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# Clinical REVIEW

## Enhanced Recovery: *Perioperative Pathways Leading to Better Outcomes*

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execution of an ERP requires coordination of the multidisciplinary teams, including surgery, anesthesiology, nursing, nutrition, physical therapy, and hospital team members.<sup>1</sup> Together, these individuals combine best practices, namely, organization of care and effective clinical management in an evidenced-based framework.

Other terminologies have been used to describe this coordination of care. These include enhanced recovery after surgery (ERAS), enhanced recovery pathways, and perioperative surgical home.<sup>1</sup> Although there are some variations in focus, the main objectives of these practices are to improve patient care and potentially reduce health care costs.<sup>1</sup>

Colorectal surgery is among the earliest surgical models to which ERP principles were applied.<sup>1</sup> The various elements of an ERP include preoperative patient education, modified preoperative fasting guidelines, preoperative medical optimization, fluid management, the role of bowel preparation, early oral intake, early ambulation, and standardized multimodal analgesic regimens. Specifically, 4 areas of patient care—preoperative medical optimization, pain management, use of bowel

An enhanced recovery program (ERP) is a set of multimodal, multidisciplinary interventions that are geared toward mitigating the undesirable effects of the surgical stress response.<sup>1</sup> The purpose of an ERP is to accelerate postoperative surgical recovery by attenuating the factors that lead to surgical stress. Successful

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preparation, and choice of intraoperative fluid type—often are overlooked under the guise of traditional dogmas. ERAS protocols aim to shift the paradigm by using the most current evidence to provide new insight into these areas.

## Preoperative Medical Optimization: Identifying “At-Risk” Patients

The focus of preoperative medical optimization begins with the question as to whether we can identify patients at risk for postoperative complications and whether that information can be used to estimate the preoperative risk in order to reduce and optimize this risk.

A variety of risk factors are associated with patient comorbidities, including age, lifestyle, patient comorbidities, type of surgery (open vs laparoscopic), cardiorespiratory fitness, nutritional status, and type of anesthesia.<sup>2</sup> According to the American College of Surgeons, the potentially modifiable risk factors include health status, body mass index (BMI), albumin level (>3.5 g/dL), and the presence of dyspnea.<sup>3</sup>

### Assessment Methods for Functional Status

There are several techniques to estimate preoperative risks through an assessment of functional status. One of these methods, the 6-minute walk test (6MWT), is an inexpensive test that simply requires a patient to walk the longest distance possible through a walking course (corridor), preferably 30 m long within a set interval of 6 minutes.<sup>4</sup> The patient has the option of stopping or slowing down at any point and then resuming the walk, depending on the degree of fatigue. Although there are other variables, such as the speed of walking, heart rate, blood pressure, oxygen saturation, the number of times the patient has to stop during testing, or changes in respiratory gases, the distance walked in 6 minutes is considered the most useful.<sup>4</sup>

Because the 6MWT lasts for a short duration and the actual walking is on a flat surface rather than an incline or a rugged surface, the 6MWT has come to be considered a submaximal test with the argument that walking 6 minutes on a flat surface would not allow the patient to reach their maximal capacity; however, most studies show a medium-to-high correlation with the actual oxygen consumption measured at the peak of the 6MWT.<sup>4</sup>

An alternative method for evaluating a patient’s functional status is the use of biomarkers. Hemoglobin A1c (glycated hemoglobin), in particular, is a known predictor of postoperative complications such as infections,<sup>5,6</sup> and can be assessed in various patient populations including patients without diabetes.

Nutritional status is another facet that should be considered when assessing preoperative risk. Malnutrition in patients undergoing surgery has been associated with an increased risk for postoperative complications, prolonged hospital length of stay (LOS), and delayed recovery of bowel function.<sup>3,7-9</sup> Malnutrition and weight loss are common in patients undergoing colorectal surgery due to tumor-related cachexia and decreased oral food intake caused in part by GI tract obstruction. Furthermore, malnutrition continues to be a prognostic indicator of poor survival outcomes and response to surgical intervention.<sup>10-12</sup>

Although efforts have been devoted to developing the tools for preoperative nutritional risk screening, it is unclear which

methods best predict the risk of developing nutrition-related complications. Traditional anthropometric nutritional assessment using body weight, skinfold thickness, serum nutritional factor levels (eg, low serum albumin and pre-albumin), and muscle strength have fallen out of favor because of their limited value in determining actual nutritional risk before surgery.<sup>13</sup> Thus, several diverse measurements have been combined into subjective scoring systems including the Subjective Global Assessment (SGA) questionnaire, the Nutritional Risk Screening 2002, the Nutritional Risk Score, and the Nutritional Risk Index scoring systems.<sup>14-17</sup> While there are no gold standards, a combination of objective and subjective nutritional assessment tools may be better than either alone (Table 1).<sup>10,14-17</sup>

### Improving Functional Reserve

Once the functional status has been ascertained, the next step is to attempt optimization in those who are subpar. In achieving optimization, an attempt is made to improve functional reserve, which can be broadly divided into 3 categories: preexisting medical conditions (inclusive of malnutrition), exercise capacity, and psychological status. The tools available to achieve these goals are nutritional, pharmacologic/procedural, physical, and mental interventions.

