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Enhanced Recovery after Surgery Guideline: Perioperative Pain Management in Patients Having Elective Colorectal Surgery

**A Quality Initiative of the Best Practice in General Surgery
Part of CAHO's ARTIC program**

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The Canadian Association of General Surgeon (CAGS) and the Canadian Society of Colon and Rectal Surgeons (CSCRS) support the ERAS Guidelines and promote their implementation as a best practice for surgical care.



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Section 1. General Information about this Guideline

Aim

The aim of this guideline is to make recommendations for perioperative pain management to optimize the recovery for elective colorectal patients.

Outcomes of Interest

The outcomes of interest are decreased pain and complications, enhanced patient recovery, decreased length of stay and increased patient satisfaction.

Target Population

These recommendations apply to adult patients undergoing elective colorectal surgery.

Intended Users

This guideline is primarily intended for use by anesthesiologists and general and colorectal surgeons and residents who perform elective colorectal surgery. This guideline is also intended to compliment the Enhanced Recovery after Surgery guideline. Thus, all persons adhering to those recommendations should be familiar with the recommendations provided here.

Overview of Process

A review of existing guidelines for Enhanced Recovery after Surgery, or Fast Track Surgery was conducted to obtain a comprehensive list of all interventions used in established guidelines. We then conducted a systematic review of each individual ERAS intervention to assess the supporting evidence. A sub-group was created to evaluate the evidence and develop recommendations based on the evidence, expert opinion and current practice. The subgroup consisted of anesthesiologists and nurses from the University of Toronto affiliated teaching hospitals and members of the Best Practice in General Surgery Steering Committee.

Section 2. Summary of Guideline Recommendations

1. Preoperative

- 1.1** A single 1000 mg dose of acetaminophen is recommended to be given preoperatively in open and laparoscopic colorectal surgical procedures (Level of evidence: Low)
- 1.2** A single 300 mg dose of gabapentin should be given be should be given preoperatively in open and laparoscopic colorectal surgical procedures (Level of evidence: Moderate)

2. Intraoperative

- 2.1** Thoracic epidural analgesia (TEA) at level T6-9 with a combination of local anaesthetic and opioid as a continuous infusion should be considered for all patients having open colorectal surgery and for patients having laparoscopic surgery who are at high risk pulmonary morbidity. TEA should be inserted preoperatively (Level of evidence: High)
- 2.2** Intraoperative lidocaine infusion bolus of 100 mg prior to the incision and then 1-2 mg/kg/hour continuous infusion is recommended for patients having laparoscopic colorectal surgery, or open colorectal surgery cases where a TEA is contraindicated or declined. Intravenous lidocaine can be continued in the PACU where patients can be monitored but should be discontinued before discharge to the ward (Level of evidence: High)

3. Postoperative

Patients having open or laparoscopic colorectal surgery should receive a multimodal analgesia package of:

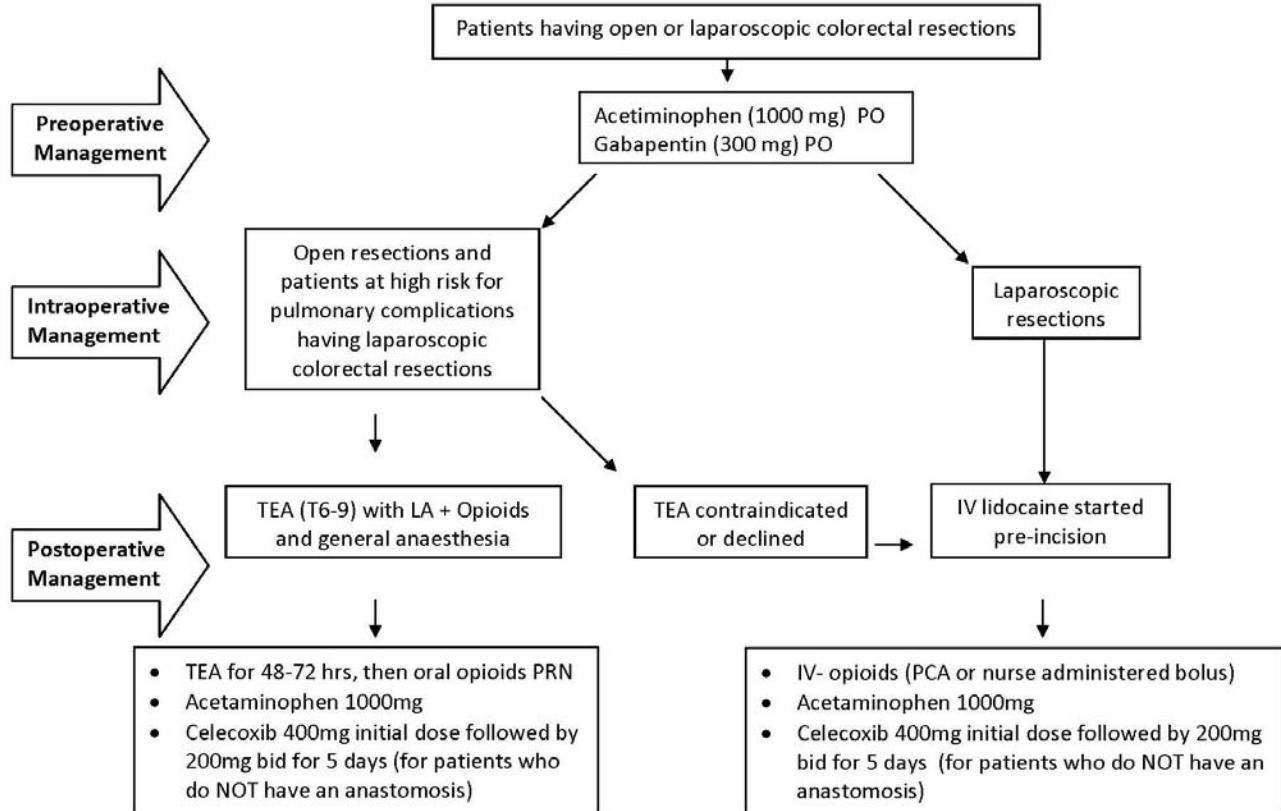
- 3.1** Acetaminophen 1000 mg given orally every 6 hours for 72-96 hours (Level of evidence: Low)
- 3.2** Prescription Post-operative celecoxib 400 mg initial dose followed by 200 mg bid for 5 days is recommended in patients having a colorectal resection where NO anastomosis is performed (for example, abdominal perineal resection) and where no contraindications to its use are present.
- 3.2b** There is inconclusive evidence about an increased risk of anastomotic leaks in patients who receive perioperative NSAIDS. However, there is some evidence linking perioperative NSAID use and anastomotic leak in patients having a colorectal resection. Thus, for patients having a colorectal resection WITH anastomosis, celecoxib (or other NSAIDS) should only be prescribed with the agreement of the surgeon, and following discussion between the surgeon and the pain team/anesthesiologist, concerning the

