

HJOG 2024, 23 (3), 195-204 | DOI: 10.33574/HJOG.0566

# Intraperitoneal analgesia to reduce pain after laparoscopic hysterectomy: Randomized Controlled Trial

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## Abstract

**Background:** Laparoscopic hysterectomy patients report high levels of postoperative pain and inadequate pain relief. This minimally invasive procedure is difficult to manage and leads to increased opioid use, limited mobility, and higher risks of complications, delayed rehabilitation and prolonged hospital stay.

**Objective:** To determine the analgesic efficacy of bupivacaine's intraperitoneal instillation (IP) with dexmedetomidine as an adjuvant for postoperative pain management in laparoscopic hysterectomy.

**Methods:** This study is a randomized control clinical trial done at the Obstetrics and Gynecology Department, Ain Shams University Hospital, within 11 months (from September 2021 to August 2022). This study's target population was all patients enrolled in laparoscopic hysterectomy. A total of 30 patients participated in this study, and we randomly divided it into two groups equally (15 patients per group).

**Results:** There was no significant difference between groups regarding body mass index, age, parity, obstetric history, medical history, surgical history, indication of hysterectomy, type of hysterectomy, duration of surgery, and uterus size. Visual analog scores for patients at 1-, 6-, 12-, and 24-hours post-operatively increased significantly in Group B than in Group A. Furthermore, the time required for first rescue analgesia increased significantly more in Group A than in Group B. Group A required substantially less analgesic amount than Group B. Group A had significantly shorter hospital stays than Group B. There was no statistically significant difference between groups A and B in terms of adverse effects like nausea and vomiting ( $p > 0.05$ ) although they were less frequent in group A.

**Conclusion:** Intraperitoneal instillation of bupivacaine combined with dexmedetomidine during laparoscopic hysterectomy substantially reduces postoperative pain and the requirement for analgesics in the postoperative period, compared to the control group, with no adverse side effects.

**Key words:** Intraperitoneal analgesia, laparoscopic hysterectomy, postoperative pain management

## Introduction

Laparoscopic gynecological procedures have gained popularity recently due to their numerous advantages. Laparoscopy is not painless, and controlling postoperative pain is a significant concern. Yet, the small incision size, fewer complications, less disfigurement, shorter stay in the hospital, quicker recovery, and less discomfort compared to abdominal surgery have made it a popular alternative<sup>1</sup>.

Pain management following laparoscopic procedures continues to be a significant obstacle. Proper control of pain promotes early mobility, which lowers the risk of deep vein thrombosis (DVT) and pulmonary embolism (PE). The patient's ability to take deep inhalations is also improved, reducing the likelihood of respiratory conditions such as asthma and atelectasis. In addition, the incidence of palpitations and their related investigations is reduced<sup>2</sup>.

Following laparoscopic surgery, there is somatic and visceral pain. The somatic component (well localized) is due to the incisions made for the trocars in the abdominal wall, and the visceral component (poorly localized, referable, and accompanied by autonomic and motor reflexes, including nausea and vomiting) is caused by the result of surgical manipulation and diaphragmatic irritation induced by dissolved carbon dioxide.

The shoulder pain is brought on by peritoneal insufflation, and stretching of the peritoneum and diaphragm causes blood vessels to tear, nerves to be pulled (such as the phrenic nerve), and the release of inflammatory mediators, which elicits the referred shoulder pain<sup>3</sup>.

Although there are numerous therapeutic protocols for pain management today, there is still a significant challenge in preventing and managing postoperative pain.

The administration of local anesthetics intraperi-

toneally, with or without adjuncts, has emerged as an effective technique for alleviating pain following laparoscopic procedures. Despite numerous previous studies, the most effective and superior local anesthetics and adjuvants are still the subject of debate<sup>4</sup>.

In addition to blocking the visceral afferent signals and altering visceral nociception, local anesthetics also provide antinociception by affecting proteins associated with nerve membranes, preventing the secretion of prostaglandins, activating nociceptors and encouraging inflammation<sup>5</sup>.

Bupivacaine is a powerful local anesthetic with a long half-life that effectively decreases postoperative pain<sup>6</sup>. It has been demonstrated that adjuvants, such as Alpha 2 agonists (dexmedetomidine), significantly extend the duration of anesthesia by enhancing its quality and duration when combined with local anesthetics<sup>7</sup>.

