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The Effect of Intravenous Infusion of Lidocaine to Control Postoperative Pain After Gynecologic Laparoscopic Surgery: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Abstract

Background: Pain after laparoscopy may still be moderate to severe due to stretching of the intraabdominal cavity and peritoneal inflammation. Systemic Lidocaine with anti-inflammatory properties may reduce this pain.
Objectives: The aim of this study was to evaluate the effect of perioperative intravenous infusion of Lidocaine on postoperative pain relief after the gynecologic laparoscopic procedure.
Methods: A double-blind, randomized clinical trial study was conducted in Iran, during the years 2014 and 2015. A sample of 60 females with American anesthesiology association (ASA) physical class I or II, who were scheduled for gynecologic laparoscopy were selected through consecutive sampling and were randomly assigned to receive either intravenous Lidocaine or Normal saline, as placebo, prior to induction of anesthesia and until the end of surgery. The severity of postoperative pain was evaluated starting at the recovery unit until 24-hours postoperatively for a total of 8 times using the visual analogue scale (VAS) scoring system. Time to first analgesic request, total analgesic dose used in the first 24-hours, and any probable postoperative complications were recorded. Risk ratio (RR) and number needed to treat (NNT) were used to analyze the data along with the generalized linear model for multivariate analysis of repeated measurements over time.
Results: The VAS at recovery was lower at recovery with a mean score of 2.8 in the Lidocaine group versus 3.9 in the control group ($P = 0.02$). Results of generalized linear modeling revealed that pain intensity decreased over time in both groups ($P = 0.02$), and the groups had different trend slopes in pain intensity over repeated measurements at various time points up to 24 hours after laparoscopy, while controlling for the baseline VAS at recovery and ASA PS ($P = 0.016$). However, when controlling for use of the pain-killers, the trends were not found to be different. Patients in the Lidocaine group were 3.8 times more likely not to need postoperative analgesic (95% CI: 1.4 to 9.9). Mean total analgesic dose was 1.3 mg in the Lidocaine group versus 38.2 mg in the control group differing significantly between the 2 groups ($P < 0.01$). Use of Lidocaine was associated with lower postoperative nausea and agitation.
Conclusions: Systemic perioperative Lidocaine could improve the pain pattern and severity as well as nausea and agitation after gynecologic laparoscopy. Although no significant side effects were detected in this study, the benefits of the intervention should be weighed against its safety.

Keywords: Analgesia, Clinical Trials, Laparoscopy, Lidocaine, Pain Measurement

1. Introduction

Pain is one of the most common complaints in clinical medicine, and many medical procedures have been developed to reduce and control pain. On the other hand, pain is one the most important causes of disability and is the source of a significant financial burden for the patients and community (1). Not providing proper treatment for postoperative pain, leads to both unwanted physiological and psychological effects that may lead to increased morbidity and mortality. It also affects the recovery quality and increases the incidence of chronic pain after the operation (2).

Nowadays, pain is considered as a legal responsibility in the medical profession. Although the treatment of postoperative pain has benefited from many advance-

ments during the past few decades, pain is still not effectively treated in surgical patients. Gynecologic surgeries are among the most common procedures in outpatient settings and are progressively performed with laparoscopy. However, acute pain is the most critical postoperative complication that could lead to patient discomfort and dissatisfaction, and may result in delayed discharge, re-admissions, and increased costs. The severity of post-laparoscopic pain is moderate to severe, and about 35% to 65% of patients experience it as abdominal or shoulder tip pain and up to 80% of patients require analgesia. Opioids are widely used as the initial treatment of moderate to severe postoperative pain. However, the opioid administration could exacerbate postoperative ileus and hence delay patient recovery (3). Research is ongoing to introduce better alternatives for opioids after surgical procedures. Systemic Lidocaine has generally been shown to be beneficial after open surgeries, while more research would be of help to construct more solid evidence for laparoscopic operations in the field of gynecology (4-7). This is while pain pattern and management after medical procedures is highly dependent on the type of procedure, anatomical location, and pathological conditions related to the disease itself. Regardless of available evidence on the analgesic effect of perioperative Lidocaine in various surgeries, research in the field of gynecologic peri-laparoscopic analgesia is rarely available. Moreover, according to the most recent available studies, evidence for the effect of Lidocaine on another side effects/outcomes of surgical procedures, such as nausea and vomiting is insufficient (7). The aim of this study was to evaluate the effect of intraoperative infusion of intravenous Lidocaine to reduce pain after laparoscopic gynecologic surgery.

