Postoperative Recovery in Patients Undergoing Laparoscopic Colorectal Surgery: Effect of Perioperative Intravenous Lidocaine

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Abstract

Intravenous lidocaine infusion for colorectal surgery has been shown to provide superior analgesia compared with systemic opioids and facilitate hospital discharge. While epidural analgesia has definite advantages over systemic opioids in term of return of bowel function and quality of postoperative pain control, there is no study comparing lidocaine infusion with epidural technique in the setting of enhanced recovery program (ERP) for laparoscopic colorectal surgery. In addition, functional recovery and quality of life have not been assessed and compared with other analgesic techniques. This project is designed to evaluate the impact of lidocaine on surgical and functional outcomes.

In these randomized studies, patients scheduled for elective laparoscopic colorectal surgery were prospectively randomized to receive thoracic epidural analgesia (TEA group), intravenous lidocaine infusion (IL group) or patient-controlled analgesia with morphine (PCA group). All patients received similar surgical care in the context of ERP.

The average time to return of bowel function and median duration of hospital stay were similar in IL and TEA groups. TEA provided better postoperative analgesia than intravenous lidocaine in patients undergoing rectal surgery; otherwise there was no difference for colon resection. IL, TEA and PCA facilitated the return of postoperative functional walking capacity to baseline, and this was independent of the analgesic techniques use. However physical functioning and fatigue levels were impaired at 3 weeks after surgery with no difference between the 3 groups.

The present study demonstrated that the restoration of bowel function and diet intake were similar in both groups receiving either lidocaine infusion or epidural. Functional walking capacity at 3 weeks after surgery returned to baseline in all the groups and this was independent of the analgesic technique used. However, in all groups physical function decreased and fatigue increased and this was also independent of the type of analgesia used.

Résumé

Lors de chirurgie colorectale, l a été démontré que la Lidocaine intra-veineuse provoque un niveau d'analgésie comparable aux opiacés mais facilite la récupération postopératoire. L'épidurale est nettement supérieure aux opiacés systémiques en terme de fonction intestinale et d'analgésie . Il n'existe hélas pas d'étude comparant la lidocaine versus l'épidurale en termes de réhabilitation fonctionnelle et qualité de vie dans le cadre d'un programme de réhabilitation accélérée après chirurgie colorectale. L'objectif du présent protocole est d'évaluer l'utilité de la lidocaine en termes de récupération fonctionnelle et chirurgicale.

Cet essai randomisé inclut des patients requérant une chirurgie colorectale par laparoscopie. Les patients sont prospectivement randomisés en 3 groupes: Epidurale (Groupe TEA), lidocaine intraveineuse (Groupe IL) ou opiacés intraveineux (Groupe PCA). Les 3 groupes de patients reçoivent des soins chirurgicaux et anesthésique identiques dans le cadre d'un programme de réhabilitation accélérée.

La récupération fonctionnelle intestinale et la durée d'hospitalisation est similaire entre les groupes lidocaine et épidurale. L'épidurale apporte une meilleure analgésie que la lidocaine chez les patients ayant des chirurgies rectales mais l'analgésie est similaire chez les patients subissant une colectomie. Les trois stratégies furent similaires en termes de récupération fonctionnelle. Néanmoins, a 3semaines postopératoire l'état fonctionnel physique et la fatigue ne sont toujours pas retournés a leurs valeurs pré-opératoires dans aucun des groupes.

La présente étude montre que la récupération fonctionnelle intestinale et la prise alimentaire est comparable entre les 3 groupes. A 3 semaines postopératoires, la capacité à la marche est retournée aux valeurs pré-opératoires dans les 3 groupes, indépendamment de la technique d'analgésie. Néanmoins a 3 semaines l'évaluation fonctionnelle physique restait diminuée et le niveau de fatigue accru par rapport aux évaluations pré-opératoires, indépendamment de la technique d'analgésie.

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Contributions of Authors

Two manuscripts entitled “Intravenous lidocaine vs thoracic epidural analgesia. A randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program” and “Short-term functional outcomes after laparoscopic colorectal resection. Comparisons of analgesic techniques” are included in this thesis.

Dr. Mingkwan Wongyingsinn was involved in reviewing literature, preparing both study protocols, obtaining informed consent, administering anesthesia to patients in this projects, entering the data, conducting data and statistical analysis and preparing the manuscripts and the thesis.

Dr.Gabriele Baldini conducted the postoperative visits and helped to analyze the data.

Dr. Barry Stein, Dr. Sender Liberman and Dr.Patrick Charlebois operated all the subjects that are part of this project.

Dr.Franco Carli elaborated the conceptual part of the studies, administered anesthesia and revised the manuscripts and the thesis.

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A. Introduction

Colorectal resection is the most common major surgery for treatment of colorectal diseases such as cancer, diverticular disease and inflammatory bowel disease. The effect of surgery induces alterations in both physiological and immune response, and these changes can be associated with an increase in postoperative morbidity and mortality. Attempts have been made to modify and decrease these effects by minimizing the surgical stress response and optimizing postoperative recovery by intervening with different modalities.

Laparoscopic technique or minimally invasive surgery has developed to replace open surgery thus leading to less inflammatory response and less postoperative analgesic requirement as a result of less tissue manipulation, thus facilitating the recovery process and reducing hospital stay.[1-3] This technique has gained rapid popularity following the publication of large randomized studies that compared the efficacy and safety of laparoscopic colorectal resection with laparotomy technique.[4, 5] Although many studies comparing these two surgical approaches have reported beneficial effects of laparoscopy, some studies have shown that other interventions are needed to improve postoperative outcomes of colorectal surgery.

Over the last 10 years, a perioperative program named Enhanced Recovery Program (ERP) was introduced in an attempt to modify the inflammatory and metabolic stressors caused by major surgery.[6, 7] ERP is an evidence-based, multi-disciplinary, perioperative approach that encompasses the preoperative, intraoperative and postoperative periods.[6, 7] In colorectal surgery, this concept includes preoperative education and preparation, intraoperative strategies to minimize surgical stress responses, optimal choice of anesthesia and operative technique and effective postoperative analgesic technique, early feeding and mobilization.[8]

Together with the principles of ERP, epidural administration with local anesthetics has been shown to be the important roles in colorectal surgery.[9]

Thoracic epidural analgesia (TEA) also provides superior benefits in term of pain and postoperative ileus compared with systemic opioid.[10-17] Although the benefits of TEA on postoperative recovery have been confirmed, risks of epidural hematoma or abscess or neurological damage still occur.[18] Therefore there has been an interest in substituting epidural analgesia with an alternative technique, intravenous lidocaine. Since 1990, the use of intravenous lidocaine infusion has been implemented to improve postoperative paralytic ileus in abdominal surgery,[19-22] to minimize postoperative pain,[20, 22, 23] decrease postoperative opioid consumption[24] and shorten the length of hospital stay compared with systemic opioids.[20-22]

A direct comparison of the effects of TEA vs intravenous lidocaine on bowel function in laparoscopic colorectal patients using the setting or ERP has not been performed. Although intravenous lidocaine has been reported to have benefits on postoperative immediate functional walking capacity compared with placebo,[25] the functional recovery in term of long term functional activity and quality of life of intravenous lidocaine has not been compared with other techniques. This clinical investigation is designed to determine whether intravenous lidocaine improves the postoperative recovery from the clinical and functional point of view.

Therefore, the aims of this thesis are:

- To determine whether, compared with TEA, perioperative and postoperative intravenous administration of lidocaine provides differences in postoperative **surgical outcomes** in patients undergoing laparoscopic colorectal surgery and using an enhanced recovery program.

- To determine whether, compared with TEA and systemic opioid, perioperative and postoperative intravenous administration of lidocaine provides differences in postoperative **functional outcomes** in patients undergoing laparoscopic colorectal surgery and using an enhanced recovery program.

B. Literature review

1. Colorectal physiology

The colorectum (also known as the large intestine or large bowel) is the lower part of the digestive system or gastrointestinal tract located in the abdominal cavity, it consists of cecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum. The colon absorbs water, potassium and some fat soluble vitamins from solid wastes while rectum acts as a temporary storage site for feces before they are eliminated from the body.

Colorectal diseases are composed of a broad range of disorders in lower gastrointestinal tract including colon, rectum and anus; the severity varies from asymptomatic to life threatening condition. Colorectal diseases can present signs and symptoms; however each pathology has different treatment depending on the stage of diseases.

Resection of the colon and rectum removes the damage caused by various diseases of the lower digestive tract, such as colorectal cancer, intestinal polyps, diverticular disease, inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis. Below is an overview on the major colorectal diseases and treatment of choice.

2. Colorectal pathology

2.1 Colorectal cancer is a malignant tumour which abnormally grows from normal cells in the lining of the colorectal over a period of time (at least 10 years), and moves to other organs. Worldwide, this is the third most common cancer and the second leading cause of cancer-related deaths. According to recent statistic for 2009, in Canada there are 22,500 new diagnosed cases (12,400 men and 10,100 women) and 9,100 deaths (5,000 men and 4,100 women). Lifetime probability of developing colorectal cancer is one in 14 of men and in 15 of women.[26] The chance of survival in colorectal cancer increases by 90% if detected early.[27]

Staging of colorectal cancer is a method of evaluating the progress of cancer in a patient.[28] It is determined by the extent to which it has spread to other parts of the body. Colorectal cancer can be classified by TNM staging and stage grouping.[28] By TNM staging, cancer is categorized by tumour, node and metastasis. **Tumour** T1: tumour invades submucosa; T2: tumour invades muscularis propria; T3: tumour invades through the muscularis propria into the subserosa, or into the pericolic or perirectal tissues; T4: tumour directly invades other organs or structures, and/or perforates. **Node** N0: no regional lymph node metastasis; N1: metastasis in 1 to 3 regional lymph nodes; N2: metastasis in 4 or more regional lymph nodes. **Metastasis** M0: no distant metastasis; M1: distant metastasis present.

For stage groupings, there are four distinct stages, along with a fifth stage that is recurrent stage. **Stage 0** is the earliest stage of colorectal cancer. The cancer only involves the inner lining, or mucosa, of the colorectal or rectum. **Stage I**: T1-2 N0 M0 colorectal cancer involves more than just the inner lining of the colorectal and extends into the wall of the colorectal or rectum. **Stage II**: T3-4 N0 M0 cancer has spread beyond the colorectal to the tissue that surrounds the colorectal but has not spread to lymph nodes. **Stage III**: any T, N1-2, M0 cancer is spreading outside the colorectal and on to the lymph nodes in the area surrounding the colorectal but not spread to other organs in the body. In **Stage IV**: any T, any N, M1 cancer had spread to other organs in the body. This is known as metastasis. The most likely organs to experience metastasis from colorectal cancer are the lungs and liver. **Recurrent** means that cancer has returned after treatment, either in the colorectal, or in some other part of the body.

In the early stages, colorectal cancer can be removed during a colonoscopy; thus the progressing chance to later stages of cancer is eliminated. Colorectal surgery or surgical resection is recommended to remove the cancer in the later stage; lymph nodes in the mesentery will be sent to the lab to determine whether the cancer has spread. The long-term prognosis after surgery, the five-year survival rate, is 10-80% depending on whether the cancer has spread to other organs. In

addition to a surgery; chemotherapy and radiation treatment may be needed in patients with risk of tumour recurrent.

2.2 Non-cancer

a. ***Colon polyp*** consists of an abnormal growth line inside the colorectum which protrudes into the intestinal canal. Polyps in the colon are very common; they can vary in size and shape. It is estimated that 50% of the people over the age of 60 will have at least one polyp and the incidence increases as individuals get older. The significance of polyps is that some polyps can become cancerous. The polyps that become cancerous are called adenomatous polyps or adenomas which are approximately 75% of all colon polyps. Nonneoplastic polyps include juvenile, hyperplastic, inflammatory, and lymphoid polyps. Not all of these so-called nonneoplastic polyps may be innocent.

b. Diverticular disease includes two conditions: diverticulosis and diverticulitis. Diverticulosis is the presence of a diverticule which is pockets pushing out in weak areas next to the colorectum's blood vessels due to increased pressure in the colorectal from trapped gas or ongoing constipation. More than 130,000 Canadians have diverticular disease; more than 3,000 Canadians require surgical intervention annually and more than 400 Canadians die due to complications associated with diverticular disease each year. The high rate of hospitalization and surgery makes diverticular disease one of the five most expensive digestive diseases ($88.6 million per year).

c. ***Inflammatory bowel disease*** (IBD) including Crohn's disease and ulcerative colitis. ***Crohn's disease*** is the chronic inflammation of the gastrointestinal tract, from mouth to anus, but it usually locates in the lower part of the small bowel and the upper end of the colon. Patches of inflammation are interspersed between healthy portions of the gut and can penetrate the intestinal layers from inner to outer lining. This inflammation is produced by an abnormal response of body's immune system to foreign material.

Ulcerative colitis is the chronic inflammation of the inner lining of the colorectum and it almost always starts at the rectum, extending upwards in a continuous manner through the colon. The inflammation comes from a complex interaction of factors such as genetics, immune system and environment. Ulcerative colitis can be controlled with medication and surgical treatment in severe cases.

d. ***Injury, obstruction,*** and ***ischemia*** (compromised blood supply) may require a surgical removal of the damaged area.

3. Colorectal surgery

The goal of resection is to remove the section of the colorectum affected. During surgery, the diseased part of the bowel to be removed is isolated from the surrounding organs and then resected. The healthy section of the colorectum adjacent to the affected area is also resected and reattached to another healthy section just past the resected area; this portion is called an anastomosis. In patients with rectal pathology, the rectum is permanently removed. Only when it is necessary, an ileostomy (an opening of the small intestine onto the surface of the abdomen through which body wastes are eliminated) will be constructed during surgery. This temporary ileostomy allows the colorectal anastomosis having longer time to heal after surgery. The ileostomy will then be closed a few months later. If a permanent opening is needed, then a colostomy is formed.

As with any surgical procedure, surgery induces alterations in both physiological and immune responses, and these changes can be associated with an increase in postoperative morbidity and mortality. Complications can occur such as excessive bleeding, infection, injury to surrounding organs during the procedure, leakage from the anastomosis, bowel obstruction, incisional hernias and abdominal wall disruption or breakdown that would require additional surgery. Moreover there are some risks which are associated specifically with colorectal surgery such as increased incidence and duration of postoperative ileus,[29-33] and postoperative fatigue.[34-36]

4. Types of colorectal surgery

For colorectal resection, there are two surgical approach; open and laparoscopic. ***Open surgery*** is the standard procedure for colorectal resection which has been practised for a long time and includes a long abdominal incision. An 8-15 cm incision is made in the abdomen, the diseased part of the colorectum is located and removed. The surgeons reconnect the anastomosis using a surgical stapler, or it may be sutured by hand. Although the recovery process begins immediately after surgery, the long incision of open colorectal surgery can delay the recovery process.

In contrast, **laparoscopic surgery** or **minimally invasive surgery** (MIS) is a new technique developed in the early 1980s. Surgery is performed through four or five small incisions, thereby reducing the need for suturing the skin. A small video camera or "scope" is inserted into one of the incisions, and the surgeon can see on a television monitor a magnified view of the internal organs. Surgical instruments are placed inside the abdomen through small incisions, once the abdominal wall is expanded using carbon dioxide. This allows the surgeon to work inside the abdomen and remove portions of the diseased colorectum.

Minimally invasive surgery reduces surgical trauma by decreasing the extent of abdominal incisions, minimizing manual traction and manipulation of abdominal tissue and preventing excessive blood loss. This technique is considered to improve the preservation of normal immune function compared with open surgery and may be beneficial for patient's recovery. As laparoscopic technique is increasingly used, more research has focused on the postoperative outcomes. Although the long term outcomes for laparoscopic or open surgery are similar, laparoscopic surgery offers significant short-term benefits to patients, including smaller scarring, less postoperative pain, faster return of bowel function, quicker return to normal activities and shorter hospitalization. A recent meta-analysis confirms that laparoscopy colorectal surgery provides significant improvements in short-term outcomes in term of reductions in postoperative morbidity, time to restoration of bowel function, and duration of hospital stay.[37]

Like any surgery, there is a possibility of some complications arising with laparoscopic colon surgery. These complications can include bleeding and infection at the site of the operation, and formation of hernia.

Although laparoscopic technique was accepted relatively quickly for colorectal surgery because of the improvements in the short term outcomes, the application of this technique to colorectal cancer raised a lot of controversy because of the risk of cancer recurrence.[38-40] Therefore several prospective randomized trials were conducted and have finally demonstrated no difference in long-term recurrence rate between laparoscopic and open colectomy for cancer.[5, 41, 42] Another study was conducted to determine local and distant recurrence rates in laparoscopic and open colorectal resection, and did not show any difference between the two surgical approaches.[43] These findings are in agreement with the data published in the United Stated, and no significant differences in time to recurrence or overall survival were seen between the laparoscopic colectomy and the open colectomy groups.[5] A recent meta-analysis showed that the laparoscopic approach for colorectal cancer was as effective as open surgery in terms of the oncological outcomes including overall disease recurrence rates, local recurrence rates, distant metastasis rates and wound-site recurrence rates.[44] Only one study in 2002 showed an increase in cancer-related survival after laparoscopic resection.[41] This benefit was mainly attributable to differences in survival between laparoscopic and open surgery in patients with stage III tumors. In these patients, laparoscopic surgery was associated with an improvement of overall survival rates and a reduction in the tumor recurrence rate. From all these data, laparoscopic surgery can be suggested as a standard of practice when possible.

Even though numerous benefits of laparoscopic technique have been reported, a study in 1997 tried to identify other factors that delay postoperative recovery, and these were pain, postoperative ileus, immobilization, and a combination of interventions to reduce perioperative stress and organ dysfunction.[45] This program, multimodal rehabilitation program or fast-track program, was developed to optimize perioperative care in colorectal surgery and it has been demonstrated

that postoperative recovery can be enhanced, and hospital stay and costs can be reduced.[46-54] However, such protocol was not widely adopted at that time due to the delay in integrating new management strategies within routine practice.[55, 56] In 2000, the Enhanced Recovery After Surgery (ERAS) collaboration was established between five northern European centres (Denmark, the Netherlands, Norway, Sweden and the UK), with the aim to standardize the perioperative enhanced recovery program in all the participating centres.

5. Enhanced Recovery Program

The Enhanced Recovery Program (ERP), also called Enhanced Recovery After Surgery (ERAS), accelerated recovery strategy or fast-track program, was implemented in the 90s as a coordinated multimodal approach aimed to attenuate psychological and metabolic stress and with the intent to reduce intraoperative and postoperative complications and facilitate a faster return to daily activities.[10, 57] This program is an evidenced based, multi-disciplinary, perioperative approach covering preoperative, intraoperative and postoperative period.[6, 7] In colorectal surgery, this concept includes a preoperative education and preparation, intraoperative strategies to minimise surgical stress response, optimize choice of anesthesia and operative technique and effective postoperative analgesic technique, early feeding and mobilization (**Table 1**).

The systematic review and meta-analysis have shown that ERP is effective in reducing overall hospital stay from an average of 10 days to a mean of 4 days in major colorectal surgery.[58-61] The combination of laparoscopy and ERP has shown to improve short term clinical outcomes and decrease postoperative hospital stay for patients with colorectal cancer.[62] However, there is no study evaluate long term outcomes of this combination.

Table 1 Summary the important ERP principles

Phase	**Intervention**
Preoperative	Preoperative education
	Avoidance of bowel preparation
	Minimizing preoperative fasting
	Preanesthetic medication
Intraoperative	Anti-thrombotic prophylaxis
	Antibiotic prophylaxis
	Optimize choice of anesthesia
	Avoiding routine nasogastric decompression
	Prevention of intraoperative hypothermia
	Fluid management
	Abdominal and urinary drainage
Postoperative	Postoperative nausea and vomiting
	Postoperative analgesia
	Early postoperative oral intake
	Early mobilization
	Discharge criteria

The major elements of the ERP are:

Preoperative education, whereby clear information of all aspects of care are given by nurses to patients when visiting the preoperative clinic including the setting of this program, management of postoperative analgesia, early oral nutritional supplements, early ambulation, and expected time of staying in hospital.[37, 63, 64] Many studies have been shown that a clear explanation of expectations during hospitalization facilitates adherence to the care pathway and allows early recovery and discharge especially in patients with denial and anxiety.[28, 65-67]

Avoidance of bowel preparation. It has been a common practice to order bowel cleansing the day before surgery, in view of the risk of fecal contamination of the anastomosis. However bowel preparation can cause significant dehydration and electrolyte abnormalities, particularly in elderly patients.[68] A number of meta-analyss has been shown that bowel preparation is not beneficial in elective colonic surgery. Furthermore, three studied indicated that it increases the risk for anastomotic leak and prolonged postoperative ileus.[69-76] In contrast, one recent study has reported that bowel preparation protects against anastomotic leaks requiring reoperations in ultralow rectal anastomosis; however, there was increased cardiovascular mortality.[77] The present consensus seems to be on avoidance of bowel preparation in colon surgery, while the last word on bowel surgery for rectal surgery remains to be said.

