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Enhanced Recovery After Surgery in Laparoscopic Cholecystectomy – A Systematic Review

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Rezumat

Protocolul E.R.A.S. (E.R.A.S. = Enhanced Recovery After Surgery) in colecistectomia laparoscopica – revizie sistematică de literatură

Introducere/Scop: Recuperarea îmbunătățită după operație (ERAS) este un concept modern care își propune să îmbunătățească îngrijirea perioperatorie a pacientului prin implementarea unei abordări de echipă bazată pe dovezi, si centrată pe pacient. Această lucrare își propune să analizeze rezultatul, variațiile şi limitele protocoalelor ERAS utilizate pentru colecistectomia laparoscopică.
Metode: Am efectuat o revizuire sistematică pe PubMed, Google Scholar, Web of Science pentru a documenta rezultatele aplicării diferitelor protocoale ERAS în colecistectomia laparoscopică (CL). După aplicarea criteriilor de includere şi excludere, în analiza calitativă au fost incluse 8 lucrări, în total 1453 de pacienți care au fost operați prin colecistectomie laparoscopică. Protocoalele ERAS aplicate în aceste studii includ diverse măsuri pre, intra şi post-operatorii menite să stimuleze recuperarea chirurgicală a pacienților şi să le scurteze şederea în spital, fără a-i expune la întâlniri periculoase.
Rezultate: Pacienții supuşi colecistectomiei laparoscopice în cadrul unui protocol specific ERAS s-au dovedit a avea niveluri mai scăzute de durere postoperatorie, greață şi vărsături, fără o rata

diferită de complicații postoperatorii. Rezultatele postoperatorii arată că ERAS-colecistectomia laparoscopică este o procedură fezabilă şi sigură, care poate scurta recuperarea postoperatorie după LC.
Concluzii: Sunt necesare studii suplimentare pentru a stabili un consens cu privire la protocolul perioperator, înainte de implementarea ERAS pentru LC în rutina clinică.

Cuvinte cheie: recuperare îmbunătățită după intervenție chirurgicală (ERAS), colecistectomie laparoscopică, minim invazivă, durere postoperatorie, rezultate

Abstract
Background and Aim: Enhanced Recovery After Surgery (ERAS) is a modern concept that aims to improve the perioperative patient care by implementing an evidence-based, patient-centered team approach. This paper aims to analyze the outcome, variations and limits of the ERAS-protocols used for laparoscopic cholecystectomy.
Methods: We performed a systematic review on PubMed, Google Scholar, Web of Science to document the outcomes of applying various ERAS protocols in laparoscopic cholecystectomy (LC). After applying the inclusion and exclusion criteria, 8 papers, totaling 1453 patients that underwent LC, were included in the qualitative analysis. ERAS-protocols applied in those studies include various pre-, intra- and postoperative measures intended to boost the surgical recovery of the patients and shorten their hospital stay, without exposing them to hazardous encounters.
Results: Patients undergoing laparoscopic cholecystectomy within an ERAS-specific protocol are proven to have lower levels of postoperative pain, nausea and vomiting, with no statistically significant risk of postoperative complications. The postoperative results show that ERAS-laparoscopic cholecystectomy is a feasible and safe procedure, that may shorten the postoperative recovery after LC.
Conclusions: Further studies are needed to establish a consensus regarding the perioperative protocol, before implementing ERAS for LC in clinical routine.

Key words: enhanced recovery after surgery (ERAS), laparoscopic cholecystectomy, minimally invasive, postoperative pain, outcomes

Introduction

Laparoscopic cholecystectomy is one of the most performed surgical procedures worldwide (1). In 1985, German-native surgeon Erich Mühe performed a highly-criticized first laparoscopic cholecystectomy, opening the ways towards minimally-invasive gallbladder surgery (2). Over the years, it became the gold-standard treatment for gallbladder disease, with open procedure being almost abandoned.

The development of new surgical equipment and techniques and, generally, the continuous interest towards promoting minimally-invasive procedures determined that laparoscopic cholecystectomy is a procedure that can safely be performed with good postoperative results in a large variety of clinical scenarios, including day care centers, as well as emergency surgery (3-5).

With an increasing number of surgeries performed nowadays, an interest for optimizing surgical procedures and their outcomes was shown in many healthcare systems, with surgeons challenging many of the medical practices which were not supported by evidence-based studies (6). Developing multimodal strategies for improving recovery after surgery became an idea in the late 1990-early 2000 years, when Danish surgeon Henrik

Kehlet used a successful multimodal recovery strategy, in order to enhance the postoperative outcome in patients undergoing elective open sigmoidectomy, with promising results (7,8).

