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Adherence to the Enhanced Recovery After Surgery Protocol and Outcomes After Colorectal Cancer Surgery

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Objectives: To study the impact of different adherence levels to the enhanced recovery after surgery (ERAS) protocol and the effect of various ERAS elements on outcomes following major surgery.

Design: Single-center prospective cohort study before and after reinforcement of an ERAS protocol. Comparisons were made both between and across periods using multivariate logistic regression. All clinical data (114 variables) were prospectively recorded.

Setting: Ersta Hospital, Stockholm, Sweden.

Patients: Nine hundred fifty-three consecutive patients with colorectal cancer: 464 patients treated in 2002 to 2004 and 489 in 2005 to 2007.

Main Outcome Measures: The association between improved adherence to the ERAS protocol and the incidence of postoperative symptoms, complications, and length of stay following major colorectal cancer surgery was analyzed.

Results: Following an overall increase in preoperative and perioperative adherence to the ERAS protocol from 43.3% in 2002 to 2004 to 70.6% in 2005 to 2007, both postoperative complications (odds ratio, 0.73; 95% confidence interval, 0.55-0.98) and symptoms (odds ratio, 0.53; 95% confidence interval, 0.40-0.70) declined significantly. Restriction of intravenous fluid and use of a preoperative carbohydrate drink were major independent predictors. Across periods, the proportion of adverse postoperative outcomes (30-day morbidity, symptoms, and readmissions) was significantly reduced with increasing adherence to the ERAS protocol (>70%, >80%, and >90%) compared with low ERAS adherence (<50%).

Conclusion: Improved adherence to the standardized multimodal ERAS protocol is significantly associated with improved clinical outcomes following major colorectal cancer surgery, indicating a dose-response relationship.

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ALTHOUGH INTERVENTIONS within enhanced recovery after surgery (ERAS) or fast-track programs have been shown to improve postoperative recovery in colorectal surgery,[1-4] universal implementation has not yet occurred.[5] One reason could be that ERAS programs are considered complex and resource demanding.[6] Another is that the ERAS concept as such possibly appears elusive because the relative contribution of each intervention in the program remains uncertain. Nevertheless, some of the elements in the ERAS program, such as omission of routine bowel preparation for colonic resections, no routine use of postoperative drains, early removal of nasogastric tubes, and early feeding and mobilization, have already been incorporated in traditional care.[5,7] Recently, a modified fast-track protocol (RAPID) with only 4 interventions,[8] instead of 20 in the ERAS program,[9,10] was also presented.

Introducing ERAS protocols usually requires a major shift in clinical routines, and many units may have difficulties in making all these changes at once. The effect of the different perioperative ERAS interventions as well as the importance of adherence to the protocol in terms of clinical outcomes, such as postoperative symptoms, morbidity, and length of stay (LOS), remain unclear.

See Invited Critique at end of article

In this prospective cohort study, we assessed the effect of an ERAS protocol relaunch project on protocol adherence and clinical outcomes. The aim was to investigate the importance of protocol adherence and the influence of different ERAS components for clinical outcomes following colorectal cancer surgery.

METHODS

STUDY SUBJECTS

Ersta Hospital in Stockholm, Sweden, is one of the original centers in the European ERAS Study Group. The ERAS protocol for colon and rectal surgery of this collaborative group[9,10] was first implemented in 2002. Clinical data, including protocol adherence and clinical outcomes, have been prospectively captured in the Web-based international ERAS Database from the start.[11] At Ersta Hospital, all patients undergoing elective major colorectal surgery are consecutively included in the ERAS protocol, which has been the standard of care since 2002. Because of unsatisfactory compliance, the ERAS protocol was relaunched on March 1, 2005, to improve several aspects of the protocol itself and the adherence to the program. Preceding the relaunch, during autumn 2004, a site visit to the pioneering unit at Hvidovre Hospital, Hvidovre, Denmark, helped identify key areas of potential improvement. These improvements concerned a large number of details in the perioperative care protocol, as well as strategies to increase adherence (eTable, http://www.archsurg.com). All patients who underwent a colon and/or rectal cancer resection in the period from 2002 to 2004 (January 1, 2002, to February 28, 2005) and 2005 to 2007 (March 1, 2005, to December 31, 2007) were registered in the database and are included in the study. During these 2 periods, the surgical staff, consisting of 7 senior consultants, anesthetists, and nursing staff, has remained largely unchanged. The research protocol was approved by the ethics committee at the Karolinska Institutet and carried out in accordance with the 1989 World Medical Association Declaration of Helsinki.