Minimizing preoperative fasting to two hours. Although overall fasting from midnight has been standard practice to avoid pulmonary aspiration in elective surgery, several National Anesthesia Societies now recommend intake of clear fluids up until 2 hours before initiation of anesthesia and 6 hours for solid food.[78-80] Provision of a clear carbohydrate-rich beverage (12.6%) at a dose of 800 ml before midnight and 400 ml 2–3 hours before surgery has been shown to reduce preoperative thirst, anxiety and significantly reduce postoperative insulin resistance.[81] Such approach put patients in a more anabolic state with less postoperative nitrogen and protein losses as well as better-maintained lean body mass, muscle strength [82-85] Some studies have shown accelerated recovery and shorter hospital stay in patients receiving preoperative carbohydrate loading in colorectal surgery.[86, 87] However, high risk patients such as the obese should be kept fasted for at least 6 hours before a surgery since they are at higher risk of regurgitation and aspiration than normal patients.[88]

Preanesthetic medication aiming to reduce anxiety using short-acting anxiolytic drug is acceptable because of no effect to prolong recovery or length of stay.[89] However, long-acting premedication such as long-acting sedatives, opioids, and

hypnotics can affect recovery by delaying oral intake and mobilization after surgery, leading to prolonged length of stay.[89, 90]

Anti-thrombotic prophylaxis. The use of subcutaneous low-dose unfractionated heparin regimens or low-molecular-weight heparin is strongly recommended reducing deep vein thrombosis, pulmonary embolism, and mortality in patients undergoing colorectal surgery when no contraindication.[91-95] Compression elastic stocking and intermittent pneumatic compression are effective and provide an additional advantage when combined with low-molecular-weight heparin and mobilisation.

Antibiotic prophylaxis is proved to be effective in reducing infectious complications in colorectal surgery when the first dose is administered within the first 20 min prior to skin incision.[96-98] A second-generation cephalosporin and metronidazole are suggested. A single dose is as effective as multidose regimens but further doses should be given in prolonged operations, more than 3 hours.[96]

Optimize choice of anesthesia using rapid, short-acting medication can facilitate early recovery from anesthesia, improve postoperative outcomes, decrease the incidence of postoperative adverse events and minimize side effects. There is no evidence what is the optimal choice of the anesthesia based on morbidity or recovery data from colorectal procedures, both short-acting inhalational anesthesia and total intravenous anesthesia are reasonable alternative choices.

The regional anesthesia such as epidural technique has an important role in colorectal surgery in term of providing additional intraoperative analgesia and reducing the dose of general anesthetic agents, blocking sympathetic response when placing at midthoracic level (T7/8), blocking stress hormone release, attenuating postoperative insulin resistance[99] and preventing gut paralysis.[100] More information about thoracic epidural analgesia is discussed in section 6.2 page 17.

Avoiding routine nasogastric decompression. A nasogastric tube can be inserted during surgery when it is necessary such as to evacuate air which have been pushed down in the stomach during mask ventilation, and can be removed before the patient wakes up from anesthesia. Avoiding routine nasogastric decompression has been shown to decrease the incidence of fever, atelectasis and pneumonia.[101] Strong evidence from a meta-analysis also confirmed that earlier removal of nasogastric tube facilitates earlier return of bowel function.[101-104]

Prevention of intraoperative hypothermia using infusion of warmed fluids and forced-air heating cover has been associated with decrease wound infections, cardiac complications, intraoperative bleeding, and transfusion requirements.[105-109]

Appropriate management of intravenous fluids aims to optimize intravascular volume and avoid overhydration. This can be achieved by using the concept of 'goal-directed fluid therapy' whereby intravenous fluids are administered under direct measurement of cardiac index. This approach has demonstrated postoperative reduction in morbidity and hospital stay.[110-114] In contrast to overhydration, dehydration leads to functional hypovolemia, an exaggerated vasoactive hormonal response and delayed recovery.[111, 112, 115-117] There is also good evidence to support the benefit to reduce a dehydration by allowing access to oral clear fluid up to 2 hours before surgery.[118]

Administration of salt solutions can delay the return of bowel function, impair wound or anastomosis healing, increase postoperative complications and prolong hospitalization.[119-122] However, a balance has to be maintained between adequate tissue perfusion and overloading with fluids, and this can be achieved by weighing patients. Administration of intravenous fluid is discontinued as soon as adequate oral intake is established.[123]

Abdominal and urinary drains need to be removed as soon as possible. Meta-analyses have demonstrated that the use of peritoneal drains after colonic anastomosis does not reduce the incidence or severity of anastomotic leak or other complications.[124, 125] Several randomised studies have shown that indwelling

urinary catheter for a period longer than 48 hours is associated with higher urinary tract infection rate.[126-128] Remaining drainages and catheters represent a significant obstacle to achieve early and appropriate mobilisation.

Prevention of postoperative nausea and vomiting (PONV) is an important component of the ERP, in fact persistent PONV can delay the return of oral intake and therefore recovery. Prophylaxis using dexamethasone or antiemetic medication is indicated especially in high risk patients such as female sex, non-smoking status and history of motion sickness or postoperative nausea and vomiting.[129-132]

Effective postoperative analgesia allows patients start early mobilisation. It is well established from several controlled trials and a Cochrane Review that optimal analgesia for abdominal surgery is best achieved by continuous epidural analgesic techniques using local anesthetics and opioids.[133] Patient controlled analgesia (PCA) using intravenous opioids provides lower analgesic efficacy and has less physiological effects on surgical stress responses compared with epidural techniques.

The importance of multimodal analgesia has been increased in the management of perioperative pain, and it has been integrated in the ERP to enhance recovery, reduce hospital stay, and facilitate early convalescence.[134] The reason for using different classes of analgesics acting on different receptor sites, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, is to provide superior dynamic pain relief with reduced analgesic-related side effects and to avoid the use of systemic opioids which impact on bowel function, and postoperative mobilization. NSAIDs have been shown to have a significant opioid-sparing effect and provide effective analgesia during the postoperative period. Also, it has been confirmed that they do not increase the risk of epidural hematoma.

Early postoperative oral intake. It has been confirmed by a meta-analysis that there is no advantage to keeping patients fasting after elective gastrointestinal

resection. [135-138] Early feeding has been shown to reduce the risk of infection and duration of hospital stay, and is not associated with an increased risk of anastomotic leakage. One of the objectives of postoperative care is restoration of bowel function to allow adequate food intake and rapid postoperative recovery**.** To achieve this aim, patients should be encouraged to have oral intake within 4 hours after surgery. However, early feeding may cause abdominal bloating with vomiting. [139, 140]

Oral nutritional supplements have been successfully used on the day prior to operation and for at least the first 4 postoperative days to achieve recommended intakes of energy and protein.[141-143] When used in combination, preoperative oral carbohydrate loading, epidural analgesia, and early enteral nutrition have been shown to result in postoperative positive nitrogen balance without concomitant hyperglycemia.[144] This emphasises the importance of multimodal therapy in the maintenance of nutritional status following surgery.

Early mobilisation can enhance bowel motility and decrease incidences of postoperative ileus, and effective pain control is a key to encourage postoperative mobilisation. In contrast, prolonged bed rest decreases muscle strength and pulmonary function and increases the risk of thromboembolism.[145] Another useful measure for patients' compliances is the use of a diary where patients document the time spent out of bed on a daily basis. The aim is to have patients out of bed for at least 2 hours on the day of surgery and on average 6 hours per day until discharge.

Implementation of strict discharge criteria. Patients have to be aware that they will be discharged once they reach specific and safe criteria. These are good pain control with oral analgesia, intake of solid food, absence of fever, passing gas and stool and be mobile.

Although each component of the ERP has independently been shown to have some beneficial effect on patient outcome, when combined they have shown to cause a significant reduction in length of hospital stay, down to 5 days after open

colorectal surgery and to 3 days after laparoscopic surgery,[4, 58, 145-147] and also a accelerated return to normal activities.[146] Furthermore, a 50% reduction of postoperative complications associated with colectomy has been demonstrated with ERP.[148-150] A remarkable reduction in hospital day stay, from 10 days or more to 3 days in some instances, has been reported.[151] These translate into significant benefits to patients and to the health-care system.

6. Analgesic techniques for colorectal resection

The analgesic technique is one of the most important elements to improve perioperative and postoperative outcome, and multimodal analgesia is an important concept in the management of perioperative pain, in order to enhance recovery, reduce hospital stay, and facilitate early convalescence.[134, 152]

6.1 Patient-controlled analgesia

The patient-controlled analgesia (PCA) has been used for several decades, and consists in using a micro-infusion pump that allows programming of the dose, the time interval, the maximum dose per time, and the background infusion rate thus enabling patients to self-administer small bolus of analgesic medication such as opioids parenterally at the touch of a button of PCA pump. The PCA technique provides a constant level of analgesic medication and avoids the swings of regularly intermittent intramuscular opioid administration based on administration every 3 to 4 hours.

The efficacy and safety of PCA have been shown in numerous clinical trials and different populations to improve analgesic efficacy, decrease respiratory depression, minimize sedation and narcotic dependence, also accelerate postoperative recovery, and reduce nursing time compared with the conventional intramuscular opioid injection.[153-155]

Although the benefits of PCA have been confirmed in term of improving efficacy and minimizing adverse effects of systemic opioid, the direct adverse effects of systemic opioid on bowel function and postoperative mobilization are to be considered.

6.2 Thoracic Epidural Analgesia

Thoracic epidural analgesia (TEA) is the most popular technique for colon resection, as it has been demonstrated to have several beneficial aspects compared with PCA, including suppression of sympathetic hyperactivity, attenuation of surgical stress, positive effect on postoperative nitrogen balance, stable hemodynamic, improvement of peripheral circulation and reduction of blood loss.[156-159] The epidural catheter must be placed in the mid-thoracic level, at T7/8 for colonic surgery and T8/9 for rectal surgery, in order to achieve both analgesic block and sympathetic block, thus preventing gastrointestinal paralysis.[100]

TEA with local anesthetic agents activated before the onset of surgery has been shown to have a impact on bowel function after colorectal surgery either as a result of direct effect of neural blockade or the anti-inflammatory properties of the local anesthetics, this beside the attenuation of the stress response and postoperative insulin resistance associated with the epidural blockade.[99] The anti-inflammatory effects of local anesthetics inhibit prostaglandin synthesis,[160] the migration of granulocytes into the inflammatory area,[161, 162] and the granulocyte release of lysosomal enzymes.[163] Because of these effects, local anesthetics prolong an inhibition of peritoneal irritation after major abdominal surgery and maintain an inhibitory effect of intestinal reflexes responsible for the development of paralytic ileus. Epidural local anesthetics have been shown in open colorectal surgery not only to have superior analgesic effect over systemic opioid, but also to accelerate the recovery of bowel function by 1 to 2 days.[164-166] However, the benefits of TEA on accelerating the return of bowel function have not been consistently shown when applied to laparoscopy. Some authors have demonstrated the same beneficial effect of TEA as in open colon resection with excellent analgesia and shorter return of bowel function.[16, 17, 133]

When the ERP is part of the surgical care, TEA is usually used in this program and its positive effects on postoperative pain, dietary intake, bowel function and the length of hospital stay have been confirmed.[14, 17, 146, 167, 168] Therefore TEA, together with laparoscopic technique and ERP, has been considered an essential

element on the basis of optimal pain relief to facilitate the recovery process and reduce postoperative morbidity.[159, 165, 169] Small dose of epidural opioids have a synergistic effect with local anaesthetic agent in providing better analgesia[170] without significant systemic effects[133, 165, 171] in open colon surgery and ERP setting.

A study in 1990 showed that an intravenous lidocaine infusion improved postoperative paralytic ileus in abdominal surgery.[19] More recently, there has been an interest in substituting epidural analgesia with intravenous lidocaine. Several studies have investigated the use of intravenous lidocaine and the results indicated a fast return of bowel function,[20-22] less postoperative pain,[20, 22, 23] decreased postoperative opioid consumption[24] and shorter length of hospital stay compared with systemic opioids.[20-22]

6.3 Intravenous lidocaine

Intravenous lidocaine has been shown to have analgesic, anti-hyperalgesic and anti-inflammatory properties which can attenuate the excessive inflammatory response associated with visceral surgery.[21-23] Although the exact mechanism is unknown, it seems that lidocaine targets different steps within the inflammatory cascade, such as intracellular G-protein coupled receptors, complement and proinflammatory cytokines thus blocking neural transmission at the site of tissue injury.[21, 172]

Colorectal surgery is associated with increased levels of proinflammatory cytokines and postoperative ileus.[173] These proinflammatory cytokines released during inflammatory responses can produce a long lasting hyperalgesia,[174, 175] modulate pain by altering pain signal transmission via cytokine-induced release of neuroactive substances while the anti-inflammatory cytokines are also increased during surgical stress to reduce inflammation.[176]

Several studies and meta-analysis demonstrated that intravenous lidocaine could reduce postoperative pain at rest and on coughing with a significant decrease in opioid consumption in patients undergoing different types of surgeries,[177, 178]

especially in major abdominal and laparoscopic colorectal surgery.[20, 22-24, 178-180] This might be a result of the anti-inflammatory and analgesic effect of intravenous lidocaine, many evidences have shown that the effect of intravenous lidocaine in reducing postoperative pain and opioid consumption seems to be dose-dependent, and these effects persist for 72 hours after the infusion is discontinued.[19, 22, 23, 179] The postoperative opioid sparing effect of lidocaine ranges between 33 to 83%. [19, 24, 181-183]

Recently, two randomized control trails compared intravenous lidocaine with thoracic epidural analgesia in patients undergoing colorectal surgery reported inconsistent findings in term of analgesic control and opioid consumption.[180, 184] However, both studies were in the setting of open colon surgery.[180, 184]

The beneficial effect of intravenous lidocaine on bowel function in patients undergoing elective open colorectal surgery has been reported in several studies in non ERP and ERP settings.[21, 22] This benefit may come from a direct excitatory effect of lidocaine on intestinal smooth muscle which results in a blockade of inhibitory sympathetic and paravertebral reflexes, activated immediately when the parietal peritoneum is entered, of the myenteric plexus.[19, 185-187] Systemic lidocaine can significantly depress amplitude, spike activity and conduction time in both myelinated A-δ and unmyelinated C fibers.[19] Then intravenous lidocaine can inhibit the migration of granulocytes, release of lysosomal enzymes and synthesis of prostaglandin.[19, 161] The anti-inflammatory effect on bowel function is prolonged and persists after serum levels have decreased.[19]

More data have been shown that intravenous lidocaine has a positive impacts on bowel function by significantly accelerating return of bowel function and attenuating postoperative ileus after laparoscopic cholecystectomy,[179] prostatectomy,[20] colorectal surgery.[21, 22] The advantage of continuous intravenous infusion of lidocaine on decreasing the duration of postoperative ileus was confirmed by a meta-analysis published in 2008.[178] Although one study showed

that intravenous lidocaine was as good as TEA with regard to recovery of bowel function,[184] this benefit was not confirmed in another study. [180]

Duration of hospital stay is one of most important outcomes after colorectal surgery which reflects the quality of postoperative recovery. Result from five randomized controlled trials in major abdominal surgery showed significantly shorter length of hospital stay in patients receiving continuous perioperative and postoperative intravenous lidocaine infusion than in those receiving placebo.[178] The duration of hospital stay was reported to vary between 2 and 7 days in patients receiving intravenous lidocaine while the range of reduction varied from 1 to 1.1 days.[20-22, 178-180, 182] However, there was no statistically difference in the length of hospital stay in two studies comparing intravenous lidocaine with thoracic epidural technique in open colon surgery.[180, 184]

The benefit of intravenous lidocaine on functional recovery has not been studied after colorectal surgery, and there are only two studies in patients undergoing laparoscopic prostatectomy and total hip arthroplasty.[25, 188] In laparoscopic prostatectomy, intraoperative and postoperative infusion of lidocaine attenuated the deterioration in functional walking capacity[25] while no benefit of the perioperative intravenous lidocaine in terms of functional recovery after total hip arthroplasty was reported.[188]

Postoperative outcomes of intravenous lidocaine following laparoscopic colorectal surgery have not been consistently compared with thoracic epidural analgesia, and two present studies have been set up to determine the impact of intravenous lidocaine on two aspects of postoperative recovery, surgical and functional outcomes.

7. Postoperative outcomes in colorectal surgery

7.1 Surgical outcomes

Surgical outcomes following colorectal surgery can be divided in short-term and long-term outcomes.

7.1.1 Postoperative bowel function is an important outcome in patients undergoing colorectal surgery as it is related to the success of surgery and significantly affects the quality of life. Postoperative ileus (POI) is a common clinical problem occurring after this surgical procedure.[29-33] POI is defined as a transient impairment of gastrointestinal motility in the postoperative setting and characterized by abdominal distension, accumulation of gas or fluid in the bowel and delayed defecation. Many clinical studies have demonstrated that the duration of POI is related to the degree of surgical manipulation, the magnitude of the inflammatory response and the anatomical location of surgery. The duration of POI after major abdominal surgery, especially colorectal, is approximately between 48 and 72 hours.[189-191] Prolonged POI can contribute to significant postoperative morbidity including nausea and vomiting, increased postoperative pain, delayed oral intake and postoperative mobilization, prolonged hospitalization, decreased patient satisfaction and increased health care costs.

The measurements to assess bowel function are not well defined. A number of methods developed to assess function in a clinical setting have been reported in the literature; however there is no standard asseeement.[31, 192, 193] Several studies have evaluated postoperative bowel function by using clinical measures such as bowel sound, however bowel sounds may originate in the small bowel as well as in the large bowel which may be lead to misinterpretation. Passage of flatus and passage of stool are the most common methods to assess postoperative return of bowel function because these are easy to be reported by patients. However, these clinical signs are not specific, as they may indicate only distal bowel function but not necessarily the function of the entire gastrointestinal tract. For this reason, there is a need to combine this outcome measure with another functional outcome such as the ability to tolerate oral fluids and diets.

In the traditional postoperative protocol, patients were allowed to have oral diet only when bowel function was returned. In the setting of ERP, more patients are encouraged to have oral intake within 4 hours after surgery and allowed early

diets when they want to eat.[136, 194, 195] If patients feel hungry or can tolerate oral intake, then this is a positive sign indicating the return of bowel function.

