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Orthostatic intolerance in enhanced recovery laparoscopic colorectal resection

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Abstract

Background: Orthostatic hypotension (OH) and intolerance (OI) are common findings in the early postoperative period after major surgery and may delay early mobilization. The mechanism of impaired orthostatic competence and OI symptoms is not fully understood, and specific data after colorectal surgery with well-defined perioperative care regimens and mobilization protocols are lacking. The aim of this study was to investigate the prevalence, possible risk factors and the impact of OI in patients undergoing elective minimal invasive colorectal cancer resection.

Methods: A prospective single-centre study with an optimal enhanced recovery program and multimodal analgesic treatment. OI and OH were evaluated using a well-defined mobilization protocol preoperatively and 6 hour and 24 hour postoperatively.

Results: A total of 100 patients were included in the data analysis. The overall median length of stay was 3 days (1-38). OI was observed in 53% of the patients 6 hour postoperatively and in 24% at 24 hour. OI at 6 hour postoperatively was associated with younger age, lower BMI, and female gender. At 24 hour postoperatively, female gender and ASA class >1 was associated with OI. Opioid consumption and intravenous fluid during the first 24 hour was not associated with OI. Postoperative complications were equally observed between patients with and without OI. Although not statistically significant, patients with OI at 24 hour postoperatively had prolonged LOS (mean 4.0 vs 7.5 days, $P = 0.069$) compared with patients without OI.

Conclusion: Postoperative orthostatic intolerance is a common problem during the first 24 hour following laparoscopic colorectal resection and may be followed by delayed recovery.

1 | INTRODUCTION

Orthostatic hypotension (OH) and intolerance (OI) are common findings in the early postoperative period after major surgery and may delay early mobilization, which is a central part of modern perioperative care programs.[1,2] Orthostatic intolerance is characterized by subjective presyncope symptoms upon mobilization and implies a risk of fall injury. The mechanism of impaired orthostatic competence and OI symptoms is not fully understood, but includes elements of postoperative autonomic dysregulation and decreased vasopressor response with reduced cerebral perfusion.[1] However, most data come from patients undergoing prostatectomy[3] and hip replacement[4] with sparse data from other procedures, including patient-related factors and type of perioperative care regimens.

The aim of this study was to investigate the prevalence, possible risk factors and the impact of OI in patients undergoing elective laparoscopic colorectal cancer resection in an enhanced recovery after surgery (ERAS) program with a well-defined mobilization protocol and multimodal analgesic treatment.

2 | MATERIAL AND METHODS

The study was carried out as a prospective single-centre study in a high-volume colorectal cancer unit, performing more than 300 minimal invasive colorectal cancer resections yearly. All patients aged 18 years or above, scheduled for an elective minimally invasive oncologic colorectal resection were recruited for a hypothesis-generating prospective study, investigating OI in relation to optimized patient care. A maximum of four patients could be included per week due to logistics and to ensure good data quality. Patients planned for abdominoperineal resections, total colectomies, palliative resections or patients with peritoneal carcinomatosis, conversion to open surgery, and/or postoperative epidural analgesia, were not included or were excluded postoperatively. All patients were enrolled by the same study nurse without any specific selection according to age, gender, tumour location, or others. The primary outcome was prevalence of OI and secondary outcome parameters were parameters associated with postoperative OI and length of stay.

2.1 | Perioperative care program

Patients and their relatives were informed by the nursing staff team, a dietician, and a physiotherapist, about key points in the ERAS program such as postoperative mobilization, importance of early oral intake, treatment of postoperative pain and nausea, and respiratory movements and exercises. Patients met on the ward on the evening before surgery. At 6 A.M on the day of surgery, all patients received a 250 mL carbohydrate beverage (lemonade). Bowel cleansing was performed routinely only in patients undergoing low anterior resection with a diverting loop-ileostomy. Other left-sided resections were prepared with rectal enemas the evening before surgery and in the morning at the day of surgery. Venous thrombosis prophylaxis included leg compression bandage and low-molecular-weight heparin (5000 anti-Factor Xa international units Deltaparin 20.00 P.M.), starting the evening before surgery and until discharge. No other premedication was used.

