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ORIGINAL RESEARCH

Perioperative Dexmedetomidine or Lidocaine Infusion for the Prevention of Chronic Postoperative and Neuropathic Pain After Gynecological Surgery: A Randomized, Placebo-Controlled, Double-Blind Study

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ABSTRACT

Introduction: The transition of acute to chronic postoperative pain (CPP) remains a significant burden to the rehabilitation of patients. The research for adjuvants to prevent CPP continues; among others, dexmedetomidine and lidocaine seem promising agents.

Methods: This is a long-term follow-up of a randomized, placebo-controlled, double-blind study on women who underwent open abdominal gynecological surgery and received dexmedetomidine or lidocaine or placebo infusion perioperatively ($n = 81$). The effect of these adjuvants on the development of CPP and neuropathic pain was assessed during a 12-month follow-up. Eighty-one (81) women ASA I–II, aged between 30 and 70 years, were randomly assigned to receive either dexmedetomidine (DEX group) or lidocaine (LIDO group) or placebo (CONTROL group) perioperatively. Before anesthesia induction, all patients received a loading intravenous dose of either 0.6 μg/kg dexmedetomidine or 1.5 mg/kg lidocaine or placebo, followed by 0.6 μg/kg/h dexmedetomidine or 1.5 mg/kg/h lidocaine or placebo until last suture. Patients were followed up to obtain the long-term outcomes at 3, 6, and 12 months. At these time-points, pain intensity was assessed with the Numerical Rating Scale, (NRS: 0–10) and the development of neuropathic elements with the Douleur Neuropathique 4 (DN4) score. Prognostic parameters that could affect chronic pain and its components were also identified.

Results: Data from 74 women were analyzed. Dexmedetomidine significantly reduced NRS scores comparing to placebo at 3 months ($p = 0.018$), while at 6 months, lidocaine was found superior to placebo ($p = 0.02$), but not to dexmedetomidine, in preventing neuropathic pain (DN4 < 4). Regarding secondary endpoints, higher NRS cough scores at 48 h were associated with statistically significant NRS and DN4 scores at 3, 6, and 12 months ($p < 0.02$). At 6 months, a statistically significant correlation was also found between higher NRS values and older age ($p = 0.020$).

Conclusions: Dexmedetomidine was superior to placebo regarding the duration and severity

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of CPP, while lidocaine exhibited a protective effect against neuropathic elements of CPP.
Trial registration: ClinicalTrials.gov identifier, NCT03363425.

Keywords: Dexmedetomidine; Lidocaine; Chronic postoperative pain; Neuropathic pain; Long-term follow-up

Key Summary Points

The transition of acute to chronic postoperative pain remains a significant problem and there is ongoing research for adjuvants that could possibly prevent it.

We present the long-term follow-up outcomes (chronic pain/neuropathic pain) of an RCT with primary endpoint the effect of lidocaine and dexmedetomidine on acute postoperative pain after open abdominal gynecological surgery.

Dexmedetomidine significantly reduced pain scores compared to placebo at 3 months, while lidocaine was found superior to placebo in preventing neuropathic pain (Douleur Neuropathique score, DN4 < 4) at 6 months.

Increased NRS scores at 48 led to statistically significant chronic pain NRS scores at 3, 6, and 12 months.

The advanced age of patients was also identified to lead to increased chronic pain NRS scores at 6 months after surgery.

INTRODUCTION

The term chronic postoperative pain (CPP) is used to describe the pain that develops after a surgical procedure and persists beyond the healing process i.e., at least 3 months after surgery [1]. CPP is an important clinical problem that may impair patients' physical function and reduce the quality of their lives; therefore, its early prevention during the perioperative period is crucial [2]. Myomectomy and hysterectomy are common gynecological surgical procedures performed for various indications such as pain, menorrhagia, or dysmenorrhea [3]. According to the literature, the incidence of chronic pain after hysterectomy is reported to be 5–50% [4–6], while prospective studies of hysterectomy for benign conditions suggest that up to a quarter of the patients still report pain 1 year after the operation [7, 8].

Even though the transition of acute postoperative to chronic pain has been extensively investigated in the past years and the quality of studies has improved, CPP still remains an unsolved issue [9]. The identification of risk factors such as young age, female sex, psychological disorders, preoperative painful syndromes or severe acute postoperative pain, surgical factors and extent of injury, would help in the reduction of CPP incidence [10, 11].

