Impact of early mobilization on outcomes after colorectal surgery

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LIST OF ABBREVIATIONS

ERAS® : Enhanced Recovery After Surgery

ERP: Enhanced recovery pathway

GI: Gastrointestinal

IBD: Inflammatory bowel disease

LOS: Length of stay

PFT: Pulmonary function testing

POD: Postoperative day

PRO: Patient-reported outcome

RCT: Randomized controlled trial

SF-36: Short-form 36 questionnaire

TRD: Time to readiness for discharge

6-MWT: 6-minute walk test

ABSTRACT

Introduction: Early mobilization is a key aspect of postoperative care. The main benefits include prevention of the deleterious side effects of bed rest, which include venous thromboembolism, pulmonary complications, muscle wasting and physical deconditioning. Early physical activity may have many other potential benefits on different aspects of recovery after surgery, such as clinical outcomes, functional status and quality of life. The objective of the research contained within this thesis is two-fold: (1) to examine the current body of evidence regarding the impact of early postoperative mobilization protocols on outcomes after abdominal and thoracic surgery, and (2) to explore the relationship between early physical activity and specific clinical outcomes in an observational study involving patients undergoing colorectal surgery.

Methods: A systematic review of the literature was performed according to the PRISMA guidelines. Eight electronic databases were searched in order to identify studies comparing patients receiving a specific protocol of early mobilization to a control group. Methodological quality was assessed using the Downs and Black tool. An observational study was subsequently carried out by conducting a secondary analysis of data from a randomized controlled trial. Sixty consecutive, adult, postoperative colorectal resection patients cared for in a multi-interventional standardized Enhanced Recovery Program were included. All patients wore an activity monitor to collect physical activity data from postoperative day (POD) 0 to POD 3, which included step counts and time spent in the standing, sitting and supine positions. Outcomes included hospital LOS, time to passage of first flatus, time to return of GI function (i.e. tolerance of solid oral intake and defecation), and serious in-hospital complications. Statistical analysis was performed using linear and logistic regression models.

Results: Systematic review demonstrated that there are very few comparative studies evaluating the impact of early mobilization protocols on outcomes after abdominal and thoracic surgery, and that most of these studies were of poor quality. There were eight comparative studies that fit the review's inclusion criteria, and they reported inconsistent results regarding the impact of early mobilization protocols on postoperative complications, length of hospital stay (LOS), return of gastrointestinal (GI) function, performance-based functional outcomes and patient-reported outcomes. There is minimal literature to suggest a positive impact of early mobilization protocols on clinical, functional and health-related quality of life outcomes after abdominal and thoracic surgery. However, in our observational study, increased step counts, standing time, sitting time and non-supine time were each associated with a reduction in LOS. Increased standing time was also associated with a significant decrease in time to return of GI function.

Conclusion: While systematic review of the small number of previous trials did not support the use of a specific mobilization protocol to improve outcomes after abdominal or thoracic surgery, our observational study suggests an association between increased postoperative mobilization and improved in-hospital outcomes, which is encouraging for future research. High-quality comparative studies are needed to evaluate the impact of interventions to increase mobilization on postoperative outcomes. Results from these studies may help to guide clinicians and hospital administrators regarding the allocation of resources to this potentially resource-intensive intervention.

RÉSUMÉ

Introduction : La mobilisation précoce est un aspect important des soins postopératoires. Parmi les bienfaits les plus importants, on retrouve la prévention des effets secondaires néfastes du repos au lit, comme la thromboembolie veineuse, les complications pulmonaires, la perte musculaire et la diminution de la forme physique. L'activité physique précoce peut entrainer plusieurs autres bienfaits potentiels sur différents aspects de la récupération après une intervention chirurgicale, comme les résultats cliniques, l'état fonctionnel du patient et la qualité de vie. L'objectif de la thèse consiste à examiner les données probantes disponibles concernant l'impact des protocoles de mobilisation précoce postopératoire sur les résultats après la chirurgie abdominale ou thoracique, et à explorer ensuite la relation entre l'activité physique précoce et des résultats cliniques spécifiques lors d'une étude observationnelle.

