

Intraperitoneal Bupivacaine with Dexamethasone versus Bupivacaine Alone for Pain Relief after Laparoscopic Hysterectomy: A Randomized Controlled Trial

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Abstract:

Background: Laparoscopic hysterectomy is a standard gynecological surgical treatment used to treat a variety of gynecological conditions. We aimed to evaluate the efficacy and safety of adding two different doses of intraperitoneal dexamethasone to bupivacaine versus bupivacaine alone for postoperative analgesia after laparoscopic hysterectomy. **Methods:** This randomized trial included 87 females who were scheduled for elective laparoscopic hysterectomy. Patients were randomly allocated into three equal groups: group I; received bupivacaine 100 ml 0.25% + 5 ml normal saline, group II; received bupivacaine 100 ml 0.25% + 4 mg dexamethasone (1 ml) + saline 4 ml, and group III; received bupivacaine 100 ml 0.25% + 8 mg dexamethasone (2 ml) + saline 3 ml. All patients were monitored with a 5-lead electrocardiogram, pulse oximeter, and non-invasive automated blood pressure as they arrived in the operation room. **Results:** Time of the 1st rescue analgesic requirement was significantly delayed in group III compared to group I and group II ($P < 0.05$) and was significantly delayed in group II compared to group I ($P = 0.011$). Nalbuphine in the 1st 24 hrs was significantly lower in group III compared to group I and group II ($P < 0.05$) and was significantly lower in group II compared to group I ($P = 0.003$). **Conclusions:** Addition of either 4 mg or 8 mg of dexamethasone to bupivacaine (0.25%) significantly can prolong the time of first rescue analgesic requirement and reduce postoperative pain and the total consumption of rescue analgesic in 24 h in addition to reduce incidence of postoperative nausea and vomiting.

Keywords: Intraperitoneal; Bupivacaine; Dexamethasone; Pain Relief; Laparoscopic Hysterectomy

Introduction

Laparoscopic hysterectomy is a standard gynaecological surgical treatment used to treat a variety of gynaecological conditions [1]. It has distinct advantages over open surgical procedures such as decreased tissue damage, less blood loss, early ambulation, reduced analgesic requirements, avoiding big surgical incision, thereby, allowing quicker recovery, and shorter hospital stay with reduced healthcare expenditures. However, pain may still be quite severe, particularly in the early postoperative period [2].

Different modalities have been introduced to relieve postoperative pain. These include parenteral analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and intercostal nerve block as well as intraperitoneal LA and opioids. The ease of use and safety of local anaesthetics is well recognized, and collectively they act as one of the most important classes of drugs in perioperative care [3]. Local anaesthetics are commonly used by skin infiltration or epidural administration in abdominal surgery, blocking somatic afferents and providing significant benefits in reducing postoperative pain and improving recovery [4].

It is also possible, however, to install local anaesthetic solutions into the peritoneal cavity, hence blocking visceral afferent signalling and potentially modifying visceral nociception and downstream illness responses. Instillation of intraperitoneal lignocaine, bupivacaine, levobupivacaine, and ropivacaine has been used following laparoscopic gynaecological and general surgical procedures to reduce postoperative pain through randomized trials for many years [5]. Use of adjuvant drugs in combination with intraperitoneal instillation of local anaesthetic has been found to reduce postoperative pain following laparoscopic surgery more effectively [6, 7].

Dexamethasone is a glucocorticoid that has a beneficial analgesic and anti-emetic

effect with a single perioperative dose that might extend up to 2-3 days [8]. The analgesic effect of steroids was attributed to various mechanisms including suppressing bradykinin and releasing neuropeptides at nerve terminals and decreasing prostaglandin synthesis through suppressing the formation of cyclooxygenase in both peripheral tissues and central nervous system. Moreover, steroids inhibit inflammatory mediators of hyperalgesia as tumor necrosis factor- α , interleukin-17b, and interleukin-6 [9]. It was hypothesized that postoperative pain in laparoscopic surgery would be reduced by intraperitoneal instillation of bupivacaine with dexamethasone more than intraperitoneal instillation of bupivacaine alone [10, 11].

