11-1-2021

Pain and Opioid Consumption and Mobilization after Surgery: Post Hoc Analysis of Two Randomized Trials

Eva Rivas

Barak Cohen

Xuan Pu

Li Xiang

Wael Saasouh
Henry Ford Health

See next page for additional authors

Recommended Citation

Rivas E, Cohen B, Pu X, Xiang L, Saasouh W, Mao G, Minko P, Mosteller L, Volio A, Maheshwari K, Sessler DI, and Turan A. Pain and Opioid Consumption and Mobilization after Surgery: Post Hoc Analysis of Two Randomized Trials. Anesthesiology 2021.

Authors

Eva Rivas, Barak Cohen, Xuan Pu, Li Xiang, Wael Saasouh, Guangmei Mao, Paul Minko, Lauretta Mosteller, Andrew Volio, Kamal Maheshwari, Daniel I. Sessler, and Alparslan Turan

ANESTHESIOLOGY

Pain and Opioid Consumption and Mobilization after Surgery: *Post Hoc* Analysis of Two Randomized Trials

Eva Rivas, M.D., Barak Cohen, M.D., Xuan Pu, M.Sc., Li Xiang, M.D., Wael Saasouh, M.D., Guangmei Mao, M.Sc., Paul Minko, B.S., Lauretta Mosteller, B.A., Andrew Volio, M.D., Kamal Maheshwari, M.D., Daniel I. Sessler, M.D., Alparslan Turan, M.D.

ANESTHESIOLOGY 2022; 136:115–26

ABSTRACT

Background: Early mobilization is incorporated into many enhanced recovery pathways. Inadequate analgesia or excessive opioids may restrict postoperative mobilization. The authors tested the hypotheses that in adults recovering from abdominal surgery, postoperative pain and opioid consumption are inversely related to postoperative mobilization, and that postoperative mobilization is associated with fewer potentially related complications.

Methods: The authors conducted a subanalysis of two trials that enrolled adults recovering from abdominal surgery. Posture and movement were continuously monitored for 48 postoperative hours using noninvasive untethered monitors. Mobilization was defined as the fraction of monitored time spent sitting or standing.

Results: A total of 673 patients spent a median [interquartile range] of 7% [3 to 13%] of monitored time sitting or standing. Mobilization time was 1.9 [1.0 to 3.6] h/day for patients with average pain scores 3 or lower, but only 1.2 [0.5 to 2.6] h/day in those with average scores 6 or greater. Each unit increase in average pain score was associated with a decrease in mobilization time of 0.12 (97.5% CI, 0.02 to 0.24; $P = 0.009$) h/day. In contrast, there was no association between postoperative opioid consumption and mobilization time. The incidence of the composite of postoperative complications was 6.0% (10 of 168) in the lower mobilization quartile, 4.2% (7 of 168) in the second quartile, and 0% among 337 patients in the highest two quartiles ($P = 0.009$).

Conclusions: Patients recovering from abdominal surgery spent only 7% of their time mobilized, which is considerably less than recommended. Lower pain scores are associated with increased mobility, independently of opioid consumption. Complications were more common in patients who mobilized poorly.

(ANESTHESIOLOGY 2022; 136:115–26)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Early mobilization is a central component of enhanced recovery pathways
- Pain and opioids may each reduce postoperative mobilization

What This Article Tells Us That Is New

- The authors combined data from two abdominal surgery trials and evaluated pain, opioid use, and mobilization
- Pain was associated with less mobilization, but opioid consumption was not
- Overall mobilization was low, and complications were more frequent in those who mobilized poorly

Postoperative mobilization is an important component of enhanced recovery after surgery programs.[1–3] Typical enhanced recovery after surgery programs recommend many hours per day out of bed starting the day of surgery[4–7]—although the recommendations are largely based on recognized deleterious effects of bed rest[8–10] rather than strong evidence that postoperative mobilization improves outcomes.[6,11–23]

Postoperative pain remains common,[24] with about half of surgical patients reporting inadequate postoperative analgesia.[25,26] Inadequate analgesia impairs functional recovery and promotes postoperative complications.[27,28] In an attempt to address this problem, adequate analgesia was introduced as a quality measure,[29] which predictably increased opioid administration and the consequent opioid-related adverse events.[24] Opioid-related adverse events including nausea and vomiting, lightheadedness, and oversedation seem likely to reduce postoperative mobilization,[27,28,30,31] although there is currently little evidence to support the theory.

Surprisingly, there is no clear evidence of association between impaired postoperative mobilization and

This article is featured in "This Month in Anesthesiology," page A1. This article has a visual abstract available in the online version.

Submitted for publication April 22, 2021. Accepted for publication September 10, 2021. Published online first on November 15, 2021. From the Department of Outcomes Research (E.R., B.C., X.P., L.X., G.M., P.M., L.M., A.V., K.M., D.I.S., A.T.), Department Quantitative Health Sciences (X.P., L.X., G.M.), and Department of General Anesthesia (K.M., A.T.), Cleveland Clinic, Cleveland, Ohio; Department of Anesthesia, Hospital Clinic of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), University of Barcelona, Barcelona, Spain (E.R.); Division of Anesthesia, Critical Care and Pain Management, Tel-Aviv Medical Center, Tel-Aviv University, Tel-Aviv, Israel (B.C.); and Department of Anesthesiology, Henry Ford Health System, Detroit, Michigan (W.S.).

 Anesthesiology 2022; 136:115–26. DOI: 10.1097/ALN.0000000000004037

<zdoi;. DOI: 10.1097/ALN.0000000000004037>

postoperative outcomes.[11,14,16,17] One explanation may be that assessment of mobilization remains imprecise and largely based on patient or nursing subjective reports rather than objective quantitative measurement. Furthermore, patient mobilization is frequently skipped or poorly implemented.[10,32,33]

The extent to which postoperative pain and opioid consumption influence postoperative mobilization remains unknown.[16–18] We therefore tested the primary hypothesis that in adults recovering from abdominal surgery, postoperative pain is inversely associated with postoperative mobilization, defined as the number of hours per postoperative day spent sitting or standing during the initial 48 postoperative hours. Secondarily, we tested the hypothesis that postoperative opioid consumption is inversely associated with postoperative mobilization. Finally, we tested the exploratory hypothesis that postoperative mobilization is associated with fewer complications potentially related to inadequate mobilization, defined as a composite of myocardial injury, stroke or transient ischemic attack, venous thromboembolism, pulmonary complications, and all-cause mortality.

