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Comparative Study of Dexamethasone Versus Ondansetron as Adjuvants to the Intra-Peritoneal Irrigation of Bupivacaine for Reducing the Postoperative Pain in Patients Undergoing Elective Laparoscopic Cholecystectomy

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ABSTRACT

Background: Post-operative pain that follow laparoscopic cholecystectomy (LC) usually is the main complaint, also it have many benefits over open cholecystectomy in form of decrease post-operative pain, short hospital stay and better cosmetic result, but it is still painful. This study assesses the effect of intra-peritoneal irrigation of Dexamethasone and Ondansetron as adjuvant to Bupivacaine at the surgical bed to reduce post-operative pain and requirement for analgesia.

Methods and materials: This study included 75 patients underwent elective LC who prospectively randomized into 3 groups. The control group (A) (n=25) received 20 ml of bupivacaine 0.5% with 2 ml normal saline installed by the surgeon into the gallbladder bed, dexamethasone group (D) (n=25) received 20 ml of bupivacaine 0.5% and 2 ml dexamethasone (8mg) installed into the same site, ondansetron group (O), (n=25) received 20 ml of bupivacaine 0.5% and 2 ml ondansetron (4mg). Pain was assessed in 1, 3, 6, 9, 12 hours post-operatively by using visual analog scale (VAS).

Results: The pain in ondansetron group was significantly lower than the other 2 groups in 1st. 3rd, 6th and 12th hours post-operatively (P<0.001), also the pain in dexamethasone group was lower than control group.

Conclusions: In this study, the intra-peritoneal irrigation of bupivacaine with dexamethasone and ondansetron reduce the post-operative pain during the first post-operative hours after LC and also reduce the requirement for analgesia.

Keywords: Elective laparoscopic cholecystectomy,Intra-peritoneal irrigation, Bupivacaine, Dexamethasone, Ondonsetron.

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INTRODUCTION

Laparoscopic cholecystectomy (LC) is minimally invasive procedures hold an important position in nowadays surgical practice. It has become the main treatment of symptomatic cholelithiasis.[1] It represents the most common laparoscopic procedure performed all over the world and has been performed as a day-case procedure for over a decade.[2&3] LC has many advantages over open cholecystectomy (OC). These include reduced pain, better cosmetic outcomes, shorter hospital stays and earlier recovery times[4], which is reflected by the patient's return to normal activities.[5] LC is not a painless procedure, but it is less painful than OC. According to research reports, "many patients experience considerable pain after LC and improvement in the analgesic technique is desirable".[6]

Regarding the mechanism of pain in LC, there are several mechanisms have been proposed for generation of pain following laparoscopy: ruptured blood vessels caused by rapid distension of the peritoneum, traumatic traction on the nerves, release of inflammatory molecules, trauma to the abdominal wall, and when the gallbladder is removed from the abdomen, pneumoperitoneum created by use of CO_2, maintenance of high abdominal pressure, irritation of the phrenic nerve and application of cold CO_2.[7] This explains why no consensus can be reached regarding effective postoperative pain relief in patients undergoing LC, because pain is multifactorial.[8]

Pain intensity usually peaks during the first postoperative hours and usually declines over the following 2-3 days.[9] In addition to discomfort and postoperative physiological repercussions, such as respiratory restriction, tachycardia and hypertension, pain delays early ambulation and hospital discharge.[10&11]

Various methods now being utilized with variable success in the post-operative pain management after laparoscopic surgery include agents like non-steroidal anti-inflammatory drugs (NSAIDS), , infiltration of wound with local anesthetics and intermittent intra-muscular narcotics.[12]

Intra-peritoneal irrigation of the diaphragmatic surface and gallbladder bed using normal saline, bupivacaine, or lignocaine may be effectively control visceral abdominal pain after LC.[13]

Bupivacaine is indicated for local infiltration, peripheral nerve block, sympathetic nerve block, and epidural and caudal blocks. It is available mixed with a small amount of epinephrine to increase the duration of its action. It typically begins working within 15 minutes and lasts for 2 to 8 hours. [14&15]. Dexamethasone is a type of corticosteroid medication that has anti-inflammatory and immunosuppressant effects. It is used in the treatment of many conditions, including rheumatic problems, a number of skin diseases, severe allergies, asthma, chronic obstructive lung

disease, croup, brain swelling, and along with antibiotics in tuberculosis .[16&17]

