



Surgicel® fibrillar as an innovative analgesic reservoir for post-laparoscopic cholecystectomy pain management: Randomized double-blind trial

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ABSTRACT

Background: Strong analgesia is still needed after laparoscopic cholecystectomy (LC). Surgicel® is a haemostatic agent, capable of absorbing fluids several times its volume, although pain is lower than after open surgeries. We hypothesized that Surgicel® could function as an innovative carrier for sustained-release postoperative analgesia.

Methods: Ninety patients (18–65 years) scheduled for LC were randomized to receive a mixture of 20 ml bupivacaine 0.5%, 10 ml lidocaine 2%, epinephrine 5 µg/ml, and morphine 0.1 mg/kg instilled at hepatic fossa, trocar sites, and under the right copula of the diaphragm (Group-I). Group-II received similar mixture to soak Surgicel® applied at the hepatic fossa and trocar sites. Group-III received normal saline to soak Surgicel® at the same locations. Visual analog scale at 1, 2, 4, 6, 12, and 24 h postoperatively was the primary outcome, while the secondary outcomes included Verbal rating scale, time to first rescue analgesia, total 24-h analgesia, time for the return of bowel function, patients' satisfaction, and adverse effects.

Results: Group-II showed the lowest pain scores ($p > 0.05$), the longest time before requesting analgesia ($p = 0.004$), used least extra analgesia ($p \leq 0.001$), maintained highest satisfaction scores ($p \leq 0.001$), and lowest complications ($p = 0.048$). Group-I showed better results regarding pain control compared to group-III after 2 h ($p = 0.02$) with prolonged time to first analgesia ($p < 0.001$) and less analgesic consumption ($p < 0.001$).

Conclusion: Application of Surgicel® as a reservoir of analgesics at the potential pain generating sites following laparoscopic cholecystectomy, resulted in superior and extended postoperative analgesia with better patients' satisfaction, and no serious adverse effects.

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1. Introduction

Cholecystectomy is one of the most common laparoscopically performed abdominal surgical procedures [1]. Laparoscopic cholecystectomy (LC) is a well-known surgical procedure with preferable outcomes related to postoperative pain, recovery time, and morbidity [2]. It was discovered in 1987 by the French surgeon Phillipe Mouret and has become the gold standard for surgical removal of the gallbladder [3]. While it is associated with less postoperative pain compared with open cholecystectomy, patients still experience some significant pain [4]. Pain after LC may be a referred pain to the right shoulder as a result of diaphragmatic stretching after gas insufflation, visceral pain after dissection at the level of the hepatic fossa, and somatic pain related to tissue injury at the laparoscopic port sites [5,6].

Local anesthetics (LAs) were effective in reducing pain after laparoscopic abdominal surgeries including LC. LAs were comprehensively tested to not only relieve pain but also to reduce the incidence of shoulder pain and postoperative opioid consumption

after LC when used in variable concentrations and techniques. Furthermore, it was ascertained to be a safe and valid method for reducing pain after LC when instilled intraperitoneally and infiltrated at the port sites [7–11].

The medical device (SURGICEL® FIBRILLAR™ Absorbable Hemostat Johnson & Johnson) used in this study was an absorbable hemostat consisting of seven layers of oxidized regenerated cellulose. It is sterilized by gamma waves and supplied with double packing [12]. The local hemostatic material is capable of absorbing whole blood and fluids several times its volume, easily adheres to the bleeding field, and conforms to a stable sticky coagulum [13,14]. SURGICEL® FIBRILLAR™ is adjunctively used in surgical procedures to assist in the control of capillary, venous, and small arterial oozing when ligation or other conventional methods of control are impractical or ineffective [15]. Bupivacaine provides variable pain relief to irrigate the intraperitoneal space as a single analgesic or combined with opioids [16]. Lidocaine 2% solution was mixed with bupivacaine to expedite the onset and potentiate the quality of analgesia [17]. Epinephrine

was used at 5 µg/ml of the total fluid mixture to extend the blocking time [18].

Our hypothesis was to assess usefulness of applying Surgicel® as an innovative carrier for local analgesic medications delivered at pain generating sites after LC to improve the quality and extend the duration of postoperative analgesia.

