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Implementation of an ERAS Protocol on Cirrhotic Patients in Liver Resection

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Abstract

Background: The development of laparoscopic liver surgery, the improvement in the perioperative care programs, and the surgical innovation has allowed liver resections on selected cirrhotic patients. However, the great majority of ERAS studies for liver surgery have been conducted on patients with normal liver parenchyma, while its application on cirrhotic patients is limited. The purpose of this study was to evaluate the implementation of an ERAS protocol in cirrhotic patients who underwent liver surgery.

Methods: We present an analytical observational prospective cohort study, which included all adult patients who underwent a liver resection between December 2017 and December 2019 with an ERAS program. We compare the outcomes in patients Cirrhotic (CG)/Non-Cirrhotic (NCG).

Results: A total of 101 patients were included. 30 of these (29.7%) were patients ≥ 70 cirrhotic. 87% of the both groups had performed >70% of the ERAS. Oral diet tolerance and mobilization on the first postoperative day were similar in both groups. The hospital stay was similar in both groups (2.9 days/2.99 days). Morbidity and mortality were similar; Clavien I-II (CG: 44% *vs*. NCG: 30%) and Clavien ≥ III (CG: 3% *vs*. NCG: 8%). Hospital re-entry was higher in the NCG. Overall mortality of the study was 1%. ERAS protocol compliance was associated with a decrease in complications (ERAS<70%: 80% *vs*. ERAS>90%: 20%; p=0.02) and decrease in severity of complications in both study groups.

Conclusion: The application of the ERAS program in cirrhotic patients who undergo liver surgery is feasible, safe, and reproducible. It allows postoperative complications, mortality, hospital stay and readmission rates comparable to those in standard patients.

Keywords: ERAS Protocol; Cirrhosis; Liver Resection

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Introduction

Enhanced Recovery After Surgery (ERAS) is a surgical protocol which arises at the end of the 20th century by the Danish professor Henrik Kehlet in Denmark [1-7]. This program establishes the second revolution in the history of modern surgery, after laparoscopy, and has become the standard for surgical care. On June 2016, ERAS Society guidelines in liver resection were published, with specific recommendations on how to improve postoperative recovery [4,7-9], being implemented by high-volume centers. However, the great majority of ERAS studies for liver surgery have been conducted on patients with normal liver parenchyma, while its application on cirrhotic patients is limited [8]. Historically, liver resection on a cirrhotic parenchyma was feasible by assuming higher mortality rates and a higher risk of severe complications on the immediate postoperative period [10-16]. Nonetheless, the development of laparoscopic liver surgery has allowed liver resections on selected cirrhotic patients, minimizing surgical trauma, and reducing the risk of post hepatectomy liver failure [17,18], bleeding, hospital stay and postoperative complications [15].

Even though the optimization of postoperative treatment remains a challenge, the application of multimodal rehabilitation in liver surgery has proven to be successful and safe along with a shorter recovery time, fewer medical complications, and improvements in quality of life [8,9,19]. However, despite the overwhelming advantages of the protocol, its implementation in cirrhotic patients is limited and controversial due to an apparent increase in complications.

The purpose of this study was to unveil that the implementation of an ERAS protocol in cirrhotic patients who underwent liver surgery did not entail an increase in morbimortality nor hospital readmission in comparison to standard patients. Additionally, to determine patient compliance

to the protocol and prove that an adequate compliance of the ERAS program is related to a decrease in complications and their severity.

Materials and Methods

Study design and Patient selection

We present an analytical observational prospective cohort study, which included all adult patients who underwent a liver resection between December 2017 and December 2019 and who signed the informed consent form and accepted to be included in the protocol. We obtained the approval from the Experimentation Ethics Committee of Málaga (nº 2099-N-19). A total of 133 liver resections were performed.

Patients with other organ resections, hemodialysis, severe valvular heart disease, ejection fraction <35%, grade IV obstructive pulmonary disease, Klatskin tumor, Associating Liver Partition and Portal Vein Ligation for Stages Hepatectomy (ALPPS) and with intraoperative unresectability were excluded.

Data collection

The variables collected were: Demographics, etiology, American Society of Anesthesiologists Physical Status Classification (ASA), frailty, CHLID/MELD, number of lesions, surgical approach, surgical technique, transfusions, surgical time, ERAS program, blood testing, immediate and 30-day postoperative morbimortality (Clavien-Dindo), postoperative stay and readmission.