STUDY DESIGN

All patients were treated according to a standardized ERAS protocol.[9] Key components in this protocol were thoracic epidural analgesia (activated before onset of surgery and discontinued on postoperative day 2-4), preoperative oral carbohydrate treatment (a carbohydrate-rich, clear beverage, Nutricia Preop [12.5 g/100 mL^{-1} carbohydrates, 12% monosaccharides, 12% disaccharides, 76% polysaccharides, 285 $mOsm/kg^{-1}$]; Numico, Zoetermeer, the Netherlands)[12] up until 2 hours prior to surgery, and avoidance of preoperative oral bowel preparation and perioperative fluid overloading. Early oral diet (4 hours after surgery) and early mobilization (2 hours out of bed on the day of surgery and then 6 hours daily) were also part of the protocol. Altogether, 114 variables, including 21 key ERAS adherence variables, were recorded. Clinical data, including extent of postoperative mobilization, symptoms delaying discharge, length of hospital stay (LOS), and 30-day morbidity and mortality, were prospectively captured in the ERAS Database.[11] Daily dietary intake and fluid/energy balance were recorded.[13] Patients were considered fit for discharge using the following discharge criteria: postoperative pain adequately controlled with oral analgesics (visual analog pain score <40 of 100), intravenous nutrition or fluids no longer needed, mobilization (out of bed ≥ 6 hours daily), return of bowel function (stool or repeated flatus), and no complications in need of treatment in the hospital. Complications were diagnosed following the Veterans Administration Total Parenteral Nutrition Trial definitions and classifications.[14] All patients were examined by a surgeon at Ersta Hospital 2 weeks after discharge and interviewed by a trained nurse on postoperative day 30 to register any late-occurring complications. The definition of postoperative symptoms was symptoms that were not part of a complication and that clearly caused prolonged LOS (unspecified fever, pain, fatigue, constipation, dizziness, or diarrhea).

DATA ANALYSIS

Altogether, 464 consecutive patients in the first period (2002-2004) and 489 consecutive patients in the second period (2005-2007) were included in the study. Adherence to the ERAS protocol was assessed among these 953 patients and analyzed with regard to postoperative outcomes, both between as well as across the 2 periods.

Results are presented as mean (standard deviation), median, odds ratio (OR), and 95% confidence interval (CI) when appropriate. A 2-tailed *t* test was used for crude group comparisons of continuous variables and multiple linear regressions, for adjusted comparisons. Crude associations between categorical variables were analyzed with χ^2 tests or the Fisher exact test, as appropriate. Baseline characteristics were analyzed to determine the univariate predictors of the different outcome variables: postoperative symptoms, LOS, and 30-day postoperative morbidity including infection rates. Multiple logistic regression was then used to assess the adjusted association between specific interventions and each outcome.

The adjustment variables were age, sex, body mass index, American Society of Anesthesiologists score, surgical interventions, and laparoscopic/open surgery. When calculating adherence to the 12 preoperative and perioperative (day 0, day of surgery) ERAS interventions, the cut offs for adherence to the continuous variables were set as follows: intravenous fluid, colon, peroperative 2000 mL + postoperative 1000 mL = 3000 mL and rectum, peroperative 2500 mL + postoperative 1000 mL = 3500 mL; per oral fluid, more than 0 mL; intravenous kilocalories, less than 200 kcal; and per oral kilocalories, more than 0 kcal.

Adherence was calculated as the number of interventions fulfilled/12 (total number of preoperative and perioperative interventions). When calculating impact on an outcome, preoperative and perioperative interventions were added in the multiple regression model using stepwise modeling including all variables with a P value $<.15$. A P value $<.05$ was considered statistically significant. All data were analyzed using Stata version 10.0 (StataCorp, College Station, Texas).

RESULTS

CHANGES IN BASELINE CHARACTERISTICS, TYPE OF SURGERY, AND ADHERENCE

First, to assess the impact of increased adherence to the ERAS protocol, baseline characteristics and type of surgery were compared between periods. The 464 consecutive patients treated in 2002 to 2004 were at lower anesthetic risk compared with the 489 operated on in 2005 to 2007 (American Society of Anesthesiologists score of 1: 21.6% vs 14.5%; $P=.007$; American Society of Anesthesiologists score of 3: 14.6% vs 19.7%; $P=.048$). Another significant difference was a small increase in the proportion of patients operated on laparoscopically (**Table 1**).

A smaller proportion of both low anterior resection and Hartmann operations were performed in the second period compared with the first period, which in turn had a lower proportion of abdominoperineal resections ($P<.05$). Fewer patients underwent pelvic surgery in the second vs the first period (40.5% vs 47.6%; $P=.03$) (Table 1). In both periods, the surgical procedure with the highest rate of complications was abdominoperineal resection (46% vs 58.1% in the second and first periods, respectively).