Later, Professor Ken Fearon and Professor Olle Ljungqvist alongside other medical specialists set up The Enhanced Recovery After Surgery Study Group (6), which later became The ERAS Society, entity created in order to develop proof-based strategies for improving surgery outcome while minimizing the impact of the surgical act impact on the patient (6). Nowadays, the concept of Enhanced Recovery After Surgery represents a multimodal perioperative approach which sums the procedures applied in order to reduce the impact of the surgery over the physiologic functions of the body, and, in the meantime, to realize the best possible outcome for the patient. ERAS protocols summarize preoperative, intraoperative and postoperative pathways intended to give the best surgical results.

At this moment, The ERAS Society offers guidelines for 23 surgical fields; gallbladder surgery, including laparoscopic cholecystectomy, is not included at this time, being still a subject of research. It is, also, still to be determined whether ERAS protocols can safely be applied to patients that undergo laparoscopic cholecystectomy for acute cholecystitis, in an emergent setting. Emergency laparoscopic cholecystectomy is proven to be safe if performed in the first 72 hours since the symptoms occur or as soon as possible if the patient tolerates the surgery, with better outcomes and lower rates of intraoperative complications (4,5). Though, in the emergency setting, the surgeon may face cases of gallbladder disease that underlie, after a thorough exploration, systemic suffering that may severely influence the perioperative setting, the intraoperative appearance, or the postoperative outcome, and may see himself in the position to postpone the surgery in order to stabilize the already-existent disorders. The surgical approach, in those cases, may also be modified, in order to avoid damaging vital structures, with multiple techniques depicted, like fundus-first cholecystectomy, subtotal cholecystectomy or using view-enhancing tools, like cholangiography (9).

This paper aims to analyze the outcome, variations and limits of the ERAS-protocols used for laparoscopic cholecystectomy.

Materials and Methods

We performed a systematic search on PubMed, Google Scholar, and Web Of Science, by the MeSH terms: "Laparoscopic Cholecystectomy" AND "ERAS" OR "Enhanced Recovery After Surgery" OR "Multimodal recovery after surgery". All articles in English language for which full terms could be obtained were included in the initial search. A hand-search in the references of the reviews previously performed on the topic was performed to identify additional relevant studies.

We focused our search on prospective, retrospective, observational studies and randomized control studies of patients undergoing laparoscopic cholecystectomy under various ERAS protocols. We systematically excluded studies that did not meet the following criteria: using ERAS multimodal protocols for laparoscopic cholecystectomy; accurate, detailed description of the ERAS protocol; age of the patients over 18; paper written in English language.

A PICO (Population, Intervention, Comparison, Outcome) analysis was then performed in order to check that the selected papers are eligible for being included in the review. The applied criteria were: Population - individuals diagnosed with symptomatic gallbladder disease; Intervention - laparoscopic cholecystectomy performed under an ERAS protocol; Comparison - ERAS-recovery versus "traditional" recovery protocols; Outcome - hospital staying and general outcome of the ERAS-group patients.

Editorials, reviews, book chapters, case reports, case series, commentaries or letters were excluded. Two independent authors conducted a thorough analysis of the abstracts, in order to check them for eligibility. Any disagreement was solved by discussion.

Results

After duplicate removal and abstract analysis, we identified a total of 8 scientific papers (10-17), published between 2020 and 2023, that matched the criteria for our systematic review, as depicted in *Fig. 1*. The total number of patients included in the analyzed papers is 1453, with sample sizes varying from 40 (10) to 445 (14). Out of these, 684 patients made up the ERAS groups of the included papers, while the control groups summed up 667 patients. *Table 1* sum up the general characteristics of the studies that we included in our review, including demographic data.

Six out of the 8 papers included in the analysis describe ERAS-protocols applied for elective laparoscopic cholecystectomy (10-13, 16-17). One of the authors approaches the possibility of applying an enhanced recovery protocol in an emergency cholecystectomy setting, for patients undergoing laparoscopic cholecystectomy for acute cholecystitis (15). One paper describes the outcomes of 148 patients receiving an ERAS-specific care protocol after elective laparoscopic cholecystectomy combined with common bile duct exploration via choledochoscopy (14).

