Early Postoperative Low Compliance to Enhanced Recovery Pathway in Rectal Cancer Patients

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Simple Summary: This research investigates the adherence and compliance to the ERAS pathway in patients operated for rectal cancer; the results highlights the important role of early postoperative compliance to the postoperative pathway with the development of complications.

Abstract: Early postoperative low compliance to enhanced recovery protocols has been associated with morbidity following colon surgery. The purpose of this study is to evaluate the possible causes of early postoperative low compliance to the enhanced recovery pathway and its relationship with morbidity following rectal surgery for cancer. A total of 439 consecutive patients who underwent elective surgery for rectal cancer have been included in the study. Compliance to enhanced recovery protocol on postoperative day (POD) 2 was evaluated in all patients. Indicators of compliance were naso-gastric tube and urinary catheter removal, recovery of both oral feeding and mobilization, and the stopping of intravenous fluids. Low compliance on POD 2 was defined as non-adherence to two or more items. One-third of patients had low compliance on POD 2. Removal of urinary catheter, intravenous fluids stop, and mobilization were the items with lowest adherence. Advanced age, duration of surgery, open surgery and diverting stoma were predictive factors of low compliance at multivariate analysis. Overall morbidity and major complications were significantly higher (p<0.001) in patients with low compliance on POD 2. At multivariate analysis, failure to remove urinary catheter on POD 2 (OR = 1.83) was significantly correlated with postoperative complications. Low compliance to enhanced recovery protocol on POD 2 was significantly associated with morbidity. Failure to remove the urinary catheter was the most predictive indicator. Advanced age, long procedure, open surgery and diverting stoma were independent predictive factors of low compliance.

Keywords: rectal surgery; enhanced recovery; overall morbidity; ERAS compliance; low pneumoperitoneum; TAP block

1. Introduction

Enhanced recovery protocols have been associated with a significant improvement of outcome after major surgery for gastrointestinal cancer [1–3]. The elderly and patients with multiple comorbidities can be included in the enhanced recovery program, but often require a tailored protocol [4,5].

Early postoperative low compliance to an enhanced recovery protocol has been reported in about one third of patients following elective colonic resection [6,7]. Patients with early low compliance after colonic resection had significant higher morbidity and longer
hospital stays [8]. Few data are currently available on both the rate and causes of early low compliance to enhanced recovery protocols following rectal surgery and its relationship with morbidity occurring afterwards.

The first experiences with enhanced recovery protocols were carried out more than 20 years ago. New items reducing perioperative stress and invasiveness of surgery have been subsequently proposed [9,10]. Promising preliminary results have been obtained with low-pressure pneumoperitoneum, multimodal analgesia including abdominal wall blocks, and inferior mesenteric artery preservation in upper rectal cancer surgery [11–14].

The purpose of this study is to assess which variables can be associated with low compliance to enhanced recovery pathways. The relationship between low compliance and overall postoperative morbidity has also been investigated.

2. Materials and Methods

The present study is performed in accordance with STROBE guidelines [15]. Consecutive patients who underwent elective surgery for rectal cancer in seven Italian hospitals have been included in the study. Patients with combined resections (rectal and other visera) were excluded. All patients have been prospectively registered in the database of the PeriOperative Italian Society. Each hospital applied a comprehensive ERAS pathway according to the ERAS® Society recommendation in colorectal surgery [16] and followed a pathway implementation program before starting the study [8].

In 35 consecutive patients who underwent surgery for upper rectal cancer at Monza Hospital, Monza, Italy, (Monza subgroup), three operative items have been added to the study protocol: TAP (transversus abdominis plane) block instead thoracic epidural catheter, low pneumoperitoneum (8 mmHg), and inferior mesenteric artery (IMA) sparing.

Demographics, perioperative variables, adherence to each item of the protocol, and short-term outcome parameters were prospectively collected in all patients. Indicators of postoperative compliance were naso-gastric tube and urinary catheter removal, recovery of oral feeding and mobilization out of bed, and the stopping of intravenous fluids. Removal of the naso-gastric tube was planned at the end of surgery; and patients were mobilized the day of surgery. The starting of oral feeding and removal of urinary catheter were planned on postoperative day 1. Intravenous fluid infusion was discontinued as early as possible in accordance with the recovery of oral feeding. Low compliance on postoperative day (POD) 2 was defined as non-adherence to two or more items [8].

Criteria to identify each postoperative complication were defined a priori [17] and the Clavien-Dindo classification has been used to grade their severity [18]. Complications graded as IIIb to V were considered as major. Discharge criteria and time to readiness for discharge were defined according to a previous study [19]. Any hospital readmission due to postoperative complications occurring within 30 days after discharge has been registered.

