

Enhanced recovery after surgery (ERAS) protocols in patients undergoing radical cystectomy with ileal urinary diversions

A randomized controlled trial

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Abstract

Background: Enhanced Recovery After Surgery (ERAS) protocols were introduced in clinical practice to reduce complication rates and hospital stay. We performed a randomized controlled single center study to evaluate perioperative benefits of an adapted ERAS protocol in patients with bladder cancer who underwent radical cystectomy (RC) and ileal urinary diversions (IUD).

Materials and methods: Forty five from 90 consecutive randomized patients were enrolled in an adapted ERAS protocol. Length of stay, diet issues, return of bowel function, readmission rates and complications were examined.

Results: Among patients following ERAS protocol, we found a significant reduction in time to first flatus (1 vs 5 days, $P < .001$), time to first stool (2 vs 5 days, $P < .001$), time to normal diet (5 vs 6 days, $P < .001$) and length of stay (16 vs 18 days, $P < .001$). Also, postoperative ileus at less than 4 days was lower than in non-ERAS patients (15.6% vs 24.4%), but with a marginal trend toward significance ($P = .05$). Readmission rate was lower in the ERAS group, but the difference did not reach statistical significance. We also found a lower readmission and complication rate in patients with ERAS protocol (6.6% vs 11.1%, $P = .23$ and 46.6% vs 57.5%, $P = .29$, respectively).

Conclusions: Implementation of ERAS protocol for patients undergoing RC in our center was associated with a significant reduction in the time to the first flatus, time to the first stool, time to a normal diet, length of hospital stay.

Abbreviations: BMI = body mass index, ERAS = enhanced recovery after surgery, GT = naso-gastric tubing, IC = ileal conduit, ICU = intensive care unit, IQR = interquartile range, IUD = ileal urinary diversions, IV = intravenously, LMWH = low molecular weight heparin, NERAS = Non-ERAS group, ON = orthotopic neobladder, PI = povidone iodine, RC = radical cystectomy, BC = bladder cancer.

Keywords: complication rate, ERAS, hospital stay, radical cystectomy, readmission rate

Editor: Giandomenico Roviello.

All patients have been enrolled in the study after signing an informed consent. Study was approved by the hospital ethics board No.: 14862.

The authors have no potential conflict of interest to report.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Vlad O, Catalin B, Mihai H, Adrian P, Manuela O, Gener I, Ioanel S. Enhanced recovery after surgery (ERAS) protocols in patients undergoing radical cystectomy with ileal urinary diversions: a randomized controlled trial. *Medicine* 2020;99:27(e20902).

Received: 27 January 2020 / Received in final form: 14 May 2020 / Accepted: 15 May 2020

<http://dx.doi.org/10.1097/MD.00000000000020902>

1. Introduction

Even though radical cystectomy (RC) is the gold standard for muscle invasive bladder cancer (BC), the procedure is associated with an increased complication rate up to 60%, in some reports.^[1,2] It has been stated that RC is a safe procedure, with acceptable complication rates, even in the elderly, as long as experienced surgeons perform it. Even then, complication rates still remain increased in high-volume centers.^[3,4] Kehlet first implemented the perioperative program named generically "fast track", which was applied in colorectal surgery.^[5] Subsequently, it has been transformed into the standard of care in many general surgery centers, leading to a faster recovery after surgery, shorter hospital stay, lower complication rates, and decreased medical costs, compared to the standard perioperative protocols.^[6,7]

Taking over from general surgery, the ERAS Society is trying to standardize the protocol in urological surgery and mostly in RC patients due to the fact that the previous standard of perioperative measures, consisting of different types of bowel preparation, preoperative fasting, gastric decompression and post-operative bowel rest with long naso-gastric tubing (NGT) until bowel movement returns had a tendency to delay recovery in this type of patients.^[8]

Since Pruthi et al started implementing ERAS pathways in RC patients, there have been many studies that have tried to prove the efficacy of these programs, some of them having conflicting results.^[9-17] Regarding length of hospital stay, which is one of the most important outcomes after surgery, some reports showed that this issue was shorter when ERAS protocols were applied,^[9-11] but others showed the contrary.^[12-14] Similar, conflicting data concerning return of bowel movement^[11-13,15] and readmissions rates were reported.^[11-13,15-18] In an attempt to clarify and contribute with strong evidence in this field, we designed a randomized controlled single center study in which we compared 2 groups of patients, 1 with standard perioperative protocols and another one in which we implemented adapted ERAS protocols in RC patients undergoing ileal urinary diversions (IUD).