2. Methods

2.1. Study Design and Ethics

This prospective randomized placebo-controlled double-blind study was approved by the Medical Ethics Committee, Faculty of Medicine, Assiut University, Egypt (IRB17300235 on 16 October 2018). The study was registered and approved by ClinicalTrials.gov (NCT03730714 on 15 November 2018). Patients scheduled for LC under general anesthesia (from November 2018 to August 2020) were enrolled in the study after signing a written informed consent and their privacy rights were always observed.

2.2. Sample Size

G*Power 3.1.9.4 software was used to calculate the sample size. A calculated minimum sample of 26 patients was required in each group to detect an effect size of 0.5 to improve the incidence of postoperative pain after LC, which was found in previously conducted studies to be 50–80% [9,10] with an alpha error probability of 0.05 and 80% power on one-tailed test. We enrolled 30 patients in each group to account for potential patients' dropouts and to ensure statistical robustness.

2.3. Medications and Random Coding

Patients were randomly distributed into three equal groups (30 patients each) using a computer-generated table of random numbers. Neither the investigator responsible for data collection nor the participants were aware of the study group or the drugs used. An anesthesiologist (not included in the procedure, observation, or data collection) prepared the study drugs. The surgical team operated on all patients sequentially without a specific order and had a comparable level of experience in the field. All consented patients received a full explanation regarding anesthetic and analgesic techniques before signing their consent.

2.4. Inclusion/Exclusion Criteria

Eligible patients were 18–65 years old, of both genders, ASA I–II, and scheduled for LC. Patients were excluded from the study if they had a history of allergic reactions to the study medications, seizure disorders, significant

respiratory or cardiac diseases, intraperitoneal infection, or chronic use of analgesia.

2.5. Anesthetic Technique

Prior to the day of surgery, each patient attended an outpatient appointment for a full medical evaluation, description of the study protocol, and assessment their eligibility to participate in the study. All patients underwent laboratory investigations and signed an informed consent. Furthermore, all patients received the standard general anesthetic technique followed in the hospital, 8 h of preoperative fasting, premedication with a proton pump inhibitor, and an antiemetic.

At the operative theater, patients were connected and evaluated for five standard monitoring measures: electrocardiography (ECG), noninvasive blood pressure (NIBP), pulse oximetry (SpO₂), core body temperature, and end-tidal carbon dioxide (EtCO₂). Patients received intravenous normal saline 0.9% fluids infused at a rate of (6–8 ml/kg/h) during the time of the surgery via an 18 gauge i.v. cannula inserted at the dorsum of the non-dominant hand.

All patients had 3 minutes of pre-oxygenation with 100% O₂ via the appropriate size face mask and general anesthesia induced with fentanyl 1 µg/kg, propofol 2–3 mg/kg, and cisatracurium 0.15 mg/kg. Patients were intubated with the appropriate sized cuffed endotracheal tube under direct laryngoscopy after complete muscular relaxation. The maintenance of anesthesia was conducted with sevoflurane at 2–3% and 0.03 mg/kg/h of cisatracurium. Respiratory parameters were adjusted to keep the EtCO₂ at 30–40 mmHg through maintaining mechanical ventilation. At the end of the surgery, the inhalational anesthetic was discontinued and the residual neuromuscular blockade was pharmacologically reversed using 0.04 mg/kg of neostigmine plus 0.02 mg/kg of atropine. Tracheal extubation was performed once the patient showed clinical signs of clearance from the neuromuscular blockade and a train-of-four ratio of 0.9 was reached.

2.6. The Study Technique

At the end of the LC procedure, Surgicel® was cut into a large piece matching the size of the hepatic fossa and small pieces for the trocar wound sites. The large piece was folded and introduced through the big port to cover the gallbladder bed, while the small pieces were used to intersect the trocar wounds. The study mixture of medicine included a total of 32 ml: Instill was used to soak the Surgicel® at the hepatic fossa (10 ml). Splash was used on the undersurface of the right copula of the diaphragm (10 ml). Instill was used to soak the small pieces of Surgicel® intersections at the port sites (12 ml).

