxib (not approved for use in the United States) was preserved as a rescue analgesic.

Conclusions: Dexmedetomidine and lidocaine could be useful adjuvants for analgesia after abdominal surgery. Lidocaine significantly reduced postoperative opioid consumption, while dexmedetomidine prevented early postoperative nausea. However, hypotension and the need

for vasopressors was common with both agents, especially with dexmedetomidine.

Key words: Dexmedetomidine, lidocaine, postoperative pain, opioid consumption, recovery, bowel function, gynecological surgery

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Postoperative pain control continues to remain suboptimal, despite multimodal analgesia regimes, minimally invasive surgical techniques, and enhanced recovery programs. Acute postoperative pain hinders patients' functional recovery and represents one of the greatest predictive factors for transition to chronic postsurgical pain (1).

In a recent large cohort study, although multimodal analgesia was used in 86% of patients, almost all patients received an opioid for postoperative pain (2). It is well known that high doses of opioids are associated with various unwanted effects, such as respiratory depression, sedation, postoperative nausea and vomiting (PONV), pruritus, urinary retention, constipation and ileus (3), hyperalgesia, and allodynia (4,5). All these may impair patients' functional recovery, prolong hospital stay, increase health care costs (3), and may lead to inadequate postoperative pain control (6,7) and transition to chronic pain (8,9). Hence, there remains a need for trialling adjuvant therapies that could reduce the perioperative use of opioids (10-12).

Among adjuvants, dexmedetomidine, a highly selective α^2 adrenoreceptor agonist, and lidocaine, a well established local anesthetic, seem promising for this purpose. Dexmedetomidine has shown positive effects on postoperative pain intensity, opioid consumption and other recovery parameters, such as PONV, speed of recovery, and bowel function restoration (13), while lidocaine may reduce postoperative pain and duration of hospitalization (14,15).

Several trials have demonstrated that dexmedetomidine affects the function of the central nervous, cardiovascular, and respiratory systems, producing sympatholytic, sedative and opioid-sparing effects (16-21). Hypotension and bradycardia represent its main side effects, and are mostly dose dependent (22,23). Dexmedetomidine is given as an intravenous (IV) loading dose of 0.5-1 μg/kg over 10 minutes, followed by an infusion of 0.2–0.7 μg/kg/h (24).

Lidocaine has exhibited an excellent safety profile when administered as a low-dose infusion (15,25-27), for cancer or non-cancer chronic pain (28,29). Its effects are mediated via a variety of mechanisms, such as sodium channel blockade (14), inhibition of G protein (27) and N-methyl-D-aspartate receptors (30). Possible side effects include lightheadedness, somnolence, nausea, headache, perioral numbness, dry mouth, metallic taste and dysarthria, cardiac arrhythmias, and hemodynamic instability (31). In patients undergoing open abdominal surgeries, lidocaine is given as a bolus IV dose of 1.5–2 mg/kg prior to induction/incision, followed by an infusion of 1.5–3 mg/kg/h (25,26,32-36).

The existing literature on the effects of IV dexmedetomidine versus lidocaine on postoperative pain, analgesic consumption, and functional recovery is limited (37,38). The aim of the present study was to assess the effect of dexmedetomidine and lidocaine on postoperative pain and analgesic consumption, as well as on important functional recovery characteristics, such as bowel function, mobilization, sleep quality, and other parameters (i.e., PONV, sedation) in patients undergoing abdominal hysterectomy or myomectomy.

Methods

This randomized, double blind, placebo control, 3-arm trial was conducted at Aretaieio University Hospital, Athens, Greece, after receiving ethical approval by the Institutional Review Board (Protocol ID:EE-2/04/31-01-2017, Chairman Dr I. Vassileiou). It was registered on ClinicalTrials.gov (ID: NCT03363425) and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The CONSORT Guidelines for reporting randomized controlled trials were followed (Fig. 1).

