Research Article

Intraperitoneal Lidocaine versus Ketamine for Postoperative Analgesia after Gynecological Laparoscopies; Randomized Controlled Clinical Study

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Abstract
Background: Laparoscopic surgery has become the standard of care for many abdominal and pelvic surgeries. Patients undergoing laparoscopic approaches were found to receive inadequate pain relief and experience high levels of postoperative pain rather than aggressive major surgeries. **Objectives:** to compare the efficacy and safety of intraperitoneal instillation of lidocaine or ketamine for pain relief in patients undergoing gynecological laparoscopies. **Methods:** Seventy-five women scheduled for gynecological laparoscopy were randomized to receive intraperitoneal installation of 20 ml placebo (Group C), lidocaine 120 mg (Group L) or ketamine preservative free 0.2 mg/kg (Group K). The primary outcome measure was to compare pain scoring using VAS. Secondary outcomes were to evaluate the extubation time, time to first rescue analgesia, analgesic consumption during first postoperative day, and postoperative study drugs related complications. **Results:** There was a statistically significant difference in the postoperative VAS readings on arrival to the recovery room between the three groups. Women in the lidocaine and ketamine groups reported less pain scores throughout the postoperative follow up. Also, women in the lidocaine and ketamine groups experienced less need for postoperative supplemental analgesia. No significant differences regarding the postoperative adverse effects. **Conclusion:** Intraperitoneal instillation of lidocaine or ketamine at the end of gynecological laparoscopies is an effective and safe for pain relief when compared to placebo. It is associated with less need for supplemental analgesic consumption during the first postoperative day, high patients' satisfaction rate and minimal adverse effects.
Keywords: Intraperitoneal, Lidocaine, Ketamine, Postoperative pain, laparoscopies.

Introduction
Laparoscopic surgery is usually associated with less peritoneal injury and tissue trauma[(1)], decreased morbidity, shorter hospital stay, improved surgical outcomes, and improved quality of life when compared with conventional surgeries[(2)].

Upper abdominal, shoulder, and postural high back pain after laparoscopy are likely to be caused by gas retained in the peritoneal cavity. Carbon dioxide is usually used to expand the abdomen to allow surgical visualization. It can take up to two days to be absorbed from the peritoneal cavity. Pain from the residual gas is of delayed onset and may present once the patient has gone home. The worst pain after gynecological laparoscopic surgeries was felt in the shoulder in 1% of the patients, two hours after surgery, but in 70% of the patients 24 hours after surgeries[(3)].

Patients undergoing laparoscopic approaches, that have the reputation of being less painful, were found to receive inadequate pain relief and experience high levels of postoperative pain rather than aggressive major surgeries[(4)]. Procedure-specific analysis of postoperative pain characteristics is necessary to proper analgesic use and optimal dynamic pain relief, allowing fast convalescence[(5)].

Administration of local anesthetics into the abdomen may be an effective way of decreasing the pain after laparoscopy[(6)]. Ketamine is a non-specific N-methyl–D-

aspartate (NMDA) receptor antagonist with hypnotic and analgesic activity, which can be administrated in many ways[7]. It seems that intra peritoneal administration of ketamine could be an acceptable surrogate to local anesthetics such as bupivacaine as a postoperative analgesic in laparoscopic surgery[8].

The objective of this study was to compare the safety and analgesic effects of intraperitoneal instillation of lidocaine or ketamine in patients undergoing laparoscopic gynecological procedures.

Material and Methods

Eligibility: This prospective, randomized, double-blind clinical study was conducted in Women's Health Hospital in the period of June 2014 to September 2016. After approval from the Institutional Ethics Committee, Assiut University (ref: 00008718) and obtaining written informed consent from women scheduled for elective gynecologic laparoscopies, all patients were informed with complete information about anesthesia and analgesia techniques would be provided to them.

Sample Size: On basis of a pilot study, we assumed that intervention that could cause more than 50% reduction in the incidence of pain after laparoscopies was interesting. With a power of 90% and type I error of 5%, 22 patients were required in each group (α=0.05 and β=90%). To account for possible losses, the number of patients in each group was increased to 25 patients.

