Intraperitoneal Levobupivacaine Instillation Improves Outcome of Laparoscopic Cholecystectomy: A Comparative Study of Preemptive versus Postoperative Instillation

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Abstract

Objectives: The present study aimed to investigate the postoperative (PO) analgesic efficacy of intra-peritoneal (IP) levobupivacaine instillation on the frequency and intensity of shoulder tip pain (STP) and its impact on duration of hospital stay in patients assigned for laparoscopic cholecystectomy (LC) comparing preemptive (PE) versus postoperative instillation.

Patients & Methods: The study comprised 80 patients, 71 ASA I and 9 ASA II, assigned to undergo elective laparoscopic cholecystectomy (LC). Patients were randomly allocated into 4 equal groups according to timing of IP instillation: Group PE received PE instillation; Group PO received PO continuous installation of levobupivacaine at rate of 12.5 mg/h and Group PE+PO received both PE instillation and PO continuous installation; control group did not receive any form of IP instillation (Group C). No local anesthetic infiltration of wound site was applied. The intensity of postoperative STP Was assessed using a visual analogue scale (VAS) ranging from 0 (no pain) to 10 (unbearable pain). Pain assessment was conducted hourly for 12 hours and 2-hourly for another 12 hours. The duration of analgesia; defined as the time lapsed till fist request of rescue analgesia that was given when patient has VAS score of 4 was determined.

Results: Intraperitoneal LA instillation provided significantly longer duration of analgesia, significantly lower pain VAS score and significantly less consumption of PO rescue analgesia compared to control group. Patients enrolled in PE+PO group showed superior outcomes compared to both PE and PO groups with significant difference in favor of PE group. Ten patients 7 in PE+PO and 3 in PE groups did not request rescue analgesia for STP with postoperative rescue analgesic sparing effect of 12.5%. Patients received levobupivacaine IP instillation had significantly shorter PO hospital stay compared to control group and those received combined PE and PO instillation had significantly shorter postoperative hospital stay compared those received PE or PO instillation with a non-significant difference between both modalities despite being in favor of PE instillation.

Conclusion: It could be concluded that IP levobupivacaine instillation provided profound PO analgesia with rescue analgesia sparing effect of 12.5% and significantly reduced PO hospital stay. Combined PE and PO instillation provided superior outcome compared to either PE or PO instillation and is advocated as therapeutic modality for pain management after LC.

Introduction

Laparoscopic strategies for managing intraabdominal pathologies offer significant benefits compared with conventional approaches. Of interest are reports of decreased postoperative pain, resulting in shorter hospitalization and earlier return to normal activity. Compared with open procedures, laparoscopic surgery, a minimally invasive technique, is associated with reduced surgical trauma and accordingly, is often performed as day-case surgery, [1].

Nonetheless, pain after laparoscopy may be moderate or even severe for some patients. Pain can prolong hospital stay and lead to increased morbidity, which is particularly important for many centers performing these surgeries as a day-case procedure, [2].

Intraperitoneal injection of opioids for postoperative analgesia has been evaluated as an alternative approach. It has been suggested that peripheral antinociceptive effects of opioid agonists could be elicited by activation of opioid receptors localized on peripheral sensory nerves, [3]. However, *Akinci et al.*, [4] found intravenous tramadol provides superior postoperative analgesia in the early postoperative period after laparoscopic cholecystectomy compared with an equivalent dose of tramadol administered intra-peritoneally and with normal saline in patients undergoing laparoscopic cholecystectomy.

Intraperitoneal injection of local anesthetics has been proposed to minimize postoperative pain after laparoscopic surgery. Several reports are available on the efficacy of intraperitoneal local anesthetic administration for analgesia after laparoscopic gynecologic

surgery; **Ceyhan et al.**, [5] found intraperitoneal installation and periportal infiltration of bupivacaine decreased postoperative pain and shortened duration for the return of bowel function, both are crucial for comfort and discharge of the patient after laparoscopic gynecological surgeries. **Malhotra et al.**, [6] found the analgesic effect of intraperitoneal installation of bupivacaine was dose-dependent and 100 mg of intraperitoneal bupivacaine is much better than 50 mg in relieving pain after laparoscopic surgery.

