June 8, 2016

Clinical Guidance Note 4

British Columbia Enhanced Recovery Collaborative
Opioid-Sparing Technique

Postoperative pain remains an unsolved challenge: poorly controlled pain is reported in 10-50% of postoperative patients.

Opioids are the mainstay of postoperative pain treatment, as approximately 95% of patients receive an opioid-based pain management strategy. However, opioids have many unwanted side effects including nausea, vomiting, constipation, ileus, urinary retention, drowsiness, dizziness, cough suppression and respiratory depression. Further, in the western world prescription drug abuse is high and studies have demonstrated patients who receive opioid prescriptions within 7 days of their surgery have a 44% increased risk of continuing to take opioids one year later(1). Consequently, the ERAS society recommends minimizing opioid exposure and taking full advantage of multi-modal analgesia regimens(2).

This Guidance Note aims to support appropriate opioid sparing techniques in an evidence directed approach for pain management in the postoperative treatment of ERAS Colorectal patients. Guidance Note 4 was developed by the Anesthesia Community of Practice of the BC Enhanced Recovery Collaborative ('the Collaborative'). It has been reviewed by the multi-disciplinary members of the Collaborative, presented to the BC Anesthesiologists Society for feedback, and approved by the Collaborative's clinical co-chairs.

This document is not intended to serve as a comprehensive review of the literature, or a statistically driven guidelines document. The Enhanced Recovery Collaborative undertook an extensive review of current literature and practice patterns for goal-directed fluid therapy, assessed the practical implications of the various proposed algorithms, and sought to summarize evidence and advise British Columbia's clinicians as to best practice based on current evidence. In the end, each site and practitioner should base decisions on providing patient care based on consultation with local care providers, and through a multidisciplinary collaborative approach.

Neuraxial analgesia

Epidural analgesia is considered the gold standard for open abdominal procedures. There is little formal evidence to support its use in laparoscopic procedures in patients with few comorbidities; however, there is theoretical benefit in the treatment of high risk patients.

The ERAS collaborative thus recommends the use of epidurals for open abdominal surgical procedures. Given the paucity of evidence, but bearing in mind expert opinion (3, 4, 5) epidural analgesia may be considered for high-risk patients undergoing extensive laparoscopic procedures after weighing the risks and potential benefits. "High risk" patients are those with multiple

comorbidities such as cardiovascular and respiratory conditions, morbid obesity, and opioid tolerant patients. This modality may also be considered for patients undergoing a procedure that is considered to be at high risk to progress to an open procedure intraoperatively.

Obviously, excellent and timely communication between Surgical and Anesthesiology staff is essential in order to optimally prepare a pain-management plan and define the possible benefit of epidural analgesia so it can be placed in a timely fashion.

Advantages to epidural analgesia include better early postoperative pain management 24-72 hr(6), accelerated recovery of gastric function (7), reduced insulin resistance (8) and reduced cardiovascular and respiratory complications (9). Disadvantages of epidural analgesia include technical issues such as inadequate or failed epidural block, hypotension, motor blockade, pruritis urinary retention, the requirement for modification of prophylactic anticoagulation regimens, and the rare catastrophic complication such as spinal cord compromise.

The level of placement of the epidural can alter its effectiveness and should be low thoracic (T6-11), depending upon the surgical incision (10). Ideally, the epidural should be tested preoperatively; however if this is not logistically possible its function should be tested immediately postoperatively and nonfunctioning epidurals replaced prior to going to the ward. Some centers recommend the use of the Tsui test to confirm placement in the epidural space. The agent used should be a local anesthetic with or without an opioid at low doses. Optimal dosing of bupivacaine is 0.08-0.1% bupivacaine when combined with opioid; lower doses result in inadequate pain control and higher doses are associated with more of the adverse effects mentioned above. Fentanyl, although lipophilic, at doses of 2-4mcg/ml improves postoperative pain control over bupivacaine alone. Hydrophilic opioids such as morphine have increased segmental analgesia spread and may be considered for long midline incisions (11). There is little literature to support a specific dose of hydromorphone in the epidural thus a specific dose is not included in this document.

