

# A systematic review of enhanced recovery protocols in colorectal surgery

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## ABSTRACT

**INTRODUCTION** Colorectal surgery has been associated with a complication rate of 15–20% and mean postoperative inpatient stays of 6–11 days. The principles of enhanced recovery after surgery (ERAS) are well established and have been developed to optimise perioperative care and facilitate discharge. The purpose of this systematic review is to present an updated review of perioperative care in colorectal surgery from the available evidence and ERAS group recommendations.

**METHODS** Systematic searches of the PubMed and Embase™ databases and the Cochrane library were conducted. A hand search of bibliographies of identified studies was conducted to identify any additional articles missed by the initial search strategy.

**RESULTS** A total of 59 relevant studies were identified. These included six randomised controlled trials and seven clinical controlled trials that fulfilled the inclusion criteria. These studies showed reductions in duration of inpatient stays in the ERAS groups compared with more traditional care as well as reductions in morbidity and mortality rates.

**CONCLUSIONS** Reviewing the data reveals that ERAS protocols have a role in reducing postoperative morbidity and result in an accelerated recovery following colorectal surgery. Similarly, both primary and overall hospital stays are reduced significantly. However, the available evidence suggests that ERAS protocols do not reduce hospital readmissions or mortality. These findings help to confirm that ERAS protocols should now be implemented as the standard approach for perioperative care in colorectal surgery.

## KEYWORDS

Enhanced recovery Colorectal surgery

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Colorectal surgery has been associated with a complication rate of 15–20% and mean postoperative inpatient stays of 6–11 days. The principles of enhanced recovery after surgery (ERAS) are well established and have been developed to optimise perioperative care and facilitate discharge.<sup>1–5</sup>

The aims of the ERAS protocol include reducing complication rates following colorectal surgery and the acceleration of recovery. The safety of these protocols has been ratified in randomised controlled trials (RCTs)<sup>4,5</sup> and they comprise a series of measures implemented in the perioperative period that reduce the stress response associated with surgery.<sup>6</sup>

Kehlet first developed a multimodal enhanced recovery programme for elective colorectal surgery.<sup>7–9</sup> Recommendations were classified separately as pre, intra and postoperative interventions, with the intention to reduce hospital stay to a mean of four days. Subsequently, several protocols have been established by different groups consisting of different perioperative recommendations that may include preoperative counselling, carbohydrate loading, omission of bowel preparation, administration of high-inspired perioperative oxygen concentrations, prophylaxis against thromboembo-

lism, active prevention of hypothermia and an avoidance of nasogastric tubes.<sup>1,4,5,10–15</sup>

In recent years, however, it has been argued that ERAS protocols may actually increase readmission rates, have no impact on costs or duration of inpatient stay and may result in a delay in recognising complications. In an effort to clarify a role for ERAS in colorectal surgery, Varadhan *et al* conducted a meta-analysis and demonstrated a reduction in the length of stay and complication rates after colorectal surgery with no compromise in patient safety.<sup>15</sup>

The purpose of this systematic review is to present an updated assessment of perioperative care in colorectal surgery from the available evidence and ERAS group recommendations.<sup>16</sup>

## Methods

Systematic searches of the the PubMed and Embase™ databases and the Cochrane library were conducted. The search strategy comprised combining the keywords and MeSH terms: ‘enhanced recovery’, ‘fast track protocols’, ‘multimodal rehabilitation’, ‘traditional care in combination with

‘colorectal’, ‘colon’, ‘rectum’ and ‘sigmoid’. A hand search of bibliographies was conducted to identify any additional articles missed by the initial search strategy. The literature review was completed in February 2011.