Dexmedetomidine is a selective  $\alpha_2$ -adrenergic agonist with analgesic and sedative effects<sup>2</sup>. Various studies have been done about intraperitoneal (IP) instillation of bupivacaine either alone or with additives and have been shown to minimize postoperative pain after laparoscopic hysterectomy; however, adding dexmedetomidine has not been sufficiently studied.

## Aim of the study

To compare the analgesic efficacy of intraperitoneal instillation of bupivacaine (Marcaine) with dexmedetomidine as adjuvant versus bupivacaine alone for postoperative pain control in laparoscopic hysterectomy.

## Patients and methods

This randomized control clinical trial was con-

ducted at the Obstetrics and Gynecology Department, Ain Shams University Hospital, over 11 months (September 2021 to August 2022). The study protocol was approved by the Ethical Committee of the Faculty of Medicine AIN Shams University (FMASU MS), in accordance with the 1975 Declaration of Helsinki and its 2000 revision. All patients gave their informed consent. The study was registered in the PAN African clinical registry.

The target population of this study was all patients who were enrolled for laparoscopic hysterectomy. A total number of 30 patients participated in this study and were split into two groups equally (15 per group). Each patient was allocated randomly into one of the following two groups using the allocation and concealment method.

Patients included in the study were those patients indicated for laparoscopic hysterectomy at our hospital.

The exclusion criteria were a history of chronic opioid intake (due to opioid-induced tolerance & hyperalgesia), large uterus ( $\geq 12$  gestational weeks), which could lead to surgical difficulties, renal failure (RF) (bupivacaine contraindicated in RF due to the risk of hypotension), chronic alcoholism (increased dose requirement of local anesthesia), heart block (due to bupivacaine side effects of cardiotoxicity), history of left ventricular failure (due to bupivacaine side effect of cardiotoxicity and hypotension), patients taking beta-blocking drugs (due to bupivacaine side effect of hypotension), allergy to the study drugs and patients are enrolled in another pain management study.

Using the sequentially numbered, opaque sealed envelopes (SNOSE) technique, we ensured that the randomization sequence was effectively allocated and concealed. The randomization groups were written on paper and kept in a sealed, opaque envelope with a serial number. As soon as the patient gave consent to participate, the researcher opens the sealed

envelope and assigns the patient to the treatment group accordingly: Group A: Bupivacaine HCL and Dexmedetomidine (Precedex) (n:15) Group B: Bupivacaine HCL (Marcaine) alone (n:15).

The primary outcome is the postoperative pain scores in the first 24 hours using the visual analog scores at 1 hour, 6 hours, 12 hours, and 24 hours following the surgery.

The secondary outcomes are nausea and vomiting, the need for post-operative rescue analgesia within the first 24 hours, and the length of hospital stay of the patients until their discharge.

**Sample Size Justification:** The EPI Info 7 software was used to calculate the sample size, with a power of 80% and an alpha error of 0.05. Based on the study by Acharya et al. (2018), a sample size of 15 women per group was necessary to detect the difference between the two groups.

Due to modifications to the surgery that precluded inclusion, one participant from Group A was withdrawn. (Converted from laparoscopic hysterectomy to abdominal hysterectomy).

## Procedure

The medical and surgical history of the patient was briefly collected, and a general, abdomen and local pelvic examination was conducted. Routine pre-anesthetic studies and tests were performed, which included a complete blood count, clotting profile, and tests to evaluate liver and kidney function.

After obtaining consent, patients were enrolled in laparoscopic hysterectomy, which involves the establishment of intra-peritoneal insufflation of carbon dioxide through a needle inserted into the umbilical incision into the peritoneal cavity. The insufflation pressure used is 14 mmHg, allowing for adequate pelvic structure visualization. A primary port of 10mm (umbilical port) and three ancillary ports of 5mm are inserted to perform the surgery. The intra-

abdominal pressure is maintained at 12-14mmHg, ensuring it does not exceed 15mmHg<sup>3</sup>.

We used electro-surgical bipolar vessel sealing (EBVS) (Ligasure) and sutured the vaginal vault laparoscopically. Following the end of the hysterectomy, a local anesthetic was instilled intraperitoneally before removing the trocars.