Méthodes : Un examen systématique de la documentation médicale a été réalisée en suivant le protocole « PRISMA ». Une étude observationnelle a été réalisée à l'aide d'une analyse secondaire des données obtenues à la suite d'un essai à répartition aléatoire contrôlé. Les données incluses provenaient des résultats postopératoires consécutifs de soixante patients adultes ayant subi une résection colorectale et recevant les soins dans un programme multidisciplinaire de récupération accéléré. Tous les patients portaient un moniteur d'activité qui recueillait les données d'activité physique de la première à la troisième journée postopératoire, et qui incluait le nombre de pas marchés, et le temps passé en position debout, assise et allongée. Les résultats étaient la durée de l'hospitalisation, le temps passé avant le passage des premiers gaz intestinaux, le temps passé avant le retour de la fonction gastro-intestinale (c.-à-d. la tolérance aux aliments solides administrés par voie orale, et la défécation), et les complications

graves en milieu hospitalier. L'évaluation statistique a été réalisée à l'aide de modèles de régression linéaire et logistique.

Résultats : L'examen systématique de la documentation médicale a démontré qu'il existe très peu d'études comparatives évaluant l'impact des protocoles de mobilisation précoce sur les résultats après une chirurgie, et que la plupart de ces études étaient de qualité inférieure. Huit études comparatives répondaient aux critères d'inclusion de l'examen, et elles présentaient des résultats contradictoires concernant l'impact des protocoles de mobilisation précoce sur les complications postopératoires, la durée de l'hospitalisation, le retour de la fonction gastro-intestinale, les résultats fonctionnels basés sur la performance et les résultats fournis par les patients. Il existe peu de documentation médicale démontrant un impact positif des protocoles spécifiques de mobilisation précoce sur les résultats cliniques, fonctionnels et la qualité de vie reliée à la santé après une chirurgie abdominale ou thoracique. Toutefois, lors d'une étude observationnelle, une association importante a été démontrée entre l'activité physique et la durée de l'hospitalisation, ainsi que le temps passé avant la récupération de la fonction gastro-intestinale. Une augmentation du nombre de pas, du temps passé debout, assis et non allongé a été associée à une diminution de la durée d'hospitalisation. L'augmentation du temps passé debout a également été associée à une réduction importante du temps passé avant la récupération de la fonction gastro-intestinale.

Conclusion : Il est important d'effectuer des études comparatives de qualité supérieure à l'avenir afin d'évaluer l'impact des protocoles de mobilisation précoce sur une grande variété de résultats postopératoires. Les résultats de ces études pourraient guider les cliniciens et les administrateurs des hôpitaux en matière d'allocation des ressources pour cette intervention postopératoire qui requiert beaucoup de main-d'œuvre. Des résultats encourageants démontrent qu'une augmentation de la mobilisation postopératoire précoce pourrait réduire la durée de l'hospitalisation et le temps passé avant la récupération de la fonction gastro-intestinale, que l'identification de stratégies efficaces pour promouvoir la mobilisation précoce après une chirurgie pourrait améliorer davantage ces résultats.

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PREFACE

This thesis is presented in a manuscript-based format, evaluating the impact of early postoperative mobilization on a variety of clinical, functional and patient-reported outcomes. The abstract of the first manuscript was presented as a poster presentation at both the Enhanced Recovery After Surgery (ERAS®) annual congress in May 2015 and the Canadian Surgical Forum annual meeting in September 2015. The associated manuscript was accepted for publication in Surgery in November 2015. The second manuscript has not yet been submitted for publication.

CONTRIBUTION OF AUTHORS

Dr. Tanya Castelino: Development of protocols for both studies, data extraction/collection/entry, data analysis, drafting and revisions of manuscripts

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CHAPTER 1:

INTRODUCTION

1.1 Early mobilization to combat the surgical stress response

The act of performing surgery on a patient induces a biochemical cascade in the body similar to that of traumatic injuries, burns, or widespread infection and sepsis. The surgical stress response is triggered upon incision, which causes activation of the sympathetic nervous system and subsequent release of pro-inflammatory cytokines and neuroendocrine hormones that are responsible for the systemic inflammatory response[1]. Acute inflammatory markers, for example white blood cell counts and C-reactive protein (CRP) levels, increase after surgical insult, and other biochemical markers, such as triglycerides, albumin and pre-albumin levels, decrease after surgery[2].

