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RESEARCH ARTICLE

CLINICAL OUTCOMES OF ENHANCED RECOVERY AFTER SURGERY PROTOCOL FOR HEPATO- PANCREATO- BILIARY SURGERY; A FIVE-YEAR EXPERIENCE FROM A HELLENIC ONCOLOGICAL HOSPITAL

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Abstract

Background: The development of enhanced recovery after surgery protocols (ERAS) for surgical intervention has contributed to reducing hospital length of stay and improved patient outcomes. Aim of the study was the assessment of the recovery time and cost-effectiveness of an ERAS protocol in oncological patients undergoing hepato- pancreato- biliary surgery (HPB) compared to conventional (CON) care.

Methods: This prospective, open label, randomized trial, enrolled 283 patients who required hepatectomy or pancreatoduodenectomy. Eligible patients were stratified into hepatectomy or pancreatectomy groups then, randomly assigned to ERAS protocol (intervention) or CON care (control). The primary outcome of interest was post-operative recovery time (composite of; time to mobilization and oral intake) and secondary outcomes were cost effectiveness, dependance on post-operative opioids and post-operative complications (using the Clavien- Dindo classification).

Results: The rate of complications for the patients underwent hepatectomy and treated in ERAS group was 18.2% compared to CON group, which was 40.9%. Whilst, of complications for the patients underwent pancreatectomy and treated in ERAS group was 15.95% compared to CON group, which was 38.03%.

Conclusions: The ERAS protocol in this study significantly improved post-operative recovery time, reduced opioid dependance and reduced post-operative complications in patients undergoing HPB surgery.

Key-words: cost-effectiveness; eras program; fast track protocol; liver and pancreatic surgery

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INTRODUCTION

The development of enhanced recovery after surgery protocols (ERAS) has contributed to reducing health care costs and improving morbidity and mortality rates.[1] These new perioperative protocols have positively influenced post-surgical and post hospitalization rehabilitation.[2,3] The goal of the ERAS protocols is to utilize a multi-disciplinary approach and optimize patient perioperative care using a combination of evidence-based clinical interventions to expedite postoperative recovery. [4–6]

ERAS programs have improved perioperative management of patients through better collaboration among healthcare professionals. The implementation of ERAS protocols includes pre-anesthesia evaluation, anti-nausea and emesis prophylaxis, use of opioid-sparing and regional anesthesia where appropriate, and better regulation of body temperature to avoid intra and postoperative shivering hypothermia. [7]

The ERAS protocol also combines early oral nutrition, early mobilization, and optimal pain control postoperatively. As an infection prevention strategy, early removal of abdominal, urinary and nasogastric drainage catheters is encouraged, as is patient mobilization on the day of surgery. [8] Many clinical benefits have been observed with the implementation of ERAS protocols that include reduced intraoperative bleeding, decreased need for fluid resuscitation, better pain management facilitating early ambulation, as well as reduced length of hospital stay facilitating early hospital discharge, typically within 5 to 6 days after surgery. [5,9]

A number of studies have evaluated the concept of fast track protocols in a different patient cohorts, including hepato-pancreato-biliary surgery (HPB), and have found them to be safe and effective. [10–15] The aim of our study was to assess the effectiveness of an ERAS protocol for oncological patients undergoing HPB surgery in Greece.

MATERIALS AND METHODS

Study design and participants

This was a prospective, open-label, randomized controlled study that compared the ERAS protocol for HPB surgery with conventional (CON) care. The study was carried out in a surgical ward of a large oncological hospital in Athens, Greece, between May 2012 and November 2017, when there were 450 beds. The study was conducted and the results reported using the CONSORT 2010 guidelines, which include the CONSORT guidelines for reporting economic evaluation alongside randomized controlled trials.[16-17]

The research was approved by the Scientific Committee of the hospital where it was carried out and the Ethical Committee of the Faculty of Nursing of the National and Kapodistrian University of Athens, Greece (ID: 4051/448 and ID: 87) (clinical trial; Registration Number: NCT02524925). The study was conducted in accordance with the Helsinki Declaration for conducting medical research involving human subjects.[18] In order to be included in the study, all participants provided written and signed informed consent. All data collected was de-identified and patients were allocated unique study numbers to guarantee confidentiality.