Statistical Analysis

Continuous variables were reported as median along with the interquartile range (IQR) and compared with a Mann-Whitney’s U test, while categorical variables were reported as percentages and compared with the Chi square test. Variables predictive of complications were individuated with uni and multiple logistic regression methods. The analysis of factors associated with low compliance on POD2 was carried out in uneventful patients. Statistics were performed with SPSS 25 (IBM Corp. Released 2017, IBM SPSS Statistics for Windows, Version 25.0. IBM Corp: Armonk, NY, USA).

3. Results

The present analysis includes 439 consecutive cancer patients who underwent elective rectal resection. An (American Society of Anesthesiology) ASA score of 3–4 was found in 141 (32.1%) patients, neoadjuvant chemo-radiotherapy was carried out in 113 (25.7%) patients, and laparoscopic surgery was successfully performed in 373 (82.7%) patients (Table 1).
Table 1. Patients’ characteristics.

| Variable            | Median | IQR    | N  | %  |
|---------------------|--------|--------|----|----|
| Age                 | 68.00  | 59.76–76.5 | 276 | 62.9% |
| Sex                 |        |        |    |    |
| M                   |        |        | 276 | 62.9% |
| F                   |        |        | 163 | 37.1% |
| BMI class           |        |        |    |    |
| <25                 |        |        | 223 | 50.8 |
| 25–29               |        |        | 164 | 37.4 |
| >30                 |        |        | 52  | 11.8 |
| BMI                 | 24.82  | 22.59–27.68 | 248 | 50.8 |
| ASA score           |        |        |    |    |
| 1                   |        |        | 60  | 13.7% |
| 2                   |        |        | 238 | 54.2% |
| 3                   |        |        | 127 | 28.9% |
| 4                   |        |        | 14  | 3.2% |
| Diabetes            |        |        | 53  | 12.1% |
| Neoadjuvant CT-RT   | 113    | 25.7%  | 113 | 25.7% |
| Mechanical bowel preparation | 172 | 39.3% |
| Surgery             |        |        |    |    |
| Anterior resection  | 403    | 91.8%  | 403 | 91.8% |
| Abdominoperineal amputation | 36  | 8.2%  |
| Duration of Surgery (min) | 243 | 191–300 |
| Intraoperative inotropes | 23  | 5.3%  |
| Successful laparoscopy | 363 | 82.7% |
| Laparoscopy converted to open surgery | 10  | 2.7%  |
| Diverting Stoma     | 241    | 54.9%  | 241 | 54.9% |
| Drain               | 345    | 78.8%  | 345 | 78.8% |

The overall adherence to preoperative and operative items was 81.3%. No patient received oral antibiotics before surgery. Mechanical bowel preparation was carried out in 172 (39.3%) patients, while an abdominal drain was placed in 345 (78.8%). The naso-gastric tube was removed at the end of surgery in 398 (90.8%) patients.

Table 2 shows that a low protocol compliance on POD 2 was found in one-third of patients. The items with the lowest adherence were removal of the urinary catheter, the stopping of intravenous fluids, and mobilization.

Table 2. Cumulative compliance with postoperative era items.

| Item                              | POD 0 | POD 1 | POD 2 | POD 3 | POD 4 |
|-----------------------------------|-------|-------|-------|-------|-------|
| Naso-gastric tube removal         | 90.8  | 96.6  | 97.5  | 99.1  | 99.5  |
| Solid Diet                        | 7.3   | 60.0  | 81.2  | 91.8  | 95.4  |
| Stop IV infusion                  | 1.6   | 41.2  | 65.0  | 79.2  | 85.4  |
| Urinary Catheter removal          | 1.7   | 41.1  | 64.5  | 84.9  | 91.7  |
| Mobilization > 4 h                | 8.0   | 43.2  | 65.0  | 74.6  | 81.4  |

Table 3 shows that advanced age, long surgical procedure, open surgery, and diverting stoma were significantly associated to low compliance on POD 2, whereas operative volemia monitoring was associated with high compliance (p = 0.06).