relative risks and benefits of NSAIDS for that particular patient. (Level of evidence: Moderate)

And one of following alternatives:

- 3.3 Thoracic epidural analgesia (TEA) at level T6-9 with a combination of local anaesthetic and opioid as a continuous infusion should be considered for all patients having open colorectal surgery and for patients having laparoscopic surgery who are at high risk pulmonary morbidity. TEA should be continued postoperatively for 48-72 hours (Level of evidence: High)
- 3.4 In patients where TEA is contraindicated or declined, IV Patient Controlled Analgesia (PCA) should be given as part of a multimodal analgesia package. Alternately, oral sustained release opioids may be given in addition to or instead of PCA to increase duration of analgesia and sleep (Level of evidence: Moderate)

Recommendations for Perioperative Pain Management for Colorectal Resections



Summary of Evidence

Patients who undergo abdominal surgery often face several days to weeks of prolonged pain, of which many are dependent on analgesics for pain relief. Furthermore, it has been reported that approximately 80% of patients experience postoperative pain, of which 86% report this pain as moderate to severe.^{1,2} The use of opioids has long been viewed as the standard of care for treating postoperative care for most surgeries, including abdominal surgery. The lack of a ceiling dose allows opioids to be the most effective agent at reducing moderate-to-severe postoperative pain. Although opioids are the mainstay for acute postoperative pain, their many adverse effects such as respiratory depression, nausea, vomiting, and bowel dysfunction, limits their use. This creates a challenging scenario as administration of too much opioid can lead to severe adverse effects, whereas insufficient analgesia can lead to physiologic and psychological manifestations, including the increased risk for the pain to progress to a chronic state.^{1,3} In addition, the multitude of adverse effects that accompany opioids often lead to a prolonged hospital stay for patients.

A safe, effective pain management plan, with emphasis on minimizing the use of systemic opioids, and the risk of postoperative sedation, is a key component of a best practice strategy in general surgery patients. A patient that is comfortable and alert will be better able to meet the other stated ERAS recommendations of early oral intake, ambulation, and timely discharge. Effective pain control in the early postoperative period is a key element in avoiding chronic post surgical pain, which has a reported rate as high as 18% in benign and oncologic gastrointestinal surgery patients four years postoperatively⁴.

Pre- and Post-Operative use of NSAIDs

Non-steroidal anti-inflammatory agents (NSAIDs) are often a part of the analgesic regimen. The use of NSAIDs in a multimodal analgesia regimen provides several advantages including its anti-inflammatory properties, improved analgesia, and a reduction in the use of opioids.⁵ Furthermore, the addition of NSAIDs has been shown to reduce the need for opioids by 20-30% in postoperative patients.⁶

It is well known that opioids can reduce bowel activity, as such; one of the major concerns with the use of opioids in abdominal surgery is the prolongation of postoperative ileus.^{7,8} Interestingly, NSAIDs may have an added benefit in reducing postoperative ileus, besides its opioid sparing effect. Abdominal surgery causes an enteric molecular inflammatory response which leads to the recruitment of leukocytes into the muscularis of the intestinal segments. This inflammation can impair local neuromuscular function and activate neurogenic inhibitory pathways, thus leading to reduced bowel motility.⁹ Furthermore, it is postulated that NSAIDs may assist in reducing the duration of a postoperative ileus by attenuating this inflammatory response.

There is a lack of consensus for the exact regimen for NSAID administration. Many clinicians believe that preoperative NSAID administration will act as pre-emptive analgesia and will be more effective than if the drug is only given postoperatively.¹⁰ As such, there have been multiple studies that have examined this topic in order to determine when it is appropriate to initiate NSAID therapy. In addition, the class of NSAID used often varies as some trials opted for Cox-II selective NSAIDs (coxibs), whereas other trials used non-selective NSAIDs from different classes, such as ibuprofen (propionic acid derivative) and ketorolac (acetic acid derivative). It appears that the recent concern over the cardiovascular complications associated with coxibs has encouraged more clinicians to use non-selective NSAIDs.

In 2005, Straube et al.¹⁰ conducted a systematic review of the randomized controlled trials that examined the preoperative use of Cox-II NSAIDs (coxibs) on postoperative outcomes. They found 24 trials with a total of 2246 patients, of which 1227 received preoperative coxibs, 753 received preoperative placebo and the rest received other treatments. The review included a large variety of procedures including: spinal surgery, prostatectomy, hysterectomy, colectomy, total knee replacement, thyroid surgery, and laparoscopic cholecystectomy. In regards to pain scores, they found 20 trials that assessed pain in the first 24h and 16 of these reported significantly lower pain scores at one or more time points in patients given a preoperative coxib. Furthermore, amongst patients undergoing major surgery, 7 out of 10 trials reported a significant reduction in postoperative pain, while 9 out of 10 trials involving minor surgery had a reduction. A total of 20 trials assessed analgesic consumption in the first 24h, 16 of which reported significantly higher consumption with placebo than with preoperative coxib. The weighted mean reduction in postoperative analgesic consumption was 41% with rofecoxib, 32% with celecoxib, and 21% with parecoxib. They also found a significant reduction in the frequency and/or severity of postoperative nausea or vomiting in 4 out of the 17 trials that reported this outcome. Although there was not a significant difference in anti-emetic use between the groups, there was a statistically significant difference in the pooled data (20% of patients needed postoperative antiemetic with coxib compared with 30% with placebo, RR=0.6, 0.5-0.9). In addition, patient satisfaction with pain and/or anesthesia was measured in 7 trials, and in each case there was significant benefit of preoperative coxib over preoperative placebo. Finally, the authors did not note any significant differences in regards to adverse events, including hemorrhagic episodes.