Materials and Methods

Study Design

We conducted a retrospective analysis of data from two randomized trials: Effect of Intravenous Acetaminophen on Postoperative Hypoxemia After Abdominal Surgery: the FACTOR Randomized Clinical Trial (NCT02156154; Alparslan Turan; registered on June 5, 2014),[34] which evaluated the effect of intravenous acetaminophen on postoperative opioid-related complications after colorectal surgery; and Transversus Abdominis Plane Block with Liposomal Bupivacaine versus Continuous Epidural Analgesia for Major Abdominal Surgery: the EXPLANE clinical trial (NCT02996227; Alparslan Turan; registered on December 19, 2016), which compared the effect of continuous epidural analgesia and transversus abdominis plane blocks on postoperative analgesia and opioid consumption after abdominal surgery. Both trials enrolled patients who had abdominal surgery and used a continuous vital sign recording system that also captures mobilization information, and were approved by the Cleveland Clinic Institutional Review Board (IRB; Cleveland, Ohio). The current analysis was approved by the IRB with waived individual consent and was designed before completing the trial enrollment (Cleveland Clinic IRB No. 19-341; approval date March 19, 2019).

Patients were managed according to Cleveland Clinic enhanced recovery after surgery protocols. Orogastric tubes were removed before endotracheal extubation. Patients were encouraged to walk on the evening of surgery and were offered noncarbonated liquids *ad libitum*. On the first postoperative day, patients were encouraged to walk at least one round of the nursing floor (approximately 60 m) up to five times, to sit out of bed between walks, and to perform regular incentive spirometry. Liquids were allowed and solid food offered if tolerated. Intraoperative analgesia was provided with short-acting opioids, and intravenous patient-controlled analgesia was used during the postoperative period. Oral analgesia was started, and the Foley catheter was removed on postoperative day 1.[35–37]

Study Population

We included adult inpatients having elective open or laparoscopic abdominal surgery scheduled to last at least 2 h with general anesthesia at the Cleveland Clinic between February 2014 and September 2019 who participated in FACTOR or EXPLANE and had continuous postoperative activity monitoring. We excluded patients who had less than 12 h of continuous activity monitoring during the initial 48 postoperative hours, along with patients who had missing pain assessments or lacked important confounding variables.

Measurements

Postoperative pain was recorded using the numerical rating scale, which is an 11-point Likert scale from 0 (no pain) to 10 (worst imaginable pain). Pain scores were recorded at least every 30 min while patients remained in the postanesthesia care unit, and at least every 4 h while hospitalized. All available pain scores during the monitoring period were collected from patients' electronic medical records, and time-weighted average pain score was calculated for each patient. Opioid consumption during the initial 48 postoperative hours was also collected from patients' electronic records and converted into milligram of intravenous morphine equivalents.[38,39]

Our primary outcome was duration of mobilization, defined as hours per monitoring day spent sitting or standing. Position and activity were continuously monitored and recorded at 15-s intervals from postanesthesia care unit admission until the earlier of 48 postoperative hours or hospital discharge using the ViSi Mobile monitoring system (Sotera Wireless, Inc., USA), which is cleared by the U.S. Food and Drug Administration (Silver Spring, Maryland) for noninvasive continuous vital sign monitoring.[40]

The ViSi Mobile monitoring system includes a three-axis accelerometer that characterizes patients' orientation and activity.[41] It captures posture status as upright 90 degrees, upright 45 degrees, supine, lying on the side, walking, and fallen. We defined mobilization as standing or sitting position, with standing defined "walking" posture and sitting as "upright 90 degrees" posture. When more than one posture was detected during a 15-s interval, a combined posture was recorded. For example, if a patient walked and sat upright 45° during a single 15-s interval, the posture would be recorded as upright 45 degrees and walking. Combined

postures were considered as mobilization if one of the components was eligible. Neither patients nor clinicians had access to mobilization data.

The exploratory outcome was a composite of postoperative complications, including myocardial injury (defined as either a postoperative peak fourth-generation troponin T concentration 0.03 ng/ml or greater within the first 7 days after surgery, apparently of cardiac origin, or an International Classification of Diseases code for myocardial infarction)[42]; stroke or transient ischemic attack; venous thromboembolism; pulmonary complications; and all-cause in-hospital mortality (appendix, table A1). Data were extracted from patients' electronic medical records, the anesthesia record-keeping system, and pharmacy records.

Statistical Methods

Gaps in activity/posture monitoring were removed and subtracted from total monitoring time, so that each patient's mobilization was calculated as hours of mobility per day by multiplying average mobilization minutes per monitoring hour by 24 h/day. Around 4% of all postures were recorded as unknown and were treated as missing and removed. Demographic and clinical characteristics of patients were summarized and presented by time-weighted average pain score category in table 1, only for presentation purposes.

For the primary analysis, a quantile regression model was used to assess the association between time-weighted average pain score and mobilization time, in hours per day. A similar model was used to secondarily assess the association between opioid consumption during the first 48 postoperative hours and mobilization time. The associations were adjusted for all demographics and surgical variables in table 1.

We conducted four sensitivity analyses. The first evaluated associations between time-weighted average pain scores and opioid consumption and postoperative mobilization, restricted to patients older than 65 yr. Second, we restricted the definition of mobilization to include only standing position. Third, we restricted the analysis to daytime, defined as 7 AM to 10 PM. For our final sensitivity analysis, we restricted the analysis to the first 24 postoperative hours.

For our exploratory analysis, the incidence of a composite of myocardial injury, stroke or transient ischemic attack, venous thromboembolism, pulmonary complications, and all-cause in-hospital mortality was summarized by quartiles of mobilization time.

Table 1. Demographic, Surgical, and Postoperative Characteristics of Patients, Presented According to Time-weighted Average Pain Scores during the Initial 48 Postoperative Hours

Factor	Overall (N = 673)	Pain ≤ 3 (N = 195)	3 < Pain < 6 (N = 354)	Pain ≥ 6 (N = 124)
Demographics				
Age, yr	51 ± 15	55 ± 16	50 ± 15	46 ± 14
Body mass index	27 ± 5	27 ± 5	27 ± 5	27 ± 6
Female	361 (54)	76 (48)	197 (56)	70 (57)
Race, white	622 (92)	152 (95)	327 (92)	111 (90)
Surgical characteristics				
ASA Physical Status				
I or II	243 (36)	72 (37)	123 (35)	48 (39)
III	413 (61)	116 (60)	224 (63)	73 (59)
IV or V	17 (3)	7 (3)	7 (2)	3 (2)
Surgery type				
Colorectal	601 (89)	173 (89)	317 (90)	111 (89)
Gynecological	31 (5)	10 (5)	15 (4)	6 (5)
Urological	9 (1)	1 (1)	7 (2)	1 (1)
Other	32 (5)	11 (5)	15 (4)	6 (5)
Procedure type				
Open	446 (66)	131 (67)	224 (63)	91 (73)
Laparoscopic	227 (34)	64 (33)	130 (37)	33 (27)
Surgery duration, min	272 [197–365]	260 [186–355]	279 [202–375]	271 [191–329]
Estimated blood loss, cc	75 [25–200]	50 [25–150]	100 [30–200]	75 [50–200]
Intraoperative ketorolac use	10 (2)	5 (3)	4 (1)	1 (1)
Postoperative characteristics				
Time-weighted average pain score	4.3 ± 1.9	2.0 ± 0.8	4.6 ± 0.8	6.9 ± 0.8
Opioid consumption (mg of IV morphine equivalents)	36 [10–97]	8 [0–50]	39 [16–101]	67 [34–171]
Any use of (%)				
NSAID	430 (64)	126 (65)	226 (64)	78 (63)
Acetaminophen	230 (34)	64 (33)	123 (35)	43 (35)
Gabapentin	355 (53)	95 (49)	190 (54)	70 (57)