### Nutritional Status

Oral nutritional supplementation should be initiated in patients identified as nutritionally “at risk,” and a dietitian should be involved in any supplemental nutritional care for a patient. Although there is a lack of consensus in the interval when nutritional supplementation should occur, a period of 5 to 7 days appears to be the most commonly recommended time interval.<sup>18</sup> If the patient is deemed to be at severe nutritional risk (ie, weight loss >10%-15%/6 months; BMI <18.5 kg/m<sup>2</sup>; SGA grade C; serum albumin <30 g/L), it would be reasonable to consider delaying surgery until the nutritional deficit is corrected, even if only partially.<sup>18</sup>

Studies focused on preoperative nutritional state have shown that those patients who are severely malnourished and not treated with enteral or parenteral nutrition before surgery have a significantly higher rate of complications than their cohorts who have received enteral or parenteral nutrition.<sup>10</sup>

Although enteral nutrition stimulates hormone secretion, enhances portal circulation, and maintains the barrier and immune function of the intestinal mucosa, it is not often possible because of preexisting gut dysfunction.<sup>19</sup> Therefore, enteral support combined with parenteral nutrition is often considered an alternative to just enteral feeding alone.<sup>20</sup>

Total parenteral nutrition (TPN) is often used for nutritional support to compensate for any deficiency of enteral nutrition.<sup>20</sup> TPN solutions provide complete nutritional support because they contain fat emulsion, vitamins, and trace elements. However, risks associated with TPN use include hemothorax, pneumothorax, electrolyte imbalances, refeeding syndrome, and central vein catheter infection; thus, preoperative TPN should only be administered for 7 to 10 days.<sup>19</sup>

Peripheral parenteral nutrition (PPN) also has been used because of its relative ease compared with TPN. Unfortunately, PPN solutions generally do not provide enough energy and nutrients for full nutritional support.<sup>19</sup> Modified PPN solutions have been tried using 2-in-1 (dextrose plus amino acids) formulas or fat emulsion; however, multiple vitamins and trace elements are often omitted with these formulations.<sup>19</sup>

## Managing Chronic Conditions

Multiple guidelines exist to guide the management of the various chronic conditions, including cardiovascular diseases, coronary stents, and preoperative anemia. According to the American College of Cardiology/American Heart Association guidelines, it is recommended that patients on  $\beta$ -blockers continue receiving treatment during surgery<sup>21,22</sup>; however, routine administration of  $\beta$ -blockers is not necessary or advisable for all patients.<sup>22</sup> For patients with coronary stent placement, specific guidelines have been reported to determine the optimal timing for surgery and what medications should be continued.<sup>23</sup> Specifically, the type of stent (bare metal vs drug eluting), the time from stent placement, and the type of surgery (emergent vs elective) are important when assessing a patient's preoperative risk. For example, if a patient with a drug-eluting stent has

antiplatelet agents stopped within the first year of stent placement, the risk for intrastent thrombosis is 89%. For patients who smoke, quitting even 4 weeks before surgery improves wound healing and reduces complications.<sup>24,25</sup>

Preoperative anemia also should be treated before surgery, if possible.<sup>26</sup> According to the National Surgical Quality Improvement Project database, 30% of patients who underwent noncardiac surgery were anemic.<sup>26</sup> These patients had a higher 30-day morbidity and mortality after adjusting for any confounding variable.<sup>26</sup> Blood transfusion itself cannot be used to improve the outcomes in these patients, as it carries its own inherent risks to patients. One unit of packed red blood cells increases the risk for sepsis (odds ratio [OR], 1.29;  $P < 0.05$ ) and pneumonia (OR, 1.29;  $P < 0.05$ ).<sup>26</sup> Thus, treating anemia "preoperatively" rather than planning for intraoperative blood transfusion may

**Table 1.** Various Scoring Systems for Assessing Nutritional Status

Scoring System	Indices Tested	Scores
Subjective Global Assessment	<p><b>Medical history:</b></p> <ul style="list-style-type: none"> <li>• Weight change</li> <li>• Dietary intake change</li> <li>• GI symptoms</li> <li>• Changes in functional capacity</li> </ul> <p><b>Physical examination:</b></p> <ul style="list-style-type: none"> <li>• Loss of subcutaneous fat</li> <li>• Muscle wasting</li> <li>• Ankle or sacral edema</li> <li>• Ascites</li> </ul>	<p><b>A:</b> well nourished</p> <p><b>B:</b> moderately malnourished</p> <p><b>C:</b> severely malnourished</p>
Nutritional Risk Screening 2002	A patient is characterized by scoring the components "undernutrition" and "severity of disease" in 4 categories: (1) absent, (2) mild, (3) moderate, and (4) severe. The patient can have a score of 0-3 for each component and a total score of 0-6. Any patient with a total score $\geq 3$ is considered to be at nutritional risk.	<p><b>Score 1:</b> The patient was admitted to the hospital with complications associated with a chronic disease. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral supplements in most cases.</p> <p><b>Score 2:</b> The patient was confined to bed due to illness (eg, infection). Protein requirement is substantially increased but can be covered by oral supplements, although artificial feeding is required in many cases.</p> <p><b>Score 3:</b> The patient is in the ICU with assisted ventilation and inotropic drugs.</p>
Nutritional Risk Score	<ul style="list-style-type: none"> <li>• Weight loss (amount and duration)</li> <li>• Stress factors (effect of medical condition on nutritional requirements)</li> <li>• BMI for adults (weight in kg/height in <math>m^2</math>)</li> <li>• Percentile charts for children</li> <li>• Food intake (appetite and ability to eat and retain food)</li> </ul>	<p><b>7-15:</b> high risk</p> <p><b>4-6:</b> moderate risk</p> <p><b>0-3:</b> low risk</p>
Nutritional Risk Index	<p>Recent weight loss and serum albumin concentration</p> <p><math>NRI = (1.489 \times \text{serum albumin [g/L]}) + (41.7 \times \text{current weight/usual weight})</math></p>	<p><math>\geq 97.5\%</math>: well nourished</p> <p><b>83.5%-97.5%:</b> moderately malnourished</p> <p><b>&lt;83.5%:</b> severely malnourished</p>

**BMI**, body mass index; **NRI**, Nutritional Risk Index  
Based on references 14-17.

reduce mortality and morbidity.<sup>27,28</sup> Identifying patients who have a high probability of requiring a transfusion can be determined using the transfusion risk index, which uses various physiologic variables (Figure).<sup>27</sup> Once identified, these patients should be medically managed preoperatively. According to the American Society of Anesthesiologists, clinicians should test patients for anemia at least 2 weeks before surgery in order to allow sufficient time to manage symptoms.<sup>29,30</sup>

### Psychological Assessment

Psychological status as it is related to medical optimization should be explored. For example, psychosocial issues regarding smoking cessation preoperatively need to be appreciated, and simple measures may not be adequate in achieving this goal. Nicotine therapy along with counseling and a support system should be used to achieve this goal.<sup>31</sup>

### Prehabilitation

Patients who are identified as not being medically optimized can undergo prehabilitation training through a multimodal program aimed at improving the nutritional status and exercise capacity.