However, a controversy exists over the effectiveness and clinical value of intra-peritoneal analgesia for pain control after laparoscopic cholecystectomy. Thus, the present study aimed to investigate the postoperative analgesic efficacy of IP levobupivacaine instillation on the frequency and intensity of STP and its impact on duration of hospital stay in patients assigned for laparoscopic cholecystectomy comparing preemptive versus postoperative instillation.

Patients & Methods

This randomized, prospective study was conducted at Anesthesiology and General Surgery Departments, Benha University Hospital. After obtaining written fully informed consent, 80 patients (ASA physical status I-II) assigned to undergo elective laparoscopic cholecystectomy (LC) were enrolled in the study. Patients had acute cholecystitis, the presence of pneumoperitoneum, sensitivity for the study drugs or the administration continuous preoperative analgesia for any indication resulted in exclusion from the study.

Patients were randomly allocated into 4 equal groups (n=20) according to timing of IP instillation: Group PE included patients assigned to receive preemptive (PE) instillation of local anesthetic with postoperative continuous installation of 0.9% saline as placebo; Group PO included patients assigned to receive preemptive instillation of 0.9% saline as placebo and postoperative (PO) continuous installation of local anesthetic and Group PE+PO included patients assigned to receive preemptive instillation with postoperative continuous installation of local anesthetic. Twenty patients were enrolled as control group and did not receive any form of IP local anesthetic instillation (Group C).

All patients received a standardized anesthetic technique with propofol 2–4 mg/kg, a non-depolarizing muscle relaxant, morphine 10 mg IV, and ondansetron 4 mg IV. Their lungs were ventilated with nitrous oxide and isoflurane 1%−1.5% in oxygen via a cuffed tracheal tube. Patients received lactated Ringer's solution at a rate of 10 ml/kg/hr during anesthesia and 2ml/kg/hr after anesthesia until patients tolerated oral fluids. At the end of surgery, atropine sulphate 0.02 mg/kg and neostigmine 0.04 mg/kg were administered I.V. for reversal of muscle relaxation and the trachea was extubated. Following extubation the patients were maintained on supplemental O_2 until awake in the recovery room.

Laparoscopic cholecystectomy was performed according to the European "four-puncture" technique described by **Dubois, et al.**, [7]. Intraperitoneal insufflation of CO_2 was conducted via Verres needle inserted into a small umbilical incision. Prior to peritoneal insufflation, with patient in 15-20º Trendlenburg's position and tilted to the right side; local anesthetic was sprayed through Verres needle and allowed to be distributed to the right upper abdominal quadrant and the undersurface of diaphragm. Thereafter, an electronic variable-flow insufflator was used to insufflate the peritoneal cavity up to 15 mmHg intra-abdominal pressures and a cannula was inserted in place of the needle to provide and maintain intra-abdominal pressure of 13-15 mmHg. A video laparoscope was inserted through the cannula and the operative field was seen. The patient's position was changed to steep reverse Trendlenburg position, with a lateral tilt to facilitate retraction of the gall bladder fundus. After completion of surgery and prior to withdrawal of the laparoscope; a multi-hole catheter was inserted through the right hypochondrial trochar site and the tip of the catheter was placed under vision in the sub-diaphragmatic space so as to allow sub-diaphragmatic instillation of the local anesthetic fluid that is allowed to run on to the gall bladder fossa. The catheter was fixed to the skin during skin closure of the port site. All the patients were treated by allowing the carbon dioxide to escape after the surgery and prior to removal of the needles.