NSAIDs include ketorolac, ibuprofen, and celecoxib. Summary statistics presented as No. (%) of patients, mean ± SD, or median [quartile 1–quartile 3] for factors, symmetric continuous variables, and skewed continuous variables, respectively (N = 673).

ASA, American Society of Anesthesiologists; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

We did two *post hoc* analyses. First, we fitted a quantile regression model with interaction between surgical approach (open or laparoscopic) and both exposures (pain and opioid consumption) with mobilization time as the outcome; and second, we explored the relationship between the mobilization time in hours per day and the composite of postoperative complications through a logistic regression model adjusting for age, sex, race, and surgery duration.

We performed a complete case analysis, as participants with missing data were excluded. Data were assumed to be missing at random. The significance level was 0.025 for each association (pain and mobilization/opioid consumption and mobilization) after Bonferroni correction for the primary and secondary analyses. All analyses were conducted using the Statistical Analysis System (SAS) statistical software package, version 9.04.01 (SAS Institute Inc., USA).

Power Consideration

We did a simulation using quantile regression to calculate the effect size we could detect. With the current sample size, we had more than 90% power for detecting a 0.2-h reduction in mobilization per day for each unit increase in pain score, or to detect a 0.13-h reduction in mobilization per day for each doubling of morphine consumption at a significance level of 0.025.

Results

A total of 984 patients who had elective open or laparoscopic abdominal surgery were enrolled in the

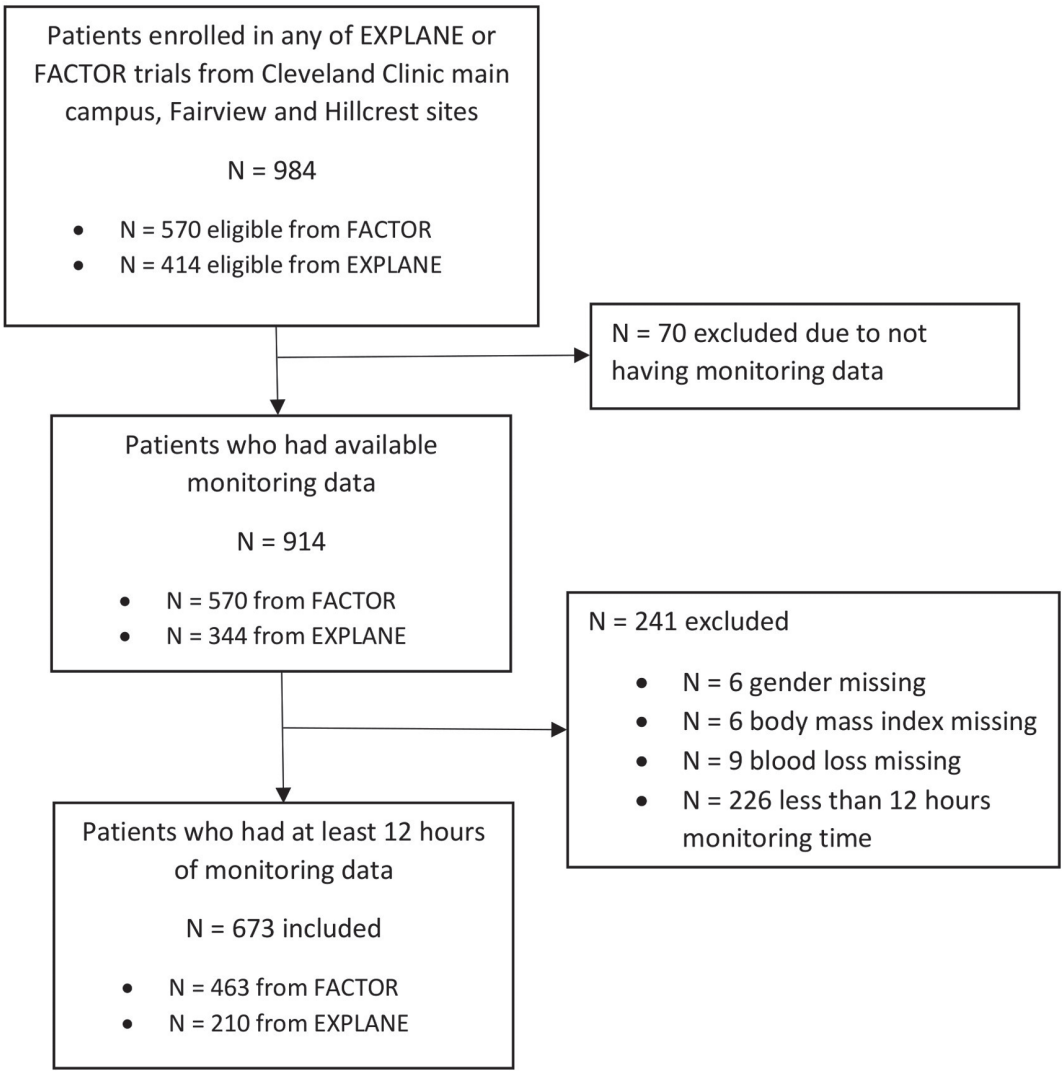

Fig. 1. Flowchart of study population. EXPLANE, Transversus Abdominis Plane Block with Liposomal Bupivacaine versus Continuous Epidural Analgesia for Major Abdominal Surgery: the EXPLANE clinical trial; FACTOR, Effect of Intravenous Acetaminophen on Postoperative Hypoxemia After Abdominal Surgery: the FACTOR Randomized Clinical Trial.

underlying trials, 570 from FACTOR and 414 from EXPLANE. Our analysis was restricted to 673 patients among the 914 who had ViSi Mobile monitoring (fig. 1). Baseline medical, demographic, anesthetic, and surgical data are presented in table 1, divided by time-weighted average pain scores.