2. Material and methods

2.1. Study aim

The aim of our study was to evaluate the perioperative benefits of ERAS protocols implementation and complications in patients with BC who performed RC and IUD.

2.2. Study design

We performed a prospective, single center, randomized controlled trial on 90 consecutive patients with BC who had indication for RC and IUD. Between January and July 2017, 152

patients performed RC in our center. Exclusion criteria were: RC performed in an emergency setting; salvage RC, patients who refused ERAS. Ninety patients remained for randomization after the exclusion criteria was applied, the manner of randomization was 1:1, 45 patients adhered to ERAS group and 45 patients to a standard per operative protocol (Non-ERAS group-NERAS) (Fig. 1). The study was approved by the local ethical institutional board review (No. 14862) and all the patients have read and signed the informed consent. Length of stay, diet issues, return of bowel function, readmission rates, and complications were evaluated.

2.3. Protocols

2.3.1. Surgical technique. RC was performed transperitoneal in a classic manner and in most patients, in an antegrade fashion. Sometimes, a bilateral approach was used, depending on the surgeon experience (antegrade and retrograde). The technique consists of the removal of the bladder, prostate, and seminal vesicles in males and removal of bladder, uterus, and anterior vaginal wall in females. An extended lymph node dissection was performed in all cases. The ileal conduit (IC) was constructed in a classical manner and the ureters were implanted in a direct fashion. In orthotopic neobladder (ON) patients, most of our surgeons preferred a modified Camey II technique with a direct implantation of the ureters. In some patients, bilateral or unilateral nerve sparing procedures was also performed mostly in ON patients.