The aim of the present study was to evaluate the efficacy and safety of adding two different doses of intraperitoneal dexamethasone (4 mg or 8 mg) to bupivacaine (0.25%) versus intraperitoneal bupivacaine (0.25%) alone for postoperative analgesia after laparoscopic hysterectomy.

Patients and methods

This double-blind, prospective, randomized controlled trial was conducted on 87 females aged from 30 to 65 years at Benha University hospitals and at Ganna private centre in Benha city, with American Society of Anaesthesiologists physical status (ASA) I-II who were scheduled for elective laparoscopic hysterectomy under general anaesthesia. The patients provided informed written consent before participating in the study. The research was conducted within the approved guidelines of the institutional ethical committee of Benha University Hospitals (RC 42-11-2023) during the period from February 2023 to February 2024. This manuscript adheres to the CONSORT guidelines.

Exclusion criteria were patients with known sensitivity to the study treatment,

body mass index of more than 40kg/m², a history of chronic analgesic, opioid, or other antiemetic drug usage, motion sickness, central nervous system problems, cardiovascular disease, or a history of psychiatric illness.

Randomization and blindness:

Randomization was done by computer-generated system. The list was concealed in sealed envelopes that were numbered and opened sequentially after obtaining patient's consent. Patients were randomly allocated using computer generated randomization tables into three equal groups, group I (Bupivacaine group) received bupivacaine 100 ml 0.25% + 5 ml normal saline, group II received bupivacaine 100 ml 0.25% + 4 mg dexamethasone (1 ml) + saline 4 ml, and group III received bupivacaine 100 ml 0.25% + 8 mg dexamethasone (2 ml) + saline 3 ml.

The pharmacist who prepared study drugs not involved in the study. The anaesthesiologist who observed the patient was unaware of the study drug.

On the night before surgery, all patients were given oral alprazolam 0.5 mg as a preanesthetic drug. Thirty minutes before surgery, all patients were premedicated with Ondansetron 8 mg IV was given to guard against PONV. Patients also received single dose of antibiotic. All patients were monitored with a 5-lead electrocardiogram, pulse oximeter, and non-invasive automated blood pressure as they arrived in the operation room.

Induction of anaesthesia was done using 1 µg/kg fentanyl, propofol 1.5 - 2 mg/kg, and 0.6 - 1.2 mg/kg rocuronium to facilitate endotracheal tube insertion. Anaesthesia was maintained using 1 MAC sevoflurane, fentanyl 1 µg/kg/hours, and rocuronium 0.1 mg/kg IV (subsequent doses of 0.01 mg/kg were given if needed according to TOF response). End-tidal carbon dioxide (EtCO₂) levels were kept between 35 and 40 mmHg by maintaining ventilation.

A bolus dose of fentanyl 0.5 µg/kg was given to patients who had hypertension (mean arterial pressure, >20% higher than baseline) or tachycardia. After accomplishment of surgery, the surgeon intraperitoneally administered drugs as per group allocation before laparoscopic trocar withdrawal. The drugs were prepared by in a sterile manner by personnel not involved in the patient management and handed over to scrub nurse for instillation at the end of the surgery before trocar withdrawal.

Just before reversal of muscle relaxation, ondansetron 4 mg IV was given. Reversal of muscle relaxant was done using neostigmine 0.04–0.07 mg/kg + 0.01-0.02 mg/kg atropine sulphate. Patients voided before surgery, and Foley's catheters was inserted intraoperatively.

Postoperatively, all patients were admitted to postanesthetic care unit (PACU) for at least 1 hour. Then, patients were transferred to surgical intensive care unit (SICU) for the first postoperative day (POD 1) before being transferred to the ward. Ketorolac 30 mg IV every 6 hours (with maximum dose of 120 mg/day). Paracetamol IV 1 g every 8 hours was given to all patients. If NRS ≥4 using nalbuphine 5 mg IV. If NRS remained ≥4 after 15 min, another 5 mg IV was given. Nalbuphine regimen was repeated after 6 hours as when needed. The degree of pain was assessed according to numeric rating scale (NRS) score where 0 is no pain and 10 is the worst possible pain^[12].

