

# Multi-Modal Analgesic Technique for Pain Control in Patients Undergoing Diagnostic Gynecological Laparoscopy: Randomized Controlled Clinical Trial

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## Abstract

**Citation:** Refaat S, Mawgood AA, Al Sonbaty MA, Gamal M, Ahmed A. Multi-Modal Analgesic Technique for Pain Control in Patients Undergoing Diagnostic Gynecological Laparoscopy: Randomized Controlled Clinical Trial. Open Access Maced J Med Sci. <https://doi.org/10.3889/oamjms.2019.184>

**Keywords:** Diagnostic laparoscopy; Multi-modal analgesia; Intraperitoneal lidocaine; Pulmonary recruitment

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**Received:** 23-Feb-2019; **Revised:** 14-Apr-2019; **Accepted:** 15-Apr-2019; **Online first:** 30-Apr-2019

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**Funding:** This work was funded by Cairo University

**Competing Interests:** The authors have declared that no competing interests exist

**BACKGROUND:** Advancement in minimally invasive laparoscopic surgeries make it one of the best choices for both the surgeon and the patient. The anesthesiologist had to improve the techniques used to control post-operative pain.

**AIM:** In this study, we hypothesized that multi-modal analgesic technique which is a combination of two simple techniques (intraperitoneal lidocaine and pulmonary recruitment) allow better result than using only one of them.

**PATIENTS AND METHOD:** This randomised controlled, double-blind study was conducted in Kasr-Alainy hospital, faculty of medicine, Cairo University, Egypt from September 2017 till February 2018. Fifty female patients, scheduled for diagnostic gynecologic laparoscopy were included in the study. Patients were randomly allocated using random computer allocation with numbered closed opaque envelopes into four study group. GM (n = 12): Patients received pulmonary recruitment maneuver and intra-peritoneal Lidocaine, GL (n = 13): Patients received intra-peritoneal Lidocaine, GP (n = 13): Patients received Pulmonary Recruitment Maneuver, GC (n = 12): Patients received passive exsufflation through the port site. In the ward, patients were asked to fulfil a questionnaire about pain severity using (VAS) at 1, 3, 6-hour post-operative both the patients and the anesthesiologist that assess the (VAS) were blind of the patient group

**RESULTS:** Regarding pain score between groups VAS 1 (the primary outcome) was lowest in GM {4.5 (3-5)} in comparison with other groups (P value = 0.015). While VAS 3 & VAS 6 wasn't statistically significant between groups. Regarding Time of first rescue analgesia; GM {3 (1.75-4)} showed the longest time in between groups (P-value = 0.042). As regard nausea and vomiting; there was no statistically significant difference in in-between groups.

**CONCLUSION:** Application of Multi-modal analgesic technique allows better analgesia for a longer duration than the use of the sole technique for control of abdominal pain in patients undergoing diagnostic gynaecological laparoscopy.

## Introduction

The advancement of laparoscopy and minimal access surgeries has greatly influenced the evolution of anaesthetic techniques. However, postoperative pain intensity may be significant, with up to 40% of patients being unsatisfied with routine analgesia and up to 80% requiring rescue opioids during their hospital stay. Pain relief after diagnostic laparoscopy, being a day case, is an issue of great practical importance [1], [2].

Pain after laparoscopy arises from three main sources: the incision site (50% to 70%), the pneumoperitoneum (20% to 30%) (in association with

peritoneal and diaphragmatic stretching, ischemia, and acidosis), and the procedure site (10% to 20%). Pain can also be referred from the sub-diaphragmatic region as shoulder pain, which is often mild in intensity and can remain for 24 hours [3], [4].

Local anaesthetics (LA) that are infiltrated pre-incisional can only eliminate incision postoperative pain. In contrast, intraperitoneal local anaesthetic installation is a good method for providing post laparoscopy pain relief. Several mechanisms of action of intraperitoneal local anaesthetic have been proposed either by a sensory neural block of peritoneal pain receptors, through a block of vagal nerve afferent that transmit visceral stimulation or through the anti-inflammatory analgesic effect of LA.