2.7. Study groups

Group (I): patients received 20 ml of bupivacaine 0.5% (maximum of 2 mg/kg), 10 ml of lidocaine 2% (maximum of 3 mg/kg), 5 µg/ml of epinephrine (maximum of 150 µg) combined with 0.1 mg/kg Morphine (maximum of 10 mg), in a total volume of 32 ml, instilled into the assigned areas according to the technique (no Surgicel® was used). Group (II): patients received the same mixture as group I to soak the Surgicel® according to the previously planned technique. Group (III): patients received 0.9% normal (32 ml) saline to soak the Surgicel® according to the planned technique.

2.8. Outcomes Measures

The primary outcome of this trial was the efficacy of the Surgicel® as a potential analgesic drug reservoir to prolong of analgesia after LC, measured by Visual Analogue Scale (VAS) at the end of the first postoperative day. The secondary outcomes included the Verbal Rating Scale (VRS), the time to first rescue analgesic request, the total analgesic requirements during the first 24 h postoperatively, patients' satisfaction, and any possible adverse effects.

2.9. Data Collection

- The pain score was measured at 1, 2, 4, 6, 12, and 24 h postoperatively: Post-operative abdominal and shoulder pain was determined using the Visual Analogue Scale (VAS) at rest, based on a 0–10 scale (with 0 indicating no pain and 10 as the most severe pain ever experienced) and the 4-point Verbal Rating Scale (VRS) at rest (0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain).
- Postoperative rescue analgesic requirements (intravenous 0.1 mg/kg of nalbuphine every 6 h on a PRN basis, if the VAS pain score was ≥ 4).
- Time for the return of bowel function: Time of recovery of bowel function as defined by the time from the end of anesthesia until the first passage of gas.
- Recorded postoperative complications, e.g., nausea and vomiting.
- Patients' satisfaction score: All participants were asked to rate their satisfaction with pain control 24 h after surgery using the 5-point Likert scale (1 = very satisfied, 2 = satisfied, 3 = neither satisfied nor dissatisfied, 4 = dissatisfied, 5 = very dissatisfied).

2.10. Statistical Analysis

Data were collected, verified, and analyzed using IBM-SPSS 21.0 (IBM-SPSS Inc., Chicago, Illinois, USA). The

calculated descriptive statistics included means, standard deviations, and percentages. The difference in the frequency distribution among the different groups was conducted using the Chi-square test. For continuous variables with more than two categories, the one-way ANOVA test was performed to test the mean differences between groups, repeated measure ANOVA (RM-ANOVA) analysis was calculated to test the mean differences for data that followed a normal distribution and had repeated measures (between groups, within groups and overall difference), and a post-hoc test was calculated using the Bonferroni corrections for pairwise comparisons between each of the two study groups. The median differences between groups with more than two categories were calculated using the non-parametric Kruskal Wallis test. A *p*-value of less than 0.05 was considered significant.

3. Results

The study enrolled 90 patients who were investigated and statistically evaluated. The flow diagram of CONSORT for this study is shown in Figure 1. The demographic characteristics of these patients were comparable and were demonstrated in Table 1, with no statistically significant differences between the three study groups regarding age, gender, and body mass index (*p*-value <0.05). The mean duration of anesthesia was 70.37 ± 13.3 , 73.17 ± 13.9 , and 70.20 ± 12.1 min in the groups I, II and III, respectively, with no statistically significant difference (*p*-value = 0.618). For the duration of surgery, there was also no statistically significant difference between the study groups (*p*-value = 0.719). The mean duration of surgical procedure was 62.00 ± 13.2 min in group-I, 64.40 ± 12.7 minutes in group-II, and 62.27 ± 11.6 minutes in the group-III. All groups were analogous with no statistically significant differences (*p*-value <0.05) for the intraoperative hemodynamic parameters at the induction of general anesthesia (baseline) until the end of the surgery including the heart rate, mean blood pressure, SpO₂, and EtCO₂.