There is some evidence in the obstetrical, thoracic and hepatic surgery literature that patient controlled bolus epidural analgesia is superior to continuous epidural infusion with-out patient controlled bolus (12, 13, 14); however, there are no specific studies in the colorectal literature.

Thoracic epidurals do not increase the risk of bladder re-catherization or urinary infection when urinary catheters are removed on day 1(15). Epidural infusions should be continued 48-72 h but patients should be transitioned to oral medications as soon as this is tolerated. Postoperative hypotension as a result of a general anesthetic and surgical inflammatory response may be exacerbated by epidural anesthesia and is often more appropriately treated with vasopressors in the first 24-48h rather than intravenous volume boluses. Patients developing hypotension after leaving the recovery room require re-assessment to determine the cause of hypotension rather than reflexive fluid loading.

Occasionally, the epidural doses do not cover the entire surgical area because of placement location, patient anatomy, or extension of the surgical incision, or is inadequate in the opioid-tolerant patient. In these cases it may be necessary to use other adjuncts along with the epidural to improve analgesia. These may include systemic lidocaine, ketamine, or opioids. The addition

of systemic opioid increases the risk of respiratory depression and no specific opioid is better than another. It is for this reason preferable to adjust or replace the epidural prior to adding systemic opioids. If this is not feasible the clinician should consider the risk of leaving the opioid in the epidural solution. This requires assessment on an individual basis considering the patient comorbidities, the surgical procedure and the ability of the center to comprehensively monitor the patient.

Currently the literature does not support the use of intrathecal opioid or local anesthetic as an adjunct for pain control in ERAS patient. Available studies offer conflicting data. Significant side effects include pruritis, respiratory depression, urinary retention and hypotension. Currently, the BC ERAS collaborative does not recommend intrathecal analgesia as a first line adjunct.

Monitoring

All patients receiving systemic analgesia (PCA, epidural, ketamine or lidocaine infusions) require similar levels of monitoring. These include regular monitoring of sedation level, heart rate, blood pressure and oxygen saturation. None of the methods discussed in this document require continuous ECG monitoring or a high acuity ward in the absence of co-morbid disease. Patients with severe pain not responding to initial standard management may require admission to a higher acuity setting to safely manage their pain.

Systemic Analgesics and Adjuncts

Intravenous patient control analgesia with opioid remains a tool for pain management immediate postoperatively in patients inadequately managed by other means. The oral route for administration is generally preferable as soon as the patient has re-established reliable gastric absorption. Independent of route of administration the dose of opioid should be kept to the lowest possible while maintaining adequate pain control. Opioid dose has been demonstrated to be an independent predictor of postoperative ileus in radical cystectomy with ilieal conduit surgery patients (16).

Remifentanil has been associated increased pain intensity scores at 1 and 4 hours postoperatively and increased visual analog scores at 24hrs, as well as, increased morphine use 24hr postoperatively. Intraoperative remifentanil should be avoided or, if used, should be run at a low dose with a propofol infusion to reduce the risk of opioid induced hyperanalgesia (17).

With regards to the specific opioid used postoperatively there is little evidence to support one being superior to another.

Intravenous lidocaine infusion has been demonstrated to be an effective adjunct to pain management for both open and closed colorectal surgeries (18, 19). Intravenous lidocaine has been shown to improve postoperative pain, reduce opioid consumption by up to two-thirds and reduce duration of postoperative nausea, ileus and hospital stay. Further, systemic lidocaine has been shown to reduce the physiological stress response (as measured by total leukocyte count, c-reactive protein and interleukin-6 (20). A suggested regimen includes a loading dose of 1.5-2mg/kg 30 min before or at the time of induction of anesthesia, continuing with an infusion of 2

mg/kg/hr (21). The majority of studies have run the lidocaine infusion postoperatively in the post-anaesthetic recovery unit and on to the ward. If possible infusions should be run for a minimum of 4hrs, but up to 24hr appears to provide the best pain relief results. Care needs to be taken in the patient with pre-existing cardiac conduction abnormalities and liver dysfunction. Intravenous lidocaine has been used without continuous ECG monitoring in higher doses for longer periods for chronic pain, and in some centres at similar doses for acute pain.