Consecutive patients requiring HPB surgery were screened for eligibility. Inclusion criteria: identified need for HPB surgery, age of at least 18 years, and ability to provide informed consent. Exclusion criteria: minors (under 18 years of age), inability to provide informed consent. Eligible patients were stratified into hepatectomy or pancreatectomy groups and then randomly assigned to the ERAS protocol (intervention) or CON care (control). Random allocations were generated by a computer using the 'Random sampling' tool from SPSS 22.0 (IMB SPSS software, Chicago, Illinois) and kept hidden from investigators and patients until enrolment.

The primary outcome of interest was post-operative recovery time (composite of: time to mobilization and oral intake) and secondary outcomes were cost effectiveness, dependance on post-operative opioids, and post-operative complications using the Clavien-Dindo classification (composite of vomiting/nausea, diarrhea, fever, postoperative ileos, atelectasis, rapture of anastomosis, hemorragia, cholorrhea, pancreatic fistula, gastric paresis)

Protocol

Two perioperative care protocols were applied: ERAS and CON care (Table 1).[6]

Patient demographic and anthropometric data were recorded.

Additionally, during the postoperative period, the presence or absence of nausea/emesis as well as any complications (Clavien-Dindo classification) were recorded. For economic evaluation, hospital length of stay was recorded (bed days).

Statistical analysis

Statistical analysis was carried out by SPSS 22 (IMB SPSS Software, Chicago, Illinois) and the mean (standard deviation) of variable values is reported. In all statistical analyses, a nominal significance level of = 0.05 was used. Descriptive statistics were used to report the data. We used the Spearman ranked order correlation to measure the association of patient recovery times between the treatment and control groups.

Sample size calculations were based on a desired level of power of 0.8, a significance level of 0.05 and a large effect size based on data derived from previous studies in similar groups of patients.[19-20] The desired sample size was estimated as n = 61 per group.

RESULTS

Between May 2012 and November 2017, a total of 307 oncology patients requiring a hepatectomy or pancreatoduodenectomy were screened for eligibility. Twenty-four patients refused to participate in the research, leaving 283 patients (143 requiring hepatectomy and 140 requiring pancreatectomy) to be stratified into the 2 groups for randomization (Figure). Patients were randomized into two groups. In group ERAS (N = 146), the ERAS protocol was applied, while in group CON (N = 137), conventional perioperative care was followed.

Table 2 reports participants' demographic and anthropometric data. No differences were found between gender, age, and body mass index (BMI).

We found the ERAS protocol significantly improved post-operative recovery for patients requiring hepatectomy and pancreatectomy. Patients were mobilized earlier [Hepatectomy: mean 0.05 days (ERAS) versus mean 1.39 days (CON), p<0.001. Pancreatectomy: mean 0.09 days (ERAS) versus mean 1.23 days (CON), p<0.001] and progressed sooner to a normal diet [Hepatectomy: mean 3.62 days (ERAS) versus mean 6.76 days (CON), p<0.001. Pancreatectomy: mean 5.04 days (ERAS) versus mean 8.38 days (CON), p<0.001] (Table 3).

We observed the rate of complications (based on the Clavien-Dindo Classification) was to twice as high in patients who underwent hepatectomy in the CON group compared to those treated in ERAS group (40.9% versus 18.2%, p=0.002) and similar comparisons were found in patients receiving pancreatectomy (38.03% versus 15.95%, p=0.003) (Table 4). Also, the analgesia which was administrated to the patients of each group is presented in Table 5. On the day of the surgery, patients were administered analgesics according to clinical practice. Patients who underwent hepatectomy and pancreatectomy and followed the ERAS protocol received opioid medication.

