

Randomized Controlled Trial of Extended Perioperative Counseling in Enhanced Recovery After Colorectal Surgery

Running head: Counseling and colorectal surgery

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HMF, CE, and FP initiated the study and were the principle investigators. HMF, CE, and AR coordinated the study activities. AR and HMF collected all data. HMF analyzed all data and designed the figures. HMF, CE, FP, AR, JMT and HK were actively involved in the study design. HMF, CE, FP, AR, JMT and HK as the writing team were responsible for the interpretation of data and the writing of the manuscript. All authors reviewed and commented on a draft version of the final report and gave the approval for publication.

Benign colorectal disease

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ABSTRACT

BACKGROUND: Enhanced recovery after surgery program reduce the length of hospital stay in patients who undergo elective colorectal resection, but the reasons for this reduction are not well understood.

OBJECTIVE: The aim of this randomized controlled trial was to assess the impact of extended perioperative counselling in treatment groups that were otherwise the same with respect to enhanced recovery after surgery criteria.

DESIGN: Patients eligible for open or laparoscopic colorectal resection were randomized to extended counseling (repeated information and guidance by dedicated nurse) or standard counselling.

SETTINGS: This study was conducted at a single institution.

PATIENTS: Patients ($n=164$) were randomly assigned to enhanced recovery after surgery plus extended counseling ($n=80$) or enhanced recovery after surgery with standard counseling ($n=84$).

MAIN OUTCOME MEASURES: The primary endpoint was total length of hospital stay. Discharge criteria were defined. Secondary endpoints were postoperative complications, postoperative length of hospital stay, readmission rate, and mortality.

RESULTS: Total hospital stay was significantly shorter among patients randomized to enhanced recovery after surgery plus extended counselling (median 5 [range 2–29] days vs. 7 [range 2–39] days, $p<0.001$). The two treatment groups differed in adherence to postoperative enhanced recovery after surgery elements such as mobilization and total oral intake. The two treatment groups did not differ in overall, major, and minor morbidity; reoperation rate; readmission rate; and 30-day mortality.

LIMITATIONS: The main limitation of this study was the absence of blinding.

CONCLUSIONS: Perioperative information and guidance was an important factor in enhanced recovery after surgery care and was associated with a significantly shorter length of hospital stay. Our findings suggest that perioperative counselling enables patients to comply with postoperative enhanced recovery after surgery elements and thereby reduces the length of hospital stay. This study was registered with ClinicalTrials.gov (NCT01610726).

INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols were created to enhance patient recovery by expediting the restoration of normal physiological function and by attenuating the surgical stress response, with consequent reduced postoperative morbidity and length of hospital stay. Randomized trials have shown that patients recover faster with ERAS care and have a reduced length of hospital stay. Most of these trials reported no differences in the complication rate¹⁻⁸, but some reported a reduction in minor complications with ERAS⁹⁻¹². Meta-analyses have shown reduction in minor, but not in major complications^{13,14}.

We previously reported the results of a randomized controlled trial that compared patients treated with ERAS to those treated with standard care¹⁵. In the absence of differences in mortality, major or minor morbidity, readmission, and reoperation rates, other factors like improved perioperative counseling might have caused the shorter hospital stay in the ERAS group. We also found no between-group differences in surgical stress, as measured by postoperative C-reactive protein levels (CRP) or bowel function in terms of time to tolerance of enteral nutrition. These similarities between the groups suggest that obtaining accurate perioperative information and providing continuous guidance about the elements of ERAS are important core factors associated with reduced length of hospital stay. However, the results did not enable us to make firm conclusions about whether a single ERAS item or several ERAS items were more effective than other interventions, and it was apparent that further studies would be necessary to understand the impact and specific role of counseling in ERAS.

To the best of our knowledge, no trials reported in the literature have addressed counseling specifically in the context of colorectal or general surgery. We wanted to investigate if we can find a relationship between perioperative counseling by a dedicated ERAS nurse as an independent strategy and the reduction in length of hospital stay.