In order to maintain quality control, the selection of studies was limited to randomised or clinical controlled trials (CCTs) with a prospective intervention group that compared an ERAS perioperative programme with traditional care in adult patients undergoing open or laparoscopic elective colorectal surgery, regardless of indication. The studies were required to document the multimodal enhanced recovery protocol implemented and are listed in Tables 1–4. They reported at least one of the following outcome measures:

- > length of primary postoperative hospital stay in days following surgery
- > length of total postoperative stay expressed as total days spent in hospital, including readmission
- > postoperative complications (morbidity expressed as a percentage)
- > readmission rates (expressed as a percentage)
- > mortality (expressed as a percentage)

Included studies contained a minimum of four elements covering the pre, intra and postoperative periods of the ERAS protocol pathway.

#### Data extraction

The following data were extracted from each study: year of publication, author, study design, inclusion and exclusion criteria, and the number of subjects included in each type of care. Data published in recent meta-analyses of RCTs<sup>14,15,17</sup> were also used for comparison of outcomes of the two care pathways.

## Results

A total of 59 relevant studies were identified, including six RCTs<sup>4,5,10,12,18,19</sup> and seven CCTs<sup>7,15,20–24</sup> that were deemed suitable for inclusion in the analysis. These 13 studies are listed in Table 1. The remaining 46 studies were case reports, meta-analyses or systematic reviews; although relevant and worthy of mention, they did not meet the inclusion criteria and were therefore excluded from rigorous analysis.

A previous meta-analysis<sup>15</sup> of the RCTs identified 452 patients with 226 in each group. None of the trials were blinded but all were appropriately randomised (either by random number generator or sealed envelope methods). All six of the RCTs selected had specified inclusion and exclusion criteria and all had at least one outcome measure as previously listed. Each RCT had a minimum of four ERAS elements implemented in the intervention group. The number of ERAS protocol elements used in the RCTs ranged from 4 to 14, with a mean of 9. Seven non-randomised CCTs were selected for review.<sup>7,15,20–24</sup> These involved small numbers of patients at solitary centres, resulting in low-powered results. All studies included in our analysis reported a 30-day

follow-up period except Khoo *et al*,<sup>5</sup> who reported outcome measures at 14 days.

#### Primary hospital stay

Eleven studies reported on primary hospital stay,<sup>4,5,8,10,12,15,18–20,25,24</sup> ten of which<sup>4,5,8,10,13,18–20,25,24</sup> reported statistically significant reductions in duration of inpatient stays in the ERAS groups compared with more traditional care. A meta-analysis of the data demonstrated that patients who underwent major open colorectal surgery managed with ERAS protocols had a reduction in primary hospital stay of 2.53 days less than those managed with traditional care pathways (95% confidence interval [CI] -35.4 to -1.47 days,  $p < 0.00001$ ).<sup>15</sup> This finding was replicated by Gouvas *et al*, who established a 2.62 day reduction in primary hospital stay in the ERAS group compared with standard care (95% CI -3.74 to -1.50 days,  $p < 0.00001$ ).<sup>14</sup> Five studies reported on total hospital stay.<sup>5,8,12,13,25</sup> A meta-analysis of these data demonstrated a shorter stay in the ERAS group of 2.46 days compared with the traditional care group (95% CI -5.43 to -1.48 days,  $p < 0.00001$ ).<sup>14</sup>

#### Postoperative complications

From the reviewed studies, morbidity rates of the ERAS protocol groups ranged from 4% to 47% while traditional care groups demonstrated morbidity rates between 8% and 75%. Only two RCTs<sup>18,19</sup> and one CCT<sup>7</sup> revealed a statistically significant difference in morbidity rates that favoured the ERAS protocol. All other reviewed studies showed a favourable trend in reduced morbidity rates in the ERAS groups that lacked statistical significance.