We used commercially available study drugs, which included a 50 ml vial of Bupivacaine 0.25% (Bupivacaine HCL) equivalent to 2.5mg/ml. The registration number for this drug is 04/2011, and Sunny Pharmaceutical Industries, Egypt, manufactured it. We also used a 2 ml vial (200 mcg) of Precedex (Dexmedetomidine HCL registration number 974233/01), equivalent to 100 mcg/ml. Hospira, Inc. USA manufactured this drug.

The Visual Analog Scale (VAS) is a commonly used tool to measure patients' pain levels. Medical professionals explain VAS to patients before the induction of anesthesia. VAS is a graphical rating scale that ranges from 0 to 10 with a 10-cm baseline. The scale is divided into ten equal parts, with labels varying from 0 (no pain) to 10 (extreme pain)<sup>8</sup>.

The visual analog score was recorded at 1 hour, 6 hours, 12 hours, and 24 hours following the surgery. If any patient reported a VAS score higher than four after the operation, a bolus of 75 milligrams of diclofenac was given intravenously as rescue analgesia to all patients. Moreover, intravenous ondansetron (4 milligrams) was administered if there was any complaint of vomiting or nausea. The complete postoperative analgesic requirements (type, dosage, and timing), fre-

quency of nausea and vomiting, incidence of adverse effects, and patient satisfaction were recorded for both groups within the first 24 hours of the surgery.

Statistical Analysis: We utilized the Statistical Package for Social Sciences (SPSS) to record and analyze the data. Each group was subjected to an Intention-to-Treat (ITT) analysis. An intention-to-treat (ITT) analysis also calculated the odds ratio (OR), relative risk (RR), absolute risk reduction (ARR), and number-needed-to-treat/harm (NNT/NNH).

## Results

The demographic characteristics in the first group were age  $48.6 \pm 6.1$  years, while in the second group, it was  $48.8 \pm 5.8$  years with no statistically significant difference between them ( $P=0.935$ ). The BMI in both groups was ( $27.6 \pm 1.7$  vs  $28.4 \pm 1.4$  with no statistically significant difference between them ( $P= 0.148$ ). The parity and the number of previous caesarean section (CS) or vaginal deliveries did not differ significantly between the 2 groups ( $P= 0.4657, 0.305, 0.406$ , respectively) [data not tabulated].

There was no significant differences in the past medical or surgical history between the groups. The indications for total laparoscopic hysterectomy (TLH) were as follows: endometrial adenocarcinoma, abnormal uterine bleeding, postmenopausal bleeding, endometrial hyperplasia, premenopausal bleeding, endocervical adenocarcinoma, and adenomyosis. There was no statistically significant difference between the two groups regarding the

Table 1. Pain scores in both study groups.

Variable	Time	Group A (n=14)		Group B (n=15)		Mean Difference	95% CI		P-value*
		Mean	SD	Mean	SD		Lower	Upper	
VAS	1 h	1.214	0.4258	3.13333	0.743	-1.91905	-2.3851	-1.452	0.00
	6 h	2.642	0.6333	5.4000	0.736788	-2.75714	3.282	-2.231	0.00
	12 h	3.928	0.4746	6.533333	1.302	-2.60476	-3.362	-1.847	0.00
	24 h	4.142	0.9492	7.466	1.884	-3.32381	-4.474	-2.173	0.00

Table 2. Nausea and vomiting in both studied groups.

		Nausea and Vomiting			Relative Risk	0.76
		Yes	No	Total	Odds ration	0.6
Group	Group A	4	10	14	<b>Absolute risk reduction</b>	0.1142
	Group B	6	9	15	<b>Number needed to harm</b>	8.75
Total		10	19	29	<b>P-Value</b>	0.518

indication for hysterectomy (P =0.508909).

Different techniques of laparoscopic hysterectomies were used as total laparoscopic hysterectomy, total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, radical laparoscopic hysterectomy with bilateral salpingo-oophorectomy, and total laparoscopic hysterectomy with salpingectomy with no statistically significant difference between the two groups (P=0.218).

There was no statistically significant difference between 2 groups regarding the operative time in hours ( $2.14 \pm 0.532$  vs  $2.7333 \pm 0.96$ , P =0.053).

Based on table (1), significant differences in VAS scores were observed between groups (P<0.05). Group B had notably higher VAS values at 1, 6, 12, and 24 hours after surgery.