The perioperative care included ERAS-specific counseling in all studies. The pre-

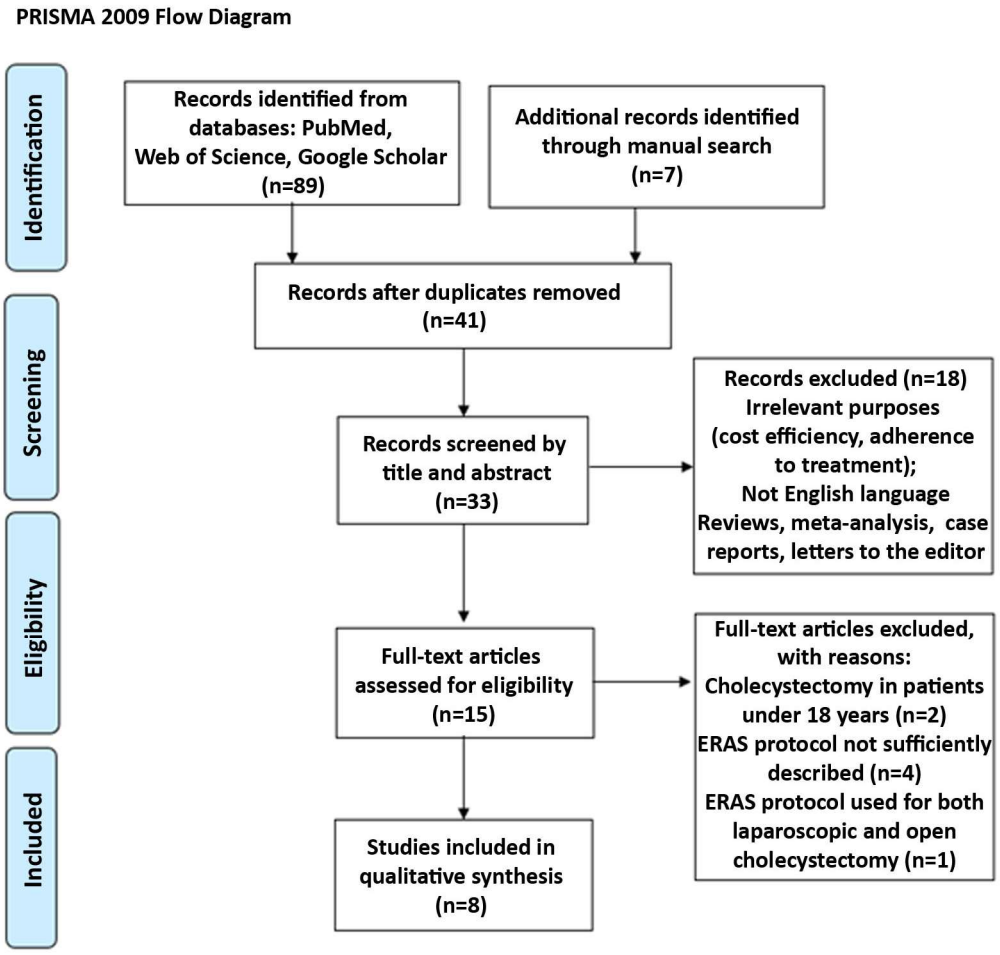

Figure 1. PRISMA flowchart for the studies included in the review

Table 1. General characteristics of the studies included in the review

Study, year	Study type	No of patients (ERAS; control)	Age (mean) ± SD	Sex (M%)	Type of LC
Rajareddy GV et al., 2023 (10)	Prospective, RCT	40(20;20)	47.87	35%	Elective LC
Udayasankar M et al., 2020 (11)	Prospective, RCT	50(25;25)	39.56	44%	Elective LC
Akhtar MS et al., 2020 (12)	RCT	147(73;74)	44.57	49%	Elective LC
Yu J et al., 2022 (13)	RCT	200(100;100)	42.05	62%	Elective LC
Zhang N et. al, 2020 (14)	Retrospective	445(148;297)	54.47	43%	Elective LC + choledocoscopy
Nechay et al., 2021 (15)	Prospective, RCT	189(88;101)	48.8	32%	Emergency LC
Mendoza-Velız M et al., 2022 (16)	Prospective	160(160;0)	36.8	17%	elective LC
Chen X et al., 2023 (17)	RCT	140(70;70)	48.8	36%	Elective LC

Footnote: RCT: randomized control trial; LC laparoscopic cholecystectomy

operative nutrition included intravenous carbohydrate loading at a variable interval, from 12 to 2 hours before surgery, and a limited fasting period of 2h for liquids and 6h for solid food. Low pressure pneumoperitoneum was used in 3 studies (10,14,15), in order to minimize the postoperative pain and analgesic consumption. The detailed settings of the ERAS-protocols used in the analyzed studies are presented in *Table 2*.

