The role of peritoneal lavage in benign gynecologic laparoscopic surgery

C. DE CICCO NARDONE[1], F. FICAROLA[1], F. PLOTTI[1], R. MONTERA[1],
L. FEOLE[1], S. RAMPELLO[1], G. MESSINA[1], D. LUVERO[1], R. MARCI[2],
R. ANGIOLI[1], C. TERRANOVA[1]

[1]Department of Gynecology, Campus Bio-Medico University Hospital Foundation, Rome, Italy
[2]Department of Transitional Medicine, University of Ferrara, Ferrara, Italy

Abstract. – **OBJECTIVE:** Laparoscopic surgery offers many advantages compared to invasive surgery but one of the main problems is postoperative pain, partially resulting from the peritoneal inflammatory process mediated by inflammatory cytokines. The rationale of this study is that intraperitoneal washing could remove inflammatory mediators that are the cause of postoperative pain and could help in the removal of CO_2 from the abdominal cavity. This article aims to analyze the effects of peritoneal lavage in the reduction of postoperative shoulder pain.

PATIENTS AND METHODS: 277 patients enrolled to undergo laparoscopic gynecologic surgery were included in the study. Women are randomized into two groups, according to the use or non-use of peritoneal lavage with saline solution at the end of laparoscopic gynecological major procedures.

RESULTS: Data show that the peritoneal lavage can significantly reduce postoperative pain in the first 36 hours after surgery, as well as patients' requests for analgesics: during the first 3 postoperative days, requests for paracetamol were lower in the YW (Yes Washing) group than the NW (No Washing) group (77 *vs.* 101; *p*<0.05); similar results are obtained considering ketorolac administration (62 *vs.* 71; *p*<0.05).

CONCLUSIONS: Peritoneal lavage after gynecological laparoscopic procedures may be effective in the reduction of postoperative pain and use of analgesics.

Key Words:
    Laparoscopy, Postoperative pain, Peritoneal lavage, Gynecologic surgery.

Introduction

Mini-invasive surgery offers many advantages if compared to traditional laparotomy. Laparoscopic surgery provides fewer scars, as well as reduced morbidity, pain and post-operative hospital stay compared to laparotomy. Furthermore, laparoscopy offers better visualization of the abdominal structures. At the same time, laparoscopy is related to some complications too, such as reduced cardiac function, reduced blood supply to vein and peripheral vessels, increased risk of deep venous thrombosis and pulmonary embolism, hypothermia and gaseous embolism. Laparoscopy can also induce alterations in pulmonary function, due to CO_2 retention and diaphragm stress due to air insufflation in the abdomen[1].

Despite the great role that laparoscopy plays among surgical procedures, post-operative pain is still one of the main problems related to this mini-invasive technique, despite it is less intense than in laparotomy[2-4]. Visceral pain after laparoscopy can be caused by peritoneal and diaphragm stretching induced by pneumoperitoneum and inflammatory cytokines produced by blood present in the abdomen. It is a dull and widespread ache, located in the abdominal or thoracic region with frequent shoulder irradiation. Pain could increase hospital stay and alter respiratory functions and hemodynamics. It is also linked to higher use of analgesics following the strategies regarding Enhanced Recovery After Surgery in the preoperative and postoperative phase[5-7]. Hysterectomy is a procedure that usually lasts longer than other laparoscopic procedures and, for this reason, the patient is exposed for a longer amount of time to pneumoperitoneum effects, like oxidative stress[8]. Moreover, the Trendelenburg position can increase shoulder pain, with a higher diaphragm irritation caused by pneumoperitoneum.

The rationale of this study is that intraperitoneal washing could remove inflammatory mediators causing pain (like Nerve Growth Factor, Prostaglandin E2, bradykinin and tryptase) and help in

Corresponding Author: Fernando Ficarola, MD; e-mail: ficarola.fernando@gmail.com

the removal of CO_2 from the abdominal cavity. In this way, inflammatory processes and nociceptive stimuli could be significantly reduced. This study aims at providing evidence about the role of intraperitoneal washing with saline solution in laparoscopic gynecological procedures to reduce postoperative shoulder pain. Secondary outcomes were the evaluation of peritoneal inflammatory state with postoperative laboratory data (Hemoglobin, C-reactive protein and White Blood Cells) on the first, second, and third postoperative days, as well as a lower request of perioperative analgesics (of both Ketorolac and Paracetamol).