General anaesthesia was induced with propofol, fentanyl, and rocuronium. After endotracheal intubation, anaesthesia was maintained with propofol and ramifentanil in a propofol-based total intravenous anaesthesia. A single prophylactic intravenous dose of 1 gram metronidazole and 240 mg gentamicin was administered at induction and intraoperative fluid therapy was managed with 0.9% saline or Ringer's lactate at the discretion of the anaesthesiologist. Blood transfusion followed the national transfusion guidelines and thresholds with haemoglobin threshold for red blood cell transfusion: < 4.3 mmol/L for adults, <5.0 in chronic stable ischemic heart disease and < 5.6 mmol/L in life-threating ongoing bleeding.

Editorial Comment

Postoperative recovery for individual patients presumably is supported by good cardiovascular performance. This study explored orthostasis and orthostatic intolerance in a specific surgical cohort. The findings demonstrate that the problem occurs in a large number of patients during the first postoperative day, though a common mechanism is not yet clear.

Ondansetron was given routinely to all patients and dexamethasone was only administered on indication (eg. PONV prophylaxis). A transurethral indwelling urinary catheter and a nasogastric tube were placed during surgery, but the nasogastric tube was removed after extubation.

Pain management in the postanaesthesia care unit (PACU) included routine administration of acetaminophen and intravenous opioid when necessary. Removal of the bladder catheter was done in the PACU following colonic resections and on postoperative day 1 following rectal resections. No routine use of intra-abdominal drain. Patients were allowed to drink and eat freely immediately after surgery without restrictions. After discharge from PACU, intravenous fluids were only administered on the indication of limited overall oral fluid intake.

All patients were administered nasal oxygen supply (2 L/min) during the first two postoperative nights. The standard postoperative mobilization protocol started when the patients arrived on the ward and included rising from supine to sitting, from sitting to standing and walking on the ward with assistance from a nurse.[5] All patients were urged to use chewing gum for a minimum of 5 minutes three times a day. All patients received 2 gram magnesium oxide daily and 4 gram paracetamol daily, starting on the day of surgery. Opioids were not administered routinely but only on demand, and nausea was treated with ondansetron orally on demand.

2.2 | Data sampling and measurements

Data concerning resection type, postoperative opioid consumption, perioperative intravenous fluid administration, duration of surgery and anaesthesia, patient weight, height and performance score, comorbidity and intraoperative bleeding, were measured and collected by the study nurse and the nursing team. Postoperative opioid consumption was calculated as oral morphine equivalent (omeq) dose. Opioid use was differentiated into opioid use in the PACU and total opioid use on the day of surgery (postoperative day 0, POD 0), calculated from patient arrival in the PACU until 23.59 P.M. Perioperative intravenous fluid administration was defined as 'i.v fluid OR+PACU' containing the amount of fluid administered from induction of anaesthesia until departure from the PACU, and 'i.v fluid POD0' containing the amount of fluid administered from induction of anaesthesia until 23.59 P.M on POD0. Patient frailty was assessed by using the validated “Timed Up and Go”- test, TUG-test.[6]

2.3 | Orthostatic hypotension and intolerance

A standardized lying-to-standing orthostatic blood pressure measurement was performed preoperatively and 6 hour and 24 hour postoperatively to assess OH and OI. A beat-to-beat noninvasive continuous blood pressure measurement was performed using a pulse oximeter (Nexfin, BMeye) attached to the patients third finger and placed around heart level. After 5 minutes of rest in the supine position, patients were mobilized to sitting position and after further 3 minutes the patients were mobilized to upright position. OH was defined as a decrease in systolic blood pressure ≥20 mm Hg or a decrease in diastolic blood pressure ≥10 mm Hg in the sitting or upright position.[5] Presence of OI was defined as appearance of one of the following presyncope symptoms upon mobilization to sitting and upright position during the orthostatic test: dizziness, nausea or vomiting, feeling of heat or blurred vision. The test was stopped if symptoms of OI or a decrease in systolic blood pressure ≥30 mm Hg was measured (compared to blood pressure at test start).