Ondansetron is a selective serotonin subtype 3 (5-HT3) receptor antagonist, is currently used for the prophylaxis and treatment of post-operative nausea and vomiting in perioperative management. [18&19] Ondansetron was found to have a local anesthetic effect. It could block sodium channels similar to local anesthetics and has an antinociceptive effect. It binds to the opioid μ receptors and acts as an agonist.[20]

A Visual Analogue Scale (VAS) is commonly used as the outcome measure for postoperative pain assessment. It is usually presented as a 100-mm horizontal line on which the patient's pain intensity is represented by a point between the extremes of "no pain at all" and "worst pain imaginable." Its simplicity, reliability , make the VAS the optimal tool for describing pain severity or intensity.[21] No pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75– 100 mm).[22]

METHODS AND MATERIALS

This study was done at AL-Hussain teaching hospital-Samawa city/Iraq for about 12 months duration (from 15th of November 2018 – 15th of November 2019) when 75 adult patients, aged 18-50 years, ASA I and II are scheduled for elective LC are involved in this study. Exclusion criteria include Patient with ASA > II, refusal of the patients, pregnancy, open cholecystectomy, acute cholecystitis, patients receiving analgesics, patients with significant cardiac, respiratory, hepatic, renal, or hematological disorders, allergy to local anesthetics, any patient with postoperative drain were excluded from this study.

Informed consent had been taken from these patients. All patients were subjected preoperatively to medical history including personal, present illness, past and family history, followed by physical examination then preoperative investigation including :complete blood count, liver function test, coagulation profile, renal function test, Chest x-ray, ECG and upper abdominal ultrasound. All patients were referred to the operating room without premedication. The patient was placed in supine position and dextrose saline (dextrose 5% with 0.9% sodium chloride) was started at a rate of 2 ml/kg/hr through a 20 G intravenous cannula. Monitoring include pulse oximetry (SPO2), ECG lead II, capnography and blood pressure monitoring. Patients were preoxygenated with 100% 0xygen for 3 minutes. Induction of anesthesia was performed by an intravenous administration of fentanyl (2 μg/ kg), propofol (2 mg/kg) and atracurium (0.5 mg/kg). Maintenance of anesthesia with sevoflorane 2 MAC then endotracheal intubation done after 3 minutes. Controlled ventilation introduced to the patients, tidal volume (7 ml/kg), respiratory rate 12 breathe/minute, I: E ratio 1:2.

A standard operative method was used with a 4-trocar technique in all patients. Pneumoperitoneum was achieved in every case with the use of a veress needle through the periumbilical incision using carbon dioxide, while the patient in a reverse Trendelenburg position with 30º tilting to the left, and maintained at 14 mm Hg during the entire surgical procedure. After removal of gallbladder, hemostasis was performed at the surgical bed then the position of the patient was changed to the Trendelenburg position, the patients were randomly allocated into three groups:

Group A (control) (n=25): 25 patients received 20 ml of bupivacaine 0.5% with 2 ml normal saline (total volume = 22 ml) installed by the surgeon into the gallbladder bed. Group D (Dexamethasone) (n=25): 25 patients received 20 ml of bupivacaine 0.5% with 2 ml of dexamethasone (8 mg) (total volume = 22 ml) installed by the surgeon into the gallbladder bed. Group O (Ondansetron) (n=25): 25 patients received 20 ml of bupivacaine 0.5% with 2 ml of ondansetron (4mg) (total volume = 22 ml) installed by the surgeon into the gallbladder bed. Instruments and trocars were removed, and the patient remain in this position for 10 minutes then changed to supine position. Volatile anesthetic agent was switched off and (neostigmine 2.5 mg + atropine 1.2 mg I. V) were given for reversing the effect of muscle relaxant then an endotracheal extubation was done.The patients are assessed postoperatively for the following:

I/ Visual analog scale (VAS), heart rate, blood pressure and episodes of nausea and vomiting (N&V) were assessed at 1,3,6,9,12 hours postoperatively.

II/ Time for the first request of analgesia (tramadol 50 mg i.m).

III/ Number of requests for analgesia/24 hours.

IV/ total dose of requested analgesia/24 hours.

Pain was assessed using VAS of 0 to 10.

VAS was explained to every patient, the number (0) was equivalent to no pain and (10) was the worse pain they ever felt. Administration of analgesics was correlated with the reading of VAS (4-5).