Levobupivacaine at a concentration of 0.75% (volume, 20 ml/ampoule) was used for the study; one ampoule was used for preemptive instillation (Group PE) and 5 ampoules (100 ml) were mixed with 200 mL of 0.9% saline to provide 750 mg of levobupivacaine in 300 ml

(2.5 mg/ml). The solution was infused at 5 ml/h, i.e., 12.5 mg/h for 24 h in group PO. Both modalities of instillation was used in group PE+PO. For groups PE and PO a similar amount of normal saline was used as preemptive placebo instillation in group PO and placebo continuous instillation in group PE. No local anesthetic infiltration of wound site was applied.

The primary outcome of the study was the duration of analgesia; defined as the time lapsed until the first request for rescue analgesia. Rescue analgesia in the form of intravenous tenoxicam (Epicotil, EPICO, 20 mg vial) was given diluted in 10 ml saline when patient has VAS score of 4.

The secondary outcome was the intensity of postoperative shoulder-tip pain (STP) assessed using a visual analogue scale ranging from 0 (no pain) to 10 (unbearable pain). The pain scale was constructed without numeration, allowing the patient to mark a point along the scale that represented their STP at that time, [8]. Patients were aware that the scale served to analyze the presence and intensity of STP alone and not a representation of generalized discomfort. Pain assessment was conducted at 1 hour after the patients had been arrived to the recovery room and then hourly for the first 12 hours and every 2-hourly for another 12 hours. Vital signs (RR, SpO$_2$, HR, SAP) and adverse effects were assessed prior to and immediately after surgery and then every 30 min for 2 hours and 2-hourly for 24 hr postoperatively.

Statistical analysis

Data were analyzed using Chi-square (X^2 test) and ANOVA (f) test tests. Statistical analysis was conducted using the SPSS (Version 10, 2002) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

The study comprised 80 patients; 16 males and 64 females with mean age of 37.6±9.6; range: 25-61 years. Only 9 patients were ASA II, while the remaining 71 patients were ASA I. There was a non-significant difference between studied groups as regards age, sex, ASA class or body mass index. Mean operative time was 53.25±8.4; range: 35-70 min with a non-significant difference between studied groups, (Table 1).

All patients passed smooth intraoperative course without complications related to surgical procedure or anesthetic modalities. Throughout postoperative observation period, there was non-significant difference between studied groups as regards hemodynamic or respiratory parameters.

Intraperitoneal local anesthetic instillation provided significantly longer duration of analgesia (duration till first request of rescue analgesia) irrespective of timing of instillation compared to control group. However, patients received combined modalities of instillation had significantly longer duration of postoperative analgesia compared to those received PE or PO instillation alone with significantly longer duration of analgesia on preemptive compared to postoperative instillation, (Table 2, Fig. 1).

All patients enrolled in groups C and PO and 17 patients (85%) in group PE requested rescue analgesia for STP, while 13 patients (65%) in group PE+PO requested rescue analgesia for STP, (Fig. 2). Thus, the use of levobupivacaine IP instillation completely spared postoperative rescue analgesic by 25%. Combined PE and PO significantly reduced the number of patients requested rescue analgesia compared to control and PO group, but non-significantly compared to PE group that showed non-significant difference compared to control and PO groups.

Moreover, 10 patients (12.5%); 7 in PE+PO and 3 in PE groups did not request rescue analgesia; while 7 patients (8.75%); 6 in control and one in PO groups requested it trice. Thus, the use of levobupivacaine IP instillation significantly reduced the number of requests of rescue analgesia compared to control group with non-significant difference between applied modalities despite being in favor of combination group, (Table 3, Fig. 3).

Intraperitoneal local anesthetic instillation provided significantly lower pain VAS score irrespective of timing of instillation compared to control group. However, patients received PO instillation had significantly higher pain VAS scores compared to those received

PE or PE+PO instillation with non-significantly lower pain VAS scores in PE+PO group compared to PE group, (Table 4, Fig. 4).

Patients received levobupivacaine IP instillation had significantly shorter postoperative hospital stay compared to control group and those received combined PE and PO instillation had significantly shorter postoperative hospital stay compared those received PE or PO instillation with a non-significant difference between both modalities despite being in favor of PE instillation, (Table 5, Fig. 5).