It has been shown that patients who are fitter and more physically active have better outcomes as they relate to a number of medical conditions, such as coronary artery disease, heart failure, hypertension, chronic obstructive pulmonary disease, obesity, and colorectal cancer.<sup>32-36</sup> Despite the slight increase in the risk for complications such as myocardial ischemia or even death during physical training, the overall benefit of enhanced physical status outweighs this short-lived period of elevated risk.<sup>32</sup>

Preoperative exercise training enables patients with a spectrum of severe pulmonary and cardiac diseases to tolerate surgical stress safely.<sup>37</sup>

Patients with malignancy often receive neoadjuvant chemotherapy and radiation therapy, which are administered weeks before a surgical procedure and usually require 6 to 12 weeks of recovery.<sup>37</sup> This has opened a window of opportunity to educate patients before major cancer surgeries, whereas previously, the pressure of reducing the time between diagnosis

and surgery prevented such an intervention. Preliminary non-randomized data from patients undergoing elective colorectal cancer surgery within an ERAS program have shown the feasibility of providing a cardiopulmonary exercise testing, a guided responsive interval-exercise training program.<sup>37</sup> Such a program is delivered 3 times a week for 6 weeks in a hospital setting after neoadjuvant chemoradiation therapy and before surgery.<sup>38</sup> The control population consisted of patients unable to engage in the exercise program for logistical reasons (eg, distance of residence from the hospital).

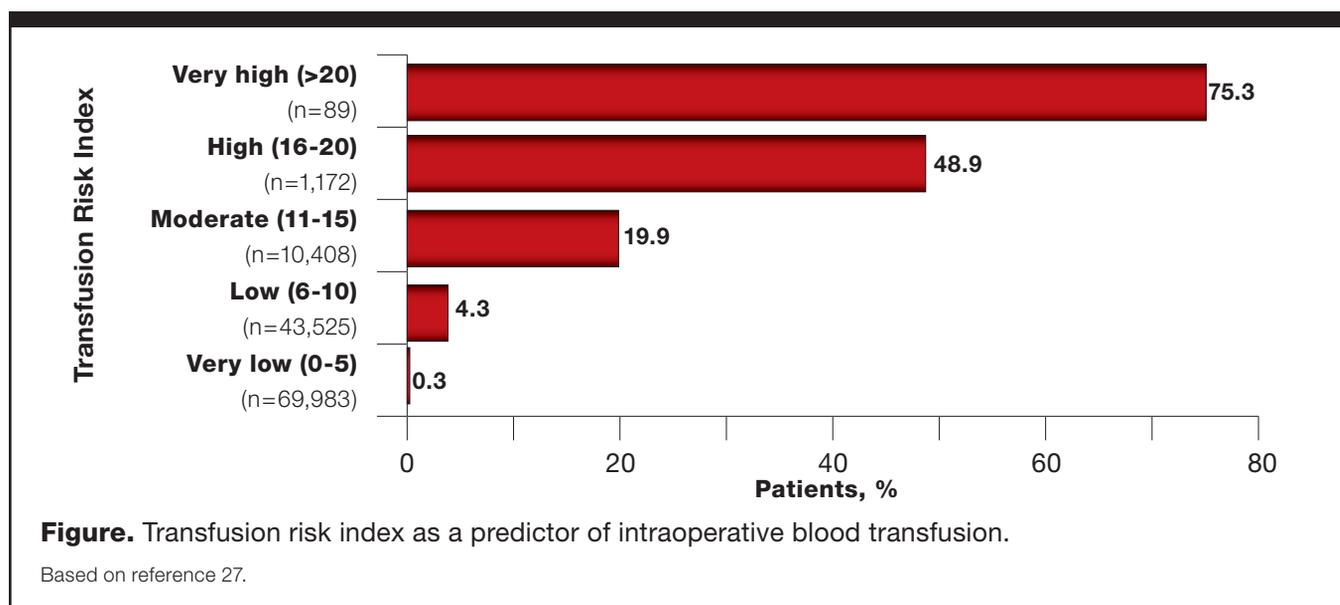
The incremental exercise test can be used to measure the efficacy of prehabilitation exercise training programs. An effective training program would be expected to result in an increase in the anaerobic threshold and/or maximum oxygen consumption.<sup>37</sup> These variables can be reliably measured and used to compare patient groups from different clinical centers and outcomes in clinical trials.