Other opinions refer to the analgesic effect was due to systemic absorption of LA through the peritoneum. Intraperitoneal local anaesthetic should not be administered to patients who have allergy for LA [4], [5].

The Pulmonary Recruitment Maneuver (PRM) is a simple manoeuvre that can reduce post laparoscopic shoulder and upper abdominal pain. Various mechanisms of action of PRM were proposed, but all were focused on mechanical removal of residual carbon dioxide (CO<sub>2</sub>). As CO<sub>2</sub> produce phrenic nerve irritation moreover the accumulated residual CO<sub>2</sub> that persist between the liver and the diaphragm irritate both diaphragm and the peritoneum. PRM should not be done in patients have increased intracranial pressure or right-side heart failure [5], [6].

The Multi-modal analgesic technique applied through a combination of two simple and safe methods (intraperitoneal local anaesthetic and pulmonary recruitment) as analgesia for post laparoscopic pain has not been discussed before. Therefore, this study aimed to investigate the effect of Multi-modal analgesic technique on postoperative pain following diagnostic gynecologic laparoscopy to gain the benefit of both techniques, compared to intraperitoneal instillation of lidocaine alone and pulmonary recruitment manoeuvre alone.

## Patients and Method

This randomised controlled, double-blind study was conducted in Kasr-Alainy hospital, faculty of medicine, Cairo University, Cairo, Egypt (one centre) from September 2017 till February 2018. After obtaining approval from the Institutional Research Committee by code, N-61-2017 registered the study at clinical trials.gov by trial number: NCT03241602.

Informed written consent was taken from 48 female patients, aged 18-45 years, ASA I or II, scheduled for diagnostic gynecologic laparoscopy.

Patients were randomly allocated to either of four study groups, 12 per group, using random computer allocation with numbered closed opaque envelopes.

- GM (n = 12): Patients received Multi-modal technique by applying pulmonary recruitment manoeuvre and intra-peritoneal Lidocaine.

- GL (n = 12): Patients received only intra-peritoneal Lidocaine.

- GP (n = 12): Patients received only Pulmonary Recruitment Maneuver.

- GC (control) (n = 12): Patients had passive

exsufflation through the port site and did not receive intra-peritoneal lidocaine nor pulmonary recruitment.

Patients younger than 18 or above 45 years old, patients with (ASA) physical status  $\geq$  III, and who were allergic or hypersensitive to amide-type local anaesthetics were excluded. Also, patients with pre-existing chronic pain disorders, or with history of alcohol or drug abuse, including opioids or tranquillisers for > 1 week preoperatively, were excluded. If the laparoscopy included any interventional procedure or was converted to an open procedure, the patient was also excluded from the study.

Patients attended the pre-anaesthesia room 1 hour before the procedure. A twenty-gauge intravenous cannula was inserted peripherally, and each patient was pre-medicated with intravenous Midazolam 0.02 mg/kg, Ranitidine 50 mg and 10 mg Metoclopramide .

In the operative room, standard monitoring (electrocardiography, pulse oximetry, capnography and non-invasive blood pressure measurement) was applied to the patient. Anaesthesia was induced with propofol 2 mg kg<sup>-1</sup>, Fentanyl 1 mcg kg<sup>-1</sup>, Atracurium 0.5 mg kg<sup>-1</sup> and the trachea were intubated after bag-mask ventilation for 3 minutes. Anaesthesia was maintained with isoflurane 1-2%, and muscular relaxation was maintained with Atracurium 0.1 mg kg<sup>-1</sup> every 15 minutes, and mechanical ventilation (volume control mode) started to keep end-tidal CO<sub>2</sub> at normal values. Depth of anaesthesia was adjusted according to clinical signs.

Laparoscopy was done using CO<sub>2</sub> as a distension medium. Veress needle was introduced at first through the lower border of the umbilicus, and a water test was done to ensure intra-peritoneal placement. Then, reaching proper distension pressure was ensured by the disappearance of dullness over the lower border of the liver — the pressure adjusted to be about 15 mmHg. The patient was placed in a Trendelenburg position to provide optimum conditions for the laparoscopic view. A 10 mm laparoscopic trocar was introduced with 45 degrees towards the pelvis, and zero cameras were introduced through the cannula-trocar. The second puncture could be done through the right or left iliac fossa.