2.4 | Statistics and ethics

No formal power calculation could be made due to nature of a hypothesis-generating study without any previous data in the literature. Statistical analysis was performed using IBM SPSS version 21 software (IBM Corp., Armonk, NY, USA). All data are presented as medians (range), if not stated otherwise. A *P*-value <0.05 was considered significant. All continuous variables were tested by using the nonparametric Mann-Whitney test. Categorical data were analysed using the chi-square test or Fisher's exact test when appropriate. Oral and written informed consent was obtained from all participants. The study was a quality assurance study of nature and has been reported to the Danish Data Protection Agency (REG-044-2018) but did not require further approvals. All patients received standard perioperative care and follow-up.

3 | RESULTS

A total of 115 patients were included in the study from September 2016 to June 2017, of which 15 patients were excluded due to peritoneal carcinomatosis (n = 2), withdrawal of consent after surgery (n = 2), change of surgical procedure (abdominoperineal excision, n = 3 and total colectomy, n = 1), conversion into open surgery (n = 5) and epidural analgesia (n = 2). One patient received a peripheral nerve block in the PACU following a colonic resection. Patient characteristics and other relevant parameters are presented in detail in Table 1.

Preoperatively, data regarding OH and OI were measured in 99 and 98 patients (of 100 patients), respectively. Postoperatively, OI data were measured in 87 of 100 patients at 6 hour and 91 of 100 patients at 24 hour. Correspondingly, OH data were measured in 81 patients at 6 hour and 91 patients at 24 hour postoperatively. The missing data were caused by lack of mobilization due to other reasons than OI at the time of measurement and logistical reasons.

OI was observed in 53% of the patients 6 hour postoperatively but declined to 24% after 24 hour (Figure 1). Overall, 60% experienced OI during the first 24 hour postoperatively (Figure 1). The combined presence of OH and OI was observed in 50% of the patients 6 hour postoperatively, and in 16% after 24 hour.

TABLE 1 Patient characteristics and relevant perioperative parameters and outcomes

	N = 100
Male	59
Age, years	70 (52-88)
Body mass index, kg/m^2	27.1 (16.7-40.2)
ASA group	
1	35
2	51
3	14
Performance score	
0	93
1	6
2	1
Comorbidity	
Hypertension	36
Diabetes	15
Surgical procedure	
Rectal resection	28
Colonic resection	72
Primary surgical approach	
laparoscopic	76
robotic-assisted	24
Patients with anastomosis	93
Patients with stoma	19
Patients with nerve block	1
Perioperative blood transfusion	0
Reoperation, number of patients	9
Readmission, number of patients	6
Surgical complications, CD ≥3, number of patients	12
Medical complications, CD ≥ 3, number of patients	6
LOS, days	
Colonic resection	3 (1-38)
Rectal resection	3.5 (1-21)

ASA, American Society of Anaesthesiologists; CD, Clavien-Dindo; LOS, length of stay.
Values are reported as median (range) and as numbers for categorical variables.

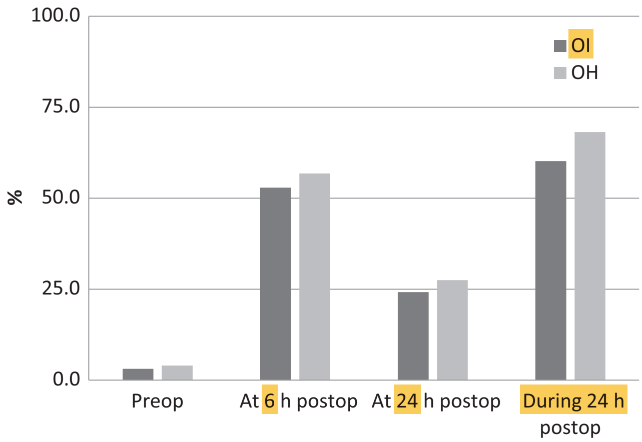

FIGURE 1 Prevalence of orthostatic hypotension (OH) and intolerance (OI) preoperatively, 6 h and 24 h after surgery and during the first 24 h postoperatively. Data are presented as percent (%) of patients observed