### Pain Management

Postoperative pain has significant clinical implications on a patient's overall recovery including anxiety, nausea, hospital discharge time, and delay in achieving the various recovery milestones.<sup>39</sup> Specifically, the delays in meaningful milestones such as ambulation have significant implications, especially in orthopedic surgical patients in whom rehabilitation can be delayed and even compromised.<sup>40</sup>

Traditionally, opioids have been the primary treatment modality for postoperative pain.<sup>41-43</sup> Although they provide profound analgesia, undesirable dose-related side effects such as postoperative nausea and vomiting (PONV), respiratory depression, sedation, and urinary retention have limited their use.<sup>42</sup> Also, although opioids provide an initial analgesic effect, there is a subsequent development of opioid-induced hyperalgesia that results in the use of higher doses.<sup>44,45</sup> Finally, opioid-related side effects lead to higher hospital costs and increased readmission rates.<sup>41</sup> Patients would rather endure continued pain and discomfort simply to avoid opioid-related side effects from the use of opioid therapy.<sup>46</sup>

Enhanced recovery guidelines seek to reduce postoperative



pain, minimize opioid-related adverse effects, and accelerate postsurgical recovery with rapid attainment of postoperative milestones and decrease hospital LOS.<sup>43</sup> Different pain management regimens have been employed for the various types of surgical procedures (Table 2).<sup>1,43,47</sup>

Various centers have employed slightly differing strategies for their ERAS programs with respect to pain management, but all adhere to the same core principle of multimodal analgesia—the use of multiple nonopioid analgesics with different mechanisms of action and/or concurrent use of regional and systemic analgesia to obtain satisfactory pain relief—while avoiding high doses of opioids (if any opioids at all) and, consequently, reducing or eliminating opioid-related side effects.<sup>43,48</sup> Therefore, it is suggested here that opioid therapy be reserved for the management of breakthrough pain.

### Nonopioid Strategy

The following drugs have been used in a multimodal approach for pain management: nonsteroidal anti-inflammatory drugs (NSAIDs)/selective cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, lidocaine, *N*-methyl-*D*-aspartate (NMDA) antagonists, gabapentinoids, and  $\beta$ -blockers.<sup>43</sup>

#### NSAIDs and COX-2 Inhibitors

In the absence of any contraindication, NSAIDs and COX-2 inhibitors are recommended in an ERP. By reducing inflammation and pain at the site of surgical trauma, these drugs are effective in the prevention and treatment of pain. Of note, although studies have shown that NSAIDs such as ibuprofen, diclofenac, and ketorolac reduce opioid consumption by as much as 30%, a direct link to reducing the duration of postoperative ileus is still lacking.<sup>49</sup> According to a retrospective data analysis, NSAIDs also have been associated with an increased risk for anastomotic leak (eg, patients with stapled anastomoses) following bowel surgery.<sup>50</sup> Of interest, selective COX-2 inhibitors were not associated with such a risk.<sup>50</sup> More studies are needed to clarify this finding.

Use of COX-2 inhibitors has demonstrated a reduction in opioid consumption and a modest reduction in postoperative ileus.<sup>51</sup> One explanation for the marked decrease in opioid use without a proportional decrease in the duration of the ileus may be that the development of the ileus is multifactorial and not as heavily dependent on opioid consumption as was once believed, although opioid use clearly contributes to it.<sup>49</sup> Other side effects of NSAIDs include increased bleeding tendency, renal dysfunction (especially in those with preexisting renal dysfunction), and allergic potential. Although long-term use of both drugs may be associated with adverse cardiovascular events, their use is generally considered safe for up to 5 days postoperatively.<sup>52</sup>

#### Acetaminophen

Acetaminophen is an effective analgesic agent for the treatment of mild to moderate pain. The mechanism of action of acetaminophen is mediated via stimulation of serotonergic pathways in the spinal cord through enhancement of the cannabinoid receptors.<sup>53</sup> Although the 3 different routes eventually achieve comparable analgesic efficacies, there is a significant difference in the maximum plasma concentrations and time to peak plasma concentrations, with the IV route achieving a 4-fold highest peak plasma concentrations compared with the oral route, and the peak plasma concentration is reached within 0.25 hour (IV route) versus 1 hour (oral route) and 2.5 hours via the rectal

route.<sup>54</sup> Hence, the IV route has become more widely used in recent years. However, the added cost of this formulation should be weighed against any potential benefit.<sup>55</sup> A recent meta-analysis found that prophylactic IV acetaminophen (typically a 1-g dose) as part of a multimodal analgesic regimen reduces nausea if administered before surgery or arriving to the PACU, but not after the onset of pain.<sup>56</sup> However, that the decrease in nausea could be secondary to a reduction in pain score and not necessarily a reduction in opioid usage.

Furthermore, acetaminophen possesses synergistic properties if given with NSAIDs.<sup>57</sup> In dental surgery, the combination of single-dose acetaminophen (0.5-1 g) and ibuprofen (200-400 mg) provides better postoperative analgesia than either drug alone with reduced analgesic needs and reduced risk for adverse events.<sup>58</sup> Overall, acetaminophen has a favorable safety profile.

#### Lidocaine Infusions

Intravenous lidocaine infusion has been associated with a reduction in acute postoperative pain (ie, 6 hours postoperatively) at rest, with cough, and with movement.<sup>59</sup> Additionally, IV lidocaine infusion also leads to a reduction in postoperative opioid (morphine) consumption, as well as opioid-related side effects such as shortened time to first flatus, shortened time to first bowel movement, and decreased PONV and hospital LOS.<sup>60</sup>

#### NMDA Receptor Antagonists

Ketamine, memantine, and magnesium sulfate are all NMDA receptor antagonists. Ketamine is often used for its analgesic properties.

Ketamine in subanesthetic doses has analgesic properties without the undesirable side effect of tolerance and delayed hyperalgesia. Ketamine is a useful adjunct when used as part of a multimodal analgesic regimen in postsurgical patients with high opioid requirements or opioid-refractory pain. It can be administered either as a bolus dose at the beginning of surgery (0.5 mg/kg) or as a continuous infusion at 10 to 20 mcg/kg per minute.<sup>61</sup> Undesirable side effects such as sedation, delusions, nightmares, and psychiatric disorders that are commonly associated with ketamine when used in anesthetic doses are not manifest at these low doses.<sup>62</sup> Of interest, an epidural regimen consisting of ketamine and bupivacaine was found to be superior to an opioid containing bupivacaine-fentanyl combination in fast-track colonic resection with shorter PACU and hospital LOS, as well as fewer opioid-related side effects.<sup>63</sup>