The postoperative measurement included degree of postoperative pain that was evaluated and recorded using NRS score during rest and movement postoperatively, at PACU, 2, 4, 6, 12 and 24 hours. Postoperative hemodynamic (mean arterial blood pressure and heart rate) at the same times of NRS. Number of patients requiring supplementary analgesia in each group. Time to first analgesic request of supplementary analgesia if NRS ≥4. Total postoperative consumption of

nalbuphine after 24 hours was recorded in each group.

Complications were recorded and managed if occurred including, hypotension (systolic blood pressure below 85 mmHg) and was planned to be managed with IV fluid infusion and IV ephedrine 5 mg increments and check the cause, bradycardia (heart rate < 60 b/min) was planned to be managed by atropine sulphate 0.01 mg/kg, respiratory rate (RR) depression for bradypnea (RR < 12 breath/min) that was managed by non-invasive mechanical ventilation, hypoxemia (decreased oxygen saturation (SPO₂) below 91% on room air) was planned to be managed by applying O₂ nasal cannula 3 L/min or continuous positive airway pressure CPAP in resistant cases and postoperative nausea and vomiting (PONV) which was treated by IV 8 mg ondansetron.

Patient satisfaction was evaluated using 5-point Likert scale, (1=extremely dissatisfied; 5=extremely satisfied) at 24 hrs. postoperatively^[13].

Outcomes:

The primary outcomes were time to first analgesic request of supplementary analgesia if NRS ≥ 4 and total postoperative consumption of nalbuphine after 24 hours and postoperative pain NRS score during rest and movement. The secondary outcomes were evaluation of postoperative hemodynamic (mean arterial blood pressure and heart rate), and incidence of adverse effects as (PONV, bradycardia, hypotension) and patients' satisfaction.

Sample size calculation:

The sample size calculation was performed using G. power 3.1.9.2 (Universität Kiel, Germany). The sample size was calculated according to the time of the 1st rescue analgesic requirement (primary outcome), where the mean time of the first rescue analgesia was (9.2 \pm 0.14 hr.) in group BD8 (Bupivacaine+ 8 mg dexamethasone

group) versus (6.1 \pm 0.19 hr.) in Group B (Bupivacaine group) and versus (7.4 \pm 0.55 hr.) in Group BD4 (Bupivacaine+ 8 mg dexamethasone group) (P<0.001), according to a previous study^[14]. Based on the following considerations: 0.05 α error and 90% power of the study. Eight cases were added to overcome dropout. Therefore, 87 patients were allocated.

Statistical analysis:

Statistical analysis was done by SPSS v28 (IBM©, Armonk, NY, USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analysed by ANOVA (F) test with post hoc test (Tukey). Quantitative non-parametric data were presented as median and interquartile range (IQR) and were analysed by Kruskal-Wallis test with Mann Whitney-test to compare each group. Qualitative variables were presented as frequency and percentage (%) and were analysed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

Results

In this study, 119 patients were assessed for eligibility, 19 patients did not meet the criteria and 13 patients refused to participate in the study. The remaining 87 patients were randomly allocated into three groups (29 patients in each). All allocated patients were followed-up and analyzed statistically, Figure (1).

Table (1) shows that there was an insignificant difference among the studied groups regarding the baseline characteristics (age, weight, height, BMI, and ASA) and duration of surgery.

The postoperative NRS at rest and movement was significantly different among the studied groups at all time measurement (at 2, 4, 6, 12 and 24h) (P<0.05), with no significant difference at PACU. Firstly, at rest, NRS at 2h was significantly lower in both group II and

group III compared to group I ($P < 0.001$, < 0.001) with no significant difference between group II and group III. At 4, 6, 12 and 24h, NRS was significantly lower in group III compared to both group I and group II ($P < 0.05$) with no significant difference between group I and group II. Secondly, at movement, NRS at 2h was significantly lower in both group II and group III compared to group I ($P < 0.001$, < 0.001) with no significant difference

between group II and group III. At 4, 6, and 24h, NRS was significantly lower in group III compared to both group I and group II ($P < 0.05$) with no significant difference between group I and group II. At 12h, NRS was significantly lower in group III compared to group I ($P = 0.006$) with no significant difference between group I and group II and between group II and group III.