From June 2017 through January 2020, 136 women, with an American Society of Anesthesiologists Physical Status of I or II, aged between 30 and 70 years, scheduled for abdominal hysterectomy or myomectomy, were assessed for eligibility to participate. Exclusion criteria were a patient's refusal or contraindication to the use of local anesthetics, Body Mass Index > 35 kg/m^2, cardiovascular disease, significant renal/hepatic impairment, insulin-dependent diabetes mellitus, central nervous system or psychiatric disease, chronic use of opioids/steroids/clonidine/other α^2 agonist/analgesics or any drugs acting on the central nervous system during the previous 2 weeks, drug/alcohol abuse,

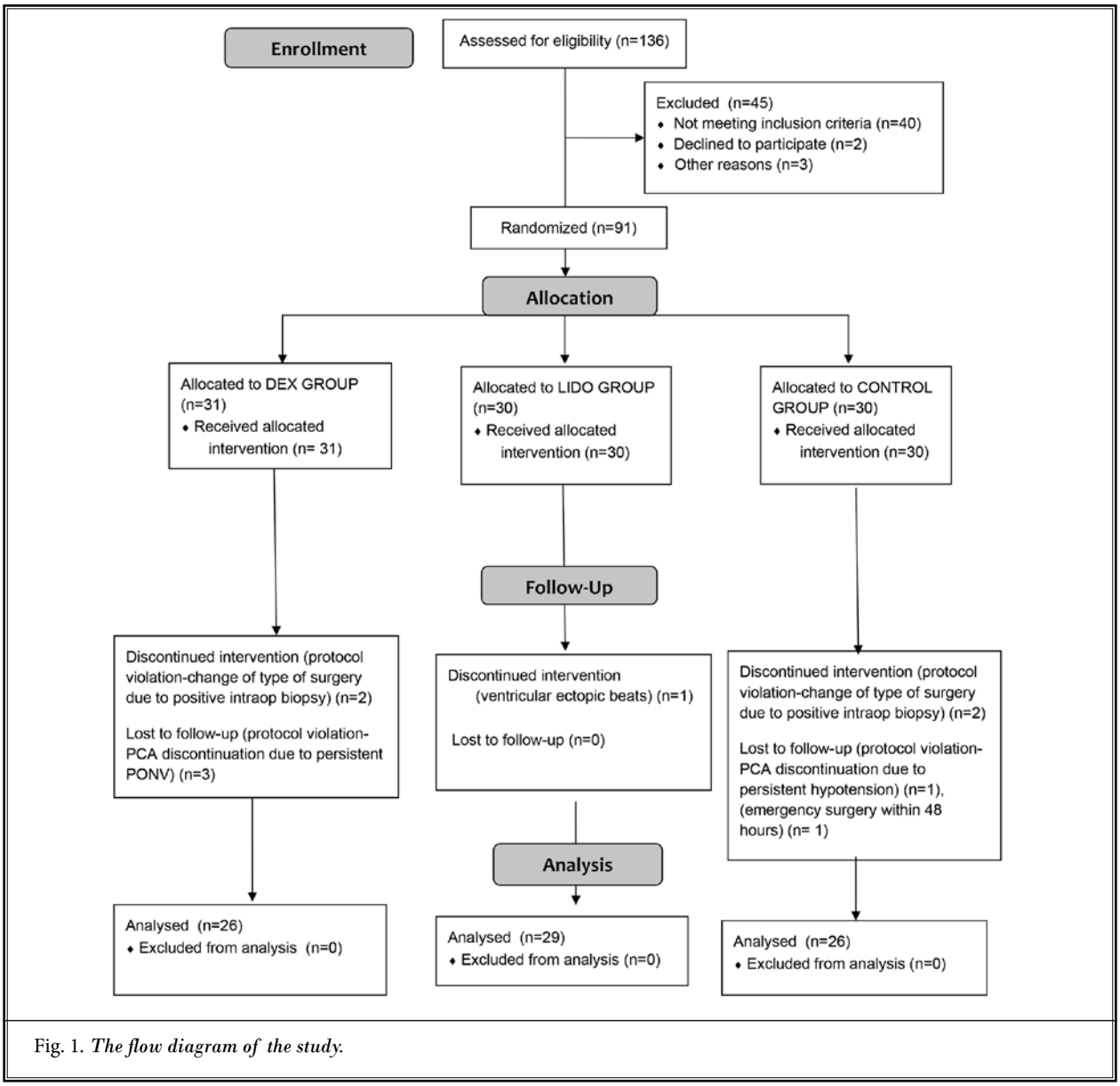

Fig. 1. *The flow diagram of the study.*

language/communication barrier or inability to comprehend the pain assessment scale and/or the use of a patient-controlled analgesia (PCA) pump.