Table 4 reports short-term outcomes. Postoperative morbidity occurred in 149 (32.6%) patients and major complications occurred in 27 (6.2%) patients. Twenty-four (5.5%) patients underwent reoperation. Median time to readiness for discharge and length of hospital stay were 5 (4–8) and 6 (5–8) days. The readmission rate was 3.0% (13 patients).
### Table 3. Variables associated with low compliance on postoperative day 2.

| Variable                        | Postoperative Compliance | Univariate Analysis | Multivariate Analysis |
|--------------------------------|--------------------------|---------------------|-----------------------|
|                                | High Compliance          | Low Compliance      | OR        | 95% CI  | Sign. | OR        | 95% CI  | Sign.  |
|                                | N/Median | %/IQR  | N/Median | %/IQR  |        |        |          |        |        |
| Men                            | 67       | 38.1%  | 36       | 40.9%  | 1.126  | 0.668  | 1.899    | 0.656  | 0.018  |
| Age (years)                    | 67       | 58.2%  | 71.9%    | 61.7%   | 1.032  | 1.007  | 1.057    | 0.011  | 1.036  | 1.006  | 1.067  | 0.018  |
| BMI                            | 24.82    | 22.2%  | 24.10    | 22.1%   | 0.992  | 0.926  | 1.062    | 0.808  |        |        |        |        |
| BMI class <25                  | 89       | 51.4%  | 51       | 58.0%  | 1.032  | 1.007  | 1.057    | 0.011  | 1.036  | 1.006  | 1.067  | 0.018  |
| ASA score 1                    | 27       | 15.3%  | 10       | 11.4%  | 1.036  | 1.006  | 1.067    | 0.018  |        |        |        |        |
| ASA score 2                    | 99       | 56.3%  | 48       | 54.5%  | 1.309  | 0.586  | 2.923    | 0.511  |        |        |        |        |
| ASA score 3                    | 42       | 23.9%  | 29       | 33.0%  | 1.864  | 0.784  | 4.433    | 0.159  |        |        |        |        |
| Diabetes                       | 36       | 20.5%  | 19       | 21.6%  | 1.071  | 0.573  | 2.030    | 0.830  |        |        |        |        |
| Neoadjuvant CT/RT              | 71       | 40.6%  | 33       | 37.5%  | 0.879  | 0.519  | 1.488    | 0.631  |        |        |        |        |
| Mechanical bowel preparation   | 108      | 61.4%  | 59       | 67.0%  | 1.281  | 0.748  | 2.194    | 0.367  |        |        |        |        |
| Preoperative glucic drink      | 47       | 26.9%  | 26       | 29.5%  | 1.142  | 0.648  | 2.013    | 0.646  |        |        |        |        |
| Haemoglobin (g/dL)             | 13.70    | 12.8%  | 13.10    | 12.3%  | 0.829  | 0.696  | 0.989    | 0.037  | 0.913  | 0.742  | 1.124  | 0.392  |
| Neoadjuvant CT/RT              | 5        | 2.9%   | 4        | 4.5%   | 1.619  | 0.424  | 6.186    | 0.481  |        |        |        |        |
| Mechanical bowel preparation   | 172      | 98.3%  | 88       | 100.0% | 1.760  | 0.769  | 2.356    | 0.897  |        |        |        |        |
| Preoperative glucic drink      | 215      | 175.5% | 256      | 210%    | 1.906  | 1.003  | 1.009    | 0.000  | 1.006  | 1.002  | 1.010  | 0.002  |
| Epidural catheter              | 15       | 8.5%   | 20       | 22.7%  | 3.157  | 1.526  | 6.531    | 0.002  | 2.732  | 1.173  | 6.362  | 0.02   |
| Intraoperative advanced volemia monitoring | 12 | 6.8% | 12 | 13.6% | 1.071 | 0.868 | 1.343 | 0.321 | 1.036 | 1.067 | 0.018 |
| Operative isotropes            | 164      | 93.2%  | 76       | 86.4%  | 0.463  | 0.199  | 1.079    | 0.074  |        |        |        |        |
| Operative warming              | 70       | 39.8%  | 58       | 65.9%  | 2.928  | 1.716  | 4.995    | 0.000  | 1.907  | 1.033  | 3.518  | 0.039  |
| Duration of Surgery            | 141      | 80.1%  | 76       | 86.4%  | 1.572  | 0.771  | 3.206    | 0.213  | 1.293  | 0.573  | 2.916  | 0.536  |

ref: reference.
Table 4. Patient’s outcomes.