2. Methods

2.1. Participants

In a double-blind, randomized clinical trial, 60 females needing elective gynecologic laparoscopic surgery (either diagnostic or therapeutic) were enrolled (Figure 1). The study setting was Alzahra University Hospital, which is a governmental referral obstetrics and gynecology hospital affiliated to Tabriz University of Medical Sciences, Tabriz, Iran. The study was conducted between February 2014 and February 2015.

Sixty patients referred for laparoscopic gynecologic surgery, who were classified to be in I or II classes, according to the American anesthesiology association physical status (ASA-PS I and II), were enrolled using the consecutive sampling method. The patients' age ranged from 18 to 60 years old. The exclusion criteria were ASA-PS III or higher, presence of cardiovascular diseases, pulmonary diseases, renal, hepatic and endocrine dysfunctions, hypertension, psychiatric diseases, epilepsy, hypersensitivity to Lidocaine, use of opioid or non-opioid analgesics prior to the operation, and a history of prior laparotomies more than once. The aim of the ASA-PS grading system is to assess the degree of a patient's "sickness" or "physical state" before choosing the anesthetic or before starting the surgery. A summary of this grading is given below yet further details could be obtained from the websites of the American Society of Anesthesiologists:

2.2. ASA PS 1: Normal Healthy Patient

No organic, physiologic, or psychiatric disturbance, excludes the very young and very old, healthy with good exercise tolerance.

2.3. ASA PS 2: Patients with Mild Systemic Disease

No functional limitations have a well-controlled disease of one body system, controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD), mild obesity, pregnancy.

2.4. ASA PS 3: Patients with Severe Systemic Disease

Some functional limitation has a controlled disease of more than one body system or one major system, no immediate danger of death, controlled Congestive Heart Failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure, and bronchospastic disease with intermittent symptoms.

2.5. ASA PS 4

Patients with severe systemic disease that is a constant threat to life has at least one severe disease that is poorly controlled or at end stage; possible risk of death, unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure.

2.6. ASA PS 5

Moribund patients, who are not expected to survive without the operation not expected to survive > 24-hours without surgery; imminent risk of death; multi-organ failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy.

2.7. ASA PS 6

A declared brain-dead patient whose organs are being removed for donor purposes.