Study Design and Randomization: A prospective randomized double-blind controlled study using a computer-generated randomization program was carried out on 75 patients scheduled for elective gynecologic laparoscopies. Neither the investigator nor the participant was aware of the group allocation or the drug used. Drugs were prepared by one investigator (not included in the anesthesia procedure, observation or in the data collection).

Patients were randomly allocated into three equal groups; Group C: included 25 patients received intraperitoneal installation of 20 ml of normal saline (NaCl 0.9%). Group L: included 25 patients received intraperitoneal installation of lidocaine 120 mg (diluted with normal saline to 20 ml total volume). Group K: included 25 patients received intraperitoneal installation of ketamine preservative free 0.2 mg/kg (diluted with normal saline to 20 ml total volume). All study drugs were installed intraperitoneally immediately after the end of the procedure and before removal of surgical trocars.

Inclusion criteria: Age 20-40 years, ASA (American Society of Anesthesia) physical status I-II, elective gynecologic laparoscopies.

Exclusion criteria: Patient refusal, women with history of any allergy to study drugs, scar of previous surgeries, chronic opioid use, cardiac disease, diabetes mellitus, hepatic impairment or any other contraindication for laparoscopies.

Anesthetic Technique: Without premedication all patients were pre-oxygenated with 100% O_2 for three minutes via facemask and intravenous access was inserted and secured. Normal saline 0.9% 4 ml/kg/h was infused intraoperatively. General anesthesia was induced by Fentanyl 1 µg/kg, Propofol 2 mg/kg and Atracrium Besylate 0.5 mg/kg. Endotracheal intubation then was done, using oral endotracheal tube of appropriate size under direct laryngoscopy and secured at the angle of the mouth. Isoflurane inhalational anesthetic (1-2 %) in 100% oxygen and Atracrium Besylate 0.1 mg/kg were used for maintenance of anesthesia. The lungs were mechanically ventilated to keep intraoperative EtCO2 35-40 mmHg.

Surgical Technique: Under complete antiseptic condition, a small cut is made just below the umbilicus (navel) through which the operating telescope was inserted. CO_2 gas was used for distension of the abdominal and pelvic cavities. When necessary, separate small incisions were made low down and at the sides of the abdomen to allow insertion of other fine instruments. At the end of the surgery, instillation of the study drugs was done. CO_2 gas was encouraged to escape from the

abdominal cavity. The incisions were closed with fine stitches and covered with sterile dressings.

Intraoperative Monitoring: ECG, heart rate, non-invasive blood pressure, SpO_2 and end-tidal CO_2 were regularly recorded every 5 minutes during the whole procedure.

Postoperative Analgesia: All pain scores were obtained during rest. To assess postoperative pain, visual analogue score (VAS) was used by means of a 10 cm line with score (0) indicated no pain and score[10] indicated worst pain ever. If VAS ≥ 4, rescue analgesia was indicated. VAS was used immediately at the recovery room (Time 0), 1, 2, 4, 6, 12 and 24 hours postoperatively. VAS was performed to assess global abdominal pain. Double-sided print or photocopy ensuring that the lines are exactly 10 cm in length and superimposed[9]. Intravenous infusion of paracetamol 1g (perfalgan, paracetamol 1000 mg. UPSA laboratories, France) was used for postoperative supplemental analgesia. The supplemental analgesia was given directly by the anesthesiologist over 15 minutes and the total amount of paracetamol used within 24 hours post-operatively was recorded. Patient's satisfaction was also recorded at the end of the first 24 hours postoperatively.

Postoperative Assessment: The length of postoperative ileus was evaluated by asking the patient when they recovered the ability to pass flatus, to tolerate a normal diet and be fully mobile. Any adverse effects were observed as regarding sweating, nausea, vomiting, dizziness, vertigo, dry mouth, headache, dyspnea, hallucination or confusion.

Statistical Analysis: Data were verified, coded by the researcher and analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA) for Windows. Quantitative data were compared using One-way ANOVA and Student's t-test. Qualitative data were analyzed using the Chi-square test. VAS was compared using the Wilcoxon ranked sum test. P-values < 0.05 were considered statistically significant.

