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**-Implementation of an Enhanced Recovery After Surgery (ERAS) protocol for acute complicated and uncomplicated appendicitis**

**Short title: ERAS program in appendicitis**

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## Abstract:

**Background:** Enhanced Recovery After Surgery (ERAS) protocols are well-documented logistic programs in elective surgery, but it is still uncertain whether ERAS can benefit emergency patients, because of significant challenges facing its application to emergency surgery.

The aim of this study was to evaluate the implementation of an ERAS protocol for patients with acute appendicitis (AA), both complicated and uncomplicated..

**Methods:** A prospective observational study was performed at 2 university hospitals in Spain, between 2015 and 2019. Inclusion criteria were patients with diagnosis of AA, undergoing appendectomy following an ERAS protocol of perioperative care. The different items of the ERAS protocol were recorded and their implementation was separately evaluated. Analyzed variables also included postoperative complications, hospital stay and readmission rate. Levels of acute phase reactants were assessed as predictors of implementation for the ERAS protocol.

**Results:** Eight hundred fifty patients were included.;498 males (58.5%) and 302 females (41.5%), with a mean age of  $34,95 \pm 17$  years. The implementation of all the items of the protocol was achieved in 770 patients(90.6%), 86.8% of patients with complicated AA and 93.1% of patients with uncomplicated AA ( $p=0.02$ ). Higher preoperative C reactive protein(CRP) levels were significantly associated with the impossibility of implementing all the items of the ERAS protocol( $p<0.001$ ), establishing a cut-off point at  $CRP=13.5mg/dl$ .

**Conclusions:** The implementation of ERAS protocols is safe and feasible in patients with AA. Although the implementation rate of all the items is lower in patients with complicated AA, it can be completed in 86.8% of these patients. CRP levels over 13.5

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mg/dl are predictors of difficulties in the implementation of all the items of ERAS protocols.

**Key words:**

ERAS; Acute appendicitis; Implementation

**Introduction:**

Acute appendicitis (AA) is the most frequent abdominal emergency, with over 11 million of cases reported every year worldwide<sup>1</sup>. Laparoscopic appendectomy (LA) is a widely used surgical procedure. Unlike open appendectomy, the laparoscopic approach results in less postoperative pain and complications, and consequently shorter hospital stay and recovery<sup>2,3</sup>. Notwithstanding, postoperative pain and delay in oral intake are often reported after LA, interfering with recovery and delaying hospital discharge, even in uncomplicated cases<sup>3</sup>. Recovery can also be delayed by postoperative complications. Although appendectomy is considered a safe operation, the complication rate can still reach up to 10%<sup>4</sup>.

Enhanced Recovery After Surgery (ERAS) protocols are well-documented logistic programs in elective surgery, with most evidence developed in colorectal procedures. The protocols are “evidence-based” approaches of perioperative care, leading to faster recovery and shorter hospital stay, with improved patients’ well-being. Although the contents of different ERAS programs can vary, common factors include minimally invasive approaches, multimodal analgesia, optimal anti-emetic prophylaxis and early oral nutrition and ambulation. The rationale is to reduce the body’s perioperative stress response and to induce early restoration of vital organ function, leading to a quicker recovery of the patient<sup>5,6</sup>.

However, it is uncertain whether ERAS can benefit emergency patients, because of significant challenges facing the application of ERAS protocols to emergency surgery. Up to date, the literature evidence on this problem is scarce, but the few studies available

tend to show that ERAS programs are safe and feasible for emergency surgery and could reduce the length of in-hospital stay and postoperative complications<sup>7-10</sup>.

The aim of the present study was to assess the safety and feasibility of the implementation of an ERAS protocol to AA, and to identify preoperative predictive factors of difficulties in the application of the protocol.

### **Materials and Methods:**

A prospective observational study was performed, based on the experience of 2 surgeons at 2 -university hospitals in Spain, between 2015 and 2019. The patients were provided with comprehensive information about the ERAS protocol, including the surgical approach, postoperative recovery and eventual complications.

The severity of AA was determined following the Gomes scale: AA with redness, edema or fibrin were regarded as uncomplicated AA, whereas necrosis of the appendix, perforation, abscess and peritonitis were regarded as complicated AA<sup>11</sup>.