The median [interquartile range] monitoring duration (after removal of gaps) was 32 [23 to 40] h during the first 48 postoperative hours. Overall, patients spent a median [interquartile range] of 7% [3 to 13%] of the total monitoring time sitting or standing, corresponding to 1.7 [0.7 to 3.1] h/day.

In patients with time-weighted average pain scores 3 or less, mobilization time was 8% [4 to 15%], corresponding to 1.9 [1.0 to 3.6] h/day. In patients with time-weighted average pain scores between 3 and 6, mobilization time was 7% [3 to 13%], corresponding to 1.7 [0.7 to 3.1] h/day. In patients with time-weighted average pain scores 6 or greater, mobilization time was 5% [2 to 11%], corresponding to 1.2 [0.5 to 2.6] h/day (fig. 2). Each unit increase in time-weighted average pain score was associated with an adjusted median decrease of 0.12 (97.5% CI, 0.02 to 0.24) h/day ($P = 0.009$; table 2).

The opioid consumption ranged from 8 [0 to 50] mg of morphine equivalents in patients with low pain scores to 67 [34 to 171] mg of morphine equivalents in patients with the highest pain scores (table 1). The main opioids used and their morphine equivalents are shown in table A2. There was no significant association between postoperative opioid consumption and mobilization time, with an estimated adjusted median change of –0.04 (97.5% CI, –0.12 to 0.08) h/day for a twofold increase in morphine equivalent opioid consumption ($P = 0.508$; fig. 2; table 2).

There was no significant association between time-weighted average pain score or opioid consumption and postoperative mobilization among patients more than 65 yr old (table 2). We did not find significant associations between time-weighted average pain score and standing position; opioid consumption was inversely associated with standing, although not by a clinically meaningful amount (estimated adjusted median change of –0.01 [97.5% CI, 0.01 to –0.004] hours per day with each twofold increase in opioid consumption). Daytime (from 7 AM to 10 PM) mobilization was inversely associated with both time-weighted average pain score and opioid consumption. The estimated adjusted median change was –0.40 (97.5% CI, –0.72 to –0.08) hours per daytime day for each unit increase of time-weighted average pain score and –0.32 (97.5% CI, –0.56 to –0.08) hours per daytime day for each doubling of opioid consumption. Mobilization during the first 24 postoperative hours was not associated with time-weighted average pain score or with opioid consumption.

We found a significant interaction between pain score and surgical approach ($P = 0.033$; table 2). For patients who had open procedures, each unit increase in pain score was associated with 0.17 (97.5% CI, 0.06 to 0.28; $P < 0.001$) fewer hours of mobilization per day; this association was no longer significant for patients who had laparoscopic surgery,

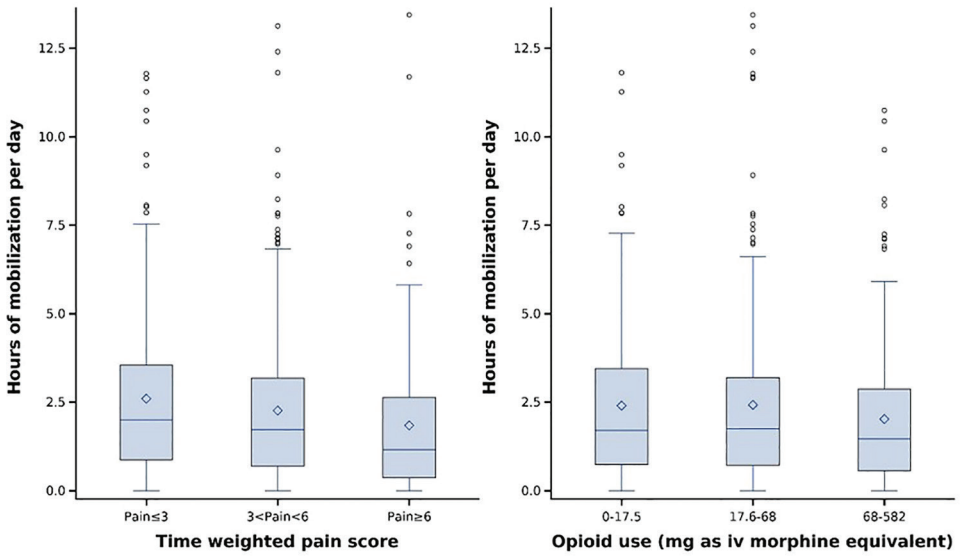

Fig. 2. Mobilization time based on time-weighted pain scores/opioid use. (*Left*) Mobilization time in hours per day, based on time-weighted average pain score during the initial 48 postoperative hours. (*Right*) Mobilization based on opioid use in milligrams of intravenous morphine equivalents during the initial 48 postoperative hours. *Boxes* represent interquartile ranges; *middle bars*, medians; *diamonds*, averages; *whiskers* extend to the most extreme value within 1.5 times the interquartile range below the first or above the third quartile. More extreme values (outliers) are represented by *circles*. iv, intravenous.

Table 2. Associations of Time-weighted Average Postoperative Pain Score or Opioid Administration and Postoperative Mobilization Hours per Day

	Pain Score (97.5% CI)*	*P* Value†	Opioid Consumption (97.5% CI)*	*P* Value†
Primary analysis				
Mobilization, h/day	Unadjusted	0.004	Unadjusted	0.586
	–0.16 (–0.24 to –0.04)		0.04 (–0.12 to 0.08)	
	Adjusted*	0.009	Adjusted*	0.508
	–0.12 (–0.24 to –0.02)		–0.04 (–0.12 to 0.08)	
Sensitivity analysis‡				
Mobilization, h/day	Adjusted*	0.805	Adjusted*	0.227
(> 65 yr old)	–0.03 (–0.36 to 0.28)		0.12 (–0.12 to 0.36)	
Mobilization, h/day	Adjusted*	0.028	Adjusted*	<0.001
(only standing position)	–0.01 (–0.01 to 0.0001)		–0.01 (–0.01 to –0.004)	
Mobilization, h/day	Adjusted*	0.003	Adjusted*	0.007
(daytime only)	–0.40 (–0.72 to –0.08)		–0.32 (–0.56 to –0.08)	
Mobilization, h/day	Adjusted*	0.026	Adjusted*	0.077
(initial postoperative 24 h)	–0.04 (–0.08 to 0.0002)		–0.02 (–0.04 to 0.01)	
Post hoc subgroup analysis§				
Open surgery	Adjusted*	<0.001	Adjusted*	0.540
	–0.17 (–0.06 to –0.28)		–0.03 (–0.12 to 0.07)	
Laparoscopic approach	Adjusted*	0.628	Adjusted*	0.816
	0.05 (–0.15 to 0.25)		0.02 (–0.15 to 0.18)	

*The association was estimated using a quantile regression model adjusted for confounders in table 1. The associated mobilization change estimates were based on unit increase of postoperative time-weighted average pain score or a twofold increase in morphine equivalent opioid consumption.