There was no difference in OI between patients undergoing colonic or rectal resection at any time postoperatively (Tables 2 and 3). Patients with OI 6 hour postoperatively were significantly younger, with lower BMI and included more females compared with patients without OI (-OI), Table 2. At 24 hour postoperatively, female gender and ASA class >1 were predominant in the +OI group, Table 3. Postoperative complications were equally observed between patients with and without OI (Table 4) but patients with OI at 24 hour had an insignificant prolonged LOS (P = 0.069) compared with patients without OI (Table 4).

There was a significant increase in TUG-score from preoperative testing to discharge (9.3 seconds vs 10.7 seconds, P = 0.002). The number of patients with TUG-score >14 seconds increased from 5/100 (5%) preoperatively to 17/86 patients (20%) at discharge, P = 0.002. We found no association between TUG-score and postoperative OI. Opioid consumption, intravenous fluid administration, duration of surgery and anaesthesia, performance score, intraoperative bleeding, preoperative TUG-score >14 seconds and prevalence of hypertension and diabetes were not associated with postoperative OI (Tables 2 and 3).

TABLE 2 Univariate analysis of possible predictors for *orthostatic intolerance 6 h postoperatively*

	−OI (n = 41)	+OI (n = 46)	*P*-value
Resection type			
Colonic	29	34	0.740
Rectal	12	12	
Opioid PACU (omeq), mg	0 (0-84)	21 (0-88)	0.311
Opioid POD0 (omeq), mg	25 (0-156)	34 (0-130)	0.701
I.v fluid OR+PACU, mL	2083 (818-4941)	2170 (962-4417)	0.831
I.v fluid POD0, mL	2702 (1329-6341)	2886 (1662-5417)	0.529
Male: female ratio	30:11	23:23	**0.027**
Age, years	73 (65-84)	69 (54-88)	**0.008**
Operative time, min	167 (117-304)	180 (93-430)	0.637
Anaesthetic time, min	230 (177-403)	242 (177-543)	0.654
Body mass index, kg/m^2	27.1 (18.4-39.4)	25.0 (16.7-39.4)	**0.022**
ASA			
1	16	17	0.814
2	20	25	
3	5	4	
Performance score			
0	39	41	0.129
1	1	5	
2	1	0	
Intraoperative bleeding, mL	25 (0-200)	25 (0-1500)	0.623
Preop. TUG-test time > 14 s	1	4	0.211
Hypertension	15	15	0.697
Diabetes	6	4	0.386

+OI, OI present; ASA, American Society of Anaesthesiologists; −OI, no OI present; OI, orthostatic intolerance; omeq dose, oral morphine equivalent dose; PACU, postanaesthesia care unit; POD, postoperative day.
OI was measured in 87 of 100 patients at 6 h postoperatively. TUG test, timed up and go test. Values are reported as median (range) and as numbers for categorical variables. Statistical significant values are high-lighted with bold font.

4 | DISCUSSION

The main finding of this prospective observational study was that orthostatic hypotension and intolerance had a high prevalence in the early postoperative period following fast-track laparoscopic colorectal resection, since 60% of the patients experienced OI during the first 24 hour postoperatively. Female gender, lower age and BMI and ASA class >1 were associated with postoperative OI.

We found a low association between postoperative OH and OI, which has also been shown in patients with epidural analgesia after major abdominal and thoracic surgery.[7] Thus, OI may be the most clinical relevant parameter for postoperative orthostatism, and consequently the focus for future interventional studies.