| Variable                          | Median | IQR  | N   | %   |
|----------------------------------|--------|------|-----|-----|
| Postoperative Pain (NRS)         |        |      |     |     |
| POD 1                            | 2      | 1–4  |     |     |
| POD 2                            | 2      | 0–3  |     |     |
| POD 3                            | 1      | 0–2  |     |     |
| POD 4                            | 0      | 0–1  |     |     |
| Overall morbidity                | 149    | 32.6%|     |     |
| Major complication               |        |      |     |     |
| 0                                | 27     | 6.2% |     |     |
| 1                                | 290    | 67.0%|     |     |
| 2                                | 54     | 12.5%|     |     |
| IIIa                             | 44     | 10.2%|     |     |
| IIIb                             | 18     | 4.2% |     |     |
| Iva                              | 22     | 5.1% |     |     |
| Ivb                              | 3      | 0.7% |     |     |
| V                                | 2      | 0.5% |     |     |
| Anastomotic leak                 | 27     | 6.2% |     |     |
| Abdominal abscess                | 8      | 1.8% |     |     |
| Respiratory complication         | 11     | 2.5% |     |     |
| Wound infection                  | 16     | 3.7% |     |     |
| Urinary infection                | 12     | 2.8% |     |     |
| Reoperation                      | 24     | 5.5% |     |     |
| Readmission                      | 13     | 3.0% |     |     |
| Day Fit for Discharge            | 5      | 4–8  |     |     |
| Length of stay                   | 6      | 5–8  |     |     |

Figure 1 shows that patients with low compliance on POD 2 had higher overall morbidity and major complications. At multivariate analysis, failure to remove the urinary catheter on POD 2 was significantly correlated with postoperative complications (Table 5).
Table 5. Variables associated with any complication.

| Variables                      | Univariate Analysis | Multivariate Analysis |
|--------------------------------|---------------------|-----------------------|
|                                | OR      | 95% CI | Sign. | OR      | 95% CI | Sign. |
| ASA score 3–4                  | 1.211   | 0.793  | 1.849 | 0.375   |         |       |
| Age                            | 1.000   | 0.983  | 1.018 | 0.968   |         |       |
| Men                            | 1.513   | 0.990  | 2.312 | 0.056   |         |       |
| Diabetes                       | 1.420   | 0.787  | 2.564 | 0.245   |         |       |
| BMI < 25                       | 1 (ref) |       |       |         |         |       |
| BMI 25–29                      | 1.142   | 0.735  | 1.774 | 0.555   |         |       |
| BMI ≥ 30                       | 1.707   | 0.918  | 3.175 | 0.091   |         |       |
| Neoadjuvant CT/RT              |         |       |       |         |         |       |
| Mechanical bowel preparation   | 1.037   | 0.690  | 1.561 | 0.860   |         |       |
| Surgery                        | 1 (ref) |       |       |         |         |       |
| Abdominoperineal amputation    | 1.107   | 0.529  | 2.318 | 0.787   |         |       |
| Successful laparoscopy         | 0.693   | 0.416  | 1.155 | 0.159   |         |       |
| Failure to remove NG tube on POD2 | 1.784 | 0.535  | 5.949 | 0.346   |         |       |
| Failure to have solid diet on POD2 | 2.113 | 1.293  | 3.452 | 0.003   | 1.357   | 0.737  | 2.498 | 0.327 |
| Failure to stop IV fluids on POD2 | 2.191 | 1.445  | 3.321 | 0.000   | 1.518   | 0.895  | 2.574 | 0.122 |
| Failure to remove urinary catheter on POD2 | 2.359 | 1.550  | 3.591 | 0.000   | 1.806   | 1.133  | 2.878 | 0.013 |
| Failure to mobilize >4 h on POD 2 | 1.835 | 1.206  | 2.793 | 0.005   | 1.466   | 0.936  | 2.295 | 0.095 |
| Poorly controlled pain on POD2 (NRS > 3) | 1.882 | 1.142  | 3.101 | 0.013   | 1.430   | 0.839  | 2.438 | 0.189 |

ref: reference.

Table 6 reports data on patients of the Monza subgroup who have a higher rate of ASA 3 compared to the overall series. The TAP block and IMA sparing technique were successfully performed in all patients, while low pneumoperitoneum failed in 5 (14.2%) patients who needed an increase up to 12 mmHg. Lymph-node collection and postoperative pain score were similar to the overall series, while early mobilization was observed in 32 (91.4%) patients. No anastomotic leak occurred.