Patient management

All patients were discussed at the Multidisciplinary Digestive Tumors Committee meeting and considered candidates for curative intention surgical treatment.

ERAS program

ERAS program was explained in the clinic by the surgeons (Appendix No. 1). Patients were given an informative leaflet concerning the different steps and guidelines of their intervention. We encouraged a prehabilitation based on a) Respiratory Physiotherapy: Deep breathing ≥ 4 times a day using a flow incentive spirometry, b) Motor Physiotherapy: Walks (30-60 min, 5 times a week) and c) Nutrition: All patients regardless their nutritional status were prescribed protein shakes 3 times a day, as improvements in postoperative results have been proven [20]. The mean time between the clinic visit and the surgery ranged between 2 and 4 weeks.

Audit

We considered an adequate compliance when patients achieved at least 70% to 90% of the stablished items in order to evaluate the compliance of the ERAS protocol, as it has been previously described in the Pisarka study [21].

Discharge criteria and postoperative follow-up

To discharge patients, they had to achieve several criteria: The ability to tolerate solid diet, pain controlled using oral analgesia, normal blood tests (hemoglobin, leukocytes, liver enzymes and synthetic factors) and an active mobility. One-week follow-up was performed by nursing personnel, and 1-month follow-up in the medical clinic. The data gathered was pain severity [Visual Analogous Scale (VAS)], analgesia requirements, complications, reincorporation to normal life, blood tests and re-entry rates.

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences program (SPSS). Categorical variables were expressed as numbers and percentages and quantitative variables as mean and standard deviation. Bivariate analysis was performed using Student t test to compare quantitative variables and the χ^2 test to compare qualitative variables. A multivariate logistic regression model was conducted including postoperative complications as the outcome variable. $p<0.05$ was considered statistically significant.

Results

116 patients had indication for liver resection. Among these, 15 (13%) were excluded from the study due to intraoperative unresectability (7), diaphragm infiltration (3) or intestinal suture association (5). 101 resections were included, being 30 of them included in the Cirrhotic Group (CG).

Demographic variables

Of all the patients included in the cirrhotic group, men were the predominant sex (p=0.005). 70% of the patients in the CG had an ASA III status in comparison to a 41% in the Non-Cirrhotic

Table 1: Demographic and intraoperative variables.

	Cirrhotic (n=30)	Non-Cirrhotic (n=71)	P
Sex (M/F)			**0.005**
Male	87% (26)	58% (41)	
Female	13% (4)	42% (30)	
Age	65 (+/-9.8)	63 (+/-10.33)	0.71
ASA			
I	3% (1)	4% (3)	**0.026**
II	27% (8)	55% (39)	
III	70% (21)	41% (29)	
Abdominal surgery			**0.001**
Yes	47% (14)	85% (60)	
No	53% (16)	15% (11)	
Etiology			**0.01**
Metastasis		78% (55)	
CRC		48	
Other		7	
HCC	90% (27)	6% (4)	
Cholangiocarcinoma	10% (3)	1% (1)	
Gallbladder adenocarcinoma		1% (1)	
Benign lesions		14% (10)	
Laparoscopy	100% (30)	79% (56)	0.006
Conversion	3% (1)	3% (2)	0.889
Liver Resection			0.667
Major Liver Resection	17% (5)	23% (16)	
Limited Resection	57% (17)	55% (39)	
Segmentectomy	23% (7)	15% (11)	
Left lobectomy	3% (1)	3% (2)	
Cystopericystectomy		4% (3)	
Pringle	80% (24)	87% (62)	0.344
Time	61 min	59 min	
Transfusion	3% (1)	20% (7)	0.267
Drainage system	50% (15)	42% (30)	0.474

Table 2: ERAS protocol compliance and items.