Patients and Methods

This is a prospective randomized clinical trial (RCT) (Registration No. NCT03290521) conducted in the Gynecology Department of Campus Bio-medico of Rome, following CONSORT (CONsolidated Standards of Reporting Trials) guidelines. All patients undergoing major laparoscopic surgery for benign pathologies from January 10th, 2019, to December 27th, 2019 were consecutively enrolled. This study is conducted by the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996) and it was approved by the Internal Review Board of Campus Bio-medico of Rome (No 39/17 INT ComEtCBM, date 12/07/2017). Written informed consent was obtained from the patients included in the study.

Inclusion and Exclusion Criteria
Inclusion criteria were patients undergoing major laparoscopic surgery (hysterectomy, hysterectomy and oophorectomy, and myomectomy), aged between 18-70 years, with no previous abdominal surgery. Exclusion criteria were age <18 or >70 years, previous use of opioids for chronic pain, cancer diagnosis, pelvic inflammation, or neurological/cognitive dysfunctions. After consent was obtained, patients were randomly assigned to either the Yes washing (YW) or No washing (NW) group by the clinical research nurse, using a computer-generated random number series with Excel 2016, software version 16.0. Patients, nurses and doctors evaluating postoperative data were unaware of patients' group.

Study Procedure
Before surgery, patients' anamnestic data, preoperative hemoglobin and C-reactive protein

(CRP) blood levels were registered. Antibiotic prophylaxis consisted in Cefazolin 2 g/iv, infused 30 minutes before surgical incision.

Operative phase
During the operative phase, each patient received general anesthesia. Drugs used during induction were fentanyl 3 mcg/kg, rocuronium bromuro, 0.6 mg/kg, and propofol 2 mg/kg. In the maintenance phase, after intubation, patients received desflurane 6% and remifentanil. Then, the second phase of preemptive analgesia was done, with paracetamol 1 gr, dexamethasone 1 mg/kg, clonidine 2 mcg/kg, granisetron 1 mg, ketorolac 30 mg. Surgery was done according to classic procedures, as described elsewhere[9,10]. The procedures were performed by 5 different surgeons (C.D.C.N, F.P., R.M., R.A. and C.T.), with more than fifteen years of work experience in the field of gynecological surgery. The two groups did not receive different procedures in terms of peritoneal access, number of trocars, intra-abdominal pressure, model of the uterine manipulator, electrosurgery and suture threads. Patients needing laparotomy were excluded from the analysis.

After the removal of the surgical specimen, accurate hemostasis was performed. Patients of the YW group underwent intraperitoneal washing, with the introduction of at least 2,000 cc of saline isotonic solution at 37°C in the peritoneal cavity. Patients were placed in Trendelenburg position and reverse Trendelenburg position, to allow contact between the liquid and all abdominal structures, including the diaphragm and surgical wounds. At the end of the procedure, all the introduced liquid was carefully removed.

Postoperative phase
During the postoperative phase, laboratory findings (Hemoglobin, white blood cells, CRP, the corporeal temperature on the 1st-, 2nd-, and 3rd-postoperative days), the timing of intestinal function recovery, painkillers requests and postoperative abdominal pain at rest, during movements and during coughing were registered. A visual analogue scale (VAS) was used to evaluate postoperative shoulder pain. Each patient received postoperative analgesia with 90 mg ketorolac in continued infusion for the first 24h. 1st-, 2nd-, and 3rd-postoperative days were considered as 24h, 48h, and 72h after surgery. During the 1st-postoperative day, rescue doses with 1 g paracetamol intravenously were considered if VAS >5. During the 2nd- and 3rd-postoperative days, rescue doses

of analgesics were used – 1 g paracetamol when VAS >5; if the pain was not reducing, ketorolac 30 mg was administered. If pain was persisting with NRS >8, opioids were used.

Normally distributed data are presented as mean +/- SD. VAS scores are compared with the Mann-Whitney test. Patients underwent medical examination 7 days post-surgery to check the safety of surgical procedures. No surgical complications were found in the two groups. Data Safety and Monitoring Board controlled every month all the patients with medical examination to check the safety of surgical procedures. No surgical complications were found during the follow-up period in the two study arms.