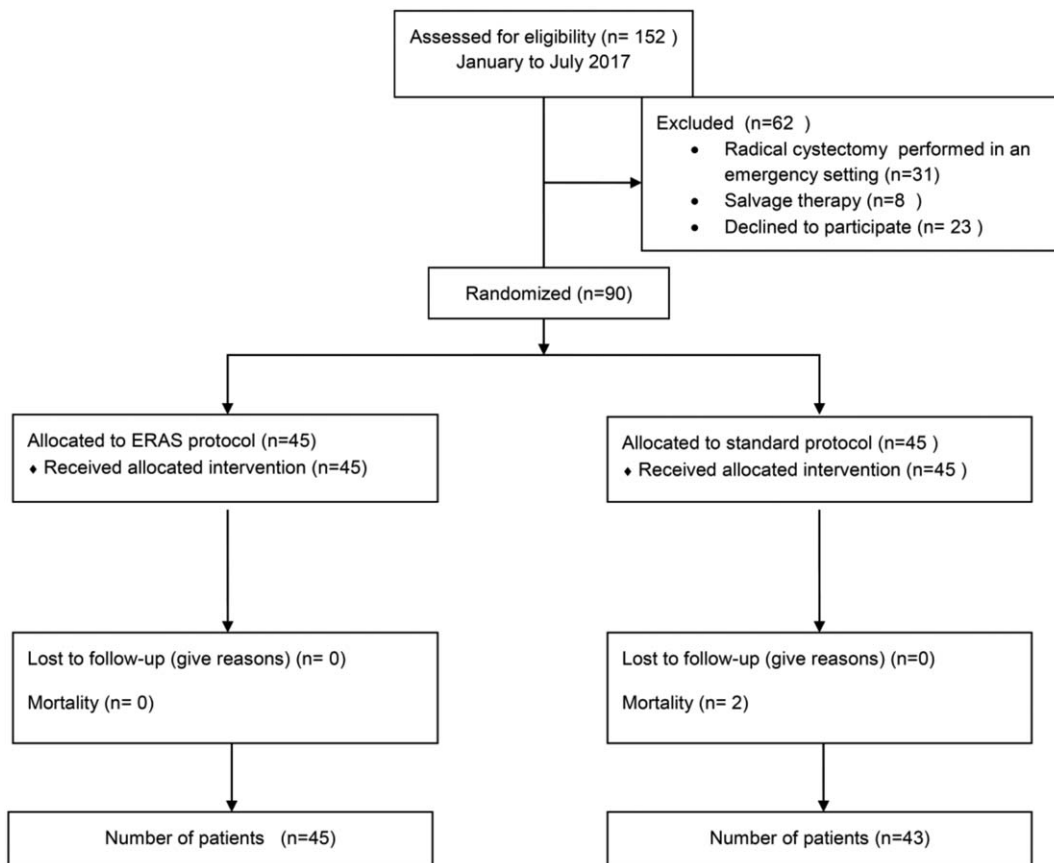


Figure 1. Randomization 1:1 was applied after exclusion criteria. ERAS-Enhanced recovery after surgery.

2.3.2. ERAS protocol. The ERAS protocol was adapted to the ERAS society recommendations and consisted of pre, intra, and post operative measures.^[8]

2.3.3. Preoperative measures. The preoperative measures consisted of: counseling and education, informing the patients about the procedure, stoma location, stoma prosthesis and care, advantages and disadvantages of ON, role of early mobilization, early nutrition, surgery, psychology, role of chewing gum, and magnesium tablets. Preoperative optimization included management of medical conditions, of comorbidities, anemia and nutritional support, counseling about smoking cessation, alcohol intake, physical exercise, and weight loss. NO oral mechanical bowel preparation was adapted to all of our patients, none received oral bowel solutions and 1 enema was performed in the morning of surgery. We used NO preoperative fasting, allowing a normal diet in the day before surgery with a 300g carbohydrate dinner, and an early morning liquid carbohydrate intake 2 to 3 hours before surgery. Pre-anesthesia medication was less based on long acting sedatives. Thoracic epidural analgesia was used in most of our patients. The antimicrobial prophylaxis was done with a single cephalosporin dose approximately 1 hour before surgery and the skin preparation was made using alcohol based solutions instead of normal povidone iodine (PI). The pulmonary thromboembolism prophylaxis was made with compression stockings also after surgery and patients received low molecular weight heparin (LMWH) up to 4 weeks.

2.3.4. Intraoperative measures. Fluid intake during surgery was limited to 1ml/kg/hour in order to lower bowel edema and minimize blood loss.

2.3.5. Postoperative measures. The nasogastric tube (NGT) was suppressed immediately after surgery in all patients.

In order to prevent ileus, chewing gum and magnesium chewable tablets were recommended after surgery. All patients have been instructed and helped to mobilize from the first day after surgery in the intensive care unit (ICU) and to stay seated at least 60% of the time. A liquid carbohydrate rich diet was started the first day after surgery and in patients with good compliance, a crushed solid diet was initiated the second or third day after surgery, in some cases even the first day in small amounts.

2.3.6. Non-ERAS (NERAS) protocol. In the NERAS group, a classical perioperative approach was implemented.

Preoperative measures consisted of a liquid diet and 12 hours fasting the day before surgery, an oral mechanical bowel preparation was performed in the day before surgery and all patients benefited from normal general anesthesia with endotracheal intubation and NGT. The NGT was kept in place normally at least 3 days or until return of bowel function. The liquid intake was normal during surgery. Intraoperative antimicrobial prophylaxis was made with cephalosporin before surgery and at least 7 to 10 days after surgery and skin preparation was made using PI. After surgery, patients received no fluids by oral intake; pain medication was administered intravenously (I.V.) using mostly non-opioid drugs. Mobilization was mostly started after pain relief from surgery, after at least 2 to 3 days. A normal diet was started after return of bowel movement.