Southwood et al.¹¹ conducted a randomized controlled trial that assessed the effects of IV administered ibuprofen on postoperative pain management. The trial included 406 patients who were scheduled to undergo elective, single-site orthopedic or abdominal surgery. Each patient received morphine that was administered via a patient controlled analgesia (PCA) or by hospital staff at the request of the patient. Patients were randomly assigned to receive ibuprofen (IBU) 400mg IV, 800mg IV, or placebo. The first dose was administered intraoperatively at the initiation of wound closure, followed by subsequent doses every 6 hours for a total of 8 doses over the first 48 hours of the study. The authors found that the median quantity of morphine used was significantly reduced during the first 24hrs after administration of the study drug in patients who received IBU 800mg (reduction of 22% compared to placebo, p=0.03). In addition, the use of IBU 800mg was associated with significant reductions in pain at

rest and with movement across 3 time periods (1-24, 6-24, 12-24hr). The effects of IBU 400mg were limited, with a significant reduction in pain at rest and with movement during the 6-24h and 12-24h time periods compared with placebo. Finally, they did not note a significant difference in adverse effects between the study drug and the placebo group.

Colorectal Surgery

Sim et al.¹² conducted a randomized controlled trial in which they aimed to demonstrate the opioid-sparing effect and reduction in postoperative ileus obtained with valdecoxib 40mg administered pre- and postoperatively in patients undergoing colorectal resection. A total of 79 patients, who were scheduled for elective colorectal resection, were randomized to receive either valdecoxib or placebo with standard PCA. In the study arm, the first dose of valdecoxib 40mg was administered approximately 1 hour prior to the start of surgery with subsequent doses at 24 hour intervals, for up to 120 hours. The mean PCA doses 12 and 24 hours were 18.6 and 28.3 mg in the study arm compared to 26.2 and 41.2mg in the controls, representing a 33% reduction in opioid use ($p=0.001$). In regards to bowel motility, bowel sounds appeared at a median of 12 hours and time to first bowel movement at a median of 72 hours in the study arm compared to 24 and 84 hours in the controls ($p<0.05$ and 0.041, respectively). Finally, tolerance of solid diet occurred at a median of 60 hours and discharge at a median of 4 days in the study arm compared to 72 hours and 6 days in the controls ($p<0.05$ and $p<0.01$) respectively. A study by Chen et al.¹³ randomized 102 patients, who were undergoing elective colorectal surgery, to receive IV PCA morphine or IV PCA morphine and ketorolac. They found that the total morphine consumption during the first 3 days was significantly lower in the ketorolac group (66 +/-132.5mg compared to 80.8 +/-32.6mg). In addition, there was a significant difference in the time to first bowel movement (1.8 +/-1 days compared to 2.4+/-1.1 days) and the time to the first passage of flatus (3.3+/-1.3 days compared to 4+/-1.2 days). There was no difference in adverse effects, such as amount of bleeding or opioid-induced complications, between the groups. An earlier trial by Chen et al.¹⁴ reported similar findings, specifically that the total morphine consumption was significantly lower in their ketorolac group (71.4 (55-96.1)mg) compared to their morphine only group (93.3 (70.4-127.1)mg). The time to first bowel movement (1.5 (0.7-1.9) compared to 1.7 (1-2.8) days, $p<0.05$) and first ambulation (2.2 +/-1 vs 2.8+/-1.2d, $p<0.05$) were also significantly earlier in the ketorolac group. Schlachta et al.¹⁵ evaluated the role of NSAIDs in patients undergoing laparoscopic colorectal resection. They included 44 patients who were allocated to receive morphine PCA and either IV ketorolac or placebo for 48h after the surgery. They found that patients in the ketorolac group consumed less morphine (63mg+/-41 compared to 33mg+/-31, $p=0.011$) and had less time to first flatus (3 days compared to 2 days $p<0.001$) and full diet (3 days compared to 2.5 $p=0.033$).

In regards to the safety of the various non-selective NSAIDs, Forrest et al.¹⁶ conducted a study that examined this area of concern. The study itself was a multi-centre randomized controlled trial that evaluated the risks of death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure, and allergic reactions, with ketorolac vs diclofenac or ketoprofen administered according to their approved parenteral and oral dose and duration of treatment. They included a total of 11245 patients who underwent a variety of major surgical

procedures, including abdominal, orthopedic, gynecological, and urologic procedures. In total, 5634 patients received ketorolac and 5611 patients received one of the comparators. The authors reported that 155 patients (1.38%) had a serious adverse outcome, with 19 deaths, 117 patients who had surgical site bleeding, 12 patients who had allergic reactions, 10 patients who had acute renal failure, and 4 patients who had gastrointestinal bleeding. Of importance, there were no differences in rates between ketorolac and ketoprofen or diclofenac for any of the variables examined.

Concern has been raised about the safety of NSAIDs in colorectal surgery with respect to the effect on healing of intestinal anastomoses. This was first noted in a randomized controlled trial by Schlacta et al¹⁵. The objective of the trial was to assess the effectiveness of ketorolac for post-operative pain management in patients having laparoscopic colorectal surgery. The study arm received Ketorolac 30 mg IV every 6 hours for 48 hours beginning post-operatively. There were only 22 patients in each group (ketorolac or placebo). This was an underpowered trial but four patients (18%) in the Ketorolac group vs one (4.5%) in the control group developed an anastomotic leak ($p=NS$).