Statistical Analysis

All database data was collected in an Excel® sheet (Redmond, WA, USA), software version 16.0. The statistical analysis was conducted with Stata® (CA, USA), software version 16.1. Based on the data collected from similar study previously performed, the number of patients required for the study was calculated based on 80% power (with significant level at 0.05), to detect a significant reduction in the shoulder postoperative pain of 30.8% at 48h in treatment group. The number of patients to reach statistical significance is 135 patients in each group. A 5% higher sample size was chosen to compensate for dropouts. The p-value <0.05 was considered statistically significant.

Results

From January 10th, 2019, to December 27th, 2019, 306 patients selected from the Department of Gynecology of Campus Bio-Medico of Rome to undergo laparoscopic gynecologic surgery were included. 29 of them refused to be enrolled for the study. A total of 277 were enrolled for it. Using inclusion and exclusion criteria, they were divided into two groups: "No Washing" group (NW) composed of 135 patients and a "Yes Washing" group (YW) composed of 142 patients. As shown in Figure 1, 7 patients are excluded for laparotomy conversion or malignancy: 131
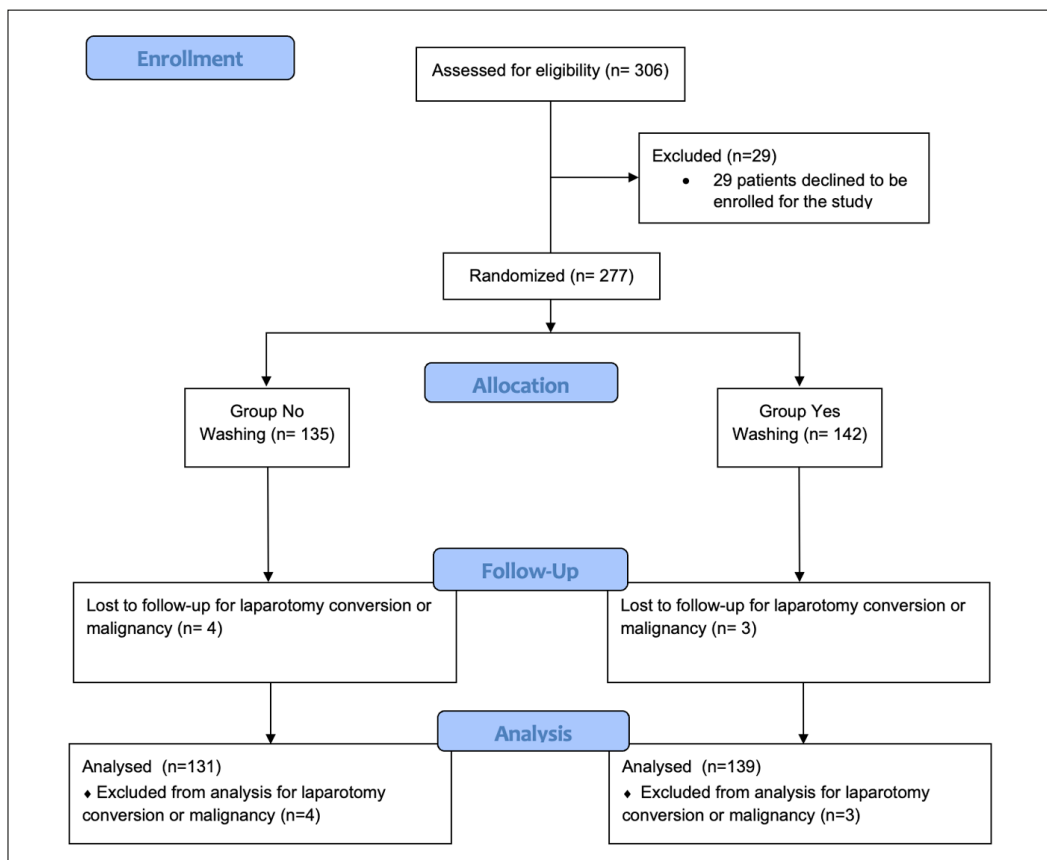

Figure 1. Study design.

Table I. Patients characteristics.