In groups GM and GL, Lidocaine (1.75 ml kg<sup>-1</sup> of 2% lidocaine (3.5 mg kg<sup>-1</sup>) was splashed under the right diaphragmatic area by the surgeon early in the procedure.

At the end of the procedure, the patient was placed back from the Trendelenburg position. In groups GM and GP, the pulmonary recruitment manoeuvre was done, and it consisted of five manual pulmonary inflations with a maximum pressure of 40 cm H<sub>2</sub>O. The anesthesiologist holds the fifth positive pressure inflation for approximately 5 seconds. In group GC, CO<sub>2</sub> was removed by passive exsufflation

through the port site, and gentle abdominal pressure was applied to evacuate the residual gas.

In all groups, after the end of the surgery, the surgeon will infiltrate the incisions with 2 ml of 0.5% bupivacaine. Residual neuromuscular block was antagonised with atropine 0.02 mg kg<sup>-1</sup> and neostigmine 0.05 mg kg<sup>-1</sup>, extubation was done according to extubation criteria.

In the recovery room, patient was asked by anesthesiologist who were both unaware of the intra-operative analgesia technique used for post-operative pain to assess Pain intensity using Visual Analogue Scale (VAS) that was described to the patients before the surgery (it is a straight horizontal line its length is 100 mm. The ends of the line defined as the extreme limits of pain as 0 is no pain, and 100 is the worst pain). The patient asked for analgesia was controlled by intravenous infusion of 1000 mg Acetaminophen. Unsatisfied Patients 30 minutes after acetaminophen received intra-venous Pethidine 1 mg kg<sup>-1</sup>.

Then, the patient was discharged to the ward according to the standard criteria.

In the ward, patients were asked to fulfil a questionnaire about pain severity using Visual Analogue Score (VAS) at 1, 3 and 6 hours postoperative. The Primary outcome of the study was the Visual Analogue Scale (VAS) at 1-hour post-operative. Secondary outcomes were Visual Analogue Scale (VAS) at 3, 6-hour post-operative, Blood pressure (systolic and diastolic), a Heart rate that recorded hourly for the first 6 hours' post-operative. Time of first rescue analgesic and Incidence of nausea and vomiting were also recorded

### Sample size

A previous study that compared intra-peritoneal Lidocaine instillation versus placebo reported 1hour postoperative VAS to be 2.2 vs 4.7 with standard deviation (1.7) [7]. The sample size was calculated using one-way analysis of variance (ANOVA). Taking the power of the study of 90% and an alpha error of 0.5, a minimum number of 10 patients will be needed for each group. This number will be increased to 12 patients per group to compensate for possible dropouts.

### Statistical analysis

Data were presented as means (stander deviation SD), medians (quartiles), frequencies (%) as appropriate. The analysis was done using one-way ANOVA for single measures, mixed model ANOVA for repeated measures, Kruskal Wallis for categorical variables. A P value of  $\leq 0.05$  was considered significant.

## Results

Fifty female patients undergoing diagnostic gynaecological laparoscopy were randomised between four groups. In both groups, GL and GP 13 patient were allocated while 12 patients were analysed as one patient in GL excluded (the patient has the additional intraoperative procedure) and one patient in GP excluded (the patient had an additional abdominal drain). In GM, GC 12 patient was allocated and analysed (Figure 1).