It has been shown in several studies, that nonadherence to one or more ERAS principles predict prolonged hospital stay and increased complication and readmission rate.[8] Early postoperative ambulation is an essential part of modern perioperative care programs and is a prerequisite to achieve a short and complication-free hospital stay.[9] However, early mobilization is delayed in patients suffering early postoperative OI, and this might explain our finding of an insignificant prolonged stay in hospital in the OI

TABLE 3 Univariate analysis of possible predictors for *orthostatic intolerance 24 h postoperatively*

	−OI (n = 69)	+OI (n = 22)	*P*-value
Resection type			
Colonic	51	15	0.600
Rectal	18	7	
Opioid PACU (omeq), mg	13 (0-84)	26 (0-88)	0.149
Opioid POD0 (omeq), mg	30 (0-156)	50 (10-130)	0.122
I.v fluid OR+PACU, mL	2083 (818-4941)	2266 (962-3964)	0.726
I.v fluid POD0, mL	2768 (1329-6341)	3108 (1662-5058)	0.875
Male:female ratio	45:24	7:15	**0.006**
Age, years	71 (52-83)	70 (56-88)	0.290
Operative time, min	178 (117-363)	176 (132-430)	0.388
Anaesthetic time, min	239 (177-403)	235 (186-543)	0.894
Body mass index, kg/m^2	27.1 (16.7-39.4)	26.2 (21.6-39.4)	0.951
ASA			
1	28	3	**0.040**
2	30	16	
3	11	3	
Performance score			
0	65	20	0.405
1	3	2	
2	1	0	
Intraoperative bleeding, mL	23 (0-1500)	25 (0-300)	0.821
Preop. TUG-test time > 14 s	3	2	0.395
Hypertension	23	11	0.159
Diabetes	9	5	0.273

+OI, OI present; ASA, American Society of Anaesthesiologists; −OI, no OI present; OI, orthostatic intolerance; omeq dose, oral morphine equivalent dose; PACU, postanaesthesia care unit; POD, postoperative day.
OI was measured in 91 of 100 patients at 24 h postoperatively. TUG test, timed up and go test. Values are reported as median (range) and as numbers for categorical variables. Statistical significant values are highlighted with bold font.

TABLE 4 Postoperative outcomes according to presence of OI

At 6 h postop (n = 87)	−OI (n = 41)	+OI (n = 46)	*P*-value
LOS, days	3 (1-21)	3 (1-27)	0.467
Surgical complications, CD ≥3, n	4	6	0.631
Medical complications, CD ≥3, n	3	1	0.253
At 24 h postop (n = 91)	**−OI (n = 69)**	**+OI (n = 22)**	***P*-value**
LOS, days	3 (1-24) mean 4.0	3 (2-38) mean 7.5	0.069
Surgical complications, CD ≥3, n	6	5	0.079
Medical complications, CD ≥3, n	3	3	0.126

+OI, OI present; CD, Clavien-Dindo; LOS, length of stay; −OI, no OI present; OI, orthostatic intolerance.
OI was measured in 87 of 100 patients at 6 h postoperatively and in 91 patients at 24 h postop. LOS data are reported as median (range) and mean values, and categorical variables as numbers.

group as also shown in prostatectomy.[10] Consequently, further focus on factors hindering early postoperative mobilization and OI is required.

Different surgical procedures imply different prevalence of postoperative OI. Following a 1-2 hour mastectomy in general anaesthesia, the incidence of early OI has been reported as low as 4%.[11] Following major procedures such as open prostatectomy, gastrectomy, total hip arthroplasty and video-assisted thoracic surgery (VATS) the prevalence of OI at 6 hour postoperatively has been reported from 42%-60% and 22-24 hour postsurgery at 12%-35%.[3,4,12,13] These results are similar to our OI prevalence at 6 hour (53%) and 24 hour (24%) postoperatively, and emphasizes that laparoscopic colorectal surgery is a major procedure with substantial impact on patient's postural competence and regulation.