The anesthetic technique has been proposed as an important factor that could reduce the incidence of CPP [12], and there is ongoing research for adjuvants that could be beneficial. Among other agents, dexmedetomidine, a highly selective α2 adrenoreceptor agonist, and lidocaine, a well-established local anesthetic, seem promising. The existing literature on the effects of dexmedetomidine versus lidocaine on CPP and neuropathic elements is very limited. Dexmedetomidine has shown positive effects on acute postoperative pain and opioid consumption [13, 14] but it has been very little investigated in the clinical setting for CPP [15–17]. Intraoperatively, it has been given as an intravenous (iv) loading dose of 0.5–1 μg/kg over 10 min, followed by an iv infusion of 0.2–0.7 μg/kg/h [18]. Lidocaine has been more extensively investigated in the chronic pain clinical setting [19, 20]. It exerts its effects through sodium channel blockade [21], inhibition of G proteins [22], and NMDA receptors [23]. In patients undergoing open abdominal surgeries, lidocaine has been 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 [24–26].

We performed a long-term (1-year) follow-up to evaluate the effects of intraoperative iv infusion of dexmedetomidine and lidocaine on the occurrence of chronic pain after abdominal gynecological surgery. The study endpoints were the development of CPP with or without neuropathic elements at 3, 6, and 12 months postoperatively. We also identified possible risk factors for the transition of acute postoperative pain to CPP. These long-term outcomes were secondary endpoints of a randomized, double-blind study investigating the effect of dexmedetomidine and lidocaine on acute postoperative pain and analgesic consumption [27].

METHODS

The key features of the original trial [27], including design, setting, eligibility, interventions, outcome measures, and sample size calculation are summarized in Table 1. Patients were contacted at 3, 6, and 12 months postoperatively by telephone for a brief interview to assess any residual pain or uncomfortable sensation. The researcher that conducted the telephone interviews was blinded regarding the intervention group of each patient. First, the patients were asked if they had any residual pain in the surgical area or around the surgical incision. If they answered "yes", then they were asked to provide further information regarding pain site and pain intensity using a numerical pain scale (NRS) from 0 (no pain) to 10 (the worst pain imaginable). To identify possible neuropathic characteristics of the pain, the participants were asked the ten questions from the Greek version of the DN4 [28]. We adapted the questionnaire for telephone interview (Table 2) according to a previous study [29]. The collection of the chronic pain data was completed in January 2021.

Statistical Analysis

Means and standard deviations were used to describe all scale measurements such as age, NRS, or the DN4 scale. Categorical variables were described with the use of counts and percentages. Repeated measures general linear models examined the differences, in NRS and DN4 scales, observed across time and between the three study groups, adjusting for the effect of age, surgery duration, and the NRS scores during the first 48 h following the surgery and the Bonferroni correction was applied to adjust for multiple comparisons. To identify parameters that could affect the DN4 scores, a repeated measures model was applied, which included the duration of the surgery, the age of the patients and the NRS cough scores measured at 48 h after surgery. Firth's penalized logistic regression was used to assess the differences in the odds of having neuropathic pain at 6 months after surgery, depending on the study group [30, 31]. Statistical significance was equal to 0.05 in all cases, including the analyses carried out under the Bonferroni correction. All analyses were conducted with the use of STATISTICA v12.0, except for the penalized logistic regression that was carried out on R.

RESULTS

Data from 74 women (24 patients in the DEX group, 25 in the LIDO group and 25 in the Control group) were included in chronic pain analysis (see attached Flowchart). Seven patients were lost to follow-up as we were unable to contact them on the given telephone number in any of the three occasions (3, 6, or 12 months) after three attempts. Patient's characteristics did not differ among the three groups ($p > 0.05$) (Table 3). Also, there was no statistical difference regarding the type of surgery ($p = 0.962$) among the groups. The surgical team included four senior surgeons with at least 15 years of experience.

At 3 months, the DEX group showed statistically significant lower pain scores compared to CONTROL group ($p = 0.018$). No other statistically differences were observed regarding pain scores at 3, 6, and 12 months among the groups (Table 4).

The repeated-measures model that was applied at each time point to identify parameters that could affect the outcomes included the NRS scores (rest and cough), the duration of the

Table 1 Summary of primary trial design, methods, randomization, and outcome measures