Therefore, in this randomized controlled study we compared patients who received ERAS care with extended pre- and postoperative counseling to patients who received ERAS care with standard counseling. Our aim was to determine whether counselling alone was associated with decreased total length of hospital stay.

MATERIALS AND METHODS

This study was registered with ClinicalTrials.gov (NCT01610726). Patients > 18 years of age treated with elective laparoscopic or open colorectal surgery for malignant or benign disease, with or without stoma, at Haukeland University Hospital in Bergen, Norway were eligible for inclusion. We obtained written consent when patients were informed about the study 1–3 weeks before surgery. Exclusion criteria were pregnancy, emergency operation, difficulty providing informed consent because of impaired mental capacity, American Society of Anaesthesiologists (ASA) grade IV, and planned multivisceral resection. If the intended surgery was not performed, the randomized patients were excluded. The regional ethics committee of western Norway approved this trial (reference number 2010/2079).

Randomization

We randomized patients who consented to participate in the study and fulfilled the inclusion criteria to ERAS care plus extended counseling or ERAS care with standard counseling. Randomization with an allocation ratio of 1:1 was generated with random block sizes of ten, and an independent statistician prepared the sequence in advance. Allocation assignments were deposited in consecutively numbered and sealed envelopes and stored locked in the study office. The patients were informed of the study and randomized by one of the two study surgeons at the outpatient clinic, 1–3 weeks before surgery, and were informed of their treatment group. The information provided by the study surgeon and nurse was

identical for both groups. We told the patients that it was unknown whether one of the two types of counseling was potentially superior. Neither patients nor physicians were blinded to the group assignment due to the nature of the study.

Outcomes

The primary outcome of this trial was total length of hospital stay (THS), defined as the number of days of postoperative hospital stay (PHS) plus any additional hospitalization period if readmission was necessary within the first 30 days after surgery. Discharge criteria were defined equally for both treatment groups and were as follows: (1) postoperative pain adequately controlled with oral medication (visual analog scale < 4), (2) mobilized and out of bed >6 hours each day, (3) tolerance of enteral nutrition, and (4) no complications requiring treatment in hospital. Furthermore, patients with a stoma had to be comfortable with stoma care before discharge. Secondary outcomes were PHS, postoperative complications, readmission rate, and mortality. Definitions of complications were predefined and recorded prospectively and were also graded by severity in accordance with the Clavien–Dindo classification¹⁶.

We recorded parameters beginning on the day of surgery (before the operation commenced) and daily thereafter until discharge. Moreover, we recorded adherence to various ERAS items that could possibly be affected by counseling. On postoperative day 30, all patients had an outpatient clinic appointment. To minimize observer-related bias, the same dedicated nurse and two surgeons conducted all outpatient clinic visits. No important changes to the methods or trial outcomes occurred after the trial was commenced.

Counselling and perioperative care

There were no differences between the groups in any of the various ERAS items except for extended perioperative counseling and guidance as the study intervention. Patients in both groups were informed of the principles of ERAS care and informed of their own role in retraining so that they understood the importance of their efforts. All patients were informed that they would eat on the same day as the operation, that they would preferably do without intravenous fluids, and that mobilization and drinking were important. Patients were also informed about nutritional drinks, when the urinary catheter would be removed, epidural analgesia and drains, discharge criteria, and expected length of stay. Both groups were treated in accordance with the ERAS protocol described in the Enhanced Recovery After Surgery Society Guidelines^{17,18}. Table 1 lists the ERAS items used in the study.

The extended counseling study intervention comprised one or two additional consultations with a dedicated ERAS nurse before surgery. The ERAS nurse had undergone rigorous training and had nursing experience with ERAS pathways. The nurse repeated information about the course of the operation and described the expectations of the staff regarding mobilization and oral intake. Pain was an important item, and postoperative pain control was described in detail. Postoperative course and expected hospital stay were also discussed. Patients were asked to describe their expectations and concerns about the operation, their home situation, readmission, and expected absences due to illness. Each consultation lasted 30–45 minutes. After the consultation, patients received a written information leaflet that summarized the most important items. Postoperatively, the patients had a daily checklist/diary that registered pain control, weight, fluid intake, nutritional drink, mobilization, nausea and vomiting, bowel function, and tolerance of enteral nutrition without nausea. Patients randomized to extended counseling during hospitalization were admitted to a separate ward. The nurses who worked in this ward had undergone special training and

education in the principles of ERAS. The same dedicated nurse who provided preoperative information supervised the postoperative course and saw all the patients on a daily basis.