Table (1): Patients characteristics and operative variables

	Group C	Group PO	Group PE	Group PE+PO	p
Age (years)	36.7±12.1	35.4±12.3	38.8±12.6	39.5±11.9	0.7(NS)
Sex, M:F	5:15	3:17	4:16	4:16	0.8(NS)
Weight (Kg)	77.8±11.6	77.6±11.6	76.2±10.9	76.2±10.9	0.9(NS)
Height (m)	159.6±8.4	159.1±7.4	160.1±8.2	162.2±9.8	0.6(NS)
BMI (Kg/m^2)	32.1±3.9	32±3.8	30.8±4.6	30.1±4.7	0.4(NS)
Operating time (min.)	49±13.1	55±11.8	53.3±10.6	55.7±12.5	0.3(NS)

Data were represented as mean±SD and frequency, range in parenthesis   BMI: Body Mass Index

Table (2): Mean (±SD) of duration of postoperative analgesia

	Group C	Group PO	Group PE	Group PE+PO	p
Mean±SD (hours)	1.7±0.6	5.4±1.9	10.6±4.5	17.4±4.4	<0.001 (HS)

Table (3): Patients' distribution according to number of requests of postoperative rescue analgesia

	Group C	Group PO	Group PE	Group PE+PO	p
No	0	0	3 (15%)	7 (35%)	<0.001 (HS)
Once	4 (20%)	13 (65%)	13 (65%)	11 (55%)	
Twice	10 (50%)	6 (30%)	4 (20%)	2 (10%)	
Trice	6 (30%)	1 (5%)	0	0	

Table (4): Mean (±SD) of total VAS score estimated throughout the postoperative 24-hours

	Group C	Group PO	Group PE	Group PE+PO	p
Mean±SD (hours)	1.6±0.05	1.2±0.1	0.6±0.05	0.7±0.05	<0.001 (HS)

Table (5): Mean (±SD) of duration of postoperative hospital stay

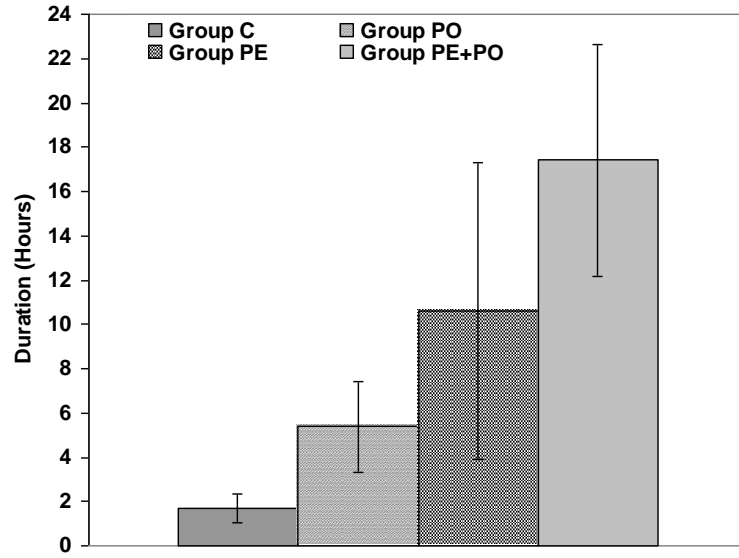|	Group C	Group PO	Group PE	Group PE+PO	p
Mean±SD (hours)	57.6±10.2	52.8±9.5	49.2±7.2	34.2±6.7	<0.001 (HS)