Despite the analgesic properties that ketamine provides, the specific use of ketamine for patients with chronic pain, whether perioperatively or otherwise, is currently off-label and not well studied. Ketamine is FDA approved for diagnostic and surgical procedures that do not require skeletal muscle relaxation when inducing anesthesia before the administration of other general anesthetic agents, and as a supplement for agents with low potency, such as nitrous oxide.<sup>43</sup> Memantine is more potent, better tolerated, and more slowly eliminated than ketamine.<sup>64</sup>

#### Gabapentinoids

Gabapentin and pregabalin  $\gamma$ -aminobutyric acid are both (GABA) analogues that have been shown to reduce postoperative opioid requirements and decrease acute and chronic postoperative pain when used as part of a multimodal analgesic technique for a broad range of surgeries (eg, gynecologic, abdominal, orthopedic, and dental).<sup>65,66</sup> Oral gabapentin

(900-1,200 mg) has been shown to lead to a decrease in reducing patient-controlled analgesia (PCA) morphine and postoperative pain after lumbar laminectomy.<sup>65</sup> One 3-armed study compared 1,200 mg prophylactic gabapentin, ketamine, and a control group, and found that preoperative use of gabapentin and ketamine reduced postoperative pain and PCA morphine consumption (42% and 35%, respectively) after hysterectomy,<sup>67</sup> whereas gabapentin alone was associated with a reduction in chronic incisional pain at 1, 3, and 6 months.<sup>67</sup>

Pregabalin possesses not only analgesic properties but also some anxiolysis. It has better bioavailability, and achieves therapeutic levels faster than gabapentin. A meta-analysis confirmed that both pre- and postoperative pregabalin reduce postoperative opioid consumption and incidence of PONV, although without a reduction in postoperative pain.<sup>66</sup> The disadvantages of the GABA analogues are their side effects—sedation, visual disturbances, dizziness, and headaches—thus limiting their use.<sup>66</sup>

### Long-Acting Bupivacaine

A liposomal formulation of long-acting bupivacaine is currently approved by the FDA for single-dose infiltration into the surgical site to produce postsurgical analgesia.<sup>68</sup> It uses DepoFoam technology of lipid-based encapsulated bupivacaine to deliver the agent over a longer period of time than conventional bupivacaine.<sup>68</sup> It sustains safe therapeutic levels of bupivacaine for up to 72 hours after initial administration,

thereby allowing prolonged analgesia and earlier hospital discharge.<sup>68</sup> When compared with conventional bupivacaine, liposomal bupivacaine led to a reduction in postoperative pain, opioid consumption, and opioid-related adverse events after surgeries such as hemorrhoidectomy by about 30%.<sup>69</sup> Similar results have been seen in patients undergoing bunionectomy of which the need for rescue pain medication was significantly lower in the liposomal bupivacaine group versus placebo.<sup>70</sup> These results also have been demonstrated in patients undergoing laparoscopic colectomies with an improvement in pain scores and a reduction in opioid consumption when compared with IV opioid PCA.<sup>71</sup> More research is needed to evaluate the safety and efficacy of the drug when administered as a peripheral nerve block.

Other novel formulations of long-acting bupivacaine are currently under development, for example, a formulation that features SABER technology, a biodegradable delivery system consisting of sucrose acetate isobutyrate,<sup>72</sup> and a bupivacaine meloxicam combination, which uses Biochronomer technology, which consists of both agents encapsulated in bioerodible polymers.<sup>73,74</sup> may play a role in further reducing opioid consumption and improving analgesia.

### β-Blockers

β-blockers may also have a role in perioperative analgesia. Esmolol, once considered a purely hemodynamic agent, has shown promise as an antinociceptive agent as well. Both

**Table 2.** ERAS Pain Management Protocols for Different Surgical Procedures

Procedure	Preoperative Analgesia	Intraoperative Analgesia
Open or laparoscopic colorectal surgery	Thoracic epidurals are placed at the T8-T10 level preoperatively with small doses of midazolam and fentanyl to facilitate epidural insertion and maintain patient comfort (ie, thromboprophylaxis with subcutaneous heparin 5,000 IU after epidural placement and before incision).	<ul style="list-style-type: none"> <li>A single epidural bolus of hydromorphone is administered at induction (0.4-0.8 mg based on body weight) followed by bupivacaine infusion (2.5 mg•mL<sup>-1</sup> at 3-6 mL•h<sup>-1</sup>).</li> <li>No intraoperative IV opioids are given after induction unless approved by attending anesthesiologist.</li> </ul>
Spine surgery	<ul style="list-style-type: none"> <li>Acetaminophen 2 g po (sustained release)</li> <li>Celecoxib 400 mg po</li> <li>Gabapentin 900 mg po</li> </ul>	<ul style="list-style-type: none"> <li>Remifentanyl and propofol</li> <li>Morphine IV 0.3 mg•kg<sup>-1</sup> at 45 min before end of surgery</li> <li>S-ketamine IV 0.5 mg•kg<sup>-1</sup> + 0.3 mg•kg•h<sup>-1</sup> until 45 min before end of surgery</li> <li>Epidural catheter is placed at middle tip of surgical field, boluses of bupivacaine 0.5 mg•mL<sup>-1</sup> at 10 mL.</li> <li>If an epidural is not possible, administer subfascial local infiltration (40 mL of bupivacaine 2.5 mg•mL<sup>-1</sup>).</li> <li>PONV prophylaxis with dexamethasone IV 24 mg</li> </ul>

ERAS, enhanced recovery after surgery; IQR, interquartile range; LOS, length of stay; NSAIDs, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; po, oral; POD, postoperative day; PONV, postoperative nausea and vomiting; SD, standard deviation

Adapted from references 1, 43, and 47.