All patients included in the trial signed a written informed consent. Eligible patients were randomly allocated to one of the 3 study groups, according to the administered solution: dexmedetomidine (DEX), lidocaine (LIDO) or sodium chloride (NaCl) 0.9% (CONTROL). A computer generated list (https://www.randomizer.org) was used for randomization. An independent nurse who did not further participate in the study prepared the solutions and syringes according to group allocation. Identical 50 mL syringes were prepared for infusion by an automatic pump. The solution volumes, appearance and infusion rates were the same in all groups, thus the intervention was masked to the investigators, patients, and personnel. Postoperative outcomes were assessed by a researcher who remained blinded throughout the study. The surgical team included 4 senior surgeons with at least 15 years of experience.

The prefilled 50 mL syringes contained either dexmedetomidine 4 μg/mL or lidocaine 10 mg/mL or NaCl 0.9%. Ten minutes before anesthesia induction all patients received an IV infusion at a rate of 0.9mL/kg/h for

10 minutes. This rate corresponded to 0.6 μg/kg dexmedetomidine or 1.5 mg/kg lidocaine. Afterwards, all patients received an infusion at a rate of 0.15mL/kg/h until the final stitch; this rate corresponded to 1.5 mg/kg/h of lidocaine or 0.6 μg/kg/h of dexmedetomidine.

Premedication was omitted and anesthesia was standardized for all patients. Routine monitoring was applied, including electrocardiogram, noninvasive blood pressure measurement, and pulse oximeter (S/5 Anesthesia Monitor, Datex-Ohmeda, Helsinki, Finland). A BIS™ sensor was attached to the patient's forehead and connected to a Bispectral Index monitor (BIS Complete Monitoring System, Covidien LLC, Mansfield, MA). Ranitidine 50 mg (no longer approved for use in the US) and metoclopramide 10 mg IV were given before induction. Fentanyl 2 μg/kg and propofol 2–2.5 mg/kg IV were used for anesthesia induction, while tracheal intubation was facilitated with rocuronium 1 mg/kg. Mechanical ventilation was applied, with the parameters adjusted to maintain normocarbia (end-tidal CO_2 35–40 mmHg). Sevoflurane concentration in an oxygen/air mixture (FiO2: 0.4, total gas flow: 2 L/min) was titrated to maintain BIS values between 40-50. Intraoperative analgesia was supplemented with additional fentanyl 3 μg/kg in divided doses (total dose was 5 μg/kg). Intermittent extra IV boluses of rocuronium 10 mg were given for maintenance of neuromuscular blockade (Train of Four between 1-2). Neuromuscular transmission (NMT) monitoring was performed via the NMT-module of the S/5Anesthesia Monitor. Thirty minutes before the end of the surgery, IV morphine 0.1 mg/kg, acetaminophen 1 g, parecoxib 40 mg and ondansetron 4 mg were administered. Sevoflurane was discontinued at final stitch. The neuromuscular block was reversed with sugammadex. All monitored parameters were recorded every 5 minutes until the patient's transfer to the Postanesthesia Care Unit (PACU). The amount of sevoflurane consumed was measured by weighing the vaporizer using an electronic scale before and after the surgical procedure.

Atropine 0.6 mg was administered in case of bradycardia (heart rate [HR] < 60beats/min) associated with hypotension (systolic blood pressure ≤ 90 mmHg) or ventricular ectopic beats; or in case of HR ≤ 40 beats/min regardless of the blood pressure. In case of hypotension not associated with bradycardia, IV boluses of ephedrine 5 mg or phenylephrine 50 μg were administered until blood pressure restoration.

In the PACU, patients received IV increments of morphine one mg until their pain was ≤ 3 on the numerical rating scale (NRS) where 0 = no pain to 10 = intractable pain. The cumulative morphine administered in the PACU was added to the total morphine consumed during the first 2 hours postoperatively via the PCA pump. All patients had access to a PCA pump to receive boluses of morphine 1 mg with a 10 minute lock-out interval. Patients also received acetaminophen 1 g every 8 hours and metoclopramide 10 mg twice daily. Rescue analgesia consisted of parecoxib 40 mg and rescue antiemetic of ondansetron 4 mg. All patients were instructed preoperatively how to use the PCA pump and how to score their pain on the NRS scale. The use of the PCA pump was strictly limited to the patient.