Fig. (1): Mean(±SD) of duration till first request of rescue analgesia
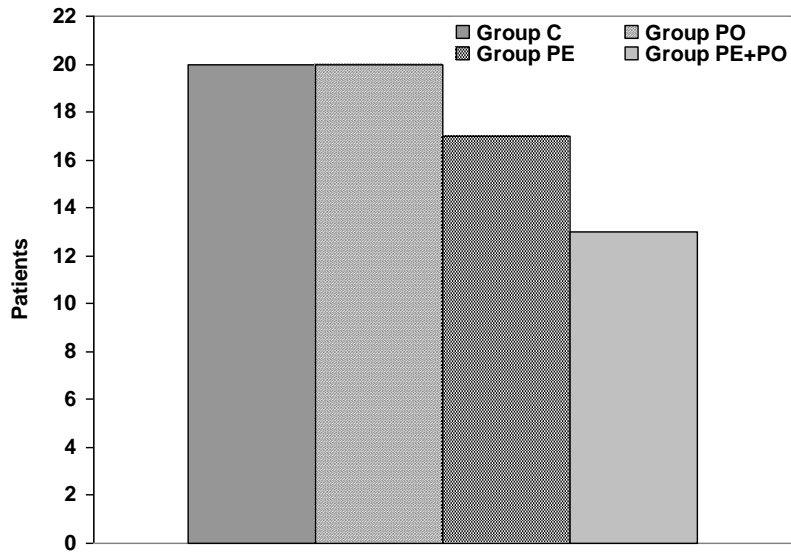

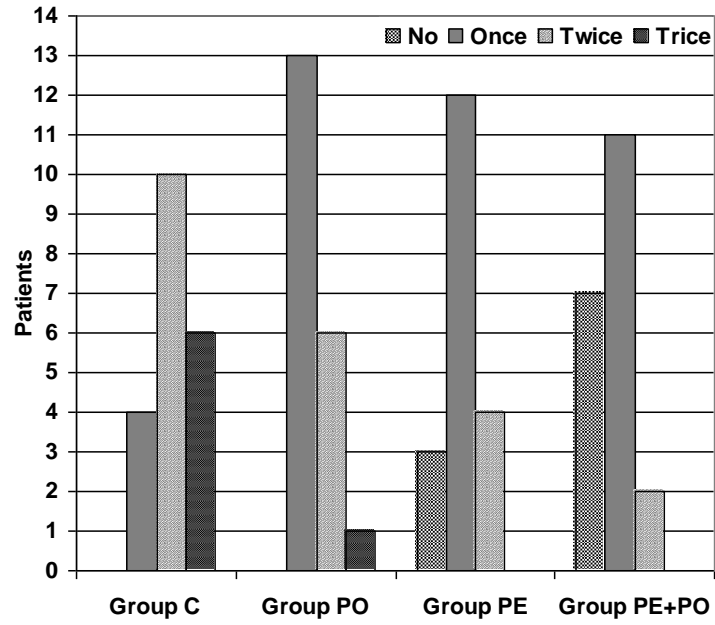**Fig. (2): Number of patients requested rescue analgesia throughout 24-hrs postoperatively**

Fig. (3): Patients' distribution according to
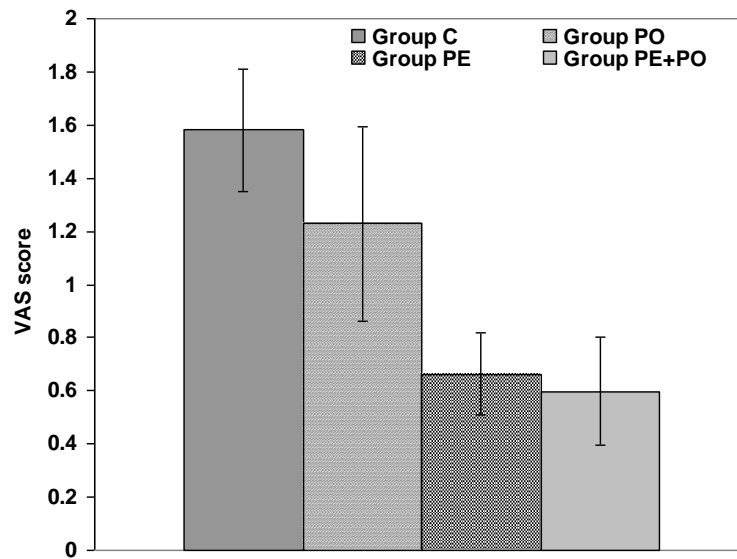number of requests of rescue analgesia