Watichow et al¹⁷ performed a randomized controlled trial to determine the impact of NSAIDs on gastrointestinal recovery after major abdominal surgery. One hundred fifty patients were randomized to celecoxib (200 mg), diclofenac (100 mg) or placebo preoperatively and continued for 7 days postoperatively. The primary outcome was the duration of paralytic ileus which was significantly reduced in the celecoxib group compared to the placebo group. Diclofenac also did not reduce paralytic ileus significantly. A secondary outcome which was reported was anastomotic leakage rate: in each of the three groups, 2 patients (4%) were withdrawn because of patients developing anastomotic leaks.

The two studies by Sim et al¹² and Chen et al¹³ which were discussed previously reported anastomotic leak rates. In the trial by Sim et al, there was 1 anastomotic leak in the valdecoxib group compared to none in the placebo group. In the study comparing ketorolac to placebo Chen (2005) reported 2 anastomotic leaks in 39 patients who received Ketorolac and one in 35 patients who received placebo. In a second trial, Chen et al reported 3 anastomotic leaks in 50 patients receiving ketorolac vs 1 in 50 patients who received placebo.

The large study by Forrest et al which was cited previously was designed to assess the side effects of ketorolac¹⁶. Approximately 2000 of the 11,000 patients included in the trial had abdominal surgery which included patients having small bowel and colon resections as well as cholecystectomy. (Further information about the procedures is not reported.) The primary outcomes were death, increased surgical site bleeding, gastrointestinal bleeding, acute renal failure and severe allergic reactions. The authors do not report on anastomotic leaks although “other adverse reports” occurred in approximately 2% of patients in all the groups.

In five of the trials which assessed ERAS protocols, patients in the ERAS groups received NSAIDS. In three trials¹⁸⁻²⁰ there were no leaks observed in trials which included 64, 25 and 39 patients respectively. In the trial reported by Serclova et al²¹, a total of 105 patients were

randomized to either an ERAS protocol or a control group. Individuals in both groups received diclofenac post operatively. The number of patients who developed anastomotic leaks was not reported but 3 patients required reoperation. The group to which these patients were allocated was not stated. Finally, in the trial by Khoo et al²², individuals in the ERAS group received ibuprofen 400 mg every 6 hours post-operatively. There were 3 (8.6%) anastomotic leaks in the control group and one (2.9%) in the ERAS group of patients.

In a prospective single cohort study, the feasibility of an ERAS program was assessed in 74 elderly patients²³. All patients received valdecoxib (20 mg bid) starting the third day post-operatively. The anastomotic leak rate was 3%.

There are several other reports based on retrospective data. Holte et al²⁴ reported on the results of 502 patients who were identified from an ERAS database maintained by Kehlet and colleagues. There were 28 leaks identified and the anastomotic leak rate was calculated for three different time periods: before celecoxib was used, during the time celecoxib was used and after celecoxib was used. They found a significantly increased anastomotic leak rate during the time period when celecoxib was used (15.1%) compared with rates of 3.3% and 1.5% before and after celecoxib use ($p<0.001$).

Rosenberg and Harvald²⁵ reported on a before-after study of patients undergoing colonic resection. Seventy eight patients received 75 mg diclofenac twice a day in order to decrease the use of morphine. The anastomotic leak rate increased significantly to 20.5% when patients received diclofenac compared with rates of 3.9% in the before and 1.3% in the after group. Neither of these latter two groups received diclofenac.

Klein et al²⁶ reported on a retrospective case-control study based on 75 consecutive patients who had a laparoscopic colorectal resection and primary anastomosis. In period one, patients received diclofenac 150 mg/day while in the second period, diclofenac was not given and patients received an opioid analgesic instead. Anastomotic leaks were confirmed at surgery. The leak rate in a group of 33 patients that received diclofenac was 21.2% (7 patients) vs 2.4% (1 in 42 patients) in the group who did not receive diclofenac. In a multivariate analysis, no other factors were associated with anastomotic leakage.

In summary, the use of NSAIDs provides a clear benefit in regards to improved pain scores and a reduction of opioid administration. The use of NSAIDs has been shown to be advantageous in abdominal surgery, especially colorectal surgery, by reducing postoperative ileus as measured by a reduced time to first flatus and bowel movement. Although the studies that have used only a postoperative NSAID regimen have shown benefit, additional literature has shown that preoperative followed by postoperative administration may provide preemptive analgesia, without increasing the complication rate. The available literature for abdominal surgery has mainly focused on colorectal procedures and cholecystectomies; however, it would be reasonable to extrapolate this information and apply it to all forms of abdominal surgery. Finally, from the available literature it appears that the choice of NSAID is of little consequence when considering the safety of the drug.

Overall, complication rates do not seem to be increased and this class of drug seems to be safe in this population of patients. The exception however, is with the safety of using them in patients with colonic or rectal anastomoses where there is conflicting evidence. There are some studies, although they are all retrospective, non randomized studies, which have suggested that the anastomotic leak rate is significantly increased. On the other hand, with the exception of one small underpowered trial, significant differences in the anastomotic leak rates have not been shown in randomized controlled trials. As well, NSAIDs have been included in many of the RCTs assessing ERAS programs and none have reported an increased leak rate. However, in none of these studies was anastomotic leak rate the primary outcome and all were small trials.

In the PROSPECT website, Kehlet et al recommend against the use of NSAIDs preoperatively prior to colonic resections but recommend their use postoperatively²⁷. Thus, in this guideline, NSAIDs are recommended although their use is controversial and therefore there should be a discussion between the surgeon and anesthesiologist prior to prescription of them regarding the potential risks and benefits.

Gabapentin

Gabapentin was introduced as an antiepileptic drug in 1993. It has been used extensively to treat painful neuropathies. The mechanism of action of gabapentin is uncertain; however, it is most likely mediated through binding to voltage gated calcium channels. It has anti-allodynic and anti-hyperalgesic properties²⁸. Several review articles have been published recently on gabapentin.

Tippana et al performed a systematic review which included 22 randomized controlled trials and 1909 patients²⁸. Gabapentin or pregabalin plus an opioid were compared to an opioid alone in most trials. Of note, there were no trials which included colorectal surgery patients. Most included patients undergoing either orthopaedic or spinal operations or hysterectomy. In addition, some were performed in patients having head and neck and breast procedures and one trial each included laparoscopic cholecystectomy or donor nephrectomy patients. Because of the heterogeneity, a meta-analysis was not performed.