Preoperative strategies are followed by a variety of intraoperative measures, meant to minimize the surgical aggression. Nasogastric tubes or drains are not a habit anymore when we are talking about ERAS surgery; their usage is minimized in ERAS laparoscopic cholecystectomy, and, when used, their removal is done as soon as possible. Low-pressure pneumoperitoneum, with values below the usual 12mmHg, helps diminish the severity of postoperative pain. Multimodal pain control starts intraoperatively, using local anesthetics, injected locally, at the trocar incision sites, or directly into the peritoneum surface.

After the surgery, fast recovery is attempted by multiple means, intended to resume intestinal motility and the ambulation of the patient as soon as possible, allowing a fast discharging of the patient. Nasogastric tubes, if used, are removed prior to waking the patient from anesthesia. A fast resuming of oral alimentation is instated as soon as possible; liquid intake is resumed as soon as 2 hours after the surgery or the patient tolerates, with solid food being reintroduced starting with 6 hours after the cholecystectomy.

The outcomes followed by the authors of the papers were heterogeneous; the main outcome followed in the articles was the length of hospital stay (LOHS); the secondary outcomes were: the number of patients presenting postoperative nausea and vomiting (PONV) (11, 14,15), the postoperative pain level measured using visual analogue pain (VAS) scale (10,11, 14,15) or the postoperative complications and readmissions (12, 15, 16), *(Tables 3, 4)*.

Postoperative results showed a medium length of hospital staying (LOHS) varying between 4.6±7.3h in the paper of Mendoza-Veléz et al., which addresses to one-day laparoscopic cholecystectomy performed under an ERAS-protocol (16), and 186.96 ± 40.8h in the study of Chen et al., approaching ERAS-laparoscopic cholecystectomy with common bile duct exploration (17). The vast majority of the papers state that LOHS is statistically significant shorter in ERAS-groups than in traditional groups ($p<0.05$) (10, 12-15,17), thus patients undergoing laparoscopic cholecystectomy under ERAS-protocols were fit for faster discharging.

Regarding postoperative pain levels, three of the studies included in our review found that pain levels were significantly lower in ERAS-groups versus control groups; Rajareddy (10), Nechay (15) and Chen (17) used Visual Analogue Scale (VAS) for measuring the pain intensity at multiple intervals, the most common of them being immediately after

Table 2. Particular features of ERAS protocols in the studies included in the review

Study, year	Rajareddy et al., 2023 (10) *	Udayasankar et al., 2020 (11)	Akhtar et al., 2020 (12) **	Yu et al., 2022 (13)	Nechay et al., 2021 (14)	Zhang et al., 2020 (15)	Mendoza-Veliz et al., 2022 (16)	Chen et al., 2023 (17)
ERAS-specific counseling	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nutritional support	Carbohydrate loading 12 and 6 hours before the surgery	Carbohydrate loading the evening and the morning before surgery; a mixture of coconut water and sugar was used	Fasting for 2h for liquids, 6h for solid food; carbohydrate loading the evening before and 2h prior to surgery	Fasting for 2h for liquids, 6h for solid food	Not specified	Fasting for 6h; carbohydrate loading with 250 ml glucose 5% solution 2h prior to surgery	No; only isotonic fluids were administered	Fasting for 2h for liquids, 6h for solid food; carbohydrate loading with 250 ml glucose 5% solution 2h prior to surgery
Pneumoperitoneum pressure reduction	Low pressure pneumoperitoneum (8-9mmHg)	Not specified	Not specified	Not specified	9 mmHg starting pressure; increasing pressure possible as needed for achieving safety view	10-12 mmHg pneumoperitoneum	Not specified	Not specified
Pain control	Trocar sites and intraabdominal anesthesia - 20 ml 0.25% Ropivacaine	Trocar sites – 10 ml of 0.25% Bupivacaine; Postoperatively - Paracetamol iv, 1g each 8 hours	Not specified	IV local anesthetics; oral non-opioids	Trocar sites - 3-4 ml of Ropivacaine 0.25%; Intraoperative - sponge with 0,25% Ropivacaine in the gallbladder bed; irrigating the subphrenic space with 0,25% Ropivacaine via puncture needle; Postoperative - 30 mg iv of Ketorolac if pain on VAS scale > 4 cm	Trocar sites - postoperative injections of Ropivacaine; the amount is not specified; Postoperative - Intramuscular injections of Opioids	Trocar sites - bupivacaine 0,5%; the amount is not specified; Postoperative - acetaminophen 1g iv; Ketorolac 30mg iv	Trocar sites - 10 ml of 0.5% bupivacaine; Postoperative - Oral/iv NSAID painkillers
PONV prophylaxis and treatment	Not specified	Prophylaxis with Ondansetron iv, 0,1mg per kg	Prophylaxis with 2 antiemetics	Not specified	Prophylaxis with Metoclopramide iv, 10 mg; if PONV persisted postoperatively, another Metoclopramide iv, 10 mg, administered	Postoperatively Metoclopramide im, 10 mg, if PONV	Prophylaxis with Dexamethasone 4 mg iv, Ondansetron 8 mg; postoperatively Ondansetron given if PONV	Prophylaxis with not specified 5HT3 antagonist
Oral feeding and ambulation resuming	Liquid diet 6 hours after surgery; ambulation within the first 6 hours after surgery	Liquid diet 1 hour after surgery; solids as soon as tolerated; limbs movement every 5 minutes	Full diet the day after surgery	Liquid diet 6 hours after surgery; semiliquid 24-36 hours after surgery; ambulation 6 hours after surgery	Liquid diet 2 hours after surgery; solid diet 6 hours after surgery if PONV not present	Liquid diet 6 hours after surgery, with gradual transition to normal diet; ambulation 6-8 hours after the surgery	Oral liquid intake and ambulation as soon as clinical status allowed	Oral fluids as soon as the patient tolerates; solids 4 hours after surgery; ambulation for 30 minutes in the surgery day and 6 hours a day the following days until leaving