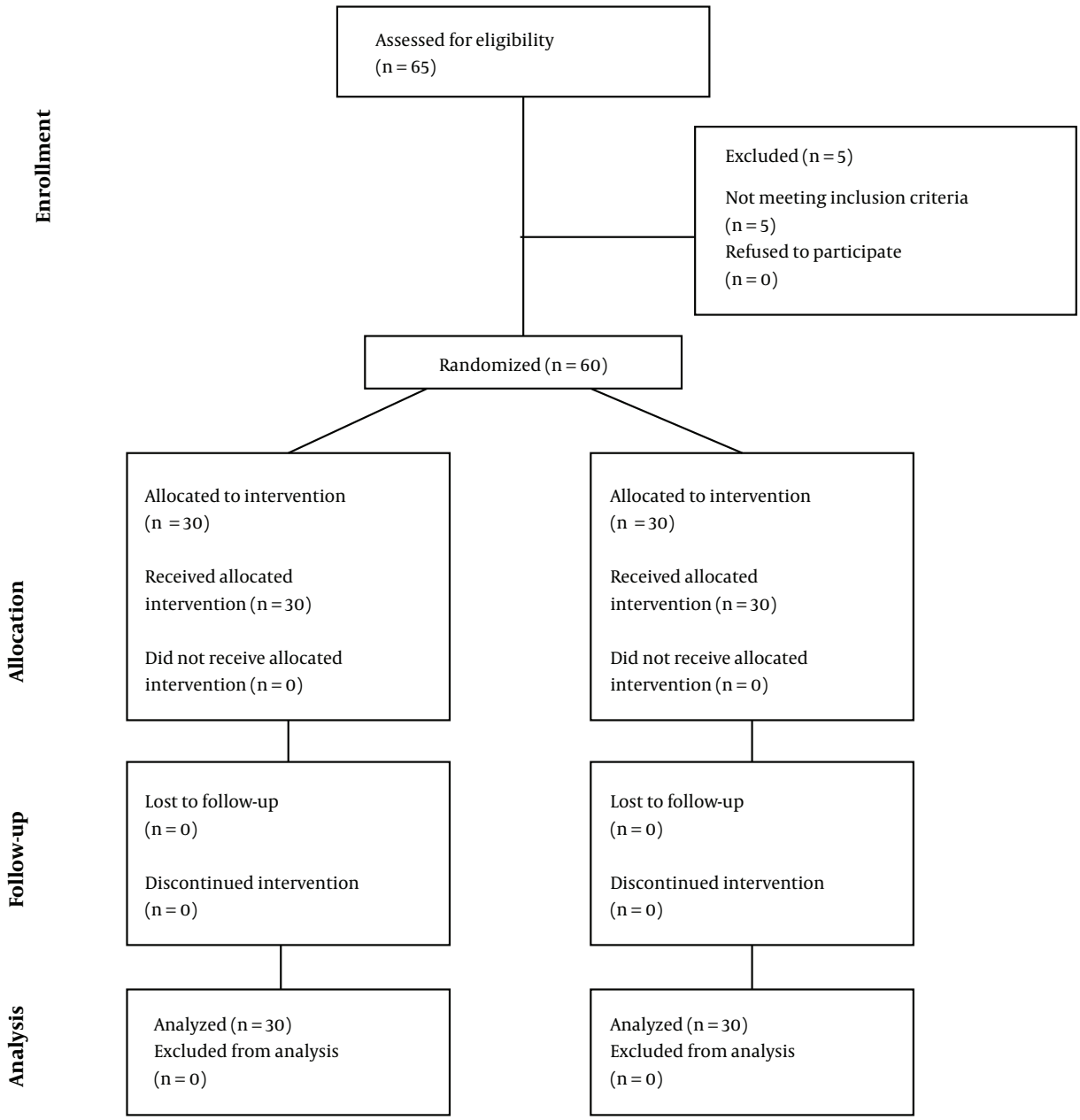

Figure 1. CONSORT diagram showing the flow of participants through each stage of the randomized trial on the effect of Lidocaine to control postoperative pain after gynecologic laparoscopic surgery

2.8. The Intervention and Randomization

The patients were randomly assigned to two equal groups of 30 patients, according to block randomization in two fixed sized blocks. The random sequence was generated using computerized methods (8).

After entering the operation room, basic vital sign assessments were performed and two upper arm intravenous lines were opened to infuse the drug and crystalloid serum throughout the operation. Patients in the Lidocaine group received an infusion of 2 mg/kg/hour of Lidocaine along with its bolus intravenous dose. However, patients in the control group only received Normal saline infusion at 2 mL/kg/hour through an infusion pump. Lidocaine infusion was started before induction and premed-

ication. Through the premedication, patients received 1 to 2 mg of Midazolam, 2 μg/kg Fentanyl, and 1.5 mg/kg Lidocaine, intravenously. To induct the anesthesia, 2 to 3 mg/kg of Propofol and 0.5 mg of Atracurium were administered, intravenously. After intubation or insertion of laryngeal mask Propofol infusion was continued at 50 to 75 μg/kg/minute. Patients were stationed at lithotomy position. The infusions were stopped at the end of the operation after removing the tracheal tube or laryngeal mask and patients were transferred to the recovery room. Vital sign assessments were performed at the recovery unit and patients were discharged from the recovery unit based on the Aldert benchmark. The first pain assessment was done at discharge from recovery (zero time point), followed by seven subsequent measurements after 1, 2, 4, 6, 8, 12, and 24 hours. The pain score was assessed across a continuum from none to an extreme amount of pain equal to 10. In case the pain score exceeded 4, a Meperidine bolus of 0.5 mg/kg was administered at each time point. The time to first analgesic use, total 24-hour Meperidine dose, and potential side effects and complications were recorded over the study period.