intra- and postoperative opioid requirements are reduced in postoperative patients,<sup>75</sup> and they have the added benefit of being able to blunt the cardiovascular responses to surgical stimuli and are cardioprotective.<sup>75</sup> Of note, perioperative esmolol has been proposed as an alternative to remifentanyl for maintaining stable intraoperative hemodynamics,<sup>76</sup> and has been proven effective in ambulatory laparoscopic cholecystectomy, resulting in decreased postoperative pain and PONV, as well as a shorter hospital LOS.<sup>77</sup>

### Reduction of Opioid-Induced Adverse Effects

Because many clinicians consider the return of bowel function to be the main factor in reducing hospital LOS, “opioid-sparing” strategies should be instituted whenever possible due to the propensity of opioids causing GI ileus. Studies have not shown a correlation between wound incision and morphine consumption. Instead, the data demonstrate that morphine consumption is inversely related to the return of bowel function. Cali and colleagues found that decreasing incision size does not result in less morphine use. Thus there is no correlation between incision length and ileus.<sup>78</sup> Thus, regardless of the size of the incision, efforts should be made to initiate a multimodal approach to pain management. More recently, the laparoscopic surgical approach has grown in popularity and is widely encouraged in an ERP. Although initial opioid use may not be different for these procedures over larger incision surgeries, the duration of pain and opioid use may be shortened due to smaller surgical incisions.<sup>78</sup>

Other pharmacologic drugs have been used specifically to reduce opioid-induced postoperative ileus. Alvimopan is a peripherally acting  $\mu$ -opioid receptor antagonist that has been shown to reduce the incidence and duration of postoperative ileus.<sup>79</sup>

### Novel PCA Delivery Systems

Newer formulations of short-acting potent opioids offer promise as an alternative to the traditional IV PCA technique for the management of acute postoperative pain. These modalities allow patients to be more mobile when recovering from surgery.

A new formulation of fentanyl, delivered via the fentanyl iontophoretic transdermal system (ITS), offers a noninvasive patient-controlled approach for the short-term management of acute postoperative pain by administering fentanyl through a technique known as iontophoresis. Iontophoresis refers to transdermal delivery of a drug through the skin via the application of a low-intensity electrical field.<sup>80</sup> Fentanyl ITS delivers preprogrammed analgesic doses that are based on patient control.

The fentanyl ITS consists of 2 components: a top half (“controller”) containing all electronics packaged separately from a bottom half (“drug unit”) containing the hydrogels (“drug unit”). The patient has a recessed on-demand dose-activation button, red light-emitting diode (LED), green LED, and dose-counting liquid crystal display, whereas the drug unit contains fentanyl HCl (10.8 mg of fentanyl HCl equivalent to 9.7 mg of fentanyl).<sup>81</sup> The health care provider (eg, nurse,

Postoperative Analgesia	Outcome
<ul style="list-style-type: none"> <li>Epidural local anesthetic/opioid infusion (0.125% bupivacaine and hydromorphone 10 mcg/mL) administered for up to 72 h.</li> <li>Adjunctive analgesia with acetaminophen administered pre-incision and every 8 h; NSAIDs are given whenever possible.</li> <li>Transition to oral opioids after epidural is removed.</li> </ul>	<ul style="list-style-type: none"> <li>Significantly less total postoperative morphine equivalents are required (median [range], 29.8 [10-85] mg vs 120 [69-267] mg).</li> <li>Significantly lower average (SD) pain scores were reported throughout POD 0-5 (3.3 [1.9] vs 4.9 [2.1], respectively).</li> <li>Significantly shorter median hospital LOS (5 vs 7 d).</li> <li>No disadvantages were reported.</li> </ul>
<ul style="list-style-type: none"> <li>Acetaminophen 1 g <math>\times</math> 4 po</li> <li>Ibuprofen 400 mg <math>\times</math> 4 po until discharge</li> <li>Gabapentin 400 + 1,000 mg po for 5 d</li> <li>Epidural bupivacaine 2.5 mg<math>\cdot</math>mL<sup>-1</sup> with 50 mcg<math>\cdot</math>L<sup>-1</sup> of morphine 5-8 mL<math>\cdot</math>h<sup>-1</sup> for 96 h</li> <li>If no epidural, PCA morphine (bolus 2 mg, lockout 15 min for 48 h) background infusion 1 mg<math>\cdot</math>h<sup>-1</sup> during first 24 h. Hydromorphone PCA also can be used instead of morphine with the appropriate dosages.</li> <li>Sustained-release oral morphine 20 mg <math>\times</math> 2 after end of epidural or PCA</li> <li>Opioid at anesthesiologist’s discretion</li> </ul>	<ul style="list-style-type: none"> <li>Significantly less opioid consumption (oral morphine equivalent) was reported on POD 1 (median [range], 110 [55-180] mg vs 15 [0-120] mg) and on POD 2 (100 [40-149] mg vs 30 [0-120] mg), but not on POD 3-6. Pain scores not analyzed.</li> <li>Significantly earlier mobilization from bed (median [IQR], 1 [1-1] d vs 1 [1-2.5] d) and ambulation, both with and without a walking frame (2 [1-2.5] d vs 3 [1-5] d and 5 [3-7] vs 7 [5-9.3] d, respectively).</li> <li>Lower nausea, sedation, and dizziness scores were reported on POD 1-6. Significantly shorter LOS was reported in the PACU (median [range], 270 [173-353] min vs 345 [240-480] min), but there was no difference in hospital LOS.</li> <li>No postoperative infections were reported in either group.</li> <li>No disadvantages were reported.</li> </ul>

physician assistant) assembles the system by snapping the drug unit and controller together immediately before application to the patient. An adhesive is used to cover the bottom of the drug component housing and allows the system to be attached to the patient's skin.