†The significance level for each association test was 0.025 (*i.e.*, 0.05/2, Bonferroni correction).

‡For the first sensitivity analysis, 169 patients were analyzed (age greater than 65 yr). For the second sensitivity analysis (only standing position), 673 patients were analyzed. For the third sensitivity analysis (daytime), 413 patients were analyzed since people whose actual daytime monitoring duration was less than 6 h were excluded. For the last sensitivity analysis (only first postoperative 24 h), 216 patients were analyzed since people whose actual postoperative 24 h monitoring duration was less than 6 h were excluded.

§The *post hoc* subgroup analysis was completed through a quantile regression model with interaction between procedure type (open *vs.* laparoscopic) and corresponding exposure (pain score or morphine usage) adjusting for confounders in primary analysis.

where each unit increase in pain score was associated with 0.05 more hours per day (97.5% CI, –0.15 to 0.25; $P = 0.628$). We did not find an interaction between morphine use and the surgical approach ($P = 0.586$). After additional adjustment for surgical approach in our primary outcome analysis, the results were similar to our primary analysis, where a doubling of morphine use was associated with 0.04 (97.5% CI, –0.14 to 0.05) fewer hours of mobilization per day (table 2).

The composite of postoperative complications was observed in 17 patients, 9 of whom had pulmonary complications; 3 had myocardial injury; 1 had a stroke/transitional intravascular accident, and 4 had venous thromboembolism (table 3). Considering quartiles of mobilization time, the incidence of the composite outcome was 6.0% (10 of 168 patients) among patients who spent 0 to 0.7 h in mobilization per day, 4.2% (7 of 168) among patients who spent 0.7 to 1.6 h in mobilization per day, and none among the remaining 337 patients in the highest two quartiles, who had more than 1.6 h/day. There was thus a significant association between mobilization time and postoperative complications with an estimated adjusted odds ratio of 0.34 (95% CI, 0.16 to 0.72) for each hour increase of mobilization per day, adjusting for age, sex, race, and surgery duration; $P = 0.005$. Preoperative American Society of Anesthesiologists Physical Status, intensive care unit admission, length of hospital stay, surgical approach, and surgery duration were also summarized by mobilization time.

Discussion

Postoperative mobilization was inversely associated with pain scores, suggesting that inadequate postoperative analgesia impairs mobilization. Unsurprisingly, the association was threefold stronger when analysis was restricted to daytime, which is reasonable since few patients mobilize at night, irrespective of pain management. The association was also 1.5-fold stronger when patients had open surgery. In contrast, there was little association between opioid consumption and overall mobilization. To the extent that the relationship is causal, our results suggest that improving postoperative analgesia by about 3 points on an 11-point Likert scale might increase mobilization time by as much as 25%—even if opioids are used to improve analgesia.

Remarkably, all postoperative complications occurred in patients who were in the lowest two mobilization quartiles, those who spent less than 7% (1.7 h/day) of their time sitting or standing during the initial 48 postoperative hours. Importantly, potential confounders as American Society of

Table 3. Summary of Composite Outcomes by Mobilization Hours per Monitoring Day

Time of Mobilization, % (h/day)	Total (N = 673)	0–2.8 (0–0.7) (N = 168)	2.8–6.8 (0.7–1.6) (N = 168)	6.8–13 (1.6–3.1) (N = 169)	> 13 (3.1–13.2) (N = 168)
Composite outcome	17 (2.5)	10 (6.0)	7 (4.2)	0 (0.0)	0 (0.0)
Composite of pulmonary complications	9 (1.3)	5 (3.0)	4 (2.4)	0 (0.0)	0 (0.0)
Myocardial injury after noncardiac surgery	3 (0.5)	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)
Stroke/transitional intravascular accident	1 (0.2)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Venous thromboembolism	4 (0.6)	2 (1.2)	2 (1.2)	0 (0.0)	0 (0.0)
All-cause in-hospital mortality	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Post hoc summary					
Preoperative ASA Physical Status					
I or II	243 (36)	46 (27)	62 (37)	65 (38)	70 (41)
III	413 (61)	117 (70)	101 (60)	98 (58)	97 (58)
IV or V	17 (3)	5 (3)	5 (3)	6 (4)	1 (1)
ICU admission	27 (4)	15 (9)	6 (4)	3 (2)	3 (2)
Length of stay, days	4 [3–7]	6 [4–8]	5 [3–7]	4 [3–6]	4 [2–5]
Surgery procedure					
Open	446 (66)	119 (71)	114 (68)	110 (65)	103 (61)
Laparoscopic	227 (34)	49 (29)	54 (32)	59 (35)	65 (39)
Surgery duration, min	272 [197–365]	321 [237–445]	286 [196–388]	254 [191–325]	234 [185–315]

The summary statistics are presented as N (%) or median [quartile 1–quartile 3] by overall percentage of mobilization time (hour per day) The association estimate between pain score and complications was obtained through a logistic regression model with postoperative complications as the outcome and mobilization in minutes per hour as exposure of interest, adjusting for age, sex, race, and surgery duration. The adjusted odds ratio was 0.34 (95% CI, 0.16 to 0.72) associated with each hour increase in mobilization time per day.

ASA, American Society of Anesthesiologists; ICU, intensive care unit.

Anesthesiologists Physical Status as well as surgery approach and duration did not differ much among postoperative pain levels, suggesting similar surgical severity and baseline comorbidities. A difference of 0.7 h of mobilization per day between patients with low or high level of pain might seem marginal. Nonetheless, this small difference corresponded to a substantial difference in the incidence of complications. Even 1.6 h of mobilization per day are therefore associated with reduced complications.

The average mobilization time in our cohort was about 2 h/day, which is the recommended out-of-bed time for the day of surgery, but considerably shorter than the times recommended thereafter by many enhanced recovery pathways.[5–7] Low adherence to mobilization recommendations is consistent with many qualitative reports.[6,18,43,44] We note, though, that enhanced recovery after surgery mobilization recommendations are largely based on expert opinion rather than on strong evidence. Our results suggest that 2 h/day may suffice.[2,5,6]

Although postoperative mobilization is included in most enhanced recovery pathways,[16,45–47] supportive evidence remains sparse.[6] On one hand, Daskivich *et al.*[18] report in a 100-patient study that 1,000 steps/day on the first postoperative day after major abdominal surgery was associated with lower probability of a prolonged length of stay. On the other hand, in patients recovering from colorectal surgery, staff-directed out-of-bed activities did not reduce the duration of hospitalization.[12–17,19–23] Moreover, a systematic review of 500 patients concluded that current evidence is insufficient to draw strong conclusions regarding the benefits of early mobilization on postoperative outcomes.[11] Some discrepancies might be partly explained by large variability in mobilization quantification, with some reports relying on nursing or patients' subjective reports[6,47] while others used walking distance[19] or daily steps.[16–18] An important consideration for all observational analyses—including ours—is that failure to mobilize early may be a reflection of poor recovery, rather than being the cause.