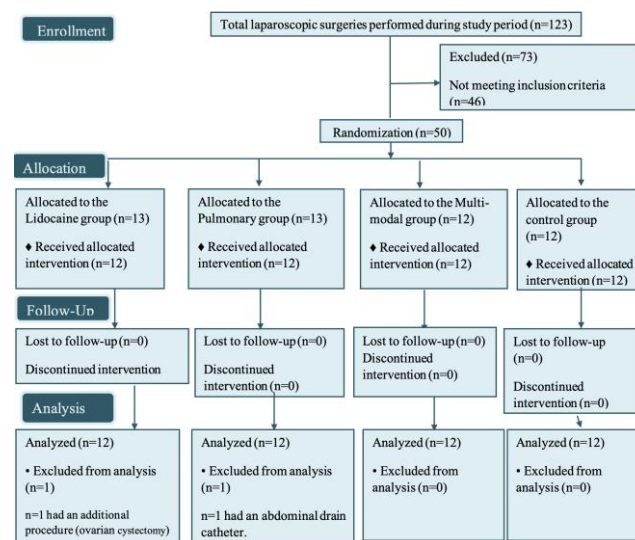


Figure 1: Flow diagram for the patients in the trial

Demographic data (Age, BMI) were comparable between groups Table (1).

Table 1: Demographic data (Age and Body Mass Index BMI) in the four groups

	Pulmonary Group GP (n = 12)	Lidocaine Group GL (n = 12)	Multimodal Group GM (n = 12)	Control Group GC (n = 12)	P value
Age (years)	23.42 ± 2.87	23.08 ± 2.15	23.42 ± 3.15	24.25 ± 2.67	0.755
BMI (kg.m <sup>-2</sup> )	29.19 ± 2.60	29.05 ± 2.26	29.37 ± 2.05	29.23 ± 2.28	0.990

Categorical data were expressed as Mean ± Standard Deviations.

Regarding the score of pain, Visual Analog Scale (VAS) was used (primary outcome). Pain complained by patients was abdominal pain. There was no incidence of shoulder pain during the assessment in the first 6 hours postoperative.

VAS 1 was lowest in GM in comparison with the other groups (P-value = 0.015). GM showed a statistically significant decrease when compared with GP, GC (P-value 0.013, 0.005) respectively.

Regarding VAS 3 & VAS 6 in all groups, the results were not statistically significant Table (2).

**Table 2: Pain score using Visual Analog Scale (VAS) in four groups**

	Pulmonary Group GP (n = 12)	Lidocaine Group GL (n = 12)	Multimodal Group GM (n = 12)	Control Group GC (n = 12)	P value
Visual Analog Scale after first hour (VAS 1)	5.5 (5-7)	5 (4-6)	4.5 (3-5) #	7 (5-7)	0.015
Visual Analog Scale after third hour (VAS 3)	3 (2.5-5)	2.5 (0-5)	3 (1-3.5)	5 (3-5)	0.248
Visual Analog Scale after sixth hour (VAS 6)	0 (0-3)	0 (0-0)	0 (0-3)	3 (0-5)	0.089

Categorical data were expressed as Median and range; statistically significant in comparison with G<sub>C</sub>; # statistically significant in comparison with G<sub>P</sub>; \*\* statistically significant in the comparison between the four groups.

Regarding Time of first rescue analgesia; GM showed the longest time in between groups, and that was statistically significant (P value = 0.042). GP shows less time in comparison to GM and was statistically significant (P value = 0.04) (Table 3).

**Table 3: Time of first rescue analgesia between four groups**

	Pulmonary Group GP (n = 12)	Lidocaine Group GL (n = 12)	Multi modal Group GM (n = 12)	Control Group GC (n = 12)	P value
Time of first rescue analgesia (hours)	1.75 (1-2)	2.25 (1.5-2.75)	3 (1.75-4) #	1.25 (1-2)	0.042 ***

Categorical data were expressed as Median and range; \*\*\* statistically significant in comparison to the four groups; # statistically significant in comparison to GP.

Regarding the comparison of vital signs over time in each group, Systolic Blood Pressure (SBP) in GM was statistically, but not clinically, significant in the comparison between SBP 1 – SBP 6.

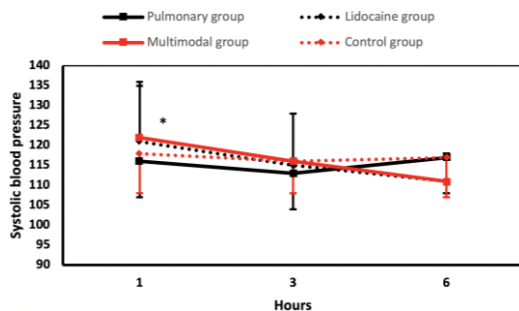


Figure 2: Systolic Blood Pressure measurement over postoperative first 6 hours. Data expressed as means ± Standard deviation

There was a decrease in Diastolic Blood Pressure DBP over time. In GP and GL there was a minimal decrease in both Systolic Blood Pressure SBP and Diastolic Blood Pressure DBP (Figure 2, and 3).