Multiple randomized controlled trials (RCTs) comparing this system with morphine IV PCA with morphine have established the safety and efficacy of fentanyl ITS in postoperative pain management.<sup>82-84</sup> Additionally, a meta-analysis of 4 active controlled RCTs concluded that fentanyl ITS and IV PCA morphine provide similar efficacy; however, patients reported significantly better relief with fentanyl ITS than IV PCA morphine.<sup>85</sup>

Another delivery system not yet FDA approved is known as the sufentanil sublingual tablet system (SSTS). Sufentanil has a rapid equilibration half-life between plasma and the central nervous system ( $t_{1/2ke0}$ =6 minutes vs 2.8 hours for morphine).<sup>86,87</sup> Unlike morphine, it lacks active metabolites and possessed a high therapeutic index in preclinical models.<sup>88</sup> Because sufentanil is highly lipophilic, a patient is able to absorb the bioadhesive tablet rapidly following sublingual administration without being invasive.<sup>89</sup> The handheld SSTS device is preprogrammed with a 20-minute lockout interval, and uses a radiofrequency identification thumb tag to allow only the patient to operate the device.<sup>89</sup> An RCT of SSTS and IV PCA with morphine showed that SSTS has a faster onset of analgesia and higher patient and nurse user satisfaction when compared with IV PCA with morphine.<sup>89</sup>

Although these novel devices may provide better patient mobility following surgery, the real effect is not yet defined because there have not been any studies conducted with these devices in the context of an ERP.

## Bowel Preparation

Mechanical bowel preparation (MBP) is not routinely recommended in enhanced recovery guidelines. In the early 1930s, mortality associated with colonic surgery was at least 20%. With the introduction of chemotherapy agents and antibiotics, however, the mortality decreased to less than 5% later in the decade.<sup>90</sup> Studies in the 1970s focused on which preparation would be most useful in clearing the bacteria.<sup>91</sup>

A study by Nichols and colleagues in 1971 evaluated the role of oral antibiotics with MBP.<sup>91</sup> Washington and colleagues sought to develop a better protocol combining oral antibiotics with MBP.<sup>92</sup> Both of these studies showed that the addition of oral antibiotics to MBP resulted in lower rates of infection.<sup>92</sup>

In the 1980s, there was a paucity of literature evaluating the efficacy of IV antibiotics in conjunction with MBP. This was primarily due to the fact that in the early part of the decade, data had already been generated that firmly established the efficacy of IV antibiotics, and future studies omitting their use in control groups could not be conducted from an ethical standpoint.<sup>93</sup> Thus, studies from the 1990s onward looked at MBP combined with various formulations of IV antibiotics. From 2003 to 2011, a series of studies that were based on the Cochrane databases concluded that there is no benefit to MBP if given in conjunction with IV antibiotics.<sup>94-96</sup>

During this time, studies were also published that refuted this claim. However, these studies looked solely at surgical site infections (SSIs) rather than overall mortality or other indices of relevance to patients (eg, hospital LOS, readmission, and overall mortality).<sup>97</sup>

Despite this evidence, close to 80% to 100% of patients in the United States and many western European countries (France, Spain, and Italy) are recommended to undergo MBP.<sup>98</sup> In the United Kingdom, the number is 86%.<sup>98,99</sup> The reason for this heterogeneity in practice is unclear. One possible explanation can be that the available literature addressing this issue often focuses on different end points and the overall conclusions are not clearly specified. The wide breadth of studies lack common, well-defined outcomes, common perioperative protocols, evaluation of outcomes except SSIs, and finally prospective RCTs comparing no preparation versus preparation.

The existing evidence points to the fact that MBP results in fluid shifts, messy liquid stool, and increased secondary morbidity.<sup>100</sup> Additionally, outcomes have been different for the various studies, and no study has looked at the outcomes for colon versus rectal surgery. The overall conclusions, however, have been to omit MBP and recognize that medical outcomes are more important than the occasional benefit of SSIs.

As a result of the available evidence, the 2009 ERAS guidelines for colonic surgery recommend that routine oral bowel preparation should not be done for patients undergoing elective colonic resection above the peritoneal reflection, and for low rectal resections where a diverting stoma is planned a bowel preparation may be considered.<sup>101</sup> These guidelines were updated in 2012 to include no mechanical or oral antibiotic bowel preparation in colonic resection, and for rectal resections an enema preparation selectively and when diversion is planned.<sup>102</sup>

Thus, the overall ERAS recommendations as they relate to MBP are to understand the complications inherent with MBP, including the physiologic stress that the patient is put under when undergoing this process. Overall, MBP should be avoided for proximal resections, and bowel preparations should be focused on the individual patient instead of routine. Finally, routine and audited systemic antibiotics at the start of colorectal surgery should be done. Future directions should focus on randomized studies that are adequately powered to evaluate the compliance of MBP, evaluating the best MBP versus no MBP, and analyzing the medical and surgical cost outcomes, as well as different operations, type of preparations, and patient populations.

## Intraoperative Fluid Management

The goal of intraoperative fluid management is to maintain the patient in a euvolemic state. In contrast to "restrictive" fluid therapy, which may be interpreted as deliberate hypovolemia,<sup>103</sup> the aim is "zero-balance" fluid management with the goals of avoiding fluid excess and maintaining preoperative hydration and weight.<sup>104</sup>

### Maintenance Fluid Therapy

Maintenance fluid should be administered to maintain a patient's preoperative baseline weight by replacing losses from urine, sweat, and other routes. Infusions of balanced crystalloid should not exceed 3 mL/kg<sup>-1</sup>·hr<sup>-1</sup>, as evaporative losses are typically only 0.5-1.0 mL/kg<sup>-1</sup>·hr<sup>-1</sup> during major abdominal surgery, lower than traditionally thought.<sup>105</sup> Replacement of "third-space" loss, describing a nonfunctional compartment that can sequester a significant amount of fluid intraoperatively,<sup>106</sup> is not supported

by tracer studies because fluid is either intravascular or interstitial.<sup>103,107</sup>