Cumulative morphine consumption (mg) and NRS scores at rest and after cough were measured in the PACU at 2 hours, 4 hours, 8 hours, 24 hours, and 48 hours postoperatively. The primary endpoint of the study was cumulative morphine consumption and pain scores at 24 hours. Secondary outcomes were: cumulative morphine consumption and pain scores at the PACU, 2 hours, 4 hours, 8 hours, and 48 hours; patient's subjective sedation feeling (0-10 scale); nausea (0-10 scale); sevoflurane consumption (grams); time (hours after extubation) to first passage of flatus/stool (patients were instructed to document the exact time, while the investigators and nurses also regularly asked them); time of getting up from bed (hours after extubation); sleep quality (0-10 scale); as well as patient satisfaction (0-10 scale) at 24 hours and 48 hours; discharge time; need for rescue analgesia and rescue antiemetic. Any drug side effects and complications associated with the interventions were also recorded: e.g., bradycardia, hypotension, arrhythmias, conduction disturbances, delirium, and signs of local anesthetic systemic toxicity.

Statistical Analysis

The sample size was calculated after the recruitment of 50 patients (DEX: 16, LIDO: 17, CONTROL: 17), by analyzing the data of 44 (4 dropouts in the DEX group and 2 dropouts in the CONTROL group). The study was powered for a reduction of 20% in NRS at rest at 24 hours postoperatively. It was estimated that approximately 26 patients were needed per group in order to achieve a statistical power of 0.80. To compensate for possible future drop out of patients, a total number of at least 30 patients per group was planned.

Statistical analysis was performed with the SPSS v.23 software (IBM Corporation, Armonk, NY). Means and standard deviations were used to describe scale demographics (age, weight, and height), as well as

NRS scores, sedation, and morphine consumption. Categorical variables were presented as frequencies and percentages. Univariate analysis included the Pearson χ^2 test to examine associations between categorical variables, while an Analysis of Variance (ANOVA) followed by multiple comparisons under the Bonferroni criterion was applied to examine differences in all scale measurements in group categories or other categorical variables. The differences between groups at all times were examined using repeated measures analysis for each outcome. Statistical significance was set at 0.05. Microsoft Word and Excel (Microsoft Corp., Redmond, WA) were used to generate graphs and tables.

Results

Data from 81 women were analyzed. Patients' demographic and operative characteristics did not differ among the groups (Table 1). The difference in cumulative morphine consumption was statistically significant between the LIDO and CONTROL groups in the PACU, at 24 hours and at 48 hours (Table 2). The NRS at rest and NRS cough scores did not differ significantly among the 3 groups at any time point (Table 3).

Nausea scores showed a statistically significant difference ($P = 0.04$) between the DEX and CONTROL groups in the PACU (0.08 ± 0.39 versus 1.58 ± 3.36, respectively), while no difference was found between the DEX and LIDO groups at any time point. The use of rescue antiemetic did not differ significantly among the 3 groups at any time point. Throughout the 48 hour period, rescue antiemetic use was in 23.1% of the DEX group, 13.8% of the LIDO group, and 15.4% of the CONTROL group ($P = 0.63$). Similarly, rescue analgesia did not differ; throughout the 48 hours rescue analgesic was used in 23.1% of the DEX group, 27.6% of the LIDO group, and 11.5% of the CONTROL group ($P = 0.328$).