Footnote: PONV: postoperative nausea and vomiting

Table 3. The rate of PONV, postoperative complications and re-admission in the papers included in the review

Study, year	PONV			Postoperative complications			Readmission		
	ERAS group	Control group	P value	ERAS group	Control group	P value	ERAS group	Control group	P value
Rajareddy GV et al., 2023 (10)	-	-	-	7 complications totally described; no significant statistical difference between groups		>0.05	-	-	-
Udayasankar M et al., 2020 (11)	5 (25%)	3 (13%)	0.46	-	-	-	-	-	-
Akhtar MS et al., 2020 (12)	-	-	-	2 (2.7%)**	4 (5.4%)**	0.414	3 (4.1%)	6 (8.1%)	0.31
Yu J et al., 2022 (13)	-	-	-	Overall complication rate lower in ERAS group than in control group		<0.05	-	-	-
Zhang N et. al, 2020 (14)	6 (4.05%)	35 (11.78%)	<0.05	12 (8.11%)	55 (18.52%)	<0.05	-	-	-
Nechay et al., 2021 (15)	14 (15.90%)	43 (42.5%)	<0.35	6 (6.8%)	5 (5.7%)	0.757	1 (1.1%)	0	0.466
Mendoza-Velız M et al., 2022 (16)	-	-	-	5 (3.1%)	-	-	2 (1.2%)	-	-
Chen X et al., 2023 (17)	-	-	-	-	-	-	-	-	-

waking from anaesthesia and 24 hours after (10,15,17). On the other hand, Udayasankar (11) reports measuring pain levels with a numeric scale from 1-10, with no statistically significant difference between the two groups (ERAS: 3.70 ± 1.32; 3.57 ± 1.3; p=0.52); the authors state that this may be the result of analgesic management of both groups, or the laparoscopic cholecystectomy itself may be a painful procedure for the subjects regardless of the perioperative management (11). Postoperative nausea and vomiting (PONV) was also found to be lower by Zhang (14) and Nechay (15) while being comparable in the paper of Udayasankar (p = 0.46) (11).

The postoperative complications were comparable between the groups; three of the papers do not find a statistically significant difference between the ERAS and traditional groups (p>0.05) (10,12,15) while the articles of Yu (13) and Zhang (14) state lower rates of complications in the ERAS groups.