2.4. Statistical analysis

Data were reported as percentages for binary variables, as mean and standard deviations for continuous normal distributed

variables and as median and interquartile range (IQR) for continuous skewed ones. To compare the variables Chi-Squared, *t* Student test and Mann–Whitney *U* were used. A statistically significant value of $P < .05$ was considered. Statistical analysis was made by SPSS IBM version 20 (Chicago, Illinois).

3. Results

3.1. Patient general data

The characteristics of the 90 patients were described in Table 1. The mean age was 62.6 ± 6.5 years, male was the dominant gender (87.7%) and the median body mass index (BMI) was 25 kg/m^2 (22.7–28.2). Regarding TNM (tumor-node-metastases) staging and tumor grading, most of the patients were pT3 and pT4 and 25.6% of them had grade 3 (G3) degree. Bricker urinary diversion was performed in 74.4% of patients. The median length of hospital stay was 17 days (16–19) and the readmission rate was 7.8%. At group comparison analysis between ERAS and NERAS protocol (Table 1) we found no statistical difference in terms of age, gender, BMI, TNM and grading, derivation type, operative time, preoperative hemoglobin, oral feeding intolerance, and readmission rate. In the ERAS group, we found a significant lower mean of postoperative hemoglobin level ($11.9 \pm 1.7 \text{ g/dl}$ vs 12.8 ± 2.2 , $P = .03$). Also in this group, there was a significant reduction in median time to first flatus (1 day vs 5 days, $P < .001$), first stool (2 vs 5 days, $P < .001$), time to reach a normal diet (5 vs 6 days, $P < .001$) and a significant reduction in median length of stay (16 vs 18 days, $P < .001$). American Society of Anesthesiology (ASA) score 2 was higher and postoperative ileus < 4 days was lower in ERAS group, but both showed a marginal trend toward significance ($P = .05$ and $P = .07$, respectively).

3.2. Complications

The complications rate and the Clavien complication grades were reported in Table 2. Regarding minor complications, altered mental status (11.1% vs 8.9%) and desaturation (11.1% vs 6.6%) were more frequent in the ERAS group, while postoperative ileus (31.1% vs 44.4%), nausea and vomiting (17.7% vs 24.4%), urinary tract infections (15.5% vs 17.8%), arrhythmias (4.4% vs 11.1%), clostridium difficile enterocolitis (6.7% vs 11.1%), and wound dehiscence (11.1% vs 13.3%) were more often in the NERAS group. As for major complications, the only 2 cases of pulmonary embolism were found in the ERAS group (2.2%) and death was found only in the NERAS group (2.2%). According to Clavien classification, grades 1 and 4 were described more often in the ERAS group (Fig. 2), but the overall complication rate was higher in the NERAS group (46.6% vs 57.7%). Comparison analysis showed only clinical significance and no statistical significance between all complications.

3.3. ERAS protocol implementation

The average compliance with the ERAS protocol in our patients was 79.1%. Analysis of the implementation of the various elements of the ERAS protocol is presented in Table 3. The most difficult measure to achieve was the optimization of medical conditions that was applied in only 35.5% of patients in the preoperative protocol. Also, in the preoperative period, counseling and education was implemented only in 73.3% of the patients. Regarding intraoperative compliance, 33 patients out of

Table 1
Patients general, pre, intra, and postoperative data.

