

# Multimodality Approaches to Improving Post-operative Pain and Outcomes

Ronald S Chamberlain, MD, MPA, FACS<sup>1</sup> and Robert H Blackshear, MD<sup>2</sup>

1. Chairman and Surgeon in Chief, Department of Surgery, Saint Barnabas Medical Center, and Professor, Department of Surgery, University of Medicine and Dentistry of New Jersey; 2. Chairman, Department of Anesthesiology, Skaggs Regional Medical Center

## Abstract

Pain is an inevitable complication of surgery. It not only impedes healing and recovery in the surgical patient, but also imposes a great deal of strain on healthcare resources. Post-operative ileus (POI), a frequent complication following surgery (especially of the abdomen), is intimately related to modes of pain control. Important aspects of effective pain control measures include improvement in quality of life and patient satisfaction as well as the prevention or limitation of post-operative complications, particularly POI. A comprehensive review of numerous peri-operative management methods reveals only limited benefit, if any, when employed individually. Strategies incorporating various preventive–therapeutic approaches devised to manage surgical patients in a ‘fast-track’ manner peri-operatively may provide better outcomes.

## Keywords

Pain management, ileus, fast-track, multimodality approaches

**Disclosure:** Ronald S Chamberlain, MD, MPA, FACS, is a consultant for Ethicon, Inc., and is on the speaker’s bureau of Merck, Wyeth, and sanofi-aventis. Robert H Blackshear, MD, is a member of the speaker’s bureau of Entoria, Inc (Chlorapep), on the speaker’s bureau of and a consultant for EKR Therapeutics, Inc., and on the speaker’s bureau of and a consultant for Flynn Pharma, Inc.

**Received:** February 12, 2009 **Accepted:** April 8, 2009 **DOI:** 10.17925/OHR.2009.05.1.16

**Correspondence:** Ronald S Chamberlain, MD, Chairman and Surgeon in Chief, Department of Surgery, Saint Barnabas Medical Center, 94 Old Short Hills Road, Livingstone, NJ 07039. E: rchamberlain@sbhcs.com

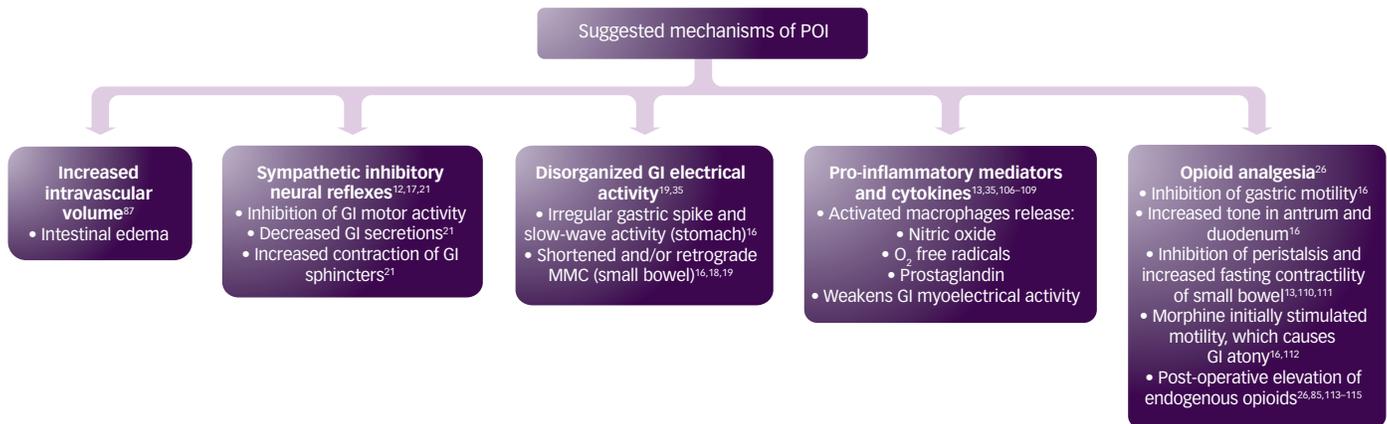
Approximately 72 million surgeries are performed in the US every year,<sup>1</sup> with over 20 million involving major inpatient procedures.<sup>2</sup> Despite the proliferation of new pain-management modalities, over 75% of all surgical patients experience moderate to severe post-operative pain.<sup>3</sup> Higher post-operative pain scores alone have been documented to be associated with longer length of hospital stay (LOS), increased post-operative medical complications, and inadequate or delayed rehabilitation.<sup>4</sup> The Joint Commission on Accreditation of Health Care Organizations (JCAHO) stated that “pain is the fifth vital sign” and has established new guidelines for the assessment and management of pain. These guidelines recognize the right of patients to appropriate assessment and treatment of pain, ensure staff competency in pain assessment and management, support appropriate use of effective pain medications, and establish quality measures for the management of pain. Consequently, healthcare providers are encouraged to continuously assess and actively treat a patient’s pain.<sup>5,6</sup>

Post-operative ileus (POI), a frequent complication following surgery, is intimately related to methods of post-operative pain management. It is the most common complication leading to prolonged LOS following abdominal surgery,<sup>7</sup> thereby overtaxing healthcare resources.<sup>8</sup> POI contributes towards post-operative complications, including delayed wound healing and ambulation, atelectasis, pneumonia, and deep vein thrombosis (DVT). The relationship between POI and DVT was

demonstrated in a clinical review of 2,949 patients who underwent 3,364 consecutive primary and revision orthopaedic surgeries.<sup>9</sup> The incidence of symptomatic DVT was 1.7%, and was higher (8.1%) in patients with POI (odds ratio [OR] 5.5; p=0.0036). Furthermore, the incidence of pulmonary embolism (PE) was 3.2% in patients with POI versus 0.24% in those without POI (OR 19.6; p<0.0082). In addition, the in-hospital mortality rate is reportedly higher in patients with POI than in those without it (6.5 versus 2.3%; p<0.01).<sup>10</sup>