2.9. Blinding

Blinding of the intervention was applied in a double-blinding procedure, such that patients were not told whether they had received Lidocaine or placebo for perioperative analgesic induction. As the surgeon could not be blinded, the outcome assessor, who was the person that asked the patients about their level of pain after the procedure, was blinded to the type of intervention and did not know, which intervention the interviewed patients had received previously.

2.10. Study Outcomes

The primary outcome of the study was the pain, which was assessed through the visual analogue scale (VAS). The pain visual analogue scale is a unidimensional scale that measures pain intensity while the patient is asked to locate a point on a graphical tool, such as a colored ruler, to show his/her pain intensity and a score of 1 to 10 is recorded for pain intensity. A higher score indicates greater pain intensity. The reliability of VAS for pain has been confirmed before with a summary intra-class correlation coefficient of paired VAS scores equal to 0.97 [95% CI = 0.96 to 0.98]. Opioid administration for pain management, such as the time to first analgesia with Meperidine, number of analgesia administrations, total Meperidine analgesic dose given over 24-hours after the operation, and the bowel function recovery were considered as secondary outcomes of the study.

2.11. Sample Size

As no similar study was available at the time of the study, the sample size was not calculated apriori and this study was an exploratory trial with a minimum sample size to allow statistical assumptions and a hypothesized effect size. To report the precisions as indicators of sample size adequacy, the 95% confidence intervals of the effect sizes were reported and an assumptive sample size was estimated using the sampsi command in the Stata version 11 statistical software package. The study was powered to detect a mean difference of 1.2 in an hourly VAS score (SD1 = 1.8, SD2 = 1.3) with a maximum type I error equal to 0.05 and maximum type II error equal to 0.2 upon an equality hypothesis testing.

2.12. Statistical Analysis

Statistical analysis in this study was done with a per-protocol approach. Data were analyzed using the Stata version 13 statistical software package (StataCorp., College Station, Tx). Through bivariate analysis, independent samples t-test and Chi-square tests were applied. Risk ratio (RR) and the number needed to Treat (NNT) were calculated along with their 95% confidence intervals. The confidence intervals were produced using the exact method of estimation. Considering repeated measurements over time, which produces multiple correlated response variable measurements over time, the generalized linear method was used to analyze and compare the trends while controlling for potential confounders. The generalized linear method generalizes linear regression model by allowing it to be related to the response variable through a link function, and by allowing the magnitude of the variance of each measurement to be a function of its predicted value. An independent interaction of time and group was considered as an evidence for different slopes of trends, as an indicator of treatment efficacy. A p-value below 0.05 was considered statistically significant.

2.13. Ethics, Consent, and Permissions

The study protocol was approved by the regional board of ethics at Tabriz University of Medical Sciences. Written informed consent was obtained from all the participants of the study.

2.14. Clinical Trial Registration

The clinical trial was registered by the Iranian Registry of Clinical Trials with the following code, IRCT2014040511700N5.

3. Results

A total of 60 females aged 18 to 60 years old with American Society of Anesthesiologists physical status (ASA PS) I and II were studied. Demographic information of the patients in both groups are shown in Table 1.

Patients in both groups underwent complete hemodynamic monitoring during the anesthesia and recovery period. A decreasing trend in mean blood pressure of the patients at different time points was observed in both groups while controlling for baseline measures in the longitudinal model ($P < 0.05$). The mean blood pressures of the patients in the group with intravenous infusion of Lidocaine as well as the controls are shown separately in Table 2.

The VAS at recovery was lower in the Lidocaine group ($P = 0.02$). Results of generalized linear modeling revealed that pain intensity decreased over time in both groups ($P = 0.022$), and the groups had different trend slopes in pain intensity over repeated measurements at various time points up to 24-hours after laparoscopy, while controlling for baseline VAS at recovery and ASA PS ($P = 0.016$). However, when adding to the model the total amount of administered painkillers, the trends were not found to be different (Figure 2 and Table 3).