Variables	Overall (n=90)	ERAS(n=45)	NERAS (n=45)	P values
Age (mean, yr)	62.6±6.5	62.1±6.2	63±6.7	.5
Gender (%)				.74
Female	12.20%	11.30%	13.30%	
Male	87.80%	88.90%	86.70%	
BMI (median, kg/m ²)	25 (22.7–28.2)	25 (23–27)	25 (22–29.5)	.88
Preoperative Hb (mean, g/dl)	14.9±1.4	14.7±1.5	15±1.2	.39
[0,1-5]ASA score (%)				
ASA 1	10%	4.40%	15.60%	.11
ASA 2	80%	86.70%	73.30%	.07
ASA 3	10%	8.90%	11.10%	.72
[0,1-5]TNM (%)				
pT1	18.90%	20%	17.80%	.78
pT2	34.40%	35.80%	33.30%	.82
pT3	35.60%	31.10%	40%	.37
pT4	11.10%	13.30%	8.90%	.5
[0,1-5]Grading (%)				
G1	35.60%	33.30%	37.80%	.66
G2	38.90%	44.40%	33.30%	.28
G3	25.60%	22.20%	28.90%	.46
Urinary diversion type (%)				.46
Bricker	74.40%	71.10%	77.80%	
ON	25.60%	28.90%	22.20%	
Surgery time (median, min)	324.5 (304–366.2)	322 (303–368.5)	331 (306.5–366)	.58
Postoperative Hb (mean, g/dl)	12.4±2	11.9±1.7	12.8±2.2	.03
Time to first flatus (median, d)	3 (1–5)	1 (1–2)	5 (3–6)	<.001
Time to first stool (median, d)	4 (2–6)	2 (2–3.5)	5 (4–7)	<.001
Time to normal diet (median,d)	5 (4–6.25)	5 (3–6)	6 (4–7)	<.001
Intolerance to oral feeding (%)	20%	15.60%	24.40%	.29
Postoperative ileus < 4d (%)	43.30%	33.30%	53.30%	.05
Length of hospital stay (median,d)	17 (16–19)	16 (15–17)	18 (16.5–21)	<.001
Readmissions (%)	7.80%	6.60%	11.10%	.23

n = number, ERAS = enhanced recovery after surgery, NERAS = non-ERAS, BMI = body mass index, ASA = American Society of Anesthesiology, TNM = tumor-node-metastasis, G = grade; Hb = hemoglobin.

45 (73.3%) adhered to fluid intake restriction to 1 ml/kg/hour. Postoperative protocol was difficult to achieve in terms of NGT remount (15%), early liquid diet (75.5%), and early solid diet (75.5%)

4. Discussion

Implementation of ERAS protocol resulted in reduction of length of hospital stay, complication, and readmission rate in general surgery, but in urological surgery the results from clinical trials are limited. Our study comes to establish the ERAS protocols in urological management of BC. We found a significant shorter time to first flatus in the ERAS group and this data is in line with the results from previous studies.^[9,13,19,20] Jensen et al reported a similar period of the bowel movement resumption.^[20] On the contrary, results reported by Smith et al^[12] showed a higher number of days (4–5 days) until first flatus was obtained in ERAS group, where patients had also underwent open procedures.

Regarding time to first stool, we observed a substantial difference between the 2 groups. Patients from ERAS group reached a 2 days median time to first stool, compared to 5 days for the NERAS patients ($P < .001$). A possible key role in obtaining an early bowel movement could be played by the use of chewing gum and magnesium tablets. Smith et al highlighted the importance of magnesium in lowering bowel inflammation subsequent to open surgery.^[11,21,22]

We also found a better time to a normal diet in the ERAS group. ERAS patients received oral fluids and crushed solids from postoperative day 1 compared to NERAS patients in which the NGT was kept in place normally for a mean of 3 days. From our experience, NGT removal immediately after surgery does not imply additional complications, patients usually have a good gastric tolerance, this resulting in an important difference between the 2 groups regarding intolerance to oral feeding only 15.6% in the ERAS group vs 24.4% in the NERAS.

Regarding length of stay, ERAS patients had a significantly lower period compared to NERAS patients (16 vs 18 days, $P < .001$). Similar results were found in series with open RC and robotic assisted RC when ERAS protocols were applied.^[13,15,19] Other authors reported a variable period of hospitalization in patients with ERAS protocol implementation, between 4 and 16 days.^[10,11,15,19,23,24]

Daneshmand et al found a median length of stay of 4 days for ERAS patients with open RC and Saar et al that obtained a median length of stay of 16 days for ERAS patients with robot-assisted RC. This large difference may appear varying from center to center due to the presence or absence of outpatient care which can sometimes be very helpful, patients being checked in domestically or over the phone in terms of drain monitoring, pain scores, wound healing status. We want to emphasize the fact that usually, in our department, patients are discharged when all drains and catheters are removed and patients are in optimal

Table 2
Complications in ERAS and non-ERAS group.