Feature	Details
Design	RCT with three treatment arms
Setting	Aretaieio University Hospital, Athens, Greece
Inclusion criteria	ASA I–II, age: 30 and 70 years, scheduled for abdominal hysterectomy or myomectomy without preoperative pain
Exclusion criteria	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 $\alpha 2$ agonist/analgesics or any drugs acting on the central nervous system during the previous 2 weeks, drug/alcohol abuse, language/communication barrier or inability to comprehend the pain assessment scale and/or the use of a patient-controlled analgesia (PCA) pump
Ethical approval and study registration	Institutional Review Board (Protocol ID: EE-2/04/31-01-2017-Chairman Dr I. Vassileiou). Study approval was obtained for short- (0-48 h) and long-term (3, 6, and 12 months) follow-up, according to the submitted protocol
	ClinicalTrials.gov (ID: NCT03363425)
Ethical standards and guidelines followed	1964 Declaration of Helsinki and its later amendments
	The Consort Guidelines for reporting *Randomized Controlled Trials*
	All patients signed a written informed consent to participate in the study and the follow-up period, according to protocol
Sample size calculation	Calculated after the recruitment of 50 patients (DEX: 16, LIDO: 17, CONTROL: 17), by analyzing the data of 44 (four dropouts in the DEX group and two dropouts in the CONTROL group)
	The study was powered for a reduction of 20% in NRS at rest at 24 h postoperatively. Approximately 26 patients were needed per group to achieve a statistical power of 0.80. A total number of at least 30 patients per group was planned to compensate for possible future dropouts
Randomization/allocation	Eligible patients were randomly allocated to one of the three study groups, dexmedetomidine (DEX), lidocaine (LIDO) or sodium chloride (NaCl) 0.9% (CONTROL) with the help of a computer-generated list (https://www.randomizer.org)
Concealment and outcome assessment during the initial 48-h period	Solutions and syringes were prepared according to group allocation by an independent nurse who did not further participate in the study
	To mask intervention, identical 50-ml syringes were prepared for infusion by an automatic pump. Solution volumes (50 ml), appearance and infusion rates (0.9 ml/kg/h loading and 0.15 ml/kg/h maintenance) were identical in all groups
	A blinded researcher assessed postoperative outcomes

Table 1 continued

Feature	Details
Interventions	Type of surgery: Abdominal hysterectomy or myomectomy
	Type (concentration) of iv infusion: dexmedetomidine (4 μg/ml) or lidocaine (10 mg/ml) or placebo (sodium chloride 0.9%)
Infusion rates	
Preoperatively	0.9 ml/kg/h for 10 min
	(Corresponding to:
	0.6 μg/kg dexmedetomidine
	1.5 mg/kg lidocaine)
Intraoperatively	0.15 ml/kg/h, until the final stitch
	(Corresponding to:
	0.6 μg/kg/h dexmedetomidine
	1.5 mg/kg/h lidocaine)
Primary outcome measures	Cumulative morphine consumption and pain scores at 24 h
Secondary outcome measures	Acute pain:
	Cumulative morphine consumption and pain scores at the Post Anesthetic Care Unit, 2 h, 4 h, 8 h, and 48 h
	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
	Time of getting up from bed (hours after extubation)
	Sleep quality (0–10 scale)
	Patient satisfaction (0–10 scale) at 24 h and 48 h
	Discharge time
	Need for rescue analgesia and rescue antiemetic
	Drug side effects and complications associated with the interventions
	Chronic pain:
	Chronic pain (NRS) at 3, 6, and 12 months
	Neuropathic pain or neuropathic elements (DN4 scores) at 3, 6, and 12 months

Table 1 continued

Feature	Details
Recruitment	91 female patients (31 in DEX, 30 in LIDO, and 30 in CONTROL group) recruited from June 2017 to January 2020
Patients assessed for CPP and neuropathic pain	81 female patients/12-month follow-up

surgery, as well as the age of the patients. The analysis showed that the cough NRS scores at 48 h had a statistically significant effect on the chronic pain NRS scores (Table 5). This correlation was revealed by the repeated measures general linear model (GLM) at all three times (Table 5; Fig. 1). Higher values of NRS pain scores at all time periods are therefore expected for higher values of NRS cough pain scores at the 48-h measurement.

A statistically significant relation ($p = 0.020$) was also found between advanced age of patients and higher values of chronic pain NRS scores at 6 months after surgery. This relationship was borderline nonsignificant at 3 and 12 months with p values equal to 0.079 and 0.092, respectively.

Analysis for the DN4 Scores

The DN4 scores across the three time points for each of the treatment groups are shown in Table 6. Even though the control group appeared to score higher at all periods compared to the other two groups (Fig. 2), these differences were not statistically significant ($p > 0.05$) (Table 6).

In our study, although many patients reported neuropathic elements, most of them did not fulfil the literature cut-off score of 4 for their pain to be diagnosed as neuropathic [32]. Therefore, at all time points, the percentage of patients suffering from neuropathic pain was relatively small, as shown in Table 7. Fisher's exact test showed a statistically significant difference at 6 months ($p = 0.031$).

The comparative bar chart in Fig. 3 shows that more patients are expected to suffer with neuropathic pain in the control group. The penalized logistic regression model also showed a statistically significant difference in the neuropathic pain depending on the treatment group ($p = 0.048$). This difference was observed between the LIDO (0%) and CONTROL (20%) group ($p = 0.02$), but not among the other groups [DEX (4.2%) vs. CONTROL ($p = 0.106$) and DEX vs. LIDO ($p = 0.442$)].

The analysis showed that the 48-h cough NRS scores had a statistically significant effect on the DN4 scores at all three times, thus 3, 6, and 12 months, with p values equal to 0.01, < 0.01, and < 0.01, respectively. Higher values of DN4 at all time periods are therefore expected for higher values of NRS cough scores at 48 h, which are depicted in Table 8.