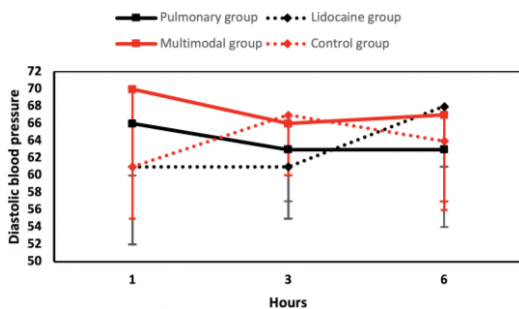


Figure 3: Diastolic Blood Pressure Measurement over postoperative first 6 hours. Data expressed as means ± Standard deviation

There were marginally significant values of decreasing heart rate from the 1<sup>st</sup> to the 3<sup>rd</sup> hour in GP (P-value = 0.053) and GM (P-value = 0.056). No significant differences in vital signs were found between groups in the 1<sup>st</sup> hour with the incidence of tachycardia around 40% (Figure 4).

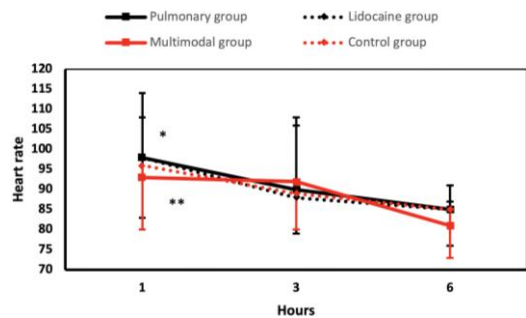


Figure 4: Heart Rate measurement over postoperative first 6 hours. Data expressed as means ± Standard deviation

As regard nausea and vomiting; There were 2 patients in GP, 1 patient in GM and 3 patients in GC who complained of nausea but that was not statistically significant. There was no incidence of vomiting in all groups (Table 4).

**Table 4: incidence of nausea and vomiting in the four groups**

	Pulmonary Group GP (n = 12)	Lidocaine Group GL (n = 12)	Multi modal Group GM (n = 12)	Control Group GC (n = 12)	P value
Nausea n (%)	2 (16.7%)	0 (0%)	1 (8.3%)	3 (25.0%)	0.476
Vomiting n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---

Numerical data were presented as number (percentage).

## Discussion

Pain after laparoscopic surgery is still considered significant, despite being markedly less than the pain after open surgery. This study was designed to find a safe, simple, and effective method to decrease pain after laparoscopy. Diagnostic gynecologic laparoscopy was chosen as our study model procedure because it is less invasive and less time-consuming than the more advanced laparoscopic procedures.

In this study, we use two simple techniques to control postoperative pain: pulmonary recruitment and intraperitoneal lidocaine. We use 1.75 ml kg<sup>-1</sup> (3.5 mg kg<sup>-1</sup>) lidocaine for intraperitoneal injection according to study done by study Yang SY, et al., [8] comparing Efficacy of intraperitoneal and intravenous lidocaine on pain relief. The study showed that 1.75 ml kg<sup>-1</sup> (3.5 mg kg<sup>-1</sup>) lidocaine dose for intraperitoneal (i.p) injection has almost the same efficacy as intravenous lidocaine for postoperative analgesia in laparoscopic

surgeries. Therefore, in this study, we hypothesise that this dose would be both effective and safe for the patients.

In our study, there was no shoulder pain detected, and for assessment of abdominal pain, Visual Analogue Scale (VAS) was used. The VAS of Multi-modal group after one hour, which showed the best result in all groups. No difference was found between the intervention groups in assessment in the 3rd and 6th hour.