Variables	NW (n = 135)	YW (n = 142)	p
Age, mean (SD)	49.73 ± 9.72	47.84 ± 14.07	0.477
Ethnicity/Race (%)			
White,	121 (89)	128 (90)	0.784
Others,	14 (11)	14 (10)	0.784
BMI (IQR), mean (SD)	23.51 (18.50-34.80)	22.98 (17.40-32.10)	0.502
Surgical indication (%)			
Menorrhagia/Metrorrhagia	68 (50)	71 (50)	0.689
Endometrial hyperplasia	35 (26)	33 (23)	0.856
Symptomatic uterine fibroids	32 (24)	38 (27)	0.794

patients in NW and 139 patients in YW were considered for the final analysis. The groups were homogeneous in terms of age, ethnicity/race, BMI (Body Mass Index) and surgery indications (Table I). Comparing the two groups, the amount of CO_2 insufflated, operative time and estimated blood loss were not significantly different (Table II). The values of postoperative pain are reported in Table III. VAS scale values for pain evaluation during abdominal examination were reduced in YW group compared to NW group at 6h, 12h and 36h after surgery (5.44 *vs.* 3.93, 4.76 *vs.* 3.28, 2.12 *vs.* 1.02 respectively; *p*=0.004, 0.008, 0.009; IC 95%). Furthermore, VAS scale values for pain evaluation during coughing show a higher reduction in YW group compared to NW group at 6h and 12h after surgery (5.61 *vs.* 4.00, 4.98 *vs.* 3.30. *p*=0.009, 0.003; IC 95%).

Secondary outcomes are reported in Table IV. The laboratory data analysis did not show a significant difference in the two groups, except for C-reactive protein (CRP) blood levels during 1st postoperative day, which were significantly lower in the YW group (NW: 1.69 *vs.* YW: 0.78 mg/dl). During 1st postoperative day, as reported in Table IV, some patients reported NRS>5 and received rescue doses of paracetamol (64 in NW *vs.* 48 in YW, *p*<0.05; IC 95%). During the second and third postoperative days, the NW group

received a total number of Ketorolac and paracetamol doses significantly higher compared to YW group's patients.

Intestinal recovery was similar between the two groups, with the greatest part of patients experiencing resolution of the ileus 24 hours(h) after surgery (YW: 60%; NW: 63%; *p*=0.176 IC 95%).

Postoperative complications, including major and minor complications, were homogeneous between the two groups with no statistical differences. One major complication was registered in the YW group (ureteral lesion). 11 minor complications occurred in the NW group and 13 in the YW one.

Discussion

Pain perception is generally due to the activation of Aδ and C fibers carried out by various substances, like inflammatory factors and cytokines (like Nerve Growth Factor, Prostaglandin E2, bradykinin, and tryptase). After laparoscopic surgery, there are two main types of pain: visceral and parietal[12]. Parietal pain is caused by surgical wounds from trocar passages. Visceral pain is due to peritoneal irritation that is caused by several factors, like pneumo-peritoneum, abdominal cavity elongation, blood in the abdomen and

Table II. Intraoperative data.

Variables	NW (n = 135)	YW (n = 142)	p
LPS procedure, total (%)			
Myomectomy	49 (36.5)	56 (39.5)	0.783
Hysterectomy	66 (49)	67 (49)	0.995
Hysterectomy + oophorectomy	20 (14.5)	19 (11.5)	0.688
CO_2, L, mean (DS)	492.73 ± 201.21	460.23 ± 215.86	0.482
Pressure, mmHg, mean (DS)	12.68 ± 1.05	12.84 ± 1.35	0.562
Operative time, min, mean (Range)	154 (80-218)	157 (87-213)	0.754
Estimated blood loss, mL, mean (Range)	163.41 (100-250)	175.58 (100-250)	0.206

Table III. Pain evaluation at rest, during movements, examination, and cough.