In patients with the intravenous infusion of Lidocaine, mean time to receive analgesic was 103.5 minutes (SD 26.5) versus 77.8 minutes (SD 12.6) in the control group, yet the difference was not statistically significant. Half of the patients in the Lidocaine group did not need analgesic during the first 24-hours after the procedure versus only 13.3% in the control group. The association between the number of analgesics and Lidocaine administrations was statistically significant ($P = 0.01$). Patients in the Lidocaine group were 3.8 times more likely not to need postoperative analgesic (95% CI: 1.4 to 9.9). The Number Needed to Treat (NNT) for such benefit was 2.7 (95% CI: 1.7 to 6.7). Mean total analgesic dose was 1.3 mg in the Lidocaine group versus 38.2 mg in the control group, differing significantly between the 2 groups ($P < 0.01$). Patients in the two groups were also studied and compared with respect to the risk of postoperative complications and possible side effects of drugs used in infusion for analgesia (Table 4).

Table 1. Demographic Specifications of Patients With Intravenous Infusion of Lidocaine to Control Postoperative Pain After Laparoscopic Gynecologic Compared With the Control Group[a]

Variable	Control Group	Lidocaine Group	P Value
Age, years	30.6 ± 7.8	33.6 ± 7.8	0.14
Weight, kg	68.4 ± 6.9	68.2 ± 7.9	0.91
ASA-PS class			0.14
Class I	27 (90)	23 (76.7)	
Class II	3 (10)	7 (23.3)	
Operation time, min	57.3 ± 19.8	59 ± 19.3	0.72
Laparoscopic operation type			0.39
Therapeutic	17 (56.7)	19 (63.3)	
Cystectomy	14 (46.7)	15 (50)	
Ectopic pregnancy	3 (10)	3 (10)	
Tubal ligation	0 (0)	1 (3.3)	
Diagnostic-Therapeutic	13 (43.3)	11 (36.7)	
Airway management type			0.39
Intubation	19 (3.63)	21 (70)	
Laryngeal Mask Airway (LMA)	11 (7.36)	9 (30)	

Abbreviations: ASA-PS, American society of Anesthesiologists physical status; SD, standard deviation.
[a]Values are expressed as mean ± SD or No. (%).

Table 2. Mean Blood Pressure Changes in Patients With and Without Intravenous Infusion of Lidocaine During Surgery After Laparoscopic Gynecologic Surgery[a,b]

Mean Blood Pressure, mmHg	With Lidocaine	Without Lidocaine	P Value
Baseline	100.4 ± 2.7	95.7 ± 2.5	0.2
After anesthesia	94.6 ± 2.1	92.2 ± 2.1	0.45
15 min later	98.9 ± 2.2	95.5 ± 2.5	0.32
At the entrance to recovery	97.8 ± 1.9	90.6 ± 1.6	0.01
At departure from recovery	97.8 ± 2.5	85.3 ± 1.3	< 0.001

[a]Values are expressed as mean ± SEM.
[b]$P < 0.05$ was considered statistically significant.

4. Discussion

The results of this study showed that intravenous infusion of Lidocaine during laparoscopic pelvic surgeries caused a significant reduction of postoperative pain, overall dosage, and frequency of painkillers after surgery, and the length of time needed to prescribe an analgesic. It was also shown that intravenous infusion of Lidocaine was associated with less postoperative nausea when compared with the control group. However, no effect of Lidocaine on recovery of bowel movement during the procedure was observed.