Table (2) shows that nausea and vomiting were not significant compared to the two groups, and the relative risk of vomiting and nausea in group A was reduced by 24% relative to group B.

Table (3) shows that the need for post-operative

rescue analgesia within the first 24 hours was statistically significant compared to groups (P<0.05). The risk of the need for postoperative rescue analgesia in the first 24 hours in group A was reduced by 86.5% relative to group B.

The following table shows a statistically significant correlation between the groups according to time, amount of post-operative rescue analgesia, and length of hospital stay, as shown in tables (4-6).

### Discussion

One of the most frequent major surgeries for women is a hysterectomy. When compared to open hysterectomy, the laparoscopic approach has fewer postoperative complications, less morbidity, quicker recovery, and shorter hospital stays<sup>9</sup>.

Although laparoscopic hysterectomies are thought to be less painful than conventional ones, patients who undergo laparoscopic procedures report high levels of postoperative pain and do not receive ade-

Table 3. Comparison between two groups according to the need for Post-Operative rescue analgesia

		Need for Post-Operative rescue analgesia			Relative Risk	0.76
		Yes	No	Total	Odds ration	0.6
Group	Group A	4	10	14	<b>Absolute risk reduction</b>	0.1142
	Group B	6	9	15	<b>Number needed to harm</b>	8.75
Total		10	19	29	<b>P-Value</b>	0.518

Table 4. Kaplan-Meier analysis time of post-operative rescue analgesia (1st 24 hr)

Groups		Total no.	No. of event	Mean	SE	95% CI		Log Rank test		Sig.
						Lower	Upper	Test value	P-value	
Groups	Group A	14.000	2.000	15.000	5.000	5.200	24.800	6.971	0.008	HS
	Group B	15.000	14.000	3.000	0.257	2.497	3.503			

Table 5. Amount of post-operative rescue analgesia cross-tabulation

		Group				P-Value
		Group A		Group B		
		Count	%	Count	%	
Total Amount of Post-Operative Rescue Analgesia.	One Dose	1	7.1%	0	0.0%	0.000
	Two Doses	10	71.4%	0	0.0%	
	Four Doses	2	14.3%	1	6.7%	
	Five Doses	0	0.0%	4	26.7%	
	Six Doses	1	7.1%	6	40%	
	Eight Doses	0	0.0%	4	6.7%	

Table 6. Kaplan-Meier analysis of length of hospital stay

Groups		Total no.	No. of event	Mean	SE	95% CI		Log Rank test		Sig.
						Lower	Upper	Test value	P-value	
Groups	Group A	14	14	2.286	0.125	2.040	2.531	13.867	0.000	HS
	Group B	15	15	3.333	0.187	2.967	3.700			

quate pain relief<sup>10</sup>.

Pain may originate from multiple sources, including the site of the wound (somatic), the surgical site (visceral), and the pneumoperitoneum (referred)<sup>11</sup>.

Many surgeons have selected IP infiltration of local anesthetic as an efficient treatment option out of the various regimens recommended for pain following surgery, such as intravenous non-steroidal anti-inflammatory drugs, local infiltration, and opioids. This pathway was chosen because visceral nociceptive transmission is inhibited. By affecting proteins linked with nerve membranes, inhibiting the secretion and action of prostaglandin and other substances that sensitize nociceptors, and promote inflammation, the local anesthetic reduces nociception. The main advantage of local anesthetics is that

they don't have the potentially delaying effects of narcotics on recovery and hospital release<sup>12</sup>.

Effective postoperative analgesia lowers postoperative stress and morbidity and enhances patient satisfaction and outcome<sup>13</sup>.

### ***Our results and the comparison to different studies***

In this study, 30 female patients undergoing laparoscopic hysterectomies were split into two groups. Group A consisted of 15 participants who received bupivacaine (Marcaine) and dexmedetomidine, and 15 patients in Group B received intraperitoneal local anesthetic (bupivacaine). Thirty patients gave informed consent. The investigators withdrew one person from Group A due to modifica-



tions to the surgery that precluded inclusion. (Converted from laparoscopic hysterectomy to abdominal hysterectomy).

Our study showed no significant differences between the groups regarding age, body mass index, parity, maternal history, medical, surgical, and family history, indication and type of hysterectomy, or duration of surgery.