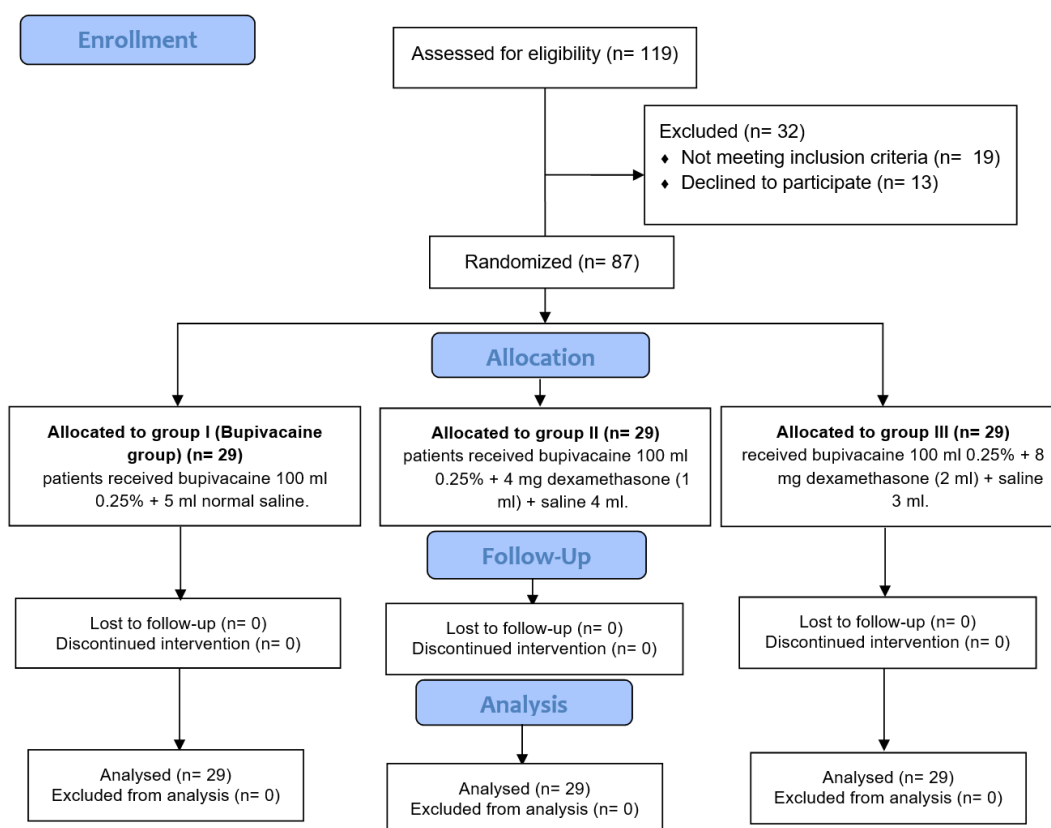


Figure 1: CONSORT flowchart of the enrolled patients

Table (1): Baseline characteristics of the studied groups.

	Group I (n=29)	Group II (n=29)	Group III (n=29)	P value
Age (years)	51.5 ± 6.72	49.1 ± 10.72	47.7 ± 9.69	0.289
Weight (Kg)	67.6 ± 12	67.2 ± 11.27	68.4 ± 11.31	0.912
Height (m)	1.6 ± 0.05	1.6 ± 0.05	1.6 ± 0.04	0.219
BMI (Kg/m ²)	25.8 ± 4.8	25.4 ± 4.73	25.5 ± 4.65	0.984
ASA	ASA I	22 (68.97%)	20 (62.07%)	0.525
	ASA II	7 (31.03%)	9 (37.93%)	
Duration of surgery (min)	117.8 ± 8.44	113.8 ± 8.54	116.2 ± 9.49	0.234

Data presented as mean ± SD or number (%), BMI: body mass index, ASA: American society of anesthesiologists.