An analysis of 161,000 major bowel resections found that in patients with POI the LOS increased by five days and the re-admission rate was higher (3.6%) compared with that of all other patients (0.2%).<sup>7,10</sup> Similarly, 17.4% of the 17,896 partial colectomy patients reviewed by Iyer and Saunders had a secondary diagnosis of POI and a significantly longer average LOS (13.75±13.33 days with POI versus 8.85±9.49 days without POI; p<0.001).<sup>11</sup> Furthermore, the hospitalization costs attributed to POI are \$1.14 billion/annum, and the expenses per patient are significantly higher (\$16,000/patient with POI versus \$10,000/patient without POI; p<0.01).<sup>7</sup> The fiscal benefit that can accrue from decreasing LOS by even a day is substantial, and warrants disciplined management of POI.<sup>11</sup>

Important aspects of effective pain control measures include improvement in quality of life and patient satisfaction and the prevention or limitation of post-operative complications, particularly

**Figure 1: Interactive Mechanisms of Post-operative Ileus**

GI = gastrointestinal; MMC = migrating motor complex; POI = post-operative ileus.

POI. Strategies incorporating numerous preventive–therapeutic approaches have been devised to manage surgical patients in a peri-operative ‘fast-track’ manner. This article will provide a comprehensive overview of currently employed strategies and discuss the strength of evidence supporting each of these approaches.

### Post-operative Ileus—Definition, Mechanism, and Risk Factors

POI is considered an iatrogenic condition and is defined as transient impairment of bowel motility following major surgery, particularly abdominal surgery.<sup>9,12-15</sup> Gastrointestinal (GI) motility normally resumes within two to three post-operative days, and POI should be suspected when it does not.<sup>16-20</sup> Nevertheless, it may be difficult to diagnose POI and distinguish it from a mechanical bowel obstruction even with the aid of radiology. Clinically, POI is characterized by abdominal distension, lack of flatus, and bowel sounds/motions,<sup>12</sup> and symptoms include nausea, vomiting, and abdominal cramps.<sup>16</sup> The underlying pathology of POI is best described as a lack of co-ordinated bowel motility that affects all segments of the GI tract.<sup>16,18</sup> Small bowel motility usually recovers within hours of surgery,<sup>16,18,19</sup> gastric motility typically recovers within 24–48 hours post-operatively,<sup>9,21</sup> and recovery of colonic motility, which is generally the limiting factor in resolving POI, usually occurs 48–72 hours post-operatively.<sup>16-20,22</sup>

Development of POI is multifactorial. These factors include disorganized GI myoelectrical activity, inhibitory sympathetic input, release of hormones, neurotransmitters, and pro-inflammatory mediators, elevated intravascular volume, and adverse effects of analgesics, particularly opioids (see *Figure 1*). Bauer and Boeckxstaens and Luckey et al. have hypothesized that intestinal inflammation in response to bowel manipulation results in activation of primary afferent neurons, which trigger inhibitory neuronal pathways leading to post-operative gut dysmotility.<sup>13,16</sup> This suggests that interactions between the above-mentioned factors are responsible for POI.

Several studies have attempted to predict the risk factors for POI. A logistical regression analysis of 666 patients with non-ruptured abdominal aortic aneurysms showed POI to be associated with

deterioration of cardiovascular–pulmonary–renal function.<sup>23</sup> While most studies have demonstrated a strong correlation between the incidence and duration of POI and opioid use, some suggest additional contributory factors including operative time, blood loss, and experience/specialization of the surgeon.<sup>24,25</sup>

Mechanical trauma of the GI tissue and release of pro-inflammatory mediators are implicated in the development of POI.<sup>13</sup> It may be reasonably expected that minimally invasive procedures would be

*Strategies incorporating numerous preventive–therapeutic approaches have been devised to manage surgical patients in a peri-operative ‘fast-track’ manner.*

associated with reduced risk for POI;<sup>24</sup> however, a review by Holte et al. found a significant association between laparoscopy and reduced POI in just two of four studies.<sup>26</sup> Although POI most often complicates abdominal surgery, it is also encountered following cardiothoracic, neurosurgical, and orthopaedic procedures.<sup>9,14,15</sup>

### Preventive and Therapeutic Strategies for Limiting Post-operative Complications and Shortening Hospital Stay

Numerous peri-operative methods have been employed to reduce the incidence and/or duration of post-operative complications such as POI. Some have shown benefits independently or if incorporated into a multimodality approach, while others have proved counter-productive and hence their use is now discouraged.

#### Pre-operative Mechanical Bowel Preparation

Pre-operative mechanical bowel preparation (MBP), a long-time practice in colonic surgery, may be unnecessary and even deleterious

according to recent studies. A systematic review by Guenaga et al., including nine randomized controlled trials (RCTs) and 1,592 patients, was performed to determine the safety and effectiveness of MBP in colorectal surgery.<sup>27</sup> They found the rate of anastomotic leaks to be higher with this intervention than without it (6.2 versus 3.2%;  $p=0.003$ ). Furthermore, another study revealed that MBP significantly increases the incidence of POI and LOS in urology patients.<sup>28</sup>

### Carbohydrate Loading, Probiotics, and Early Post-operative Feeding

Traditionally, patients are advised to fast overnight pre-operatively. However, recent evidence suggests that the administration of enteric nutrition within hours pre-operatively shortens bowel recovery time post-operatively.<sup>29-31</sup> In a study of 36 patients, Noblett et al. found that patients who consumed a carbohydrate-rich drink pre-operatively had a significant decrease in LOS versus those who fasted or drank an

*Numerous peri-operative methods have been employed to reduce the incidence and/or duration of post-operative complications such as post-operative ileus.*

equivalent amount of water.<sup>29</sup> These findings were mirrored in reviews performed by Fearon and Luff and Nygren et al.<sup>30,31</sup> Bengmark and Gil suggest that enteric administration of specific lactobacillus in the pre- and post-operative period may help maintain GI motility and prevent POI.<sup>32</sup> Probiotics are currently the most investigated nutritional aid, and further studies will determine their significance.