Mobility data were missing for 9% [3% to 20%] of the initial postoperative 48 h, in part because continuous monitoring was purely observational. Clinicians were therefore blinded to results, and to disconnections or technical failures. Missing data are always a concern in clinical research, but more so if data are missing nonrandomly. In our case, it is plausible that disconnections were most common in mobile patients, thus diminishing the apparent difference in mobility time for the highest and lowest quartiles. We adjusted for many potential confounding factors including duration of surgery, but it remains likely that larger and open procedures that cause much tissue injury simultaneously provoke pain and impair mobilization. Although few of our patients experienced complications, after adjusting for as many important confounders as we could, there was still a strong relationship between complications and mobilization, even over a small range of sitting and standing times. However, the association between postoperative complications and low levels of mobilization cannot exclude reverse causality since patients with postoperative complications surely move

less. The extent to which the association between pain and mobilization is causal, and thus amenable to intervention, remains unclear. A future trial of analgesic approaches with differing efficacies could better evaluate causality.

Conclusions

In patients recovering from abdominal surgery on an enhanced recovery pathway, lower pain scores are associated with increased mobility, even when opioid consumption is increased. Patients spent only about 2 h/day mobilized, which is considerably less than the recommended time. There appears to be little beyond expert opinion to support the recommended daily mobilization goal, and our results suggest that 2 h/day may suffice.

Research Support

The underlying Effect of Intravenous Acetaminophen on Postoperative Hypoxemia After Abdominal Surgery: the FACTOR Randomized Clinical Trial was supported by an investigator-initiated research grant from Mallinckrodt Pharmaceuticals (Hampton, New Jersey); and the underlying Transversus Abdominis Plane Block with Liposomal Bupivacaine versus Continuous Epidural Analgesia for Major Abdominal Surgery: the EXPLANE clinical trial was funded by PACIRA Pharmaceuticals (Parsippany, New Jersey). Sotera Wireless, Inc. (San Diego, California) and Respiratory Motion, Inc. (Watertown, Massachusetts) provided devices and disposables. However, this analysis was supported by internal funds only, and the sponsors had no role whatsoever in data analysis, manuscript preparation, or the decision to submit for publication. The sponsors have not reviewed this manuscript. Dr. Rivas received a grant from Instituto Salud Carlos III, Madrid, Spain (BA18/00048).

Competing Interests

Dr. Sessler is a consultant for PACIRA Pharmaceuticals (Parsippany, New Jersey). Dr. Maheshwari is a consultant for Edwards Lifesciences (Irvine, California). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: turana@ccf.org. Raw data available at: turana@ccf.org.

Correspondence

Address correspondence to Dr. Turan: Department of Outcomes Research, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, Ohio, 44195. turana@ccf.org. This article may be accessed for personal use at no charge through the Journal Web site, www.anesthesiology.org.

References

1. Kehlet H: Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth 1997; 78:606–17
2. Enhanced Recovery After Surgery Society. Available at: https://erassociety.org/guidelines/. Accessed September 10, 2021.
3. Gustafsson UO, Scott MJ, Hubner M, Nygren J, Demartines N, Francis N, Rockall TA, Young-Fadok TM, Hill AG, Soop M, de Boer HD, Urman RD, Chang GJ, Fichera A, Kessler H, Grass F, Whang EE, Fawcett WJ, Carli F, Lobo DN, Rollins KE, Balfour A, Baldini G, Riedel B, Ljungqvist O: Guidelines for perioperative care in elective colorectal surgery: Enhanced Recovery After Surgery (ERAS®) Society recommendations: 2018. World J Surg 2019; 43:659–95
4. Ljungqvist O, Scott M, Fearon KC: Enhanced recovery after surgery: A review. JAMA Surg 2017; 152:292–8
5. Lassen K, Soop M, Nygren J, Cox PB, Hendry PO, Spies C, von Meyenfeldt MF, Fearon KC, Revhaug A, Norderval S, Ljungqvist O, Lobo DN, Dejong CH; Enhanced Recovery After Surgery (ERAS) Group: Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. Arch Surg 2009; 144:961–9
6. Vlug MS, Bartels SA, Wind J, Ubbink DT, Hollmann MW, Bemelman WA; Collaborative LAFA Study Group: Which fast track elements predict early recovery after colon cancer surgery? Colorectal Dis 2012; 14:1001–8
7. Gustafsson UO, Hausel J, Thorell A, Ljungqvist O, Soop M, Nygren J; Enhanced Recovery After Surgery Study Group: Adherence to the enhanced recovery after surgery protocol and outcomes after colorectal cancer surgery. Arch Surg 2011; 146:571–7
8. Kehlet H, Wilmore DW: Multimodal strategies to improve surgical outcome. Am J Surg 2002; 183:630–41
9. Bed rest, thrombosis, and embolism. Lancet 1958; 1:465–6
10. Brown CJ, Friedkin RJ, Inouye SK: Prevalence and outcomes of low mobility in hospitalized older patients. J Am Geriatr Soc 2004; 52:1263–70
11. Castelino T, Fiore JF Jr, Niculiseanu P, Landry T, Augustin B, Feldman LS: The effect of early mobilization protocols on postoperative outcomes following abdominal and thoracic surgery: A systematic review. Surgery 2016; 159:991–1003
12. Arbane G, Douiri A, Hart N, Hopkinson NS, Singh S, Speed C, Valladares B, Garrod R: Effect of postoperative physical training on activity after curative surgery for non-small cell lung cancer: A multicentre randomised controlled trial. Physiotherapy 2014; 100:100–7