The cost of patients' hospitalization included drugs, surgical instruments, as well as medical examinations, such as laboratory tests, medical and nursing care. Likewise, the anesthesiologist's costs are accounted for in the anesthesia and operating room costs presented in the stem and leaf plot. The cost of hospitalization for patients following ERAS programs was lower in comparison to patients in the CON group, in total. The total cost in euros for the ERAS group is, as mean (SD), 6299.53 (4157.08) and the CON group 7475.43 (3603.94) (U = 7640, p = 0.001).

Bi-variate Comparison between Cost of Hospitalization and Postoperative Recovery Parameters

The cost of hospitalization was correlated at the significance level of p = 0.01. Firstly, the cost was positively correlated with the length of postoperative days (rho = 0.26, p = 0.002) for patients who underwent pancreatectomy. Additionally, the cost of patients' hospitalization who have undergone hepatectomy was positively correlated with the total days of postoperative hospitalization (rho = 0.290, p 0.001).

DISCUSSION

This study observes and compares two different groups of patients surgically treated for pancreatoduodenectomy and hepatectomy and their cost effectiveness. It was a prospective randomized trial evaluating surgical outcomes, including early ambulation and the beginning of oral alimentation, together with the evaluation of hospitalization's total cost, focusing on pan-

creatoduodenectomized and hepatectomized oncological patients. The expected benefit of the ERAS protocol was to decrease the length of hospital stay as well as the time of returning to work and normal activity. According to the findings of this study, patients who followed the ERAS protocol had a faster postoperative recovery with fewer complications, fewer readmissions, and a shorter postoperative length of hospitalization.

In the present study, patients had liquid diet 6 hours after surgery, which was in contrast to the study of Zouros et al. where patients started to their liquid diet the 2nd postoperative day, [21] but was much earlier compared to researches such as Balzano et al. [22] Also, in Abu Hilal et al. research, patients had liquid diet on the 2nd postoperative day.[23] Patients who participated in our study started the assumption of a normal diet almost 3 days earlier without any side effects such as nausea or vomiting.

In the current study patients participated in ERAS protocol presented complications in 18.2% for patients underwent hepatectomy and 15.95% of patients underwent pancreatectomy. However, in the studies of Ratti et al. [24] and Qi et al. [25] the percentage of morbidity was higher (31.4% and 28,75%, respectively), whereas in the study of Chong et al. [26] postoperative morbidity was overall less frequent but not statistically significantly different in patients treated according to ERAS protocol (p=0.661), as in the current study for patients undergoing hepatectomy. In addition, the complication rates after pancreatoduodenectomy were lower in the study of Perinel et al. but it was not significant for the ERAS group (p=0.380). [27] The ERAS program provides early mobilization, early assumption of normal meals, without more complications. Also, our study showed that ERAS program was safe and efficient for patients who underwent HPB surgery. Patients returned to their quotidian lives much earlier.

Likewise, in our study, the length of postoperative hospitalization was reduced by at least 5 to 6 days in the ERAS group, as in other studies, for patients undergoing pancreatoduodenectomy. Kowalsky et al. has showed a reduction of postoperative stay,[28] while Wu et al. has showed that hospital stay was reduced from 11 to 7 days after hepatectomy.[29] The reduction of hospitalization days demonstrated fewer complications and lower costs for patients who followed the ERAS protocol.

In the current study the cost of hospitalization of the ERAS group was statistically significant different in relation to the CON group. In the study of Kowalsky et al., it was noted that hospitalization costs for the ERAS group were USD 20,362 versus 24,277, (p=0.001) compared to the CON group.[30-31] Meanwhile, Dai et al. observed that median total hospital cost was significantly decreased in the ERAS group (yoan79790.40 versus yoan 102982.8, p<0.001). [32] Furthermore, Jing et al. mentioned a mean total cost of hospitalization for the ERAS group 7835.05±1355.45 US dollars, p<0.001, after HPB surgery.[33] Also, many studies have shown that the implementation of ERAS programs has reduced the cost of hospitalization. In particular, in the study of Ovaere et al., the cost- effectiveness analysis revealed a significant reduction in postoperative costs in the clinical pathway €1912.2, p < 0.001, [34] as well as a total mean cost reduction of €3080 per patient after ERAS implementation, in the study of Joliet et al., after pancreatoduodenectomy. [35] The present study showed that ERAS protocols in HPB surgery was a cost- effective intervention, simultaneously reducing the economic burden of patient hospitalization after major abdominal surgery but future research is needed for rigorous cost- benefit analyses.