Table 2: Postoperative numerical rating scale (NRS) at rest and movement of the studied groups

	Group I (n=29)	Group II (n=29)	Group III (n=29)	P value		
NRS at rest	PACU	1 (0 - 1)	1 (1 - 2)	1 (0 - 2)	0.693	---
	2h	3 (3 - 3)	2 (1 - 3)	2 (1 - 2)	<0.001*	P1<0.001* P2<0.001* P3=0.081 P1=0.305
	4h	3 (3 - 5)	3 (3 - 3)	2 (1 - 2)	<0.001*	P2<0.001* P3<0.001* P1=0.837
	6h	3 (3 - 5)	3 (3 - 4)	2 (2 - 3)	<0.001*	P2<0.001* P3<0.001* P1=0.223
	12h	3 (3 - 5)	3 (3 - 3)	2 (2 - 3)	0.002*	P2<0.001* P3=0.020* P1=0.648
	24h	3 (2 - 5)	3 (3 - 3)	2 (1 - 3)	0.017*	P2=0.008* P3=0.027*
	PACU	1 (1 - 2)	2 (1 - 2)	2 (1 - 3)	0.729	---
NRS at movement	2h	4 (3 - 4)	2 (2 - 3)	2 (2 - 3)	<0.001*	P1<0.001* P2<0.001* P3=0.342 P1=0.805
	4h	4 (3 - 5)	4 (3 - 5)	2 (2 - 3)	<0.001*	P2<0.001* P3<0.001* P1=0.690
	6h	4 (3 - 5)	4 (3 - 5)	3 (3 - 3)	<0.001*	P2<0.001* P3=0.001* P1=0.323
	12h	4 (3 - 5)	4 (3 - 5)	3 (2 - 4)	0.019*	P2=0.006* P3=0.075 P1=0.351
	24h	4 (3 - 5)	4 (3 - 5)	3 (2 - 4)	0.008*	P2=0.002* P3=0.035*

Data presented as median (IQR), NRS: numerical rating scale, PACU: post anesthesia care unit, *: statistically significant as P value <0.05, P1: p value between groups I&II, P2: p value between groups I&III, P3: p value between groups II&III.

The postoperative HR and MAP were significantly higher in group I compared to group II and group III all time measurement (at 2, 4, 6, 12 and 24h) (P<0.05), with no significant difference among the studied groups at PACU. The postoperative HR and MAP were higher in group II compared to group III all time measurement (at 2, 4, 6, 12 and 24h) but with no significant difference between both groups.

Time of the 1st rescue analgesic requirement was significantly delayed in group III compared to group I and group II

(P<0.001, <0.001) and was significantly delayed in group II compared to group I (P=0.011). Patients requiring rescue analgesics was significantly different among the studied groups (P=0.018), being lower in group III, followed by group II. The total dose of Nalbuphine in the 1st 24 hrs was significantly lower in group III compared to group I and group II (P<0.001, 0.001) and was significantly lower in group II compared to group I (P=0.003), Table (3).

Table (4) shows that there was a significant difference among the studied

groups regarding the satisfaction (P=0.005), being higher in group III followed by group II.

Regarding the incidence of the adverse effects, PONV occurred in 15 (51.72%) patients in group I, 7 (24.14%) patients in group II and 2 (6.9%) patients in group III.

Bradycardia, hypotension, and respiratory depression not occurred to any patients in our study. PONV was significantly different among the studied groups (P=0.007), being higher in group I followed by group II.

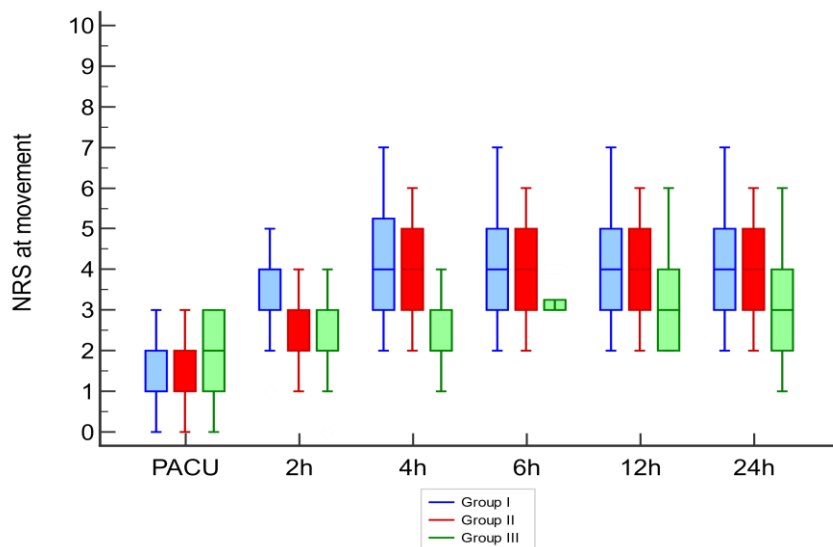


Figure (2): Numerical rating scale (NRS) at movement of the studied groups.