Laparoscopic surgery causes less postoperative pain compared to open surgery, yet according to various reports, about 35% to 63% of patients undergoing laparoscopic surgery experienced moderate to severe pain af-

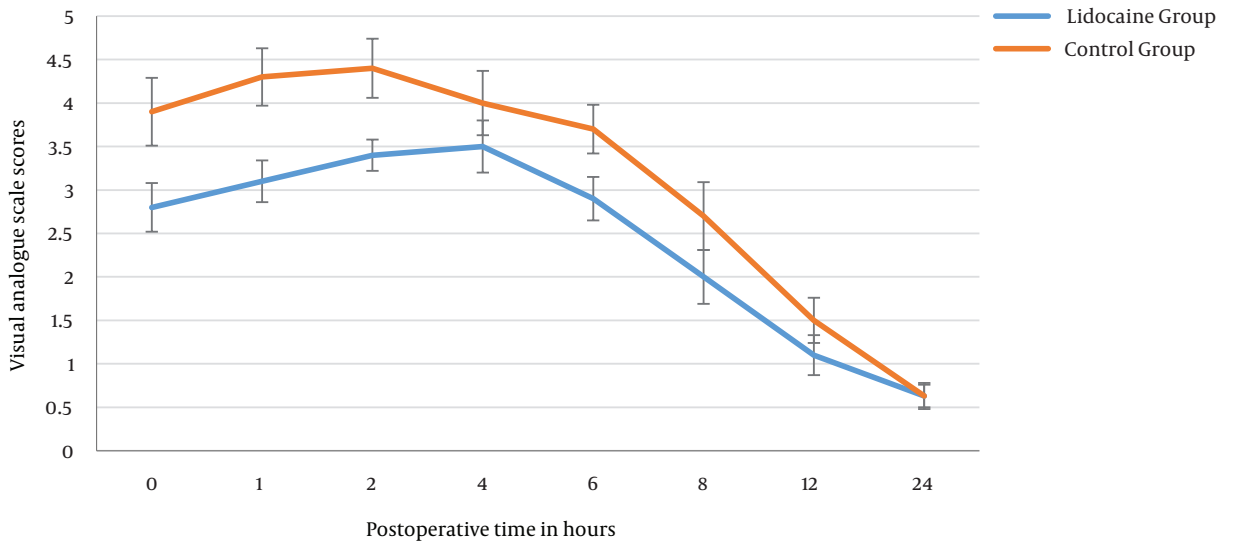

Figure 2. The trends of pain visual analogue scale scores compared between the group receiving Lidocaine infusion and control group (Error bars represent standard errors of mean)

Table 3. Details of Pain Assessment Measures Compared Between the Group Receiving Lidocaine Infusion and the Control Group

Group	VAS* at Recovery	VAS After 1 h	VAS 2 h	VAS 4 h	VAS 6 h	VAS 8 h	VAS 12 h	VAS 24 h
Lidocaine group								
Mean	2.8	3.1	3.4	3.5	2.9	2	1.1	0.63
Median	2	3	3	3	3	2	1	0.5
SD**	1.5	1.3	1	1.7	1.3	1.7	1.3	0.72
IQR***	1	2	1	2	2	1	1	1
Control group								
Mean	3.9	4.3	4.4	4	3.7	2.7	1.5	0.63
Median	4	4	4	4	4	2	1	0
SD	2.2	1.8	1.9	2	1.5	2.1	1.4	0.81
IQR	4	3	3	3	1	2	1	1
Total								
Mean	3.3	3.7	3.9	3.8	3.3	2.4	1.3	0.63
Median	3	4	4	4	3	2	1	0
SD	1.9	1.7	1.6	1.9	1.5	2	1.4	0.76
IQR	2	1.5	1	1	2	2	2	1

Abbreviations: IQR, Interquartile range; VAS, Visual analogue scale; SD, standard deviation.

ter the procedure. Postoperative pain is the most common cause of delay in discharge and even premature admission among patients undergoing laparoscopic surgery, which is often performed as an outpatient procedure (9, 10). Pain after laparoscopy is multifactorial and appears as a result of various reasons. It may be a visceral pain, maybe caused by irritation of parietal peritoneum due to blowing gas into the peritoneal cavity, or be induced due to surgical trauma to the abdominal wall. Shoulder tip pain or scapular tip pain may be caused by irritation of the diaphragm and phrenic nerve for blowing gas into the peritoneal cavity, particularly at the Trendelenburg position.