Inclusion criteria were clinical or radiological diagnosis of AA, with intraoperative confirmation based on the surgical findings and age over 18 years. Both, complicated and uncomplicated AA were included.

Exclusion criteria were refusal to follow an ERAS protocol, language barrier, preoperative hemodynamic instability, transfer to the intensive care unit (ICU) after surgery and pregnancy. Patients undergoing conversion to open appendectomy were not excluded, but the conversion to mid-line laparotomy with the performance of surgical procedures additional to appendectomy, peritoneal lavage or drainage placement, were considered exclusion criteria.

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***ERAS protocol:***

The ERAS protocol for emergency surgery, as described by the ERAS-Spain group, was implemented (Table 1)<sup>12</sup>.

***Surgical technique:***

A laparoscopic approach was initially indicated. Three ports were inserted: Hasson umbilical port, a 12mm port in left flank and a suprapubic 5mm port. Low-pressure (8–9 mmHg) pneumoperitoneum was established. Dissection of the mesentery was performed using monopolar coagulation, with eventual clip application on the appendiceal artery. The appendix stump was sectioned with Endo-Gia 45mm (Medtronic, USA). The specimen was extracted inside a bag. Secretions and intraperitoneal fluids were aspirated. In cases with peritonitis, the cavity was irrigated with 200ml of normal saline. The fascial layer of the Hasson and 12mm ports were closed with running monofilament absorbable suture. The skin was closed using staples.

***Postoperative care:***

In all patients with complicated AA, the antibiotic treatment was prolonged for 3–5 days, depending on their response to therapy. Postoperative pain intensity was assessed at rest on the visual analog scale (VAS) 24 hours after surgery. Patients with pain intensity > 50 mm (VAS), were given 3 ml morphine chloride . In those patients who had an intra-abdominal drain, it was removed 24 hours after surgery.

Discharge criteria are summarized in Table 1. A telephone survey was conducted on day 2 after discharge. The patients were asked about the presence of pain, fever and oral intake.

***Variables:***

The rate of complicated and uncomplicated AA was assessed. The different items of the ERAS protocol were recorded and their implementation was separately evaluated.

Analyzed variables also included the frequency of postoperative complications, as classified by Clavien-Dindo score, hospital stay and readmission rate. Levels of acute phase reactants were assessed as predictors of implementation for the ERAS protocol.

***Statistical analysis:***

Dichotomous variables were recorded as absolute frequencies (number of cases) and relative frequencies (percentages). Continuous variables were recorded as means and standard deviations (SD) or median plus maximum and minimum values, depending on whether or not their distribution was normal (determined by the Kolmogorov-Smirnov test). Quantitative variables were compared using the Student's t-test for independent variables (Mann-Whitney test for non-gaussian variables). P values < 0.05 were considered statistically significant.

The outcome ability of laboratory data was evaluated by a receiver operator characteristic curve. The area under the curve was given with 95% CI, and the cutoff point was calculated maximizing the sensitivity in accordance with the Youden index.

All the analyses were made using 22.0 version SPSS software (Chicago, IL, USA).

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An intention-to-treat analysis (initial application of the ERAS protocol) was used. Implementation rate was separately assessed.

### **Results:**

A total of 850 acute appendicitis, initially following an ERAS protocol, were included; 498 males (58.5%) and 302 females (41.5%), with a mean age of  $34,95 \pm 17$  years. There were 56 complications (6.6%), including 32 incisional surgical site infections (SSI), 14 organ-space SSI, 6 postoperative ileus, 2 hemoperitoneum and 2 nosocomial pneumonias. The complications, classified using the Clavien-Dindo system, are summarized in Table 2. There was no mortality. Mean hospital stay was  $2.1 \pm 0.9$  (range 0-12 days). The readmission rate was 1.9%. Histopathological analysis revealed 509 cases of uncomplicated appendicitis (58.9%) and 341 cases of complicated AA (41.1%).

