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Liberal perioperative fluid administration is an independent risk factor for morbidity and is associated with longer hospital stay after rectal cancer surgery

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ABSTRACT

INTRODUCTION Recent studies have advocated the use of perioperative fluid restriction in patients undergoing major abdominal surgery as part of an enhanced recovery protocol. Series reported to date include a heterogenous group of high- and low-risk procedures but few studies have focused on rectal cancer surgery alone. The aim of this study was to assess the effects of perioperative fluid volumes on outcomes in patients undergoing elective rectal cancer resection.

METHODS A prospectively maintained database of patients with rectal cancer who underwent elective surgery over a 2-year period was reviewed. Total volume of fluid received intraoperatively was calculated, as well as blood products required in the perioperative period. The primary outcome was postoperative morbidity (Clavien-Dindo grade I–IV) and the secondary outcomes were length of stay and major morbidity (Clavien–Dindo grade III–IV).

RESULTS Over a 2-year period (2012–2013), 120 patients underwent elective surgery with curative intent for rectal cancer. Median total intraoperative fluid volume received was 3680ml (range 1200–9670ml); 65/120 (54.1%) had any complications, with 20/120 (16.6%) classified as major (Clavien–Dindo grade III–IV). Intraoperative volume >3500ml was an independent risk factor for the development of postoperative all-cause morbidity (P=0.02) and was associated with major morbidity (P=0.09). Intraoperative fluid volumes also correlated with length of hospital stay (Pearson's correlation coefficient 0.33; P<0.01).

CONCLUSIONS Intraoperative fluid infusion volumes in excess of 3500ml are associated with increased morbidity and length of stay in patients undergoing elective surgery for rectal cancer.

KEYWORDS

Rectal – Cancer – Surgery – Intravenous – Fluid – Perioperative

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Introduction

Rectal cancer and its treatment remain significant causes of morbidity and mortality, but the past decade has seen substantial improvements, due to improved multimodal diagnostic and therapeutic interventions.[1] Moreover, the introduction of dedicated rectal cancer centres has standardised care and improved outcomes.[2,3] One critical aspect of improved care has been the implementation of protocol-driven enhanced recovery after surgery (ERAS) programmes within these dedicated centres.[4] Recent studies have shown that care pathways incorporating ERAS protocols are associated with improved outcomes, including length of hospital stay, among patients with colorectal cancer.[5] The relative contribution of each component of such pathways remains controversial. In particular, the use of perioperative fluid restriction has been the subject of significant debate and research in recent years. Earlier studies involving patients undergoing a variety of gastrointestinal operations demonstrated that perioperative fluid restriction conferred significant benefits with regard to morbidity and length of stay,[6–9] yet more recent larger studies and meta-analyses involving patients undergoing a range of major abdominal procedures, have shown little difference in outcomes between restrictive and more traditional, liberal fluid regimes.[10,11] A persistent challenge around this issue is the ability to define exactly what constitutes liberal and restrictive fluid regimes and such differences have made studies difficult to compare, adding to the debate. Equally, the heterogeneous populations in studies to date, including operations of greater and lesser complexity, means that results may not be generalizable to higher-risk populations, such as those undergoing proctectomy.

There is little evidence regarding the role or effect of different fluid regimens on outcomes after rectal cancer surgery, with only a small number of studies published to date examining this issue specifically.[12,13] Standardisation of care pathways and outcome measures used for rectal cancer resection in large-volume centres allow the opportunity to evaluate the impact of intraoperative fluid therapy in this higher-risk population.

Methods and materials

Study type and patient identification

A prospectively maintained oncological database within a single, dedicated rectal cancer tertiary referral centre, involving all patients diagnosed with primary rectal cancer over a 2-year period (1 January 2012 to 31 December 2013) was retrospectively reviewed. This was performed in keeping with guidelines proposed by the STROBE statement (**STrengthening the Reporting of OBservational studies in Epidemiology**).[14,15] Patients who underwent elective surgical resection for histologically diagnosed rectal cancer were identified. Patients were excluded if they did not have surgery, had evidence of malignancy elsewhere, underwent emergency resection or were undergoing a palliative procedure. In cases where details were absent from the database, medical charts were reviewed to ensure accuracy.

Patient characteristics recorded included date of birth (age), sex and American Society of Anesthesiology (ASA) grade. Oncological characteristics recorded included tumour location, TNM stage, use of neoadjuvant or adjuvant chemotherapy and radiotherapy (including regimen and dose/fraction respectively), surgical procedure, surgical approach, formation of ileostomy, need for reoperation, radial margin status and number of nodes (and associated positive nodes) excised. Rectal cancer was defined as a tumour ≤15cm from the anal verge, measured using a rigid proctoscope. The location of the tumour was classified as low (0–5cm), medium (5.1–10cm) and high (10.1–15cm).