Table 1. Patient Characteristics

	No. (%)		
	2002-2004 (n=464)	2005-2007 (n=489)	*P* Value
Age, mean (SD), y	69.3 (11.9)	69.0 (11.6)	.77[a]
BMI, mean (SD)	25.4 (4.3)	25.2 (4.4)	.60[a]
Male/female	231/233	237/252	.68[b]
ASA score, %			
1	21.6	14.5	.007[b]
2	63.1	64.4	.69[b]
3	14.6	19.7	.048[b]
4	0.7	1.4	.33[c]
Colorectal cancer	464 (100)	489 (100)	
Dukes stage C/D	192 (41.4)	191 (39.1)	.39[b]
Preoperative radiation	141 (30.4)	126 (25.8)	.11[b]
Complex group[d]	68 (14.7)	65 (13.3)	.52[b]
Laparoscopic surgery[b]	6 (1)	23 (5)	.002[c]
Peroperative bleeding, mean (SD), mL	363 (409)	366 (448)	.91[a]
Surgical procedure			
Right hemicolectomy	97 (21)	137 (28)	
Sigmoid resection	31 (7)	20 (4)	
Left hemicolectomy	23 (5)	39 (8)	
Anterior resection (10 cm above anus)	61 (13)	77 (16)	
Anterior resection (10 cm below anus)	128 (28)	89 (18)	
Abdominoperineal resection	49 (11)	94 (19)	
Hartmann operation	46 (10)	26 (5)	
Other	29 (6)	7 (1)	

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).
[a] Two-tailed *t* test.
[b] Pearson χ^2 test.
[c] Fisher exact test.
[d] The complex group refers to patients with additional intraoperative procedures (for example, small-bowel resection).

Table 2. Protocol Compliance

	No./Total No.[a] (%)		*P* Value
	2002-2004	2005-2007	
Preoperative compliance			
Preadmission counselling[b]	361/454 (79.5)	465/487 (95.5)	<.001[c]
Carbohydrate drink[b]	200/398 (50.3)	311/465 (66.9)	<.001[c]
Without bowel preparation[b]	66/446 (14.8)	322/481 (66.9)	<.001[c]
Without premedication[b]	100/463 (21.6)	289/486 (59.5)	<.001[c]
Active warming[b,d]	229/372 (61.6)	428/439 (97.5)	<.001[c]
EDA	446/464 (96.1)	475/487 (97.5)	.22[c]
Perioperative compliance			
Intravenous fluid day 0, mean (SD), mL[b]	5220 (1560)	3820 (1210)	<.001[e]
Per oral fluid day 0, mean (SD), mL[b]	550 (560)	790 (570)	<.001[e]
Intravenous kcal day 0, mean (SD), mL[b]	398 (193)	204 (159)	<.001[e]
Per oral kcal day 0, mean (SD), mL[b]	122 (308)	299 (379)	<.001[e]
Out of bed day 0, 2 h[b]	166/406 (40.9)	222/459 (48.4)	.03[c]
Oral nutrition supplements day 0[b]	51/413 (12.3)	271/476 (56.9)	<.001[c]
Postoperative compliance			
Intravenous fluid day 1-3, mean (SD), mL	2640 (2970)	2090 (2640)	.02[f]
EDA catheter removal, mean (SD), d	3.8 (2.4)	3.9 (2.5)	.31[f]
Urinary catheter removal, mean (SD), d	4.7 (3.8)	4.7 (3.6)	.49[f]
Per oral fluid day 1-3, mean (SD), mL	4320 (2330)	5220 (1990)	<.001[f]
Out of bed day 1, 6 h	61/260 (23.5)	111/404 (27.5)	.29[f]
Oral nutrition supplements day 1	85/433 (19.6)	276/485 (56.9)	<.001[f]
Solid food day 1	387/459 (84.3)	438/484 (90.5)	.008[f]
Without drip infusion day 1	150/457 (32.8)	286/485 (59.0)	<.001[f]
Contact with nurse day 7	304/416 (73.1)	466/486 (95.9)	<.001[f]

Abbreviations: EDA, epidural anesthesia; ERAS, enhanced recovery after surgery.
[a] The denominator represents values recorded in the database.
[b] The 12 ERAS interventions used in calculations of overall mean adherence.
[c] Pearson χ^2 test.
[d] By Bair Hugger; Arizant Healthcare, Eden Prairie, Minnesota.
[e] Two-tailed *t* test.
[f] Multiple linear and logistic regression adjusted for age, sex, American Society of Anesthesiologists score, body mass index, type of operation, and laparoscopic surgery.