### **Analytical preoperative predictors of complicated appendicitis:**

Patients with intraoperative findings of complicated AA showed a higher white blood cell (WBC) count than patients with uncomplicated AA (mean difference  $4298.65/\text{mm}^3$ ; CI95%(591.03-8006.28);  $p=0.009$ ). A cut-off point was established at  $16500 \text{ WBC}/\text{mm}^3$ , with a sensibility of 73% and specificity of 68.2%. Similarly, those patients with complicated AA showed a higher lymphocyte count (mean difference  $294.05/\text{mm}^3$ ; CI95%(16.32-571.77);  $p=0.038$ ). A cut-off point was established at  $1350 \text{ lymphocytes}/\text{mm}^3$ , with a sensibility of 67.5% and specificity of 63.2%.

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### **Implementation of the ERAS protocol:**

A complete implementation of the protocol was achieved in 770 patients (90.6%); 296 patients with complicated AA (86.8%) and 474 (93.1%) with uncomplicated AA (RR 9.6; CI95% (3.3-21.8); $p=0.02$ ). The main items of the protocol, which were more difficult to implement were the early oral intake, early mobilization and avoidance of opioids administration, caused by inadequately controlled postoperative pain and nausea or vomits. The implementation of the different items of the protocol is shown in Table 2, separating between complicated and uncomplicated AA.

Higher preoperative C reactive protein (CRP) levels were significantly associated with the impossibility of complete implementation of the ERAS protocol (mean difference 5.74 mg/dl; CI95% (2.99-8.50);  $p<0.001$ ). A cut-off point was established at CRP=13.5mg/dl, with a sensibility of 83.3 % and specificity of 78.1%. WBC and lymphocytes count failed to be associated with the implementation rate of the ERAS protocol.

### **Discussion:**

ERAS programs have revolutionized perioperative care in elective surgery, and their positive effects are globally acknowledged. However, it remains uncertain whether ERAS can also benefit emergency patients, as the evidence in literature on this problem is still scarce<sup>13,14</sup>. This is mostly due to significant challenges facing the application of enhanced recovery pathways to emergency surgery. Paduraru et al concluded from a meta-analysis that ERAS protocols were safe and feasible for emergency surgery and could reduce the length of in-hospital stay and postoperative complications<sup>7</sup>.

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Several studies have shown the benefits of diverse ERAS components for patients with AA, but Hamill et al. underlined in a review that there are no standardized ERAS algorithms for AA<sup>15</sup>. Nechay et al developed a modified ERAS protocol, including laparoscopic approach, multimodal analgesia and early oral intake and mobilization, observing results in early patient discharge and less postoperative pain as main benefits of the implementation of the protocol<sup>2</sup>. The ERAS protocol implemented in the present study, included more items than these, as described in the protocols developed by the ERAS-Spain group<sup>12</sup>. Beyond this, our protocol includes several intraoperative anesthetic measures, such as goal-directed fluid administration or strict antiemetic prophylaxis following Apfel scale.

In the present study, we evaluated the complete implementation of the protocol, but also the different items included, aiming to identify those most difficult to apply. The range of components borrowed from the ERAS programs for elective surgery varies in emergency surgery due to significant challenges facing their adaptation to the emergency setting. We obtained a complete implementation of the protocol in over 90% of the patients, which is higher than data reported by other groups for emergency surgery<sup>2</sup>. As ERAS protocols are widely implemented in many surgical procedures at our institutions, the multidisciplinary team is used to apply the different items and consequently, we have a complete or very high implementation of technical aspects, which are often the most relevant limiting factor for the application of ERAS programs at many institutions<sup>16</sup>. The most difficult issues to apply in our series were patients' related items, mainly the early mobilization, early oral intake and avoidance of opioid administration. However, these measures could be implemented in over 85% of the cases. Nechay et al reported an early oral intake in only 42% and early mobilization in 56% of the patients<sup>2</sup>. So far, it remains unclear which components of the program make the greatest contribution to the

recovery process in urgent care, but in our opinion all the components are important and show a synergistic effect. Inadequately controlled postoperative pain and nausea or vomits were the main reasons reported for the failure of implementation of the protocol. Multimodal analgesia is focused on reducing postoperative pain and consequently allowing an early mobilization. In addition, multimodal analgesia, decreases the opioid needs, which associate postoperative ileus as adverse effect. The latter delays the possibility of early oral intake, and causes nausea and vomits. Early oral intake and early mobilization also induce bowel peristalsis. Thereby all the items included in the multimodal approach interact to improve the postoperative recovery. Consequently, we do not advocate for the implementation of a single measure, but for a complete protocol<sup>17</sup>.