Hours	NW (n 135) At rest mean (Range)	YW (n 142) At rest mean (Range)	*p*	NW (n 135) Movementsmean (Range)	YW (n 142) Movementsmean (Range)	*p*	NW (n 135) Examinationmean (Range)	YW (n 142) Examinationmean (Range)	*p*	NW (n 135) Coughmean (Range)	YW (n 142) Coughmean (Range)	*p*
6	4.73 (0-10)	3.49 (0-8)	*0.015	5.05 (2-10)	3.81 (0-7)	*0.009	5.44 (2-10)	3.93 (2-8)	*0.004	5.61 (3-10)	4.00 (0-7)	*0.009
12	4.02 (0-10)	1.98 (0-6)	*0.002	4.51 (0-9)	3.07 (0-8)	*0.017	4.76 (0-9)	3.28 (0-8)	*0.008	4.98 (0-9)	3.30 (0-8)	*0.003
18	2.41 (0-8)	1.86 (0-6)	0.274	2.83 (0-8)	2.86 (0-7)	0.951	3.07 (0-8)	2.88 (0-7)	0.695	3.34 (0-8)	3.12 (0-7)	0.642
24	2.27 (0-8)	2.16 (0-7)	0.835	2.22 (0-7)	1.51 (0-6)	*0.042	2.78 (0-7)	2.95 (0-7)	0.710	2.85 (0-8)	3.28 (0-7)	0.336
36	1.95 (0-8)	0.56 (0-10)	*0.001	2.02 (0-8)	1.44 (0-6)	0.130	2.12 (0-7)	1.02 (0-10)	*0.009	2.24 (0-6)	1.53 (0-6)	0.068
48	0.85 (0-3)	0.42 (0-5)	0.071	1.39 (0-6)	1.28 (0-5)	0.776	1.56 (0-9)	0.86 (0-6)	0.076	1.73 (0-7)	1.26 (0-5)	0.170
72	0.51 (0-2)	0.19 (0-5)	0.076	0.44 (0-6)	0.58 (0-5)	0.575	0.90 (0-7)	0.70 (0-6)	0.527	1.22 (0-7)	0.91 (0-4)	0.283

* = *p* statistically significant value from data comparison between the two groups ($p < 0.05$).

Table IV. Secondary outcomes

	NW (n = 135) Mean (DS)	YW (n = 142) Mean (DS)	p
Laboratory Data			
Haemoglobin loss (g/dL)	2.21 ± 0.96	2.23 ± 0.90	0.916
PCR (mg/dL)			
1st day	1.69 ± 1.74	0.78 ± 0.46	*0.002
2nd day	2.89 ± 2.59	2.08 ± 1.29	0.081
3rd day	2.04 ± 1.83	1.54 ± 1.3	0.156
White blood cells (/uL × 10^3)			
1st day	10.99 ± 1.99	11.89 ± 2.20	0.055
2nd day	7.40 ± 1.64	7.90 ± 2.60	0.307
3rd day	6.67 ± 1.56	5.92 ± 1.88	0.053
Analgesic Use			
Paracetamol 1 gr	Doses	Doses	
1st day	64	48	*0.030
2nd-3rd day	71	62	*0.026
Ketorolac 30 mg			
2nd-3rd day	37	29	*0.023
Opioids (1st -2nd -3rd day)	8	7	0.876

* = *p* statistically significant value from data comparison between the two groups (*p*<0.05).

pelvic dissections[13]. Pneumoperitoneum causes peritoneum and diaphragm stretching that are responsible for pain genesis[4,14-16].

Blood in the abdominal cavity can cause postoperative pain too by retrieving mastocytes which, in turn, produce inflammatory cytokines that are responsible for the abovementioned mechanisms related to pain and that can be responsible for chronic pain[15,16].

To our knowledge, this is the first RCT evaluating the role of intraperitoneal washing with isotonic saline solution for postoperative pain reduction in gynecologic surgery; these data demonstrate that intraperitoneal washing could reduce pain perceived by the patients in specific postoperative intervals. 6h and 12h after surgery, patients who received peritoneal washing referred lower postoperative pain at rest, during movements, abdominal examination and coughing compared to patients who did not receive peritoneal washing. 24h after surgery, reduction of postoperative pain was perceived only during movements. 36h after surgery, patients referred reduction of postoperative pain at rest and during the abdominal examination.

Patients receiving peritoneal washing required significantly lower doses of ketorolac and paracetamol than those patients belonging to the other group. These data could indicate that peritoneal washing could reduce analgesic use during the 1st-postoperative day.

These findings correlate with previous work that highlighted greater pain and higher analgesia requirements in the immediate postoperative period after laparoscopic surgery[17,18].