Overall, the mean preoperative and perioperative (day 0) adherence to the 12 specific elements of the ERAS protocol increased from 43.3% among patients undergoing colorectal surgery in 2002 to 2004 to 70.6% in 2005 to 2007 ($P<.001$). Adherence to most of the postoperative intervention parameters also improved significantly (**Table 2**).

POSTOPERATIVE OUTCOMES BETWEEN PERIODS

Following an overall increase in mean preoperative and perioperative adherence to the ERAS protocol from 43.3% to 70.6% between study periods, the number of patients with at least 1 complication declined from 203 (43.8%) in 2002 to 2004 to 165 (33.7%) in 2005 to 2007 and the number of patients with symptoms delaying discharge also declined from 307 (66.2%) to 247 (50.5%) (**Figure 1** and **Figure 2**). Thus, a 27% increase in overall adherence to the ERAS protocol was associated with a 27% reduction in relative risk of any 30-day postoperative morbidity (OR, 0.73; 95% CI, 0.55-0.98) and a 47% reduction in relative risk of symptoms delaying discharge (OR, 0.53; 95% CI, 0.40-0.70), adjusting for confounding. Although the median LOS went from 7 days to 6 days with higher adherence to the ERAS protocol, this was not statistically significant ($P=.14$). However, the proportion of patients with LOS within the clinic target for abdominoperineal resections (<7 days) increased significantly from 35.4% to 46.8% (OR, 2.34; 95% CI, 1.01-5.38) between the first and second periods (adjusted for confounding) (Figure 1). The difference in proportion of patients with LOS within the clinic targets for colonic surgery (<3 days) (9.0% vs 12.7%) and low anterior resection (<5 days) (17.4% vs 22.7%) was not significant. No significant difference was found in the proportion of reoperations (10.6% vs 8.8%), readmissions (10.6% vs 10.2%), or 30-day mortality (1.3% vs 1.2%) between the first and second periods, respectively.

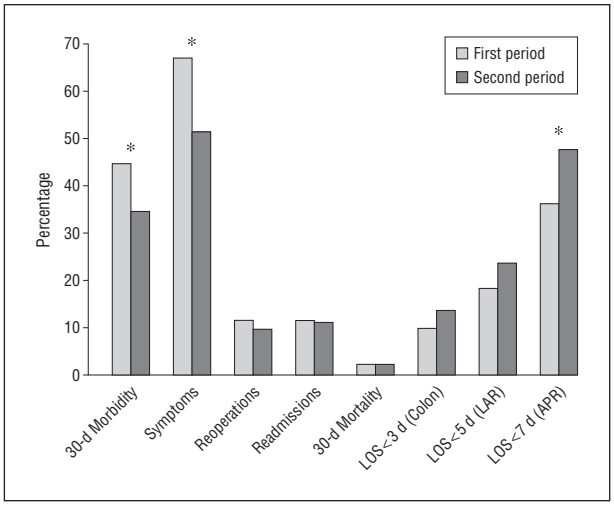

Figure 1. Postoperative outcomes. APR indicates abdominoperineal resection; LAR, low anterior resection; LOS, length of stay. *Statistically significant at $P<.05$.

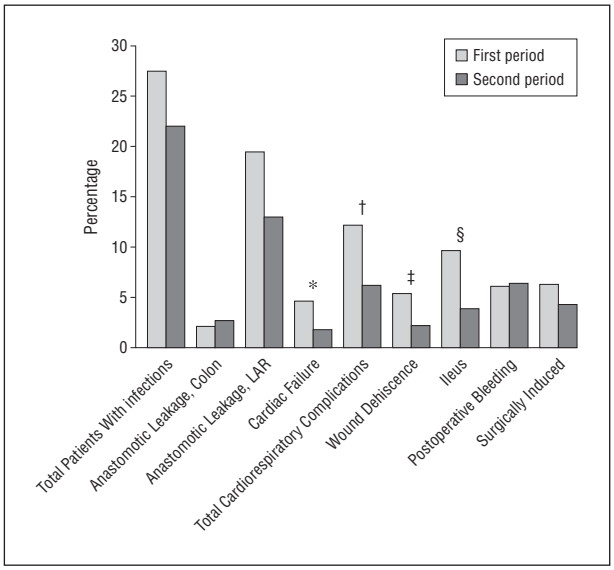

Figure 2. Postoperative complications in 2002 to 2004 (first period) vs 2005 to 2007 (second period). LAR indicates low anterior resection. *Odds ratio (OR), 0.34; 95% confidence interval (CI), 0.13-0.88; $P=.03$. †OR, 0.52; 95% CI, 0.31-0.87; $P=.01$. ‡OR, 0.31; 95% CI, 0.12-0.80; $P=.02$. §OR, 0.40; 95% CI, 0.21-0.76; $P=.005$.