Intraoperative fluid use and standard procedures

The intraoperative period was defined as beginning from induction of anaesthesia to cessation of anaesthesia, as recorded in anaesthesia records. Fluid data collected included fluid volume received, fluid type, and use of blood products intraoperatively. These details were recorded from intraoperative anaesthesia notes, which were maintained for every patient. If these notes were not available, the patient was excluded. Fluid volumes received on postoperative day 1 were also recorded. Postoperative day 1 was defined as the 24-hour period beginning at 7am the day after surgery.

All patients were treated using a standardised care pathway, including enhanced recovery protocols, and were coordinated by a dedicated enhanced recovery nurse. Operations were performed using an open or a laparoscopic method and this decision, as well as whether or not to perform sphincter-preserving surgery or abdominoperineal resection, was made by the operating surgeon, taking oncologic and patient characteristics into account. Similarly, the use of intraoperative faecal diversion with loop ileostomy was at the discretion of the operating surgeon. Every patient was discussed at a multidisciplinary team meeting pre- and postoperatively. All patients underwent standard total mesorectal excision. Lateral pelvic sidewall node dissection was performed in selected cases when nodal metastases were suspected.Abdominoperineal resection was performed in the lithotomy position. All patients had central venous lines and peripheral arterial lines inserted under aseptic technique, as well as undergoing urethral catheterisation after induction of general anaesthesia. The use of epidural blocks was at the discretion of the consultant anaesthesist. All patients also received perioperative antibiotics and underwent rectal washout with chlorhexidine intraoperatively.

Outcomes

The primary outcome was postoperative morbidity. This was defined as any morbidity, as defined by the Clavien-Dindo classification system,[16] occurring within 30 days of surgery. Secondary outcomes included major morbidity, defined as any complication meeting Clavien–Dindo grade II–IV criteria, and length of hospital stay for each patient. Complications were recorded in clinical notes by the surgical team and a rectal cancer clinical nurse specialist. Anastomotic leaks were classified as being either clinical or radiological and were defined as per the International Study Group of Rectal Cancer.[17] All patients in whom an anastomosis was formed underwent a gastrograffin enema study at postoperative Day 3–5 to assess for evidence of a leak. Morbidities were captured systematically by a nurse trained in data collection. All written and electronic clinical records were systematically examined at the time of discharge by trained data coordinators and a Dendrite (Dendrite Clinical Systems Ltd, Henley-on-Thames, Oxon) database entry was completed for every patient. Any uncertainty regarding outcomes was checked by independent anonymised parties to avoid reporting bias.

Statistical analysis

Data are presented as medians for non-normally distributed data. Categorical data were analysed using Fisher's exact test or the Chi-square test. The association between clinical factors, pathological characteristics, primary/secondary outcomes and intraoperative fluid volume received was analysed using binary logistic regression, including both univariate and multivariate analyses. All variables were included in the multivariate analyses. This was done to assess whether intraoperative fluid volume received was an independent risk factor for development of all-cause morbidity or major morbidity in the postoperative period. No subgroup analyses were performed. Correlation was performed using Spearman's correlation coefficient. A P-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 19.0 (IBM).

Results

Between 1 January 2012 and 31 December 2013, 127 patients underwent elective curative resection for rectal cancer. Seven patients were excluded from analysis owing to lack of sufficient data. Of the 120 patients remaining, 93 (77.5%) were male and 27 (22.5%) were female (male : female ratio = 3.44 : 1). The median age of patients included was 65.3 years (range: 32–86 years) with 10 patients less than 50 years, 71 between 50–70 years and 39 patients were over 70 years. ASA grade was available for 103 of 120 patients: 9 (7.5%) were ASA grade I, 70 (58.33%) were ASA grade II and 24 (20%) were ASA grade III. All patients were treated by an enhanced recovery protocol. Median preoperative body mass index was 26.2 but this was not available for all patients and so was not included as part of statistical analysis.