Limitations

It is important that limitations should be noted, since it was a single-center study and more results are needed to apply the ERAS programs to patients who are undergoing HPB surgery.

CONCLUSION

As a patient-centered approach, ERAS programs increase patients' engagement and adherence to the pathway of care, resulting in improved clinical outcomes. It is simultaneously efficient and safe for patients.

Since 2001, when the ERAS protocols were introduced to postoperative management, patients have yielded the best benefits. This study compared various parameters of the ERAS and CON perioperative protocols in oncological patients after HPB surgery. The findings of this study highlight the improvement of hospitalization conditions, in the form of safer care, fewer complications, and cost effectiveness, under the severe financial cri-

sis. In conclusion, the present study is a basis for further research. However, the implementation of ERAS protocols results in a great reduction in the cost of hospitalization in combination with improved postoperative parameters, introducing a new era in HPB surgery.

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ANNEX

Table 1. ERAS/CON protocols parameters applied to study's participants

ERAS/CON protocols parameters

Preoperatively

- Preoperative information about ERAS/CON protocol
- No pre-anesthetic medication
- No bowel preparation

ERAS protocol

Day of Surgery

- Mobilization 4 hours after operation
- Oral fluids intake (0.5 lt) 6 hours after operation
- Nasogastric tube removal as early as possible after surgery
- Administrating less opioid drug

1st Postoperative day

- Patient starts hydric diet (tea-soup-gelatin)
- Removal of urinary drainage
- Administrating paracetamol after evaluation with numeric Visual Analogue Scale (VAS) scale

2nd – 3rd Postoperative day

- Normal diet

4th -6th Postoperative day

CON protocol

Day of Surgery

- No mobilization scheme
- No oral application scheme
- Administrating opioid drug