The opioid-sparing effect during the first 24 hours after a single pre-operative dose of gabepentin (300-1200 mg.) ranged from 20-62% or the equivalent of a 30 mg decrease in morphine. The beneficial effects were not dose related²⁸. In addition, the rate of nausea, vomiting and urinary retention was decreased in the group receiving gabepentin while excessive sedation and dizziness were increased. There were no significant differences in any other adverse effects.

The combination of celecoxib and gabapentin given preoperatively is more beneficial than celecoxib alone²⁹. It is less well described what, if any benefits result from continuing gabapentin postoperatively. It is also unclear if gabapentin provides benefit to an existing multimodal analgesic regimen³⁰.

Lidocaine Infusion

Intravenous lidocaine is another option which can be used to decrease the need for opioids in patients having surgery. Intravenous lidocaine has analgesic, anti-inflammatory and anti-hyperalgesic properties. It can be given safely with few side effects. The intravenous route has advantages over epidural analgesia in that epidurals are in adequate in approximately 30% of individuals because of premature removal or malposition of the catheter. In addition, side effects and complications of epidurals are obviated.

A recent systematic review³¹ of the effect of intraoperative IV lidocaine on postoperative analgesia and recovery after surgery was published by Marret et al³². It included eight trials (320 patients) which compared intraoperative IV lidocaine to placebo in patients undergoing abdominal surgery. All of the trials were small but were otherwise of high quality including double blinding. Of the 8 trials, 2 were in patients having open colorectal surgery and one was in patients having laparoscopic colorectal surgery. In all trials, except one, a bolus of lidocaine (100 mg or 1.5-2mg/kg) was given before the surgical incision followed by continuous infusion (1.5-2mg/kg/hr or 2-3mg/minutes) stopped either at the end of the surgery or 24h postoperatively. In the other trial, lidocaine infusion was started 30 minutes before the skin incision. In four of the trials, an ERAS program was in place which included NSAIDs as well. The primary endpoint in three trials was duration of ileus. Intravenous lidocaine administration was found to decrease the duration of ileus (WMD -8.36 h, 95%CI -13.24 - -3.47) length of hospital stay (WMD -0.84 d, 95% CI -1.38 - -0.31) and postoperative pain (WMD -5.93, 95%CI -9.63 - -2.23 on a VAS 0-100). In addition, nausea and vomiting was reported in 5 trials and occurred in 52% of patients in the control group compared with 32% in the lidocaine group (OR 0.39, 95%CI 0.20-0.76).

Overall, intravenous lidocaine was safe. In one study, a single patient developed an arrhythmia, and in another study 3 patients developed intraoperative bradycardia, but remained stable³¹

A more recent systematic review published by McCarthy et al included 16 trials³³. However, only four of the 16 trials were in patients who had colorectal surgery and three of these had been included in the meta-analysis performed by Marret et al. Not surprisingly, they also reported decreased analgesia use in 5 of the 8 trials involving open intra-abdominal

surgery; shortened ileus in five of six studies which reported on bowel function; and shortened length of hospital stay in three of five studies which reported this outcome.

Thoracic Epidural Analgesia/Anesthesia (TEA)

Safe, effective pain relief is a key component of a successful fast track/ERAS program³⁴. There are 2 recent meta-analyses which have shown that TEA provides superior analgesia to IV Patient Controlled Analgesia (PCA) in open abdominal surgical procedure³⁵ globally and colorectal procedures specifically³⁶. This advantage persists for up to 72 hours post-operatively.

In a Cochrane Review, Werawatganon and colleagues included nine studies involving 711 participants who had undergone various abdominal procedures³⁵. The mean pain score (visual analogue scale) was significantly higher in the PCA group compared to that in the TEA group measured at 6, 24 and 72 hours. The weighted mean differences and 95% confidence intervals of the resting pain scores were 1.74 (95% CI 1.30 to 2.19), 0.99 (95% CI 0.65 to 1.33), and 0.63 (95% CI 0.24 to 1.01), respectively. The length of hospital stay and other adverse effects were not statistically different except that the incidence of pruritus was lower in the PCA group (OR 0.27, 95% CI 0.11 to 0.64).

In a meta-analysis by Marret and colleagues, 16 trials (total of 806 patients, range 30-116 patients/trial) were included³⁶. Fourteen included patients having open and two included patients having laparoscopic colorectal surgery. Post-operative epidural continuous infusion with opioid and local anaesthetic was used in thirteen and local anaesthetic only in three. Patients received epidural analgesia for 24 hours to 6 days. Pain was measured using visual analogue scores. When 11 trials were combined, epidural analgesia was significantly better with reduced pain scores at 24 and 48 hours (WMD -15, 95%CI -19- -11 and -18, 95% CI -26- -10 respectively). There was a significant decrease in the duration of ileus in the epidural analgesia group (WMD -1.55, 95% CI -2.27- -0.84) but there was no significant difference in the length of stay (WMD- 0.07, 95% CI -0.40-0.54). There also was an increased incidence of pruritis OR 4.8, 95% CI 1.3-17.0), urinary retention (OR 4.3, 95% CI 1.2-15.9) and arterial hypotension (13.5, 95% CI 4.0-57.7).