Adverse Effects of the Investigated Agents

Intraoperative hypotension and bradycardia were more often observed in the study groups (DEX and LIDO) compared to the CONTROL group, but the differences were not statistically significant ($p = 0.357$ and $p = 0.566$, respectively). A patient of the LIDO group developed ventricular ectopic beats, which resolved after discontinuation of the intervention.

No other adverse effects were reported during the postoperative period.

DISCUSSION

Our results showed that perioperative iv infusion of dexmedetomidine comparing to placebo had a beneficial effect on the prevention of CPP at 3 months, while lidocaine infusion prevented the development of neuropathic pain at 6 months after gynecological surgery. To our knowledge, this is the first study comparing

Table 2 Adapted DN4 questionnaire for telephone interview

Question	Adaptation
Interview of the patient:	
Q1: Does the pain have one or more of the following characteristics?	
Yes No	
(1) Burning	Not needed
(2) Painful cold	Not needed
(3) Electric shocks	Not needed
Interview of the patient:	
Q2: Is the pain associated with one of more of the following symptoms in the same area?	
(4) Tingling	Not needed
(5) Pins and needles	Not needed
(6) Numbness	Not needed
(7) Itching	Not needed
Examination of the patient:	
Q3: Is the pain located in an area where the physical examination may reveal one or more of the following characteristics?	
(8) Hypoesthesia to touch	Yes—The patient was asked to describe the feeling while touching with a cloth
(9) Hypoesthesia to prick	Yes—The patient was asked to describe the feeling while pricking with a tweezer
Examination of the patient:	
Q4: In the painful area, can the pain be caused or increased by:	
(10) Brushing	Yes—The patient was asked to describe the feeling while brushing with a soft towel

intraoperative dexmedetomidine and lidocaine with placebo with regards to CPP development. Our long-term follow-up showed superiority of the studied drugs over placebo and highlighted predisposing factors for development of chronic pain with or without neuropathic elements.

The first finding, that dexmedetomidine at 3 months prevented the development of CPP compared to placebo, is also supported by one study, which investigated perioperative infusion of dexmedetomidine in patients undergoing breast cancer surgery [15]. However, in that study, patients had received much greater doses of the investigated drug (1 μg/kg iv bolus, followed by a continuous infusion of 0.5 μg/kg/h iv till the completion of surgery, and then the

Table 3 Patient and operative characteristics of the studied groups (DEX group: dexmedetomidine, LIDO group: lidocaine and CONTROL group: normal saline)

Group (*n*)	DEX (*n* = 24)	LIDO (*n* = 25)	CONTROL (*n* = 25)	*p* value
Age (years) (mean ± SD)	45.25 ± 7.48	48.48 ± 10.89	50.16 ± 10.14	0.20
Height (cm) (mean ± SD)	163.88 ± 5.54	163.92 ± 6.58	163.56 ± 5.43	0.97
Weight (kg) (mean ± SD)	66.04 ± 10.56	67.64 ± 7.99	69.44 ± 10.00	0.47
BMI (mean ± SD)	24.55 ± 3.46	25.24 ± 3.19	26.00 ± 3.87	0.36
Surgery duration (mean ± SD)	109.17 ± 30.54	119.32 ± 48.16	118.04 ± 36.09	0.62
Type of surgery (myomectomy: hysterectomy)	13:11	13:12	13:12	0.99

Values are expressed as mean ± standard deviation (SD)
BMI body mass index, *n* number of patients
*Statistical significance ($p < 0.05$)

Table 4 NRS cough (NRS, numerical rating scale 0–10) in the three study groups (DEX group: dexmedetomidine, LIDO group: lidocaine and CONTROL group: normal saline) at 48 h and NRS scores across the three time points for each intervention group

Group	NRS			
	Mean ± SD	*p* value (DEX-CONTROL)	*p* value (LIDO-CONTROL)	*p* value (DEX-LIDO)
NRS cough 48 h				
LIDO	4.60 ± 2.62	1.0	1.0	1.0
DEX	4.19 ± 2.94			
CONTROL	4.35 ± 2.37			
NRS 3 months				
LIDO	1.84 ± 2.15	0.018*	0.79	0.68
DEX	1.08 ± 1.47			
CONTROL	2.52 ± 2.18			
NRS 6 months				
LIDO	0.84 ± 1.34	0.27	0.84	0.99
DEX	0.46 ± 0.72			
CONTROL	1.48 ± 1.66			
NRS 12 months				
LIDO	0.40 ± 1.04	0.95	0.99	1.00
DEX	0.21 ± 0.66			
CONTROL	0.72 ± 1.06			

Values are expressed as mean ± standard deviation (SD)
*Statistical significance ($p < 0.05$)