Table 3: Postoperative rescue analgesic requirement of the studied groups

	Group I (n=29)	Group II (n=29)	Group III (n=29)	P value	
Time of the 1st rescue analgesic requirement (hr.)	4 (4 - 6)	6 (4 - 6)	12 (12 - 24)	<0.001*	P1=0.011* P2<0.001* P3<0.001*
Patients requiring rescue analgesics	25 (86.2%)	20 (68.7%)	15 (51.7%)	0.018*	
Total dose of Nalbuphine in the 1st 24 hrs (mg)	10.0 ± 2.83	7.5 ± 2.56	5.0 ± 0	<0.001*	P1=0.003* P2<0.001* P3=0.001*

Data presented as median (IQR), mean ± SD or frequency (%), *: statistically significant as P value <0.05, P1: p value between groups I&II, P2: p value between groups I&III, P3: p value between groups II&III.

Table (4): Satisfaction of the studied groups.

	Group I (n=29)	Group II (n=29)	Group III (n=29)	P value
Very dissatisfied	0 (0%)	0 (0%)	0 (0%)	
Dissatisfied	9 (31.03%)	5 (17.24%)	1 (3.45%)	
Neutral	12 (41.38%)	9 (31.03%)	5 (17.24%)	0.005*
Satisfied	7 (24.14%)	11 (37.93%)	14 (48.28%)	
Very satisfied	1 (3.45%)	4 (13.79%)	9 (31.03%)	

Data presented as frequency (%), *: statistically significant as P value <0.05.

Discussion

Postoperative nausea and pain are the most common complications of laparoscopic surgery [15]. The pain reaches a maximum level within 6 h of procedure and then gradually decreases over a couple of days but varies considerably between patients [16, 17]. Visceral pain caused by pneumoperitoneum is the main source of pain following laparoscopic surgeries as reported by previous studies [18, 19].

Improving postoperative analgesia after laparoscopic surgeries by intraperitoneal instillation of a local anaesthetic has been widely investigated in previous studies [20, 21]. A study by Symons et al. [22] found that adding intraperitoneal bupivacaine reduced postoperative opioid consumption during the first postoperative day following laparoscopic gastric bypass. Another study by Alkhamesi et al. [23] showed a reduction in postoperative pain with the use of intraperitoneal bupivacaine in the same group of patients. Moreover, similar studies (29, 30) were conducted on paediatrics undergoing laparoscopic surgeries and concluded similar results [20, 24].

On the other hand, steroids have also been used successfully for postoperative pain relief in different kind of surgeries [25, 26]. Glucocorticoids play a crucial role in regulating inflammatory responses by inhibiting the synthesis of bradykinin and other neuropeptides which are responsible for causing pain [27], based on this, we used dexamethasone with bupivacaine in our study.

Sharma et al. [28] administered intraperitoneal hydrocortisone plus bupivacaine and found that adding hydrocortisone improved postoperative pain relief compared to bupivacaine alone following laparoscopic cholecystectomy.

To the best of our knowledge, there is lack of studies that evaluated the effect of addition of different doses of dexamethasone to bupivacaine in laparoscopic hysterectomy.

We found that time of the 1st rescue analgesic requirement was significantly delayed in group III compared to group I and group II ($P < 0.001$, < 0.001) and was significantly delayed in group II compared to group I ($P = 0.011$). Patients requiring rescue analgesics was significantly different among the studied groups ($P = 0.018$), being lower in group III, followed by group II. The total dose of Nalbuphine in the 1st 24 hrs was significantly lower in in group III compared to group I and group II ($P < 0.001$, 0.001) and was significantly lower in group II compared to group I ($P = 0.003$).