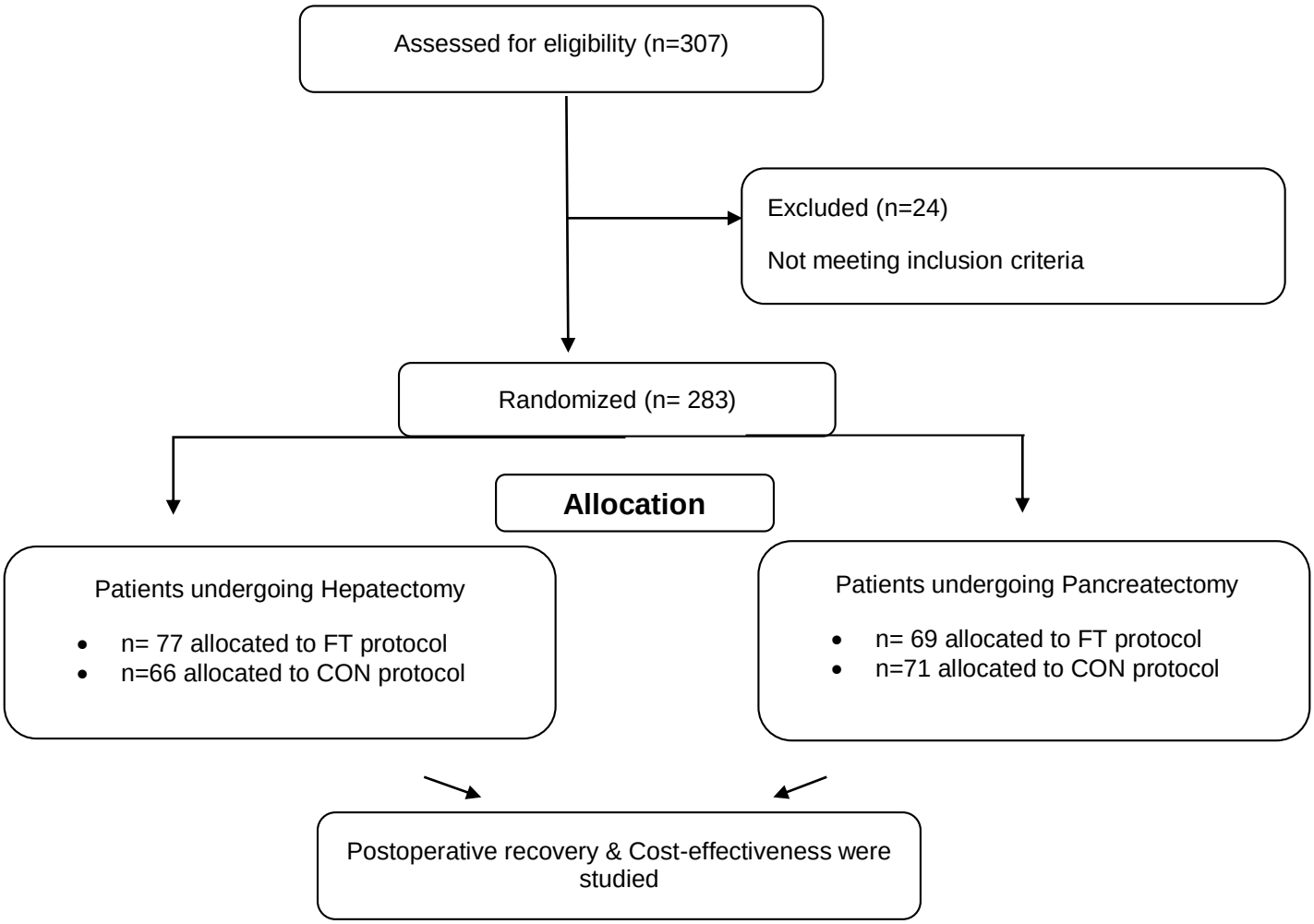
1st Postoperative day

- Oral intake after bowel mobilization
- Continue to administrate opioid drug after evaluation with numeric VAS scale
- Mobilization a after the 1st postoperative day

2nd – 3rd Postoperative day

- Evaluation bowel mobilization for oral intake

Figure. Flow-chart of patients' sample according CONSORT 2010



Stem & Leaf Plot of Patients' Total Cost of Hospitalization

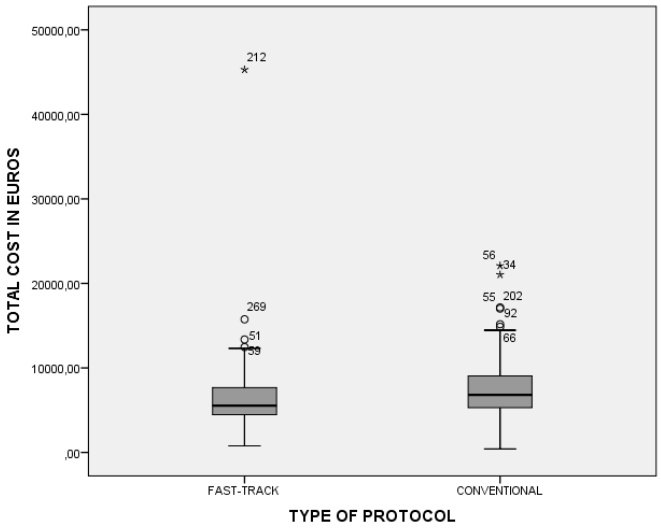


Table 2. Demographic Anthropometric and Clinical data of the participants.