A central feature of the metabolic response to injury is the development of a state of acute insulin resistance. Many of the pro-inflammatory cytokines released as a result of surgical intervention, such as interleukin-6, tumour necrosis factor-α, CRP and complement C3, are associated with increased insulin resistance[3, 4]. Insulin resistance occurs almost immediately after surgery, and the degree of resistance is proportional to the magnitude of the surgery, i.e. the more invasive the procedure, the higher the insulin resistance[5, 6]. The overall result is increased catabolism of protein, carbohydrate and fat to provide food substrate, with subsequent protein breakdown of up to 50-70 grams of muscle protein per day, as well as lipolysis and free-fatty acid oxidation[7].

Increased physical activity and exercise have been shown to decrease inflammation and improve insulin sensitivity in healthy people as well as in specific disease states, such as non-insulin dependent Type 2 diabetes and atherosclerosis[8, 9]. While there is enormous interest in the use of exercise to prevent and treat many medical conditions, research on the physiologic benefits of exercise for surgical patients in the postoperative period is lacking. However, through our understanding of the pathophysiology behind the surgical stress response and our knowledge of the benefits of physical activity in healthy people and various disease states, we can hypothesize that exercise may be beneficial in preserving insulin sensitivity and decreasing the inflammatory response in surgical patients.

In addition to the biochemical changes that could be associated with increased physical activity in postoperative patients, there are several clinical benefits that can be observed. Bed rest has been shown to have many negative effects, such as venous thromboembolism, pulmonary and cardiac dysfunction (decreased functional vital capacity, stroke volume and cardiac output), muscle wasting and fatigue[7]. Muscle mass drops by 1.5-2% per day for the first two to three weeks of enforced bed rest[10]. The earlier that patients are advised to mobilize and/or exercise after surgery, the more we are likely to prevent these deleterious side effects[11]. Venous stasis and a pro-inflammatory state are risk factors for the development of thromboembolism, which can be lowered with mobilization. By getting out-of-bed, i.e. being in the upright position, and moving around after surgery, patients can increase their vital capacity and prevent the development of atelectasis and subsequent pneumonia, as well as increase their cardiac output. Increased postoperative activity levels may also have a dual benefit in preventing muscle wasting, by preventing the atrophy that accompanies inactivity and by decreasing insulin resistance, thereby lessening catabolic effects and protein breakdown.

1.2 Knowledge gaps: Definition, quantity, and resources

There are many gaps in our current knowledge regarding postoperative early mobilization. To begin with, it is challenging to find a consistent definition of the term “early mobilization” after surgery. The concept was first described in 1899 by Dr. Emil Ries, a gynecologist who allowed his patients to get out of bed within the first 24 to 48 hours after surgery[12]. It was common practice at the time to keep patients confined to their beds for two to three weeks after surgery. The landmark paper by Ries did not change practice amongst surgeons during his time, and in fact there was no further American literature published on the topic of early mobilization after surgery until 1941 by Leithauser and Bergo[13]. They defined early mobilization as standing up out-of-bed, walking, and performing deep breathing exercises on postoperative day (POD) one. In 1966, Leithauser and colleagues described a very specific three-stage procedure for early mobilization, consisting of progressing from sitting to standing, then performing pulmonary and “stooping” exercises, followed finally by walking at least once or twice on the day of surgery. They encouraged attempts at early rising immediately after recovering from anesthesia on the day of surgery, so that the patients could “literally walk back to health”[14]. Since then however, the definition of early mobilization after surgery has become much less specific. In recent years, early mobilization has been loosely defined as “getting out-of-bed”, and not specifically as walking or doing any type of special exercise[15, 16]. While the definition of “mobilization” has been very inconsistent, there seems to be agreement that "early" should mean on the day of surgery or on POD 1 at the latest.