Table 5 Repeated measures general linear model (GLM) for the effect of group, NRS 48 cough, duration of surgery, and age at each time point on NRS scores at 3, 6, and 12 months

	Df	SS	MS	*F*	*p*
NRS 3 months					
Intercept	1	2.11	2.11	0.61	0.44
Group	2	20.77	10.39	2.97	0.06
NRS48 cough	1	27.96	27.96	8.00	0.01
Duration	1	0.87	0.87	0.27	0.62
Age	1	11.10	11.10	3.18	0.08
Error	68	237.65	3.50		
Total	73	300.72			
NRS 6 months					
Intercept	1	4.08	4.08	2.66	0.11
Group	2	9.78	4.90	3.19	< 0.05
NRS48 cough	1	9.26	9.26	6.05	0.02
Duration	1	0.06	0.06	0.04	0.85
Age	1	8.74	8.74	5.71	0.02
Error	68	104.12	1.53		
Total	73	134.66			
NRS 12 months					
Intercept	1	1.37	1.37	1.75	0.19
Group	2	2.78	1.39	1.78	0.18
NRS48 cough	1	7.74	7.74	9.89	< 0.01
Duration	1	0.51	0.51	0.66	0.42
Age	1	2.28	2.28	2.91	0.09
Error	68	53.20	0.78		
Total	73	66.28			

df degrees of freedom, *SS* sum of squares, *MS* mean squares, *F F* test

dose was tapered to 0.2 μg/kg/h for up to 24 h). The beneficial effect of dexmedetomidine has also been shown in an experimental study, where it attenuated persistent postsurgical pain by upregulating K^+–Cl^- cotransporter-2 in the spinal dorsal horn in rats [33].

The second finding of our study was that lidocaine proved to be superior to placebo regarding DN4 scores, making it a useful drug for the prevention of postsurgical neuropathic pain. For the assessment of neuropathic elements of pain, we used the DN4 questionnaire, a validated and widely used screening tool for the identification and classification of neuropathic pain [32]. It has been shown to achieve an 83% sensitivity and 90% specificity when compared to clinical diagnosis [34]. A former study had successfully performed the DN4 neuropathic pain questionnaire over the telephone to identify possible neuropathic elements [29]. In this study [29], for the first seven symptom items, the respondents answered "yes" or "no" to whether their pain could be described as burning, painful cold, electric shocks, tingling, pins and needles, numbness, and itching. The patients were also asked if their pain area was sensitive to touch, sensitive to pin prick, and sensitive to light brushing, which resembles the clinical examination. A score of 1 was given for each "yes" answer and 0 for each "no" answer. A score of < 4 suggested that the pain was unlikely to be neuropathic. This important finding might be supported by the fact that lidocaine is already a very useful drug, used as infusion in chronic neuropathic pain states, as extensively analyzed in a recent review [35] and in a metanalysis [36].

Moreover, our results showed that the pain scores (NRS cough) at 48 h had a statistically significant effect on the chronic pain scores at all three times, making acute postoperative pain an indication of transition to chronic pain. Fassoulaki et al. have demonstrated that pain during the immediate postoperative period can predict chronic pain after breast surgery for cancer [37]. However, in this study patients who developed chronic pain had experienced higher pain intensity at rest during the first nine postoperative hours rather than pain at cough at 48 h as in our study. Other studies also support our finding [38, 39].

Pain intensity at 48 h postoperatively was found to be a significant risk factor for the development of neuropathic pain, as higher

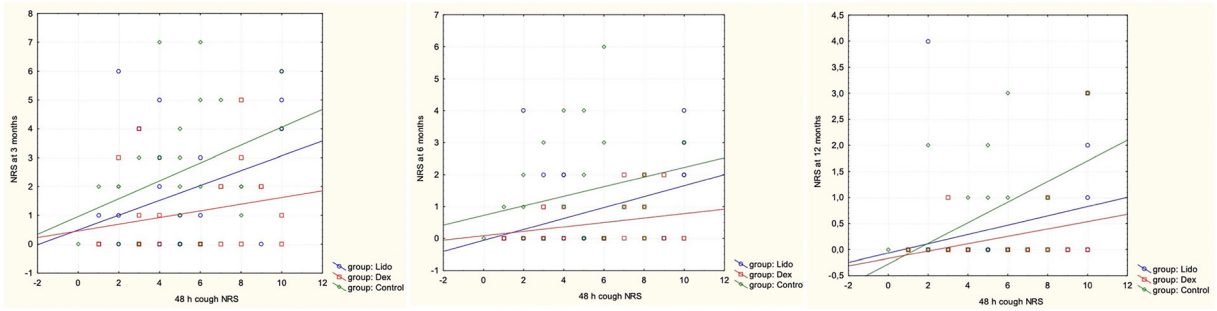

Fig. 1 NRS scores compared to 48-h NRS cough scores for all groups at 3, 6, and 12 months