Regarding clinicopathological characteristics, 45 patients (37.5%) had tumours 0–5cm from the anal verge, 40 (33.3%) had tumours at a distance of 5.1–10cm and 35 (29.16%) had tumours at a distance of 10.1–15cm. Most (*n*=92) patients underwent neoadjuvant radiotherapy, using a standard protocol of 50.4 Gy in 28 fractions over 6–8 weeks. Of these, the majority (*n*=81) received combined chemoradiotherapy with 5-fluorouracil based regimens being the most commonly administered. Regarding surgical resection, 88 patients (73.7%) underwent anterior resection, 25 (20.83%) had abdominoperineal resection (APR) and 7 (5.83%) had other procedures, including 4 local excisions (1 transanal), 2 Hartmann's procedures and a panproctocolectomy in a patient with significant premalignant morbidity; 81 patients (67.5%) had an open procedure and the remainder (*n*=39; 32.5%) had laparoscopic procedures. All but five patients (5.7%) undergoing anterior resection had a loop ileostomy fashioned. Of the patients undergoing a laparoscopic approach, none required conversion to an open approach. The median pathological tumour stage post-excision was T3 (range: 0–4) and the median number of nodes excised was 13 (range: 2–32). The median number of positive nodes was 0 (range: 0–11), 24.2% had evidence of nodal involvement and 4 patients had a positive radial margin.

The median volume of fluid administered intraoperatively was 3680ml (range: 1200–9670ml). Seventy patients (58.33%) received ≥3500ml intraoperatively, with the remainder receiving <3500ml. All patients routinely received compound sodium lactate solution (Hartmann's solution) as fluid of choice intraoperatively, per institutional practice; 38/120 patients also received Gelofusine® (B. Braun Medical Ltd, Sheffield, UK) during the operation; 13 patients required blood products during their operations. Where this occurred, the median number of pooled red blood cell units received was two; one patient also required platelets. The median volume of fluid administered on postoperative day 1 was 3335ml (range: 625–5852ml); 47.5% of patients received ≥3500ml on postoperative day 1.

A total of 65 patients experienced morbidity of any grade (Clavien–Dindo grade I–IV), of which 20 were classified as major (Table 1). The most common major morbidity was anastomotic leak (*n*=11 of 88 anterior resections), of which six were clinical and five radiological. Eight patients required reoperation during their index admission, five of whom for an anastomotic leak. The median length of stay was 8 days (range 4–49 days); 17 patients required readmission within 30 days of initial operations (14.1%). There were no postoperative mortalities.

Table 1 All-cause and major morbidity (*n*=120)

Complication	Patients (*n*)	(%)	Clavien–Dindo grade
Patients with morbidities	65	54.1	I–IV
Minor			
Wound dehiscence not requiring antibiotics	4		I
Wound infection	1		II
Urinary retention	11		I
Ileus	19		I/II
Respiratory tract infection	4		II
Atrial fibrillation requiring rate control	5		II
Persistent hypotension	6		I/II
Anaemia requiring transfusion	4		II
Sepsis requiring antibiotics	6		II
Electrolyte disturbance/renal dysfunction	5		II
Pelvic collection requiring antibiotics only	3		II
Major			
Anastomotic leak	11		III–IV
Clinical (requiring operative intervention)	6	4	
Radiological (requiring operative intervention)	5	1	
Pelvic/presacral abscess requiring drainage	2		IIIa
Postoperative haemorrhage requiring reoperation	2		IIIb
Small bowel perforation requiring reoperation	2		IIIb
Sepsis requiring intensive care admission	2		IVb
Pulmonary embolus requiring intensive care	1		IVa
Renal failure	1		IVa

Regarding primary outcome, receiving more than 3500ml of fluid intraoperatively was associated with an increased risk of all-cause postoperative morbidity (64% vs. 40%; odds ratio, OR, 2.7, P = 0.008) on univariate analysis (Table 2). The level of 3500ml was chosen because of its close proximity to the median fluid volumes received in this cohort and supporting evidence from the ERAS compliance group, indicating 3500ml as the value below which a perioperative fluid regimen for a patient undergoing elective rectal cancer resection is described as restrictive.[5] Patients with ASA

Table 2 Univariate analysis to assess effect of patient/clinicopathological factor and fluid volumes on all-cause morbidity

Factor	*P* value	Odds ratio	Confidence interval
Sex	0.48	0.73	0.31–1.72
Age (years):			
< 50	0.29	2.09	0.51–8.51
50–70	0.36	0.71	0.34–1.48
> 70	0.73	1.14	0.53–2.46
Tumour height:			
0–5cm	0.89	0.95	0.45–1.98
5.1–10cm	0.36	1.42	0.66–3.08
10.1–15cm	0.43	0.73	0.33–1.6
Neoadjuvant radiotherapy	0.22	0.58	0.24–1.39
Surgery type:			
Anterior resection	0.23	1.61	0.73–3.56
Abdominoperineal resection	0.83	0.91	0.36–2.25
Surgical method:			
Open	0.67	1.17	0.54–2.56
Laparoscopic	0.67	0.85	0.39–1.84
ASA grade:			
I	0.53	0.71	0.24–2.09
II	0.41	0.73	0.34–1.54
III	0.16	1.85	0.78–4.43
Fluids ≥ 3500ml	0.008	2.7	1.27–5.70