ANOVA showed no statistically significant differences among the 3 groups with regards to total sevoflurane consumption (g) and rate of sevoflurane consumption (g/min). The values of the test were $F_{2.78} = 0.10$ and $F_{2.78} = 0.09$, respectively. Times to pass/flatus, stool and time to first mobilization did not differ across the groups. The values derived by the ANOVA F-test were $F_{2.78} = 0.56$, $F_{2.78} = 0.29$ and $F_{2.78} = 0.31$, respectively, with all P values > 0.5. No statistically significant differences were found among the 3 groups with regards to

Table 1. *Patient and operative characteristics of the studied groups (DEX group: dexmedetomidine, LIDO group: lidocaine, CONTROL group: normal saline). BMI: Body Mass Index*

Group (n = No. of patients)	DEX (n = 26)	LIDO (n = 29)	CONTROL (n = 26)	*P* value
Age (years) (mean ± SD)	45.15 ± 7.24	47.79 ± 10.40	49.77 ± 10.13	$P = 0.21$
Height (cm) (mean ± SD)	164.27 ± 6.06	163.34 ± 6.39	163.31 ± 5.48	$P = 0.805$
Weight (kg) (mean ± SD)	66.35 ± 10.19	66.59 ± 8.10	69.46 ± 9.80	$P = 0.409$
BMI (mean ± SD)	24.56 ± 3.40	24.99 ± 3.053	26.09 ± 3.82	$P = 0.258$
Surgery Duration (min) (mean ± SD)	112.35 ± 32.47	115.28 ± 46.92	120.23 ± 37.09	$P = 0.769$
Type of surgery (myomectomy: hysterectomy)	14:12	15:14	13:13	$P = 0.962$

Values are expressed as mean ± standard deviation (SD). * Statistical significance (*P* value < 0.05).

Table 2. *Morphine consumption in the 3 study groups (DEXgroup: dexmedetomidine, LIDOgroup: lidocaine, CONTROL group: normal saline) at all measurement time points (PACU, 2h, 4h, 8h, 24h, and 48h). PACU: Postanesthesia care unit.*

	DEX mean ± SD	LIDO mean ± SD	CONTROL mean ± SD	*P* value (DEX-CONTROL)	*P* value (LIDO-CONTROL)	*P* value (DEX-LIDO)
PACU Morphine (mg)	9.02 ± 2.78	8.41 ± 1.45	10.40 ± 3.30	0.16	0.017*	0.77
2h Morphine (mg)	10.98 ± 3.79	10.93 ± 3.03	13.21 ± 4.45	0.11	0.08	1.0
4h Morphine (mg)	13.6 ± 6.79	12.66 ± 3.98	15.17 ± 5.27	0.65	0.24	0.89
8h Morphine (mg)	16.37 ± 9.87	14.31 ± 5.18	18.6 ± 7.96	0.67	0.13	0.70
24h Morphine (mg)	20.75 ± 12.21	16.86 ± 5.851	23.40 ± 9.54	0.68	0.036*	0.35
48h Morphine (mg)	25.02 ± 13.91	20.45 ± 6.58	28.87 ± 12.55	0.53	0.022*	0.36

Values are expressed as mean ± standard deviation (SD). * Statistical significance (*P* value < 0.05).

Table 3. *Pain intensity at rest and cough (NRS, numeric rating scale 0-10) in the 3 study groups (DEX group: dexmedetomidine, LIDO group: lidocaine, CONTROL group: Normal saline) at all measurement time points (PACU, 2h, 4h, 8h, 24h, and 48h). PACU: Postanesthesia care unit.*

	DEX Mean ± SD	LIDO Mean ± SD	CONTROL Mean ± SD	*P* value (DEX-CONTROL)	*P* value (LIDO-CONTROL)	*P* value (DEX-LIDO)
PACU - NRS rest	4.86 ± 3.05	5.60 ± 2.27	5.73 ± 2.62	0.76	1.0	0.96
2h NRS rest	4.69 ± 2.33	5.45 ± 2.81	5.08 ± 2.15	1.0	1.0	0.78
4h NRS rest	3.89 ± 2.25	4.20 ± 2.58	3.61 ± 2.33	1.0	1.0	1.0
8h NRS rest	3.15 ± 2.41	3.05 ± 2.36	2.73 ± 2.07	1.0	1.0	1.0
24h NRS rest	3.48 ± 2.35	2.86 ± 2.50	2.08 ± 1.60	0.07	0.57	0.9
48h NRS rest	2.15 ± 2.29	1.98 ± 1.90	1.39 ± 1.58	0.47	0.77	1.000
PACU - NRS cough	6.15 ± 3.21	6.72 ± 2.14	7.12 ± 2.18	0.53	1.0	1.0
2h NRS cough	6.50 ± 2.63	7.28 ± 2.30	7.08 ± 1.96	1.0	1.0	0.65
4h NRS cough	6.15 ± 2.78	6.17 ± 2.70	6.89 ± 2.32	0.95	0.95	1.0
8h NRS cough	6.04 ± 2.62	5.72 ± 2.79	5.77 ± 2.45	1.0	1.0	1.0
24h NRS cough	6.04 ± 2.62	6.00 ± 2.82	5.46 ± 2.44	1.0	1.0	1.0
48h NRS cough	4.19 ± 2.94	4.60 ± 2.62	4.35 ± 2.37	1.0	1.0	1.0