Due to emerging data, early feeding following intra-abdominal surgery has gained favor. Stewart et al. found that patients who were fed early post-operatively had faster bowel recovery and reduced LOS than those who were not.<sup>33</sup> In addition, Jeffery et al. found no difference in recovery of patients receiving a clear liquid diet versus regular diet beginning with the first post-operative oral intake.<sup>34</sup> Moreover, the absence of complication risks associated with early post-operative feeding has led to a growing trend toward this approach.<sup>35</sup>

### Post-operative Pain Control

#### Opioids and Opioid Antagonists

Intravenous (IV) opioids are widely used in post-operative pain management. Chronic opioid administration causes development of tolerance to its analgesic effect but not adverse GI effects.<sup>26,36</sup> Thus, limiting opioid use significantly decreases POI.<sup>19,37</sup> Opioid antagonists counteract opioid effects on gastric motility. The two opioid antagonists currently available are alvimopan and methylnaltrexone. These agents are highly selective for peripheral receptors and do not readily cross the blood-brain barrier, thereby reversing opioid effects on the GI tract without reversing pain relief (central effect).<sup>19,35,38-40</sup> Alvimopan has been shown to significantly reduce POI in bowel resection patients.<sup>41</sup> Patients were given alvimopan 6 or 12mg or placebo at least two hours pre-

operatively and twice daily for up to seven days post-operatively. Alvimopan 6 or 12mg accelerated GI recovery by 12–18 hours over placebo (hazard ratio 1.28 and 1.38, respectively;  $p<0.001$ ) and time to discharge by 16 hours for 6mg and 18 hours for 12mg ( $p<0.001$ ) from a mean of 147 hours for placebo. In addition, alvimopan-treated patients had reduced incidences of prolonged LOS or re-admission ( $p<0.001$ ). However, alvimopan is only approved for up to 15 doses as long-term treatment increases the risk for myocardial infarction within the first four months of therapy for patients treated with chronic opioids.<sup>42</sup>

A separate study with methylnaltrexone 0.3mg/kg administered as a 20-minute IV infusion every six hours for up to seven days was randomized among 65 colectomy patients.<sup>39</sup> Methylnaltrexone-treated patients experienced faster recovery of bowel function than placebo patients and the mean differences in most recovery parameters were greater than one day. No differences in opioid use, mean pain scores, or adverse events were observed between the two groups. Currently, methylnaltrexone is US Food and Drug Administration (FDA)-approved for the treatment of opioid-induced constipation only.

#### Intravenous Patient-controlled Analgesia

IV patient-controlled analgesia (IV-PCA) continues to be the most regularly used mode of analgesia delivery for post-operative pain control.<sup>43</sup> IV-PCA requires a programmable infusion pump that can deliver a pre-programmed dose of IV opioid on demand by the patient. IV-PCA drug delivery hinges on an important point: the ability of the patient to be actively engaged in his or her own pain therapy. In theory, IV-PCA is based on the principle that small patient-controlled incremental doses of an opioid will result in effective pain relief without the unwanted side effects of over-sedation and respiratory depression. The result is pain relief via a minimum effective analgesia concentration (MEAC).<sup>44</sup> In order for IV-PCA to be efficacious, two prerequisites must be established: individualize dosage and titrate to pain relief response to achieve MEAC and establish analgesia, and maintain constant plasma opioid concentrations to avoid peaks and troughs. Numerous algorithms for IV-PCA therapy have been established and are usually institution-specific.<sup>45</sup>

#### Epidural Delivery of Analgesia/Anesthesia

Epidural delivery of analgesics/anesthetics is a technique well-known to anesthesiologists throughout the US. This mode of analgesia is clearly superior to IV-PCA for most severely painful surgical

*It is hypothesized that epidural analgesics/anesthetics block afferent inhibitory and efferent sympathetics with a resultant decrease in post-operative ileus and increase in splanchnic blood flow, respectively.*

procedures.<sup>46,47</sup> Effective post-operative analgesia can be delivered via this route whether for post-operative pain control following surgeries below the umbilicus in which epidural analgesia is placed at the lumbar interspace, or above the umbilicus for upper abdominal

**Table 1: American Society of Regional Anesthesia Guidelines for Thromboprophylactic Therapy in Patients Receiving Neuraxial Analgesia<sup>61</sup>**

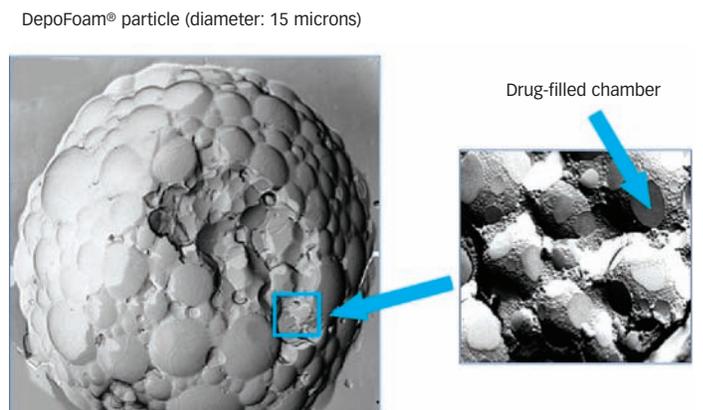
Antiplatelet Medications	Unfractionated SC Heparin	Unfractionated IV Heparin	LMWH	Warfarin
No contraindication with NSAIDs; discontinue ticlopidine 14 days, clopidigrel seven days, glycoprotein IIb/IIIa inhibitors eight to 48 hours in advance.	No contraindication; consider delaying heparin until after block if technical difficulty anticipated.	Heparinize one hour after neuraxial technique, remove catheter two to four hours after last heparin dose, no mandatory delay if traumatic needle or catheter placement.	Once-daily dosing: remove neuraxial catheter 10–12 hours after last dose of LMWH; subsequent dosing should occur minimum of two hours after catheter removal. Twice-daily dosing: LMWH 24 hours after surgery, regardless of technique; remove neuraxial catheter two hours before first LMWH dose.	Document normal INR after discontinuation (prior to neuraxial technique); remove catheter when INR $\leq 1.5$ (initiation of therapy).