7.1.2 Postoperative pain is a complex response to tissue trauma during surgery which stimulates the hypersensitivity of the central nervous system. In recent years many interventions and techniques have been developed to minimize postoperative pain, as there is sufficient evidence that postoperative pain may result in physiological and psychological consequences leading to significant morbidity short term and long term.[196] Short-term effects of postoperative pain include emotional and physical suffering, sleep disturbance, cardiovascular side effects such as hypertension and tachycardia, increased oxygen consumption, impaired bowel movement, negative effects on respiratory function leading to atelectasis, retention of secretions and pneumonia, delayed mobilisation and recovery, postponed return to normal activities of daily living and prolonged hospital stay.[170, 196, 197] Additionally, inadequate treatment of acute postoperative pain is a risk factor for the development of chronic pain in the long term period.[196, 198, 199]

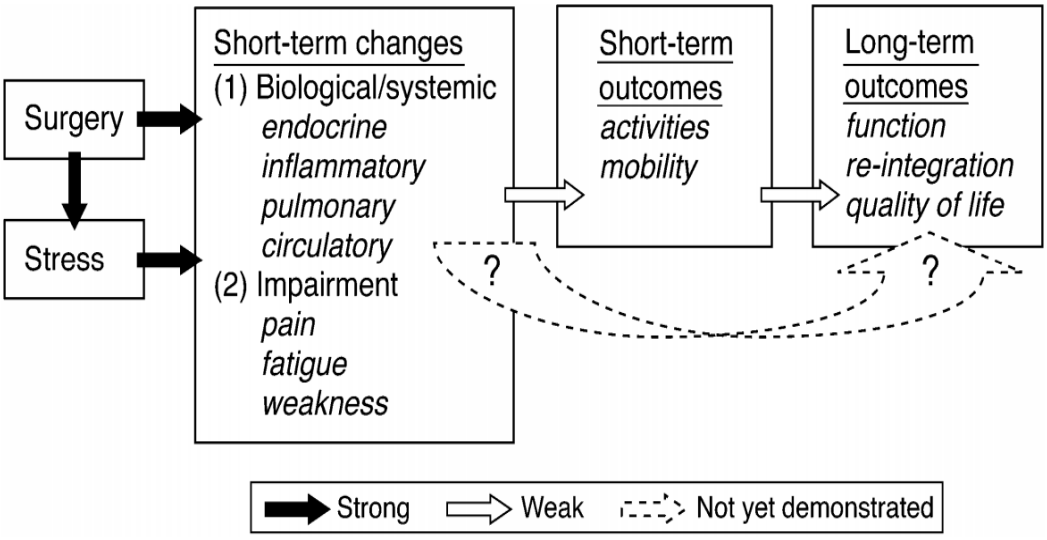
Pain is a subjective experience so pain assessment by the observer is unreliable; it should be reported by patients as far as they are able to communicate and express. Postoperative pain could be assessed and recorded by pain assessment scales which can quantify pain including the intensity of pain. Visual analogue scale (VAS) is the commonly used method of assessing acute pain. It is a unidimensional scale with several appealing characteristics,[200] easy to use and requires no verbal or reading skills.[201-203] VAS needs a 10 cm line labeled 'no pain' at one end and 'the worst possible' at another end; and it should not have other markings, numbers or words along the line because these tend to influence the results. The patient is asked to make a vertical mark on the line to indicate the intensity of their pain. Some patients with limited education or the elderly have difficulty with VAS, so it is most important to ensure that the patient understands the meaning of these two end points by giving examples of familiar pain problems. Verbal rating scale (VRS) is the most commonly used method of

assessing pain and has been derived from VAS in order to simplify the pain assessment. In practice, this method is extremely simple and easily to be understood by patients; VRS requires the patient to choose a number between 0 and 10 to represent their pain, the zero represents that the patient has no pain, and the 10 represents that the patient has the worst possible pain. VRS is more commonly used than VAS because VRS is straightforward and does not need equipments such as paper and pen to complete. A strong correlation has been shown between VRS and VAS.[204-206]

The pain assessment is used not only to measure the intensity of pain but also to measure both static and dynamic pain which provides more information about the severity of pain. In the postoperative period, static pain means pain at rest while dynamic pain means pain on walking and on coughing. Postoperative pain control aims to limit static pain at rest less than 4 and dynamic pain less than 6 because a study has reported that low dynamic pain scores accelerates more functional recovery and correlates with less postoperative complications.[204]

Surgical outcomes have traditionally been reported in terms of morbidity, length of hospital stay and complication rate, all of these have been used as a measure of outcomes but these outcomes are not the best indicators of recovery to indicate the real status of the patient's health. As a proposed model demonstration, a surgery associated with stress and that both of them produce immediate physiological and systemic biological changes (solid arrows) (**Figure 1**).[207] These short-term physiological effects have an impact on short-term function (open arrows), however, a relationship between the short- and long-term outcomes remains controversy (dash arrow).[207] And there was also no association between short-term biological changes and the long-term outcome.[207]

Figure 1 A model for measuring the outcome of surgical procedures[207]



7.2 Functional outcomes

Recently, there have been some interests in assessing the influence of surgery on the process of functional recovery returning to baseline, with patient-reported outcomes of well-being.[25, 33, 146, 192, 208-211] Functional recovery targets impairments, activity limitations, or restrictions in participation which can be referred to patients' ability to perform an activity or participate with their community in some roles. Physical activity is an important aspect of daily life; health status, pain, fatigue can influence physical activity and also affects continuously the recovery process.[25, 207] The literature of the best effective method to assess functional recovery is inconsistent, as no measurement can cover all functional recovery. Several aspects of functional recovery such as walking capacity, quality of life and postoperative fatigue have to be assessed with many measurements in order to interpret overall functional outcomes of colorectal surgery.

7.2.1 Functional walking capacity is a measure of exercise tolerance requiring muscle strength. Walk tests can be used to assess this capacity which measure the distances walked over a definite time period and reflect greater distances indicating better performance. Many walking tests are used to assess

functional walking capacity and reflect endurance and muscle force required to walk effectively.[212-214] Walk tests could be administered as part of an assessment to determine functional performance, to evaluate treatment effectiveness, or to assess readiness for discharge.[215]

The 6-Minute Walk Test (6MWT) is a performance-based test and very simple functional walking test which measures the distance (meters) that a patient can walk in a period of six minutes. This test reflects an ability to perform physical activities of daily living and correlates with measures of quality of life [216-220] The evidence still supports that the 6MWT is a useful measure of functional capacity targeted and has been widely used for preoperative and postoperative evaluation as a measure of surgical recovery.[218, 221] Although most literature focus on the 6- and 12-Minute Walk Test, only the 6MWT has data on responsiveness and sensitivity to change.[222] It is better tolerated than the 12-Minute Walk Test and more reflective of the requirements of activities of daily living than the 2-Minute Walk Test.[222] 6MWT is usually done twice, once before and once following therapeutic intervention or surgery to determine the significant improvement in functional status and assess endurance. The change in 6MWT can be presented as an absolute value, a percentage change, or a change in the percentage of predicted value; however an absolute value is the most recommended.[212, 221]

Many studies demonstrated the predicted values of 6MWT however these reference values are limited due to differences in the population studied.[223-227] One study has presented predicted 6-minute walk distance in healthy adults, and was calculated using gender-specific reference equations; for men, 6MWT distance = (7.57 × height(cm)) - (5.02 × age) - (1.76 × weight(kg)) - 309 meters, and for women, 6MWT distance = (2.11 × height(cm)) - (2.29 × weight(kg)) - (5.78 × age) + 667 meters.[223] However most patients do not achieve maximal exercise capacity which is the predicted distances during the 6MWT and most activities of daily living are performed at submaximal levels of exertion; thus the 6MWT may provide enough information to reflect the functional exercise level for daily physical activities.

The 2-Minute-Walk Test (2MWT) was originally modified from 6- and 12-Minutes Walk Test and developed to compensate in case of postoperative patients unable to ambulate for six minutes, especially early in their rehabilitation.[228] The 2MWT has been found more suitable for patients in compromised health states in the early postoperative period.[212] A greater distance of 2MWT indicates a better performance. Soon after surgery, patients have stress from surgery including postoperative pain, POI, fatigue, etc; and most of them cannot tolerate walking in 6 minutes. Therefore, 2MWT can properly replace 6MWT.

It has been shown to be comparable to the six- and twelve-minute walk tests in patients with chronic respiratory disease and correlated to measures of oxygen consumption. [212, 229] This walk test has been used to measure the functional exercise capacity of persons with lower extremity amputation and cardiac surgery, and it is responsive to change to rehabilitation with adequate correlation with measures of physical functioning.[214, 230] The 2MWT is usually measured before surgery and only for short-term period after surgery to assess muscle strength especially lower extremities and the obstacles to walking recovery.

7.2.2 Health-related quality of life (HRQL) can be assessed by using **SF-36 questionnaire** which is a short-form health survey of patients with 36 questions (appendix). This measure was created to assess the health-related quality of life in the general population in 1992.[231] This evaluation scale was developed to be as an indicator of perceived health status for using in general and specific population. In the present, the SF-36 is the most commonly used generic instrument and has been translated into more than 50 languages for measuring quality of life.[232]

SF-36 has 8 multi-item scales profile composed of Physical Functioning (PF) (10 items), Role-Physical (RP) (4 items), Bodily Pain (BP) (2 items), General Health (GH) (5 items), Vitality (VT) (4 items), Social Functioning (SF) (2 items), Role-Emotional (RE) (3 items) and Mental Health (MH) (5 items); which are aggregated to two summary measures, physical and mental component summary.

Each scale profile provides individual information such as performing physical activities including the most vigorous without limitations due to health for PF scale, problems with work or other daily activities as a result of physical health for RP scale, feeling full of energy for VT scale, performing normal social activities without interference due to physical or emotional problems for SF scale, problems with work or other daily activities as a result of emotional problems for RE scale and feeling peaceful, happy, and calm for MH scale.[233-236] Information about SF-36 scales, PCS and MCS is present in **Table 2**.

This measure is targeted at a specific age, nationality and disease or treatment group. The interpretation of the results has been made with the standardization of mean scores and standard deviations for all SF-36 scales. Specifically, norm-based scoring has been proven to be very useful when interpreting differences across scales in the SF-36 profile and for monitoring disease groups over time. Linear transformations were performed to transform scores to a mean of 50 and standard deviations of 10, in the general population.[234, 235, 237] This transformation achieves the same mean and standard deviation for all eight scales and the physical and mental summary measures.

Table 2 Summary information about SF-36 scales, Physical and Mental Component Summary Measures[238]

Scales	Number of Items	Mean	SD	Definition	
				Lowest Possible Score	Highest Possible Score
Physical Functioning (SF)	10	84.2	23.3	Very limited in performing all physical activities, including bathing or dressing	Performs all types of physical activities including the most vigorous without limitations due to health
Role-Physical (RP)	4	80.9	34.0	Problems with work or other daily activities as a result of physical health	No problems with work or other daily activities
Bodily Pain(BP)	2	75.2	23.7	Very severe and extremely limiting pain	No pain or limitations due to pain
General Health (GH)	5	71.9	20.3	Evaluates personal health as poor and believes it is likely to get worse	Evaluates personal health as excellent
Vitality (VT)	4	60.9	20.9	Feels tired and worn out all of the time	Feels full of pep and energy all of the time
Social Functioning (SF)	2	83.3	22.7	Extreme and frequent interference with normal social activities due to physical and emotional problems	Performs normal social activities without interference due to physical or emotional problems

Table 2 Summary information about SF-36 scales, Physical and Mental Component Summary Measures[238] (continue)

Scales	Number of Items	Mean	SD	Definition	
				Lowest Possible Score	**Highest Possible Score**
Role-Emotional (RE)	3	81.3	33.0	Problems with work or other daily activities as a result of emotional problems	No problems with work or other daily activities
Mental Health (MH)	5	74.7	18.1	Feelings of nervousness and depression all of the time	Feels peaceful, happy, and calm all of the time
Physical Component Summary (PCS)	35	50.0	10.0	Limitations in self-care, physical, social, and role activities, severe bodily pain, frequent tiredness, health rated "poor"	No physical limitations, disabilities, or decrements in well-being, high energy level, health rated "excellent"
Mental Component Summary (MCS)	35	50.0	10.0	Frequent psychological distress, social and role disability due to emotional problems, health rated "poor"	Frequent positive effect, absence of psychological distress and limitations in usual social/role activities due to emotional problems, health rated "excellent"

7.2.3 Postoperative fatigue (POF) is an unpleasant and distressing symptom which frequently occurs after major abdominal surgery. POF has multifactorial etiology including physiological, biological and social factors; and frequently has a major impact on the patient's quality of life.[36, 239-241] It affects both physical daily activity including capacity of working, and emotion including feelings of frustration, depression, and difficulty in concentration.[242] POF occurs following uncomplicated abdominal surgery in about one-third of patients, and continues to persist for up to 3 months after uncomplicated gastrointestinal surgery.[35, 239, 243, 244]

To assess the level of fatigue, many different questionnaires have been developed. These range from single-item scales of intensity, such as Visual Analogue Scales which assesses the feeling of fatigue before and after major abdominal surgery,[35] to multidimensional measures which assess both mental and physical aspects of fatigue on the basis of severity, circumstances, consequences, and responsiveness to rest or sleep.[245, 246]

Identity-Consequence Fatigue Scale (ICFS) was developed in 2006 specifically for surgical patients to assess POF, as fatigue is one of the most common complaints during the postoperative period especially after major abdominal surgery.[34-36]

ICFS is a validated multidimensional self-report questionnaire that has 31 items including 20 items to assess the feelings and 11 items to assess the Instrumental Activities of Daily Living (IADL) (appendix).[36] The ICFS questionnaire measures 5 different subscales of POF: feeling of fatigue (5 items), feeling of vigor (4 items), impact on concentration (5 items), impact on energy (6 items), and impact on daily activities (11 items). It is summarized into two summary scores, the overall POF score which is the mean of the first 2 subscales and the Fatigue-Consequence (FC) score which is the mean of the latter 3 subscales. Both POF and FC are expressed as a percentage of the maximum possible scores.[36]

C. The aim of thesis

Intravenous lidocaine infusion, compared with systemic opioids, has been shown to have superior benefits on surgical outcomes in term of faster return of bowel movement, better postoperative pain control and shorter duration of hospital stay. TEA is a recommended technique for colorectal surgery and it is used in the setting of ERP to improve postoperative recovery.

A direct comparison between TEA and intravenous lidocaine with regard to return of bowel function after laparoscopic colorectal surgery in the context of ERP has not been performed.

Although intravenous lidocaine has been reported to facilitate the postoperative immediate functional walking capacity compared with placebo,[25] functional recovery in term of long term activity and quality of life has not been assessed and compared with other analgesic techniques. This clinical investigation is, therefore, designed to evaluate the effect of intravenous lidocaine infusion on surgical and functional outcomes. The aims of this thesis are as follows:

- To determine whether perioperative and postoperative intravenous infusion of lidocaine accelerates the return of bowel function and attenuates postoperative pain in patients undergoing laparoscopic colorectal surgery and using the enhanced recovery program.

- To determine whether perioperative and postoperative intravenous infusion of lidocaine impacts positively on postoperative functional outcomes in term of functional walking capacity, quality of life and postoperative fatigue in patients undergoing laparoscopic colorectal surgery and using the enhanced recovery program.

D. Intravenous lidocaine vs thoracic epidural analgesia. A randomized controlled trial in patients undergoing laparoscopic colorectal surgery using an enhanced recovery program

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D.1 Abstract

Background and Objective: Laparoscopy, thoracic epidural analgesia and enhanced recovery program (ERP) have been shown to be the major elements to facilitate the postoperative recovery strategy in open colorectal surgery. This study compared the effect of intra and postoperative intravenous lidocaine infusion with thoracic epidural analgesia on postoperative restoration of bowel function in patients undergoing laparoscopic colorectal resection using an ERP.

Methods: Sixty patients scheduled for elective laparoscopic colorectal surgery were prospectively randomized to receive either thoracic epidural analgesia (TEA group) or intravenous lidocaine infusion (IL group) (1mg/kg/h) with PCA morphine for the first 48 hours after surgery. All patients received a similar ERP. The primary outcome was time to return of bowel function. Postoperative pain intensity, time out of bed, dietary intake, duration of hospital stay and postoperative complications were also recorded.

Results: Mean times and standard deviation (95% confidence interval) to first flatus (TEA, 24 ± 11 [19-29] h vs IL, 27 ± 12 [22-32] h) and to bowel movements (TEA, 44 ±19 [35–52] h vs IL, 43 ± 20 [34–51] h) were similar in both groups (P=0.887). TEA provided better analgesia in patients undergoing rectal surgery. Time out of bed and dietary intake were similar. Patients in the TEA and IL groups were discharged on median day 3 [interquartile range 3-4 days], P=0.744. Sixty percent of patients in both groups left the hospital on day 3.

Conclusion: Intra and postoperative INTRAVENOUS infusion of lidocaine in patients undergoing laparoscopic colorectal resection using an ERP had a similar impact on bowel function compared to thoracic epidural analgesia.

D.2 Introduction

Laparoscopic approach to colorectal surgery has been shown to accelerate dietary intake and return of bowel function[247], to facilitate post operative mobilization[248], to reduce the length of stay in hospital [247, 249], and to impact positively on postoperative mortality.[146, 247, 249, 250] In addition, it has been shown to be safe even for malignant lesions in a number of meta-analyses and systematic reviews.[247, 251, 252] Despite all the major benefits of laparoscopy, elective colorectal resection is still associated with a complication rate varying between 20 and 30% and a postoperative hospital stay of 7–10 days.[168]

The enhanced recovery program (ERP), or enhanced rehabilitation, also called fast-track program, was initially proposed over a decade ago in order to minimize the impact of surgical stress on postoperative morbidity and to accelerate the recovery process.[148, 168] This multidisciplinary approach was initially applied in patients undergoing colonic surgery and found to be feasible and safe. In several uncontrolled trials and subsequently in randomized studies the ERP had demonstrated significant reduction in hospital stay, with low readmission rate and low morbidity.[145, 148, 168]

Thoracic epidural analgesia (TEA) with local anesthetic agents has been shown to have a positive impact on bowel function after colorectal surgery either as a result of direct effect of neural blockade or for the anti-inflammatory properties of the local anesthetics. This beneficial effect of TEA has been consistently shown in either open[164, 169] or laparoscopic colectomy,[16] and therefore this technique, together with minimally invasive approach and ERP, has been considered an essential element to facilitate the recovery process.[165, 169]

More recently, there has been some interest in the use of intravenous (IV) lidocaine in abdominal surgery as a result of its analgesic, anti-hyperalgesic and anti-inflammatory effects.[21-23] Perioperative IV lidocaine has been shown to decrease post operative pain[23], to minimize the use of opioids, to facilitate the

earlier restoration of bowel function[21, 22] and to shorten the length of stay after colorectal surgery.[22]

Both TEA and IV lidocaine infusion have independently shown to be superior to systemic opioid analgesia with regard to various outcomes following open colorectal resection[180, 184], however there is a need to establish whether these two techniques are comparable when applied to laparoscopic colorectal surgery in the context of a standardized ERP.

The present randomized trial was designed to compare the effect of TEA and IV lidocaine infusion on the return of bowel function. It is hypothesized that intra and postoperative lidocaine would result a difference in postoperative restoration of bowel function compared with TEA in patients undergoing laparoscopic colorectal resection when an ERP is implemented.

D. 3 Methods

Patient selection

After approval by the Research Ethics Boards of the McGill University Health Centre (GEN06-023) and ClinicalTrials.gov (NCT01155440), a prospective randomized study in patients scheduled to undergo elective laparoscopic colorectal resection at the Montreal General Hospital was undertaken between July 2009 and June 2010. Patients, ASA I–III, greater than 18 years old were approached in the preoperative clinic and informed written consent obtained from each of them. Exclusion criteria were allergy to lidocaine, contraindication to have thoracic epidural analgesia, chronic treatment with opioid, inability to communicate in either French or English or to understand the purpose of the study, severe physical disability or metastatic carcinoma.

Anesthesia and Analgesia

No premedication was administered. All patients underwent general anesthesia. On the day of surgery and before the induction of general anesthesia, Patients were randomly assigned, using a computer-generated number sealed in a brown envelope, to two groups, epidural (TEA) and intravenous lidocaine (IL).

In the TEA group, and epidural catheter was inserted before induction of general anesthesia in either the eight or nine thoracic intervertebral space and lidocaine 2% 3 ml followed by bupivacaine 0.25% 5-10 ml were injected in the epidural space to produce a bilateral segmental sensory block to ice and pinprick between T4 and L3 dermatomes. The neural blockade was maintained during surgery with additional infusion of 5-8 ml/h of bupivacaine 0.25%. A continuous epidural analgesia with bupivacaine 0.1% and morphine 0.02 mg/ml was started in the post anesthesia care unit (PACU) and continued for 48 hours on the surgical ward. The segmental sensory block was assessed daily by the acute pain service (APS) team using ice and pinprick, and the infusion adjusted to maintain a bilateral sensory block between T7 and L3 (area of surgical incision) and pain intensity assessed by verbal rating scale (VRS), ranging from 0 (no pain) to 10 (worse possible pain) at

rest, on walking and on coughing. If the VRS at rest exceeded 4, the rate of epidural infusion was increased by increments of 1 cc to a maximum of 15 ml/h. No rescue analgesia with systemic morphine was used.

In the IL group, patients received, via a separate IV catheter, a bolus of lidocaine 1.5 mg/kg (maximum 100 mg) just prior to the induction of anesthesia, followed by an IV infusion of lidocaine 2 mg/kg/h for the whole surgical procedure. The infusion was then decreased to 1mg/kg/h in the PACU and continued for the first 48 postoperative hours. As a rescue analgesia, patients in the IL group received patient control analgesia (PCA) using IV morphine for 48 hours. The PCA was set up at 1-2 mg every 7 minutes with no background infusion, and was increased if the VRS at rest exceeded 4 at rest.