Results

The study recruited eighty patients, five of whom were excluded before randomization. The final analysis included a total of seventy-five patients who were enrolled in the study. A flow diagram of the study is shown in (Figure 1).

All patients included in this study were discharged from the hospital about 24 hours after end of surgeries. Demographic data and clinical characteristics of these women were shown in table (1). There were no statistically significant differences between the three groups as regarding age, weight, ASA status, duration of anesthesia, duration of operation, time to extubation after end of surgery, and type of surgical procedure.

There were no statistically significant differences between the three study groups as regarding the preoperative, intraoperative or postoperative heart rate (HR), non-invasive mean blood pressure (MBP), O_2 saturation (SpO_2) and end-tidal CO_2.

Table (2) shows the postoperative VAS readings. There was a statistically signify-cant difference in the postoperative readings on arrival to the recovery room between the three groups. It was 4.80±1.40 in the control group, 2.38±0.84 in the lidocaine group and 2.40±0.91 in the ketamine group. Women in the lidocaine and ketamine groups reported less pain scores throughout the postoperative follow up, this was statistically significant only at full recovery after anesthesia (time 0) and 1 hour postoperatively.

As regards the need for postoperative supplemental analgesia, women in the lidocaine and ketamine groups experienced less need for postoperative supplemental analgesia (intravenous Perfalgan) than those in the control group; this difference was statistically significant. The difference between the three groups was also statisti-cally significant regarding the total amount of supplemental analgesia used within the first postoperative 24 hours. The different times at which postoperative supplemental analgesia was given to these cases were

shown in table (3). Most of women asked for postoperative supple-mental analgesia were in the first 2-4 postoperative hours as described in table (3).

The length of postoperative ileus was not statistically significant different in the three study groups. Women in the lidocaine and ketamine groups reported a high rate of satisfaction with the whole postoperative care and willingness to retake the same medication again in the future with a statistically significant different than the control group as described in table (4).

Women in the three study groups reported no significant differences regarding the postoperative adverse effects as bloating, nausea and vomiting, sweating, headache or abdominal cramps. The incidence of minimal adverse effects was recorded in 9/25 women (36%) of the control group, 8/25 women (32%) of the lidocaine group and 7/25 women (28%) of the ketamine group (table 5). No serious complications were recorded.

Table 1: Demographic Data and Patients' Characteristics

Parameter	Control (n=25)	Lidocaine (n=25)	Ketamine (n=25)	P value
Age (years)	23.50±3.89	24.10±4.53	23.70±3.56	NS
Weight (kg)	63.80±11.05	65.30±9.88	62.50±11.12	NS
ASA I/II	22/3	21/4	22/3	NS
Duration of anesthesia: (minutes)	55.01±34.11	60.18±27.50	57.45±30.60	NS
Duration of operation: (minutes)	43.00±29.58	46.50±26.63	45.00±32.26	NS
Time to extubation after end of surgery (minutes)	8.61±2.85	9.87±1.59	8.99±2.27	NS
Indication of operation: no. (%) Diagnostic laparoscopy PCO Drilling Peritubal Adhesolysis Endometriosis	 13(52%) 10(40%) 2(8%) 0(0%)	 11(44%) 12(48%) 2(8%) 0(0%)	 12(48%) 9(36%) 3(12%) 1(4%)	NS

Data are presented as mean ± SD, numbers or percentages

Table 2: Postoperative Visual Analogue Score (VAS)

Parameter	Control (n=25)	Lidocaine (n=25)	Ketamine (n=25)	P value
VAS at recovery (time 0)	4.80±1.40	2.38±0.84	2.40±0.91	0.000*
VAS postoperative 1 hour	3.60±0.97	3.42±1.48	2.80±1.03	0.002*
VAS postoperative 2 hours	2.95±0.63	2.50±0.34	2.75±0.60	NS
VAS postoperative 4 hours	3.15±1.05	3.05±1.27	3.00±0.90	NS
VAS postoperative 6 hours	3.10±0.97	2.60±0.87	2.80±1.03	NS
VAS postoperative 12 hours	2.55±0.60	2.47±0.52	2.40±0.44	NS
VAS postoperative 24 hours	2.80±1.03	2.30±0.83	2.20±0.65	NS