Some studies[8,14,19] evaluated the role of intraperitoneal washing in laparoscopic surgery. Barthelsson et al[19] hypothesized a positive effect of intraperitoneal administration of saline solution on abdominal and shoulder pain after laparoscopic cholecystectomy, with faster recovery after surgery. The group that received intraperitoneal washing showed a reduction of abdominal pain after 24h and a week from surgery, although data were not statistically significant[19]. Another study[20] hypothesized that the presence of inflammatory status consequent to biliary calculi could have influenced the results of these studies. In fact, stress response could be caused not only by laparoscopy, but also by pre-operative abdominal inflammatory status[20]. Considering these assumptions, patients with suspected pelvic inflammatory status were excluded from the study. This could explain why the analgesic request in our study was considerably lower compared to the abovementioned studies[17-19].

In a RCT study on laparoscopic cholecystectomy and reduction of postoperative pain, patients were divided into three groups, receiving respectively placebo, acetazolamide and intraperitoneal lavage. In the first postoperative 24h, lower pain at rest, during movements and coughing in pa-

tients undergoing intraperitoneal lavage has been reported compared to patients receiving acetazolamide orally[21]. The greater and longer reduction of pain could be explained by the prolonged effect of the saline solution (until 48h) if compared to acetazolamide (4h). What could explain these results is that peritoneal washing and its successive aspiration could guarantee the removal of residual CO_2 and dilute carbonic acid levels (H_2CO_3) in the peritoneum. Furthermore, intraperitoneal irrigation could contribute to visceral pain reduction for the probable elimination of irritative factors derived from tissue dissection, blood loss and other factors caused by surgery. Considering analgesia, in this paper, rescue analgesia was lower in the group receiving intraperitoneal washing.

Considering the removal of CO_2 and its effects on pain, some study hypothesized that the reduction of postoperative pain after intraperitoneal washing could not be explained by CO_2 removal[22]. Bala et al[21] evaluated, with X-Ray, the amount of gas that remains in the abdomen after laparoscopy in gynecological surgical procedures[21]. They found that, despite using 1,000 cc of saline solution, 96% of patients had gas residual at 24h and 76% after 48h. Furthermore, CO_2 residuals are rapidly adsorbed by the peritoneum[22]: in fact, CO_2 is absorbed in about 30 minutes. For this reason, as suggested by the authors themselves, gas visualized at X-Ray could have a different origin – probably aqueous vapor from tissue coagulation.

The evaluation of C-reactive protein (CRP) blood levels during the 1st-postoperative day were significantly lower in patients undergoing intraperitoneal washing. This could be explained by the fact that saline solution carries away inflammatory factors, hematic rests and irritant factors involved in pain perception. CRP has a typical trend after surgery with a peak at about 48h after surgery[23]. Our study found that CRP was lower in patients receiving intraperitoneal washing on the 1st-postoperative day, probably due to the removal of inflammatory cytokines and pain mediators from the abdomen at the end of the surgery. Despite this result, CRP increased during successive postoperative days equally in both groups. This fact could be explained by various factors, like tissue infarction and postoperative trauma, causing an increase in inflammatory cytokines (especially IL-6) and, consequently, higher CRP production by the liver in the successive postoperative days. Moreover, CRP increase has been associated with higher pain and opioids use[24,25].

Other studies that evaluate how reducing intrabdominal CO_2 could be effective for postoperative shoulder pain after laparoscopy were conducted by Tsai et al[26] and Van Dijk et al[27]. In particular, in a multicenter RCT[27] on women undergoing laparoscopy for benign gynecologic pathologies, patients were randomized into two groups: no intervention (i.e., removal of residual CO_2 with gentle abdominal pressure at the end of the surgery, allowing CO_2 passage through the trocars) *vs.* intraperitoneal saline infusion with pulmonary recruitment maneuver executed during surgery. The study's rationale is that the pulmonary recruitment maneuver (performed by anesthesiologists) could help eliminate CO_2 during surgery by increasing abdominal pressure. Van Dijk et al[27] demonstrated that the combination of these two procedures were effective in the reduction of postoperative pain. A reduction of rescue analgesia was also observed, but the data are not statistically significant. Tsai et al[26] obtained similar results in his study, which included women undergoing both major and minor surgical laparoscopic procedures. In both studies, 1,000 cc of saline solution were used, so a lower quantity is demonstrated to be insufficient to reduce postoperative pain. Remnant fluid in the abdominal cavity is adsorbed with a speed of 30-60 cc/h[10].