General anesthesia was induced in both groups with fentanyl 1.5 μg/kg and propofol 2 mg/kg, and orotracheal intubation was achieved with rocuronium. Intraoperative muscle relaxation was monitored with a neuromuscular nerve stimulator. Supplemental doses of 50 μg of fentanyl were administered if intraoperative blood pressure and heart rate were greater 25% baseline. Anesthesia was maintained with desflurane in a mixture of air 40% and O_2 60%, and end-tidal concentration of desflurane was adjusted to maintain Bispectral Index (BIS) within 40-60. Systolic arterial blood pressure was maintained within 20% of baseline values, and hypotension was treated with IV phenylephrine. A thermal blanket was positioned over the exposed parts of the body to maintain perioperative normothermia (T>36°C). All patients received an IV infusion of sodium chloride 0.9% at a rate of 6 ml/kg/h and 500 ml of plasma expander. Thirty minutes before termination of anesthesia, ketorolac 30 mg was given IV unless there was a contraindication (history of peptic ulcer or renal disease). Prevention of postoperative nausea and vomiting was achieved with droperidol 0.625 mg and dexamethasone 8 mg.

In both groups, multimodal analgesia included 500 mg of naproxen twice a day and acetaminophen 1g four times a day for up to 5 days. Both epidural and

lidocaine with PCA were discontinued 48 hours after surgery if VRS at rest was less than or equal to 4, and oral oxycodone 5-10 mg was then provided every 4 hours as a breakthrough medication. If the VRS at rest in both groups exceeded 4 at 48 hours after surgery, TEA or IL infusion was continued and VRS was reassessed every two hours.

Surgical care

Three experienced laparoscopic surgeons (BS, SL, and PC) performed all the procedures. All patients were same day admission. Mechanical bowel preparation was used for all sigmoid and rectal procedures. Cefazolin 2 g and metronidazole 500 mg were administered 30 min before induction of anesthesia. Antiembolic stockings were applied before positioning patients on the operating table, and unfractionated heparin 5,000 units was injected sc one hour into the surgery.

Laparoscopy was achieved using a 12 mm untipped Hasson cannula inserted under direct vision into the peritoneal cavity through a small vertical infra-umbilical incision to establish the pneumoperitoneum, which was maintained with carbon dioxide insufflation to a pressure of 12 mmHg. This incision was later extended to 4-5 cm to deliver the colon or sigmoid for resection and reanastomosis. Three additional 5-mm trocars were inserted under laparoscopic vision. For right and left colectomy, the colon was completely mobilized laparoscopically and the blood vessels divided intracorporeally. The resection and anastomosis was performed extracorporeally. For rectal resections, the anastomosis was completed extracorporeally through a 10 cm horizontal incision and using the double-shaped end-to-end anastomotic circular stapling technique. Nasogastric tube and abdominal drains were not used.

The Enhanced Recovery Program started to be implemented in 2008 in this institution and the major components of this perioperative program are composed of preoperative education, reduction of unnecessary bowel preparation and preoperative fasting, surgical stress reduction, avoidance of excess IV fluid infusion, early remove nasogastric tube, urinary catheter and other drains, early

oral intake and mobilization encouragement; which have been previously described.[168]

Outcome measures

All the postoperative data was collected daily by the research assistant unaware of the hypothesis. During the first three postoperative days, the research assistant would collect data from the patients' diary and from the patients' medication record. The APS and the ward nurses followed the clinical pathway has set up by the ERP.

The primary outcome was time to return of bowel function as measured by time (h) from the end of surgery to passage of flatus and bowel movements. The secondary outcome measure was quality of postoperative analgesia, as assessed by VRS at rest, on walking and on coughing at 24, 48 and 72 hours after an operation. Intermediate outcomes included, time to first fluid intake and full diet, time out of bed either sitting or walking, incidence of nausea and vomiting, duration of hospital stay defined as time spent in the hospital from the day of admission to the day of hospital discharge, incidence of medical and surgical complications, and readmission rate.

Complications were defined as follows: ileus as abdominal distension, no flatus or bowel movement or nausea/vomiting which prevents oral intake or requires therapeutic use of nasogastric tube. Urinary retention was failure to pass urine requiring insertion of urinary catheter. Surgical complications were categorized as anastomotic leak, intra-abdominal collection diagnosed by clinical or radiology, bowel obstruction and wound infection.

Statistical analysis

The two interventions, TEA and lidocaine infusion, have previously been shown to be superior to parenteral morphine in the colorectal surgery population and, therefore, it was decided not to include the parenteral morphine group as a control group.

The sample size was calculated base on the results previously published in patients undergoing laparoscopic colorectal resection using ERP setting. The average time to return of bowel movements in the epidural subgroup of the Basse study was 48 ± 20 hours while in the lidocaine subgroup of Kaba study, it was 32 ± 19 h. Twenty-five subjects in each group were sufficient to demonstrate a difference in time to return of the bowel movement with a type-1 error of 0.05 and a power of 80%. The number was increased to 30 patients to include dropouts.

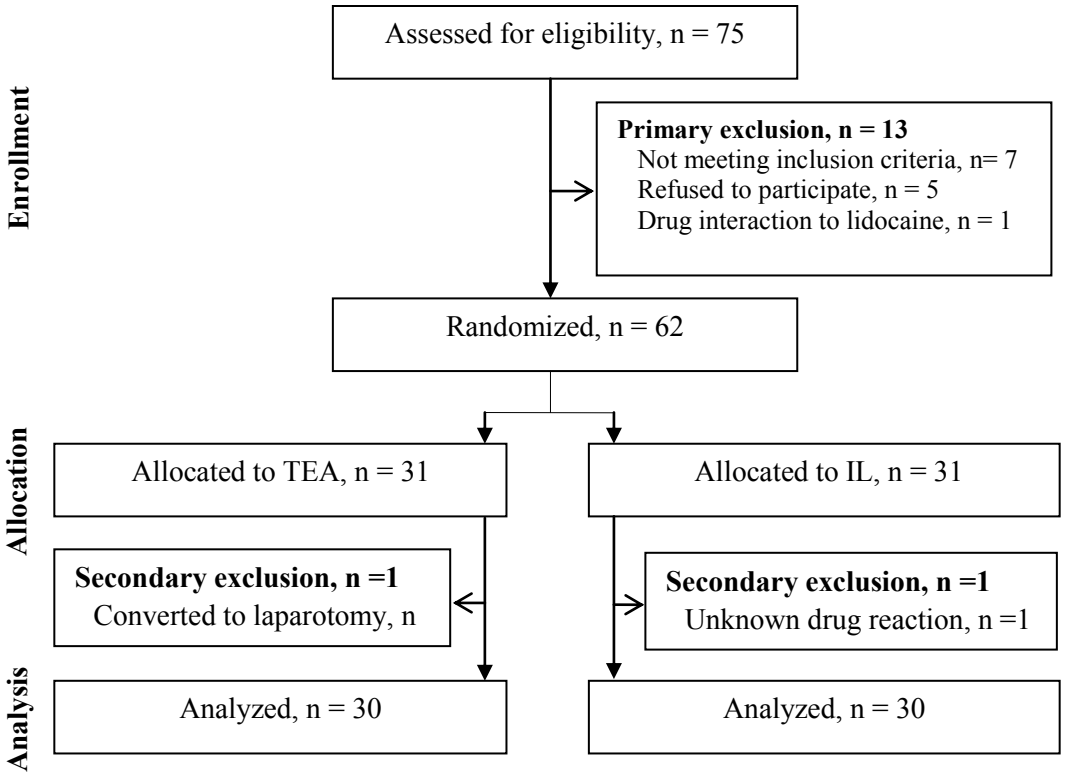
Data was collected on the standard forms and entered into a private computer database. Categorical variables were analyzed by X^2 test and Fisher's exact test. Continuous variables are presented as mean ± standard deviation (SD) [95% confidence interval, CI] or median and interquartile range (IQR) and when data was not normally distributed, and were compared between groups using either a two-tailed Student's t test or the Mann-Whitney U test. All statistical tests were two tailed at the significant level of 0.05. Statistic analysis was performed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL).

D.4 Results

Patient selection

A total of seventy-five eligible patients was enrolled in this study. Seven patients did not meet study criteria, five patients refused to participate, and drug interaction with lidocaine led to exclusion of one patient. Thus, sixty-two patients were randomized and assigned equally to both groups. Two patients had to be excluded from final analysis, one in the TEA group for conversion to laparotomy, and one patient in the IL group for unknown drug reaction (**Figure 2**).

Figure 2 Study design according to the CONSORT diagram showing the flow of participants through each stage of a randomized trial



TEA = thoracic epidural analgesia; IL = intravenous lidocaine.

The demographic characteristics and the clinical data of the two groups were similar (**Table 3**). The diagnosis, type of surgery, need of ileostomy and co-morbidities were equally distributed in both groups.

Table 3 Demographic characteristics and clinical data of two studied groups

	TEA (n=30)	**IL (n=30)**
Age (years)	61 ± 15	58 ± 16
Sex (M/F)	19/11	19/11
Weight (kg)	74 ± 15	80 ± 20
BMI ($kg \bullet m^{-2}$)	26 ± 4	28 ± 7
ASA I/ II/ III	12/14/4	9/20/1
Diagnosis		
Cancer	21 (70%)	17 (57%)
Polyps	6 (20%)	5 (16%)
Diverticular disease	1 (3%)	2 (7%)
Inflammatory Bowel Disease	2 (7%)	6 (20%)
Type of surgery		
Right hemicolectomy	10(33%)	9 (30%)
Left hemicolectomy	3 (10%)	4 (13%)
Sigmoid resection	2 (7%)	4 (13%)
Anterior resection	7 (23%)	3 (10%)
Low anterior resection	6 (20%)	6 (20%)
Proctocolectomy	2 (7%)	4 (14%)
With ileostomy	8 (27%)	9 (30%)
Co-morbidity		
Hypertension	9 (30%)	10 (33%)
Diabetes	4 (13%)	0 (0%)
Coronary artery disease	3 (10%)	1 (3%)
Dyslipidemia	2 (7%)	3 (10%)
Asthma	2 (7%)	1 (3%)
Atrial fibrillation	2 (7%)	0 (0%)
Anemia	1 (3%)	1 (3%)
Obstructive sleep apnea	1 (3%)	1 (3%)
Chronic obstructive pulmonary disease	1 (3%)	0 (0%)

Data is presented as absolute number (%) or mean ± standard deviation. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; BMI = body mass index; ASA = American Society of Anesthesiologists.

There were no differences in intraoperative opioid consumption, BIS, end-tidal desflurane concentration, amount of IV fluid replacement and blood loss, duration of surgery and number of patients who have episodes of hypotension and vasopressor use (**Table 4**). Hypotension is defined as decreasing in blood pressure below baseline more than ten minutes. No patients showed signs of lidocaine toxicity in the postoperative period.

Table 4 Intraoperative data

	TEA (n=30)	**IL (n=30)**	**P value**
Fentanyl consumption (mcg)	208 ± 60	235 ± 40	0.104
Bispectral index (BIS)	44 ± 7	44 ± 6	0.992
End tidal desflurane (%)	4.7 ±0.8	5 ± 0.9	0.343
Fluid resuscitation (L)	1.7 ± 0.6	1.9 ± 0.7	0.223
Estimated blood loss (ml)	308 ± 108	285 ± 119	0.662
Duration of surgery (min)	213 ± 90	220 ± 78	0.739
Number of patients with hypotension	4 (13%)	4 (13%)	1.000
Number of patients using vasopressor	5 (17%)	6 (20%)	0.739

Data is presented as mean ± standard deviation or absolute number (%). TEA = thoracic epidural analgesia; IL = intravenous lidocaine.

Postoperative gastrointestinal function

Postoperative return of bowel function, passage of flatus and bowel movements, showed similar results in the both TEA and IL groups (**Table 5**). Time to return of flatus was significantly faster in the subgroup who had primary rectal anastomosis compared with those who had primary colonic anastomosis (20 ± 9 [24-32] hours vs 28 ± 11 [14-26] h, P = 0.032). There was no difference in return of bowel movements between these two subgroups.

Table 5 Time to return of bowel function

Primary anastomosis	**TEA (n=22)**	**IL (n=21)**	**P value**
Time to first flatus (h)	24 ± 11 [19-29]	27 ± 12 [22-32]	0.380
Time to first bowel movement (h)	44 ± 19 [35-52]	43 ± 20 [34-52]	0.887
Primary ileostomy	**TEA (n=8)**	**IL (n=9)**	**P value**
Time to first flatus (h)	25 ± 14 [13-36]	28 ± 17 [15-42]	0.614
Time to first bowel movement (h)	39 ± 23 [19-58]	36 ± 17 [23-49]	0.794

Data is presented as mean ± standard deviation [95% confidence interval].
TEA = thoracic epidural analgesia; IL = intravenous lidocaine.

Postoperative pain relief and analgesic medication

Data on postoperative VRS pain at rest, on walking and on coughing are presented in **Table 6** for the colonic and the rectal resections. Although the two subgroups undergoing colonic resection were similar, there was a significant less pain in the TEA group at rest and on walking. Epidural catheter and PCA morphine were used for the first two postoperative days and stopped on the morning of the postoperative day 2. Epidural failure occurred in one patient within the first 24 h, and the epidural catheter was reinserted in the PACU and an adequate quality of analgesia was achieved. The consumption of morphine was recorded for each postoperative day during the first two days after surgery. In the TEA group, the median consumption of epidural morphine for the first and second 24 hours was 3.8 [3.3-4.9] mg and 2.9 [2.0-3.5] mg respectively. In the IL group, IV morphine for the same period of time was 25.5 [17-41] and 8.5 [0 -31] mg respectively. On postoperative day 3, the median value of oral oxycodone was 27.5 [20-35] mg for the TEA group and 20.0 [20-32] mg for the IL group (P = 0.434).

Table 6 VRS pain at rest, on walking and on coughing in the colon and rectal subgroups

Colon	**TEA (n=15)**	**IL (n=17)**	**P value**
VRS at rest			
At 24 h	2 [0-3]	2 [0-2]	0.556
At 48 h	0 [0-2]	0 [0-2.5]	0.789
At 72 h	1 [0-2]	1 [0-1.5]	0.426
VRS on walking			
At 24 h	2 [1-3]	3 [2-4]	0.210
At 48 h	2 [0-2]	3 [0.5-4]	0.104
At 72 h	1 [0-3]	1 [0-3]	0.798
VRS on coughing			
At 24 h	4 [2-5]	4 [3-5]	0.969
At 48 h	3 [1-4]	4 [1-5]	0.219
At 72 h	2 [0-3]	2 [0-4]	0.344
Rectal	**TEA (n=15)**	**IL (n=13)**	**P value**
VRS at rest			
At 24 h	0 [0-2]	3 [1.5-3]	***0.023***
At 48 h	0 [0-2]	3 [1-3]	***0.008***
At 72 h	2 [0-2]	2 [1-2.5]	0.248
VRS on walking			
At 24 h	2 [0-4]	4 [2.5-5]	0.207
At 48 h	2 [0-2]	4 [2.5-5.5]	***0.032***
At 72 h	1 [0-3]	3 [1.5-4.5]	***0.028***
VRS on coughing (cm)			
At 24 h	5 [0-6]	4 [1.5-6]	0.944
At 48 h	4 [0-4]	4 [2.5-6]	0.227
At 72 h	2 [1-5]	4 [2.5-5]	0.149
Morphine consumption (mg)	**via epidural (n=30)**	**via PCA (n=30)**	**P value**
At 24 h	3.8 [3.3-4.9]	25.5 [17-41]	-
At 48 h	2.9 [2.0-3.5]	8.5 [0 -31]	-
Oral oxycodone (mg)			
At 72 h	27.5 [20-35]	20.0 [20-32]	0.434

Data is presented as median [interquartile range]. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; VRS = verbal rate scale (0-10).

Postoperative clinical data, incidence of complications and readmission

There was no difference between the two groups in the time to the first fluid and full dietary intake, time out of bed either sitting or walking over the first 3 postoperative days (**Table 7**). Readiness for discharge and length of hospital stay were also similar. Postoperative nausea and vomiting occurred in both groups with the same incidence. There was a higher incidence of urinary retention in the TEA group, but similar number of medical and surgical complications.

Table 7 Clinical data of postoperative period

	TEA (n=30)	**IL (n=30)**	**P value**
Time to first drink (h)	4.25 [3-6]	3.75 [2-6]	0.252
Time to first full diet (h)	35 [22-51]	38 [22-46]	0.894
Time sitting out of bed (min)			
Day 1	90 [28-135]	120 [27-240]	0.603
Day 2	83 [28-300]	120 [30-360]	0.528
Day 3	125 [30-338]	120 [30-375]	0.801
Time walking out of bed (min)			
Day 1	10 [2 -15]	9 [3 -15]	0.788
Day 2	25 [10-40]	15 [10-46]	0.870
Day 3	30 [12-60]	30 [14-60]	0.817
Readiness to discharge (days)	3 [3-4]	3 [3-4]	0.534
Hospital stay (days)	3 [3-4]	3 [3-4]	0.744
Nausea	17 (57%)	11 (37%)	0.438
Vomiting	18 (60%)	12 (40%)	0.791
Postoperative complications in hospital			
Urinary retention	3 (10%)	0 (0%)	0.076
Ileus	2 (7%)	6 (20%)	0.129
Bleeding per rectum	1 (3%)	0 (0%)	0.313
Exudate from stoma	0 (0%)	1 (3%)	0.313
Other medical complications	2 (7%)	1 (3%)	0.554

Data is presented as median [interquartile range] or absolute number (%). TEA = thoracic epidural analgesia; IL = intravenous lidocaine.

The distribution of duration of hospital stay is presented in **Figure 3**. Sixty percent of patients in each group were discharged home on postoperative day 3 and 80% on day 4, with the maximum duration of hospital stay of nine days in both groups. The reasons for hospital discharge beyond postoperative day 3 are presented in **Table 8.**

Figure 3 Distribution of duration of hospital stay

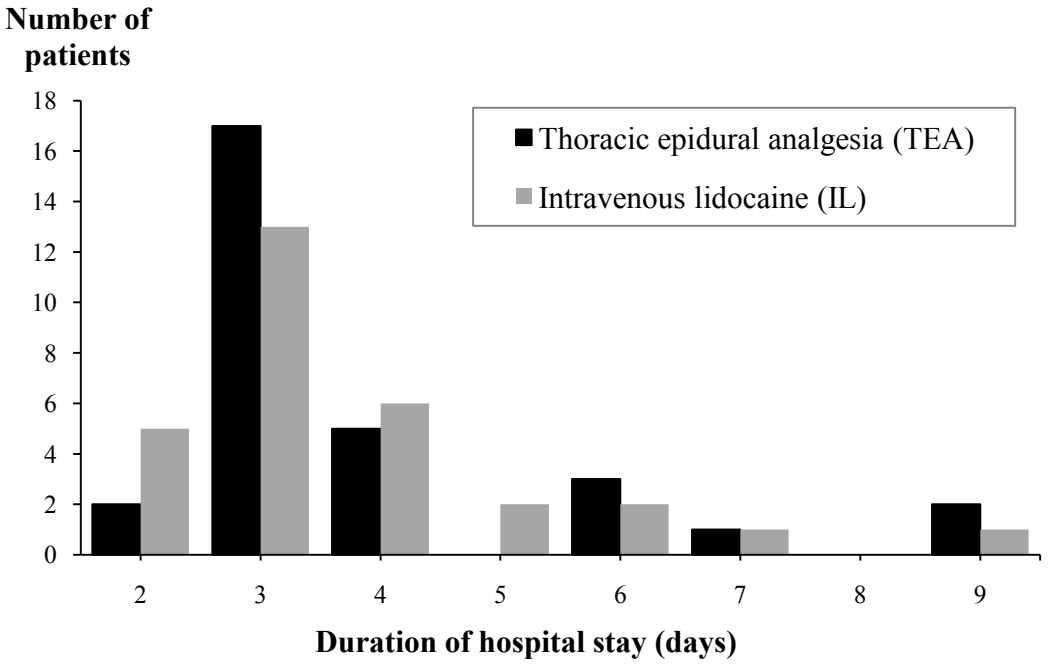


Table 8 Reasons for hospital discharge beyond postoperative day 3

TEA	Age	Sex	BMI	ASA	Diagnosis	LOS	Reason for delayed discharge
Right hemicolectomy	24	M	25	1	Polyp	4	Social reason
Sigmoid resection	60	F	14	1	Cancer	4	Urinary retention
Anterior resection	71	M	33	3	Cancer	4	Urinary retention
Low anterior resection	73	M	24	2	Cancer	4	Social reason
Anterior resection	48	M	28	1	Cancer	4	Social reason
Right hemicolectomy	64	M	33	1	Cancer	6	Urinary retention
Right hemicolectomy	78	F	23	2	Polyp	6	Bleeding per rectum
Sigmoid resection	60	F	28	2	Cancer	6	Chest pain
Low anterior resection	83	M	27	3	Polyp	7	Asthmatic attack
Low anterior resection	71	M	28	2	Cancer	9	Ileus
Proctocolectomy	63	F	21	2	IBD	9	Ileus

TEA = thoracic epidural analgesia; BMI = body mass index; ASA = American Society of Anesthesiologists; LOS = length of hospital stay after the operation; IBD = inflammatory bowel disease.