Table 6 DN4 (Douleur Neuropathique score 0–10) in the three study groups (DEX group: dexmedetomidine, LIDO group: lidocaine and CONTROL group: normal saline) at 3, 6, and 12 months

Group	DN4			
	Mean ± SD	*p* value (DEX-CONTROL)	*p* value (LIDO-CONTROL)	*p* value (DEX-LIDO)
DN4 3 months				
LIDO	1.60 ± 1.73	0.54	0.88	1.00
DEX	1.33 ± 1.49			
CONTROL	2.24 ± 2.20			
DN4 6 months				
LIDO	0.92 ± 1.19	0.57	0.69	1.00
DEX	0.83 ± 1.17			
CONTROL	1.72 ± 1.99			
DN4 12 months				
LIDO	0.40 ± 0.76	0.78	0.50	1.00
DEX	0.58 ± 1.10			
CONTROL	1.32 ± 1.91			

Values are expressed as mean ± standard deviation (SD)
*Statistical significance ($p < 0.05$)

DN4 scores at 3, 6, and 12 months were reported from patients with higher NRS cough scores at 48 h. This finding has been also identified by other studies that have highlighted the role of acute pain as a risk factor for the development of long-term neuropathic pain [40, 41].

Age may also play an important role in the development of CPP. We found that at 6 months after surgery, older patients suffered more severe pain. This is not in agreement with previous findings, as Martinez et al. have suggested the opposite, i.e., that younger age is a predictive factor for chronic pain [42]. Also, according to Schug and Bruce, younger age seems to be in most studies a relatively consistent demographic risk factor for CPP in adults [11].

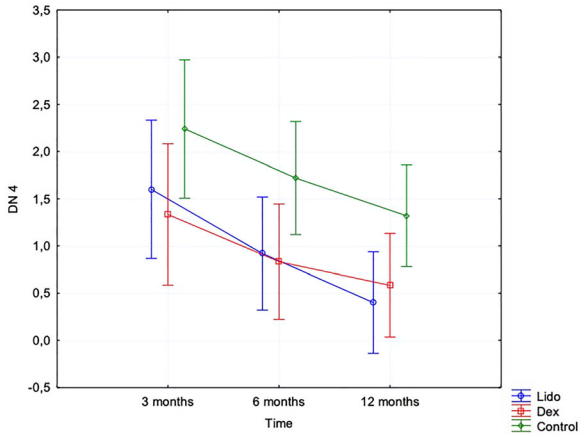

Fig. 2 DN4 scores at 3, 6, and 12 months for all groups

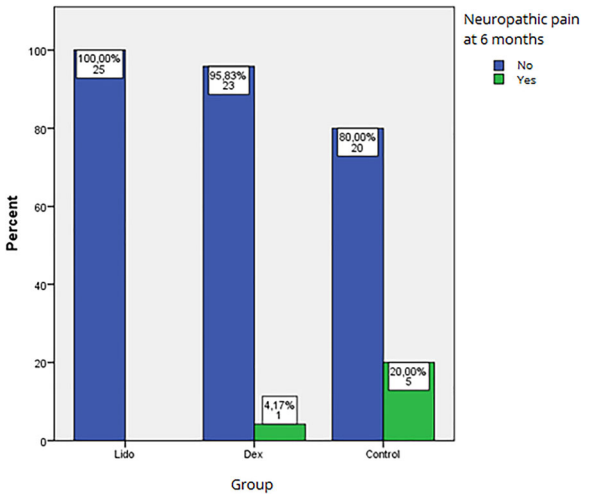

Fig. 3 Neuropathic pain at 6 months for all groups

LIMITATIONS AND STRENGTHS

This long-term study on CPP derives from a RCT that was powered to reveal differences in acute postoperative pain; thus, the sample size may be relatively small for chronic pain outcomes. Another possible limitation is that we did not study different doses of the administered drugs. Also, several possible risk factors of CPP, such as gender, preexisting pain, and psychological factors were not investigated in the present study, as it was designed to minimize these confounding factors; the studied population were all females (ASA I and II with no major comorbidities or prior disability), while patients with preexisting pain or analgesic consumption, or those treated for depression and anxiety were excluded according to protocol (Table 1). Additionally, the duration of surgery did not differ among the groups (Table 3) and the patients with surgical complications were excluded from follow-up and analysis. We did

Table 7 Neuropathic pain at 3, 6, and 12 months

	Group					
	LIDO		DEX		CONTROL	
	Count	Column *N* %	Count	Column *N* %	Count	Column *N* %
Neuropathic pain at 3 months						
No	21	84	21	87.5	16	64
Yes	4	16	3	12.5	9	36
Neuropathic pain at 6 months						
No	25	100	23	95.8	20	80
Yes	0	0.0	1	4.2	5	20
Neuropathic pain at 12 months						
No	25	100	24	100	22	88
Yes	0	0.0	0	0.0	3	12