Regarding statistical analysis, frequencies and percentages were used to present categorical variables. Means and standard deviations (SD) were given for the normally distributed variables. To analyze the difference in VAS scores, blood pressure, and heart rate among the three groups, one-way analysis of variance was used assuming unequal variances since the variables approximated a normal distribution. Kaplan-Meier curves and Log Rank test were used to assess differences over time. The descriptive variables were analyzed either by chi-square analysis or by Fisher's exact test, as appropriate. To compare the mean dose of analgesia required for each group, an ANOVA statistic was used assuming unequal variance. P value of less than 0.05 was considered statically significant. Statistical analysis was performed with SPSS version 24 (SPSS, Chicago, IL, USA).

RESULTS

Seventy-five patients were included in this study.

Seventy-two patients were females. The means of age for group A, D and O were 34.4 (8.5), 34 (7.7), 33.7 (8.4), respectively (table1).

Table 1: Demographic characteristics of patients within each group

Characteristics	Group A	Group D	Group O	P value
Sex (male/female)	2/23	1/24	0/25	
Mean age (years)	34.4 (8.5)	34 (7.7)	33.7 (8.4)	0.87

There is no statistically significant difference in the mean arterial pressure recordings at all times (Table 2).

Table 2: Mean blood pressure difference between the three groups overtime

Characteristics	Group A	Group D	Group O	P value
Mean (SD) MAP at 1st hr	77.13 (10.1)	78.32 (7.5)	74.9 (8.28)	0.381
Mean (SD) MAP at 3 hrs	80.26 (11.3)	82.8 (9.3)	78.3 (7.6)	0.263
Mean (SD) MAP at 6 hrs	85.6 (8.9)	86.6 (10.3)	81.4 (6.5)	0.087
Mean (SD) MAP at 9 hrs	88.26 (8.7)	88.36 (5.8)	87.96 (5.1)	0.063
Mean (SD) MAP at 12 hrs	89.3 (8.4)	90.1 (5.7)	86 (4.2)	0.055

Table 3 & figure 1 demonstrate the differences in VAS among the three groups. The VAS of Group O was significantly lower than the other two groups in the 1st, 3rd, 9th and 12th hours post-operatively ($P < 0.001$). However, the difference in VAS scores in the 6 hour post-operatively was not statistically significant among the three groups ($P = 0.19$).

Table 3: Differences in pain visual analogue scale over time in each group

Characteristics	Group A Mean (SD)	Group D Mean (SD)	Group O Mean (SD)	P value
Pain VAS at 1st hr	2.7 (0.66)	1.8 (0.76)	1.8 (0.55)	< 0.001
Pain VAS at 3 hrs	4.0 (0.7)	3.5 (0.81)	2.6 (0.8)	< 0.001
Pain VAS at 6 hrs	2 (1.8)	3 (2.2)	2.2 (1.9)	0.19
Pain VAS at 9 hrs	2.2 (0.7)	1.4 (0.64)	1.2 (0.4)	< 0.001
Pain VAS at 12 hrs	4.1 (1.1)	2.8 (0.9)	1.9 (0.8)	< 0.001

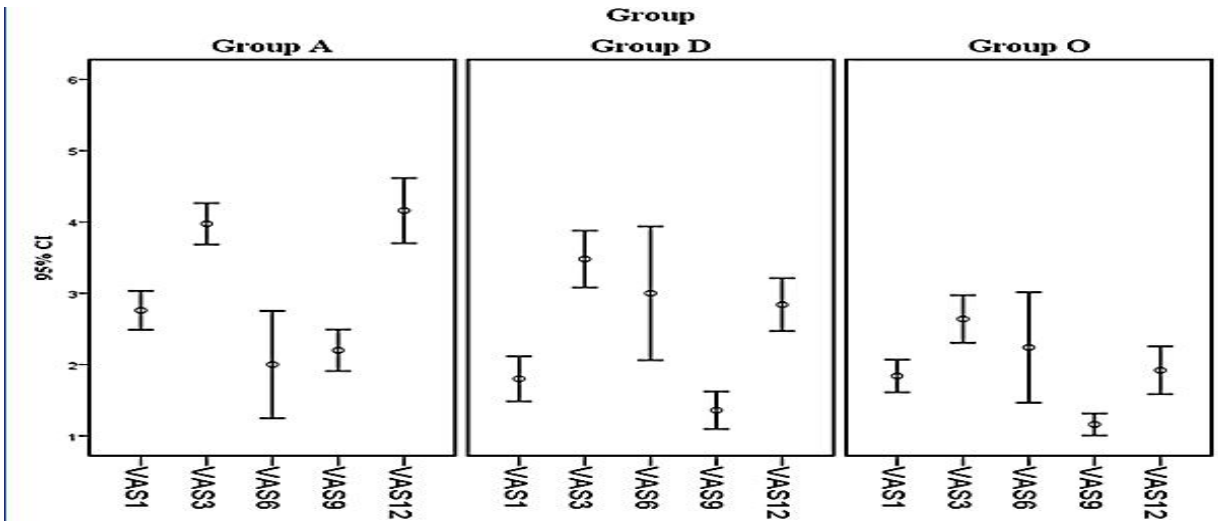

Figure 1: illustrates the VAS scores of the three groups.