Fig. (4): Mean (±SD) of total VAS score determined
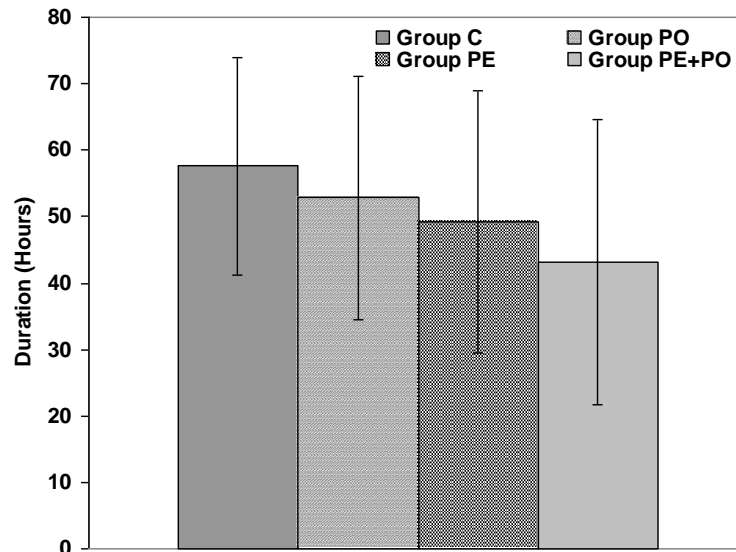throughout 24-hrs observation period

Fig. (5): Mean (±SD) of duration of postoperative hospital stay

Discussion

Laparoscopic cholecystectomy has been widely accepted as an alternative to open cholecystectomy and has many advantages including short hospital stay, and very limited surgical intervention. However, some studies suggested that significant physiologic derangements could occur during laparoscopic surgery, [9].

Postoperative pain at the shoulder following laparoscopic surgery is frequent and very distressing phenomenon. The etiology and pathogenesis of this type of pain are still not clearly understood. Some authors maintain that it may be the result of diaphragmatic irritation of a chemical nature caused by the insufflated CO_2. Carbon dioxide may be transformed by combining with fluid in the peritoneal cavity to an irritative carbonic acid, [10].

There are others, however, who believe that shoulder pain after laparoscopy could be caused by overstretching of the diaphragmatic muscle fibers owing to the high rate of insufflations. In this case, it would be the volume of the gas utilized for pneumoperitoneum that caused the diaphragmatic irritation. It was demonstrated that the degree of stretching of the intra-abdominal cavity is a significant cause of postoperative pain, and it has been shown that a low insufflation rate significantly reduces shoulder pain, [4].

The present study aimed to the effect of IP levobupivacaine instillation on the frequency and intensity of STP and its impact on duration of hospital stay comparing preemptive versus postoperative instillation. Levobupivacaine was chosen as the study drug depending on the previously reported by ***Papagiannopoulou et al.***, [11] who compared the analgesic efficacy of local tissue infiltration using ropivacaine versus levobupivacaine and saline on postoperative pain after laparoscopic cholecystectomy and found local tissue infiltration with levobupivacaine is more effective than ropivacaine in reducing the postoperative pain associated with laparoscopic cholecystectomy.