Table 3 Multivariate analysis to assess effect of patient/clinicopathological factor and fluid volumes on all-cause morbidity

Factor	*P* value	Odds ratio	Confidence interval
Gender	0.42	0.69	0.35–1.77
Age:			
< 50	0.26	2.02	0.52–8.56
50–70	0.38	0.65	0.38–1.44
> 70	0.77	1.09	0.58–2.47
Tumour height:			
0–5cm	0.9	0.97	0.46–1.99
5.1–10cm	0.38	1.37	0.69–3.15
10.1–15cm	0.48	0.76	0.38–1.7
Neoadjuvant radiotherapy	0.27	0.62	0.23–1.44
Surgery type:			
Anterior resection	0.26	1.45	0.77–3.59
Abdominoperineal resection	0.86	0.93	0.38–2.28
Surgical method:			
Open	0.69	1.12	0.57–2.59
Laparoscopic	0.69	0.88	0.36–1.89
ASA grade:	0.57	0.74	0.28–2.18
I	0.45	0.78	0.31–1.63
II	0.21	1.81	0.75–4.3
III			
Fluids ≥ 3500ml	0.018	2.6	1.67–5.18

grade 3 had a non-significant tendency towards greater complications (OR 1.9; *P*=0.16). On multivariate analysis, patients who received more than 3500ml of fluid intraoperatively were more likely to suffer complications in the postoperative period (OR 2.6, *P*=0.01). When considering secondary outcomes length of hospital stay correlated with intraoperative fluid volume received (Spearman's correlation coefficient 0.36; *P*=0.001). Patients who received more than 3500ml intraoperatively were more likely to have length of stays above the median of 8 days (Chi-square test; *P*=0.03). While receiving more than 3500ml intraoperatively was associated with higher rates of major morbidity (35.7% vs 22%; OR 2.4) this was not statistically significant (*P*=0.09). On examining individual morbidities, the rate of anastomotic leak (clinical or radiological) was higher in the group receiving more than 3500ml (11.4% vs 6%) but this was not statistically significant (Chi-square test; *P*=0.30). Of the six patients diagnosed clinically with anastomotic leaks, only one had received less than 3500ml, with a mean of 4460ml being administered intraoperatively to the remaining five. Receiving more than 3500ml on postoperative day 1 was associated with an increased risk of any morbidity but this was not statistically significant (Chi-square test; *P*=0.054). Receiving more than 3500ml on postoperative day 1 was not associated with major morbidity (Chi-square test; *P*=0.75).

Twenty-four patients received epidural anaesthetic blocks in the perioperative period. Within this group, the mean fluid volume received intraoperatively was 3198ml (range 1500–5100ml). Patients who underwent a laparoscopic approach received a mean intraoperative fluid volume of 3401ml (range 1500–7250ml) compared with a mean intraoperative fluid volume of 3787ml (range 1000–10,000ml) in those treated with an open approach. When examining resection types, patients undergoing anterior resection received a mean intraoperative volume of 3601ml (range 1500–7250ml) compared with 4213ml (range 1486–10,000ml) in the abdominoperineal resection group.

Discussion

This study shows that patients undergoing elective resection of rectal cancer with curative intent are more likely to experience complications and will have a longer hospital stay if they receive more than 3500ml of fluid intraoperatively. While other studies previously performed have focused on the effect of fluid volumes in heterogeneous general surgical populations[18–20] or the effects of fluid volumes on the incidence of specific complications in rectal cancer patients, few examine such effects on the incidence of all-cause morbidity and length of stay in rectal cancer surgery alone. Studies by Lee *et al*[12] and Boesen *et al*[13] examined the effect of perioperative fluid volumes on rates of postoperative urinary retention and anastomotic leak respectively. Both studies found results similar to our findings, yet our study, to our knowledge, is the first to examine the effect of intraoperative fluid volumes on all-cause morbidity in a rectal cancer population. On multivariate analysis, the only independent risk factor predictive of morbidity was the volume of fluid administered intraoperatively. Clinicopathological characteristics such as tumour height, resection type and the use of adjuvant and neoadjuvant therapies can influence morbidity rates[21–23] but in most cases are not modifiable. In our study, such characteristics were not found to be independent risk factors for the development of postoperative all-cause or major morbidity. The only independent risk factor found to increase such morbidity was the volume of fluid administered during the operation.