Discussions

The continuous pressure to enhance the

Table 4. The hospital stay and postoperative pain early in the ERAS group vs control group in the reviewed studies

Study, year	Hospital stay			Postoperative pain 0h after surgery*			Postoperative pain 24h after surgery*		
	ERAS group	Control group	P value	ERAS group	Control group	P value	ERAS group	Control group	P value
Rajareddy GV et al., 2023 (10)	30.35±7.36h	39.10±10.249h	0.004	5.7	7.4	<0.05	2.25	1.25	<0.05
Udayasankar M et al., 2020 (11)	-	-	-	Postoperative pain described measuring pain using a numeric scale showing no statistically significant difference between groups (p = 0.52)					
Akhtar MS et al., 2020 (12)	28.93±9.55h	40.54±11.00h	<0.01	-	-	-	-	-	-
Yu J et al., 2022 (13)	Shorter hospital staying for ERAS group than control group		<0.05	-	-	-	-	-	-
Zhang N et. al, 2020 (14)	83.76±3.36h	133.68±5.52h	<0.05	Postoperative pain described as "incisional pain"; 12 (8.11%) in ERAS group, 55 (18,52%) in control group with p < 0.05					
Nechay et al., 2021 (15)	33.3±19.6h	53.7±32.7h	<0.0001	3.7±1.8	5.4±1.3	<0.0001	2.1±1.2	3±1.2	<0.0001
Mendoza-Velız M et al., 2022 (16)	4.6±7.3h	-	-	-	-	-	-	-	-
Chen X et al., 2023 (17)	186.96±40.8h	202.32±53.28h	0.036	-	-	-	3.57	3.1	<0.001

Footnote: ERAS: Enhanced Recovery After Surgery; LOHS: Length of Hospital Stay; PP: postoperative pain; *measured using Visual Analogue Scale

quality of care and improve the cost-efficiency balance (18), were the premises to a personalized, patient-centered approach, that could allow an easy recovery. ERAS-protocols sum an ensemble of strategies with the main objective of diminishing the impact of the surgery, boosting the recovery speed. The first component that ERAS-protocols intend to optimize is the preoperative status of the patient, in order to raise their condition to the best possible and make them as fit as they can be for surgery. Addressing to each patient in a personalized manner, by carefully compensate metabolic imbalances, frailty and comorbidities are associated with improved postoperative outcomes (19,20).

Being a promising strategy, ERAS represents, at the same time, a challenging method, especially for surgeons who are committed to "traditional" perioperative care strategies. Also, it is not to be omitted that one may face difficulty when using ERAS in specific surgical setups. Our review sums 8 scientific papers that describe the technique and results of 1453 laparoscopic cholecystectomies performed under multimodal ERAS protocols. In the following sequence, we approach the specific aspects described in those papers.

An Anxiety-Free Surgery - is Preoperative Counseling Enough or is More Needed?

Anxiety is one of the factors that may exert a significant influence over a surgical act, with the risk of rising morbidity. Multiple causes were identified, with the main being the surgical act itself, the general anesthesia, as well as the lack of information regarding the postoperative outcome and possible complications (21-23); because of the general considerations of laparoscopic surgery, laparoscopic cholecystectomies are performed under general anesthesia with orotracheal intubation. The negative effects of perioperative anxiety may occur with even higher frequency in emergency surgery settings (24,25), when ERAS-specific measures are harder to apply because of the short time assigned for preoperative preparation in most of these situations. Otherwise, ERAS protocols address the risk of preoperative anxiety with multiple possible actions.

Unanimously, all of the papers that we included report providing the patients with specific ERAS-counseling prior to the surgery; mostly, they report using interactive measures, like brochures, PowerPoint slides, phone or tablet screens in order to handle many of the surgery and perioperative care details directly to the patients (10-17); extensive preoperative counseling was performed, with both surgical and anesthesia teams ready to answer the patients' questions.

ERAS-counseling was followed by measuring the anxiety levels using specific instruments. Yu et al. (13) used preoperative and postoperative levels of cortisol and adrenaline, showing lower levels of the stress hormones in both ERAS and traditional groups. Udayasankar (11) reported measuring the anxiety using a 0-10 scale, with 0 being the minimum and 10 being the maximum. The results showed that anxiety levels were lower in ERAS group prior to the surgery and 6 hours after it (11).

As a particularity, Udayasankar et al.(11) propose a preoperative treatment scheme that uses Alprazolam 0,25mg and Ranitidine 150mg prior to surgery in both control and ERAS groups in order to reduce anxiety and the risk for stress-induced gastritis, a measure that, even not described as specific to ERAS-protocol, was not found in other papers, but was applied to both control and ERAS groups. Therefore, the reported results over preoperative anxiety levels reduction should be granted to ERAS-specific measures(11).