NSAIDs = non-steroidal anti-inflammatory drugs; SC = subcutaneous; IV = intravenous; LMWH = low-molecular-weight heparin; INR = international normalized ratio.

surgeries or surgeries involving the thorax in which delivery of analgesia can be placed at either the lumbar interspace or the thoracic interspace.<sup>48</sup> Analgesics are typically placed via an indwelling epidural catheter if pain control is desired for more than 24 hours. Epidural analgesia for post-operative pain management has been clinically shown to provide control of rest and incident pain,<sup>46</sup> low incidence of pulmonary and cardiovascular complications,<sup>49</sup> better post-operative analgesia compared with parenteral opioids including IV-PCA,<sup>50,51</sup> improved post-operative outcome,<sup>52</sup> improved quality of life and patient satisfaction,<sup>53</sup> and attenuation of stress-induced immunosuppression in patients undergoing major abdominal surgery.<sup>54</sup> As with any indwelling device connected to an infusion pump, complications do occur. Medication errors are especially onerous and are monitored via the Institute for Safe Medication Practices (ISMP) and the FDA Medwatch program.<sup>55</sup> Additionally, the risk for epidural abscess or hematoma related to epidural catheterization, though low, is real, with an incidence of abscess formation of less than 0.1% and hematoma of less than 0.05%.<sup>56–59</sup> Once an abscess or hematoma causing neurological deficit is identified, the event becomes a neurosurgical emergency.

The risk for developing a hematoma is substantially greater when epidural catheters are in place in combination with post-operative thromboprophylaxis. Between May 1993 and November 1997, 30 cases of spinal hematoma in patients undergoing spinal or epidural anesthesia while receiving low-molecular-weight heparin (LMWH) were reported to the FDA. In response, manufacturers of LMWH were requested to add 'boxed warnings' to their products warning of epidural/spinal hematoma risk,<sup>60</sup> and the American Society of Regional Anesthesia (ASRA) developed specific guidelines regarding thromboprophylactic therapy in patients undergoing neuraxial analgesia (see *Table 1*).<sup>61</sup> The choice of placement of an indwelling epidural catheter in patients who will need thrombo-prophylactic therapy does not obviate their use, but does influence when an epidural catheter can be safely placed or removed. Inhibitory neural signals to the GI tract have been implicated in POI, including those originating from the incision and/or intestinal manipulation.<sup>12,17,26</sup> It is hypothesized that epidural analgesics/anesthetics block afferent inhibitory and efferent sympathetics with a resultant decrease in POI and increase in splanchnic blood flow,

**Figure 2: Micrograph View of a Single Drug-filled Multivesicular Liposomal Particle (DepoFoam®)**



DepoFoam® is a registered trademark of Pacira Pharmaceuticals, Inc. Source: Hartrick and Manvelian, 2004.<sup>64</sup>

respectively. Systemic absorption of local anesthetics may also have anti-inflammatory effects.<sup>12,49,62</sup>

The use of epidural analgesics/anesthetics has resulted in a significant decrease in POI in comparison with systemic opioid administration.<sup>26</sup> A meta-analysis of five RCTs (261 patients) concluded that epidural analgesics/anesthetics reduce the duration of POI compared with systemic and epidural opioids (by 37 and 24 hours, respectively).<sup>63</sup> A more recent meta-analysis (16 RCTs) found that while epidurals decrease the duration of POI compared with parenteral opioids in colorectal patients (weighted mean difference [WMD] -1.55 days, -2.27 to -0.84), they do not influence the LOS (WMD 0.07 days, -0.40 to 0.54).<sup>64</sup> However, if incorporated into a multimodality approach, epidurals shorten LOS following colorectal surgery.<sup>65</sup>

**Extended-release Epidural Morphine Sulfate**

Extended-release epidural morphine sulfate (EREM), introduced to the US in late 2004, is a single-shot opioid intended for epidural administration at the lumbar level for the treatment of pain following major surgery. Its extended-release properties are made possible by

encapsulation of morphine sulfate in an aqueous suspension of microscopic multivesicular liposomal (MVL) particles called DepoFoam® (see *Figure 2*).<sup>66-68</sup> After injection, reorganization of the DepoFoam liposomal membrane leads to the release of packets of morphine sulfate within the epidural space<sup>66</sup> and subsequent diffusion through the dural membranes into the cerebral spinal fluid and finally to the site of action:  $\mu$  receptors in the dorsal horn of the spinal cord.<sup>69,70</sup> Comparing the

*The clinically important point is that extended-release epidural morphine sulfate does not require an indwelling epidural catheter; therefore, appropriate patients may be immediately anticoagulated post-operatively.*

pharmacokinetics of EREM with that of conventional preservative-free (PF) morphine sulfate, the sustained-release property is readily apparent, with a 5mg epidural dose of EREM achieving a plasma maximum concentration (Cmax) of 7.1ng/ml compared with 23.8ng/ml for a 5mg dose of PF morphine sulfate for epidural injection (DepoDur® full prescribing information, EKR Therapeutics, Bedminster, NJ). The clinically important point is that EREM does not require an indwelling epidural catheter; therefore, appropriate patients may be immediately anticoagulated post-operatively.<sup>71</sup>