Table 8. Reasons for hospital discharge beyond postoperative day 3 (Continue)

IL	Age	Sex	BMI	ASA	Diagnosis	LOS	Reason for delayed discharge
Left hemicolectomy	52	M	31	1	Polyp	4	Ileus
Sigmoid resection	45	M	52	2	Cancer	4	Social reason
Anterior resection	46	F	20	1	Diverticulitis	4	Ileus
Low anterior resection	78	M	26	2	Cancer	4	Social reason
Low anterior resection + ileostomy	73	M	40	2	Cancer	4	Exudate from stoma
Low anterior resection + ileostomy	86	F	24	2	Cancer	4	Social reason
Left hemicolectomy	57	M	24	1	Diverticulitis	5	Ileus
Low anterior resection	56	F	28	1	Cancer	5	Social reason
Right hemicolectomy	68	M	29	2	Cancer	6	Ileus
Left hemicolectomy	76	M	27	2	Cancer	6	Hypertension
Proctocolectomy + ileostomy	51	M	28	2	IBD	7	Ileus
Proctocolectomy	68	F	28	2	IBD	9	Ileus

IL = intravenous lidocaine; BMI = body mass index; ASA = American Society of Anesthesiologists; LOS = length of hospital stay after the operation; IBD = inflammatory bowel disease.

Readmission occurred in seven patients (23.3%) in both TEA and lidocaine groups (**Table 9**). The highest incidence of complication was anastomotic leak which occurred in six patients, three patients had CT-guided drainage for releasing intra-abdominal collection, two patients were re-operated and the other patient received conservative treatment because of the small amount of intra-abdominal collection. Four patients having small bowel obstruction were treated by conservative treatment. Two patients revisited the hospital with abdominal pain and were treated conservatively, and no evidence of anastomotic leak was found. The rate of readmission in the two groups was similar, however, the duration of hospital stay during the readmission period was longer in the IL group ($P = 0.053$).

Table 9 Clinical data of readmission to hospital

	Age	Sex	BMI	ASA	Diagnosis	LOS[1]	Readmission		
							Reason for readmission	POD	LOS[2]
TEA									
Right hemicolectomy + ileostomy	64	M	33	1	Cancer	6	Anastomotic leak	9	12
Right hemicolectomy	77	M	29	2	Polyp	3	Urinary retention	3	2
Right hemicolectomy	64	M	30	1	Cancer	3	Anastomotic leak	17	2
Anterior resection	65	M	29	3	Cancer	3	Bleeding per wound	5	0
Low anterior resection	83	M	27	3	Polyp	7	Anastomotic leak	6	2
Proctocolectomy + ileostomy	22	M	22	1	Polyp	4	Small bowel obstruction	5	4
Proctocolectomy + ileostomy	63	F	21	2	IBD	9	Anastomotic leak	4	0
IL									
Right hemicolectomy	21	F	18	2	IBD	3	Anastomotic leak	5	2
Left hemicolectomy	57	M	24	1	Diverticulitis	5	Anastomotic leak	4	19
Sigmoid resection	59	M	24	2	Cancer	4	Anastomotic leak	2	29
Anterior resection + ileostomy	76	M	26	3	Cancer	4	Small bowel obstruction	2	11
Low anterior resection + ileostomy	53	M	34	2	Cancer	3	Anastomotic leak	4	12
Proctocolectomy + ileostomy	41	M	34	1	IBD	3	Small bowel obstruction	17	3
Proctocolectomy + ileostomy	51	M	28	2	IBD	7	Small bowel obstruction	3	5

Data is presented as absolute number. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; BMI = body mass index; ASA = American Society of Anesthesiologists; LOS[1] = length of hospital stay after the operation; LOS[2] = length of hospital stay after readmission; POD = the interval (days) between first discharge from hospital and readmission; IBD = inflammatory bowel disease.

D.5 Discussion

The results of this prospective randomized study demonstrated showed that, when the ERP was implemented, the average return of bowel movement after laparoscopic surgery was within the first 48 hours with no difference between IV lidocaine and TEA. In addition, duration of hospital stay and rate of readmission were similar with these two techniques.

During the past two decades, laparoscopic approach to colorectal surgery has gained more popularity due to better short- and long-term outcomes. A meta-analysis published in 2006,[248] and subsequently confirmed more recently by a systematic review and meta-analysis,[247, 252] showed that laparoscopy for colorectal cancer resulted in a faster return of bowel movement by 0.6 to 1.3 days, less postoperative pain thus facilitating a shorter hospital stay by approximately two days when compared with open surgery.[248] In addition, there was no increase in the rate of surgical complications and oncology outcome.[251] However, at scrutiny, return of bowel movement was still over 72 hours[248, 250, 252] with an average postoperative hospital stay of at least 7 days.[168, 248, 250]

TEA has been shown in open colorectal surgery not only to have superior analgesic effect over systemic morphine, but also to significantly accelerate the recovery of bowel function by 1 to 2 days.[164-166] It had also been the case when the laparoscopic approach was used, however the benefits of TEA on accelerating the return of bowel function have not been consistent. In some studies the use of TEA was shown to be beneficial as it provided excellent analgesia and shortened the return of bowel function[16, 17], but this was not the case in an earlier study which did not report a significant difference with parenteral morphine.[14] It has to be said that the two former studies did not incorporate in their practice an ERP, and this might explain their results. It appears therefore that when the ERP is part of the surgical care, the effects of TEA on dietary intake and bowel function are less evident. This is the case with the findings reported in 4 studies[14, 146, 167, 168] where laparoscopy, TEA and ERP positively influenced the length of hospital

stay, the return of bowel function and the quality of analgesia. Similarly, pain scores were significant lower[14, 17] and return of bowel movements occurred within two days after surgery in the ERP setting.[17, 167]

In the present study the median time to return of bowel movements and duration of hospital stay in both TEA and lidocaine groups were 44 hours and 3 days respectively, and similar to those reported by others.[14, 17, 167] These findings would imply that, although TEA appears to be an important component facilitating the recovery process after bowel surgery, the analgesic technique of IV lidocaine could provide similar benefits and a equivalent return in bowel function.

Intravenous lidocaine has been shown to have analgesic, anti-hyperalgesic and anti-inflammatory properties which can attenuate the excessive inflammatory response associated with visceral surgery.[21-23] Although the exact mechanism is not known, it seems that lidocaine targets different steps within the inflammatory cascade, such as intracellular G-protein coupled receptors, complement and pro inflammatory cytokines[21, 172] thus blocking neural transmission at the site of tissue injury. Perioperative and postoperative IV lidocaine has been shown to provide adequate postoperative pain relief with a significant decrease in opioid consumption following major abdominal surgery.[23] In the present study, the overall quality of analgesia was similar in those patients undergoing colonic resection; however it was not the case in patients with rectal resection. This might be explained by the use of an 8 cm sub-umbilical incision with greater nociception, perhaps, than produced by the 4-5 cm incision in the group without rectal anastomosis.

The beneficial effect of IV lidocaine on bowel function in patients undergoing elective open colorectal surgery has been reported in several studies in non ERP and ERP settings.[21, 22] In both instances the use of lidocaine was associated with faster return of bowel function and shorter hospital stay.[21] More recent data in colon surgery using a laparoscopic approach and an ERP have shown that IV lidocaine improved postoperative analgesia and bowel function compared with

placebo. The benefits were associated with a significant reduction in hospital stay (2 [2-3] vs 3 [3-4] days; $P = 0.001$).[22] These findings are to some extent confirmed in the present study with similar length of hospital stay even though the population in this study was composed of over 70% of cancer and 50% of all resections were rectal surgery.

ERP, also called accelerated recovery strategy or fast-track, was introduced in the mid nineties as a coordinated multidisciplinary perioperative care plan aimed to reduce postoperative complications and to allow a faster recovery of daily activities.[17] This approach included the following: revision of the traditional perioperative care, optimization of anesthetic and analgesic techniques, improved knowledge of perioperative organ dysfunction and minimally invasive surgery.[148, 168] All the major components of the ERP such as surgical stress reduction, avoidance of excess IV fluid infusion, earlier oral intake and encouraged mobilization, have independently been shown to impact positively on patient outcome,[145, 148, 168] and when combined, they have lead to a significant reduction in length of hospital stay, down to 3-5 days after open colorectal surgery[58] and to 2-4 days after laparoscopic surgery.[146, 168] Also return to normal activities was shown to be accelerated.[146]

Although the average readiness for discharge in the present study was 3 days, only 60% of all patients left the hospital on day 3 and this was independent of the analgesia group. As reported in table 7, 11 (18%) patients left on day 4 for reasons not strictly related to the surgical technique, such social reason and ileus, thus potentially amenable to modifications. The in hospital complication rate was similar in both groups averaging 26%.

Readmission rate was 23% with no difference between the two groups. Fifty-seven percent of the readmissions occurred in patients who has rectal surgery, and this is in agreement with the literature indicating a higher number of readmissions in this subgroup.[146, 168] Nine out of 14 patients (64 %) were readmitted within the first 5 days after discharge, and 43% stayed for less than 3 days. Except for one,

all reasons for readmission were surgically related, and only two patients were re-operated. These findings would indicate that perhaps some of the readmissions could have been avoided if patients were kept in hospital longer.[151]

Previous authors have commented on the difficulty to achieve sufficient adherence to the principles of the ERP, particularly in the postoperative period.[253] In the present study while return to oral dietary intake was achieved within a time-frame in over 70% of patients, few were able to mobilize out of bed effectively and for long period of time. Yet, the ability to ambulate independently is part of the discharge criteria. Preliminary attempts to introduce validated walking tests to assess functional capacity in surgical populations have indicated that these tests can be used to determine the impact of analgesia and can predict long term outcome. [25, 254] Therefore, there is a need to identify if these measures of functional outcome in the colorectal surgery population beside hospital length of stay and return of bowel function are clinically meaningful when assessing the safety of a clinical pathway.

There are some limitations associated with this study. Presence of a control group receiving PCA morphine would have facilitated the comparison of the two interventions vs what is considered standard practice in laparoscopic surgery. However, there is published evidence demonstrating the superiority of the two interventions vs systemic morphine. Because of different design and patient population studied it was difficult to hypothesize which of these two techniques, epidural or IV lidocaine would have had a greater impact on return of bowel function.

The definition and management of ileus were not standardized in the present study and these might imply that the incidence of ileus was greater than 12% reported. Recently a classification of ileus has been proposed and efforts should be made to report this important complication in a more systematic fashion.[255]

In conclusion, the findings of this study demonstrate that, in the context of an ERP, perioperative IV infusion of lidocaine has the same impact on postoperative

restoration of bowel function as TEA, with equal incidence of complications and duration of hospital stay. In addition, it can be said that IV lidocaine can be safely used instead of epidural analgesia in patients undergoing laparoscopic colorectal resection.

E. Summary of study 1 and introduction to study 2

In the first part of this thesis, I have investigated the impact of perioperative intravenous infusion of lidocaine on some of the surgical outcomes following laparoscopic colorectal surgery in the context of ERP. The findings demonstrated that perioperative lidocaine compares favourably to TEA with regard to return of bowel function. The two techniques had equal incidence of complications, readmission and duration of hospital stay. However, epidural provided better postoperative analgesia, and in particular in rectal surgery.

Since an association between quality of analgesia and postoperative functional recovery might exist, I would like to determine the impact of intravenous lidocaine on measures of short-term and long-term functional recovery. As such I intend to compare three analgesic techniques, TEA, PCA and intravenous lidocaine.

F. Short-term functional outcomes after laparoscopic colorectal resection. Comparison of analgesic techniques

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Registration number: NCT00982618 (http://www. clinicaltrials.gov)

F.1 Abstract

Background and Objective: Intravenous lidocaine infusion has been shown to facilitate the postoperative immediate functional walking capacity compared with placebo in patients undergoing laparoscopic prostatectomy. This study compared the effect of perioperative and postoperative infusion of intravenous lidocaine with thoracic epidural analgesia and systemic opioid on postoperative walking capacity and health-related quality of life in patients undergoing laparoscopic colorectal resection using an ERP.

Methods: Ninty patients scheduled for elective laparoscopic colorectal surgery were prospectively randomized to receive thoracic epidural analgesia (TEA group) or intravenous lidocaine infusion (IL group) or patients-controlled analgesia morphine (PCA group) for the first 48 hours after surgery. All patients received a similar protocol based on the ERP used in this institution. The primary outcome was functional walking capacity 3 weeks after surgery. Postoperative health-related quality of life and postoperative fatigue, pain intensity and duration of hospital stay were also recorded.

Results: Postoperative median functional walking capacity (TEA, 416 [355-462] m vs IL, 420 [372-444] m vs PCA, 400 [340-445] m) were the same as preoperative values and were similar in the three groups (P = 0.737). Health-related quality of life in term of physical functioning and postoperative fatigue were impaired at 3 weeks after surgery with no difference in the three techniques. Postoperative pain was similar in the three groups. Patients in the three groups were discharged on median day 3 [3-4] days, P = 0.885.

Conclusion: Perioperative and postoperative intravenous infusion of lidocaine in patients undergoing laparoscopic colorectal resection using an ERP had a similar impact on postoperative functional walking capacity compared to thoracic epidural analgesia and systemic opioid.

F.2 Introduction

Postoperative recovery is an important outcome after surgery. There are various indicators to reflect postoperative recovery after colorectal surgery. Surgical outcomes have traditionally been reported in terms of postoperative return of bowel function, postoperative pain score, use of pain medication, length of hospital stay and complication rate.[256] However the above mentioned outcomes are meaningful to the surgeon, but do not directly reflect the state of health of patients and their recovery. As shown in the proposed model for surgical recovery, both physiologic and systemic changes such as pain, fatigue, muscle weakness, sympathetic hyperactivity immediately occur after surgery and may affect the short-term functioning such as the ability to mobilize and perform basic activities of daily living (ADLs).[207] One of the most common measurements is the capacity for walking and a walk test, the six-minute walk test (6MWT), can be used to assess this capacity. 6MWT was validated to be a measure of surgical recovery in colorectal resection, and reflect mobility and be related to the ability to perform ADLs.[218, 257]

Although many surgical outcomes have been shown to improve following intravenous lidocaine infusion in the setting of laparoscopic colorectal surgery and ERP setting,[21, 22, 24, 178, 258] only few studies have been conducted about functional recovery associated with intravenous lidocaine,[25] and none of them have been compared with other techniques.

To address these issues, this prospective randomized controlled trial was designed to analyze the effect of intraoperative and postoperative lidocaine infusion on the postoperative functional walking capacity, quality of life and postoperative fatigue and compare with thoracic epidural analgesia and patient-controlled analgesia techniques, using the surgical model of laparoscopic colorectal surgery and within the context of the ERP. It was hypothesized that lidocaine infusion would provide a difference in the capacity to mobilize from epidural analgesia and systemic opioid, thus promoting better quality of life and reducing postoperative fatigue at 3 weeks after operation.

F.3 Methods

Patient selection

The study was approved by the Research Ethics Boards of the McGill University Health Centre (Gen06–023) and written informed consent was signed by all patients. The study was registered at ClinicalTrials.gov (NCT00982618), and conducted between July 2009 and November 2010. Patients undergoing elective laparoscopic colorectal resection at the Montreal General Hospital aged more than 18 years and ASA I–III were eligible. Exclusion criteria were allergy to lidocaine, contraindication to have thoracic epidural analgesia, chronic treatment with opioid, inability to communicate in either French or English or to understand the purpose of the study, severe physical disability making patients unable to walk, or metastatic cancer. Following at the preoperative clinic, the 2MWT, 6MWT, SF-36 and ICFS were completed to be a baseline.

Anesthesia and Analgesia

On the day of surgery and before the induction of general anesthesia, patients were randomly assigned, using a computer-generated number sealed in brown envelopes, to three groups, epidural (TEA), intravenous lidocaine (IL) and patient control analgesia (PCA).

Upon arrival in the operating theatre, all patients underwent general anesthesia and no premedication was administered. Baseline values of blood pressure, heart rate and oxygen saturation were recorded. General anesthesia was induced with fentanyl 1.5 μg/kg and propofol 2 mg/kg and orotracheal intubation was achieved with rocuronium. Intraoperative muscle relaxation was monitored with a neuromuscular nerve stimulator. Supplemental doses of 50 μg of fentanyl were administered if intraoperative blood pressure and heart rate were greater 20% baseline. Anesthesia was maintained with desflurane in a mixture of air 40% and oxygen 60%, and end-tidal concentration of desflurane was adjusted to maintain Bispectral Index (BIS) within 40-60. Systolic arterial blood pressure was maintained within 20% of baseline values, and hypotension was treated with

intravenous (IV) phenylephrine. A thermal blanket was positioned over the body to maintain intraoperative normothermia (T>36°C). All patients received an IV infusion of sodium chloride 0.9% at a rate of 6 ml/kg/h and 500 ml of plasma expander. Thirty minutes before termination of anesthesia, ketorolac 30 mg was given IV unless there was a contraindication. All patients received dexamethasone 8 mg and droperidol 0.625 mg to prevent postoperative nausea and vomiting.

In the TEA group, epidural catheter was inserted before induction of general anesthesia in either the eight or nine thoracic intervertebral space and lidocaine 2% 3 ml followed by bupivacaine 0.25% 5-10 ml were injected in the epidural space to produce a bilateral segmental sensory block to ice and pinprick between T4 and L3 dermatomes. The neural blockade was maintained during surgery with additional infusion of 5-8 ml/h of bupivacaine 0.25%. A continuous epidural analgesia with bupivacaine 0.1% and morphine 0.02 mg/ml was started in the post anesthesia care unit (PACU) and continued for 48 hours on the surgical ward. The segmental sensory block was assessed daily by the acute pain service (APS) team using ice and pinprick, and the infusion adjusted to maintain a bilateral sensory block in the area of surgical incision and pain intensity assessed by verbal rating scale (VRS), ranging from 0 (no pain) to 10 (worse possible pain) at rest, on walking and on coughing. If the VRS at rest exceeded 3, the rate of epidural infusion was increased by increments of 1 cc to a maximum of 15 ml/h. No rescue analgesia with systemic morphine was used.

In the IL group, patients received a bolus of lidocaine 1.5 mg/kg (maximum 100 mg) before the induction of anesthesia, followed by an IV infusion of lidocaine 2 mg/kg/h for the whole surgical procedure via a separate IV catheter. The infusion was then decreased to 1mg/kg/h in the PACU and continued for the first 48 postoperative h. As a rescue analgesia, patients received patient control analgesia (PCA) using IV morphine for 48 h. The PCA was set up at 1-2 mg every 7 min with no background infusion, and was increased if the VRS at rest exceeded 3.

In the PCA group, patients received neither epidural catheter nor intravenous lidocaine during intraoperative and postoperative period. As a postoperative analgesia, patients received PCA morphine using the same setting as patients in IL group for 48 hours.

Epidural, lidocaine and PCA were discontinued 48 hours after surgery if VRS at rest was < 4, and then oral oxycodone 5-10 mg was provided every 4 hours as breakthrough medication. All patients recieved multimodal analgesia included 500 mg of naproxen twice a day and acetaminophen 1g four times a day for up to 5 days.

Surgical care

All operations were performed using a standard laparoscopic technique with infiltration of bupivacaine 0.25% with adrenaline 1:200 000 at the trocar entry ports by three experienced laparoscopic surgeons (BS, SL, and PC). All patients were same day admission. Bowel preparation was used only for sigmoid and rectal procedures. Cefazolin 2 g and metronidazole 500 mg were administered 30 min before surgical incision. Antiembolic stockings were applied and unfractionated heparin 5,000 units was injected sc one hour after the insertion of the epidural catheter.