The mean postoperative VAS values were statistically and significantly different between the three study groups starting 2 after recovery from anesthesia and during the whole period of postoperative follow-up (*p*-value >0.05). The VAS score readings were the lowest in group-II than the other groups throughout the observation period. Group-I showed a significant lower VAS values than that of group-III only after 2 h postoperatively with a *p*-value of 0.02 (Table 2). Regarding postoperative VRS values, there was a statistically significant difference between the three study groups only after recovery from general anesthesia at 2 and 4 h with a *p*-value >0.05. The number of patients with no pain at the postoperative VRS score

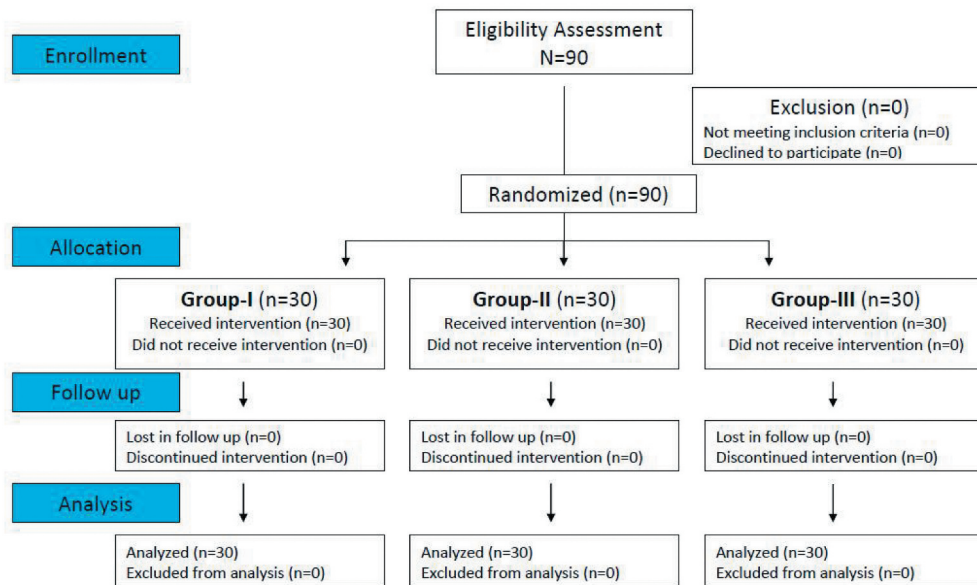


Figure 1. CONSORT flow diagram of patients in the three study groups.

Table 1. Demographic characteristics and clinical data in the studied groups.

Variable	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	p-Value
Age (years)	36.40 ± 0.8	35.30 ± 1.9	35.03 ± 1.8	0.858 ^a
p-Value ^b	I vs. II = 0.676	II vs. III = 0.919	I vs. III = 0.603	
Sex (Female/Male)	22/8	23/7	20/10	0.679 ^c
BMI	30.43 ± 2.3	30.65 ± 2.9	30.86 ± 2.0	0.791 ^a
p-Value ^b	I vs. II = 0.731	II vs. III = 0.733	I vs. III = 0.495	
Duration of Anesthesia (minutes)	70.37 ± 13.3	73.17 ± 13.9	70.20 ± 12.1	0.618 ^a
p-Value ^b	I vs. II = 0.411	II vs. III = 0.384	I vs. III = 0.961	
Duration of Surgery (minutes)	62.00 ± 13.2	64.40 ± 12.7	62.27 ± 11.6	0.719 ^a
p-Value ^b	I vs. II = 0.460	II vs. III = 0.511	I vs. III = 0.934	

^aANOVA test used to compare the mean difference between groups.

^bPost-hoc test used for pairwise comparison with Bonferroni correction.

^cChi-square test used to compare the proportion difference between groups.

p-Value is considered significant if less than 0.05.

Table 2. Postoperative VAS differences between the studied groups.

VAS	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	p-Value
VAS-1 h	1.80 ± 0.1	1.33 ± 0.2	1.67 ± 0.2	0.228 ^a
p-Value ^b	I vs. II = 0.096	II vs. III = 0.232	I vs. III = 0.631	
VAS-2 h	1.47 ± 0.2	1.27 ± 0.2	2.23 ± 0.3	0.009 ^a
p-Value ^b	I vs. II = 0.538	II vs. III = 0.004	I vs. III = 0.020	
VAS-4 h	1.60 ± 0.2	0.97 ± 0.1	1.97 ± 0.2	0.002 ^a
p-Value ^b	I vs. II = 0.024	II vs. III < 0.001	I vs. III = 0.187	
VAS-6 h	1.57 ± 0.2	1.10 ± 0.1	1.87 ± 0.2	0.033 ^a
p-Value ^b	I vs. II = 0.111	II vs. III = 0.010	I vs. III = 0.303	
VAS-12 h	1.37 ± 0.2	0.93 ± 0.1	1.60 ± 0.2	0.028 ^a
p-Value ^b	I vs. II = 0.084	II vs. III = 0.009	I vs. III = 0.949	
VAS-24 h	1.10 ± 0.1	0.93 ± 0.1	1.40 ± 0.1	0.046 ^a
p-Value ^b	I vs. II = 0.376	II vs. III = 0.015	I vs. III = 0.113	
p-Value ^c	=0.011	=0.020	=0.030	=0.002 ^d