All patients in our cohort were treated using a protocol-based care pathway including carbohydrate preloading, early mobilisation, early feeding and a standardised analgesic regime. Our study indicates that patients who receive less intraoperative fluid as part of this protocol experience less morbidity and go home sooner. A recent multicentre retrospective study published by the ERAS compliance group included details of over 860 rectal cancer cases throughout 13 centres.[5] In this cohort, increasing ERAS compliance correlated with reduced postoperative morbidity and patients managed with restrictive fluid regimens suffered fewer complications. The role of fluid restriction is likely synergistic with other aspects of the ERAS pathway in improving outcomes. For example, although not considered in this trial, use of oesophageal Doppler-guided goal directed fluid administration during such surgery may also be beneficial as previous evidence has suggested.[24–26] While a recent randomised controlled trial suggests that fluid restriction in isolation does not confer benefit,[11] even the control group in that study received less than 2500ml, suggesting that the threshold for benefit falls somewhere between the 2500ml reported in that series and the 3500ml cut-off that we report. Standardisation of the definition of restrictive fluid regimens is required to allow meta-analysis and it appears that more extreme fluid restriction beyond the range of 2500–3500ml range may confer no advantage.

This study also found that fluid volumes administered intraoperatively correlated with length of stay. Patients administered more than 3500ml intraoperatively were more likely to stay in hospital beyond the median of 8 days, even when enhanced recovery protocols were used. This is consistent with the findings of previous studies.[7] A possible explanation for this is the rate of ileus (n=19) in the postoperative period which may have delayed discharge. It has previously been shown that ileus is more common when patients receive ‘high volume’ fluid regimens.[27] Over two-thirds of patients in our cohort had an open operation, increasing the chances of postoperative ileus. The combination of a laparoscopic approach and cautious fluid regimens in the range of 2500–3500ml may reduce rates of postoperative ileus and length of stay.

Our study observed an association between fluid volumes and major morbidity, although this was not found to be statistically significant. The most common observed major morbidity was anastomotic leak with six patients requiring operative intervention. Previous studies have also found that fluid volumes directly impact upon the incidence of anastomotic leaks.[27,28] It is postulated that increased fluid volumes can cause tissue oedema thereby reducing anastomotic strength.[29] This is particularly important in rectal cancer surgery as anastomotic leakage is associated with poor outcomes.[23,30] Our study found that anastomotic leaks were more common in the group that received more than 3500ml but this was not statistically significant. Of the 11 patients with anastomotic leaks, 6 were clinically evident and 5 were diagnosed radiologically. Of the 6 patients with a clinical leak, 5 had received more than 3500ml, while only 1 patient had received less than 3500ml but again this was not statistically significant (P=0.20).

Our study has a number of limitations. We have not included operative time in our analysis. Prolonged operative time is likely to influence total fluid volume administered, and longer operative times may also be associated with adverse outcomes, but identifying causal relationships in the small cohort of patients with very prolonged theatre time is complex. We did not have complete data on the number of patients who received bowel preparation and so this was not included in our analysis, but it may have had an influence on intraoperative fluid volumes administered and, possibly, on outcomes. However, it is institutional policy that patients undergoing elective rectal cancer resection, especially anterior resection, do receive bowel preparation unless there is a significant contraindication. It is likely that the majority of the cohort above did receive bowel preparation and our results should be interpreted with this in mind. Our cohort included 120 patients and it is possible that, with more patients, a statistically significant association between fluid volumes and major morbidity would be observed. A larger study or meta-analysis involving rectal cancer patients alone is required to verify the significance of such an association.

Conclusion

This study includes a series of 120 patients undergoing rectal cancer resection with curative intent in a high-volume rectal cancer centre, using a standardised care pathway that incorporates components considered necessary for enhanced recovery after surgery. In this context, liberal intraoperative fluid regimens, defined as those where a patient receives more than 3500ml fluid intraoperatively, are associated with an increased risk of all-cause postoperative morbidity and a more prolonged length of hospital stay. In conjunction with studies by other groups, this suggests a range of intraoperative fluid administration of 2500–3500ml may be a useful threshold for future evaluations aimed at assessing relationships between intraoperative fluid volumes and patient outcomes.

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