In this study, aspirated abdominal fluid was performed almost completely and cardiovascular or pulmonary side effects due to the increasing of body fluids in patients have not been found. Furthermore, a complete and abundant washing of the peritoneal cavity was performed instead of diluting only the intraperitoneal nociceptive substances, as suggested by other authors in the literature.

The weaknesses of this study are that it is a single-center study, based on benign gynecology and, therefore, excluding malignant diseases, as well as including surgeries performed by different surgeons with different surgical expertise. Therefore, their performances of the peritoneal washings at the end of the surgery after exposure to pneumoperitoneum differed.

Conclusions

Intraperitoneal washing with saline solution, performed at the end of laparoscopic procedures in major gynecologic surgery, can reduce postoperative pain. Intraperitoneal washing determines not only a reduction of postoperative pain in the first 24h, but also a reduction in the patients' request for analgesics.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Clinical Trial Registration

This trial has been registered on ClinicalTrials.gov (No. NCT03290521).

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Approval

This study is conducted by the regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996) and it was approved by the Internal Review Board of Campus Bio-Medico of Rome (No. 39/17 INT ComEtCBM, date 12/07/2017).

Informed Consent

Informed consent was obtained from all study participants..

Authors' Contribution

C. D. C. N., F. F., F. P., R. M., L. F., S. R., G. M., D. L., R. M., R. A., C. T. conceived and designed the experiments, data collection, analyzed the data, and wrote the manuscript. All authors read and approved the final manuscript.

ORCID ID

Ficarola Fernando: https://orcid.org/0000-0002-2474-2442.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

References

1) Atkinson TM, Giraud GD, Togioka BM, Jones DB, Cigarroa JE. Cardiovascular and Ventilatory Consequences of Laparoscopic Surgery. Circulation 2017; 135: 700-710.

2) Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. Anesthesiology 2013; 118: 934-944.

3) Alexander JI. Pain after laparoscopy. Br J Anaesth 1997; 79: 369-378.

4) Lee DH, Song T, Kim KH, Lee KW. Incidence, natural course, and characteristics of postlaparoscopic shoulder pain. Surg Endosc 2018; 32: 160-165.

5) Mouton WG, Bessell JR, Otten KT, Maddern GJ. Pain after laparoscopy. Surg Endosc 1999; 13: 445-448.

6) Sjövall S, Kokki M, Kokki H. Laparoscopic surgery: a narrative review of pharmacotherapy in pain management. Drugs 2015; 75: 1867-1889.

7) Miralpeix E, Nick AM, Meyer LA, Cata J, Lasala J, Mena GE, Gottumukkala V, Iniesta-Donate M, Salvo G, Ramirez PT. A call for new standard of care in perioperative gynecologic oncology practice: Impact of enhanced recovery after surgery (ERAS) programs. Gynecol Oncol 2016; 141: 371-378.

8) Lirk P, Thiry J, Bonnet MP, Joshi GP, Bonnet F; PROSPECT Working Group. Pain management after laparoscopic hysterectomy: systematic review of literature and PROSPECT recommendations. Reg Anesth Pain Med 2019; 44: 425-436.

9) Angioli R, Terranova C, De Cicco Nardone C, Cafà EV, Damiani P, Portuesi R, Muzii L, Plotti F, Zullo MA, Panici PB. A comparison of three different entry techniques in gynecological laparoscopic surgery: a randomized prospective trial. Eur J Obstet Gynecol Reprod Biol 2013; 171: 339-342.

10) Levy L, Tsaltas J. Recent advances in benign gynecological laparoscopic surgery. Fac Rev 2021; 10: 60.

11) Tsai HW, Chen YJ, Ho CM, Hseu SS, Chao KC, Tsai SK, Wang PH. Maneuvers to decrease laparoscopy-induced shoulder and upper abdominal pain: a randomized controlled study. Arch Surg. 2011; 146: 1360-1366.

12) Zucker KA. Surgical Laparoscopy. Lippincott Williams & Wilkins, 2000.