Table 8 Repeated measures general linear model (GLM) for the effect of group, NRS48 cough, duration of surgery, and age at each time point on DN4 scores at 3, 6, and 12 months

	Df	SS	MS	*F*	*P*
DN4 at 3 months					
Intercept	1	1.73	1.73	0.55	0.46
Group	2	12.58	6.29	1.99	0.14
NRS48 cough	1	24.31	24.31	7.69	0.01
Duration	1	0.01	0.01	0.00	0.95
Age	1	0.24	0.24	0.08	0.78
Error	68	214.95	3.16		
Total	73	250.59			
DN4 at 6 months					
Intercept	1	0.72	0.72	0.36	0.55
Group	2	11.88	5.94	2.97	0.06
NRS48 cough	1	22.13	22.13	11.06	< 0.01
Duration	1	0.55	0.55	0.27	0.60
Age	1	0.52	0.52	0.26	0.61
Error	68	136.01	2.00		
Total	73	172.05			
DN4 at 12 months					
Intercept	1	0.41	0.41	0.25	0.62
Group	2	11.77	6.09	3.99	0.07
NRS48 cough	1	18.73	18.73	11.69	< 0.01
Duration	1	0.56	0.56	0.35	0.56
Age	1	0.00	0.00	0.00	0.97
Error	68	108.95	1.60		
Total	73	141.09			

df degrees of freedom, *SS* sum of squares, *MS* mean squares, *F F* test

not assess other possible predisposing factors for CPP, such as education level and lifestyle.

A strength of this study is that the patients were followed up for quite a long time (12 months) and also that we managed to have a high percentage of patients (74/81 or 91.35%) that completed the follow-up period. This is important since previous similar studies report significant dropout rates, ranging from approximately 34% [43] to 43.6% after 12 months [44].

CONCLUSIONS

The present study demonstrated that perioperative infusion of dexmedetomidine or lidocaine may exert a beneficial effect on the development and characteristics of CPP after abdominal gynecological surgery. Dexmedetomidine proved to be superior to placebo regarding the duration and severity of CPP, while lidocaine exhibited a protective effect against neuropathic elements of CPP over placebo. We consider that the findings of this RCT could provide the foundation for future studies.

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Compliance with Ethics Guidelines. Ethical approval was provided by 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 the ClinicalTrials.gov (ID: NCT03363425). The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. All subjects provided informed consent to participate in the study. All participants provided consent for publication if any identifying information is included in the manuscript.

Data Availability. All data generated during the current study are available on request by Martina Rekatsina at mrekatsina@gmail.com.

REFERENCES

1. Treede RD, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003–7.
2. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287–98.
3. Parker WH. Uterine myomas: management. Fertil Steril. 2007;88(2):255–71.
4. Brandsborg B, et al. Chronic pain after hysterectomy. Acta Anaesthesiol Scand. 2008;52(3):327–31.
5. Han C, et al. Incidence and risk factors of chronic pain following hysterectomy among Southern Jiangsu Chinese Women. BMC Anesthesiol. 2017;17(1):103.
6. Pinto PR, et al. Risk factors for persistent postsurgical pain in women undergoing hysterectomy due to benign causes: a prospective predictive study. J Pain. 2012;13(11):1045–57.
7. Gimbel H, et al. Randomised controlled trial of total compared with subtotal hysterectomy with one-year follow up results. BJOG. 2003;110(12):1088–98.
8. Humalajärvi N, et al. Quality of life and pelvic floor dysfunction symptoms after hysterectomy with or without pelvic organ prolapse. Eur J Obstet Gynecol Reprod Biol. 2014;182:16–21.
9. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth. 2008;101(1):77–86.
10. Lavand'homme P. Transition from acute to chronic pain after surgery. Pain. 2017;158(Suppl 1):S50-s54.
11. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017;2(6): e627.
12. Searle R, Simpson K. Chronic post-surgical pain. Contin Educ Anaesth Crit Care Pain. 2009;10(1):12–4.
13. Jessen Lundorf L, Korvenius Nedergaard H, Møller AM. Perioperative dexmedetomidine for acute pain after abdominal surgery in adults. Cochrane Database Syst Rev. 2016;2: CD010358.

14. Galvin IM, et al. Pharmacological interventions for the prevention of acute postoperative pain in adults following brain surgery. Cochrane Database Syst Rev. 2019;2019(11): CD011931.

15. Jain G, et al. Effect of the perioperative infusion of dexmedetomidine on chronic pain after breast surgery. Indian J Palliat Care. 2012;18(1):45–51.

16. Liu Y, et al. Dexmedetomidine relieves neuropathic pain in rats with chronic constriction injury via the Keap1-Nrf2 pathway. Front Cell Dev Biol. 2021;9: 714996.