As a reference, Appendix 2 provides the approved submission to the Vancouver Acute Regional Pharmacy & Therapeutics Committee to allow systemic lidocaine to be used on surgical wards as an analgesic.

N-Methyl-d-Aspartate Receptor Antagonists (ketamine, magnesium) have been used to provide analgesia. Ketamine administered at subanesthetic doses reduces rescue analgesic requirements, pain intensity, 24 H PCA morphine consumption and postoperative nausea or vomiting (PONV)(22). Adverse effects are minimal at dosages 0.1-0.4 mg/kg/hr. Concern has been raised regarding the risk of delirium with ketamine use, however, the existing literature does not report an increased risk of delirium. This is consistent with repeated observations that pain is a risk factor for delirium and non-opioid treatment can reduce the risk of delirium(23). However, there is a lack of well-designed large safety studies in the general population, and therefore we currently recommend the use of ketamine primarily in patients who are unsuitable for neuraxial analgesia or who are opioid tolerant. The use of ketamine infusions in conjunction with lidocaine infusions has not been specifically studied, but it is reasonable to believe that the combination would provide enhanced benefit as they function by different mechanisms: however, this requires further study as there is no data to confirm their safety in combined use.

Magnesium bolus and infusions have been shown to reduce opioid consumption and pain scores in first 24 h(24). It is unclear what the optimal dosing regimen as it appears single dose may be as good as bolus plus infusion thus we recommend a 40-50 mg/kg bolus during surgery if chosen as an alternate to ketamine. Care must be taken in patients with neuromuscular disorders and renal dysfunction to minimize complications.

NSAIDs and COX-2 inhibitors have been shown to improve postoperative analgesia, reduce opioid consumption and reduce opioid related side effects by 30% (25, 26), however some concerns have been raised with regards to the risk of anastomotic leakage (27). In the context of this controversy and without clear safety data, we recommend that NSAIDs and COX-2 inhibitor use be considered, but discussed with the surgeon and possibly be reserved for patients without bowel anastomoses.

Acetaminophen has been shown to improve postoperative analgesia, reduce opioid consumption but not reduce opioid side effects (28). IV acetaminophen reduces the risk of PONV (29). The ERAS collaborative recommends use of regular acetaminophen perioperative unless there are contraindications. For patients who can take an oral dosage form, no clear indication exists for preferential prescribing of IV acetaminophen (30). Intravenous acetaminophen is not currently available in Canada but would be advantageous for patients unable to take oral or rectal acetaminophen.

Other systemic agents include Gabapentinoids, clonidine, dexmedetomidine and high dose steroids. Gabapentinoids have been shown to reduce pain scores and morphine consumption postoperatively but are associated dizziness and sedation (31). Clonidine and dexmetdetomidine have been shown to reduce morphine consumption after surgery (25% clonidine, 30% dexametatomadine), reduce pain scores within the first 24 hour but not after, and reduce nausea. They have side effects of sedation and hypotension(32). Currently, there is not enough literature to support the use of these agents in the ERAS patient. They may be agents to consider in patients that do not respond to conventional treatment.

Regional Anesthesia

Local anesthestic administered peripherally via transversus abdominis plane blocks (TAP), rectus sheath blocks, interperitoneal instillations and wound catheters have all been suggested to be useful in abdominal surgery. Currently literature is not strong enough for the collaborative to support regular use at this time. It would be potentially advantageous to obtain liposomal local anesthetic as it would extend the anesthetic block.