POSTOPERATIVE OUTCOMES ACROSS PERIODS

The effect of overall adherence to the ERAS protocol, regardless of period, was also analyzed comparing patients with an overall adherence of more than 90% (n=76), more than 80% (n=183), and more than 70% (n=284) with patients with a low overall adherence less than 50% (n=333). Across periods, the proportions of patients with symptoms delaying discharge and 30-day morbidity were significantly reduced with higher levels of ERAS adherence using multivariate logistic regression adjusting for age, sex, American Society of Anesthesiologists score, body mass index, type of operation, and laparoscopic surgery (**Figure 3**). The ORs for postoperative symptoms were 0.35 (95% CI, 0.25-0.51), 0.34 (95% CI, 0.22-0.52), and 0.31 (95% CI, 0.17-0.55) with more than 70%, more than 80%, and more than 90% adherence, respectively. The ORs for 30-day morbidity were 0.62 (95% CI, 0.43-0.89), 0.57 (95% CI, 0.37-0.89), and 0.33 (95% CI, 0.16-0.66) with more than 70%, more than 80%, and more than 90% adherence, respectively, and the ORs for readmissions were 0.36 (95% CI, 0.17-0.76), 0.38 (95% CI, 0.15-0.95), and 0.16 (95% CI, 0.02-1.19) with more than 70%, more than 80%, and more than 90% adherence, respectively, vs less than 50% adherence.

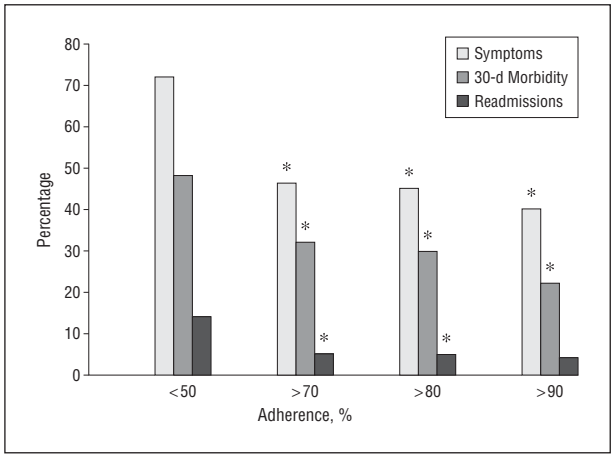

Figure 3. Association between adherence to the enhanced recovery after surgery protocol and postoperative outcomes. *Statistically significant at $P<.05$.

In univariate analysis, mean LOS was significantly shorter in patients with high ERAS protocol adherence (>70%, 7.4 days; $P<.001$; >80%, 7.0 days; $P<.001$; and >90%, 6.0 days; $P<.001$) compared with patients with low adherence (<50%, 9.4 days). Multiple regression revealed a significant difference in LOS among patients with adherence more than 90% ($P<.03$) vs less than 50% adherence, while the difference among patients with adherence more than 70% ($P=.07$) and more than 80% ($P=.08$) was borderline significant.

THE IMPACT OF SINGLE ERAS ELEMENTS

The effect of each intervention on postoperative symptoms, complications, and LOS was analyzed across periods. Multiple regression analysis adjusted for basic characteristics and other protocol interventions revealed that perioperative intravenous fluid management (intravenous day 0=day of surgery) (Table 2) and receiving a preoperative carbohydrate drink were major independent predictors of postoperative outcomes. The amount of fluids given the day of surgery was concurrently associated with preoperative oral bowel preparation. Patients receiving bowel preparation had a mean amount of 1000 mL of additional fluids given during the day of surgery (OR, 1.33; 95% CI, 1.14-1.54) while patients given preoperative carbohydrates received a mean 450 mL less fluids on average (OR, 0.75; 95% CI, 0.66-0.87). For each additional liter of fluids given during the day of operation, the risk of postoperative symptoms delaying recovery increased by 16% (OR, 1.16; 95% CI, 1.02-1.31) and the probability of postoperative complications increased by 32% (OR, 1.32; 95% CI, 1.17-1.50). In particular, fluid overload in-

creased the risk of cardiorespiratory complications (OR, 1.20; 95% CI, 1.10-1.31). If patients were treated with preoperative carbohydrates, the risk of postoperative symptoms was reduced by 44% (OR, 0.56; 95% CI, 0.40-0.77). In particular, preoperative carbohydrates significantly reduced the risk of postoperative nausea and vomiting, pain, diarrhea, and dizziness. Also, the risk of postoperative wound dehiscence was reduced by the preoperative carbohydrate drink (OR, 0.16; 95% CI, 0.05-0.50). Most of the other preoperative and perioperative ERAS interventions had a positive effect on the different outcome parameters, but the majority did not retain statistical significance in multivariate analyses adjusting for confounding.