	ERAS	NERAS	P value
[0,1-4]Major complications			
Eviscerating	2 (4.4%)	3 (6.7%)	.60
Acute renal failure	0 (0%)	0 (0%)	–
Cardiac ischemia	1 (2.2%)	1 (2.2%)	1
Death	0 (0%)	2 (4.4%)	.15
Postoperative bleeding	0 (0%)	1 (2.2%)	.31
Pulmonary embolism	1 (2.2%)	0 (0%)	.31
Mechanical bowel obstruction	1 (2.2%)	1 (2.2%)	1
[0,1-4]Minor complications			
Postop Ileus	14 (31.1%)	20 (44.4%)	.19
Nausea/Vomiting	7 (17.7%)	11 (24.4%)	.43
Urinary tract infection	7 (15.5%)	8 (17.8%)	.77
Arrhythmias	2 (4.4%)	5 (11.1%)	.23
Atelectasis/desaturations	5 (11.1%)	3 (6.6%)	.45
Altered mental status	5 (11.1%)	4 (8.9%)	.72
Deep vein thrombosis	0 (0%)	0 (0%)	–
Urine leak	1 (2.2%)	1 (2.2%)	1
Clostridium difficile enterocolitis	3 (6.7%)	5 (11.1%)	.46
Pneumonia	2 (4.4%)	2 (4.4%)	1
Wound dehiscence	5 (11.1%)	6 (13.3%)	.75
Fever of unknown origin	6 (13.3%)	6 (13.3%)	1
[0,1-4]CLAVIEN complication grade			
Grade 1	5 (11.1%)	11 (24.4%)	.10
Grade 2	11 (24.4%)	9 (20%)	.61
Grade 3	3 (6.7%)	3 (6.7%)	1
Grade 4	2 (4.4%)	1 (2.2%)	.56
Grade 5	0 (0%)	2 (4.4%)	.15
Clavien overall	21 (46.6%)	26 (57.7%)	0.29

ERAS = enhanced recovery after surgery, NERAS = non-ERAS.

condition, outpatient care in our country not being frequently used. Osawa et al showed in a large study which included over 700 individuals with RC that a length of stay equal or less than 5 days was correlated with an increased risk of complications and

readmissions rates. Our overall readmission rate was 7.8% and 6.6% in the ERAS group, which is lower than in other studies. Smith et al reported a greater readmissions rate for ERAS patients, this imposing what we stated above.^[11]

In our study, postoperative hemoglobin level was lower in the ERAS group (11.9g/dl vs 12.8g/dl) but this did not lead to a higher rate of transfusion.

The average compliance with the ERAS protocol in our patients was 79.1%. The most difficult point of the program to carry out was represented by preoperative optimization of medical conditions that was implemented in 35.5% of the patients. This fact could be associated with a low compliance to stop smoking, lose weight, stop drinking, control their diabetes, and stick to their medication plan. Another point to be taken into consideration is represented by counseling and education which can be very challenging sometimes for the practitioner due to low patient education and reluctance to new things like epidural anesthesia, early mobilization and so on.

Another pathway that we tried to implement is the fluid intake restriction to 1 ml/kg/hour in an effort to reduce bleeding, bowel inflammation, liquid imbalance. We obtained it in a considerable amount of our subjects (73.3%) and in other patients the anesthesiologist considering it inappropriate to take in consideration, due to patient fragility and hydro-electrolytic imbalance before surgery. Early mobilization was also a challenge in implementing the ERAS pathway; the most difficult part was encountered in the ICU due to multiple drains, catheters and presence of epidural catheter, personnel compliance to new methods. Most of the patients were mobilized early (77.7%), meaning that in the first day after surgery they stood on the side of the bed, after they stood up, they were administered while being seated clear fluids and in the second part of the day crushed solids at will. NGT was suppressed right after surgery, but in 15.5% of cases was remounted due to heavy abdominal distension and pain.