Low-Pressure Pneumoperitoneum and its Effects

Alongside all its known effects on cardiovascular and pulmonary physiology, occurring due to the combination of hypercarbia and elevated intra-abdominal pressure, that may raise problems in patients with lower cardiac and pulmonary reserve (26-28), other data shows that higher values of intra-abdominal pressure created through pneumoperitoneum could

worsen the postoperative pain, thus hindering the recovery process. The pneumoperitoneum represents an aggression over the peritoneal cavity physiology, raising the risks for peritoneal hypoperfusion, adhesion formation and peritoneal acidosis (29). The physiopathology of this phenomenon is still subject to research, with some of the hypotheses indicating that the carbon dioxide distending the peritoneum cause consecutive trauma of both the diaphragm and phrenic nerve; consecutively, left shoulder pain, a known side effect of laparoscopic surgery, may occur (30). Data shows that lowering the pneumoperitoneum pressure is the best adjustment of technique in ERAS protocol for diminishing left shoulder postoperative pain (31). Thus, scientists state that intra-abdominal pressure may be safely lowered without additional risks for the patient (32). The ERAS-protocols applied in the papers included in our review suggest, as an effective measure, lowering the pressure values from the standard 12 mmHg of intra-abdominal pressure established through pneumoperitoneum induction; this adjustment is reported in the papers of Rajareddy (10), Chang (14) and Nechay (15).

An important element of harmlessness that must be taken into consideration is obtaining the critical view of safety (CVS), term introduced in 1995 by Strasberg et al.(33), who proposed dissecting Calot's triangle with individualization of cystic duct and artery; those actions must be performed prior to cystic duct stapling and transection, in order to correctly identify the regional anatomy and differentiate the cystic duct and the common bile duct (34,35). The intra-abdominal pressure should always be sufficient in order to achieve CVS.

In acute settings when early surgery is recommended as safe and effective by protocols, the intraoperative aspect of the gallbladder and surrounding viscera, including the risk of advanced adhesions, may raise problems for the surgical team. Thus, achieving CVS may be difficult without an optimal workspace. Nechayet al. (14), in their study on patients with acute cholecystitis undergoing laparoscopic cholecystectomy, recommend a 9-mm starting pressure that may be raised, successively, with 1-mm steps, until the surgical team obtains a safe view of vital structures; as an additional precaution, they state that the workspace must be enough for placing the instruments anytime at least 1-cm away from the common bile duct (14).

Perioperative Nutrition Aspects in ERAS - Laparoscopic Cholecystectomy

Preoperative fasting, a concept belonging to "traditional" perioperative protocols, represents an important part of the preoperative preparation of any patients, being mainly intended to reduce the risk of pulmonary aspiration. Though, it was proven that prolonged fasting prior to surgery may alter the recovery process by multiple means, including dehydration, hunger, rising postoperative insulin resistance and higher catabolic response rates (8,36,37). Guidelines state that a 6-hours fasting for solids and a 2-hours fasting for liquids, the so-called "6-2 rule", represents the optimal approach for surgery (8,36).

On the other hand, ERAS-protocols allow the usage of carbohydrate loading solutions as a nutritional support, in order to reduce postoperative insulin resistance, with an improvement in the matter of postoperative outcome (37). Rajareddy et. al (10) used carbohydrate loading solutions 12 and 6 hours prior to surgery, and Udayasankar et. al (11) who states using a mixture of coconut water and sugar, summing up to 1200 mL of liquids, given to the patient the evening and the morning before the surgery. Mendoza-Velez et. al (16) state using only isotonic fluids, in amounts specific to each patient, in order to avoid dehydration.

ERAS protocols support an early-feeding resume strategy; it was shown that patients can safely resume liquid intake 2 hours after surgery and solid meals after 6 hours (38). Early resuming of oral intake of liquids and solids is reported to enhance the recovery of the patient, decreasing the surgical stress and the risk of further complications (39,40).

Multimodal Controlling Pain Strategies in ERAS-Protocols

It is already known that higher levels of postoperative pain exert a negative influence amid recovery time and quality of postoperative life, as it may persist long after surgery (41,42). ERAS-protocols use multimodal strategies in order to offer various options for pain control and optimize analgesia management (8). In ERAS strategies, the postoperative pain level is one of the established criteria not only for discharging the patients, but also for measuring the protocol efficacy. The papers we included in our review describe strategies that include multiple measures intended to minimize the impact of postoperative pain over the patient's recovery and life quality.