13. Ahn H, Weaver M, Lyon DE, Kim J, Choi E, Staud R, Fillingim RB: Differences in clinical pain and experimental pain sensitivity between Asian Americans and Whites with knee osteoarthritis. Clin J Pain 2017; 33:174–80
14. Le H, Khankhanian P, Joshi N, Maa J, Crevensten H: Patients recovering from abdominal surgery who walked with volunteers had improved postoperative recovery profiles during their hospitalization. World J Surg 2014; 38:1961–5
15. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW: Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum 2003; 46:851–9
16. Fiore JF Jr, Castelino T, Pecorelli N, Niculiseanu P, Balvardi S, Hershorn O, Liberman S, Charlebois P, Stein B, Carli F, Mayo NE, Feldman LS: Ensuring early mobilization within an enhanced recovery program for colorectal surgery: A randomized controlled trial. Ann Surg 2017; 266:223–31
17. Balvardi S, Pecorelli N, Castelino T, Niculiseanu P, Alhashemi M, Liberman AS, Charlebois P, Stein B, Carli F, Mayo NE, Feldman LS, Fiore JF: Impact of facilitation of early mobilization on postoperative pulmonary outcomes after colorectal surgery. Ann Surg 2021; 273:868–75
18. Daskivich TJ, Houman J, Lopez M, Luu M, Fleshner P, Zaghiyan K, Cunneen S, Burch M, Walsh C, Paiement G, Kremen T, Soukiasian H, Spitzer A, Jackson T, Kim HL, Li A, Spiegel B: Association of wearable activity monitors with assessment of daily ambulation and length of stay among patients undergoing major surgery. JAMA Netw Open 2019; 2:e187673
19. Ni CY, Wang ZH, Huang ZP, Zhou H, Fu LJ, Cai H, Huang XX, Yang Y, Li HF, Zhou WP: Early enforced mobilization after liver resection: A prospective randomized controlled trial. Int J Surg 2018; 54:254–8
20. Jurt J, Hübner M, Pache B, Hahnloser D, Demartines N, Grass F: Respiratory complications after colorectal surgery: Avoidable or fate? World J Surg 2018; 42:2708–14
21. Haines KJ, Skinner EH, Berney S; Austin Health POST Study Investigators: Association of postoperative pulmonary complications with delayed mobilisation following major abdominal surgery: An observational cohort study. Physiotherapy 2013; 99:119–25
22. Browning L, Denehy L, Scholes RL: The quantity of early upright mobilisation performed following upper abdominal surgery is low: An observational study. Aust J Physiother 2007; 53:47–52
23. Ahn KY, Hur H, Kim DH, Min J, Jeong DH, Chu SH, Lee JW, Ligibel JA, Meyerhardt JA, Jones LW, Jeon JY, Kim NK: The effects of inpatient exercise therapy on the length of hospital stay in stages I-III colon cancer patients: Randomized controlled trial. Int J Colorectal Dis 2013; 28:643–51
24. Kaafarani HMA, Han K, El Moheb M, Kongkaewpaisan N, Jia Z, El Hechi MW, van Wijck S, Breen K, Eid A, Rodriguez G, Kongwibulwut M, Nordestgaard AT, Sakran JV, Ezzeddine H, Joseph B, Hamidi M, Ortega C, Flores SL, Gutierrez-Sougarret BJ, Qin H, Yang J, Gao R, Wang Z, Gao Z, Prichayudh S, Durmaz S, van der Wilden G, Santin S, Ribeiro MAF Jr, Noppakunsomboom N, Alami R, El-Jamal L, Naamani D, Velmahos G, Lillemoe KD: Opioids after surgery in the United States *versus* the rest of the world: The International Patterns of Opioid Prescribing (iPOP) Multicenter Study. Ann Surg 2020; 272:879–86
25. Apfelbaum JL, Chen C, Mehta SS, Gan TJ: Postoperative pain experience: Results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97:534–40
26. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL: Incidence, patient satisfaction, and perceptions of post-surgical pain: Results from a US national survey. Curr Med Res Opin 2014; 30:149–60
27. Regenbogen SE, Mullard AJ, Peters N, Brooks S, Englesbe MJ, Campbell DA Jr, Hendren S: Hospital analgesia practices and patient-reported pain after colorectal resection. Ann Surg 2016; 264:1044–50
28. Boekel RLM Van, Warlé MC, Nielen RGC, Vissers KCP, Sande R Van Der, Bronkhorst EM, Lerou JGC, Steegers MAH: Relationship between postoperative pain and overall 30-day complications in a broad surgical population: An observational study. Ann Surg 2019; 269:856–65
29. Phillips DM: JCAHO pain management standard are unveiled. J Am Med Assoc 2000; 284:428–9
30. Andersen HL, Gyrn J, Møller L, Christensen B, Zaric D: Continuous saphenous nerve block as supplement to single-dose local infiltration analgesia for postoperative pain management after total knee arthroplasty. Reg Anesth Pain Med 2013; 38:106–11
31. Andersen LW, Berg KM, Chase M, Cocchi MN, Massaro J, Donnino MW; American Heart Association's Get With The Guidelines(®)-Resuscitation Investigators: Acute respiratory compromise on inpatient wards in the United States: Incidence, outcomes, and factors associated with in-hospital mortality. Resuscitation 2016; 105:123–9
32. Kalisch BJ, Landstrom GL, Hinshaw AS: Missed nursing care: A concept analysis. J Adv Nurs 2009; 65:1509–17
33. Callen BL, Mahoney JE, Grieves CB, Wells TJ, Enloe M: Frequency of hallway ambulation by hospitalized older adults on medical units of an academic hospital. Geriatr Nurs 2004; 25:212–7
34. Turan A, Essber H, Saasouh W, Hovsepyan K, Makarova N, Ayad S, Cohen B, Ruetzler K, Soliman LM, Maheshwari K, Yang D, Mascha EJ, Ali Sakr Esa W,

Kessler H, Delaney CP, Sessler DI; FACTOR Study Group: Effect of intravenous acetaminophen on postoperative hypoxemia after abdominal surgery: The FACTOR randomized clinical trial. JAMA 2020; 324:350–8