Values are expressed as mean ± standard deviation (SD). * Statistical significance (*P* value < 0.05).

sleep quality and satisfaction. According to the ANOVA implemented for satisfaction at 24 hours and 48 hours, the values of the test were $F_{2.78}$ = 1.529 (*P* = 0.22) and $F_{2.78}$ = 0.688 (*P* = 0.51), respectively. For sleep quality at 24 hours and 48 hours, the values of the test were $F_{2.78}$ = 0.23 (*P* = 0.77) and $F_{2.78}$ = 0.01 (*P* = 0.99), respectively. Finally, discharge time also did not differ significantly among groups. The value derived from the ANOVA F-test was $F_{2.78}$ = 0.20 and the *P* value was 0.82. The mean values obtained were substantially similar, and the total mean discharge time was 3.34 days (standard deviation: 1.41 days).

Regarding side effects, the highest incidence of hypotensive episodes was observed in the DEX group (13/26, 50%) compared to the LIDO group (11/29, 37.93%) and the CONTROL group (8/26, 30.76%), but was not statistically significant (*P* = 0.357) according to Pearson's χ^2 test. However, a significant difference was observed in the use of vasoactive agents in both the DEX and LIDO groups compared to the CONTROL group. Vasoactive agents were used in 14/26 patients in the DEXgroup (53.85%), in 12/29 patients (41.38%) in the LIDO group, and in only 5/26 patients (19.23%) in the CONTROL group (*P* = 0.034). Logistic regression showed that there was a statistically significant higher use of ephedrine/phenylephrine in the DEX group compared to the CONTROL group (*P* = 0.012), but not between the DEX and LIDO groups (*P* = 0.356) or between the LIDO and CONTROL groups (*P* = 0.082). The odds of using vasoactive agents were 4.9 times higher in the DEX group compared to the CONTROL group (odds ratio = 4.9, 95% confidence interval [CI] 1.413-16.988). Notably, although not statistically significant, there was also a clear trend towards higher use of vasoconstrictors in the LIDO group versus the CONTROL group. The highest incidence of bradycardic episodes was recorded in the DEX group (3/26, 11.54%), followed by LIDO (2/29, 6.90%) and CONTROL-group (1/26, 3.85%), without statistical significance (*P* = 0.566), even though the incidence was 3 times higher in the DEX group compared to the CONTROL group. Accordingly, no significant differences were detected among the groups in the use of atropine (*P* = 0.798). Finally, regarding postoperative sedation, the differences among the groups were statistically insignificant at all time points (*P* > 0.05).

Discussion

The important finding of our study was the superiority of lidocaine, in terms of exhibiting a significant morphine-sparing effect postoperatively. Dexmedetomidine, in the used dose, failed to decrease morphine consumption, but significantly reduced patients' nausea in the early postoperative period. We did not find a significant difference in postoperative pain among patients receiving dexmedetomidine or lidocaine or placebo, as NRS scores at both rest and cough were comparable at all times. This finding was somewhat expected, since all patients had access to morphine via a

PCA pump, and thus they could easily and promptly get adequate pain relief. A disadvantage of dexmedetomidine was the increased vasoconstrictor requirements to maintain normotension intraoperatively.