The results of our study agree with Rokhgireh et al., 2019<sup>14</sup> who found that there was no significant difference in terms of body mass index, age, type, and duration of the surgery among the study groups.

This result is also supported by Arden (2013)<sup>15</sup>, who found no significant differences between the bupivacaine and placebo groups in age, race/ethnicity, body mass index, reason for hysterectomy, and number of previous operations.

Based on the current study, patients in group B had significantly lower visual analog scores at 1, 6, 12, and 24 hours after the surgery compared to the other groups, with a p-value of less than 0.001. This result is consistent with the findings of a study conducted by Rokhgireh et al. in 2019, which also showed lower VAS scores in the first 24 hours in group 3 (bupivacaine plus dexmedetomidine) compared to the other two groups ( $P < 0.001$ ). This result is also supported by Chiruvella and Nallam, who found that VAS scores at various time intervals were consistently lower in the RD (ropivacaine + dexmedetomidine) group than in the R group<sup>2</sup>.

According to a study by Gupta et al. in 2021, the pain verbal rating score was analyzed at different intervals of 1, 2, 4, 6, and 8 hours. The study found that the B group had a higher VRS than the BD and BF groups. This difference was significant when comparing bupivacaine to the dexmedetomidine group<sup>16</sup>.

There was a significant difference between Group A and Group B in terms of the need for rescue analgesia after the operation. Only 14% of patients in Group A required rescue analgesia within the first 24

hours, while 93% of patients in Group B needed it at different intervals.

Moreover, Group A needed significantly fewer analgesics than Group B, and the time before the first rescue analgesia was needed was significantly longer in Group A than in Group B. Additionally, the hospital stay was significantly shorter in Group A than in Group B.

Our findings are consistent with those of prior research by Shukla et al., 2015<sup>17</sup>, which also found that Group BD patients required more time before requesting pain medication. Group BD used less diclofenac than Group B.

The result is also supported by [18], which found that rescue analgesia was given to all patients in group R at varying points, but only a subset of patients in group RD got it.

Although we discovered that the negative effects of group A, such as vomiting and nausea, were less severe than those of group B, the difference was not statistically significant.

The study results align with Acharya et al., 2016, which found no significant differences between the three groups in terms of post-operative side effects such as nausea and vomiting<sup>18</sup>.

El-Bahnassy et al., 2019 [19], also supported the study finding, finding that the RD group experienced fewer adverse effects, such as nausea and vomiting, compared to the ropivacaine group, but the difference was not significant.

Clinical implications of the study: We encourage all Gynecologists and minimally invasive surgeons to use the intraperitoneal instillation of bupivacaine combined with dexmedetomidine during laparoscopic hysterectomy.

Strengths and limitations of the study: the strengths point of our research are appropriate methodology and proper randomization. The limitations of our study are the relatively small number of patients and the fact that it is a single-center study, which could lead to a statistical bias.

Recommendations for further studies: Larger numbers of patients are needed, and we recommend similar studies to be multi-centric for better results.

### Conclusion

Intraperitoneal instillation of bupivacaine combined with dexmedetomidine during laparoscopic hysterectomy substantially reduces postoperative pain and the requirement for analgesics in the postoperative period, compared to the control group, with no adverse side effects.

### Authors Contribution

All authors jointly contributed to the conception and design of the study.

OI K: Design of the study, helped in the review of literature, revision of results and data analysis, writing the manuscript, and submission to the journal.

HM S: design of the study, revision of literature review, and revision of the manuscript.

MF G: registration of the Trial, obtaining ethical committee approval, reviewed the literature, sharing in the collection of data, patient recruitment

SA M: design of the study, revision of the review of literature and revision of the manuscript.

### Funding

This research received no external funding.

### Study registration

The study was registered in the Pan-African Clinical Trial.

### Disclosure of Interest

The authors declare no conflict of interest.

### Ethics Approval

Following local regulations, the protocol gained ethical and research approval from the Faculty of Medicine Ain Shams University, FMASU.MS511/2021.

### Informed Consent to Participate

All patients were given and signed the informed consents. We confirm that all methods were performed according to the relevant guidelines and regulations according to the Declaration of Helsinki.

### Data Sharing

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

### Acknowledgment

Not applicable.

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*Received 5-5-2024*

*Revised 25-5-2024*

*Accepted 29-5-2024*