13) Zakka TM, Teixeira MJ, Yeng LT. Abdominal visceral pain: clinical aspects. Rev Dor 2013; 14: 311-314.

14) Sao CH, Chan-Tiopianco M, Chung KC, Chen YJ, Horng HC, Lee WL, Wang PH. Pain after laparoscopic surgery: Focus on shoulder-tip pain after gynecological laparoscopic surgery. J Chin Med Assoc 2019; 82: 819-826.

15) Anaf V, Simon P, El Nakadi I, Fayt I, Simonart T, Buxant F, Noel JC. Hyperalgesia, nerve infiltration and nerve growth factor expression in deep adenomyotic nodules, peritoneal and ovarian endometriosis. Hum Reprod 2002; 17: 1895-1900.

16) Nicol GD, Vasko MR. Unraveling the story of NGF-mediated sensitization of nociceptive sensory neurons: ON or OFF the Trks? Mol Interv 2007; 7: 26-41.

17) Ruiz-Tovar J, Llavero C, Muñoz JL, Zubiaga L, Diez M. Effect of Peritoneal Lavage with Clindamycin-Gentamicin Solution on Post-Operative Pain and Analytic Acute-Phase Reactants after

Laparoscopic Sleeve Gastrectomy. Surg Infect 2016; 17: 357-62.

18) Ekstein P, Szold A, Sagie B, Werbin N, Klausner JM, Weinbroum AA. Laparoscopic surgery may be associated with severe pain and high analgesia requirements in the immediate postoperative period. Ann Surg 2006; 243: 41-46.

19) Barthelsson C, Sandblom G, Ljesevic-Nikoletic S, Hammarqvist F. Effects of Intra-abdominally Instilled Isotonic Saline on Pain, Recovery, and Health-Related Quality-of-Life Following Laparoscopic Cholecystectomy: A Randomized Prospective Double-Blind Controlled Study. World J Surg 2015; 39: 1413-1420.

20) Blobner M, Felber AR, Gögler S, Feussner H, Weigl EM, Jelen G, Jelen-Esselborn S. The resorption of carbon dioxide from the pneumoperitoneum in laparoscopic cholecystectomy. Anaesthesist 1993; 42: 288-294.

21) Bala I, Bhatia N, Mishra P, Verma GR, Kaman L. Comparison of preoperative oral acetazolamide and intraperitoneal normal saline irrigation for reduction of postoperative pain after laparoscopic cholecystectomy. J Laparoendosc Adv Surg Tech A 2015; 25: 285-290.

22) Adcock J, Martin DC. Resolution of subdiaphragmatic gas. J Am Assoc Gynecol Laparosc 1999; 6: 501-503.

23) Cole DS, Watts A, Scott-Coombes D, Avades T. Clinical Utility of Peri-Operative C-Reactive Protein Testing in General Surgery. Ann R Coll Surg Engl 2008; 90: 317-321.

24) Choi HR, Song IA, Oh TK, Jeon YT. Perioperative C-reactive protein is associated with pain outcomes after major laparoscopic abdominal surgery: a retrospective analysis. J Pain Res 2019; 12: 1041-1451.

25) Liu Y, Sun ZR, Lu LH, Zhang X, Gao LL, Wu JM, Yang L, Xu PB. Comparison of effects of transversus abdominis plane block and thoracic epidural anesthesia mediated activation of inflammasome on postoperative medication, pain, and recovery in patients undergoing laparoscopic colorectal surgery. Eur Rev Med Pharmacol Sci. 2023; 27: 2794-2807.

26) Tsai HW, Wang PH, Yen MS, Chao KC, Hsu TF, Chen YJ. Prevention of postlaparoscopic shoulder and upper abdominal pain: a randomized controlled trial. Obstet Gynecol 2013; 121: 526-531.

27) van Dijk JEW, Dedden SJ, Geomini PMAJ, Meijer P, van Hanegem N, Bongers MY. POstLAparoscopic Reduction of pain By combining intraperitoneal normal salinE And the pulmonary Recruitment maneuver (POLAR BEAR trial). RCT to estimate reduction in pain after laparoscopic surgery when using a combination therapy of intraperitoneal normal saline and the pulmonary recruitment maneuver. BMC Womens Health 2017; 17: 42.