All patients were enrolled in the Enhanced Recovery Program which was implemented in this institution in 2008 and the major components of this perioperative program included preoperative education, reduction of unnecessary bowel preparation and preoperative fasting, surgical stress reduction, avoidance of excess IV fluid infusion, early remove nasogastric tube, urinary catheter and other drains, early oral intake and encouraged mobilization; which have been previously described.[168]

Outcome measures

Demographic data, BMI, American Society of Anesthesiology classification, comorbidities, type of surgery and operation were collected. The intraoperative and immediate postoperative data was also recorded: operative time, estimated

blood loss, fluid resuscitation, intraoperative and postoperative opioid consumption, time out of bed either sitting or walking, duration of hospital stay, early complication (<30 days) incidence of medical and surgical complications and readmission rate. Some specific complications were defined as follows: 1.ileus characterized by abdominal distension, absence of flatus or bowel movement, or nausea/vomiting which prevented oral intake or required therapeutic use of nasogastric tube; 2.urinary retention as failure to pass urine with and bladder volume over 600 ml (as per bladder scanner) requiring insertion of urinary catheter; 3.anastomotic leak characterized by an intra-abdominal collection diagnosed either clinically or radiologically; 4.bowel obstruction and 5.wound infection. All data was collected by the research assistant unaware of the hypothesis. The research assistant visited the patient in the preoperative clinic, and daily during the first three postoperative days, then at postoperative 3, 4-wk follow up and called the patients 6-8 weeks after surgery.

Walking capacity was assessed by using the 6-Minute Walk Test which was measured before surgery and at 3 weeks after surgery. The test was administered in a quiet corridor where patients walked back and forth along a 15 m distance as much as they can over a 6-minute period. Standard encouragement with the standardized statements such 'you are doing well' or 'good' or 'keep going' was given every 30 seconds. Patients were provided with clear instructions and were allowed to use their regular walking aids and rest, if required. Walking distance was recorded in meters. Baseline predicted 6MWT distance was calculated using gender-specific reference equations for the 6MWT.[223]

Health-related quality of life (HRQL) was measured by using SF-36 health survey which was completed by all patients in three groups before surgery, at the 3-week and 6-week follow up. The questionnaire is a well-validated instrument in a healthy population which consists of 36 questions relating to 8 domains: physical functioning (limitations in performance of physical activities), role-physical (limitations in daily activities as a result of physical health), bodily pain (measures pain-related functional limitations), general health (measures an

individual's perception of his or her overall health), vitality (measures energy level), social functioning (limitations in social functioning), role-emotional (limitations in daily activities as a result of emotional problems) and mental health (measures the presence and degree of depression and anxiety).[233, 235] These 8 subscale scores can be further aggregated into two composite summary scale scores: physical composite score (PCS) and the mental composite score (MCS). Normative data have been generated for the PCS, MCS, and the 8 subscale scores and compared with a group of health population in the same age interval because the SF-36 has not been validated in the postoperative population.[259, 260]

Postoperative fatigue was assessed by using Identity-Consequence Fatigue Scale (ICFS) which was completed by the patient before surgery and at the 3-week and 6-week follow up. This questionnaire is specifically designed to measure postoperative fatigue with 20 items assessment of feelings and 11 items assessment of instrumental activity of daily living.[36] The ICFS questionnaire measures 5 different subscales of POF: feelings of fatigue (5 items), feelings of vigor (4 items), impacts on concentration (5 items), impacts on energy (6 items), and impacts on daily activities (11 items); and summarized to two summary scores, overall POF score which is the mean of the first 2 subscales and the Fatigue-Consequence (FC) score which is the mean of the latter 3 subscales. Both POF and FC are expressed as a percentage of the maximum possible scores.[36]

Statistical analysis

The primary outcome was functional walking capacity as measured by the 6MWT at postoperative 3 week. Calculations for sample size were based on previous studied in which a change in 20 meters in 6MWT was considered to be clinically meaningful.[25, 169] Twenty four subjects in each group were sufficient to detect a 20 meters difference in 6MWT distance between each group, with a type-1 error of 0.05 and a power of 80%. The number was increased to 30 patients to include dropouts.

Data was collected on the standard forms and entered into a private computer database. Categorical variables were analyzed by X^2 test. Continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) and when data was not normally distributed. Comparison between groups used either an analysis of variance (ANOVA) or a Kruskal Wallis test. All statistical tests were two tailed at the significant level of 0.05. Statistic analysis was performed using SPSS version 18 for Windows (SPSS Inc., Chicago, IL).

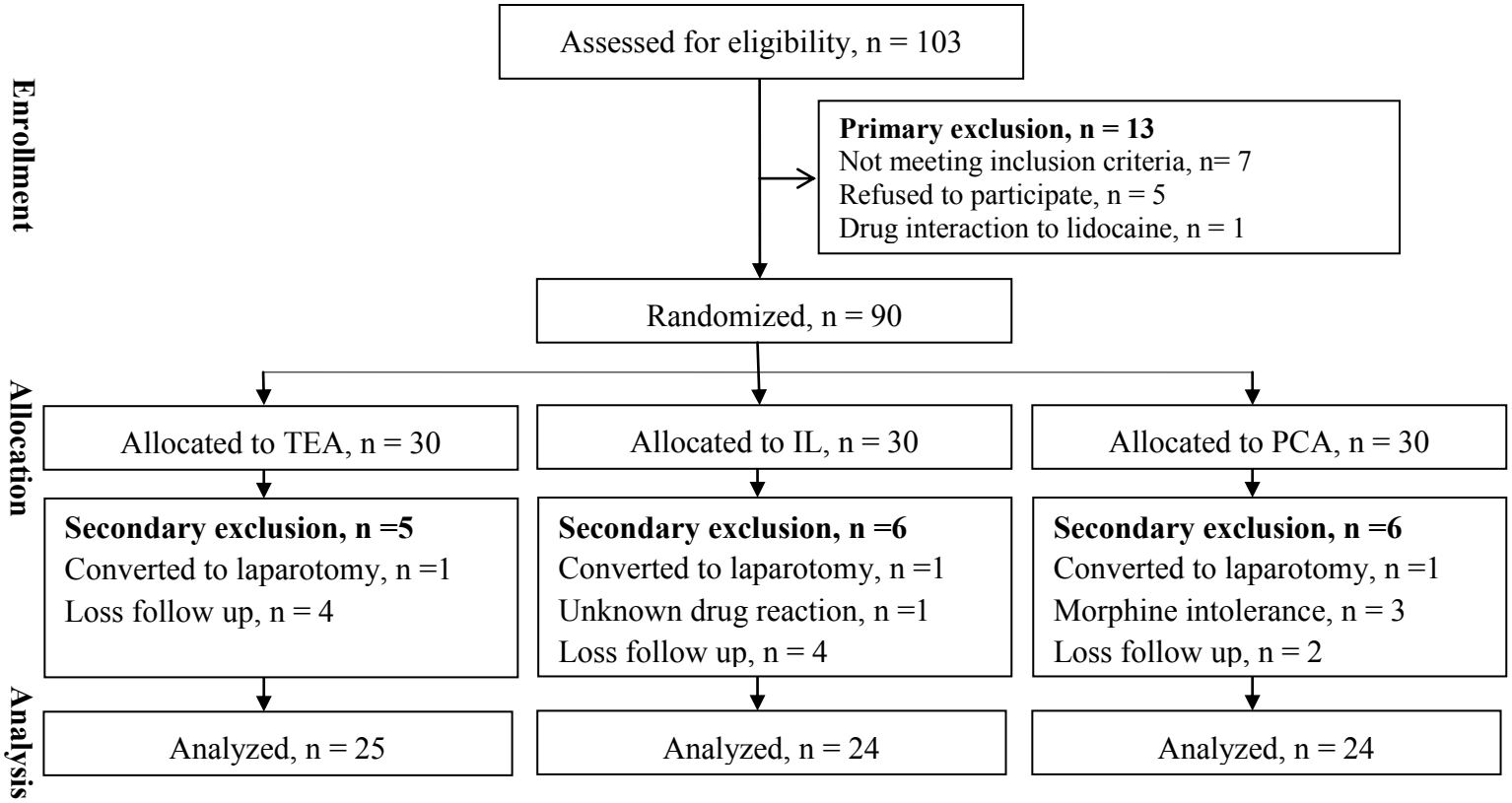
F.4 Results

Patient selection

A total of one hundred and three eligible patients was enrolled in this study. Seven patients did not meet the study criteria, five patients refused to participate, and drug interaction with lidocaine led to exclude one patient. Thus, ninety patients were randomized and assigned equally to three groups. Seventeen patients had to be excluded from the final analysis, one in each group for conversion to laparotomy, four patients in the TEA group, two patients in the IL group and two patients for the PCA group because patients were absent at 3 weeks follow up clinic, one patient in the IL group for unknown drug reaction and three patients in the PCA group for morphine tolerance (**Figure 4**).

The three groups were similar in patients' demographic characteristics (**Table 10**). The diagnosis, type of surgery and co-morbidities were equally distributed in the three groups.

Figure 4 Study design according to the CONSORT diagram showing the flow of participants through each stage of a randomized trial



TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia.

Table 10 Demographic characteristics and clinical data of three studied groups

	TEA (n=25)	**IL (n=24)**	**PCA (n=24)**	**P value**
Age (years)	60 ± 12	58 ± 16	66 ± 11	0.143
Sex (M/F)	13/12	18/6	13/11	0.196
Weight (kg)	75 ± 16	79 ± 15	71 ± 19	0.260
BMI ($kg•m^{-2}$)	26 ± 4	28 ± 6	25 ± 5	0.218
ASA I/ II/ III	12/11/2	7/16/1	6/14/4	0.252
Diagnosis				
Cancer	17 (68%)	14 (59%)	15 (63%)	0.781
Polyps	5 (20%)	2 (8%)	6 (25%)	0.301
Diverticular disease	1 (4%)	2 (8%)	1 (4%)	0.755
Inflammatory Bowel Disease	1 (4%)	6 (25%)	1 (4%)	***0.027***
Colo-vesicle fistula	1 (4%)	0 (0%)	1 (4%)	0.604
Type of surgery				
Right hemicolectomy	8 (32%)	4 (17%)	8 (33%)	0.353
Left hemicolectomy	4 (16%)	4 (17%)	1 (4%)	0.331
Sigmoid resection	4 (16%)	2 (8%)	2 (8%)	0.610
Anterior resection	8 (32%)	9 (37%)	10 (42%)	0.781
Proctocolectomy	1 (4%)	5 (21%)	3 (13%)	0.201
Co-morbidity				
Hypertension	7 (28%)	4 (13%)	4 (13%)	0.524
Diabetes	2 (8%)	0 (0%)	2 (8%)	0.354
Coronary artery disease	3 (12%)	2 (8%)	2 (8%)	0.880
Dyslipidemia	2 (8%)	2 (8%)	0 (0%)	0.354
Asthma	2 (8%)	2 (8%)	1 (4%)	0.817
Atrial fibrillation	1 (4%)	0 (0%)	1 (4%)	0604
Anemia	1 (4%)	1 (4%)	1 (4%)	1.000
Obstructive sleep apnea	1 (3%)	0 (0%)	1 (4%)	0.604

Data is presented as absolute number (%) or mean ± standard deviation. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia; BMI = body mass index; ASA = American Society of Anesthesiologists.

Intraoperative data

There were no differences in operative time, estimated blood loss and amount of IV fluid replacement. Intraoperative fentanyl consumption in the TEA and IL group was less than the PCA group significantly (TEA vs. PCA, P = 0.001; IL vs. PCA, P = 0.023) but the difference of intraoperative fentanyl consumption between TEA and IL was not significant (P = 0.306).

Postoperative clinical data

No patients showed signs of lidocaine toxicity in the postoperative period. There were no significant differences between the three groups in postoperative opioid consumption, postoperative pain at rest, on walking and on coughing, time out of bed over the first three postoperative days, duration of hospital stay, incidence of complications and readmission rate (**Table 11**).

Readmission occurred in 4 (16%), 6 (25%) and 1 (4%) patients in the TEA, IL and PCA groups respectively. The highest incidence of complication was anastomotic leak which occurred in four patients, two patients had CT-guided drainage for releasing intra-abdominal collection, two patients were re-operated. Three patients having small bowel obstruction were treated by conservative treatment. One patient was readmitted with abdominal pain and treated conservatively, and no evidence of anastomotic leak was found. Three patients in the TEA revisited the hospital with wound infection, bleeding per wound and urinary retention respectively.

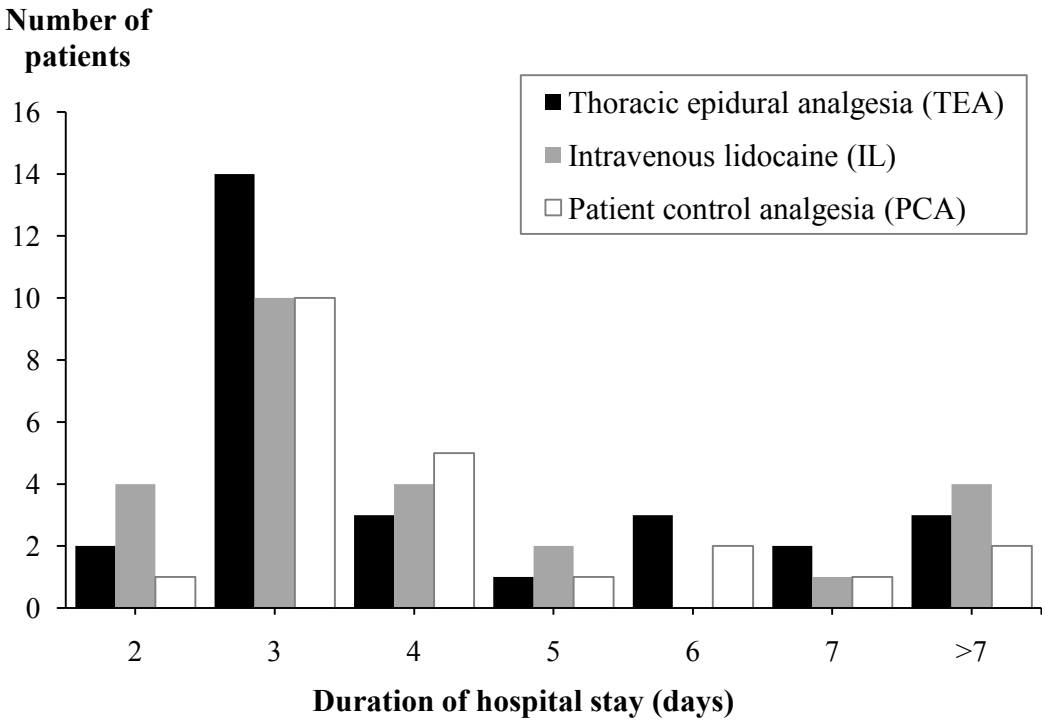
Table 11 Intraoperative data

	TEA (n=25)	IL (n=24)	PCA (n=24)	P value
Intraoperative data				
Duration of surgery (min)	200 ± 86	240 ± 75	200 ± 82	0.081
Estimated blood loss (ml)	282 ± 170	300 ± 182	270 ± 200	0.348
Fluid resuscitation (L)	1.8 ± 0.7	2.0 ± 0.7	1.8 ± 0.6	0.359
Fentanyl consumption (mcg)	216 ± 86	256 ± 88	323 ± 117	***0.001***
Postoperative data				
Morphine equivalent dose (mg)	90 ± 21	75 ± 45	83 ± 50	0.441
VRS pain at rest	1.5 [1-3]	2 [1-3]	1.5 [1-3]	0.534
VRS pain on walking	2 [1-4.5]	3 [2-4]	1.5 [1-4]	0.388
Time spent out of bed (min)	485[168-940]	612[207-947]	495[243- 607]	0.769
Hospital stay (days)	3 [3-6]	3 [3-5]	3.5 [3-5]	0.885
Complications in hospital				
Ileus	4 (16%)	5 (21%)	5 (21%)	0.883
Urinary retention	3 (12%)	0 (0%)	0 (0%)	0.056
Pneumonia	2 (8%)	0 (0%)	0 (0%)	0.139
Bleeding per rectum	1 (4%)	0 (0%)	1 (4%)	0.604
Sepsis	1 (4%)	0 (0%)	0 (0%)	0.378
Exudates from stoma	0 (0%)	1 (4%)	0 (0%)	0.355
Intraabdominal hematoma	0 (0%)	1 (4%)	0 (0%)	0.355
Atrial fibrillation	0 (0%)	0 (0%)	1 (4%)	0.355
Readmission	4 (16%)	6 (25%)	1 (4%)	0.170

Data is presented as mean ± standard deviation or median [interquartile range] or absolute number (%). TEA = thoracic epidural analgesia; IL = intravenous lidocaine.

The distributions of duration of hospital stay were the same in the three groups (**Figure 5**). Fifty percent of patients in each group were discharged home on postoperative day 3 and 70% on day 4, with the maximum duration of hospital stay of 22, 20 and 14 days in TEA, IL and PCA group respectively.

Figure 5 Distribution of duration of hospital stay



Walking capacity

Baseline predicted 6MWT and 2MWT distances calculated using gender-specific reference equations were presented in **Table 12**.[223] Preoperative and postoperative value of 6MWT and 2MWT were similar in the three groups.

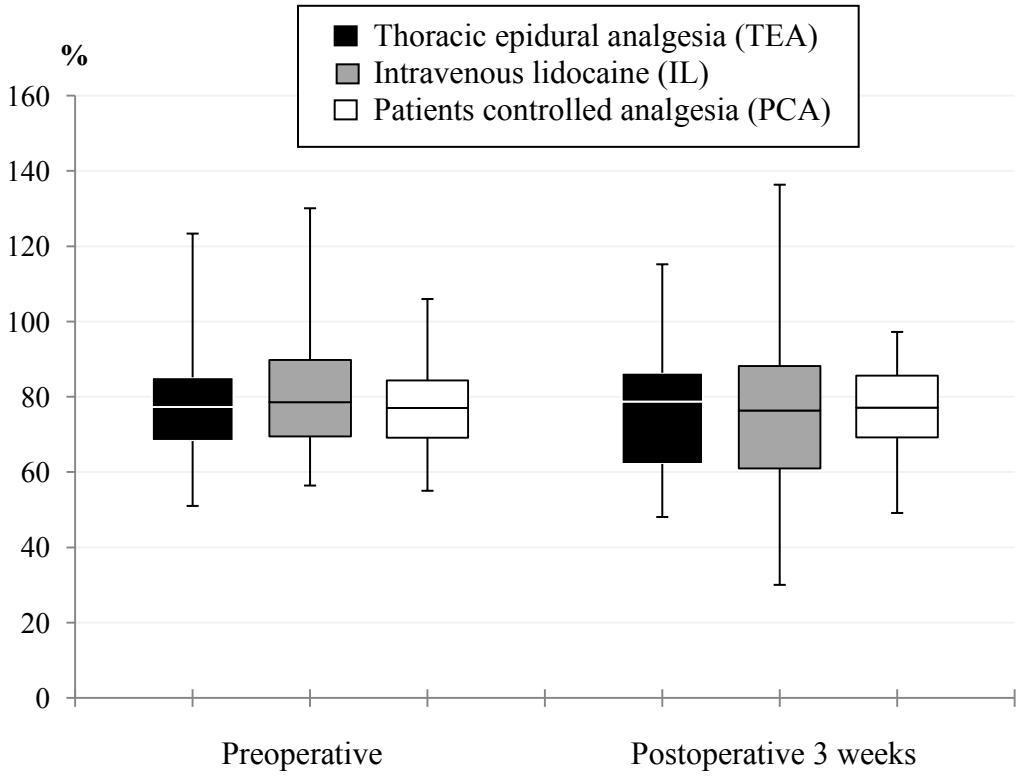
Table 12 Predicted and measured 6MWT and 2MWT distances (meters)

	TEA (n=25)	**IL (n=24)**	**PCA (n=24)**	**P value**
6MWT				
Predicted value	515 [458- 596]	536 [452-627]	532 [469-572]	0.771
Preoperative baseline	407 [375-470]	420 [390-450]	392 [355-450]	0.255
Postoperative at 3 weeks	416 [355-462]	420 [372-444]	400 [340-445]	0.736
2MWT				
Predicted value	172 [153-199]	179 [151-209]	177 [156-191]	0.769
Preoperative baseline	135 [121-158]	135 [128-150]	126 [112-148]	0.177
Postoperative day 1	48 [21-63]	49 [0-72]	35 [0-77]	0.897
Postoperative day 2	61 [39-84]	67 [48-84]	63 [40-92]	0.867
Postoperative day 3	72 [45-96]	79 [51-93]	67 [43-101]	0.731

Data is presented as median [interquartile range]. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia.