COMMENT

In this large prospective observational study of more than 900 consecutive patients undergoing major surgery for colorectal cancer within an ERAS program, we found an association between improved protocol adherence and improved postoperative outcomes. Patients with high adherence to the ERAS protocol had a 25% lower risk of postoperative complications and nearly 50% lower risk of postoperative symptoms delaying discharge. They also had a higher tendency toward reaching LOS within the target limits compared with patients operated on under less optimal ERAS protocol adherence. Overall, there was a strong indication of a dose-response relationship between enhanced adherence to the protocol (>70%, >80%, and >90% compared with <50%) and improved surgical outcomes, reducing the relative risk for postoperative symptoms delaying discharge, 30-day morbidity, and readmissions between 38% and 69%. Nearly all preoperative and peroperative ERAS interventions influenced postoperative outcomes beneficially, but intravenous fluid management and intake of a preoperative carbohydrate drink were the major independent predictors.

It is possible, although unlikely, that factors other than improved adherence to the ERAS protocol could explain the observed differences in outcomes between periods. However, the turnover of surgical staff was minimal between periods. Second, although the mix of surgical procedures and the frequency of laparoscopy differed slightly between periods, the proportions of patients who underwent pelvic and laparoscopic surgery were adjusted for in the multivariate analysis. Also, because abdominoperineal resection, the procedure with the highest morbidity and longest recovery, was more frequent in the late study period, this would reduce the observed improvement in outcomes over time. However, the strongest argument for an independent association between overall adherence to the ERAS protocol and improved clinical outcomes is the indication of a dose-response relationship between level of adherence and postoperative morbidity, independent of study period.

The main explanation for the apparently high overall morbidity is that both major and minor complications were prospectively recorded, the patients were relatively old, and a large proportion underwent major pelvic surgery.

Several studies have demonstrated that the ERAS protocol is associated with earlier recovery and discharge after colonic resection,[15-22] while the recovery benefits following pelvic surgery remain uncertain.[20,23,24] It has not previously been convincingly shown that an ERAS protocol reduces postoperative complications after colorectal surgery, although 2 systematic reviews and 2 smaller uncontrolled studies[1,2,18,24] indicate a decline in surgical morbidity. It was recently found that a modest improvement in ERAS protocol adherence does not improve postoperative outcome,[25] but the present study shows a decline not only in complication rates and postoperative symptoms delaying recovery but also a shorter LOS following enhanced protocol adherence.

The ERAS protocol includes approximately 20 evidence-based care elements aimed at reducing surgical stress and postoperative catabolism.[9,10] We prospectively audited 21 index elements to assess protocol adherence, 18 of which were significantly improved after the program relaunch. Randomized studies on the importance of the different ERAS components are lacking and evaluating the impact of each single intervention is cumbersome since they influence each other, confounding interpretation. However, in the present study, most of the ERAS elements were found to significantly improve outcome parameters in univariate analysis but failed to do so after adjustment for confounding in the subsequent multivariate analysis where only 2 factors remained independent predictors: perioperative intravenous fluid management and preoperative carbohydrate treatment. Preoperative carbohydrate loading to avoid preoperative fasting reduces postoperative insulin resistance by approximately 50%[26] and attenuates postoperative nitrogen losses, lean body mass, and impairment of muscle function.[27-29] The carbohydrate drink, in addition to its metabolic effect, improves patient well-being (thirst, hunger, and anxiety) preoperatively.[30] We found that a carbohydrate drink not only reduced the need for perioperative intravenous treatment but also lowered the risk of postoperative symptoms delaying discharge by 44%. Moreover, fluid overloading in patients also played a major role, increasing the risk of postoperative complications by 32% for each additional liter of perioperative intravenous fluid administered. This is in line with previous reports of deleterious effects of fluid overload,[31,32] but our data show that controlling intravenous fluids is important even within an ERAS setting.