Levy and colleagues performed a systematic review of post-operative analgesia following laparoscopic colorectal surgery³⁷. Six studies were randomized controlled trials. The other two were non-randomized comparative studies. Overall, the quality of the studies was poor. Three randomized controlled trials compared epidural analgesia to PCA. The length of stay was not significantly different in these three trials. With regards to pain, in one trial, this outcome was not measured while in the other two, a significant difference which favored TAE was found while in the other there was no significant difference between the two groups. The authors concluded that “further studies are required to determine the most appropriate analgesic regime following laparoscopic colorectal surgery.”³⁷

Local anaesthetics delivered via mid-thoracic epidural reduce the incidence of paralytic ileus, blunt the surgical stress response, improve dynamic pain relief, and reduce systemic opioid requirements, thereby optimizing the patient's ability to successfully navigate through a fast track/ERAS/ protocol by facilitating early oral intake, ambulation and return of bowel function³⁸. Thus, TEA is recommended in most ERAS guidelines. Adamina and colleagues included 6 randomized controlled trials comparing ERAS pathways to standard post operative care following colorectal surgery³⁹. The interventions included in the pathways varied amongst the trials. However, in all 6 trials, pain management was part of the protocol although TEA was used in only 5 of the trials. As well, multiple modalities were used including ketoralac, acetaminophen, ibuprofen, prn morphine. As well, the duration of the epidural ranged from 24-72 hours. Overall, hospital stay was reduced by 2.5 days (95%CI -3.92- -1.11) and 30 day morbidity was significantly decreased (RR=0.52, 95% CI 0.36-0.73)³⁹.

Various guidelines have included TEA as part of the ERAS protocol. A February 2010 update of the PROSPECT website, developed by Henrik Kehlet and others continues to recommend TEA for open colorectal surgery²⁷. Two consensus review articles from 2005⁴⁰ and 2009⁴¹ recommend TEA be used in patients having colon and colorectal resection in an ERAS setting.

While the reported rates of hypotension and urinary retention are increased, overall TEA is safe. Kehlet and colleagues studied the risk of anastomotic leaks in patients having an epidural compared to patients receiving IV-PCA^{24,36}. No significant difference was observed with an observed rate of 6.0% (95%CI 3.5-9.6%) in the TEA group compared to 3.4% (95% CI 1.6-6.1%) in the PCA group. The authors did acknowledge that the study was underpowered²⁴. Major risks following TEA are extremely rare and their exact rate is difficult to determine and varies depending on the type of epidural, patient factors and setting. However, the risk of epidural bleeding in perioperative patients is estimated to be approximately 1:10,000. The estimated risk of an epidural abscess is even lower at 1:24,000⁴².

Acetaminophen

Most ERAS protocols include multimodal protocols for pain management. This approach leads to improved post operative pain control as well as lower opioid use and thus fewer side effects. Acetaminophen has very few contraindications and is relatively free from side effects so it is a good addition to a multimodal pain management plan.

Remy et al performed a meta-analysis comparing acetaminophen plus PCA morphine versus PCA morphine alone⁴³. Seven randomized controlled trials with 513 patients were included. Five of the trials were performed in orthopaedic patients and one each in patients

having elective Caesarean sections or hepatic resections. The 24 hour morphine consumption in the patients who received acetaminophen was decreased with a mean reduction of 9 mg (95% CI -15-3 mg.). However, while this was a statistically significant decrease ($p=0.003$), the clinical significance of this decrease is not certain. Furthermore, morphine related side effects were not decreased; approximately 25% of patients in both groups reported post operative nausea and vomiting and the rate of urinary retention was approximately 5%. Sedation was reported less frequently in the acetaminophen group but the difference was not statistically significant (OR 1.3, 95% CI 0.79-2.16, $p=0.30$).

Section 4. External Review Process

Reviewer comment: I'm concerned about the routine use of NSAIDS. Although the evidence is not bullet proof, there are suggestions from various authors of increased anastomotic leaks from NSAID use. In 25 years of practice I've never buried someone from post op pain, but I've unfortunately seen some very bad outcomes from anastomotic leak. As a colorectal surgeon, I would really like to see any avoidance of any drug which there is a hint of anastomotic complications. A large RCT would be nice to answer this question. I'm sure that we will have differences of opinion on this. The NSAIDS are a useful adjunct as part of multimodal pain relief. If we do use NSAIDS there probably has to be some consideration to avoiding them in patients with elevated Cr and ACE inhibitor use etc.

Author's response: We agree that there is conflicting evidence regarding whether there is an increased risk of anastomotic leak with the use of NSAIDs in the perioperative period. In response to these concerns, we have presented a review of the published evidence on this topic to assist clinicians in decision making regarding their use (page 6). As well, recognizing that there is lack of consensus on this issue, we have modified the guideline to state: "Prescription of celecoxib 400 mg as a loading dose should be considered in all open and laparoscopic colorectal procedures after ***discussion between the surgeon and anesthesiologist regarding the potential risks and benefits***"

Reviewer comment: Almost all evidence cited is derived from patients undergoing orthopaedic and spinal procedures and no trials included colorectal surgery patients. Is it really appropriate to extrapolate this data to a firm recommendation in favour of gabapentin for all patients?

Author's response: Agree that there are no RCTs assessing the use of gabapentin in elective colorectal surgical procedures. However, there is Level I evidence showing effectiveness in patients having abdominal hysterectomy and therefore, we believe the data can be extrapolated to patients having colorectal procedures.

Reviewer comment: I think if we are going to administer pre-op drugs the gabapentin dose needs to be considered in renal failure - even celebrex dosing may need consideration and adjustment on a case by case basis. Surgeons will need to ensure their patients are seen in PAU and a pre-operative medication order can be signed by an anesthesiologists and modified where appropriate. We should also consider adding a dose of acetaminophen pre-operatively too if we are giving gabapentin and celebrex.

Author's response: We have recommended a relatively small dose of gabapentin (300 mg) preoperatively only and therefore, dose adjustment should not be required in patients with renal insufficiency. However, both gabapentin and celecoxib should only be prescribed after considering the age and comorbidities of the patient and the risks and benefits of the medication. We have not recommended acetaminophen preoperatively because it is unlikely a dose given preoperatively will provide any benefit in postoperative pain management. We agree that anesthesiologists should see patients in the PAU and that they discuss pain

management with them and at the same time a preoperative pain medication order can be signed by the anesthesiologist.