^aANOVA test used to compare the mean difference between groups; VAS, visual analogue scale.

^bPost hoc test used for pairwise comparison with Bonferroni correction.

^cRM-ANOVA test used to compare the mean difference within the group over time.

^dInteraction between Group and Time.

p-Value is considered significant if less than 0.05.

was lower in group II compared to the other two groups at any time point of postoperative follow-up (Table 3).

The number of patients that required supplemental analgesia within the first postoperative day was smaller in group-II (2 patients) compared to the other two study

Table 3. Postoperative VRS differences between the studied groups.

VRS	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	p-value ^a
VRS-1 h				0.263
● No Pain	13 (43.3%)	18 (60%)	18 (60%)	
● Mild	17 (56.7%)	10 (33.3%)	10 (33.3%)	
● Moderate	0 (0%)	2 (6.7%)	3 (10%)	
● Severe	0 (0%)	0 (0%)	1 (3.3%)	
VRS-2 h				0.006
● No Pain	14 (46.7%)	20 (66.7%)	17 (56.7%)	
● Mild	15 (50%)	9 (30%)	6 (20%)	
● Moderate	0 (0%)	1 (3.3%)	7 (23.3%)	
● Severe	1 (3.3%)	0 (0%)	1 (3.3%)	
VRS-4 h				0.013
● No Pain	19 (63.3%)	21 (70%)	12 (40%)	
● Mild	11 (36.7%)	9 (30%)	14 (46.7%)	
● Moderate	0 (0%)	0 (0%)	3 (10%)	
● Severe	0 (0%)	0 (0%)	1 (3.3%)	
VRS-6 h				0.373
● No Pain	16 (53.3%)	23 (76.7%)	17 (56.7%)	
● Mild	11 (36.7%)	7 (23.3%)	10 (33.3%)	
● Moderate	1 (3.3%)	0 (0%)	2 (6.7%)	
● Severe	2 (6.7%)	0 (0%)	1 (3.3%)	
VRS-12 h				0.138
● No Pain	16 (53.3%)	24 (80%)	18 (60%)	
● Mild	14 (46.7%)	6 (20%)	11 (36.7%)	
● Moderate	0 (0%)	0 (0%)	1 (3.3%)	
● Severe	0 (0%)	0 (0%)	0 (0%)	
VRS-24 h				0.166
● No Pain	22 (73.3%)	23 (76.7%)	17 (56.7%)	
● Mild	8 (26.7%)	7 (23.3%)	13 (43.3%)	
● Moderate	0 (0%)	0 (0%)	0 (0%)	
● Severe	0 (0%)	0 (0%)	0 (0%)	

^aChi-square test used to compare the proportion difference between groups;VRS, verbal rating scale. P-value is considered significant if less than 0.05.

groups (7 patients in group-I and 17 patients in group-III) with a statistically significant difference between the three groups (p -value = 0.004). One patient (3.3%) in group-I and four patients (13.4%) in group-III required two doses of postoperative analgesia. In contrast, no patient (0%) in group-II required more than one treatment of postoperative analgesia. The mean total amount of rescue analgesic requirements was 1.34 ± 0.1 , 0.51 ± 0.1 , and 5.60 ± 1.1 mg in groups I, II, and III, respectively, at a statistically significant level (p -value <0.001). Regarding the time passed before the first analgesic requirement, there was a statistically significant difference between the three study groups (p -value = 0.004) (Table 4).

The postoperative period recorded for the return of bowel function showed no statistically significant difference between the three study groups (p -value = 0.198). For the postoperative complications between the three groups, nausea and vomiting reported a statistically significant difference with a p -value of 0.048. This study recorded no other complications or serious adverse effects along the observation period (Table 5).