Patients in the standard counseling group were treated in the regular colorectal unit with different nursing personal than in the extended counseling group. The nurses in this unit had also been educated in ERAS principles. All nurses in this ward were responsible for the counseling and adherence to the ERAS program, and all patients in this group were introduced to ERAS criteria when they were admitted to the hospital. However, in the standard counseling group, a dedicated nurse did not supervise ERAS care. Postoperatively, patients in the standard group had the same daily checklist/diary as in the extended group. There was no interchange between the nurses and paramedic staff of the two wards. Ward personnel were kept separate to minimize the possibility of introducing confounders into treatment effects. In both groups, nurses equally experienced in colorectal surgery provided the care.

All of the patients received preoperative systemic antibiotics, perioperative hypothermia prevention, and thromboembolic prophylaxis (5000 IE of low molecular weight heparin [Dalteparin] daily). In the first study period, intraoperative fluid loading included 800 ml of antibiotics. In the last study period, antibiotics were given per os preoperatively. In both groups, patients were allowed to drink clear fluids until 2 hours before surgery. All patients were encouraged to drink a carbohydrate-loaded beverage (200 ml of ProvideXtra®) the evening before surgery and 2 hours before surgery. We did not use preoperative glucocorticoid as part of perioperative management.

Thoracic epidural anaesthesia was used in both groups only in open surgery. Epidural anaesthetic agents were injected at Th9–Th11 and comprised continuous dosages of 1 mg/ml bupivacaine, 0.002 mg/ml fentanyl, and 0.002 mg/ml adrenaline. General anaesthesia for both

groups consisted of gas with propofol or thiopental, fentanyl, and isoflurane or sevoflurane. Nasogastric tubes were removed immediately after extubation in both groups.

For colon surgery, the main surgeon preoperatively determined the bowel preparation on an individual basis. For rectal surgery, standard mechanical bowel preparation procedures were used. In both groups, patients who underwent rectal resection received a pelvic drain, while patients with colon resection had no drain. A colorectal surgeon either performed or supervised all operations. The operating surgeon decided the surgical approach. While five surgeons performed both open and laparoscopic surgery, two surgeons performed open surgery only. Open surgery was performed through a midline incision. The operating surgeon had no active role in the protocol, i.e. extended counselling and guidance. The surgeon provided the same pre- and postoperative information to both groups. All patients in both groups were allowed to start drinking and eating immediately after surgery and were encouraged to mobilize starting directly after surgery.

Statistical analysis

The primary outcome measure of counseling was THS. Sample size calculation was based on a pilot study of 20 patients, prior to our previous randomized controlled trial. The difference in mean THS was 2.5 days (7.7 days, SD 6.0 in ERAS care and 10.2 days, SD 8.3 in standard care). To detect a difference of 2.5 days, with a SD of 6.0 in one group and 8.3 in the other group, with the power of 0.8 and a significance level of 0.05, this would require 133 patients in each group. Assuming about 15% dropout would lead to a total sample size of 300 patients. We used IBM SPSS SamplePower2.0, t-test for 2 independent groups to calculate the sample size. Based on the results of our previous randomized controlled trial, we planned an interim analysis once we had included at least half of the required patients. We therefore carried out an interim analysis when we had included and followed-up 164 patients. We

performed the interim analysis with the statistical program R 3.3 and group sequential design with gsDesign 3.0^{19,20}. With an estimated total patient number of 300, a power of 0.8, and a nominal significance level of 0.05, our statistician predicted that we should have a marginal significance level of <0.006 if we stopped the trial. The sample size for final analysis after the interim analysis would then increase to 303 if the trial was not stopped. The *p* value for the difference in primary outcome (THS) was <0.001, and the criterion for termination of the study was fulfilled.