It has been widely described that patients with complicated AA are more prone to develop postoperative complications and these lead to increased postoperative pain. Furthermore, organ-space SSI are associated with prolonged postoperative ileus<sup>18</sup>. Both, uncontrolled postoperative pain and prolonged ileus, impede the implementation of several items of ERAS protocols<sup>19</sup>. The latter has been also confirmed in our patients. Notwithstanding, a complete implementation of the protocol could be achieved in over 85% of our cases of complicated AA. Therefore, we think that the intraoperative finding of complicated AA must not prevent surgeons from implementing an ERAS approach, as many patients may benefit from these measures in their postoperative recovery.

Another factor that prevents complete implementation of ERAS protocols is the conversion from laparoscopic to open approach. However, the conversion is not a contraindication for implementing the rest of the items from the protocol. In our series, in complicated AA the conversion rate reached 2.3%, whereas there was no conversion in uncomplicated AA. The conversion to open approach implies a lengthening of the operative time, delayed meal intake, increased postoperative pain and a longer hospital

stay. Consequently, it is an independent prognostic factor for difficulties in implementing an ERAS protocol. Elevated CRP values have been associated with an increased risk of conversion<sup>20</sup>. In our series, we failed to demonstrate such an association, as few patients required conversion. However, we determined that CRP values over 13.55 mg/dl were associated with more frequent failure to complete the ERAS items. As complicated AA is usually associated with higher preoperative CRP levels<sup>21</sup>, it could be recommended that the surgery is performed by an experienced surgeon given the higher risk of technical complexity and eventual possibility of conversion.

In the present study, we observed that higher WBC levels were associated with increased risk of having complicated AA. The predictive value of WBC for the severity of AA still remains controversial<sup>22, 23</sup>. Recently, the neutrophil-to-lymphocyte ratio (NLR) has been proposed as a simple inexpensive marker of subclinical inflammation, which is easily calculated from the differential WBC counts, providing information regarding two different immune and inflammatory pathways which may make it a potential marker for predicting AA and its severity. The neutrophil count highlights active and continuing inflammation, whereas the lymphocyte count highlights the regulatory pathway. As AA is **mostly** an acute inflammation, it is expected that neutrophil count is higher whereas, lymphocyte count remains at lower levels. Consequently, the greater the NLR ratio, the greater is the risk of complicated AA<sup>24</sup>. We failed to demonstrate this hypothesis. In our series, we found that overall WBC count, including neutrophil and lymphocyte counts, was directly associated with and increased risk of having complicated AA, but an elevated lymphocyte count was also related to the presence of complicated AA. Obviously, as the lymphocyte count is in the denominator of the NLR formula, the greater the lymphocyte count, the lower the value of the ratio. As complicated AA usually represent an evolved process of inflammation, which often lasts for several days, we hypothesize that this is

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time enough to start a lymphocyte-mediated regulatory process. Anyway, further studies should evaluate the impact of lymphocyte count on the severity of AA.

#### Limitations:

Most of the items included in our ERAS protocol can be considered as normal clinical management. In our experience, the most relevant differences between this protocol and the historic standard of care were based on 4 items: Goal-directed fluid administration, multimodal analgesia, start of oral fluids intake 6 hours after surgery and active mobilization 8 hours after surgery. Unfortunately, data from a historic cohort of patients following a standard of care were not available, preventing a comparison of results, which may have shown the clinical advantages of implementing an ERAS protocol in cases of AA. Further studies must be conducted, preferably randomized clinical trials, to show the clinical impact of the implementation of these protocols.

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#### Conclusions:

The implementation of ERAS protocols is safe and feasible in patients with AA. Although the implementation rate of all the items is lower in patients with complicated AA, the entire protocol can be completed in 86.8% of these patients. CRP levels over 13.5 mg/dl are predictors of difficulties in the implementation of all the items of ERAS protocols. However, this should not prevent use of these protocols.

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#### *Declarations*

**Funding:** The authors did not receive any funding for the conduction of the study.

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**Conflicts of interest/Competing interests:** The authors do not have conflicts of interests for the publication of this study.