Previous research from Andjelković et al (38) compared the same drugs in laparoscopic intestinal resections (dexmedetomidine: 0.5 μg/kg/h, lidocaine: 1.5 mg/kg/h – without loading doses). Similar to our findings, lidocaine was found superior to placebo regarding total opioid consumption during the 2 postoperative days, but not superior in reducing pain intensity. Also, in accordance to our findings, none of the drugs improved bowel function. Neither dexmedetomidine nor lidocaine decreased intraoperative fentanyl consumption, but both significantly reduced propofol requirements for maintenance of BIS scores between 40-55 (38). We failed to demonstrate a sevoflurane sparing effect, possibly owing to differences regarding the pharmacological profile of propofol and sevoflurane and the different targeted BIS limits (we had a strict BIS range: 40-50). Another difference was that in that previous study (38), ephedrine or atropine was not required intraoperatively in any of the groups. Nevertheless, these investigators omitted the loading doses, which are more likely to cause hemodynamic changes, while they also used a lower dexmedetomidine dose (38).

In a study by Xu et al (37) the 2 agents and their combination were used in abdominal hysterectomies; lidocaine was administered at the same dose as in our study, while dexmedetomidine was used at a lower dose (0.5 μg/kg loading, 0.4 μg/kg/h infusion). Although the design of this study is closer to the design of ours, the results are inconsistent; these investigators found that both drugs reduced postoperative pain intensity and opioid (fentanyl) consumption, while their combination (dexmedetomidine plus lidocaine) potentiated and prolonged this analgesic effect to 24 hours and further reduced fentanyl requirements postoperatively. No significant difference was found between the 2 adjuvants, while the duration of their effect was rather short. Interestingly, the postoperative opioid-sparing effect of lidocaine did not exceed 4 hours, while our results showed a significantly longer effect, up to 48 hours. Another contrary finding from that study was that both drugs exhibited an intraoperative anesthetic/opioid sparing effect (37). However, their anesthetic protocol differed significantly from ours, since they used total intravenous anesthesia. Moreover, we used a standard dose of fentanyl and variation in individual analgesic needs was addressed with morphine boluses in the PACU. Finally, this study showed that lidocaine (either alone or combined with dexmedetomidine) accelerated bowel function, which we failed to demonstrate.

Previous studies have shown that dexmedetomidine might reduce postoperative pain (39,40) and analgesic requirements (39-43). We were unable to demonstrate similar findings in our study. These differences could be explained by the deeper anesthetic level (lower targeted BIS values) in other studies or prolonged administration of dexmedetomidine (up to 72 hours postoperatively) (39-41). One of our positive findings was that dexmedetomidine reduced PONV, in accordance with previous studies (43). However, in a meta-analysis of 12 randomized controlled trials (RCTs), results were inconclusive regarding such PONV reduction (42). Kim et al (44) reported sparing of sevoflurane as an advantage of this adjuvant in pediatric patients. In the study by Kim et al (44), the initial bolus dose was significantly higher than in our study (1 μg/kg), while sevoflurane consumption was estimated by the end-tidal sevoflurane concentration titrated to achieve a BIS score of 45-50 during surgery, rather than weighting the exact amount of sevoflurane consumed, as in our study.

Dexmedetomidine also improved patients' satisfaction in the study of Dong et al (41), where its infusion was continued during the postoperative period. We also failed to show any beneficial effect of dexmedetomidine on sleep quality and other parameters of postoperative functional recovery, such as restoration of bowel function and patient mobilization (42). Finally, regarding its side effects, the most commonly reported were hypotension (41,42) and bradycardia (43,44). Similarly, in our study the use of vasopressors in the DEXgroup was significantly increased, while the incidence of bradycardia was higher but not statistically significant. In agreement with a recent meta-analysis, no significant residual sedation was observed (42).

Regarding perioperative lidocaine infusion, a recent Cochrane review concluded that its impact on early postoperative pain and opioid consumption remains uncertain (45). However, a meta-analysis of 5 RCTs (46), and 2 individual studies (47,48), showed that lidocaine significantly reduced postoperative pain scores and opioid consumption up to 24 hours after laparoscopic cholecystectomy (46), subtotal gastrostomy (47), or laparoscopic inguinal hernioplasty (48). Our results are in accordance with the above regarding the

opioid sparing effect, but in our study this effect lasted longer (up to 48 hours), while the NRS pain scores were not significantly reduced at any time point. Possibly the invasiveness of surgery and the different levels of pain involved, along with the use of a morphine PCA, may account for the differences.