There was a significant difference between all groups regarding the mean of the time (hours post-operatively) to the first request of analgesia, 3.8 (0.65) hours in group A, 4.9 (0.87) hours in group D, and 5.3 (0.69) hours in group O (Table 4 & figure 2).

Table 4: Time to the first request of analgesia in the three groups

Group	N (%)	Mean (in hours)	SD	*P* value
Group A	25 (33.3)	3.8	0.65	< 0.005
Group D	25 (33.3)	4.9	0.87	

Group O	25 (33.3)	5.3	0.69	

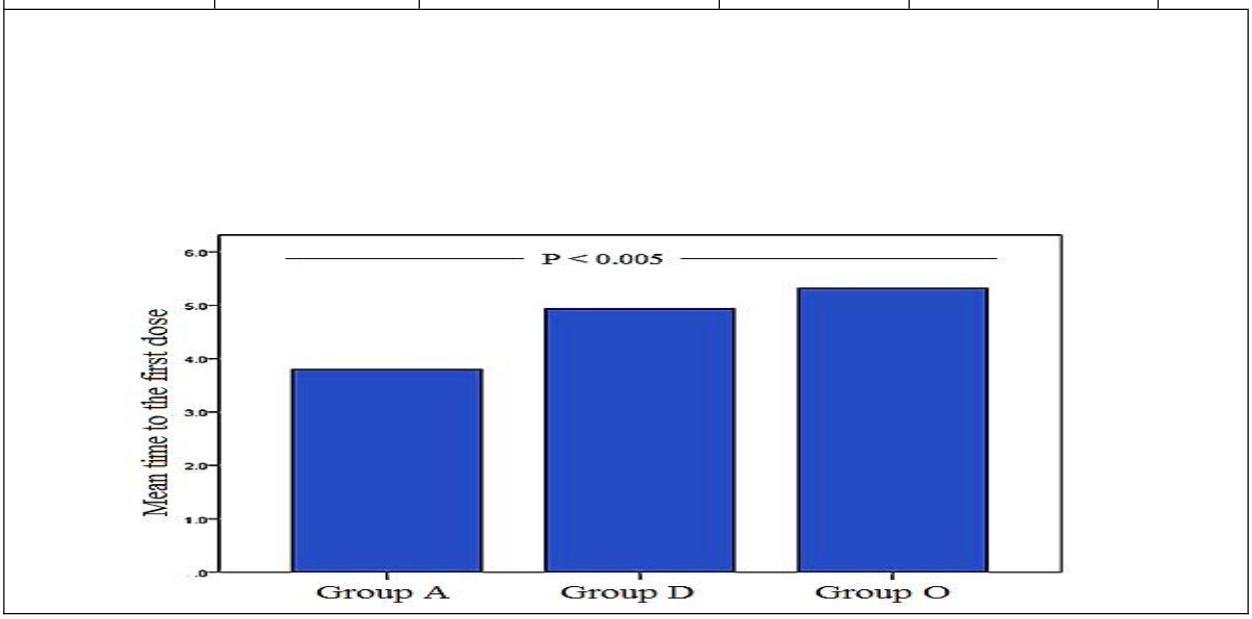

Figure 2: Time to the first request of analgesia

The mean dose of analgesia was 142 mg in the control group, 102 mg in the dexamethasone group, and 94 mg in the ondansetron group (Table 5 & figure 3). There is a statistically significant difference in the mean dose of analgesia required for the three groups ($P < 0.005$).