	Cirrhotic (n=30)	Non- cirrhotic (n=71)	P
ERAS Compliance			0.374
100%	37%	26%	
70%-90%	50%	65%	
<70%	13%	9%	
ERAS ITEMS			
Signed informed consent form	100%	100%	n.s.
Preoperative assessment	100%	100%	n.s.
Preoperative nutrition	100%	100%	n.s.
6-hour fast	100%	100%	n.s.
Preanesthetic Medication	100%	100%	n.s.
Compression stockings	100%	100%	n.s.
Antibiotic prophylaxis	100%	100%	n.s.
Perioperative Steroids	97%	97%	n.s.
Glycemic control	100%	100%	n.s.
Guided fluid therapy	100%	100%	n.s.
Laparoscopic Surgery	100%	79%	n.s.
Nausea and vomiting prevention	100%	100%	n.s.
Active heating	100%	100%	n.s.
Drainage avoidance	50%	58%	n.s.
Intraoperative nasogastric tube withdrawal	93%	94%	n.s.
Analgesia Pump (epidural or intravenous)	13%	25%	n.s.
NSAIDs as adjuvant treatment	100%	100%	n.s.
Respiratory physiotherapy	100%	100%	n.s.
Diet tolerance 6h after surgery	73%	76%	n.s.
Early mobilization	73%	76%	n.s.
Urinary catheter withdrawal on 1st postoperative day	77%	80%	n.s.
Active mobilization on 1st postoperative day	54%	59%	n.s.
Audit	100%	100%	n.s.

Group (NCG). 11 patients (37%) included in the CG had pulmonary hypertension. 97% of them were child class A and the mean value of MELD was 7 (r: 6-14). Hepatocellular Carcinoma (HCC) was the most frequent indication in the CG (90%) as opposed to metastasis in the NCG (78%).

Laparoscopic approach was performed in all the cirrhotic patients (100%). Limited Resection (LR) was the most common surgical technique, however a 17% and 23% of Major Liver Resection (MLR) were performed in both groups respectively. The use of surgical drainage systems was comparable in both groups without statistically significant differences. A detailed distribution of the different etiologies and intraoperative variables is presented in Table 1.

ERAS program compliance

87% of the cirrhotic patients showed an adequate compliance of the ERAS protocol (70%), similarly to the non-cirrhotic group (91%) (Table 2). Along with a higher compliance of ERAS protocol, a significant decrease in complication rates (ERAS<70%: 80% *vs.* ERAS 70%-90%: 45% *vs.* ERAS>90%: 20%; p=0.002) and complication severity Clavien >III was observed (ERAS<70%: 20% *vs.* ERAS 70%-90%: 8.2% *vs.* ERAS>90%: 3.3%; p=0.03).

Table 3: Diet advancement and ambulation.

	Cirrhotic (n=30)	Non-cirrhotic (n=71)	P
Tolerance			0.829
Afternoon after surgery	73% (22)	76% (54)	
1 POD	24% (7)	22% (15)	
2 POD	3% (1)	2% (2)	
Liquid diet			0.490
Afternoon after surgery	3% (1)	3% (2)	
1 POD	87% (26)	90% (64)	
2 POD	7% (2)	7% (5)	
3 POD	3% (1)	0	
Regular diet			0.083
Afternoon after surgery	3% (1)	0	
1 POD	47% (14)	51% (36)	
2 POD	37% (11)	48% (34)	
3 POD	10% (3)	1% (1)	
4 POD	3% (1)	0	
Afternoon after surgery sitting (Early mobilization)	73% (22)	76% (54)	0.772
Armchair			0.309
Afternoon after surgery	30% (9)	18% (13)	
1 POD	60% (18)	75% (53)	
2 POD	7% (2)	6% (4)	
3 POD	3% (1)	0	
5 POD	0	1% (1)	
Ambulation (Active mobilization)			0.275
1 POD	54% (16)	59% (42)	
2 POD	43% (13)	34% (24)	
3 POD	0	6% (4)	
≥ 4 POD	3% (1)	1% (1)	

Diet advancement and ambulation

All items evaluated (tolerance, liquid diet, regular diet, early mobilization, sitting out of bed and active mobilization) were comparable in both groups (Table 3).

Complications, hospital stay and readmission

Table 4 shows morbimortality. In the cirrhotic group a small increase of type I/II complications was observed (44%) mainly due to ascites and renal function deterioration. Overall mortality of the study was 1%. The mean hospital stay was 2.90 days in the CG compared to 2.99 days in the NCG. Hospital re-entry was significantly higher in the non-cirrhotic group caused by intra-abdominal collection or undrained biliary fistula.