With regards to postoperative bowel function, lidocaine was found to be beneficial in patients undergoing hand-assisted laparoscopic colon surgery (49,50). However, the optimal dose and duration of infusion was not identified, while studies which continued the infusion after skin closure were also included. Staikou et al (51) found no benefit on bowel function after open large bowel surgery, as in the present study.

A recent study (52) involving pediatric patients undergoing major spinal surgery showed that lidocaine decreased sevoflurane consumption by 15%, as calculated by the end-tidal sevoflurane concentration, while sevoflurane concentration was adjusted according to hemodynamic and BIS values. The different age group and method of assessing sevoflurane consumption may explain why we did not find such an effect. Regarding our other findings (i.e., no effect on PONV, patient satisfaction, length of stay), previous results are equivocal. Ghimire et al (48) reported that lidocaine (1.5 mg/kg bolus, 2 mg/kg/h infusion) was associated with less PONV and higher patient satisfaction compared to control. However, in Yon et al's study (47), where the same doses of lidocaine were used, no significant differences were detected in PONV and patient satisfaction. A relatively recent Cochrane review concluded that there is still uncertainty regarding PONV and gastrointestinal recovery in patients receiving lidocaine (45).

Recent research suggests that both lidocaine and dexmedetomidine have significant anti-inflammatory effects, which could at least partly explain their analgesic activity. In vitro, dexmedetomidine was found to suppress the expression of inflammatory mediators such as cyclooxygenase-2, prostaglandin E2 and cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (53), while in an experiment of induced inflammatory pain in rats, lidocaine was associated with lower levels of TNF-α, IL-1β and IL-6 (54). Similarly, clinical trials have shown that both lidocaine (55) and dexmedetomidine (56,57) attenuate the perioperative secretion of inflammatory cytokines (ILs, TNF-α). Moreover, Xu et al (58) recently demonstrated that the combination of the 2 agents exerts a synergistic effect on supressing the postoperative inflammatory response (further reduced plasma levels of IL-1, IL-6, and TNF-α).

Our study has a number of limitations that should be considered. We did not assess different doses of the studied medications, therefore we cannot exclude that different doses might be more beneficial. Also, we administered the drugs only pre- and intraoperatively, because we were concerned about safety issues associated with prolonged infusion into the postoperative period. In this regard, we used doses that were reported in previous studies, taking into consideration both safety and efficacy. Another possible limitation is that we did not manage postoperative pain according to the WHO pain relief ladder; nevertheless, all patients were adequately covered with PCA morphine and regular doses of acetaminophen, while parecoxib was preserved as rescue analgesic in order to identify more accurately possible differences in postoperative analgesic requirements. Finally, although the sample size of our study was determined by a power analysis, further research with a larger number of patients is needed to confirm the usefulness of lidocaine and dexmedetomidine as analgesic adjuvants.

Conclusions

This study showed that both dexmedetomidine and lidocaine could be considered as useful adjuvants for abdominal non-malignant gynecological surgery. Lidocaine significantly reduced postoperative opioid consumption for up to 48 hours, while dexmedetomidine prevented PONV in the early postoperative period. Hypotension and the need for vasopressors was common, especially with dexmedetomidine, so careful patient selection is advisable when considering the use of these adjuvants. Further studies assessing different dosing regimens or simultaneous administration of both drugs in low doses would be useful to clarify their safety and efficacy.

Authorship

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with Ethics Guidelines

Approval was received from: The Institutional Review Board (IRB) of Aretaieio University Hospital, Athens, Greece on 31st of January 2017 (Protocol ID: EE-2/04/31-01-2017, Chairman Dr I, Vassileiou).

The trial was registered on ClinicalTrials.gov (ID: NCT03363425)

The trial was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

The CONSORT Guidelines for reporting randomized controlled trials were followed for the presentation of the study.

All the patients included in the trial signed a written informed consent for the study and publication, while no identifying information was included in the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Trial Registration

Ethical approval was provided by the Institutional Review Board (IRB) of Aretaieio University Hospital, Athens, Greece on January 31, 2017. (Protocol ID: EE-2/04/31-01-2017, Chairman Dr I, Vassileiou). The trial was registered with ClinicalTrials.gov (ID: NCT03363425).

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