Table 4. Potential Side Effects in Patients With and Without Intravenous Infusion of Lidocaine During Surgery to Control Postoperative Pain After Gynecologic Laparoscopy

Event	Lidocaine Group	Control Group	P Value	Risk Ratio	95% CI
Nausea	3 (10)	13 (43.3)	0.004	0.23	(0.07 - 0.73)
Vomiting	2 (7/6)	3 (10)	0.64	0.67	(0.12 - 3.7)
Chills	5 (7/16)	6 (20)	0.74	0.83	(0.28 - 2.4)
Fidget	5 (7/16)	12 (40)	0.045	0.42	(0.17 - 1.04)
Ileus	3 (10)	6 (20)	0.28	0.5	(0.14 - 1.8)

Abbreviation: CI, confidence interval (calculated using exact method).

Visceral and parietal pain peaks in early hours after laparoscopic surgery and is exacerbated by coughing and after body movement. Shoulder tip pain occurs mostly around 8-hours after laparoscopic surgery, often the night after surgery. The use of multi-drug regimens or drugs with different mechanisms of analgesia is effective in the prevention and treatment of such pain (11).

The sodium channel binding property of Lidocaine is assumed to yield an important mechanism of action to decrease ectopic neural activity, peripherally. Lidocaine is known as a drug with analgesic and anti-inflammatory properties through different mechanisms of action, including blocking the NA receptors, inhibitory effects on G-protein coupled receptors and on N-methyl-D-aspartate receptors. This will suppress the excitability of dorsal horn neurons, reduce the amplitude and nerve conduction time of both myelinated and demyelinated nerve fibers. Lidocaine may also suppress central sensitization yet has strong anti-inflammatory effects. Interestingly, the analgesic effect of Lidocaine continues for some time even after cessation of the infusion due to inhibition of spinal or environmental sensitivity or both. This is possibly achieved through inhibiting the N-methyl-D-aspartate receptor or priming leukocytes or both (10, 12-14).

In this study, patients, who received Lidocaine during laparoscopic surgery compared with the control group, experienced significantly less severe postoperative pain at all timepoints during the first 12-hours after laparoscopy. A thorough exploration of pain severity trend compared between the groups in the present study showed that both groups had a decreasing trend of postoperative pain similarly ending in its lowest level after 24-hours. The most important difference in this trend is the return to the pain level at first measurement showing that Lidocaine leads to a substantially higher analgesic effect early after the operation. The lower pain severity scores at the first measurement could effect consequent scores that were found to be lower in the Lidocaine group except for the last measurement, which could be assumed as the final effect point. This was while patients in the control group received higher total doses of analgesics as well as having a higher need for receiving analgesics. Although primary analysis showed a slightly steeper decreasing trend for the control group, it disappeared in multivariate longitudinal analysis while controlling for the analgesic use. This pattern of Lidocaine is in line with the expected effects of Lidocaine to appear at earlier hours and mainly on visceral pain (9, 11, 15, 16). It has been shown that the effect may last even up to three days (15). However, a recent study showed that although Lidocaine may give rise to a mean reduction of 0.8 to 0.3 in VAS at 1 to 4 hours and 24 hours, no difference could be expected after 24-hours of surgery (7). Lidocaine is shown to also be effective after open surgery as well as tonsillectomy, arthroplasty, coronary artery bypass surgery, supratentorial tumor surgery, and nephrectomy; nevertheless, well-documented detailed evidence has not been reported on its effect after laparoscopic surgery (17-21). Furthermore, there have been studies, such as that by Gregory L Bryson showing no effect for Lidocaine infusion on postoperative pain (5). The current study showed that the time to need analgesics was longer in the Lidocaine group although not found to be statistically significant. However, the number of people needing analgesics and the total dose of analgesics revealed a beneficial effect of Lidocaine.

Studies conducted by Walid EL- Sherbiny et al. from the infiltration of small abdominal laparoscopic surgery using Lidocaine and Bupivacaine, and Yin-You Chou, using drug infiltration, also showed the greatest effect of Lidocaine in the early hours (5, 10). On the other hand, Grady P et al. showed that intravenous infusion of Lidocaine caused a significant and prolonged decrease in laparoscopic abdominal pain that continues even up to 3-days after surgery, such that postoperative Morphine consumption also decreases dramatically (18). Baral et al. in their study on the effect of Lidocaine on postoperative analgesia in the upper abdomen showed the meantime to receive the first analgesic dose for postoperative pain control in patients receiving Lidocaine was considerably longer than the control group (6).