Preoperative values of 6MWT were accounted for approximately 75% of predicted baseline (**Figure 6**). At the postoperative 3 weeks, the median 6MWT distances in all three groups were similar to preoperative values and there was no significant difference between preoperative and postoperative values.

Figure 6 6MWT-the percent difference from predicted baseline

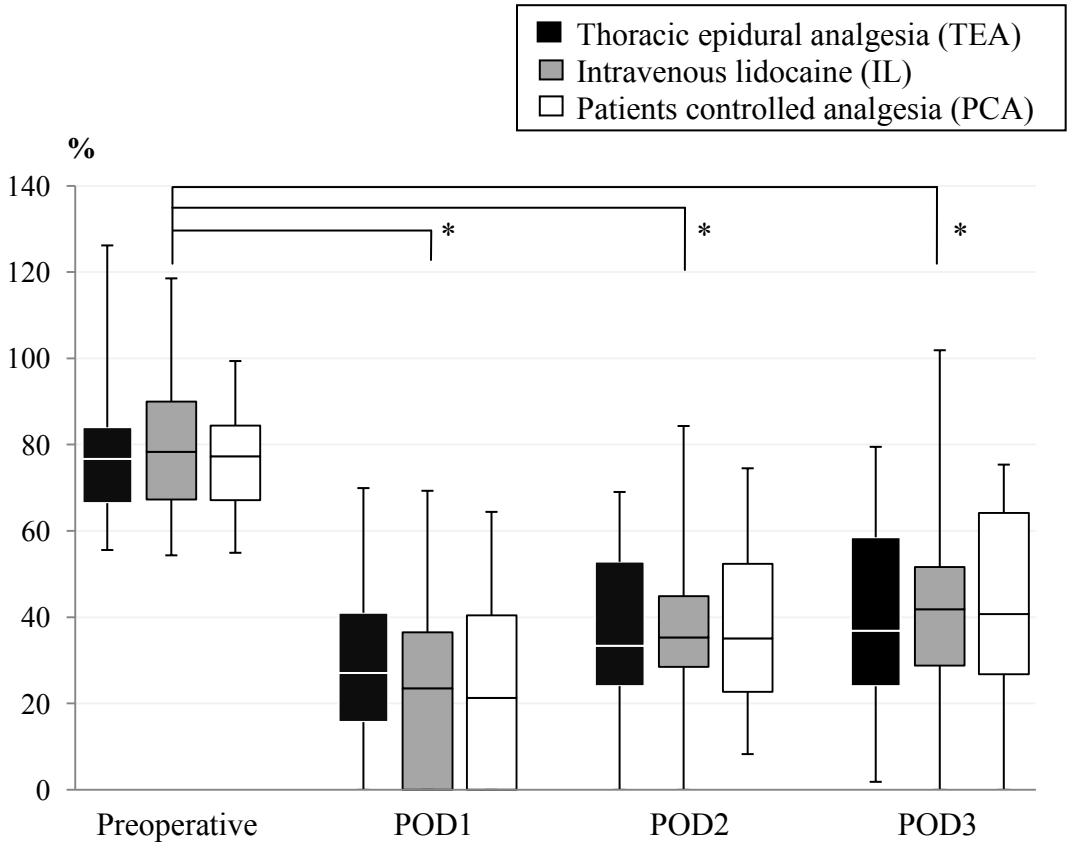


Data is presented as a box plots showing median and interquartile range.

Bars represent 95% confidence intervals.

For 2MWT, the preoperative median distances in the three groups were approximate 75% of the predicted baseline as same as 6MWT (**Figure 7**). On the first day after surgery, the median 2MWT distances in the three groups decreased significantly to approximately 25% of the predicted baseline (P<0.001). The 2MWT distance increased to 35% and 40% of the predicted baseline on the postoperative day 2 and 3 respectively; however the percent differences of postoperative 2MWT to predicted baseline were still significantly lower than preoperative values.

Figure 7 2MWT-the percent difference from predicted baseline



Data is presented as a box plots showing median and interquartile range.

Bars represent 95% confidence intervals. POD = postoperative day. * P < 0.001.

Health-related quality of life

The Canadian norms of SF-36 scores at the age interval of 55-64 yr, preoperative and postoperative SF-36 scores of patients in the three groups were presented in the **Table 13.** The preoperative scores were slightly lower than Canadian norms in five of eight domains except physical function, bodily pain and general health were not affected at preoperative baseline in the three groups; however there was no significant difference of all scale scores with Canadian normative data (**Figure 8**). In additional, the preoperative SF-36 scores of all eight domains and two summarize components were similar between three groups.

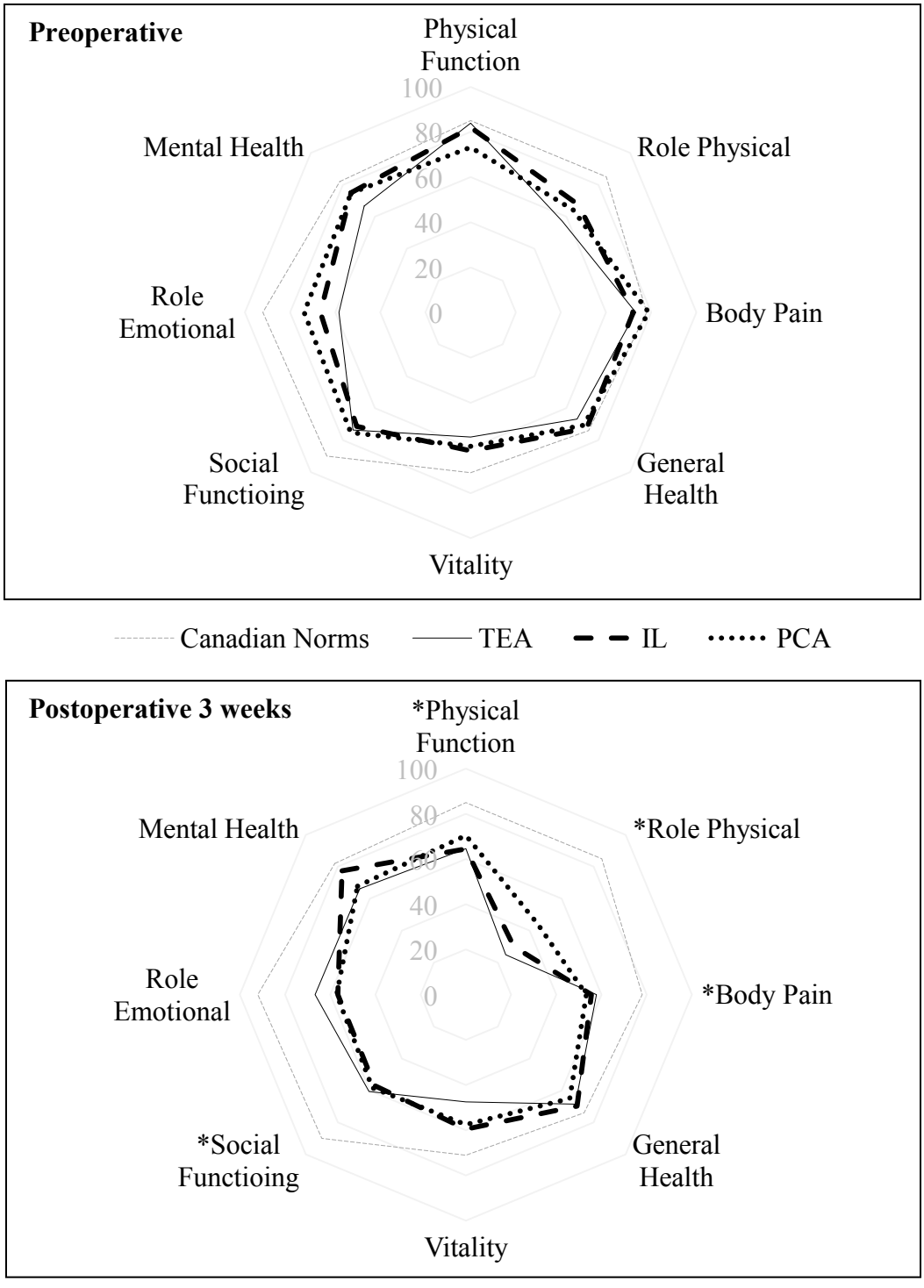
At 3 weeks after surgery, SF-36 scores in eight domains decreased from preoperative baseline but only four of eight domains (physical functioning, role-physical, bodily pain and social functioning) were significantly different (**Figure 8**). Moreover the summary scores of postoperative physical component significantly decreased, but the summary scores of mental component were not affected. The scores in eight domains and two component summaries were not significantly different between groups. The analgesic techniques did not affect the different change of postoperative SF-36 scores in all eight domains and two component summaries (**Table 14**).

Table 13 Preoperative and Postoperative SF-36 scores

SF-36	Canadian Norms (n= 645)	Preoperative			At 3-wk follow up			P value
		TEA (n=25)	IL (n=24)	PCA (n=24)	TEA (n=25)	IL (n=24)	PCA (n=24)	
Physical Functioning	85 ± 18	83 ± 21	82 ± 21	82 ± 27	67 ± 34	64 ± 29	74 ± 24	***<0.001***
Role-Physical	85 ± 30	55 ± 46	61 ± 42	75 ± 40	29 ± 40	28 ± 41	38 ± 44	***<0.001***
Bodily Pain	78 ± 23	74 ± 25	75 ± 31	78 ± 24	61 ±27	55 ± 22	57 ± 25	***<0.001***
General Health	74 ± 19	65 ± 22	72 ± 22	76 ± 19	69 ± 20	66 ± 20	70 ± 20	0.422
Vitality	71 ± 16	57 ± 24	61 ± 24	62 ± 23	50 ± 25	57 ± 25	58 ± 21	0.061
Social functioning	90 ± 17	74 ± 25	70 ± 30	77 ± 21	65 ± 33	57 ± 32	62 ± 27	***<0.001***
Role-Emotional	92 ± 23	61 ± 46	61 ± 44	79 ± 38	68 ± 46	53 ± 50	62 ± 45	0.406
Mental Health	82 ± 13	69 ± 22	73 ± 22	75 ± 20	69 ± 25	74 ± 22	72 ± 19	0.681
Physical Component Summary	50 ± 9	47 ± 10	48 ± 10	49 ± 10	40 ± 11	37 ± 9	41 ± 8	***<0.001***
Mental Component Summary	55 ± 8	43 ± 14	44 ±14	47 ± 11	45 ± 14	46 ± 14	45 ± 12	0.568

Data is presented as mean ± standard deviation. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia. P values are analyzed compared with preoperative baseline.

Figure 8 Polar graph of SF-36 scores before surgery and at 3 weeks after surgery



TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia. * $P < 0.05$ postoperative vs preoperative value

Table 14 Difference from preoperative values of SF-36 at 3 weeks after surgery

SF-36	TEA (n=25)	IL (n=24)	PCA (n=24)	P value
Physical Functioning	-15.5 ± 27	-18.6 ± 28	-8.4 ± 29	0.453
Role-Physical	-26.8 ± 42	-33.0 ± 63	-36.4 ± 52	0.806
Bodily Pain	-12.7 ± 26	-19.8 ± 33	-21.4 ± 31	0.540
General Health	4.9 ± 17	-6.2 ± 21	-5.1 ± 16	0.057
Vitality	-6.8 ± 22	-3.6 ± 27	-4.1 ± 16	0.859
Social functioning	-8.9 ± 26	-13.6 ± 45	-15.8 ± 22	0.752
Role-Emotional	7.2 ± 51	-8.0 ± 50	-16.7 ± 49	0.238
Mental Health	-0.6 ± 14	1.3 ± 17	-3.1 ± 12	0.594
Physical Component Summary	-7.7 ±9	-10.5 ± 14	-8.3 ± 11	0.627
Mental Component Summary	1.8 ± 11	1.9 ± 14	-1.8 ± 9	0.467

Data is presented a median and interquartile range or mean ± standard deviation. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia.

Postoperative fatigue

At preoperative baseline, there were no differences between the three groups in all five subscales, overall fatigue and fatigue consequence scores as measured by ICFS. Three weeks after surgery, the level of fatigue in all five subscales increased from preoperative baseline in all three groups, but there were only three subscales (feeling of fatigue, impact on energy and impact on daily activities) significantly increased (**Table 15**). Both postoperative overall fatigue and fatigue consequence scores also increased at 3 weeks after surgery, but only fatigue consequence score was significantly different from the preoperative baseline.

Intravenous lidocaine infusion tended to eliminate an increase in fatigue level more than other two techniques in four of five subscales, but there were no significant differences between groups (**Table 16**). There was only one subscale, impacts on daily activity, which had a significant increase in patients receiving intravenous lidocaine compared with receiving PCA ($P = 0.027$). However, an increase in postoperative overall fatigue and fatigue consequence scores had no significant difference between groups.

Table 15 Preoperative and postoperative identity-consequence fatigue scales

ICFS	Preoperative			At 3-wk follow up			P value
	TEA (n=25)	**IL (n=24)**	**PCA (n=24)**	**TEA (n=25)**	**IL (n=24)**	**PCA (n=24)**	
Feeling of fatigue	43 ± 19	40 ± 19	41 ± 19	50 ± 19	43 ± 19	46 ± 19	***0.013***
Feeling of vigor	61 ± 18	55 ± 22	56 ± 21	65± 19	57± 21	62 ± 22	0.105
Impact on concentration	40 ± 12	37 ± 14	35 ± 17	42 ±15	34± 15	35 ± 14	0.529
Impact on energy	52 ± 20	48 ± 23	47± 19	64± 23	54± 23	56± 20	***<0.001***
Impact on daily activities	27 ± 15	32 ± 16	31 ± 19	38 ± 23	48± 25	31 ± 14	***<0.001***
Postoperative overall fatigue	52 ± 17	48 ± 15	48 ± 19	58 ± 18	49 ± 19	54 ± 19	***0.028***
Fatigue consequence	40 ± 13	39 ± 16	38 ± 15	48 ± 15	45 ± 19	45 ± 13	***<0.001***

Data is presented a mean ± standard deviation. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia. P values are analyzed to compare with preoperative baseline.

Table 16 Different values of identity-consequence fatigue scales between preoperative and postoperative values

ICFS	TEA (n=25)	IL (n=24)	PCA (n=24)	P value
Feeling of fatigue	6.8 ± 14	2.8 ± 23	5.0 ± 10	0.689
Feeling of vigor	4.8 ± 17	0.9 ± 25	5.6 ± 16	0.668
Impact on concentration	1.4 ± 9	-3.5 ± 10	-0.5 ± 14	0.274
Impact on energy	11.2 ± 19	5.4 ± 19	8.8 ± 19	0.539
Impact on daily activities	11.4 ± 24	16.1 ± 25	0.5 ± 13	***0.049***
Postoperative overall fatigue	5.5 ± 15	2.5 ± 20	5.3 ± 11	0.786
Fatigue consequence	8.0 ± 13	5.9 ± 16	7.0 ± 12	0.442

Data is presented a mean ± standard deviation. TEA = thoracic epidural analgesia; IL = intravenous lidocaine; PCA = patient control analgesia..

F.5 Discussion

The results of this prospective randomized study showed that the median distances of postoperative walking capacity at 3 weeks after laparoscopic colorectal surgery were similar to preoperative baseline values with no difference between analgesic techniques, TEA, IL and PCA. In addition, postoperative HRQL (the physical and the mental components) decreased in the three groups at 3 weeks after surgery and this was similar among these three techniques. Moreover, both postoperative fatigue and fatigue consequence scores increased to a similar level in the three groups.

Over the last two decades, there have been numerous techniques which have been developed to improve postoperative recovery. Laparoscopy, ERP, epidural technique and intravenous lidocaine have been accepted to have a positive effect to facilitate surgical outcomes in terms of postoperative return of bowel function, postoperative pain score, use of pain medication, length of hospital stay and complication rate,[256] however these outcomes do not actually represent the postoperative health status in the patient's perspective. Many measures have been used to describe the functional recovery after surgery such as the ability to mobilize, walk and perform basic daily activities, and the level of postoperative fatigue.[207]

Functional walking capacity, as measured by walk tests, was chosen in this study as the primary outcome. An ideal index of postoperative recovery should be consistent with a biologic model and relate to the long term outcomes.[218] As a biologic model for surgical recovery, intraoperative physiologic and systemic changes which occur immediately after surgery affect the short-term functioning such as the ability to mobilize, walking and performing daily activities.[218] Walk tests are an effective indicator to assess the impact on exercise tolerance and patients' deterioration as a result of surgical stress, pain and fatigue.[218, 261] In the present study, the preoperative distances in 2MWT and 6MWT were approximately 75% of predicted baseline which well correlated with those

reported by others.[169, 218] In recent studies, TEA and intravenous lidocaine have been shown to attenuate the deterioration in functional walking capacity over systemic morphine in various types of operations, as measured by 6MWT and 2MWT.[25, 169, 218] In the present study, the median distances of postoperative 6MWT were similar to preoperative values with no difference between the 3 groups. These results contrasted with those reported in a previous study which presented the deterioration of walking capacity at 3 weeks after open colonic surgery.[169] The discrepancy can be explained by the positive effects of ERP on postoperative walking capacity, implying that functional activity can be restored when multidisciplinary interventions are implemented and independent of the type of analgesia. These results would be in agreement with the findings reported by Basse.[146, 262]

The pattern of acute deterioration of functional walking capacity while in hospital, as measured by the 2MWT, was similar to that observed in those patients who underwent laparoscopic prostatectomy.[25] In the present study, the deterioration in 2MWT distance was greater than 50% on the first postoperative day and decreased over time with no impact of analgesic techniques. One would therefore assume that, in spite the introduction of laparoscopy and ERP, the type of analgesia had no effect in improving the acute deterioration of walking capacity after surgery.

For HRQL in this study, the preoperative SF-36 scores in the three groups were within the normal range for Canadians of the age between 55-64 yr.[259] The statistically significant decline in physical health (PSC) from preoperative baseline in the three analgesic techniques by 7.7 points for TEA group, 10.5 points for IL group and 8.3 points for PCA group were clinically difference because a two-point change in PSC is associated with clinically meaningful impact in the general population.[238] At preoperative baseline, the patients on the average 60 yr of age were within the Canadian norms for this age group, however by 3 weeks this decline put patients well below the norms for Canadians older

than 75 yr.[259] In the present study, these declined levels were less than those reported in a study on patients who underwent open colonic surgery.[169]

In the present study, there were significant postoperative impairments in four out of eight domains, and three domains (physical functioning, role-physical and bodily pain) which highly correlated with the physical component and contributed to the scoring of the PCS measure. [238] These findings confirm that the immediate postoperative period is limiting the activities of patients undergoing this type of surgery and that these outcomes qualify the extent of this decreased ability to mobilise and perform the daily activities.[207] At three weeks after operation, the most affected domains were role-physical, bodily pain and physical functioning respectively. It is interesting that this significant decline in these reported outcomes did not correlate with the changes in 6MWT distance measured at the same time. In fact the latter returned to baseline values while patients still reported decreased physical functioning. This implies that the two measures have a different meaning; while patients were capable of conducting their activity, walking, activity if they were asked to do so, they reported problems with work as a result of limitation in performing physical activities and pain, and this was independent of the analgesic technique used.

In this study, an attempt was made to quantify fatigue levels and the impact on daily function. As such we used a scale previously validated in surgical patients which has been shown to have face validity and reproducibility. The ICFS has five subscales, feeling of fatigue and feeling of vigor subscales represent fatigues level while impacts on concentration and impacts on daily activities represent fatigue consequences dimension; greater the score greater the fatigue.[36] The results in this study demonstrated that fatigue levels and the fatigue consequence (ability to do activity) at 3 weeks after surgery significantly increased in the three groups, and these correlated with the findings reported in 2 studies in colonic resection using the setting of ERP.[146, 262] The increase in fatigue level was more substantial in patients receiving TEA and PCA than in those patients who had IL. In contrast, patients receiving IL had a significant impairment on the impact on

daily activities however this group of patients had less increase in the fatigue level than TEA and PCA techniques. These results are to some extent in agreement with the changes in the physical component of the SF36 and can explain the decrease in physical functioning.