Discharge Planning

Care must be taken around transition from the hospital setting with nursing support for analgesia to home management of analgesics to present inadequate analgesia and addiction or abuse. Patients who continue on opioid analgesia 7 days after discharge are likely to have long term problems with opioid use (1). Changing analgesics on discharge from hospital can lead to confusion and inadequate analgesia. Not all patients will require discharge with a prescription for opioid analgesics. Patients should be discharged on the same medications they have been using effectively in the hospital with good education regarding use and side effects as well as a clear weaning plan.

Summary of Recommendations

1. Patients without contraindication should be offered thoracic epidural analgesia for all open colorectal surgical procedures laparoscopic procedures which are likely to be converted intraoperatively to an open procedure.

    a. Epidural analgesia should generally be placed in the low thoracic region and be based primarily on a continuous infusion of low dose local anesthetic (bupivacaine 0.08-0.1%.) In addition epidural narcotic may be added at the lowest effective dose.
    b. It is reasonable to consider patient controlled epidural analgesia.
    c. Epidural effectiveness should be confirmed with a test dose preoperatively or postoperatively before the patient leaves the recovery room.
    d. Epidural analgesia may also be considered in high risk patients for extensive laparoscopic procedures.

2. Patients who do not receive thoracic epidural analgesia for open procedures and patients for laparoscopic procedures should be offered a lidocaine infusion.
    a. The ERAS collaborative recommends a loading dose of 1.5-2mg/kg followed by a continuous infusion of 2mg/kg/hr started intraoperatively and continued postoperatively for 24-48h. This can be safely administered in a ward setting without continuous cardiac monitoring in the patient without a history of cardiac conduction abnormalities or liver dysfunction.

3. All patients without contraindication should be offered acetaminophen prior to surgery this should continue at an appropriate dose at regular intervals for 48h post operatively.

4. PCA is appropriate for analgesia in patients who have not received epidural analgesia.
    a. PCA should be transitioned to oral narcotics as soon as possible and the minimal necessary doses used.
    b. Care should be taken with transition from the hospital setting to home in order to minimize opioid use and reduce the risk of issues with tolerance and addiction or changing opioids and inadequate analgesia.

5. Patients who are opioid tolerant, have chronic pain with opioid tolerance, are otherwise high risk for poorly managed post-operative pain or fail with initial analgesic management may be offered ketamine infusions for analgesia.
    a. Intra-operative ketamine with a loading dose of 0.5mg/kg and an infusion of 0.1-0.25mg/kg/h intraoperatively.
    b. This may be continued postoperatively at a rate of 10mg/h up to 30mg/h and can be used in a ward setting with monitoring similar to that for a PCA.

6. A discussion between surgical and anaesthetic personnel is recommended regarding the risks and benefits of the use of NSAIDs in patients with bowel anastomosis.

7. There is inadequate or conflicting evidence, or risk of significant side effects, which does not allow us to recommend the use of TCAs, gabapentanoids, intrathecal narcotics, demedetomidine, clonidine, or regional analgesia (TAP or single shot rectus sheath blocks) routinely for the ERAS population.

8. A careful plan for transition to home should be in place.
    a. Patients requiring opioid analgesia on discharge should be discharged on the same opioid they used in hospital and with education on the use and side effects of the medication.
    b. All patients discharged on opioids should have a clear weaning plan in place.
    c. Patients discharged on opioids should continue with appropriate adjunct analgesics to minimize opioid use and aid weaning.

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Appendix 1: Description of the Enhanced Recovery Collaborative

From November 2014 to January 2016, eleven BC surgical sites worked together as the BC Enhanced Recovery Collaborative ('the Collaborative'). The Collaborative aimed to improve outcomes for elective colorectal surgery patients by collectively implementing the evidence-based Enhanced Recovery protocol: a multi-modal perioperative care pathway designed to achieve early recovery after surgical procedures by maintaining pre-operative organ function and reducing the profound stress response following surgery. Sponsored by the Specialist Services Committee (SSC), the BC Enhanced Recovery Collaborative applied the Institute for Healthcare Improvement Breakthrough Series model to integrate evidence into practice by promoting cross-site learning and teaching, efficient sharing of resources and tools, and development of a multi-disciplinary network of Enhanced Recovery clinicians and champions.