Reviewer comment: Lidocaine provides similar benefits to thoracic epidural. Some of our anaesthesiologists have started to use it recently and I think I'm a big fan. Easy, cheap and so far the patients seem quite comfortable

Author's response: Agree that the evidence supports the use of lidocaine for peri-operative pain management and it is included as one option for pain management intra-operatively and in the PACU. Since TEA has been an integral component of all ERAS protocols and included in all ERAS RCTs, it is also recommended as another option in patients having open surgery

Reviewer comment: Overall they seem very biased towards epidural catheters and do not seem to rely on strong evidence nearly as much as the other guidelines in this series. In fact they do not mention the level of evidence, while the ERAS guidelines are very explicit about the level of evidence and strength of each recommendation

Author's response: As outlined in Recommendation 2.1, there is level 1 evidence to support the use of TEA to manage post-operative pain in patients undergoing abdominal surgery. The results of nine (Werawatganon et al) and twelve (Marret et al) studies were combined in two meta-analysis which showed that epidural analgesia is effective in reducing post-operative pain at 24 and 48 hours in patients undergoing open colorectal surgery. There also was a significant decrease in the duration of ileus although there was no significant decrease in the length of stay. As well, TEA has been a component of all ERAS RCTs. The grade of evidence has been included for all recommendations.

Reviewer comments: Using epidural catheters in patients undergoing laparoscopic surgery, even if they are at high risk of pulmonary complications, seems excessive. I could not find any evidence to support this in the document

Author's response: We agree that there is no direct evidence supporting the use of TEA in patients undergoing laparoscopic resection who are at high risk for pulmonary complications. This is recommended as an option but if there are contraindications or the patient declines a TEA, other options (IV lidocaine) can be used

Reviewer comments: In future we should look for a protocol on peri-operative ketamine. This too has been shown to reduce opioid use, and reduce phenomenon like hyperalgesia and the development of chronic pain. It is particularly effective in patients on high opioid doses where their opioid receptors are down regulated and where opioids may be ineffective for analgesia (many IBD patients). There is a benefit to running IV lidocaine or ketamine beyond the OR and recovery room and for a 24-48 hr period post-operatively but hospital nursing ward requirements need to be adjusted appropriately so this can occur and maximum benefit to the patients can be obtained - currently the only site in the hospital where we can run IV lidocaine

and/or ketamine infusions (even low dose) are in the OR, PACU and ICU. This bears consideration and revision if appropriate.

Author's response: Agree that there is evidence supporting the use of ketamine. However, at this time, we chose not to include it in the guideline. While there is a benefit to running IV lidocaine beyond the OR and recovery room and for a 24-48 hour period postoperatively, we are recommending that lidocaine only be used in the operating room and PACU. In the future, we may modify the guideline to recommend the use of lidocaine postoperatively in monitored beds. However, most centers do not use lidocaine presently and we felt a stepwise approach to implementation might be better.

Reviewer comment: I'm particularly concerned about section 4 – Management of hypotension in patients with epidurals. This section reads more like an anaesthesiology lecture than a set of evidence-based guidelines.

Author's response: This section has been removed from the guideline because we agree that it is not evidence based. Instead we have made it a separate "Contingency Plan" document to provide guidance on the management of hypotension.

Reviewer comments: I'm concerned with the recommendation to use pressors to treat epidural related hypotension. Most of these patients are not going to monitored beds where pressors can be used, and the use of pressors in bowel anastomoses causes significant vasospasm in "my coronaries". I know of one article from Sunnybrook where there was a strong association between vasoactive drugs and anastomotic leaks. We also are trying to avoid "overhydration" and if we use epidurals routinely won't the fluid boluses be a contributing factor here.

Author's response: This is no longer a guideline recommendation, but instead will be part of a "Contingency Plan" to provide guidance on the management of hypotension. It is recommended that initially one dose of ephedrine 5-10 mg IV be given to patients who are hypotensive. The half of life of ephedrine is approximately 15 minutes and it is expected that a member of the Pain Service will be in attendance during this time. A maximum of 2 doses of ephedrine are recommended and a member of the Pain Service should be in attendance during this time to monitor the hemodynamic response. With regards to the Sunnybrook data, a paper by Tremblay et al included ICU patients only who received vasopressors for a more prolonged period of time.

Reviewer comments: Section 4.3 - "Hypotension related to epidurals may be avoided by ..." This should probably read "reduced" instead of "avoided", or the statement eliminated entirely because the evidence supporting it seems quite weak.

Author's response: Agree and the recommendation has been modified to state "minimized" instead

Reviewer comments: Section 4.4 – This seems like a relatively complex patient management decision being broken down into four simple, but perhaps not accurate steps. I am very concerned by 4.4.d – “If vasodilation from an epidural infusion is thought to be a contributing factor to postoperative hypotension, vasopressors should be considered and administered by the Pain service”. I certainly would not want the Pain service administering my patients vasopressors in the early postoperative periods with bowel anastomoses rather than turning down/off the epidural and switching to a IVPCA if necessary. From what I can see the only evidence this is based on is an animal model of hepatosplanchnic blood flow. Surely not enough to be the basis for a clinical guideline.