Logistic regression analysis

We analyzed the different possible factors that could influence the ERAS protocol compliance: Age, laparoscopy, cirrhosis, etiology, sex, surgical history, MLR and ASA. We proved how being cirrhotic was not a risk factor for an adequate compliance. However, MLR was a risk factor in the compliance of ERAS protocol (OR: 6.618, IC 95% 2.176-20.129, p=0.001).

We also analyzed possible factors related to the development of postoperative complications. The compliance of the ERAS protocol

Table 4: Postoperative Clavien complications.

	Cirrhotic (n=30)	Non-cirrhotic (n=71)	P
Complications			0.165
None	50% (15)	62% (44)	
I/II	44% (13)	30% (21)	
Ascites	4	2	
Disorientation	1	2	
Renal function deterioration	2	2	
Respiratory	1	2	
Anemia (iron)	0	2	
Postoperative ileus	1	3	
Sinusal tachycardia	0	2	
A-fib with rapid ventricular response	0	3	
Biliary fistula	2	0	
Transfusion	1	1	
Hyperbilirubinemia	1	0	
Postoperative collection	0	1	
Jugular vein thrombosis	0	1	
III/IV	3% (1)	8% (6)	
Hematoma	0	1	
Abscess	0	1	
Biloma	0	2	
Grade B liver insufficiency	0	1	
Hemodynamic instability	0	1	
Epistaxis due to NG tube	1	0	
Exitus	3%	0%	0.112
Re-entry	0	11%	0.055
Biliary fistula		3	
Postoperative collection		4	
Fever syndrome		1	
Stay (days)	2.9	2.99	0.149

was a protective factor: Achieving over 70% resulted in a 0.091 risk reduction of complication development (OR: 0.091, IC 95%: 0.01-0.868; p=0.037). On the contrary, patients requiring blood transfusions had 13.925 times more risk of developing complications (OR: 13.925, IC 95%: 1.442-134.473; p=0.023).

Discussion

The application of ERAS program was first described in the beginning of the 20th century [22], however, its integration and implementation into clinical practice has been slower than other disciplines. The development of laparoscopy and its benefits, clearly demonstrated at the Southampton Conference [17], have significantly broaden the application of the ERAS protocol, allowing its implementation to certain subgroups previously excluded, such as cirrhotic patients.

The greatest surgical risk of cirrhotic patients depends on the severity of liver insufficiency and comorbidity, instead of the cirrhosis itself as described by El-Serag [23]. Our cirrhotic patient group had satisfactory functional results as 97% of them were Child Class A with a mean value of MELD of 7, yet signs of portal hypertension were described in 37% of them.

The improvement of surgical techniques along with minimal invasive approach have allowed liver resection in this group of patients. Consequently, 100% of the cirrhotic patients in this study underwent laparoscopic approach, as described in the literature [24]. However, we showed superior results compared to Lunel [25], Zheng [10] and Teixeira [26] who described a laparoscopic approach in 26% to 45% of the patients. Regarding the type of liver resection, there were no statistically significant differences in the LR (CG 17% *vs.* NCG 23%). Texeira [26] describes MLR in 25.7% of the patients, whilst Lunel [25] and Zheng [10] showed slightly superior percentages (40.3% and 37.5% respectively). Zheng does not specify MLR and has a low percentage of laparoscopic approach in both groups (34.2% and 26%).

With the Pringle maneuver we prioritized the reduction of blood loss over the consequences driven by the intermittent ischemia, as there is no postoperative functional repercussion. The use of the Pringle technique was similar in both groups, which led to a low blood transfusion rate in this group (3%). These results are similar to those described by Al Saeedi [27] and Ortiz Galindo [28], with a 76% of Pringle maneuver in cirrhotic patients who underwent conventional liver resection.

The restriction in the use of drainage systems is one of the key elements in the ERAS program, however we must admit a high use of them (50%). Nonetheless, our results were lower than those described by Lunel [25] and Texeira [26], with a 72% and 68.6% respectively. Our high implementation of drainage systems in this group was due to their risk of developing postoperative ascites as a clinical sign of liver insufficiency. However, this did not lead to an increase in morbidity nor longer hospital stay. Therefore, in relation to the results shown in this study, we recommend the use of drainage systems in cirrhotic patients at least during the first 48 h to identify an edemo-ascitic decompensation. In our group, 33% of them were discharged with a drainage system (as a result of liver insufficiency grade A presented as ascites).