A single injection of EREM has been shown to provide effective analgesia for up to 48 hours after administration, thus resulting in continuous pain control without need for an indwelling epidural catheter.<sup>72-76</sup> Administered prior to thromboprophylaxis, EREM is able to provide the benefits of neuraxial analgesia in the immediate post-operative period without introducing an additional risk for spinal or epidural hematoma. Lack of an epidural catheter also eliminates the need for infusion pump and tubing, virtually eliminating the risk for medication error into the epidural space. Use of EREM may also reduce the incidence of post-operative PE through fewer restrictions on anticoagulant administration and earlier patient mobilization in the post-operative period.<sup>77</sup> Clinical studies with EREM have shown efficacy across an array of surgical procedures in which epidural catheters are indicated, including lower abdominal surgical procedures.<sup>72</sup>

As with all neuraxial opioids, the most serious complication is respiratory depression. Monitoring of respiratory status according to American Society of Anesthesiologists (ASA) 2009 guidelines is encouraged not only for EREM but also for all neuraxial opioid delivery, whether epidural or intrathecal.<sup>78</sup> In all clinical trials with EREM and in the experience of the authors, the onset of respiratory depression requiring the use of an opioid antagonist occurred within 16 hours of administration of FDA-approved EREM doses.<sup>72-77</sup> Side effects of EREM are consistent with any neuraxial opioid, with nausea, emesis, and pruritus at the top of the list.<sup>79</sup> Pre-emptive treatment of these side effects is important for both patient satisfaction and improved outcomes. Post-operative orders should include a means to closely monitor the patient for respiratory depression as well as a

means to treat respiratory depression if necessary. Avoidance of additional sedatives or anti-emetics with sedative properties (prochlorperazine, promethazine, and droperidol) is recommended. Use of a low-dose continuous infusion of naloxone (0.5–1mcg/kg/hour) has been shown to reduce unwanted side effects of neuraxial opioids without reversing analgesia.<sup>80</sup>

### Cyclo-oxygenase-2 Inhibitors

Given the role of prostaglandins in inflammation, cyclo-oxygenase-2 (COX-2) inhibitors can be useful for post-operative pain control.<sup>26</sup> Peri-operative administration of COX-2 inhibitors independently<sup>81</sup> or in combination with PCA<sup>82,83</sup> has been effective in reducing the need for opioids in pain management. Although data on the use of COX-2 inhibitors following abdominal surgery are limited, a study with 40 patients showed that these agents have opioid-sparing effects and reduce ileus after colorectal resection.<sup>84</sup> In these patients, first bowel sounds and motions appeared at medians of 12 and 72 hours versus 24 and 84 hours, respectively, in comparison with controls ( $p < 0.05$ ). Tolerance of solid diet and hospital discharge occurred at a median of 60 hours and four days in the experimental group versus 72 hours and six days in the control group ( $p < 0.05$  and  $p < 0.01$ , respectively). It must be noted that both rofecoxib and valdecoxib have been withdrawn from the market due to their adverse cardiovascular effects.

### Minimally Invasive Surgery

Laparoscopy results in reduced production of endogenous opioids and cytokines compared with open surgery.<sup>85</sup> Hence, it may reasonably be expected that laparoscopy would be associated with a lower incidence of POI. Two of the four studies reviewed by Holte et al. found a significant association between laparoscopy and reduced

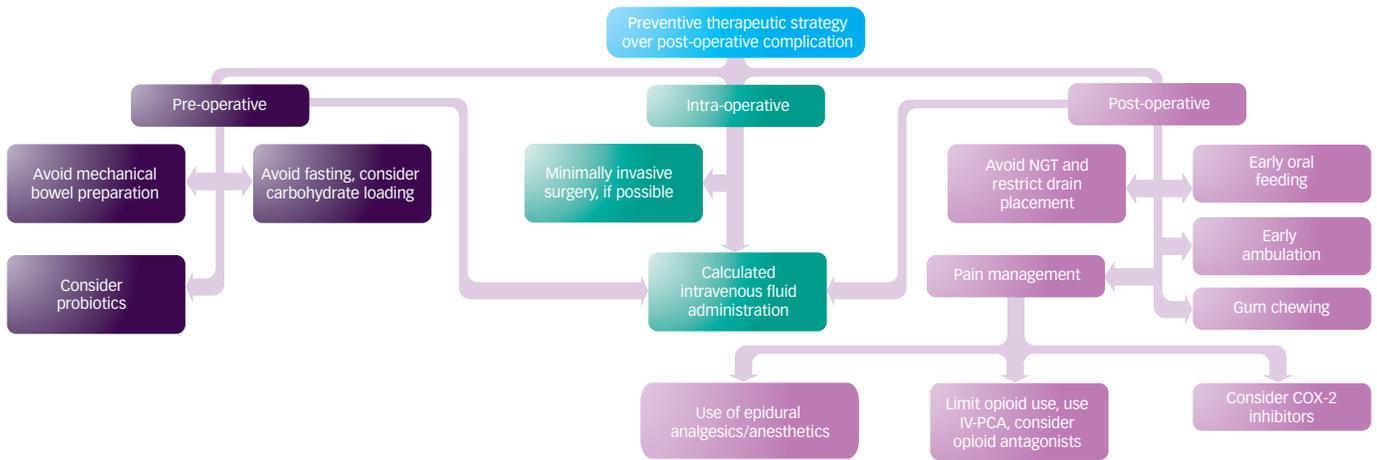
*Post-operative orders should include a means to closely monitor the patient for respiratory depression as well as a means to treat respiratory depression if necessary.*

POI.<sup>26</sup> A meta-analysis of 49 non-randomized studies (6,438 colorectal resections) comparing laparoscopic resection with open procedure for colorectal cancer revealed that patients who undergo laparoscopic resection have a faster GI recovery time until passage of first flatus (cumulative weighted difference [CWD] -1.2 days, cumulative weighted ratio [CWR] 0.67), bowel movement (CWD -1.3 days, CWR 0.73), and tolerance to oral fluids (CWD -1.6 days, CWR 0.63) and solid diet (CWD -1.4 days, CWR 0.74).<sup>86</sup> Laparoscopy not only reduced the pain measurements and narcotic requirements (16–35% reduction), but also shortened the LOS (CWD -3.4 days, CWR 0.71).