We used IBM SPSS, version 23 for statistical analyses and descriptive statistical methods to characterize the sample. Data are presented as median and range. We used chi-squared test to compare discrete variables, independent-sample *t*-test for continuous, normally distributed variables, and Mann–Whitney U test for continuous, non-normally distributed variables. The reported *p* values are based on two-sided tests.

RESULTS

Between 10 March 2015 and 5 December 2016, 179 patients were randomly assigned to ERAS plus extended counseling or ERAS with standard counselling. In the interim analysis, we calculated that we needed at least 152 patients. After 15 exclusions, 164 patients remained for the final analysis. Of 416 eligible patients, we did not include 237, mainly because of logistical reasons and a lack of resources at our study outpatient clinic (Figure 1). Because of the summer vacations of the responsible study surgeons and nurse, patients who underwent surgery in July and August were not included. However, treatment routines continued throughout the summer months. Patients who met the inclusion criteria (*n* = 176) but were not included in the study were similar in age (median 69 years) and male:female ratio (91:85) to included patients. There were fewer laparoscopies (70/176 [39.8%] vs. 71/163 [43.6%]), as well as a larger proportion of rectal operations (94/176 [53.4%] vs.

68/163 [41.7%], in patients not included in the study. The distribution of ASA classification was the same among included and not-included patients. Table 2 summarizes the patient characteristics and surgical details of the included patients. Baseline characteristics between the two treatment groups did not differ significantly.

THS was significantly shorter among patients randomized to the ERAS plus extended counseling group compared to the ERAS with standard counseling group (median 5 [range 2–29] vs. median 7 [range 2–39] days; $p < 0.001$) (Table 3). The discharge criterion pain control with oral medication was achieved earlier in the extended counselling group, while the criterion tolerate solid food without nausea did not differ between the two groups (Table 3).

There were no significant differences between the two treatment groups in overall, major, and minor morbidity; reoperation rate; readmission rate; and 30-day mortality (Table 4). The frequency of Clavien–Dindo complications \geq grade 3b was similar in both groups (Table 5). A separate analysis excluding patients with severe complications also demonstrated a significant difference in THS between treatment groups (median 5 [range 2–21] vs. median 7 [range 2–25] days; $p < 0.003$).

Table 6 summarizes the ERAS parameters affected by counseling. There were no differences in intraoperative fluid load or intravenous fluid administered during the first 24 postoperative hours. The groups differed significantly 24 hours after surgery and on postoperative days 2 and 3, with a higher total oral intake and longer periods of mobilization in the extended counseling group.

DISCUSSION

This randomized controlled trial demonstrated a significantly shorter THS in patients treated with ERAS care plus extended perioperative counseling compared to ERAS care with standard counseling after elective colorectal surgery. We initiated this trial specifically to

compare ERAS programs with and without extended perioperative information and guidance in the daily practice of laparoscopic and open colorectal surgery. Previously published randomized controlled trials and cohort studies have shown that ERAS programs are associated with decreased hospital stay. Like many of the other randomized controlled trials¹⁻⁸, our previous randomized trial compared ERAS care to standard care¹⁵ and found no differences in mortality, major or minor morbidity, reoperation, or readmission, which may explain the shorter THS in the ERAS group. The results of the previous study did not allow us to confirm which part of the ERAS intervention was responsible for the beneficial effects, but the results of the current randomized trial strongly suggest that extended counseling alone may decrease THS significantly. Included in the term counseling are preoperative information and education, as well as postoperative guidance. Preadmission information and counselling are considered as core factors in an ERAS protocol, even if the evidence levels are considered low^{17,18}. The perioperative counseling evaluated in this study is more extended than the preoperative counseling and information described in the ERAS guidelines. Detailed information about anesthetic and surgical procedures has shown to reduce anxiety and fear, and enhance postoperative recovery with reduced length of hospital stay²¹⁻²³. Personal counselling or multimedia information including information of the course of the procedure with expectations and tasks to patients may improve pain control, early postoperative mobilization, pre- and postoperative feeding, and respiratory physiotherapy, and thus reduce complications²⁴⁻²⁶. However, patient counseling and education as an independent strategy to reduce the length of hospital stay has received little attention; to our knowledge, this is the first randomized trial to demonstrate that the length of stay of patients undergoing colorectal surgery can be decreased significantly by focusing on counseling in an ERAS setting.