87% of the cirrhotic patients complied with >70% of the ERAS protocol items, similarly to non-cirrhotic patients. Our results were higher than those showed by Texeira [26] and Lunel [25] who described a compliance rate of 65% and 60.3% respectively (both based on the accomplishment of different items of the protocol, as specified in our study).

As a result of the ERAS program, early diet reintroduction has been feasible in liver surgery [29-33]. In our study being cirrhotic did not affect diet reintroduction, as we observed diet tolerance 6 h after surgery similarly in both groups (CG: 73%). The same occurred regarding liquid diet on 1st Postoperative Day (POD) (CG: 90%) and regular diet on 2nd POD (CG: 87%). Similar results are observed by Teixeira [26], who reintroduced oral diet in 82% of the total of their patients.

In relation to mobilization, similar results were thrown in both groups: either respecting early mobilization (on the afternoon of the surgery →CG: 73% *vs.* NCG: 76%), sitting (2nd POD →CG: 90% *vs.* NCG: 93%) or ambulation (2nd POD →CG: 97% *vs.* NCG: 93%). These results are comparable to those described by Texeira [26], with 82% of the patients with an early mobilization, however not describing what was considered as early mobilization. On the contrary, our results were higher to those described by Lunel [25], who showed early

mobilization on the afternoon of the surgery in 32% of the patients, and on the second postoperative day in 45% of them.

A slightly higher percentage of Clavien I/II complications was observed in the cirrhotic group (CG: 44% *vs.* NCG: 30%), appearing as ascites and renal function deterioration. Such results are higher to those from Lunel [25] and Liang [24] who described a 22 and 28% each. Our higher percentage of complications can by justified with our thorough data collection, as no impact on diet, tolerance, mobilization nor hospital stay was observed. In relation to Clavien ≥ III no differences between both groups were observed (CG 3% *vs.* NCG 8%). These results were lower than those published in different articles concerning ERAS program in liver resections [10,25,26,30] with complication rates oscillating between 7.5 and 20%. We believe our lower morbidity is due to our high percentage of laparoscopic approach and the preventive use of drainage systems on the first 48 h after surgery.

Overall mortality of our study was of 1%, only one patient, which in the cirrhotic group implied a 3%. No overall mortality was also seen by Teixeira [26] and Liang [24]. On the contrary, Lunel [25] described in the ERAS group an overall exitus rate of 5% and 12% in the cirrhotic group. It has been proved in the literature that cirrhotic patients who undergo liver surgery have a higher mortality risk, being also supported that mortality cannot be reduced with the application of the ERAS protocol as it is related to comorbidities and technical complications [26,34,35]. The only exitus in our series was a cirrhotic patient with frailty criteria (physical frailty phenotype → 4) and multiple comorbidities, therefore considering it as a poor selection to undergo liver surgery.

There were no statistically significant differences between both groups regarding hospital stay (CG 2.90 days *vs.* NCG 2.99 days), being lower than those in the literature. Teixeira [26] presented a high percentage of laparotomy approach (73.75%) which could justify their 5 days mean hospital stay, similarly to Lunel [25] with a mean stay of 8 days after surgery due to a low laparoscopic rate (34.2%) and a low compliance percentage of the ERAS program (60%). However, Liang [24] despite describing the use of laparoscopy in the total of the patients (100%), a 36% of cirrhotic patients and a 29% of MLR, which is comparable to our study, they report a mean stay of 5 days. 66% of the cirrhotic patients of our sample were discharge on the first three postoperative days. No re-entries were described in our cirrhotic patients (CG 0% *vs.* NCG 11%), oppositely to Lunel [25] and Liang [24] who had an 8.5% and 6.9% of re-entry rates respectively. We believe re-entry, as well as exitus, is not related to ERAS protocol, but to technical complications and comorbidities as described by Ahmed [36].

This study has a few limitations: 1) Unicentric study with limitations concerning patient recruitment. 2) The lack of analysis about the influence of prehabilitation on the development of complications in the overall sample due to the lack of data collection.

Conclusion

The application of the ERAS program in cirrhotic patients who undergo liver surgery is feasible, safe, and reproducible. It allows postoperative complications, mortality, hospital stay and readmission rates comparable to those in standard patients. An adequate compliance of the ERAS protocol results in a decrease of complications and their severity.

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