Intraperitoneal local anesthetic instillation provided significantly longer duration of analgesia, significantly lower pain VAS score and significantly less consumption of postoperative rescue analgesia. These findings go in hand with who ***Alkhamesi et al.***, [1] compared postoperative analgesia in patients undergoing laparoscopic cholecystectomy using aerosolized bupivacaine, aerosolized normal saline and local bupivacaine infiltration in the bladder bed and found aerosolized bupivacaine significantly reduced postoperative pain in comparison with all other treatments, while local injection of bupivacaine into the gallbladder bed did not result in a significant difference from the control condition and with ***Sherwinter et al.***, [12] who evaluated the efficacy of intraperitoneal local anesthetic instillation in patients undergoing laparoscopic adjustable gastric banding and reported a statistically significant decrease in patient's subjective reports of pain by visual analog and remained significant until the end of the study.

The obtained results were contradictory to the minimal or no effect of IP instillation reported in some preliminary studies; **Schulte-Steinberg et al.**, [13] compared IP or intra-pleural routes of opioid administration versus intravenous administration for postoperative analgesia after LC and reported that neither IP or intra-pleural morphine produced significant analgesia after LC and attributed the lack of effect of IP injections to the small dose and to a rapid dilution within the peritoneal cavity. Also, **Szem et al.**, [14] reported that IP bupivacaine offered a detectable, albeit subtle benefit to patients undergoing LC and the effect was transient and had little impact upon the patient's convalescence. **Fuhrer et al.**, [15] tried to overcome these problems by increasing the dose of local anesthetic and found IP administration of 0.6 ml/kg of 0.375% bupivacaine is ineffective in reducing postoperative pain after LC and these high doses of bupivacaine may result in toxic plasma concentrations, thus this technique is not safe and cannot be recommended.

However, through the present study, these problems were overcome using continuous instillation of local anesthetic through catheter applied at the target site. In support of this, patients received PE+PO or PO local anesthetic IP instillation showed superior results compared to placebo or PE groups. As regarding the dose used, levobupivacaine was instilled hourly in a dose of 12.5mg/hr and adjusting this dose to the mean patients' weight the dose was 0.15 mg/kg/hr which is lower than that used by **Fuhrer et al.**, [15] who instilled bupivacaine in a dose of 0.23 mg/kg. Moreover, they used bupivacaine without dilution so the instilled dose was acutely high. In support of the safety of technique and dosing; all patients passed smooth intra and postoperative course without complications or manifestations of toxicity and showed a significantly shorter hospital stay compared to control group.

As regards timing of IP instillation, preemptive instillation alone provided superior postoperative analgesia compared to postoperative instillation alone manifested as significantly longer duration of analgesia and lower pain VAS scores. This difference could be attributed to the facts that CO_2 insufflation is widely considered to be responsible for postoperative pain. In particular, shoulder-tip pain is presumed to be linked to CO_2 insufflation and its intensity is often so strong that analgesics must be administered frequently, [16]. Shoulder pain after laparoscopy could be caused by overstretching of the diaphragmatic muscle fibers owing to the high rate of insufflations and the degree of stretching of the intraabdominal cavity is a significant cause of postoperative pain, [17]. Thus, preemptive instillation prior to pneumoperitoneum could prevent stimulation of stretch receptors in the peritoneum and concomitant STP. Moreover, preemptive instillation allowed block of the release of the nociceptive mediators released on tissue injury during surgery.

In support of these data; **Pasqualucci et al.**, [18] reported that IP local anesthetic blockade administered before or after surgery preempts postoperative pain relative to an untreated placebo-control condition; however, the timing of administration is also important in that postoperative pain intensity and analgesic consumption are both lower among patients treated with local anesthetic before versus after surgery. **Barczyński et al.**, [10] reported that preemptive analgesia with bupivacaine peritoneal instillation is much more effective for pain relief if used before creation of pneumoperitoneum and although the effect of bupivacaine peritoneal instillation is also noticeable when used after creation of pneumoperitoneum, it confers significantly lower benefits.

It could be concluded that IP levobupivacaine instillation provided profound postoperative analgesia with rescue analgesia sparing effect of 25% and significantly reduced postoperative hospital stay. Combined PE and PO instillation provided superior outcome compared to either PE or PO instillation and is advocated as therapeutic modality for pain management after LC.

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