Excessive fluid administration can cause significant harm.<sup>108,109</sup> Hypervolemia increases intravascular hydrostatic pressure, damaging the endothelial glycocalyx that mediates vascular permeability, contributing to fluid shift into the interstitial space.<sup>110</sup> Edema of the gut wall with resultant ileus is the most common manifestation of excessive fluid therapy after major bowel surgery. In humans, a modest 3-kg fluid weight gain after elective colonic resection is associated with delayed recovery of GI function, an increased rate of complications, and a prolonged hospital LOS.<sup>109</sup>

### **Bolus Fluid Therapy**

Blood loss and fluid shifts must be accounted for and replaced as necessary. Signs or symptoms of intravascular hypovolemia should be treated with a fluid challenge.<sup>103</sup> Patients with hemodynamic instability are not necessarily volume depleted, and rapid infusion should only be administered when hypovolemia is evident or likely. However, clinicians are always successful at diagnosing hypovolemia based on “clinical ground,” as rapid infusion of a fluid bolus only improves hemodynamic stability in fewer than half of the patients.<sup>111,112</sup> Additional administration of vasopressors may help to determine the effect of reduced vascular tone in causing relative hypovolemia once real hypovolemia is excluded.

Heart rate, blood pressure, urine output, and central venous pressure (CVP) are not reliable measures of volume status. Acute blood loss up to 25% of the circulating volume, for example, may not be associated with rapid or significant changes in heart rate and/or blood pressure because splanchnic vasoconstriction maintains core perfusion.<sup>113</sup> A systematic review has concluded that CVP does not accurately identify which patients require fluid therapy, how much they require, or whether routine monitoring of CVP is of value in the operating room, emergency department, or the ICU.<sup>114</sup> Neurohormonal responses to surgical stress reduce urine output below 0.5 mL/kg<sup>-1</sup>·hr<sup>-1</sup> without indicating a need for fluid administration.<sup>115</sup>

### **Goal-Directed Fluid Therapy**

Goal-directed fluid therapy (GDFT) extrapolates fluid responsiveness from measurable hemodynamic changes, according to the Frank-Starling law in patients without myocardial disease.<sup>103</sup> Several meta-analyses of multiple studies have concluded that GDFT reduces complications such as nausea, postoperative hemodynamic instability, and shorter hospital LOS after major surgery.<sup>116,117</sup>

Fluid responsiveness also can be predicted without administration of a fluid bolus. A number of cardiovascular measurements, such as stroke volume, pulse pressure, and systolic pressure, vary during the ventilatory cycle with the amplitude of their variation indicating the degree of hypovolemia. These are more sensitive for hypovolemia than changes in heart rate and blood pressure, allowing for earlier therapeutic intervention.<sup>118,119</sup> Variation in the stroke volume or pulse pressure greater than 13% predicts fluid responsiveness<sup>120</sup> in the presence of fairly constant R-R intervals<sup>121</sup> with constant intrathoracic pressure and tidal volumes above 8 mL/kg<sup>-1</sup>.<sup>122</sup> When lower tidal volumes are used, as is often the case in clinical practice, the predictive value of these dynamic indices decreases.<sup>123</sup> These indices should not be

used in isolation, but should be combined with other clinical measurements to determine the presence of hypovolemia.

GDFT reduces the rate of GI complications and the hospital LOS (by about 2 days) after major elective surgery among patients treated conventionally without adopting an ERP.<sup>124</sup> More recent studies suggest a reduced effect of GDFT in the presence of an ERP, probably because the patient is less likely to be severely hypovolemic at induction of anesthesia.<sup>125</sup>

### **Postoperative Fluid Management**

Postoperative fluid management aims to maintain a euvolemic state and continues to assess fluid responsiveness, particularly in high-risk patients.<sup>126</sup> Most patients are less able to excrete fluid and sodium postoperatively, which they retain.<sup>109</sup>

Eating and drinking soon after GI resection should be encouraged, as feeding is associated with a reduced risk for infection and a decreased hospital LOS, without an increase in the risk for anastomotic dehiscence.<sup>103</sup> Intravenous fluids should be discontinued and not restarted unless there is a clinical indication. Patients without ongoing fluid deficit or losses should drink at least 1.75 L water each day.<sup>127</sup> Normovolemic patients who are hypotensive as a result of neuraxial anesthesia should not be treated with additional fluid.<sup>128</sup> Instead, the dose or concentration of epidural local anesthetic should be reduced, accompanied by vasopressor infusion. Postoperative oliguria should not automatically trigger IV fluid infusion, as fluid retention is a normal neurohormonal response to stress.

### **Perioperative Urine Output**

Traditionally, intraoperative urine output has been assumed to correlate with intravascular volume, with oliguria predicting postoperative renal failure. Postoperative acute renal failure is commonly attributed to prerenal acute tubular necrosis, treated by maintaining renal blood flow with IV infusions of fluid and vasoconstrictors. However, an observational study of over 65,000 patients undergoing noncardiac surgery suggests that these assumptions are incorrect, finding no significant correlation between the prevalence of postoperative acute renal failure and intraoperative urine output less than 0.5 mL/kg<sup>-1</sup>·hr<sup>-1</sup>, regardless of the preoperative risk for developing acute renal failure. Additionally, a positive postoperative fluid balance is associated with increased risks for acute kidney injury and GI dysfunction.<sup>129</sup> Within an ERP, the presence of short-term oliguria should be monitored but not immediately be treated with additional administration of crystalloid.

### **Conclusion**

ERPs have revolutionized perioperative surgical care. The shift in paradigm that is required to reassess old concepts often is met with resistance among some in the medical community who have become accustomed to providing care under old and dated guidelines. Preoperative optimization can reduce the risk for postoperative complications; multimodal analgesia is superior to opioid-based analgesic techniques for postoperative pain management; and MBP has not been shown to achieve the goals for which it was designed and in fact can lead to longer hospital LOS and complications. ERPs should be considered the new standard of care for patients undergoing major elective surgery.

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