Data are presented as mean ± SD

* statistically significant difference

Table 3: Supplemental Analgesia (intravenous paracetamol)

Parameter	Control (n=25)	Lidocaine (n=25)	Ketamine (n=25)	P value
Need for supplemental analgesia: no. (%)				0.000*
Yes	25(100%)	18(72%)	16(64%)	
No	0(0%)	7(28%)	9(36%)	
Time to 1st analgesic requirement (hours)	0.05±0.12	1.35±0.63	2.40±1.45	0.000*
Total amount of supplemental analgesia within 24 hours (range)	1200.0±210.8 (1000-1500)	900.0±516.4 (0-1500)	675.0±334.4 (0-1000)	0.002*

Data are presented as mean ± SD, numbers, percentages or range
* statistically significant difference

Table 4: Patients′ Satisfaction with technique and medications

Parameter	Control (n=25)	Lidocaine (n=25)	Ketamine (n=25)	P value
Postoperative ileus (hours)	3.7±1.81	3.9±1.54	3.5±1.95	NS
Patients′ Satisfaction with medications				0.021*
No	14(56%)	6(24%)	5(20%)	
Yes	11(44%)	19(76%)	20(80%)	
Willingness to retake the same analgesic medication in future				0.013*
No	12(48%)	5(20%)	4(16%)	
Yes	13(52%)	20(80%)	21(84%)	

Data are presented as mean ± SD, numbers and percentages
* statistically significant difference

Table 5: Postoperative data and adverse effects

Parameter	Control (n=25)	Lidocaine (n=25)	Ketamine (n=25)	P value
Postoperative ileus (hours)	3.7±1.81	3.9±1.54	3.5±1.95	NS
Adverse Effects: no. (%)				NS
None	16(64%)	17(68%)	18(72%)	
Nausea & vomiting	4(16%)	5(20%)	4(16%)	
Bloating	1(4%)	2(8%)	1(4%)	
Sweating	0(0%)	0(0%)	1(4%)	
Headache	2(8%)	1(4%)	1(0%)	
Abdominal Cramps	2(8%)	0(0%)	0(0%)	