Author's response: This has been removed from the guideline

References

1. Rahbari NN, Zimmermann JB, Schmidt T, et al. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg.* 2009;96:331–341.
2. Lobo DN, Bostock KA, Neal KR, et al. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomized controlled trial. *Lancet.* 2002;359:1812–1818.
3. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg.* 2003; 238:641–648.
4. Bruce, J. and Z.H. Krukowski, Quality of life and chronic pain four years after gastrointestinal surgery. *Diseases of the colon and rectum,* 2006. **49**(9): p. 1362-70.
5. Oberhofer D, Skok JM Neseck-Adam V. Intravenous ketoprofen in postoperative pain treatment after major abdominal surgery. *World J Surg* 2005;29:446-9.
6. Kehlet K, Holte K. Effect of postoperative analgesia on surgical outcome. *Br J Anaesth* 2001;87:62-72.
7. Ferraz AA, Cowles VE, Condon RE et al. Nonopioid analgesics shorten the duration of postoperative ileus. *Am Surg* 1995;61:1079-83.
8. Petros JG, Realica R, Ahmed S. Patient-controlled analgesia and prolonged ileus after uncomplicated colectomy. *Am J Surg* 1995;170:371-4.
9. Bauer AJ, Boeckxstaes GE. Mechanisms of postoperative ileus. *Neurogastroenterol Motil* 2004;16(S2):54-60.
10. Straube S, Derry S, McQuay HJ, et al. Effect of preoperative Cox-II selective NSAIDs (coxibs) on postoperative outcomes: a systematic review of randomized studies. *Acta Anaesthesiol Scand* 2005;49:601-13.
11. Southwood S, Peters J, Rock A, et al. A mutlicenter, randomized, double-blind, placebo-controlled trial of intravenous ibuprofen 400 and 800 mg every 6 hours in the management of postoperative pain. *Clinical Therapeutics* 2009;31:1922-35.
12. Sim R, Cheong DM, Wong KS, et al. Prospective randomized, double-blind, placebo-controlled study of pre- and postoperative administration of a COX-2-specific inhibitor as opioid-sparing analgesia in major colorectal surgery. *Colorectal Diseases* 2005;9:52-60.
13. Chen JY, Ko, TL, Wen YR, et al. Opioid-sparing effects of ketorolac and its correlation with the recovery of postoperative bowel fundtion in colorectal surgery patients. *Clin J Pain* 2009;25:485-9
14. Chen JY, Wu GJ, Mok MS, et al. Effect of adding ketorolac to intravenous morphine patient-controlled analgesia on bowel function in colorectal surgery patients – a prospective, randomized, double blind study. *Acta Anaesthesiol Scand* 2005;49:546-51.
15. Schlachta CM, Burpee SE, Fernandez C, et al. Optimizing recovery after laparoscopic colon surgery (ORAL-CS). *Surg Endosc* 2007;21:2212-9.
16. Forrest JB, Camu F, Greer A, et al. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. *Br J Anaesth* 2002;88:227-33.
17. Wattchow, D.A., et al., Clinical trial: the impact of cyclooxygenase inhibitors on gastrointestinal recovery after major surgery - a randomized double blind controlled trial of celecoxib or diclofenac vs. placebo. *Alimentary pharmacology & therapeutics,* 2009. **30**(10):

- p. 987-98.
18. 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 Jul;46(7):851-9.
 19. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. *Br J Surg*. 2003 Dec;90(12):1497-504.
 20. Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. *Br J Surg*. 2005 Nov;92(11):1354-62.
 21. Serclová Z, Dytrych P, Marvan J, Nová K, Hankeová Z, Ryska O, Sléglrová Z, Buresová L, Trávníková L, Antos F. Fast-track in open intestinal surgery: prospective randomized study (Clinical Trials Gov Identifier no. NCT00123456). *Clin Nutr*. 2009 Dec;28(6):618-24.
 22. Khoo CK, Vickery CJ, Forsyth N, et al. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. *Annals of Surgery* 2007;245(6):867-72.
 23. Scharfenberg, M., et al., "Fast-track" rehabilitation after colonic surgery in elderly patients—is it feasible? *International Journal of Colorectal Disease*, 2007. **22**(12): p. 1469-1474.
 24. Holte K, Kehlet H. Epidural analgesia and risk of anastomotic leakage. *Regional anesthesia and pain medicine*, 2001. **26**(2): p. 111-7.
 25. Rosenberg J, Harvald T. Severe complications with diclofenac after colonic resection. *Dis Colon Rectum* 2007;50:685.
 26. Klein M, Andersen LP, Harvald T, Rosenberg J, Gogenur I. Increased risk of anastomotic leakage with diclofenac treatment after laparoscopic colorectal surgery. *Dig Surg*. 2009;26(1):27-30.
 27. PROSPECT website (www.postoppain.org)
 28. Tiippana, E.M., et al., Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesthesia and analgesia*, 2007. **104**(6): p. 1545-56, table of contents.
 29. Parsa, A., et al., Combined Preoperative Use of Celecoxib and Gabapentin in the Management of Postoperative Pain. *Aesthetic Plastic Surgery*, 2009. **33**(1): p. 98-103.
 30. Clarke, H., et al., Adding gabapentin to a multimodal regimen does not reduce acute pain, opioid consumption or chronic pain after total hip arthroplasty. *Acta anaesthesiologica Scandinavica*, 2009. **53**(8): p. 1073-83.
 31. McCarthy, G.C., S.A. Megalla, and A.S. Habib, Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs*, 2010. **70**(9): p. 1149-63.
 32. Marret, E., et al., Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *The British journal of surgery*, 2008. **95**(11): p. 1331-8.
 33. McCarthy, G.C., S.A. Megalla, and A.S. Habib, Impact of intravenous lidocaine infusion on postoperative analgesia and recovery from surgery: a systematic review of randomized controlled trials. *Drugs*, 2010. **70**(9): p. 1149-63.

34. Kehlet, H. and D.W. Wilmore, Evidence-based surgical care and the evolution of fast-track surgery. *Annals of surgery*, 2008. **248**(2): p. 189-98.
35. Werawatganon, T. and S. Charuluxanun, Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. *Cochrane database of systematic reviews*, 2005(1): p. CD004088.
36. Marret, E., C. Remy, and F. Bonnet, Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. *The British journal of surgery*, 2007. **94**(6): p. 665-73.
37. Levy BF, Tilney HS, Dowson HM, Rockall TA. A systematic review of postoperative analgesia following laparoscopic colorectal surgery. *Colorectal Dis*. 2010 Jan;12(1):5-15.
38. Kehlet, H. and J.B. Dahl, Anaesthesia, surgery, and challenges in postoperative recovery. *Lancet*, 2003. **362**(9399): p. 1921-8.
39. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. *Surgery*. 2011 Jun;149(6):830-40.
40. Fearon, K.C., et al., Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clinical nutrition*, 2005. **24**(3): p. 466-77.
41. Lassen, K., et al., Consensus Review of Optimal Perioperative Care in Colorectal Surgery: Enhanced Recovery After Surgery (ERAS) Group Recommendations. *Arch Surg*, 2009. **144**(10): p. 961-969.
42. Freise, H. and H.K. Van Aken, Risks and benefits of thoracic epidural anaesthesia. *British journal of anaesthesia*, 2011. **107**(6): p. 859-68.
43. Remy, C., E. Marret, and F. Bonnet, Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *British journal of anaesthesia*, 2005. **94**(4): p. 505-13.