Despite the fact that the more complex multimodal ERAS programs repeatedly have been found to improve recovery after major surgery, old traditions prevail. Hoping to reach the same results with less effort, some clinics select a few components of the ERAS program and incorporate these into traditional care.[8,10] The RAPID protocol[8] is an example of a modified fast-track protocol where most of the enhanced recovery interventions are omitted. Using only 4 intervention arms (removal of tubes, ambulation, analgesia, and diet introduction), the protocol resulted in enhanced recovery after surgery. However, the target of removal of intravenous fluids on postoperative day 2, ambulation of more than 100 m on postoperative day 2, a patient-controlled analgesia pump instead of epidural anesthesia, and introduction of diet on postopera-

tive day 2 is a clinical pathway that differs from the multimodal pathway previously described by the ERAS Study Group.[10] As the enhanced recovery field develops, certain interventions may turn out to be nonessential. However, before omitting specific components in the protocol, such a decision should be based on a closer understanding of the importance of each element in the program. This study has shown that adherence to the ERAS protocol as a whole results in improved outcomes and identified some elements of the protocol as being more crucial than others. However, our findings reflect the specific circumstances that prevailed during the study and do not contradict that it may be the combination of each of the different elements that makes an effective regimen rather than the single element on its own. This may also be worth considering when implementing the ERAS protocol in other abdominal surgical procedures.[33,34]

In conclusion, better adherence to the elements of the ERAS protocol is crucial to improve surgical outcome. In this study in particular, restricted perioperative intravenous fluid management and a preoperative carbohydrate drink were found to be of specific importance for beneficial outcomes.

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Online-Only Material: The eTable is available at http://www.archsurg.com.
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REFERENCES

1. Varadhan KK, Neal KR, Dejong CH, Fearon KC, Ljungqvist O, Lobo DN. The Enhanced Recovery After Surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: a meta-analysis of randomized controlled trials. *Clin Nutr*. 2010;29(4):434-440.
2. Wind J, Polle SW, Fung Kon Jin PH, et al; Laparoscopy and/or Fast Track Multimodal Management Versus Standard Care (LAFA) Study Group; Enhanced Recovery after Surgery (ERAS) Group. Systematic review of enhanced recovery programmes in colonic surgery. *Br J Surg*. 2006;93(7):800-809.
3. Kehlet H, Wilmore DW. Evidence-based surgical care and the evolution of fast-track surgery. *Ann Surg*. 2008;248(2):189-198.
4. Eskicioglu C, Forbes SS, Aarts MA, Okrainec A, McLeod RS. Enhanced Recovery After Surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. *J Gastrointest Surg*. 2009;13(12):2321-2329.
5. Lassen K, Hannemann P, Ljungqvist O, et al; Enhanced Recovery After Surgery Group. Patterns in current perioperative practice: survey of colorectal surgeons in five northern European countries. *BMJ*. 2005;330(7505):1420-1421.
6. Polle SW, Wind J, Fuhring JW, Hofland J, Gouma DJ, Bemelman WA. Implementation of a fast-track perioperative care program: what are the difficulties? *Dig Surg*. 2007;24(6):441-449.
7. Arsalani-Zadeh R, Ullah S, Khan S, Macfie J. Current pattern of perioperative practice in elective colorectal surgery: a questionnaire survey of ACPGBI members. *Int J Surg*. 2010;8(4):294-298.
8. Lloyd GM, Kirby R, Hemingway DM, Keane FB, Miller AS, Neary P. The RAPID protocol enhances patient recovery after both laparoscopic and open colorectal resections. *Surg Endosc*. 2010;24(6):1434-1439.
9. Fearon KC, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005;24(3):466-477.
10. Lassen K, Soop M, Nygren J, et al; Enhanced Recovery After Surgery (ERAS) Group. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg*. 2009;144(10):961-969.
11. Maessen J, Dejong CH, Hausel J, et al. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. *Br J Surg*. 2007;94(2):224-231.
12. Nygren J, Thorell A, Jacobsson H, et al. Preoperative gastric emptying: effects of anxiety and oral carbohydrate administration. *Ann Surg*. 1995;222(6):728-734.