35. Delaney CP, Brady K, Woconish D, Parmar SP, Champagne BJ: Towards optimizing perioperative colorectal care: Outcomes for 1,000 consecutive laparoscopic colon procedures using enhanced recovery pathways. Am J Surg 2012; 203:353–5; discussion 355–6
36. Wen Y, Jabir MA, Dosokey EM, Choi D, Petro CC, Brady JT, Steele SR, Delaney CP: Using Modified Frailty Index to predict safe discharge within 48 hours of ileostomy closure. Dis Colon Rectum 2017; 60:76–80
37. Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH: "Fast track" postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery. Br J Surg 2001; 88:1533–8
38. Farag E, Ghobrial M, Sessler DI, Dalton JE, Liu J, Lee JH, Zaky S, Benzel E, Bingaman W, Kurz A: Effect of perioperative intravenous lidocaine administration on pain, opioid consumption, and quality of life after complex spine surgery. Anesthesiology 2013; 119:932–40
39. Turan A, Atim A, Dalton JE, Keeyapaj W, Chu W, Bernstein E, Fu A, Jae Ho L, Saager L, Sessler DI: Preoperative angiotensin-converting enzyme inhibitor use is not associated with increased postoperative pain and opioid use. Clin J Pain 2013; 29:1050–6
40. Sotera. ViSi Mobile - technical specifications. Available at: https://www.soterawireless.com/faqs. Accessed September 10, 2021.
41. Dhillon MS, McCombie SA, McCombie DB: Towards the prevention of pressure ulcers with a wearable patient posture monitor based on adaptive accelerometer alignment. Annu Int Conf IEEE Eng Med Biol Soc 2012; 2012:4513–6
42. Deveraux PJ, Chan MTV, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Buse GL, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S: Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. J Am Med Assoc 2012; 307:2295–304
43. Smart NJ, White P, Allison AS, Ockrim JB, Kennedy RH, Francis NK: Deviation and failure of enhanced recovery after surgery following laparoscopic colorectal surgery: Early prediction model. Colorectal Dis 2012; 14:e727–34
44. Tasheva P, Vollenweider P, Kraege V, Roulet G, Lamy O, Marques-Vidal P, Méan M: Association between physical activity levels in the hospital setting and hospital-acquired functional decline in elderly patients. JAMA Netw Open 2020; 3:e1920185
45. Perlas A, Kirkham KR, Billing R, Tse C, Brull R, Gandhi R, Chan VW: The impact of analgesic modality on early ambulation following total knee arthroplasty. Reg Anesth Pain Med 2013; 38:334–9
46. Vlug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, Gerhards MF, van Wagensveld BA, van der Zaag ES, van Geloven AA, Sprangers MA, Cuesta MA, Bemelman WA; LAFA Study Group: Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: A randomized clinical trial (LAFA-study). Ann Surg 2011; 254:868–75
47. Wind J, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ, van Berge Henegouwen MI, Fuhring JW, Dejong CH, van Dam RM, Cuesta MA, Noordhuis A, de Jong D, van Zalingen E, Engel AF, Goei TH, de Stoppelaar IE, van Tets WF, van Wagensveld BA, Swart A, van den Elsen MJ, Gerhards MF, de Wit LT, Siepel MA, van Geloven AA, Juttmann JW, Clevers W, Bemelman WA: Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management *versus* standard care (LAFA trial). BMC Surg 2006; 6:16

Appendix

Table A1. Composite of Postoperative Complications

Component of the Composite Outcome	ICD9/ICD10 Code or Definition
Pulmonary complications	
Respiratory complications	997.31/J95851 997.32/J9589 997.39/J95859, J9588, J9589
Pulmonary infection, pneumonia	481/J13, J181 482/J150 483/J157, J160, J168 484/B250 485/J180 486/J189
Respiratory failure and distress	518.3/J82 518.51/J95821, J9600 518.52/J952, J953 518.53/J95822, J9620 518.81/J9600, J9690 518.84/J9620
Tracheitis and bronchitis	466/J209 464/J040
Hypoxemia	799.02/R0902 Or one of the following: •Saturation < 90% •Use of face mask with > 6 l O_2 flow •Nonrebreather mask/Venturi mask •Continuous positive airway pressure/ bilevel positive airway pressure use
Pleural effusion	511.9/J918
Atelectasis	518.0/J9811, J9819
ARDS	518.5/J80 518.82/J80
Acute COPD exacerbation, acute asthma exacerbation	491.21/J441 493.92/J45901
Other continuous invasive mechanical ventilation	Z99.1/Z99.11
Reintubation	Defined by: reintubation surrogate search •Intubation note •Propofol bolus >100 mg •Etomidate •Muscle relaxant
Transfusion-related acute lung injury	518.7/J9584
Pulmonary embolism, respiratory acidosis	415.1/I2699 276.2/E872
Myocardial injury after noncardiac surgery	410 I21–I23 Or postoperative peak troponin T concentration ≥ 0.03 ng/ml within the first 7 days after surgery, apparently of cardiac origin
Stroke or transitional intravascular accident	430–435 I60–I66
Venous thromboembolism	4534 I824
All-cause mortality	Defined as any death before discharge, regardless of the cause

ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; ICD9, International Classification of Diseases, Ninth Revision; ICD10, International Classification of Diseases, Tenth Revision.

Table A2. Most-used Opioids and Conversion Doses

Name	Route	Units	Equivalent Dose	Name	Route	Units	Equivalent Dose
Morphine	IV	Milligrams	10	Codeine	Oral	Milligrams	200
Morphine	Oral	Milligrams	30	Propoxyphene	Oral	Tablets	1
Fentanyl	IV	Milligrams	0.1	Percocet 5/325	Oral	Tablets	6
Fentanyl	Epidural	Milligrams	0.1	Hydrocodone	Oral	Milligrams	30
Fentanyl	Oral	Milligrams	0.229	Vicodin 5/500	Oral	Tablets	6
Remifentanil	IV	Milligrams	0.1	Vicodin 7.5/500	Oral	Tablets	4
Methadone	Oral	Milligrams	20	Tramadol	Oral	Milligrams	150
Hydromorphone	IV	Milligrams	1.5	Meperidine	IV	Milligrams	75
Hydromorphone	Oral	Milligrams	7	Meperidine	Oral	Milligrams	333
Alfentanil	IV	Milligrams	0.67				

IV, intravenous.

ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Gauging the Herrick-Pender Thermistor: Marvelous Monitoring, from Open Fridge to Open Heart

After completing his World War II Navy assignment, John William Pender, M.D. (1912 to 2002, *lower right*), returned in 1946 to anesthesiology training at Mayo Clinic. While trialing hypothermia protocols in cardiac surgery, Pender and his team used thermistors from electric refrigerators ("fridges")—modern marvels of the mid-twentieth-century kitchen. By encapsulating metallic oxide beads in epoxy, these "thermal resistors" were more responsive and less toxic than mercury-based thermometers. Unfortunately, these "resistors" lacked a proper temperature gauge. Pender reached out to Julia F. Herrick, Ph.D. (*upper right*), a biophysicist recently back from the war effort and now studying physiologic thermometry. She lent him a prototype thermistor (*left*) until commercial models became available. The two collaborators would emerge as leaders in their respective fields. Dr. Herrick became President of the Engineering in Medicine and Biology Society and founding editor of their journal in 1954; Dr. Pender became President of the Academy of Anesthesiology in 1965. (Photos of Drs. Herrick and Pender by permission of Mayo Foundation for Medical Education and Research. Courtesy of The W. Bruce Fye Center for the History of Medicine, Mayo Clinic, Rochester, Minnesota. Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology. www.woodlibrarymuseum.org)

Melissa L. Coleman, M.D., Assistant Professor, Department of Anesthesiology and Perioperative Medicine, Penn State College of Medicine, Hershey, Pennsylvania.