### Intravenous Fluids, Gastric 'Decompression,' and Use of Drains

A review by Holte et al. raised concerns that overhydration from peri-operative fluid therapy might cause cardiopulmonary dysfunction

**Figure 3: Algorithm Outlining the Various Strategies that Can Be Used in the Prevention and Therapeutic Management of Post-operative Complications and Post-operative Ileus**



COX-2 = cyclo-oxygenase type 2; ELA = epidural local anesthetics; IV-PCA = intravenous patient-controlled analgesia; NGT = nasogastric tube.

and gut edema, which would worsen POI.<sup>87</sup> However, recent RCTs by these same authors found no correlation between either POI or LOS and volume of peri-operative fluid therapy.<sup>88,89</sup> Nasogastric tube (NGT) decompression and advancement of oral diet after return of bowel sounds and/or flatus are long-standing surgical practices. A meta-analysis comparing selective versus routine nasogastric decompression following laparotomy revealed an increased incidence of fever, atelectasis, and pneumonia associated with the latter practice.<sup>90</sup> Only 5% of patients stood to benefit from NGT decompression, hence the authors recommended against its routine use. It is reasonable to expect that decreased NGT use would increase ambulation, which may decrease POI. Intra-operative drain placement is a common practice in abdominal surgery. While drains effectively eliminate fluid from surgical sites, they are also a source of wound infection, which can increase LOS.<sup>91</sup> Kumar et al. randomized 180 patients undergoing subtotal gastrectomy into two groups—drain and no drain—and found no significant difference between them in terms of GI recovery, LOS, or overall mortality.<sup>91</sup> Similar findings were reported by Bafna et al. in patients undergoing surgery for gynecological malignancies.<sup>92</sup> Both studies concluded that drains are usually unnecessary.

**Early Ambulation**

It is a long-held belief that ambulation increases GI motility, consequently reducing POI. Waldhausen and Schirmer evaluated the effects of early ambulation on post-laparotomy patients via intra-operatively placed seromuscular bipolar electrodes on the stomach, jejunum, and colon.<sup>93</sup> Electrical recordings indicated no independent benefit of early ambulation on recovery of GI motility. Nevertheless, early ambulation is vital in other ways, and is a major component of multimodal fast-track peri-operative care models.

**Chewing Gum**

Gum chewing aids post-operative recovery of GI function by serving as a ‘sham feeding,’ thereby stimulating associated neuronal pathways. A meta-analysis of five RCTs showed that gum chewing shortened mean time to flatus (WMD -20 hours, range 13–27) and

defecation (WMD -29 hours, range 19–39) with a trend towards shortening LOS (WMD -1.3 days, 0.6–3.2).<sup>94</sup>

**Prokinetic Agents**

Prokinetics primarily alter upper GI motility and are generally ineffective for treating POI.<sup>13</sup> A systematic review by Traut et al. that included 39 RCTs (4,615 patients) assessed the benefits of systemic prokinetics in treatment of POI.<sup>95</sup> Of the 15 agents examined, the authors concluded that most lacked adequate effect. They suggested that alvimopan may be beneficial, and further studies on IV lidocaine and neostigmine are essential to determine their significance in

*Considerable progress is necessary in educating today’s surgeons and implementing steps known to ameliorate post-operative ileus and other complications.*

treatment of POI. Zingg et al. randomized bisacodyl (colon-stimulating laxative) among colectomy patients and found the drug accelerated GI recovery post-operatively (three days versus 3.7 days in non-treatment group; p=0.007).<sup>96</sup>

**What Should We Do?**

Fast-track multimodal peri-operative strategies including epidural analgesia have been developed with the goal of reducing post-operative complications, in particular POI, and associated healthcare costs. In Europe, the efficacy of such strategies, which include various combinations of the management strategies reviewed here, were evaluated in patients undergoing abdominal surgery.<sup>97–101</sup> These studies showed that patients who followed fast-track multimodal approaches had reductions in GI recovery time and LOS compared with those treated conventionally. In two separate studies, Basse et

al. compared management-related (fast-track versus conventional) outcomes in colectomy patients, and demonstrated accelerated bowel function recovery ( $p < 0.05$  and  $p < 0.001$ , respectively) and shortened LOS ( $p < 0.05$  and  $p = 0.001$ , respectively) in fast-track patients.<sup>102,103</sup> Similarly, use of fast-track strategies by Delaney et al. in complex colorectal and pelvic surgeries yielded shortened LOS ( $p < 0.0001$ ).<sup>104</sup> Despite the benefits of such approaches, surgeons have been slow to adopt these methods. An extensive survey across 295 European and North American hospitals revealed that NGTs were left *in situ* and pre-operative MBPs were used in 40–60% and 85% of colectomy patients, respectively,<sup>105</sup> and POI and LOS extended beyond five and seven days, respectively, in nearly half of these patients. Thus, considerable progress is necessary in educating today's surgeons and implementing steps known to ameliorate POI and other complications. *Figure 3* outlines the various suggested components of a fast-track multimodal approach that physicians should undertake to reduce post-operative complications and LOS. ■



Ronald S Chamberlain, MD, MPA, FACS, is Chairman and Surgeon in Chief at Saint Barnabas Medical Center in Livingston, New Jersey, and a Professor of Surgery at the University of Medicine and Dentistry of New Jersey (UMDNJ) and St George's University School of Medicine (SGSOM). His research interests are in the fields of cancer vaccines, hepatobiliary surgery, surgical infections, and surgical education.