13. Olin AO, Osterberg P, Hådell K, Armyr I, Jerström S, Ljungqvist O. Energy-enriched hospital food to improve energy intake in elderly patients. *JPEN J Parenter Enteral Nutr*. 1996;20(2):93-97.
14. Buzby GP, Knox LS, Crosby LO, et al. Study protocol: a randomized clinical trial of total parenteral nutrition in malnourished surgical patients. *Am J Clin Nutr*. 1988;47(2)(suppl):366-381.
15. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. *Am J Surg*. 2002;183(6):630-641.
16. Basse L, Hjort Jakobsen D, Billesbølle P, Werner M, Kehlet H. A clinical pathway to accelerate recovery after colonic resection. *Ann Surg*. 2000;232(1):51-57.
17. Basse L, Raskov HH, Hjort Jakobsen D, et al. Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition. *Br J Surg*. 2002;89(4):446-453.
18. Basse L, Thorbøl JE, Løssl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. *Dis Colon Rectum*. 2004;47(3):271-277, discussion 277-278.
19. Stephen AE, Berger DL. Shortened length of stay and hospital cost reduction with implementation of an accelerated clinical care pathway after elective colon resection. *Surgery*. 2003;133(3):277-282.
20. Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH. 'Fast track' postoperative management protocol for patients with high comorbidity undergoing complex abdominal and pelvic colorectal surgery. *Br J Surg*. 2001;88(11):1533-1538.
21. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg*. 2003;90(12):1497-1504.
22. DiFronzo LA, Yamin N, Patel K, O'Connell TX. Benefits of early feeding and early hospital discharge in elderly patients undergoing open colon resection. *J Am Coll Surg*. 2003;197(5):747-752.
23. Schwenk W, Neudecker J, Raue W, Haase O, Müller JM. "Fast-track" rehabilitation after rectal cancer resection. *Int J Colorectal Dis*. 2006;21(6):547-553.
24. Nygren J, Soop M, Thorell A, Hausel J, Ljungqvist O; ERAS Group. An enhanced-recovery protocol improves outcome after colorectal resection already during the first year: a single-center experience in 168 consecutive patients. *Dis Colon Rectum*. 2009;52(5):978-985.
25. Ahmed J, Khan S, Gatt M, Kallam R, MacFie J. Compliance with enhanced recovery programmes in elective colorectal surgery. *Br J Surg*. 2010;97(5):754-758.
26. Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate postoperative insulin resistance. *Am J Physiol Endocrinol Metab*. 2001;280(4):E576-E583.
27. Crowe PJ, Dennison A, Royle GT. The effect of pre-operative glucose loading on postoperative nitrogen metabolism. *Br J Surg*. 1984;71(8):635-637.
28. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively: a randomised clinical trial. *Clin Nutr*. 2005;24(1):32-37.
29. Svanfeldt M, Thorell A, Hausel J, et al. Randomized clinical trial of the effect of preoperative oral carbohydrate treatment on postoperative whole-body protein and glucose kinetics. *Br J Surg*. 2007;94(11):1342-1350.
30. Hausel J, Nygren J, Lagerkranser M, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. *Anesth Analg*. 2001;93(5):1344-1350.
31. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet*. 2002;359(9320):1812-1818.
32. Brandstrup B, Tønnesen H, Beier-Holgersen R, et al; Danish Study Group on Perioperative Fluid Therapy. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens. a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5):641-648.
33. Borendal Wodlin N, Nilsson L, Kjølhede P; for the GASPI study group. The impact of mode of anaesthesia on postoperative recovery from fast-track abdominal hysterectomy: a randomised clinical trial [published online September 14, 2010]. *BJOG*. doi:10.1111/j.1471-0528.2010.02697.x.
34. Lassen K, Kjaeve J, Fetveit T, et al. Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. *Ann Surg*. 2008;247(5):721-729.

INVITED CRITIQUE

Enhanced Recovery Programs

Major Benefits Demonstrated Again

On its face, the ERAS program is a combination of simple, low-risk interventions that, when used in an integrated approach, can reduce LOS and major complications. The benefits have been proven in multiple studies, mostly from Europe, on colorectal surgery patients, not limited to patients with cancer. Gustafsson et al contribute additional information on a large number of patients who underwent resection of colorectal cancers. The data compare an earlier phase (2002-2005) during which ERAS was poorly implemented with a more recent phase (2005-2007) during which more substantial efforts achieved significantly higher compliance with the protocol. Fewer major complications, fewer debilitating postoperative symptoms, and more frequent discharges within LOS targets were seen during the more recent phase of practice and in patients with better compliance with ERAS components. Causality can be questioned since patients who have major complications are ill and less likely to participate in various postoperative ERAS activities such as ambulation and early refeeding. However, multivariable analysis showed 2 early interventions in the process of surgery and recovery to be independent predictors of postoperative outcomes: preoperative carbohydrate loading and perioperative fluid restriction.

The ERAS programs are not known to be widely adopted in the United States. An ERAS program requires a multidisciplinary collaboration between surgeons, anesthesiologists, and nurses. Preoperative carbohydrate loading involves oral intake up until 2 hours prior to induction, which may not be accepted among anesthesiologists. Limiting fluid administration during surgery is also primarily under control of the anesthesiologist. Nearly all ERAS programs include a preoperative education session to promote patient participation in postoperative components of the proto-