The current study reported higher patients' satisfaction scores in group-II patients compared to group-I or group-III, with a statistically significant difference (p -value <0.001). The cumulative satisfaction results showed that 29 patients (96.7%) in the group-II were very satisfied and satisfied compared to 28 patients (93.3%) in the group-I and 17 patients (56.7%) in the group-III (Table 5).

4. Discussion

The use of a gelatin-based hemostatic agent capable of absorbing approximately 40–50 times its volume of fluids or blood inspired the research team to invest in this criterion and innovate with a local carrier of analgesic medication [19]. To our knowledge, it is the first use of this innovative method of delivering analgesic medications to optimize pain relief after LC with minimal systemic effects.

This study introduced a new and promising tool that will have an appealing clinical application for pain management, as shown in its main outcome. Patients who received the study medicine to soak Surgicel® at the hepatic fossa and trocar sites experienced optimized and statistically significant lower VAS pain scores compared to those who received the same medication without Surgicel® in group-I or received placebo to soak Surgicel® (group-III). This difference was more robust after 2 h of recovery and probably when the effect of the analgesic medication received during anesthesia had worn off. Also, the VRS demonstrated better values regarding postoperative pain (no pain or mild pain) during 24 h of the study in group-II, especially at 2 and 4 h after recovery. There were 93.3% of group-II patients required no breakthrough analgesia with a significantly low total analgesic consumption.

Bupivacaine has been the most commonly used local anesthetic for analgesia after LC through

Table 4. Postoperative analgesia in the three studied groups.

Variable	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	p-Value
Number of patients required postoperative analgesia				0.004 ^a
• No	23 (76.7%)	28 (93.3%)	13 (43.3%)	
• One Dose	6 (20%)	2 (6.7%)	13 (43.3%)	
• Two Doses	1 (3.3%)	0 (0%)	4 (13.4%)	
The total amount of analgesic requirements (mg)				<0.001 ^c
• Mean \pm SD	1.34 \pm 0.1	0.51 \pm 0.1	5.60 \pm 1.1	
• p-Value ^b	I vs. II = 0.424	II vs. III <0.001	I vs. III <0.001	
Time to first postoperative analgesia (h)				0.004 ^d
• Median (range)	0.0 (0–6)	0.0 (0–2)	1.0 (0–6)	
• P-value ^b	I vs. II = 0.897	II vs. III <0.001	I vs. III <0.001	

^aChi-square test used to compare the proportion difference between groups.

^bPost hoc test used for pairwise comparison with Bonferroni correction.

^cANOVA test used to compare the mean difference between groups.

^dKruskal–Wallis test used to compare the median difference between groups.

p-Value is considered significant if less than 0.05; mg, milligrams; SD, standard deviation; h, hour.

Table 5. Postoperative outcomes of the studied groups.

Variable	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	P-value
Time for the return of bowel function (h)				0.198 ^c
• Mean \pm SD	3.20 \pm 0.2	2.93 \pm 0.2	3.37 \pm 0.3	
• p-Value ^b	I vs. II = 0.271	II vs. III = 0.075	I vs. III = 0.491	
Postoperative Complications (nausea and vomiting)				0.048 ^a
• Yes	4 (13.3%)	3 (10%)	6 (20%)	
• No	26 (86.7%)	27 (90%)	24 (80%)	
Patients' Satisfaction Score				<0.001 ^a
• Very Satisfied	4 (13.3%)	7 (23.3%)	0 (0%)	
• Satisfied	24 (80%)	22 (73.4%)	17 (56.7%)	
• Neutral	2 (6.7%)	1 (3.3%)	8 (26.7%)	
• Unsatisfied	0 (0%)	0 (0%)	5 (16.6%)	
• Very Unsatisfied	0 (0%)	0 (0%)	0 (0%)	

^aChi-square test used to compare the proportion difference between groups.

^bPost hoc test used for pairwise comparison with Bonferroni correction.