Robert H Blackshear, MD, is Chairman and Medical Director of the Skaggs Regional Medical Center Department of Anesthesiology and President Elect of the Medical Staff. He is also a member of the Medical Executive Committee at Skaggs. He pioneered the cardiac anesthesia program at Skaggs Regional Medical Center in 2002 and was board-certified in peri-operative transesophageal echocardiography at that time. He has carried out extensive research including numerous clinical trials on access devices and skin antiseptics, including chlorhexidine.

- Ambulatory and Inpatient Procedures in the United States, 1996.
- National Center for Health Statistics, CDC website. Available at: [www.cdc.gov/hchs/fastats/insurg.htm](http://www.cdc.gov/hchs/fastats/insurg.htm) (accessed August 20, 2008).
- Warfield CA, et al., *Anesthesiology*, 1995;83:1090–94.
- Morrison RS, et al., *Am Geriatr Soc*, 2009;57(1): 1–10.
- Phillips DM, *JAMA*, 2000;284:428–9.
- Koo PJ, *Am J Health Syst Pharm*, 2007;64:S11–15.
- Post-operative Ileus Management Council, Postoperative ileus: profiles, risk factors and definitions, Clinical consensus update in general surgery. Available at: [www.clinicalwebcasts.com/pdfs/GenSurg\\_WEB.pdf](http://www.clinicalwebcasts.com/pdfs/GenSurg_WEB.pdf) (accessed May 1, 2008).
- Senagore AJ, *Am J Health Syst Pharm*, 2007;64:S3–S7.
- Berend KR, et al., *J Arthroplasty*, 2004;19:82–6.
- Health Care Financing Administration. Federal Register, 1999–2000. Available at: [www.gpoaccess.gov/fr/](http://www.gpoaccess.gov/fr/) (accessed May 1, 2008).
- Iyer S, Saunders WB, Impact of postoperative ileus (POI) on hospital length of stay in colectomy surgery patients, Abstract presented at American College of Gastroenterology Annual Scientific Meeting, October 16, 2007, Philadelphia.
- Holte K, Kehlet H, *Br J Surg*, 2000;87:1480–93.
- Bauer AJ, Boeckxstaens GE, *Neurogastroenterol Motil*, 2004;16:54–60.
- Bianchi C, et al., *Ann Vasc Surg*, 2003;17:137–42.
- Shapiro G, et al., *Curr Opin Pediatr*, 2001;13:36–41.
- Luckey A, et al., *Arch Surg*, 2003;138:206–14.
- Livingston EH, Passaro EP Jr, *Dig Dis Sci*, 1990;35:121–32.
- Waldhausen JH, et al., *Ann Surg*, 1990;211:777–84.
- Behm B, Stollman N, *Clin Gastroenterol Hepatol*, 2003;1:71–80.
- Wilson JP, *Gut*, 1975;16:689–92.
- Person B, Wexner SD, *Curr Probl Surg*, 2006;43:6–65.
- Woods JH, et al., *Surgery*, 1978;84:527–33.
- Johnston KW, *J Vasc Surg*, 1989;9:437–47.
- Artinyan A, et al., *World J Surg*, 2008;32:1495–1500.
- Gervaz P, et al., *Int J Colorectal Dis*, 2006;21:542–6.
- Holte K, Kehlet H, *Drugs*, 2002;62:2603–15.
- Guenaga KF, et al., *Cochrane Database Syst Rev*, 2005;CD001544.
- Shafiq M, et al., *BJU Int*, 2002;89:879–81.
- Noblett S, et al., *Colorectal Dis*, 2006;8:563–9.
- Nygren J, et al., *Curr Opin Clin Nutr Metab Care*, 2001;4:255–9.
- Fearon KC, Luff R, *Proc Nutr Soc*, 2003;62:807–11.
- Bengmark S, Gil A, *Nutr Hosp*, 2006;21:72–84.
- Stewart BT, et al., *ANZ J Surg*, 1998;68:125–8.
- Jeffery KM, et al., *Am Surg*, 1996;62:167–70.
- Clevers GJ, et al., *J Gastroenterol Hepatol*, 1991;6:253–9.
- Yuan CS, Foss JF, *Reg Anesth Pain Med*, 2000;25:639–42.
- Ferraz AA, et al., *Am Surg*, 1995;61:1079–83.
- Delaney CP, *Neurogastroenterol Motil*, 2004;16:61–6.
- Yuan CS, Israel RJ, *Expert Opin Investig Drugs*, 2006;15:541–52.
- Yuan CS, *Ann Pharmacother*, 2007;41:984–93.
- Delaney CP, et al., *Ann Surg*, 2007;245:355–63.
- Food and Drug Administration, [www.fda.gov/cder/foi/label/2008/021775REMS.pdf](http://www.fda.gov/cder/foi/label/2008/021775REMS.pdf)
- Marcio A, et al., Presented at: 24th Annual Scientific Meeting of the American Pain Society, March 30 – April 2, 2005, Boston.
- Austin KL, et al., *Anesthesiology*, 1980;53:460–66.
- Grass JA, *Anesth Analg*, 2005;101:S44–S61.
- Block BM, et al., *JAMA*, 2003;290:2455–63.
- Provenzano DA, et al. In: Fleisher LA (ed.), *Evidence-based Practice of Anesthesiology*, Philadelphia: WB Saunders, 2004;441–8.