#### Readmission rates

Readmission rates ranged from 0% to 24% for the ERAS protocol groups and for the traditional care groups it ranged from 0% to 20%. Gouvas *et al* failed to establish a significant difference in the readmission rates between the two groups following their meta-analysis.<sup>15</sup> Nevertheless, a subgroup analysis confirmed lower readmission rates in those patients subjected to more traditional postoperative pathways. In contrast, however, in their CCT, Teewen *et al* were able to demonstrate a trend towards reducing readmission rates between the ERAS protocol and traditional care groups ( $p < 0.6$ ).<sup>20</sup>

#### Mortality

Eight studies reported on mortality rates.<sup>4,5,8,10,15,20–22</sup> Within ERAS protocol groups, mortality ranged from 0% to 5%, while mortality rates in the traditional care group ranged from 0% to 9%. No statistical difference was identified between the two groups.

## Discussion

Review of the published data reveals that the ERAS protocols have a role in reducing postoperative morbidity and result in an accelerated recovery following colorectal surgery. Similarly, both primary and overall hospital stays are

Table 1 Study design and reviewed data

Author	Design	Year	Number of patients		PHS (days)		THS (days)		Morbidity (%)		Readmission (%)		Mortality (%)	
			TC	ERAS	TC	ERAS	TC	ERAS	TC	ERAS	TC	ERAS	TC	ERAS
Teewen <sup>20</sup>	CCT	2010	122	61	9	6					2	3	1.6	0
Muller <sup>18</sup>	RCT	2009	75	76	10.3	6.7			49	21	3	4		
Serclova <sup>19</sup>	RCT	2009	52	51	10.4	7.4			48	22	0	0		
Khoo <sup>5</sup>	RCT	2007	35	35	7	5	7	5	46	26	3	9	6	0
Polle <sup>13</sup>	CCT	2007	52	55	6	4	6.5	4	31	27	6	11	0	0
Kariv <sup>21</sup>	CCT	2007	97	97							20	24	0	0
Wichmann <sup>24</sup>	CCT	2007	20	20	9.7	6.7								
Gatt <sup>4</sup>	RCT	2005	20	19	9	6.6			75	47	20	5	0	5
Basse <sup>7</sup>	CCT	2004	130	130	10	3.3	13	5.5	55	26	12	21	3	5
Raue <sup>22</sup>	CCT	2004	29	23					21	4	3	9	0	0
Anderson <sup>10</sup>	RCT	2003	11	14	7	4			45	29	0	0	9	0
Delaney <sup>12</sup>	RCT	2003	33	31	5.8	5.2	7.1	5.4	30	23	18	10		
Stephen <sup>23</sup>	CCT	2003	52	86	6.6	3.7	6.9	4.2	25	11	2	9		

PHS = primary hospital stay; THS = total hospital stay; TC = traditional care; ERAS = enhanced recovery after surgery; CCT = clinical controlled trial; RCT = randomised controlled trial  
 Continuous data variables expressed as a mean

Table 2 Elements of enhanced recovery protocol included per study in the preoperative period

Author	Design	Preoperative			
		Synbiotics	Preoperative feeding	No bowel preparation	Preoperative preparation
Teewen <sup>20</sup>	CCT	x	x		x
Muller <sup>18</sup>	RCT		x	x	
Serclova <sup>19</sup>	RCT		x	x	
Khoo <sup>5</sup>	RCT				x
Polle <sup>13</sup>	CCT		x	x	
Kariv <sup>21</sup>	CCT				x
Wichmann <sup>24</sup>	CCT		x		
Gatt <sup>4</sup>	RCT	x		x	
Basse <sup>7</sup>	CCT				x
Raue <sup>22</sup>	CCT				x
Anderson <sup>10</sup>	RCT	x	x	x	
Delaney <sup>12</sup>	RCT				x
Stephen <sup>23</sup>	CCT				x

CCT = clinical controlled trial; RCT = randomised controlled trial

Table 3 Elements of enhanced recovery protocol included per study in the perioperative period