The main strengths of our study are the randomized controlled trial design and the utilization of two completely different wards for patients allocated to the two study arms. To

minimize the possibility of introducing confounders into treatment effects, different nursing personnel attended the two wards. Moreover, the department had a colorectal unit with a stable staff of seven senior surgeons responsible for both wards during the entire study period. To minimize observer-related bias, the same dedicated nurse and the same two surgeons attended all outpatient clinic visits on day 30. One surgeon and one nurse performed all prospective data registration. Due to the nature of the study (counseling and guidance), neither the physicians and nurses nor the patients were blinded to the treatment assignment.

More than 160 patients were included over a 1.5-year period. The main reason for not including patients was logistical; there was limited capacity at our study outpatient clinic. Further, we did not include any patients in the study during summer vacation. A smaller proportion of the included patients underwent rectal resection and more laparoscopic procedures were performed compared to patients not included in the study. Patient randomization and inclusion was a continuous process, but these differences may reflect a selection bias. We included both rectal and colon resections in this study because we believe that it should be possible to apply ERAS criteria independent of the surgical procedure. The adherence to preoperative (except counseling/information) and peroperative ERAS items should be the same in both treatment groups. We therefore did not register the adherence to these elements, but this might be a weakness in the study. Although there were more complications in the standard counseling group, the difference was not statistically significant. In our previous trial we had the opposite finding, with more complications in the ERAS care group compared to the standard care group, also without statistical significance.

The ERAS approach comprises a combination of multimodal interventions, rather than one specific strategy. However, it is unclear whether all elements are equally important; a large systematic review and meta-analysis was unable to show that programs with more elements were more successful than those with fewer components²⁷. Compliance with

postoperative rather than preoperative ERAS elements is likely to be of particular importance for good progress and accelerated postoperative recovery²⁸. Other studies have suggested an association between early mobilization and better postoperative outcome²⁹⁻³². The two treatment groups in our study were significantly different with respect to adherence to postoperative ERAS elements such as mobilization and total oral intake. We think it is highly likely that the differences in counseling and guidance between the groups have been responsible for this effect, as follow-up and guidance by the nurses largely determined the patients' degree of mobilization and intake of fluid and nutrition. A "local champion", as in our case a dedicated nurse, has been shown to be an important success factor³³. This perioperative patient coaching provided by dedicated nurses is the key factor for the reduced THS.

In most previous studies of ERAS, as in the present study, the length of hospital stay was the primary outcome; however, the causes for delays in discharge are generally not provided. Even with established discharge criteria, not all patients are discharged in daily practice when they meet the criteria for readiness for discharge. This can be due to logistical challenges or to the patient's own wishes. Making sure that the same dedicated nurse provides both preoperative information and postoperative supervision appears to be essential in order to achieve early discharge. Early discharge may not be an appropriate goal in itself; what matters for the patient is a safe treatment course with minimal complications. However, length of hospital stay has major economic consequences. Good patient information and education can reduce hospital costs significantly.

In our previous study detailed preoperative information, as well as ensuring continuous counseling and repetition by trained personnel throughout the care pathway seemed to be important for the reduced THS¹⁵. In the current study our hypothesis was that THS can be reduced by perioperative counseling by dedicated nurses as an independent

strategy. And this is what we can demonstrate. The reduction in THS in this study, and probably also in our previous study, is most likely caused by counseling and coaching. Introduction of an ERAS program without local ERAS champions will not be successful. Our results suggest that well counseled patients comply more strongly, particularly with respect to postoperative ERAS criteria, which have an important impact on both recovery and time to discharge from hospital.

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