Data are presented as mean ± SD, numbers and percentages

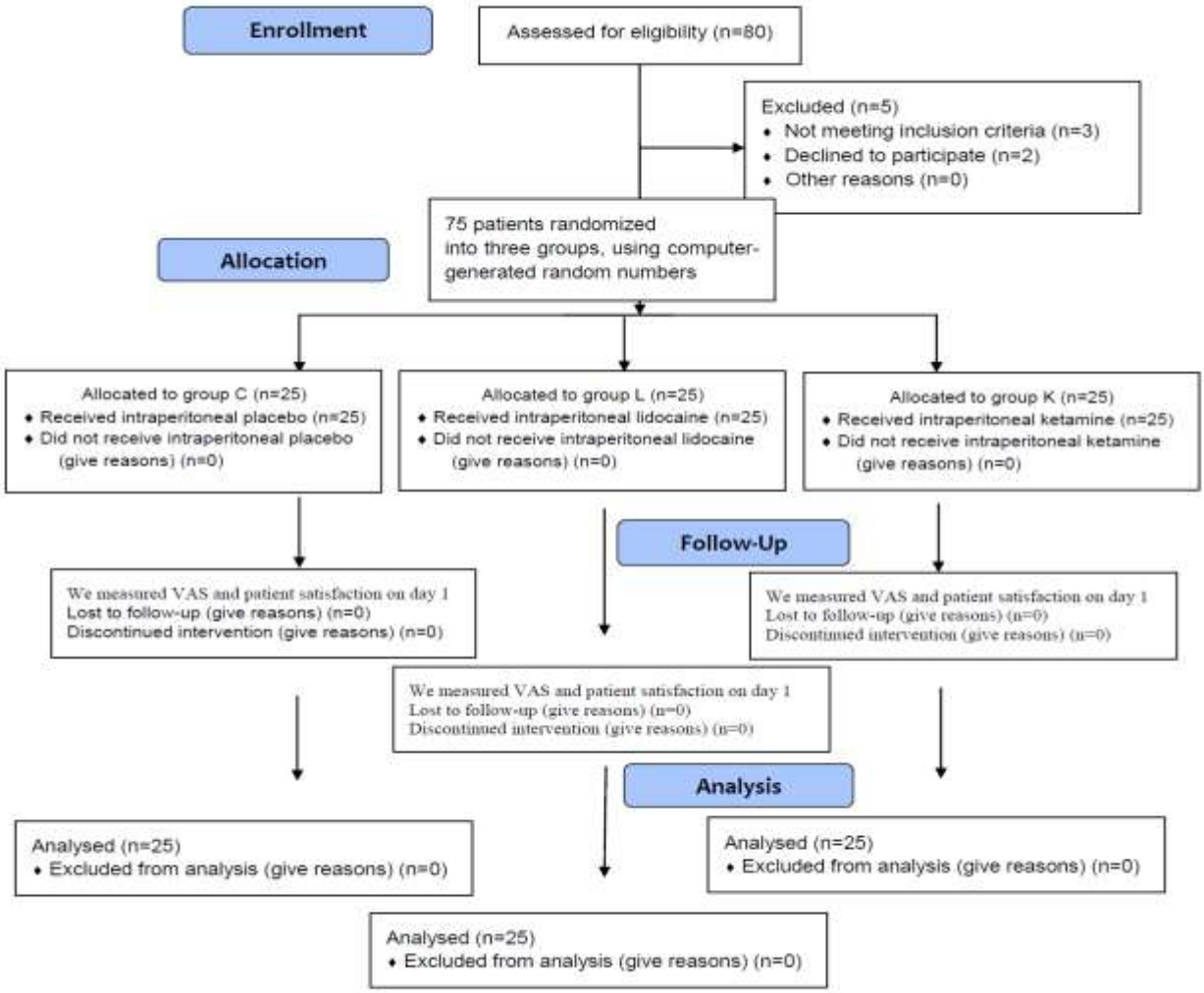

Figure (1): Flow diagram of all patients included in the three study groups

Discussion

Procedure-specific analysis of characteristics on early postoperative pain is necessary for proper analgesic use and optimal dynamic pain relief, allowing fast convalescence[6]. The pain characteristics have been previously described in the literature concerning laparoscopic cholecystectomy, laparoscopic ventral hernia repair, laparoscopic inguinal hernia repair, laparoscopic fundoplication, neurosurgeries, and cesarean section[10].

Early postoperative pain after laparoscopic procedures is common[11]. Some laparoscopic procedures are performed on a day-case or fast track basis, and this emphasizes the importance of improving early postoperative pain relief. The use of local anesthetic infiltration for post-operative analgesia may allow widespread use of laparoscopic day-case surgery[12]. Intraperitoneal administration of local anesthetics has been shown to be effective in some previous studies[11,13]. However, other investigators have not been able to confirm the analgesic efficacy of intraperitoneal local anesthetics[14].

Preoperative administration of ketamine, an NMDA-receptor antagonist, should prevent central sensitization and may improve postoperative pain relief. This is termed preemptive analgesia. However, despite the

overwhelming success in animal experiments[15], clinical report confirming the preemptive analgesic effects of ketamine have not been forthcoming[16]. Minimally invasive surgery produces less tissue trauma. A smaller dose of ketamine may be sufficient to block perioperative noxious input without additional psychotomimetic side effects[17].

The efficacy of intra peritoneal Ketamine S (+) was superior to the intra peritoneal lidocaine. N-methyl –D-aspartate (NMDA) receptor activation is considered one of the mechanism of postoperative pain, and the hypersensitivity through both peripheral (intraperitoneal), and central effects (intravenous route)[18].

Peripheral (peritoneal) NMDA receptors blockade by S (+) Ketamine was involved in reduction of postoperative pain, and analgesic requirement following bariatric surgery[8].

In this study, we compared the postoperative analgesic requirement in patients receiving intraperitoneal lidocaine and patients receiving intraperitoneal ketamine. We found that intraperitoneal lidocaine (120mg) or small dose of ketamine (0.2 mg/kg) improves the postoperative pain relief (p value <0.001) especially in the first second hour postoperatively and it really decrease the need for further analgesia.