In the lidocaine group, the VAS 1 was 5 (4-6), which was better than that of the pulmonary group. Many studies were done to show the efficacy of i.p. Lidocaine in gynaecological surgeries and general abdominal surgeries. In consistency with our results, a study was done by M. Parsanezhad et al., [9] and study done by W. Elsherbiny et al., [10] use intraperitoneal instillation of lidocaine for pain control after diagnostic gynecologic laparoscopy.

Regarding the pulmonary group, in our study, during the assessment of abdominal pain, VAS 1 was 5.5 (5-7), and VAS 3 was 3 (2.5-5). In consistency with our results, a study was done by S. Sharami et al., [11] showed a shoulder pain score of  $1.28 \pm 1.7$ , recorded 4 hours postoperatively.

In contrast with our study, a study was done by H. Liu et al., [12] investigated the effect of combining local anaesthetic infiltration of ropivacaine with pulmonary recruitment manoeuvre on postoperative pain following diagnostic hysteroscopy and laparoscopy. The postoperative pain score was significantly lower in this study: 1st hour,  $1.6 \pm 1.3$ ; a 3rd hour,  $0.5 \pm 0.8$ . They added 20 ml of 0.5% ropivacaine injected preincisionally before placing the trocars.

In the following studies [7], [13], [14], [15] that record the effect of intraperitoneal lidocaine or pulmonary recruitment in abdominal pain after laparoscopic surgeries, the patients had received an oral, intravenous or intraperitoneal analgesic drug from the beginning of the procedure with either pulmonary recruitment or intraperitoneal lidocaine. While in Multi-modal analgesic technique, the patients received two simple and safe manoeuvres. The intraperitoneal local anaesthetic blocks the nociceptors involved in phrenic irritation by CO<sub>2</sub> and diaphragmatic and peritoneal stretching. The pulmonary recruitment manoeuvre washes the CO<sub>2</sub> content from under the diaphragm, so it decreases the local effect and washes CO<sub>2</sub> from the abdomen, decreasing its systemic absorption.

Regarding the need for analgesia, in this study, the time of first rescue analgesia was the longest in GM compared to the other groups. That proves the efficacy of the combination of the two simple techniques. That also allows early ambulation of the patient and early discharge from the hospital.

Concerning the vital signs, we found

marginally significant values of decreasing heart rate from the 1st to the 3rd hour in the pulmonary group and the combined group. There were a small number of studies that showed the importance of vital signs to assess the effect of analgesic techniques.

M. Khan [16] showed that there was no significant difference in the mean heart rate and blood pressure at any time between the groups, with the incidence of tachycardia being 5% at 0 hours and 2% at 4 hours in the lidocaine group.

Regarding nausea, there was no significant incidence in the lidocaine group (0%), GP (16.7%), and GM (8.3%). Vomiting was not reported in any patient over the first 6 hours.

In consistency with our results, a study did H. Liu et al., [12] used the PRM manoeuvre to wash CO<sub>2</sub>. Nausea and vomiting were reported in 26.7% of patients. However, intravenous propofol and remifentanyl were used for maintenance of anaesthesia, and no inhalational agents were used. Propofol infusion was associated with less postoperative nausea and vomiting.

A study was done by H. Tsai et al., [17] on the analgesic effect of PRM after laparoscopic surgeries for the benign gynaecological lesion. They reported nausea and vomiting in 50.9% of patients. This high incidence may be due to the more invasive procedure than our selected diagnostic one as the surgical site adds to the complexity of pain, in contrast, other studies reported a higher incidence of nausea and vomiting.

In this study, we hypothesize that multimodal technique offer to the patient the benefits of the two simple techniques pulmonary recruitment and intraperitoneal lidocaine, the results showed the effectiveness of the multimodal technique.

### **Limitations of the study**

In this study we include only female patients due to the type of procedure; we did not Record the total consumption of postoperative analgesics.

In conclusion, application of Multi-modal analgesic technique allows better analgesia for a longer duration than the use of the sole technique for control of abdominal pain in patients undergoing diagnostic gynaecological laparoscopy.

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