The differences in the results of various studies may be due to dose differences or differences in duration of infused drug. In addition, the central and peripheral sensitization pattern could vary according to the type of surgery, due to the difference in the analgesic effect of Lidocaine in different surgeries.

Postoperative ileus is due to several factors, such as postoperative opioid consumption, visceral inflammation associated with surgery, and postoperative sympathetic stimulation. Reduction of postoperative ileus after use of Lidocaine has been reported in various studies and could be explained by its effect on postoperative pain as well as lower consumption of opiates, anti-inflammatory properties of Lidocaine, and direct inhibition of sympathetic myenteric plexus (14). In this study, despite the better control of postoperative pain and lower postoperative opioid consumption in the group receiving Lidocaine, no difference in the incidence of postoperative ileus was observed between the two groups perhaps due to the nature of the procedures performed in the present study, a limited laparoscopic pelvic procedure with less manipulation of the digestive tract. However, in studies with procedures more extensive than ours, the effect of Lidocaine on postoperative pain coexisting with faster return of bowel function was reported for perioperative Lidocaine administration (10, 14, 15, 22).

Additionally, in this study the possible complications after laparoscopic surgery that could be affected by the administration of Lidocaine were evaluated. The incidence of nausea in patients receiving Lidocaine was significantly lower than the control group. This is in line with most previous studies and could be explained by lower postoperative opioid consumption (23-26).

Local anesthetic agents could be responsible for serious and potential lethal complications; the most feared is local anesthetic systemic toxicity (LAST), thus use of such drugs should be cautious and limited. They may have a direct membrane stabilization effect on heart rate and compromise heart function. Although no major side effects were detected in this study, the benefits of the intervention should be weighed against its safety, especially among the elderly (27). In the study by Daykin on older patients with Lidocaine analgesia, it was shown that patients with malignancy had a greater likelihood of developing adverse effects, yet no patients required treatment for Lidocaine toxicity (27).

The present study reported the NNT for not receiving postoperative analgesic to be 2.7, meaning that at least one person out of three receiving intravenous Lidocaine would benefit from treatment. This provides a good decision-making hint for its use, along with other statistics of its advantage, in endoscopic gynecologic surgery.

4.1. Conclusions

The findings of this study indicate that intraoperative Lidocaine infusion during laparoscopic pelvic surgery leads to lower pain severity and frequency after surgery as well as the need for painkillers, especially in the early hours after laparoscopic pelvic surgery. In addition, patients receiving Lidocaine were less likely to experience postoperative nausea. Although no major side effects were detected in this study, the benefits of the intervention should be weighed against its safety.

4.2. Strengths and Limitations

This study had a number of limitations, including the lack of measurement of depth of the anesthesia using BIS, which could have been of help to assess the effect of intraoperative Lidocaine infusion on the amount of anesthetic agents needed. However, this was not considered as the aim of the current study. Moreover, the effect of Lidocaine on metabolic and endocrine responses, associated with anesthesia and surgery, was not investigated in this study. The current study seems to be among the first trials in this specific field. This, could also be considered as a limitation due to the exploratory design of the trial that limits the extrapolation power of the trial.

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Footnotes

Authors' Contribution: All the authors contributed in design and interpretation of results and drafting the manuscript. Farnaz Moslemi, Sousan Rasooli and Marjan Dehdilani had a major role in data collection. Homayoun Sadeghi-Bazargani and Mahnaz Dehdilani performed the analysis and had a major role in drafting the manuscript. All authors read and approved the final manuscript.

Availability of Data and Materials: All the data was gathered by the corresponding author. Data could be shared upon request, conditional on agreement from the committee of ethics and organizational approvals.

Conflict of Interests: The authors declare that they had no conflict of interests with respect to this study.

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