For more information on the BC Enhanced Recovery Collaborative, please refer to the detailed **Final Report** and Final Report –**Highlights**, which describe the background, structure, activities, results, and lessons learned from the Collaborative experience.

Specialist Services Committee (Sponsor)

- Dr. Ron Carere, SSC, Co-Chair
- Dr. Sean Virani, SSC, Co-Chair
- Adrian Leung, SSC, Executive Lead
- Angie Chan, SSC, Project Manager, Surgical Improvement
- Elizabeth Babcock, SSC, Assistant

Participating Collaborative Sites

- Campbell River Hospital
- Kelowna General Hospital
- Langley Memorial Hospital
- Mills Memorial Hospital (Terrace)
- Mount St. Joseph's Hospital (Vancouver)
- Nanaimo Regional General Hospital
- Royal Columbian Hospital (New Westminster)
- Royal Inland Hospital (Kamloops)
- St. Paul's Hospital (Vancouver)
- Surrey Memorial Hospital
- Vancouver General Hospital

Participating Health Authorities

- Fraser Health Authority
- Interior Health Authority
- Island Health Authority
- Northern Health Authority
- Providence Health Care
- Vancouver Coastal Health Authority

Advisory Panel

- Dr. Ron Collins, Enhanced Recovery Collaborative Anesthesia Co-Chair, Interior Health
- Dr. Ahmer Karimuddin, Enhanced Recovery Collaborative Surgery Co-Chair, Providence Health Care
- Garth Vatkin, Enhanced Recovery Collaborative Nursing Co-Chair, Interior Health
- Andrea Bisaillon, Vancouver Coastal Health
- Dr. Jean Lauzon, Fraser Health
- Dr. Willem Lombard, Northern Health
- Valerie MacDonald, BC Hip Fracture Initiative
- Kimberly McKinley, BC Patient Safety & Quality Council
- Dr. Samaad Malik, Island Health
- Dr. Kelly Mayson, Vancouver Coastal Health
- Dr. Richard Merchant, Fraser Health
- Dr. Jill Osborn, Providence Health Care
- Stephen Parker, Providence Health Care
- Brenda Poulton, Fraser Health
- Geoff Schierbeck, BC Patient Safety & Quality Council
- Dr. Jacques Smit, Island Health
- Dr. Tom Wallace, Interior Health
- Dr. Garth Warnock, Vancouver Coastal Health
- James Watson, Island Health
- Deborah Bachand, Island Health (former member)
- Ly Truong, Island Health (former member)

Anesthesia Community of Practice

Anesthesia

- Dr. Ron Collins, Kelowna General Hospital
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- Dr. David Hadid, Mills Memorial Hospital
- Dr. Maha Iyer, Surrey Memorial Hospital
- Dr. Bruce Kilpatrick, Royal Inland Hospital
- Dr. Magda Lipowska, Lion's Gate Hospital
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- Dr. Kelly Mayson, Vancouver General Hospital
- Dr. Andrew Meikle, Vancouver General Hospital
- Dr. Richard Merchant, Royal Columbian Hospital
- Dr. Clare Morrison, Lion's Gate Hospital
- Dr. Michael Negraeff, Vancouver General Hospital
- Dr. Scott Neilson, Nanaimo Regional General Hospital
- Dr. Jill Osborn, St. Paul's Hospital
- Dr. Sarah Pearce, Campbell River Hospital
- Dr. Steve Petrar, St. Paul's Hospital
- Dr. Chris Pollitt, Campbell River Hospital
- Dr. Curt Smecher, Abbotsford Regional Hospital
- Dr. Jacques Smit, Royal Jubilee Hospital
- Dr. Cornel Van West, Richmond Hospital
- Dr. Annika Vrana, Lion's Gate Hospital
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- Jan Muir, Providence Health Care
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Patient Partners

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- BC Patient Safety & Quality Council