There are many unanswered questions regarding early postoperative mobilization, in addition to the lack of a clear definition of the term. For example, are certain types of activity better than others, i.e. is walking better than sitting out-of-bed? While we know that physical activity has many potential benefits in the postoperative period, we do not know how much activity is required in order to see beneficial effects. Furthermore, if more mobilization is better for surgical patients, how do we achieve these levels, i.e. can patients mobilize or exercise by themselves, or do they require assistance and supervision? If extra personnel are required in order to facilitate patients' early mobilization after surgery, should additional resources be devoted to these interventions?

Recent studies have attempted to quantify early mobilization in postoperative patients. A multicentre study evaluating colon surgery patients demonstrated that only 53% of European patients were walking by POD 3 and approximately 71% of American patients were walking by POD 2[17]. But how much walking is actually achieved may be very minimal. A prospective observational study in postoperative upper abdominal surgery patients showed median "uptimes" of only 3 minutes on POD 1 to 34.4 minutes by POD 4[18]. These values raise another important question, which is how do we quantify mobilization in the postoperative period? There are several methods to measure physical activity levels after surgery and these will be discussed further in section 1.4.

1.3 A new era: Enhancing recovery after surgery

Perioperative care has evolved immensely since earlier mobilization became a routine aspect of postoperative therapy. The concept of enhanced recovery after surgery emerged in the last twenty years, and has revolutionized the way we deliver perioperative care to our patients. Enhanced recovery programs (ERPs) are multidisciplinary care pathways that combine many different interventions before, during and after surgery with the goal of reducing the perioperative stress response in order to hasten the patient's recovery, as well as preventing postoperative organ dysfunction and complications[19]. Preoperative interventions include patient education and counseling, smoking and alcohol cessation, avoidance of fasting, preoperative carbohydrate drinks and avoidance of bowel preparation when possible. Intraoperative interventions include prevention of hypothermia, antimicrobial prophylaxis, minimally invasive surgery whenever possible and fluid optimization. Postoperative components of ERPs include early oral feeding, multimodal analgesia, avoidance of drains, early removal of urinary catheters, standard laxatives and "early mobilization". Generally, adherence to the postoperative elements is lower than for the pre- and intraoperative components[20].

There is a lot of variability between different institutional ERPs in terms of how many elements are included, as well as how each element, including "early mobilization", is defined. This is illustrated by the studies included in a 2011 Cochrane review[21] evaluating the impact of ERPs compared to conventional care on postoperative morbidity and length of hospital stay (LOS) after colorectal surgery. Table 1-1 summarizes how each of these randomized trials defined early mobilization, demonstrating significant variability in the way this element is defined and implemented, with some programs potentially requiring extra resources, especially if allied health professionals are required to be involved in mobilizing patients.

Table 1-1. Variability of benchmarks for early mobilization in ERP protocols.

Study	Early mobilization definition
Anderson et al.[22]	• Sit out-of-bed for 20 minutes on day of surgery • Walk the length of the ward on POD 1 with help of physiotherapist • Further daily mobilization as per patient tolerance
Delaney et al.[23]	• Mobilization only as tolerated on day of surgery • Walk at least one circuit of the nursing floor (60 metres) up to 5 times on POD 1 • Sit out-of-bed between walks
Gatt et al.[24]	• Sit out-of-bed on day of surgery • Walk the length of the ward on POD 1 • Further mobilization as per patient tolerance • Described as an “active intervention by the physiotherapist”
Khoo et al.[25]	• Mobilization “encouraged” from the night of the operation • “Predefined mobility targets over the postoperative days”
Muller et al.[26]	• “Encouraged to early mobilization starting immediately after surgery”
Serclova et al.[27]	• “Immediately after postoperative stabilization”, encouraged to “exercise in bed as well as out of it”

The Enhanced Recovery After Surgery (ERAS®) Society has specific guidelines for early postoperative mobilization after colon and rectal surgery, which consist of getting the patient out-of-bed for two hours on the day of surgery and for six hours per day on each subsequent postoperative day until hospital discharge[28]. This benchmark is given a strong recommendation despite the low level of evidence[29] and the selection of those targets is essentially arbitrary.