Author	Design	Postoperative				
		Active prevention of hypothermia	Epidural analgesia	Perioperative high FiO <sub>2</sub>	Minimally invasive surgery	
Teewen <sup>20</sup>	CCT	x	x			x
Muller <sup>18</sup>	RCT		x			
Serclova <sup>19</sup>	RCT		x			
Khoo <sup>5</sup>	RCT		x			
Polle <sup>13</sup>	CCT	x	x			x
Kariv <sup>21</sup>	CCT					
Wichmann <sup>24</sup>	CCT	x	x	x		x
Gatt <sup>4</sup>	RCT		x	x		x
Basse <sup>7</sup>	CCT		x			x
Raue <sup>22</sup>	CCT		x			x
Anderson <sup>10</sup>	RCT		x	x		x
Delaney <sup>12</sup>	RCT					
Stephen <sup>23</sup>	CCT		x			x

CCT = clinical controlled trial; RCT = randomised controlled trial

Table 4 Elements of enhanced recovery protocol included per study in the postoperative period

Author	Design	Postoperative						
		No use of drains	Enforced postoperative mobilisation	No routine use of nasogastric tubes	No systemic morphine	Enforced postoperative oral feeding	Early removal of catheter	Laxatives
Teewen <sup>20</sup>	CCT		x	x	x	x		x
Muller <sup>18</sup>	RCT	x		x	x			
Serclova <sup>19</sup>	RCT	x	x	x	x	x		
Khoo <sup>5</sup>	RCT		x	x	x		x	
Polle <sup>13</sup>	CCT	x	x	x	x	x	x	x
Kariv <sup>21</sup>	CCT		x	x				
Wichmann <sup>24</sup>	CCT		x					
Gatt <sup>4</sup>	RCT	x	x	x	x			
Basse <sup>7</sup>	CCT		x		x	x	x	x
Raue <sup>22</sup>	CCT		x	x	x		x	x
Anderson <sup>10</sup>	RCT	x	x	x	x			
Delaney <sup>12</sup>	RCT		x	x				
Stephen <sup>23</sup>	CCT		x	x	x		x	x

CCT = clinical controlled trial; RCT = randomised controlled trial

reduced significantly. However, the available evidence suggests that ERAS protocols do not reduce hospital readmissions or mortality.

Despite these observations, a study from 2007 argued against the use of enhanced recovery protocols in clinical practice on the basis of cost-effectiveness and patient safety.<sup>26</sup> This may stem from a reluctance to reject surgical dogma decreeing a period of postoperative enteral resting with the concurrent maintenance of a hypervolaemic state. Kehlet *et al*, the architects of the ERAS protocol, hypothesise that audit is an inherent and essential component of each step in the procedure.<sup>1</sup>

A potential weakness of our systematic review is that only four elements of the ERAS protocol were required for studies to be assessed. This leads to variations in the number of elements of the ERAS protocol utilised in each study. It is unlikely that each element is of equal importance in determining a patient's perioperative course.

The study by Delaney *et al* incorporated four elements of the ERAS protocol in the intervention group.<sup>12</sup> This was the only trial of all those reviewed that did not demonstrate a statistically significant difference in primary length of hospital stay. Other reviewed studies included up to fourteen elements<sup>15</sup> of the ERAS protocol and all demonstrated a statistically significant reduction in primary length of hospital stay of at least two days.

Reviewed studies also assessed other elements of the ERAS protocol including preoperative counselling, epidural use, minimally invasive/transverse incisions, absence of nasogastric tubes with enforced postoperative mobilisation and oral feeding. Laparoscopically assisted surgery demonstrates improvements in outcome measures, including length of primary hospital stay and morbidity.<sup>25</sup>

Laparoscopic resectional surgery is currently considered to be the key interventional change in traditional care that has led to improvements in recovery rates and reductions in morbidity following colorectal surgery. RCTs have demonstrated a reduction in primary length of hospital stay in association with laparoscopic colorectal surgery.<sup>56–58</sup> The combination of ERAS protocols and laparoscopically assisted colonic resections has been evaluated in three separate trials<sup>27–29</sup> that, unfortunately, have not yielded a pervasive message. These trials failed to elicit significant differences in outcome between groups that had undergone open as compared with laparoscopic colorectal resection within the context of an ERAS protocol. The study by Basse *et al*, in which laparoscopy was introduced into a well-established ERAS protocol, showed no significant difference in the length of postoperative stay or rate of readmissions in the laparoscopic group.<sup>27</sup>