We reported that intraperitoneal instillation of ketamine has no statistically significant difference regarding the hemodynamic changes. In agree with our study, De Kock et al., who used ketamine (0.15 mg/kg) and they reported that ketamine did not change hemodynamic or respiratory variables. Patients were not sedated, and there was no difference in the incidence of postoperative nausea and vomiting among groups[19].

We recorded a statistically significant difference in the postoperative VAS readings on arrival to the recovery room and one hour postoperatively between the three groups with lower pain scores in lidocaine and ketamine groups.

Our study evaluated the effect of local anesthetics effect of intraperitoneal administration of (120 mg per dose) lidocaine for postoperative pain relief after minor gynecologic laparoscopic surgery. The rationale for intraperitoneal administration of drugs for treatment of the pain following laparoscopic surgery is that the small incisions in the abdominal wall cause the visceral component of the pain to be more prominent. Many clinicians have tried to diminish pain via the peritoneal route[20].

Intraperitoneal administration of drugs is considered to be safe, to improve patient comfort, and to shorten the duration of stay in the postoperative care unit. However, some studies have reported that administration of intraperitoneal local anesthetics do not provide adequate postoperative analgesia. They reported that administration of local anesthetics under direct vision at the beginning of laparoscopy in the right sub-diaphragmatic peritoneum has been shown to decrease postoperative shoulder pain. However, it has not been able to decrease visceral pain after laparoscopic cholecystectomy[21,22].

In gynecological studies, lower postoperative pain scores after local anesthetic administration have been reported. Sharon et al.,[13] used continuous intraperitoneal insufflations of lidocaine, and they found that it could reduce pain significantly in the initial stage of postoperative recovery. In addition, Zadah et al.,[23] used intra--peritoneal 10 ml 2% lidocaine and found that this too provided effective analgesia.

Zahran et al., in 2011, concluded that the combined use somatic (trochar site) and visceral (intraperitoneal) lidocaine blockade is superior to intraperitoneal lidocaine alone in managing postoperative pain for laparoscopic gynecological procedures. It led to lower VAS scores, less need for additional analgesics and higher patients' satisfaction[24].

The postoperative pain induced by minor gynecologic laparoscopic procedures had a considerable visceral component, owing to

surgical handling and irritation of the diaphragm by dissolved carbon dioxide, and a lesser somatic component from the holes made in the abdominal wall for the trocars[25].

The present study showed that intra-peritoneal instillation of lidocaine at the end of laparoscopic gynecological surgery led to significantly lower pain scores. Similarly, Sharon et al.,[13], Ahmed et al.,[26], and Moiniche et al.,[27] concluded that instillation of local anesthetic at the end of laparoscopic surgery reduced post-operative pain and markedly reduced the need for postoperative analgesia.

Studies regarding acute pain have recommended the use of multimodal thera-peutic regimens, in order to enhance the efficacy of analgesic regimens while decreasing the untoward side effects[28].

Women in lidocaine and ketamine groups reported higher rate of satisfaction with the postoperative care and willingness to retake the same medication in the future and this was statistically significant than the control group.

Women in all groups reported no difference regarding the duration of postoperative ileus and incidence of postoperative adverse effects as bloating, nausea and vomiting, sweating, headache or abdominal cramps. These were statistically not significant. The incidence of adverse effects was reported in 9 cases (36%) of the control group, in 8 cases (32%) in the lidocaine group and in 7 cases (28%) in the ketamine group.

In conclusion, intraperitoneal instillation of lidocaine or ketamine at the end of gynecological laparoscopies is effective and safe for pain relief when compared to placebo. It is associated with decrease postoperative amount of supplemental analgesic consumption during the first postoperative day, high patients' satisfaction rate and minimal adverse effects.

Limitations: Small sample size, larger studies with a larger sample size may be helpful to confirm and validate our results. Another limitation is that we did not record the shoulder pain intensity and relief as we selected minimally invasive laparoscopic surgeries in which the visceral component of pain is important.

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