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**Ethics approval:** The study was approved by the local Ethics Committee (FUNMEL 845).

**Consent to participate:** All the participants signed an Informed Consent form for the participation in the study, allowing the publication of the data in an Anonymous manner.

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Table 1: ERAS protocol for acute appendicitis

Time	Procedure
Preoperative	<p>Laboratory data, including White blood cell count (WBC) and C reactive protein (CRP)</p> <ul style="list-style-type: none"> <li>• Empiric antibiotic treatment according to the severity of the infection</li> </ul>
Intraoperative	<ul style="list-style-type: none"> <li>• Maintenance: Oxygen/air with FiO<sub>2</sub> 60-80%</li> <li>• Goal-directed fluid administration</li> <li>• Active heating with thermal fluid heater and thermal blanket</li> <li>• Prophylaxis of postoperative nausea and vomits following Apfel scale</li> <li>• Multimodal analgesia: Port-sites infiltration with local anesthetics (Bupivacaine 0.5%, 20 ml), before ports placement.</li> <li>• Laparoscopic surgery</li> </ul>
Immediate postoperative period	<ul style="list-style-type: none"> <li>• Maintenance of FiO<sub>2</sub> 50% for 2 hours after surgery.</li> <li>• Intravenous analgesia: Acetaminophen + NSAIDs. Avoid opioids</li> <li>• Oral fluids 6 hours after surgery</li> <li>• Active mobilization 8 hours after surgery</li> </ul>
Postoperative day 1, Discharge and Follow-up	<ul style="list-style-type: none"> <li>• Start oral analgesia</li> <li>• Progression to complete diet</li> <li>• Drainage removal, when present</li> <li>• Analytic evaluation of C reactive protein and/or procalcitonin</li> </ul> <p>Discharge criteria: No surgical complications, no fever, pain controlled with oral analgesia, full deambulation, no needs of prolonged intravenous antibiotic treatment, patient acceptance.</p> <p>Recommendations at discharge:</p> <ul style="list-style-type: none"> <li>• Telephone monitoring for 48 hours.</li> <li>• Coordination with General Practitioner</li> <li>• First out-patient visit 15 days after discharge</li> </ul>

ERAS= Enhanced Recovery After Surgery

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Table 2: Clavien-Dindo classification of postoperative complications, hospital stay and readmission rate

Clavien Dindo stage	Total (n=850)	Complicated AA (n=341)	Uncomplicated AA (n=509)	p
I	6 (0.71%)	4 (1.17%)	2 (0.39%)	0.183
II	2 (0.24%)	1 (0.29%)	1 (0.2%)	0.775
IIIa	42 (4.9%)	32 (9.4%)	10 (1.96%)	<0.001
IIIb	4 (0.47%)	3 (0.88%)	1 (0.2%)	0.154
Hospital stay	2.1 ± 0.9	2.9 ± 1.3	1.4 ± 0.5	<0.001
Readmission	16 (1.9%)	11 (3.2%)	5 (1%)	0.018

AA= acute appendicitis

Table 3: Implementation of the ERAS protocol in complicated and uncomplicated appendicitis

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	Complicated AA (n=341)	Uncomplicated AA (n=509)	p
Intraoperative FiO <sub>2</sub> 60-80%	100%	100%	NS
Goal-directed fluid administration	100%	100%	NS
Prophylaxis of postoperative nausea and vomits following Apfel scale	100%	100%	NS
Port-sites infiltration with local anesthetics	100%	100%	NS
Laparoscopic surgery	97.7%	100%	0.0005
Avoid opioids	86.8%	93.1%	0.002
Oral fluids 6 hours after surgery	87.7%	93.7%	0.0022
Active mobilization 8 hours after surgery	86.8%	93.1%	0.002
Start oral analgesia 24 hours after surgery	90.6%	93.1%	NS
Progression to complete diet 24 hours after surgery	88%	96.1%	<0.001
Drainage removal, when present, 24 hours after surgery	87.5%	-	
Analytic evaluation of C reactive protein and/or procalcitonin 24 hours after surgery	100%	100%	NS
Telephone monitoring for 48 hours after discharge	100%	100%	NS

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ERAS=Enhanced Recovery After Surgery; FiO<sub>2</sub>= fraction of inspired oxygen

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