The LAFA trial is a randomised multicentre trial with a 2 x 2 balanced factorial design.<sup>42</sup> Patients are blinded for the type of intervention, ie laparoscopic or open surgery. The aim is to determine whether laparoscopic surgery, fast track perioperative care or a combination of both is to be preferred over open surgery with standard care in patients undergoing a segmental colectomy for malignant disease. Similarly, the EnROL trial aims to randomise patients to

open or laparoscopic surgery with an enhanced recovery programme to try to establish best practice.<sup>45</sup> These trials will go some way in answering these issues.

The inclusion of other aspects of the ERAS protocol is well supported by robust evidence from previous trials and meta-analyses. Bowel preparation is known potentially to cause significant fluid shifts that may result in dehydration and electrolyte deficiencies.<sup>50</sup> Two RCTs have shown no benefit with the routine use of bowel preparation in elective colorectal surgery<sup>51,52</sup> with another suggesting an increased risk of postoperative anastomotic breakdown.<sup>55</sup> The evidence for avoiding routine nasogastric tube decompression and implementation of epidural anaesthesia postoperatively has been ratified by meta-analyses.<sup>54,55</sup>

Factors affecting the quality of data reviewed include a relative lack of RCTs and CCTs that compare the ERAS and traditional care pathways, and also the low numbers of patients involved. Given the nature of the ERAS interventions being compared, blinding of patients and staff is unfeasible.

Eleven trials reported the length of hospital stay as either a primary or secondary outcome measure. It was, however, unclear whether primary length of stay was measured from the admission date to the point of fulfilling discharge criteria and therefore the social circumstances of each patient may have influenced results artificially.

Another factor that may limit data homogeneity includes the fact that discharge criteria were not always clarified or, when specified, varied between trials. In the RCTs<sup>4,10,12</sup> discharge criteria were defined for both ERAS and traditional care groups. This consisted of full mobilisation, oral analgesia and an ability to tolerate solids without nausea and vomiting. Delaney *et al* included the additional prerequisite of passage of flatus, prior to discharge.<sup>12</sup> Of the CCTs, Teewen *et al* described identical discharge criteria for both groups, including adequate pain relief with non-opioid oral analgesia, normal food intake and a return to the preoperative mobility level,<sup>20</sup> while Khoo *et al* additionally required bowel or stoma function.<sup>5</sup>

Other causes of inconsistency in the data were that two RCTs<sup>12,19</sup> included patients who had undergone a small bowel resection. Serclova *et al* also limited participation in the trial to patients aged 18–70 years and to those who were undergoing bowel resection and stoma formation for non-malignant colorectal disease.<sup>19</sup>

There is evidence that the incorporation of single elements of the ERAS protocol leads to a decrease in morbidity and a reduction in primary length of hospital stay.<sup>54,59–60</sup> Results of the RCTs, CCTs and meta-analyses reviewed in this paper strengthen those conclusions. Other, less comprehensively investigated elements of the ERAS protocol, such as the use of synbiotics and withholding premedication, may also have contributed to the reduction in morbidity and length of hospital stay. However, evidence for this is lacking and further RCTs with emphasis on total protocol compliance and homogenisation of study populations is necessary to investigate all individual elements.

## Conclusions

Following an extensive review of the literature, the available evidence supports the contention that ERAS protocols reduce healthcare costs<sup>21,41</sup> and, importantly, that there is a significant reduction in patient morbidity with an acceleration of postoperative recovery. These findings help to confirm that ERAS protocols should now be implemented as the standard approach to perioperative care in colorectal surgery. To develop the evidence base further, future RCTs of ERAS protocols with strict pathway compliance will be required.

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