When talking about perioperative analgesia, the general principles that rule ERAS protocols emphasize that there should be a variety of actions that surgeons may opt from, for an optimal control of perioperative pain (8). As no agreement was set for a standardized protocol, the papers we included in our study approached multiple possibilities for surgeons to choose from. It's important to notice that one of the key principles of ERAS analgesia is avoiding the usage of opioids; the gastrointestinal side effects of opioid drugs, including nausea, vomiting and the prolonging of postoperative ileus, may interfere with the clinical evolution of the patient and may hinder their recovery (43,44). Yu (13) and Chen (17) opted in their studies for classic oral analgesia using non-steroid drugs. Udayasankar (11), Nechay (14) and Mendoza-Veléz (16) chose the intravenous administration of painkiller medication. Zhang et al (15), in the paper approaching laparoscopic cholecystectomy with common bile duct exploration, offered the possibility of using opioids for pain relieving.

Wound management using anesthetic infiltration with Ropivacaine or Bupivacaine in various amount at the incision sites is, also, one of the components of the multimodal pain control strategies of ERAS-protocols, not only in laparoscopic cholecystectomy, but generally in laparoscopic surgery carried out under an enhanced-recovery multimodal recovery strategy. Nechay et al (14) also report placing a sponge soaked in Ropivacaine directly into the cystic plate. Instillations of local anesthetics directly into the peritoneum were used by Rajareddy (10) in a dose of 20 ml of 0.25% Ropivacaine, while Nechay injected the subphrenic space with Ropivacaine via puncture needle (14).

Postoperative Nausea and Vomiting - Prophylactic or Expectative Management?

Postoperative Nausea and Vomiting (PONV) is one of the most common postoperative complications, with a complex physiopathology; it is estimated that up to 20-30% of the patients have PONV, a redoubtable complication that may significantly affect the recovery of the patients after surgery (45). PONV prophylaxis and fast treatment, if occurring, are important goals for the surgeons working under ERAS protocols (46,47).

The studies included in our research adopt in their vast majority the PONV prophylactic strategy. Authors reported using 5HT3 inhibitors (11,16,17) or Metoclopramide, as a dopamine receptor antagonist (14), with the possibility of further treatment if PONV persisted.

Emergency Cholecystectomy for Acute Cholecystitis under ERAS - Is it Possible?

As defined by the actual guidelines, surgery for acute cholecystitis can safely be performed as soon as possible, in order to avoid gallstone-related complications, with little contraindications specified, like shock or general anesthesia contraindications (4,5). Even though, surgery in acute cholecystitis may become technically difficult because of the local inflammation, the visceral adhesions or the intraperitoneal fluid, complications that could alter the anatomic perspective and harden gaining the critical view of safety (9). ERAS protocols, even with their promising results, were mostly designed for elective settings (47, 48). There is limited experience regarding

whether emergency laparoscopic cholecystectomy for acute cholecystitis can safely be performed using an ERAS-perioperative protocol.

In our research, only one paper investigated the safety and efficacy of performing ERAS laparoscopic cholecystectomy for acute calculous cholecystitis (14), with another paper being removed in the screening stage because of not accurately depicting the ERAS applied protocol. The study showed that patients in the ERAS group had lower rates of postoperative pain, including shoulder pain for patients undergoing low-pressure pneumoperitoneum cholecystectomy, with similar rate of complications. Early recovery was associated with an early discharge, with 54,5% of the patients being discharged in the first 24 hours after the surgery, versus 19,8% of the patients within the control group (14). Nevertheless, the promising results of this study should be fulfilled by further research into the field, as the authors state the need for more prospective studies and meta-analyses, in order to elaborate an ERAS-specific emergency laparoscopic cholecystectomy protocol.

Conclusions

ERAS protocols could optimize the recovery after laparoscopic cholecystectomy, ensuring a decreased postoperative pain and shorter hospital stay. Further studies are needed to establish a consensus regarding the perioperative protocol, before implementing ERAS for LC in clinical routine.

Nevertheless, the emergency laparoscopic cholecystectomy settings represent a challenge for the supporters of ERAS-protocols, as they are, generally, meant for use in elective surgeries, when the perioperative scenario is, somehow, controlled, and the unknown does not occur as often as it does when performing emergency laparoscopic cholecystectomy. Further research into the field must clearly determine the ERAS-measures that may be safely applied for patients that present with acute cholecystitis with improved outcomes.

Despite those drawbacks, ERAS-laparoscopic cholecystectomy remains a promising approach and may become a standard in healthcare as research progresses into the field.

Authors' Contributions

All authors contributed to the article according to the ICMJE criteria: 1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; 2) drafting the work or revising it critically for important intellectual content; 3) final approval of the version to be published; 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Full approval of the manuscript by all authors should be explicitly stated by including the following statement.

Conflicts of Interest

The authors declared no potential conflicts of interest.

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