The postoperative inflammatory response generated by a surgical procedure may be a potential pathogenic factor for postoperative OI. However, one randomized study investigating the effect of low (i.v hydrocortisone equivalent to preoperative oral dosing, followed by taper) vs high (100 mg hydrocortisone i.v every 8 hour, followed by taper) dose steroid on postoperative OH included 92 patients undergoing open or laparoscopic benign bowel resection,[14] and reported a low overall prevalence of postoperative OH and no difference in OH after low (4%) vs high (5%) dose steroid administration. These results cannot be directly transferred to include other patients groups due to the heterogeneity of the study and lack of clinical relevant OI data. A recent study in hip arthroplasty found no effect of a preoperative high-dose of 125 mg methylprednisolone i.v on OI or OH despite a significant reduction in the inflammatory response.[15]

We did not find any differences in administered perioperative intravenous fluid volume between patients with or without OI. Many approaches to perioperative fluid management have been proposed, including "zero-fluid balance", restrictive fluid regimens and intraoperative goal-directed fluid therapy (GDFT). However, avoidance of potential hypovolaemia by GDFT did not prevent OI in patients undergoing open prostatectomy.[10] These results were confirmed in a recent double-blinded randomized trial investigating patients undergoing laparoscopic colorectal resection within the context of an ERAS protocol (median LOS 4 days), as GDFT did not affect the prevalence of OH, postoperative ileus, length of stay, 30-day morbidity or mortality.[16] However, OH and OI were not assessed in detail hindering exact interpretation.

Postoperative opioid consumption have been associated with postoperative OI, but the present studies were not designed to explore this association in detail,[12,13] especially with respect to opioid dose and time and way of opioid administration. Thus, we were not able to demonstrate any relation between opioid consumption and postoperative OI. Improved analgesic techniques with local nerve and compartment block might reduce postoperative opioid use and thereby reduce orthostatic intolerance, but future studies should clarify such important issues. Preoperative TUG-score >14 seconds has been associated with an increased risk of postoperative morbidity of 70% and death of 25%.[6] We therefore speculated that TUG-score >14 seconds (as a frailty measure) could predict postoperative OI or OH, but this hypothesis was not confirmed by our results. Many patient-related risk factors have been described and contribute to the understanding of OI as a multifactorial problem. Female gender is a well-described risk factor for OI,[12,13] which we also found in our study, but also younger age[13] and lower BMI[17] has been proposed as risk factors. Side-effect to antihypertensive agents, vascular rigidity in patients with hypertension, and potential cardiovascular autonomic dysfunction in diabetic patients may also theoretically contribute to postoperative OH and OI, but have not been evaluated in detail. In relation to the last two issues, we did not find an increased prevalence of OI among patients with hypertension or diabetes, although we have no power to support this statement.

The effect of oral midodrine hydrochloride, an α_1-receptor agonist, on postoperative OH has been evaluated in one randomized study with 120 patients undergoing fast-track hip arthroplasty,[18] but only a nonsignificant reduction in the prevalence of OH or OI was found at mobilization 6 hour postoperatively. However, a standard leg compression bandage may reduce postural hypotension and symptoms at mobilization, as shown in a heterogeneous cohort of hospitalized nonsurgical patients with various acute conditions.[19] Furthermore, wearing an automated inflatable abdominal binder may improve orthostatic competence in nonsurgical patients with orthostatic hypotension, and with the same effect as midodrine alone.[20]

The strength of our study is the standardization of the perioperative care protocol, including standardized mobilization, analgesic regimens, and surgical technique, as illustrated by the short length of stay and readmission rate. Furthermore, this is the first study to describe postoperative OH and OI in details including potential risk factors after minimally invasive colorectal surgery within an ERAS program. Limitations include the low number of patients and a few missing data.

In conclusion, postoperative orthostatic intolerance is a common problem in the immediate postoperative period following colonic and rectal resection and may be associated with a risk of prolonged recovery and stay in hospital. Future studies are warranted concerning strategies aiming at reduction of postoperative orthostatic intolerance through different mechanisms.

CONFLICTS OF INTEREST

None.

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