	Hepatectomy			Pancreatectomy		
	Group ERAS (N=77)	**Group CON (N=66)**	**p-value**	**Group ERAS (N=69)**	**Group CON (N=71)**	**p-value**
Gender (N)			chi^2=0.11 p=0.736			chi^2=0.04 p=0.835
Male	41	37		42	42	
Female	36	29		27	29	
Age (yrs) mean(SD)	60.58(13.45)	62.98(11.5)	0.316	62.64(12.45)	66.1(10.95)	0.091
BMI mean(SD)	25.31(4.24)	26.11(5.23)	0.491	26.12(4.92)	25.65(4.72)	0.662
Body weight (kg) mean(SD)	70.53(15.19)	73.62(18.41)	0.45	74.12(18.33)	71.39(14.44)	0.522
Body height (cm) mean(SD)	166.26(9.17)	167.27(10.33)	0.69	167.59(10.44)	166.68(9.42)	0.782
Kind of surgery N(%)			chi^2=6.54, p=0.088			chi^2=4.53, p=0.339
Right hepatectomy	33(42.9)	16(24.2)				
Left hepatectomy	13(16.8)	15(22.7)				
Extended hepatectomy	12(15.6)	18(27.3)				
Segmental hepatectomy	19(24.7)	17(25.8)				
Whipple				51(73.9)	58(81.7)	
Total pancreatectomy				5(7.25)	3(4.22)	
Peripheral pancreatectomy				13(18.85)	10(14.08)	

Table 3. Patients' Postoperative Recovery Parameters and Cost expenses' results.

	Hepatectomy			**Pancreatectomy**		
Mean(SD)	**Group ERAS (N=77)**	**Group CON (N=66)**	**p-value**	**Group ERAS (n=69)**	**Group CON (N=71)**	**p-value**
Mobilization (days)	0.05(0.22)	1.39(1.7)	**<0.001**	0.09(0.332)	1.23(1.01)	**<0.001**
Diet (days)						**<0.001**
Clear liquids	0.27(0.83)	3.15(3.32)	**<0.001**	0.54(1.31)	3.73(2.58)	**<0.001**
Full liquid diet	2(1.25)	5(3.45)	**<0.001**	3.22(1.58)	5.94(4.27)	**<0.001**
Normal meal	3.62(1.33)	6.76(3.75)	**<0.001**	5.04(1.59)	8.38(5.27)	**<0.001**
Length of post-operative days (days)	5.13(1.71)	11.71(7.03)	**<0.001**	6.48(2.36)	11.44(7.19)	**<0.001**
Cost of postop-erative hospital-ization (euros)	6431.81(2787.1)	8448.49(4200.29)	**0.003**	6151.91(5303.4)	6570.9(2670.16)	**0.016**

Table 4. Patients' Complications (Clavien- Dindo classification)

	Hepatectomy			**Pancreatectomy**		
N (%)	**Group ERAS (N=77)**	**Group CON (N=66)**		**Group ERAS (n=69)**	**Group CON (N=71)**	
			chi^2=8.97 **p=0.002**			chi^2=8.33 **p=0.003**
No	63(81.8)	39(59.1)		58(84.05)	44(61.97)	
Yes	14(18.2)	27(40.9)		11(15.95)	26(38.03)	
I	-	-		1(1.45)	-	
II	11(14.28)	20(30.3)		8(11.6)	17(23.95)	
III	1(1.29)	1(1.51)		-	2(2.82)	
IV	2(2.59)	6(9.09)		2(2.9)	8(11.26)	

Table 5. Patients' Analgesia Medicine the day of the surgery

	Hepatectomy			**Pancreatectomy**		
N	**Group ERAS (N=77)**	**Group CON (N=66)**		**Group ERAS (n=69)**	**Group CON (N=71)**	
			chi^2=24.76 **p<0.001**			chi^2=8.33 **p=0.003**
No	2	3		5	1	
Epidural analgesia	2	0		3	2	
Morphine	25	27		18	17	
Pethidine	9	8		2	10	
Morphine + Paracetamol	9	8		21	25	
Pethidine + Paracetamol	19	13		10	7	
Morphine+ Parecoxibe	0	4		2	1	
Paracetamol	8	1		5	5	
Dextropropoxyphene Hydrochloride+ Paracetamol	9	8		3	2	
Dextropropoxyphene Hydrochloride+ Parecoxibe	1	0		-	-	