Table 5: The difference in the mean dose of analgesia required in the three groups

Group	**N (%)**	**Mean**	**SD**	***P* value**
Group A	25 (33.3)	142.0	18.7	
Group D	25 (33.3)	102.0	17.6	< 0.005
Group O	25 (33.3)	94.0	16.6	

There was a significant difference in the number of requests for analgesia between groups D and O in comparison with group A. (Table 6)

Table 6: Number of requests for analgesia in the three groups

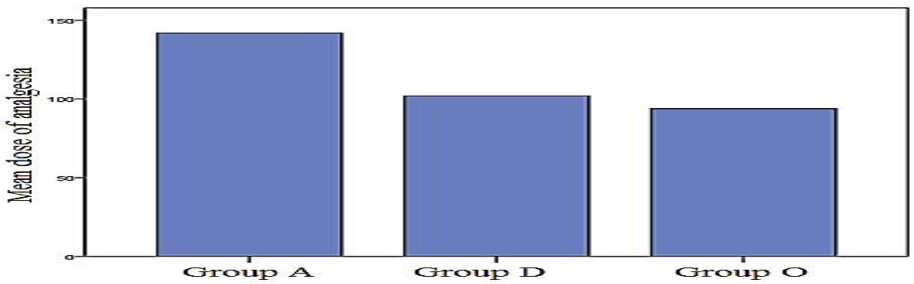

Figure 3: Mean dose of analgesia in the three groups

Number of requests

	Once	Twice	Three times
	N (%)	N (%)	N (%)
Group A	0 (0)	4 (16)	21 (84)
Group D	1 (4)	22 (88)	2 (8)
Group O	3 (12)	22 (88)	0 (0)

DISCUSSION

Although minimally invasive surgery is characterized by reduced pain, it is not at all painless.[23]Patients undergoing LC suffer significant pain on the day of surgery, frequently requiring narcotic analgesics. However, the average pain scores of the entire group in our series was 2.1 in a scale of 1 to 10 in 1 hour, 3.7 in 3 hours, 2.4 in 6 hours, 1.6 in 9 hours and 3 in 12 hours post-operatively. These values were lower than the ones obtained in other studies mainly because bupivacaine was used in all groups.[24]

The pain characteristics suggest an intra-abdominal origin, and it seems unlikely that this pain is generated mainly by the small skin incisions. Studies of local anesthetics infiltrated into the skin wounds report reduced postoperative pain only to a minor degree.[25&26] Pain may be generated by stretching of the abdominal wall during the pneumoperitoneum, by the local dissection, or by irritation of the peritoneum from blood, bile spillage, or by the CO_2 used for creation of the pneumoperitoneum.[7]

Studies that examine the use of bupivacaine to reduce pain after LC demonstrated mixed results. While Zmora et al and Al-Saad et al[27]showed that the application of intra-peritoneal bupivacaine did not attenuate pain following LC, Castillo-Garza et al[28] and Ravishankar et al[29]found that the use of bupivacaine irrigated over the surgical bed was an effective method for reducing pain during the first postoperative hours after LC. In our study, we assumed that the addition of dexamethasone or ondansetron have an additional analgesic effect when combined with bupivacaine. We believe this to be a novel investigation seeing as no similar studies have previously been conducted. Actually, the main key of this study has been based on the control and treatment of postoperative pain after LC.[30]

Intra-peritoneally administered dexamethasone was used in this study. Although application of these drugs is controversial, but most experts believe that the inflammatory process in the peritoneal cavity is the best reason for shoulder pain after laparoscopic surgery. Thus, non-inflammatory agents such as corticosteroids are able to relieve pain severity via reduction of inflammation after LC.[31]

The VAS was significantly lower when ondansetron or dexamethasone were added to bupivacaine compared to bupivacaine alone. These findings are consistent with Azgari and colleagues who found that dexamethasone significantly reduced pain in patients underwent gynecological laparoscopy in the 2-24 hours post-operatively when compared to controls. Furthermore, the use of ondansetron was not thoroughly studied in the reduction of post-operative pain when administered locally. One study showed that ondansetron, as an adjunct to lidocaine, have anti-inflammatory effects and can be administered to reduce postoperative pain in intravenous regional anesthesia.[32]The time to first request of analgesia was significantly longer in the ondansetron group compared to the dexamethasone and control groups. These finding indicate that ondansetron considerably delayed the first request for analgesia when added to bupivacaine compared to dexamethasone. Patients in the control group required significantly higher doses of analgesia than the other two groups. Furthermore, most patients in the control group requested analgesia more frequently. These results reflect the higher pain scores in the control group.

CONCLUSIONS

This study demonstrates that irrigation with either ondansetron or dexamethasone at the surgical bed in patients with LC will significantly lower the intensity of post-operative pain as well as the analgesic consumption when compared to bupivacaine alone, especially in the first hours postoperatively. Ondansetron and, to a lesser extent, dexamethasone delayed the first request for analgesia compared to bupivacaine alone.

RECOMMENDATION

We recommend using the combination of ondansetron and bupivacaine to irrigate the surgical bed in all LC.

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