It is clear that in the present study the postoperative decrease in functional outcomes was significantly less compared to that reported in a study using a model of open colorectal surgery,[169] and the decrease in functional outcome was irrespective of the type of analgesia used. This could be explained by the implementation of the ERP in this study.

Assessment of postoperative functional recovery has not received great attention, probably as a result of the difficulty to understand the meaning of recovery. Conventionally length of hospital stay is used as a measure of recovery, but this outcome is very much dependent upon the administrative and social structure of the institution and organization. From the patient point of view recovery would mean the ability to attend the daily chores, to return to work and to function socially. The present study is an attempt to determine whether analgesia can impact on short- and long-term functional recovery and verify whether the context of the ERP encompasses all aspects of care, and with analgesia playing only a part. Two other studies have measured functional recovery in colon surgery and return to baseline function was better in those patients who were enrolled in the multidisciplinary ERP program.[146, 262]

In conclusion, within the context of the ERP program, functional walking capacity at 3 weeks after surgery are similar to baseline in all the groups, and this is independent of the analgesic techniques used. It is evident in this study that PCA demonstrated to be as good as both TEA and IV lidocaine. Physical functioning and fatigue levels are impaired at 3 weeks after surgery implying that the process of recovery following colorectal surgery takes time; and more research needs to be conducted to better understand the mechanism of recovery.

G. Conclusion

The main goals of this project were to determine the impact of perioperative and postoperative intravenous infusion of lidocaine on surgical outcomes and functional outcomes compared with other analgesic techniques. It was found that the average return of bowel movement after laparoscopic colorectal surgery was within the first 48 hours with no difference between IL and TEA techniques. In addition, duration of hospital stay and rate of readmission were similar with these two techniques. Intravenous lidocaine infusion, within the context of the ERP, also facilitated the return of postoperative functional walking capacity to baseline, and this was independent of the analgesic techniques used, TEA, IL and PCA. However, physical functioning and fatigue levels are impaired at 3 weeks after surgery with no difference in the three techniques.

In conclusion, these findings suggest that perioperative and postoperative infusion of intravenous lidocaine may be used as an alternative to TEA in accelerating the return of bowel function and the postoperative walking capacity. The benefits of intravenous lidocaine on health-relate quality of life and postoperative fatigue still remain unclear, therefore further studies should be continued to evaluate the short-term and long-term benefits of intravenous lidocaine compared with other analgesic techniques in this population.

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I. Appendices

SF-36 HEALTH STATUS SURVEY / CANADA

Questionnaire

Date: _____

INSTRUCTIONS: This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.

Answer every question by marking the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

1. In general, would you say your health is:

(circle one)

Excellent…… 1

Very good…… 2

Good…… 3

Fair…… 4

Poor…… 5

2. Compared to one year ago, how would you rate your health in general now?

(circle one)

Much better now than one year ago …… 1

Somewhat better now than one year ago …… 2

About the same as one year ago …… 3

Somewhat worse now than one year ago …… 4

Much worse now than one year ago …… 5

SF-36 HEALTH STATUS SURVEY / CANADA

Questionnaire

3. The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

(circle one number on each line)

ACTIVITIES	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
a. **Vigorous activities**, such as running, lifting heavy objects, participating in	1	2	3
b. **Moderate activities**, such as moving a table, pushing a vacuum cleaner,	1	2	3
c. Lifting or carrying groceries	1	2	3
d. Climbing **several** flights of stairs	1	2	3
e. Climbing **one** flight of stairs	1	2	3
f. Bending, kneeling, or stooping	1	2	3
g. Walking **more than a kilometre**	1	2	3
h. Walking **several blocks**	1	2	3
i. Walking **one block**	1	2	3
j. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

(circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or	1	2
b. **Accomplished less** than you would like	1	2
c. Were limited in the **kind** of work or other activities	1	2
d. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

SF-36 HEALTH STATUS SURVEY / CANADA

Questionnaire

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

(circle one number on each line)

	YES	NO
a. Cut down the **amount of time** you spent on work or other activities	1	2
b. **Accomplished less** than you would like	1	2
c. Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one)

Not at all..... 1

Slightly..... 2

Moderately..... 3

Quite a bit..... 4

Extremely..... 5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

(circle one)

None..... 1

Very mild 2

Mild..... 3

Moderate 4

Severe..... 5

Very severe..... 6

SF-36 HEALTH STATUS SURVEY / CANADA

Questionnaire

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

(circle one)

Not at all ……..…..…… 1

A little bit ……..…… 2

Mild……...……..…… 3

Moderately…… 4

Quite a bit..……..…….…… 5

Extremely..……..…….…… 6

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 week?

(circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
a.Did you feel full of pep?	1	2	3	4	5	6
b.Have you been a very nervous person?	1	2	3	4	5	6
c.Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
d.Have you felt calm and peaceful?	1	2	3	4	5	6
e.Did you have a lot of energy?	1	2	3	4	5	6
f.Have you felt downhearted and blue?	1	2	3	4	5	6
g.Did you feel worn out?	1	2	3	4	5	6
h.Have you been a happy person?	1	2	3	4	5	6
i.Did you feel tired?	1	2	3	4	5	6

SF-36 HEALTH STATUS SURVEY / CANADA

Questionnaire

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one)

All of the time 1

Most of the time..... 2

Some of the time..... 3

A little of the time..... 4

None of the time 5

11. How **TRUE** or **FALSE** is each of the following statements for you?

(circle one number on each line)

	Definitely True	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
a. I seem to get sick a little easier than other people	1	2	3	4	5
b. I am as healthy as anybody I know	1	2	3	4	5
c. I expect my health to get worse	1	2	3	4	5
d. My health is excellent	1	2	3	4	5

QUESTIONNAIRE SUR L'ÉTAT DE SANTÉ SF-36

DIRECTIVES: Les questions qui suivent portent sur votre santé, telle que vous la percevez. Vos réponses permettront de suivre l'évolution de votre état de santé et de savoir dans quelle mesure vous pouvez accomplir vos activités courantes.

Répondez à toutes les questions en suivant les indications qui vous sont données. En cas de doute, répondez de votre mieux.

1. En général, diriez-vous que votre santé est:

(encerclez une seule réponse)

Excellent	1
Très bonne	2
Bonne	3
Passable	4
Mauvaise	5

2. Par comparaison à l'an dernier, comment évaluez-vous, maintenant, votre santé générale?

(encerclez une seule réponse)

Bien meilleure maintenant que l'an dernier.	1
Un peu meilleure maintenant que l'an dernier	2
À peu près la même que l'an dernier	3
Un peu moins bonne maintenant que l'an dernier	4
Bien moins bonne maintenant que l'an dernier	5

QUESTIONNAIRE SUR L'ÉTAT DE SANTÉ SF-36

3. Les questions suivantes portent sur les activités que vous pourriez avoir à faire au cours d'une journée normale. Votre état de santé actuel vous limite-t-il dans ces activités? Si oui, dans quelle mesure?

(encerclez un seul chiffre par ligne)

ACTIVITÉS	Mon état de santé me limite beaucoup	Mon état de santé me limite un peu	Mon état de santé ne me limite pas du tout
a. Dans les activités exigeant un effort physique important comme courir, soulever des objets lourds, pratiquer des sports violents	1	2	3
b. Dans les activités modérées comme déplacer une table, passer l'aspirateur, jouer aux quilles ou au golf	1	2	3
c. Pour soulever ou transporter des sacs d'épicerie	1	2	3
d. Pour monter plusieurs étages à pied	1	2	3
e. Pour monter un seul étage à pied	1	2	3
f. Pour me pencher, me mettre à genoux ou m'accroupir	1	2	3
g. Pour faire plus d'un kilomètre à pied	1	2	3
h. Pour faire plusieurs coins de rue à pied	1	2	3
i. Pour marcher d'un coin de rue à l'autre	1	2	3
j. Pour prendre un bain ou m'habiller	1	2	3

QUESTIONNAIRE SUR L'ÉTAT DE SANTÉ SF-36

4. Au cours des quatre dernières semaines, avez-vous eu l'une ou l'autre des difficultés suivantes au travail ou dans vos autres activités quotidiennes à cause de votre état de santé physique?

(encerclez un seul chiffre par ligne)

	OUI	NON
a. Avez-vous dû consacrer moins de temps à votre travail ou à d'autres activités?	1	2
b. Avez-vous accompli moins de choses que vous l'auriez voulu?	1	2
c. Avez-vous été limité(e) dans la nature de vos tâches ou de vos autres activités?	1	2
d. Avez-vous eu du mal à accomplir votre travail ou vos autres activités (par exemple vous a-t-il fallu fournir un effort supplémentaire)?	1	2

5. Au cours des quatre dernières semaines, avez-vous eu l'une ou l'autre des difficultés suivantes au travail ou dans vos autres activités quotidiennes à cause de l'état de votre moral (comme le fait de vous sentir déprimé(e) ou anxieux(se))?

(encerclez un seul chiffre par ligne)

	OUI	NON
a. Avez-vous dû consacrer **moins de temps** à votre travail ou à d'autres activités?	1	2
b. Avez-vous **acccompli moins** de choses que vous l'auriez voulu?	1	2
c. Avez-vous fait votre travail ou vos autres activités avec moins de soin qu'à l'habitude?	1	2

QUESTIONNAIRE SUR L'ÉTAT DE SANTÉ SF-36

6. Au cours des quatre dernières semains, dans quelle mesure votre état physiques ou moral a-t-il nui à vos activités sociales habituelles (famille, amis, voisins ou autres groupes)?

(encerclez une seule réponse)

Pas du tout……..1

Un peu……....2

Moyennement…….3

Beaucoup……..…..4

Enormément……...5

7. Au cours des quatre dernières semaines, avez-vous éprouvé des douleurs physique?

(encerclez une seule réponse)

Aucune douleur……...1

Douleurs très légères……2

Douleurs légères……..3

Douleurs moyennes…….4

Douleurs intenses…….5

Douleurs très intenses.…….6

7. Au cours des quatre dernières semaines, dans quelle mesure la douleur a-t-elle nui à vos activités habituelles (au travail comme à la maison)?

(encerclez une seule réponse)

Pas du tout……..1

Un peu……...2

Moyennement…….3

Beaucoup……4

Enormément……...5

QUESTIONNAIRE SUR L'ÉTAT DE SANTÉ SF-36

9. Ces questions portent sur les quatre dernières semaines. Pour chacune des questions suivantes, donné la réponse qui s'approche le plus de la façon dont vous vous êtes senti(e). Au cours des quatre dernières semaines, combien de fois:

(encerclez un seul chiffre par ligne)

	Tout le temps	**La plupart du temps**	**Souvent**	**Quel-que-fois**	**Rare-ment**	**Jamais**
a. Vous êtes-vous senti(e) plein(e) d'entrain (de pep)?	1	2	3	4	5	6
b. Avez-vous été très nerveux(se)?	1	2	3	4	5	6
c. Vous êtes-vous senti(e) si déprimé(e) que rien ne pouvait vous remonter le moral?	1	2	3	4	5	6
d. Vous êtes-vous senti(e) calme et serein(e)?	1	2	3	4	5	6
e. Avez-vous eu beaucoup d'énergie?	1	2	3	4	5	6
f. Vous êtes-vous senti(e) triste et abattu(e)?	1	2	3	4	5	6
g. Vous êtes-vous senti(e) épuisé(e) et vidé(e)?	1	2	3	4	5	6
h. Vous êtes-vous senti(e) heureux(se)?	1	2	3	4	5	6
i. Vous êtes-vous, senti(e) fatigué(e)?	1	2	3	4	5	6

QUESTIONNAIRE SUR L'ÉTAT DE SANTÉ SF-36

10. Au cours des quatre dernières semaines, combien de fois votre état physique ou moral a-t-il nui à vos activité sociales (comme visiter des amis, des parents, etc.)?

(encerclez une seule reponse)

Tout le temps.....1

La plupart du temps.....2

Parfois.....3

Rarement.....4

Jamais.....5

11. Dans quelle mesure chacun des énoncés suivants est-il VRAI ou FAUX dans votre cas?

(encerclez un seul chiffre par ligne)

	Tout à fait vrai	**Plutôt vrai**	**Ne sais pas**	**Plutôt faux**	**Tout à fait faux**
a. Il me semble que je tombe malade un peu plus facilement que les autres	1	2	3	4	5
b. Je suis aussi en santé que les gens que je connais	1	2	3	4	5
c. Je m'attends à ce que ma santé se détériore	1	2	3	4	5
d. Ma santé est excellente	1	2	3	4	5

Investigating tiredness

Some things to be aware of while you complete this questionnaire:

- There are **no right or wrong answers** to the questions.
- It is best not to spend long thinking about any one answer; normally the first response is best.
- Some questions may seem very similar, but for measurement purposes it is often important to ask a question in slightly different ways. We would appreciate your patience and willingness to answer all of the questions.

Thank you for taking the time to fill out this questionnaire

Part 1

Please think about the **last two days** and tick the box that best describes how you have been feeling.

During the last two days…

	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
1. I have been feeling drained	☐	☐	☐	☐	☐	☐
2. I start things without difficulty then get tired	☐	☐	☐	☐	☐	☐
3. I have been feeling energetic	☐	☐	☐	☐	☐	☐
4. I have had trouble paying attention	☐	☐	☐	☐	☐	☐
5. I have been feeling worn out	☐	☐	☐	☐	☐	☐
6. I have been feeling refreshed	☐	☐	☐	☐	☐	☐
7. My body has been feeling heavy all over	☐	☐	☐	☐	☐	☐
8. I have been feeling vigorous	☐	☐	☐	☐	☐	☐
9. I have been forgetful	☐	☐	☐	☐	☐	☐
10. It has been hard for me to get motivated to do my regular activities	☐	☐	☐	☐	☐	☐

Part 1 (continue)

Please think about the last two days and tick the box that best describes how you have been feeling.

During the last two days…

	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
11. I do very little in a day	☐	☐	☐	☐	☐	☐
12. I have been able to concentrate on things	☐	☐	☐	☐	☐	☐
13. My thoughts have wandered easily	☐	☐	☐	☐	☐	☐
14. I lack the energy to do things I normally do	☐	☐	☐	☐	☐	☐
15. I have been feeling fatigued	☐	☐	☐	☐	☐	☐
16. I have had the energy to do lots of things	☐	☐	☐	☐	☐	☐
17. Physically, I have felt tired	☐	☐	☐	☐	☐	☐
18. I have made more mistakes than usual	☐	☐	☐	☐	☐	☐
19. I have had to restrict how much I try and do in a day	☐	☐	☐	☐	☐	☐
20. I have been feeling lively	☐	☐	☐	☐	☐	☐

Part 2

The following questions ask how much **fatigue** interferes with the things you can do.

For activities you aren't doing, for reasons other than fatigue, tick the box labelled "N/A" (not applicable).

Examples of why you might tick the "N/A" box include:

- You are still in hospital and are not required to do things like run errands.
- You are not the person who usually cooks in your household.
- Or, you have a wound that is vacuum-sealed and you are not able to do household chores because of this.

During the last two days, I have had enough energy to...	Not at all ▼	Almost Never ▼	Some of the time ▼	Fairly Often ▼	Very Often ▼	All of the time ▼
21. Read a newspaper/book or watch TV	☐	☐	☐	☐	☐	☐
22. Bath/wash	☐	☐	☐	☐	☐	☐
23. Dress	☐	☐	☐	☐	☐	☐
24. Do household chores	☐	☐	☐	☐	☐	☐
25. Cook	☐	☐	☐	☐	☐	☐
26. Work	☐	☐	☐	☐	☐	☐
27. Visit or socialize with family and friends	☐	☐	☐	☐	☐	☐
28. Engage in leisure or recreational activities	☐	☐	☐	☐	☐	☐
29. Shop or do errands	☐	☐	☐	☐	☐	☐
30. Walk	☐	☐	☐	☐	☐	☐
31. Exercise other than walk	☐	☐	☐	☐	☐	☐

Investigation de la fatigue

Des choses que vous devez souligner en remplissant ce questionnaire:

- Il n'y a pas de bonne ou de mauvaise réponse.
- Il est mieux de ne pas trop penser sur les réponses, normalement, le premier est correct
- Quelques questions peuvent paraitre similaires, mais pour des raisons de formalité, il est important quelquefois de poser une question de façon différente. On apprécie votre patience de répondre aux questions

Merci de prendre le temps de remplir ce questionnaire

la première partie

Veuillez penser s'il vous plait des deux derniers jours et cocher les cases qui convient le plus possible de la façon dont vous vous sentiez

Pendant les deux derniers jours …	Jamais ▼	Presque jamais ▼	Parfois ▼	Souvent ▼	Très souvent ▼	Tout le temps ▼
1. Je me sentais épuisé(e)	☐	☐	☐	☐	☐	☐
2. Je commence les choses sans difficultés et après devient fatigué(e)	☐	☐	☐	☐	☐	☐
3. je me sentais énergétique	☐	☐	☐	☐	☐	☐
4. j'au eu des problèmes de concentration	☐	☐	☐	☐	☐	☐
5. Je me sentais affaibli(e)	☐	☐	☐	☐	☐	☐
6. je me sentais rafraichi(e)	☐	☐	☐	☐	☐	☐
7. Mon corps faisait mal partout	☐	☐	☐	☐	☐	☐
8. je me sentais vigoureux (se)	☐	☐	☐	☐	☐	☐
9. je me sentais distrait(e)	☐	☐	☐	☐	☐	☐
10. C'était dur pour trouver la motivation pour accomplir mes taches quotidiennes	☐	☐	☐	☐	☐	☐

la première partie (continuer)

Veuillez penser s'il vous plait des deux derniers jours et cocher les cases qui convient le plus possible de la façon dont vous vous sentiez

Pendant les deux derniers jours …	Jamais ▼	Presque jamais ▼	Parfois ▼	Souvent ▼	Très souvent ▼	Tout le temps ▼
11. Je fais presque rien pendant la journée	☐	☐	☐	☐	☐	☐
12. je suis capable de bien me concentrer sur des choses	☐	☐	☐	☐	☐	☐
13. Je suis dans la lune	☐	☐	☐	☐	☐	☐
14. je manque d'énergie pour accomplir pour accomplir mes taches quotidiennes	☐	☐	☐	☐	☐	☐
15. Je me sentais fatigué(e)	☐	☐	☐	☐	☐	☐
16. J'ai eu l'énergie pour accomplir plein de chose	☐	☐	☐	☐	☐	☐
17. Physiquement, je me sentais déprimé(e)	☐	☐	☐	☐	☐	☐
18. J'ai fait beaucoup d'erreur que d'habitude	☐	☐	☐	☐	☐	☐
19. J'ai du limité(e) combien et ce que j'essaie de faire pendant une journée	☐	☐	☐	☐	☐	☐
20. je me sentais vivant (e)	☐	☐	☐	☐	☐	☐

la deuxième partie

Les questions suivantes vous demandent combien la **fatigue** à de l'effet sur vos activités quotidiennes

Pour des activités que vous ne faites par, pour des raisons d'autre que la fatigue, cochez la case marquée "N/A" (not applicable).

Des exemples de chose qu'on pourrait marquer "N/A" box sont:

- Vous êtes toujours à l'hôpital et vous n'êtes pas recommander de magasiner.
- Vous êtes pas la personne désigné pour faire la cuisine.
- Or, vous avez une plaie qui est bien fermer et vous n'êtes pas capables faire des taches ménagères a cause de cela.

Pendant les deux derniers jours, j'ai eu assez d'énergie pour…..	Jamais ▼	Seulement occasionnellement ▼	Quelquefois mais moins que souvent ▼	Le plus souvent possible ▼	Très souvent ▼	N/A ▼
21. lire un journal/ livre ou regarder la télé	☐	☐	☐	☐	☐	☐
22. Prendre une douche/	☐	☐	☐	☐	☐	☐
23. S'habiller	☐	☐	☐	☐	☐	☐
24. Faire des taches ménagères	☐	☐	☐	☐	☐	☐
25. Cuisiner	☐	☐	☐	☐	☐	☐
26. Travailler	☐	☐	☐	☐	☐	☐
27. Visiter et socialiser avec amis/famille	☐	☐	☐	☐	☐	☐
28. Engager dans des activités récréationelles	☐	☐	☐	☐	☐	☐
29. Magasiner/faire des courses	☐	☐	☐	☐	☐	☐
30. Marcher	☐	☐	☐	☐	☐	☐
31. Exercise other than walk	☐	☐	☐	☐	☐	☐