- Popping DM, et al., *Br J Anaesth*, 2008;101:832–40.
- Liu S, et al., *Anesthesiology*, 1995;82:1474–1506.
- Kelhet H, et al., *Br J Anaesth*, 2001;87:62–72.
- Correll DT, et al., *Reg Anesth Pain Med*, 2001;26:444–9.
- Moraca RJ, et al., *Ann Surg*, 2003;238:663–73.
- Carli F, et al., *Anesthesiology*, 2002;97:540–49.
- Ahlers O, et al., *Br J Anaesth*, 2008;101:781–7.
- Cohen MR, Medication errors: prevention and management issues. Platform presentation of the American Pharmaceutical Association Annual Meeting, Washington, DC, March 10–14, 2000.
- Yuan HB, et al., *Anesthesiology*, 2008;108:130–37.
- Augoustides JGT, *Anesthesiology*, 2007;107:1034–5.
- Cameron CM, et al., *Anesthesiology*, 2007;106:997–1002.
- Meikle J, et al., *Br J Anaesth*, 2008;101:400–404.
- Horlocker TT, et al., *Anesth Analg*, 1998;86:1153–6.
- Horlocker TT, et al., *Reg Anesth Pain Med*, 2003;28:172–97.
- Steinbrook RA, *Anesth Analg*, 1998;86:837–44.
- Jorgensen H, et al., *Cochrane Database Syst Rev*, 2000;CD001893.
- Marret E, et al., *Br J Surg*, 2007;94:665–73.
- Wind J, et al., *Br J Surg*, 2006;93:800–809.
- Hartrick CT, Manvelian G, *Today's Therapeutic Trends*, 2004;22:167–80.
- Keck S, *Orthopaedic Nursing*, 2007;26:86–92.
- Alam M, Hartrick CT, *Pain Pract*, 2005;5:349–53.
- Slover RB, Phelps RW. In: Brown DL (ed.), *Regional Anesthesia and Analgesia*, Philadelphia: WB Saunders Company, 1996;145–9.
- Cousins MJ, Mather LE, *Anesthesiology*, 1984;61:276–310.
- Geerts WH, et al., *Chest*, 2008;133:3815–453S.
- Gambling D, et al., *Anesth Analg*, 2005;100:1065–74.
- Carvalho B, et al., *Anesth Analg*, 2007;105:176–83.
- Carvalho B, et al., *Anesth Analg*, 2005;100:1150–58.
- Viscusi ER, et al., *Anesthesiology*, 2005;102:937–47.
- Hartrick CT, et al., *J Bone Joint Surg Am*, 2006;88:273–81.
- Blackshear R, Crosson C, *Reg Anesth Pain Med*, 2008;32:1.
- American Society of Anesthesiologists Task Force on Neuraxial Opioids, *Anesthesiology*, 2009;110:218–30.
- Hartrick CT, Hartrick KA, *Expert Rev Neurother*, 2008;8:1641–8.
- Gan TJ, et al., *Anesthesiology*, 1997;87:1075–81.
- Buvanendran A, et al., *JAMA*, 2003;290:2411–18.
- Malan TP Jr, et al., *Anesthesiology*, 2003;98:950–56.
- Reynolds LW, et al., *J Pain Symptom Manage*, 2003;25:133–41.
- Sim R, et al., *Colorectal Dis*, 2007;9:52–60.
- Yoshida S, et al., *Surg Endosc*, 2000;14:137–40.
- Abraham NS, et al., *ANZ J Surg*, 2007;77:508–16.
- Holte K, et al., *Br J Anaesth*, 2002;89:622–32.
- Holte K, et al., *Br J Anaesth*, 2007;99:500–508.
- Holte K, et al., *Anesth Analg*, 2007;105:465–74.
- Cheatham ML, et al., *Ann Surg*, 1995;221:469–76.
- Kumar M, et al., *World J Gastroenterol*, 2007;13:3738–41.
- Bafna U, et al., *Int J Gynecol Cancer*, 2001;11:143–6.
- Waldhausen JH, Schirmer BD, *Ann Surg*, 1990;212:671–7.
- de Castro SM, et al., *Dig Surg*, 2008;25:39–45.
- Traut U, et al., *Cochrane Database Syst Rev*, 2008;CD004930.
- Zingg U, et al., *Int J Colorectal Dis*, 2008;23:1175–83.
- Merat S, et al., *Ann Fr Anesth Reanim*, 2007;26:649–55.
- Kehlet H, Wilmore DW, *Am J Surg*, 2002;183:630–41.
- Wind J, et al., *BMC Surg*, 2006;6:16.
- Wilmore DW, Kehlet H, *BMI*, 2001;322:473–6.
- Kehlet H, Wilmore DW, *Br J Surg*, 2005;92: 3–4.
- Basse L, et al., *Dis Colon Rectum*, 2004;47:271–7.
- Basse L, et al., *Br J Surg*, 2002; 89:446–53.
- Delaney CP, et al., *Br J Surg*, 2001;88:1533–8.
- Kehlet H, et al., *J Am Coll Surg*, 2006;202:45–54.
- Kalff JC, et al., *Ann Surg*, 1998;228:652–63.
- Schwarz NT, et al., *Ann Surg*, 2002;235:31–40.
- Schwarz NT, et al., *Gastroenterology*, 2001;121:1354–71.
- Kalff JC, et al., *Surgery*, 1999;126:498–509.
- Bauer AJ, et al., *Gastroenterology*, 1991;101:970–76.
- Bauer AJ, Szurszewski JH, *J Physiol*, 1991;434:409–22.
- Borody TJ, et al., *Gastroenterology*, 1985;89:562–70.
- Brix-Christensen V, et al., *Int J Cardiol*, 1997;62:191–7.
- Brix-Christensen V, et al., *Acta Anaesthesiol Scand*, 2000;44:1204–8.
- Kehlet H, *Acta Anaesthesiol Scand*, 2000;44:1167–8.