In our institution a large number of RC are performed each year. Giving that we are a high volume center, we felt the need to

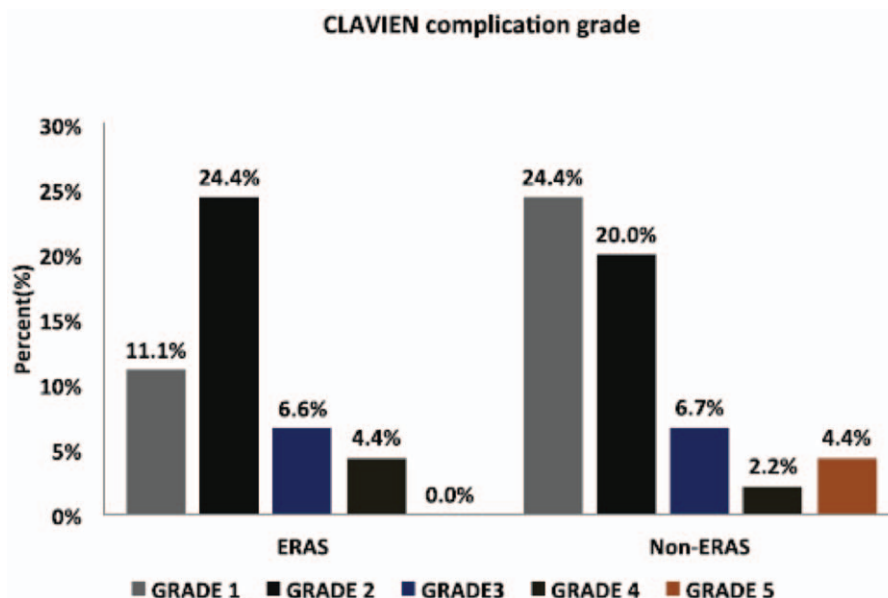


Figure 2. Postoperative complications were assessed using the Clavien classification system. Comparative analysis showed no significant statistical difference between ERAS and NERAS group (data shown in Table 2). ERAS = enhanced recovery after surgery, NERAS = non-ERAS.

Table 3
ERAS implementation protocol.

	ERAS items	N (%)
Preoperative	Counseling and education	33 (73.3%)
	Preoperative optimization of medical conditions	16 (35.5%)
	NO oral mechanical bowel preparation	45 (100%)
	Preoperative carbohydrates loading	41 (88.8%)
	NO preoperative fasting	45 (100%)
	Pre-anesthesia medication	41 (88.8%)
	Epidural analgesia	39 (86.6%)
	Antimicrobial prophylaxis and skin preparation	43 (95.5%)
	PE prophylaxis	42 (93.3%)
	Intraoperative	Fluid intake restriction to 1ml/kg/hour
Postoperative	NGT out	45 (100%)
	NGT remounted	7 (15.5%)
	Ileus prevention	39 (86.6%)
	Early mobilization	35 (77.7%)
	Liquid diet in number of days after surgery- Early diet	1 day after surgery- 34 (75.5%)
	Solid diet in number of days after surgery	2 days after surgery-34 (75.5%)
	Average ERAS compliance	79.1%

N= number, PE = pulmonary embolism, NGT = nasogastric tube.

improve perioperative care in an effort to reduce complications and thus hospital stay. After we started implementing randomly our ERAS program, we observed a better postoperative course for our patients.

Although our study has considerable advantages due to the fact that it was prospective and randomized controlled, it has several limitations: it was unicentric, and the number of patients was quite low.

5. Conclusion

In conclusion, we showed that the implementation of ERAS protocol in patients with BC who undertake RC with IUD, reduced significantly the time to the first flatus, time to the first stool, time to a normal diet, length of hospital stay, and was associated with a lower rate of complications.

Author contributions

The authors contributed equally to this manuscript. All authors read and approved the final paper.

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