17. Wang X, Liu Q. Dexmedetomidine relieved neuropathic pain and inflammation response induced by CCI through HMGB1/TLR4/NF-κB signal pathway. Biol Pharm Bull. 2021. https://doi.org/10.1248/bpb.b21-00329.

18. Dholakia C, et al. The impact of perioperative dexmedetomidine infusion on postoperative narcotic use and duration of stay after laparoscopic bariatric surgery. J Gastrointest Surg. 2007;11(11): 1556–9.

19. Bailey M, et al. Perioperative lidocaine infusions for the prevention of chronic postsurgical pain: a systematic review and meta-analysis of efficacy and safety. Pain. 2018;159(9):1696–704.

20. Kendall MC, et al. The effect of intraoperative systemic lidocaine on postoperative persistent pain using initiative on methods, measurement, and pain assessment in clinical trials criteria assessment following breast cancer surgery: a randomized, double-blind placebo-controlled trial. Pain Pract. 2018;18(3):350–9.

21. Hollmann MW, Durieux ME. Local anesthetics and the inflammatory response: a new therapeutic indication? Anesthesiology. 2000;93(3):858–75.

22. Hollmann MW, et al. Local anesthetic inhibition of G protein-coupled receptor signaling by interference with Galpha(q) protein function. Mol Pharmacol. 2001;59(2):294–301.

23. Sugimoto M, Uchida I, Mashimo T. Local anaesthetics have different mechanisms and sites of action at the recombinant *N*-methyl-D-aspartate (NMDA) receptors. Br J Pharmacol. 2003;138(5): 876–82.

24. Toner AJ, et al. A pilot multicentre randomised controlled trial of lidocaine infusion in women undergoing breast cancer surgery. Anaesthesia. 2021;76(10):1326–41.

25. Herroeder S, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. Ann Surg. 2007;246(2):192–200.

26. Koppert W, et al. Perioperative intravenous lidocaine has preventive effects on postoperative pain and morphine consumption after major abdominal surgery. Anesth Analg. 2004;98(4):1050–5.

27. Rekatsina M, Theodosopoulou P, Staikou C. 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. Pain Physician. 2021;24(7):E997-e1006.

28. Sykioti P, et al. Validation of the Greek version of the DN4 diagnostic questionnaire for neuropathic pain. Pain Pract. 2015;15(7):627–32.

29. Zghoul N, et al. Prevalence of chronic pain with neuropathic characteristics: a randomized telephone survey among medical center patients in Kuwait. J Pain Res. 2017;10:679–87.

30. Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993;80(1):27–38.

31. Wang X. Firth logistic regression for rare variant association tests. Front Genet. 2014;5:187.

32. Bouhassira D, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1–2):29–36.

33. Dai S, et al. Dexmedetomidine attenuates persistent postsurgical pain by upregulating K(+)–Cl(−) cotransporter-2 in the spinal dorsal horn in rats. J Pain Res. 2018;11:993–1004.

34. Harifi G, et al. Validity and reliability of the Arabic adapted version of the DN4 questionnaire (Douleur Neuropathique 4 Questions) for differential diagnosis of pain syndromes with a neuropathic or somatic component. Pain Pract. 2011;11(2):139–47.

35. Kandil E, Melikman E, Adinoff B. Lidocaine infusion: a promising therapeutic approach for chronic pain. J Anesth Clin Res. 2017;8(1):697.

36. Zhu B, et al. Intra-venous lidocaine to relieve neuropathic pain: a systematic review and meta-analysis. Front Neurol. 2019;10:954–954.

37. Fassoulaki A, et al. Acute postoperative pain predicts chronic pain and long-term analgesic requirements after breast surgery for cancer. Acta Anaesthesiol Belg. 2008;59(4):241–8.

38. Shipton E. Post-surgical neuropathic pain. ANZ J Surg. 2008;78(7):548–55.

39. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. Anesthesiology. 2018;129(3):590–607.

40. Lavand'homme PM, et al. Pain trajectories identify patients at risk of persistent pain after knee arthroplasty: an observational study. Clin Orthop Relat Res. 2014;472(5):1409–15.

41. Juwara L, et al. Identifying predictive factors for neuropathic pain after breast cancer surgery using machine learning. Int J Med Inform. 2020;141: 104170.

42. Martinez V, et al. Risk factors predictive of chronic postsurgical neuropathic pain: the value of the iliac crest bone harvest model. Pain. 2012;153(7): 1478–83.

43. Cutler RB, et al. Identifying patients at risk for loss to follow-up after pain center treatment. Pain Med. 2001;2(1):46–51.

44. Beyaz SG, et al. Chronic postsurgical pain and neuropathic symptoms after abdominal hysterectomy: a silent epidemic. Medicine (Baltimore). 2016;95(33): e4484.