Table 6. Monza subgroup patients’ characteristics.

| Variable                        | Value | Median | IQR     | N   | %  |
|---------------------------------|-------|--------|---------|-----|----|
| Men                             | 18    | 51     |         |     |    |
| Age ≤ 25                        | 16    | 46     |         |     |    |
| BMI class ≥ 30                  | 11    | 31     |         |     |    |
| ASA score 1                     | 8     | 23     |         |     |    |
| IMA sparing                     | 2     | 5.7    |         |     |    |
| TAP-block                       | 13    | 37     |         |     |    |
| Failure Low Pneumoperitoneum    | 19    | 54     |         |     |    |
| Successful laparoscopy          | 2     | 5.7    |         |     |    |
| Lymph nodes harvested           | 15    | 12–21  |         |     |    |
| POD 1                           | 2     | 2–5    |         |     |    |
| POD 2                           | 2     | 2–5    |         |     |    |
| POD 3                           | 1     | 1–3    |         |     |    |
| POD 4                           | 0     | 0–2    |         |     |    |
| NRS                             |       |        |         |     |    |
4. Discussion

Low compliance to an enhanced recovery protocol was found in about one-third of patients after rectal surgery. Patients with low compliance on POD 2 had higher overall morbidity and major complications. Variables associated with early low compliance were advanced age, long procedure, open surgery, and diverting stoma. Upon multivariate analysis, failure to remove the urinary catheter on POD 2 was significantly correlated with postoperative complications.

Operative fluid overload and inadequate pain control can be determinants of postoperative low compliance to enhanced recovery protocol [20–22]; however, low compliance can also be considered an early sign for underlying complications. In a series of colon cancer patients, the failure to remove the urinary catheter and to stop intravenous fluids on POD 2 was a predictive indicator of morbidity [8]. To detect an early low compliance might yield to identify patients with higher risk to develop complications afterwards. These patients could benefit from proper diagnostics and the early treatment of complications. This is very important, especially in patients with advanced age and multiple comorbidities.

Previous studies found that minimally invasive colorectal surgery had an independent role to favor early postoperative recovery, to reduce overall morbidity, and to shorten the hospital stay [9,10,23,24]. In the present series, successful laparoscopic surgery was widely performed and conversion to laparotomy was necessary in only 2.7% of patients. A multivariate analysis showed that open surgery was the most important variable associated with low compliance to enhanced recovery protocol on POD 2. Our data also suggest that the elderly and patients who were given a long surgical procedure or diverting stoma had a lower compliance rate. Therefore, a tailored approach with a tight postoperative monitoring should be performed in these patients.

The rate of low compliance on POD 2 was similar to that reported following colonic surgery [8]. The lowest protocol adherence was found for removal of the urinary catheter and the stopping of intravenous fluids, whereas the highest adherence was found for nasogastric tube removal and oral feeding recovery. Early low compliance to postoperative protocol was significantly associated with overall morbidity and major complications. In particular, failure to remove the urinary catheter on POD 2 played an independent role to favor postoperative morbidity. A delayed removal of urinary catheter increases urinary tract infections, and reduces the patient’s mobilization favoring respiratory complications [25].

The impact of the three additional operative items was positive. Both TAP block and IMA sparing were successfully performed in all patients, allowing good pain control, no anastomotic leak, and a lymph-node collection comparable to the overall series. A failure of low pneumoperitoneum was recorded in 14% of patients. These promising results and previous reports [20–22] should encourage the incorporation of a TAP block, low pneumoperitoneum, and IMA sparing in the enhanced recovery protocols.

A possible limitation of the present study is that participating hospitals could differ in the degree of enhanced recovery pathway implementation. However, the high adherence

| Variable                              | Value | Median | IQR    | N  | %  |
|---------------------------------------|-------|--------|--------|----|----|
| Mobilization > 4 h POD2               | 32    | 21     | 60     |    |    |
|                                       | 0     | 4      | 11     |    |    |
|                                       | 2     | 6      | 17     |    |    |
| Clavien Dindo                         | 3a    | 1      | 2.8    |    |    |
|                                       | 3b    | 1      | 2.8    |    |    |
|                                       | 4     | 0      | 0      |    |    |
|                                       | 5     | 0      | 0      |    |    |
| Anastomotic leak                      | 0     | 0      | 0      |    |    |
| Fit for discharge, d                  | 6     | 4–7    |        |    |    |
| LOS, d                                | 7     | 5–8    |        |    |    |
| Readmission                           | 3     | 8.6    |        |    |    |

Table 6.

Cont.
to preoperative and operative items indicates that the vast majority of patients followed a comprehensive protocol. The wide range of patients’ age and ASA score suggests a small likelihood of selection bias.

5. Conclusions

In conclusion, early low compliance to postoperative enhanced recovery protocols was associated with overall morbidity and major complications following rectal surgery. Variables associated with early low compliance were advanced age, long procedure, open surgery and diverting stoma, suggesting a tailored and careful approach in these patients.

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