Nasr et al. [14] performed a randomized clinical trial to evaluate efficacy and safety of adding intraperitoneal dexamethasone to bupivacaine for postoperative pain relief after laparoscopic bariatric surgeries. Patients were randomly allocated into three groups, group B (Bupivacaine group), group BD4 (Bupivacaine+ 4 mg dexamethasone group) and group BD8 (Bupivacaine+ 8 mg dexamethasone group). They found that pain was lower in group BD8. Sedation was deeper in Group B. Time to first supplementary analgesia was longer in group BD8 than groups B or BD4, and longer in group BD4 compared to group B. Patients requiring supplementary analgesia were less in group BD8 than group B or BD4. Total postoperative consumption of nalbuphine in the first postoperative day (POD 1) was less in group BD8 than group B or BD4, and less in group BD4 than group B.

Additionally, Jadav et al. [11] performed a randomized prospective trial on a total of 100 patients scheduled for laparoscopic cholecystectomy (LC) who were randomized into two equal groups, group RD received 0.2% ropivacaine 30 ml plus 8 mg dexamethasone, and group RS received 0.2% ropivacaine 30 ml plus 2 ml normal saline intraperitoneally to evaluate the intraperitoneal ropivacaine with dexamethasone versus ropivacaine alone for pain relief after LC. They found a

significant difference in mean NRS score was observed among two groups at 6, 12, and 24 h. Only 52% in group RD demanded rescue analgesia as compared to 76% in group RS ($P= 0.0004$). Evaristo-Méndez et al. ^[29], in their study, found that ropivacaine with dexamethasone for local infiltration decreased incisional pain intensity after 12 h post elective laparoscopic cholecystectomy with a good safety profile which is similar with Jadav et al. ^[11] study.

Sarvestani et al. ^[30] showed that intraperitoneal injection of hydrocortisone before gas insufflation in laparoscopic cholecystectomy can reduce postoperative pain with no significant postoperative adverse effect.

Regarding PONV, it occurred in 15 (51.72%) patients in group I, 7 (24.14%) patients in group II and 2 (6.9%) patients in group III. PONV was significantly different among the studied groups ($P=0.007$), being higher in group I followed by group II.

Dexamethasone at a dose of 8 mg intraperitoneally was administered by Ismail et al. ^[31] in their study to reduce postoperative nausea after gynaecological laparoscopy. Similar to intravenous dexamethasone, there is no specific mechanism of dexamethasone's role in preventing PONV, but it affects glucocorticoid receptors that play a role in the vomiting pathway; prostaglandin secretion inhibition by central mechanism and decrease in the central serotonin activity are a few of the plausible causes of beneficial effects ^[32].

Jadav et al. ^[11] showed that dexamethasone and intraperitoneal ropivacaine significantly reduces the incidence of PONV in LC as compared to ropivacaine use alone.

Srivastava et al. ^[33] reported that intraperitoneal administration of dexamethasone, dexmedetomidine, and a combination of dexamethasone–dexmedetomidine in laparoscopic hysterectomies significantly reduces both

PONV and postoperative analgesics requirements compared with the control group.

Our study had some limitations as relatively small sample size Bupivacaine is associated with cardiotoxicity when used in high concentration or when accidentally injected intravascularly. Also, the patients in our study were followed up to 24h after surgery, the presence of any nausea and vomiting after the period of observation was not studied. Because there are so few studies on the use of intraperitoneal dexamethasone for the reduction of PONV in the literature, more research with different doses of these drugs and a combination of other postoperative antiemetic is needed to provide the best results in terms of PONV relief and postoperative pain relief after laparoscopic surgeries. Further larger blinded randomized studies are needed to validate our findings.

Conclusions:

The addition of either (4 mg or 8 mg) of dexamethasone to bupivacaine (0.25%) significantly can prolong the time of first rescue analgesic requirement and reduce postoperative pain and the total consumption of rescue analgesic in 24 h in addition to reduce incidence of postoperative nausea and vomiting following hysterectomy, with 8 mg being superior to 4 mg of dexamethasone with no added side effects.

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