^cANOVA test used to compare the mean difference between groups.

p-Value is considered significant if less than 0.05.

installation into the intraperitoneal space below the right diaphragm and the hepatic fossa at different concentrations, volumes, and in combination with other medications. When injected at the gallbladder area, either alone or combined with opioids, bupivacaine is an effective and promising mode of analgesia for pain associated with LC [20,21]. Nevertheless, bupivacaine is reported to show poor results when used in the same route of administration for pain relief after LC, which could partially be explained by the use of low concentration, low volume, or even missing areas that could be a potential source of pain [22,23]. Recent research used the LAs ropivacaine or bupivacaine, and showed a significant statistical efficacy of LAs in reducing different types of postoperative pain after LC versus the placebo, especially in the first 8 h [24,25].

The effect of intraperitoneal LAs for post abdominal laparoscopic pain was verified even more in recent studies compared to the placebo and showed a clear benefit in reducing pain encountered after abdominal laparoscopic surgery [26]. The outcome of using bupivacaine for the same purpose after intraperitoneal injection after LC demonstrated a statistically significant reduction in the figures of pain assessment using VAS, NRS, use of additional analgesia, and patients'

satisfaction, specifically in the first postoperative 8 h. However, they used a 500 ml volume of 0.02% to obtain such an effect and satisfactorily improved analgesia in the early 8 h after the surgery compared to the placebo [27]. Using large volumes and low concentrations, bupivacaine reduced pain after LC and demonstrated equivalent results and a better analgesic profile in early postoperative period, delayed the claim for the first analgesia, and cut the overall backup analgesia consumption over the first postoperative 24 h in the study group versus placebo [28].

The main objective of the literature over the last decade was to extend the time of analgesia obtained from bupivacaine/ropivacaine when instilled intraperitoneally through the addition of drugs that can boost analgesia quality and time with minimal side effects. In this context, buprenorphine was studied in combination with bupivacaine, plain bupivacaine, and a placebo; these studies found that LA with buprenorphine elicited a statistically significant and extended superior quality of postoperative pain relief with a low rescue analgesic requirement compared to plain LA and a placebo [4].

Intraperitoneal morphine, when used in addition to bupivacaine versus plain LA and the placebo, has proven efficacy in extending expressive postoperative

analgesia (VAS < 3), delayed the request for rescue analgesia, and reduced the dose compared to the other two groups in the study in patients undergoing laparoscopic abdominal surgery in favor of the morphine plus LA group with no substantial increase in side effects [29]. Morphine, when used a long time before and in a similar protocol to manage postoperative pain after LC, reported good analgesic profiles in the study group but for only the first 6 h after recovery. A low dose of morphine used in that study may explain the short period of pain relief [30].

We assume that the use of Surgicel® as a reservoir for the study medication is the main reason for this optimized and extended pattern of analgesia maintained for 24 h of the current study; it probably released the drug slowly at the target sites. The added epinephrine possibly have slowed the rate of absorption of the analgesics as well, besides the effect of morphine used in the drug mixture of the study group (medication plus Surgicel).

Nevertheless, this mixture of medication was not associated with any significant adverse effects compared to the other two groups (drug instillation or placebo), possibly due to the slow release of the medicine from the Surgicel® reservoir. This may have reduced the reported rate of statistically significant side effects in the Surgicel® study group versus the other groups. The superiority and validity of this approach of pain management after LC is evidenced by a 96.7% positive patients' satisfaction score reported in the group-II (very satisfied and satisfied) compared to the other two study groups.

The strength points of the study include the use of a strict protocol to select patients of both genders; exclusion of patients whose severe renal, hepatic, or respiratory diseases might affect the results; the study was conducted with one surgical team to avoid an additional surgical confounder; all patients were monitored closely over 24 h postoperatively; low dropout rate; and prompt surveillance of any postoperative adverse effects.

Limitations

A larger number of patients would enhance the power of our results and state for safety of this technique. Another limitation was the difficulty in conducting a multicenter protocol which is recommended for future work. Finally, the lack of long-term follow-up regarding pain assessment or postoperative complication. Further research is recommended as one type of surgery was encountered in this comparative study and intensity of pain could have been different with other surgeries.

Conclusion

Application of Surgicel® as a reservoir for analgesics at the potential pain generating sites following laparoscopic cholecystectomy resulted in superior and

extended postoperative analgesia with better patients' satisfaction, and no serious adverse effects.

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