The McGill University Health Centre (MUHC) introduced a multimodal ERP for colorectal patients in 2009[30]. The program includes 22 interventions, of which early mobilization plays a key role in postoperative care (Table 1-2). Patients are educated in the preoperative phase regarding the importance of early mobilization after surgery and given daily benchmarks to achieve based on the ERAS® Society guidelines, i.e. to stay out-of-bed for 2 hours on the day of surgery and for 6 hours per day from POD 1 until discharge. Patients are assisted with early mobilization by the nursing staff, and if additional assistance is required, the medical team requests a consultation from the physiotherapy team.

Table 1-2. MUHC ERP elements for colorectal patients

Intervention	Definition
Preoperative elements	
Preadmission patient education	Counseling from a nurse and a physician at preoperative clinic visit, and receiving a booklet outlining recovery goals and benchmarks during hospital stay.
Selective mechanical bowel preparation (MBP)	MBP reserved for patients undergoing planned stoma during rectal resection.
Carbohydrate loading	Preoperative carbohydrate drink up to two hours prior to induction of anesthesia (at least 50 grams of carbohydrate in at least 400 mL of fluid).
No long-acting sedation	No long-acting sedative medication prior to surgery (e.g. opioids, benzodiazepines).
Intraoperative elements	
Antibiotic prophylaxis	Antibiotic prophylaxis prior to surgical incision.
Epidural anesthesia	Thoracic epidural analgesia prior to surgical incision.
Minimally invasive approach	Laparoscopic resection whenever possible.
Balanced intravenous fluids	Intraoperative maintenance fluids excluding replacement of blood loss: for laparoscopy <3 mL/kg/hour; for open surgery <5 mL/kg/hour. If bowel preparation used, an extra 1000 mL of fluids is allowed to cover losses.
Postoperative nausea and vomiting (PONV) prophylaxis	Multimodal PONV prophylaxis administered according to Apfel score[31].
Avoidance of abdominal or pelvic drainage	No resection site drainage.
Normothermia	Body temperature $\geq$36°C at the end of surgery.

Thromboembolic disease prophylaxis	Prophylaxis with low molecular-weight heparin.
Avoidance of nasogastric tube drainage	Nasogastric tube removed at the end of surgery.
Postoperative elements	
Multimodal analgesia	Use of opioid-sparing strategies including thoracic epidural analgesia, abdominal trunk blocks, IV lidocaine, acetaminophen, NSAIDs.
Oral liquids on POD 0	Clear liquids postoperatively on the day of surgery.
Oral nutritional supplements on POD 0	Nutritional drinks (e.g. Boost, Ensure) postoperatively on the day of surgery.
Early mobilization	Patient mobilized out-of-bed within 24 hours of surgery.
Early termination of IV fluid infusion	Termination of IV fluids by the morning of POD 1.
Early termination of urinary drainage	Termination of urinary drainage by POD 1.
Full diet on POD 1	Patient received at least one meal of solid food by POD 1.
Chewing gum	Patient chewing gum at least three times a day for thirty minutes by POD 1.
Laxatives	Laxative medication started by POD 1.
Transition to oral analgesia by POD 2	Termination of thoracic epidural analgesia or patient-controlled analgesia with transition to oral medication by POD 2.

However, compliance with these targets is relatively low. For example, in a multi-institutional ERAS® society registry, compliance was reported as 48% on postoperative day (POD) 0 and 28% on POD 1[20]. Perhaps the lack of compliance with early mobilization relates to the many barriers to it that exist in the postoperative period. These include pain, fatigue, lack of motivation and surgical attachments such as drains, nasogastric tubes, urinary catheters, and intravenous lines and epidurals that require a pole to be transported by the patient or caregiver[32, 33]. Despite having a low adherence rate, early mobilization has been shown to be an independent predictor of "early recovery", which was defined as a reduction in total hospital stay i.e. number of days during initial admission plus readmission days within 30 days of index operation. Vlug et al. found that compliance with early mobilization, defined as a minimum of 540 minutes out-of-bed during POD 1, 2 and 3 in total (49% of patients in the ERP group), was independently associated with a 32% reduction in total hospital stay[34]. These results are encouraging, however may be less meaningful as the authors do not comment on how adherence to early mobilization was measured.

1.4 Measuring physical activity and postoperative recovery

1.4.1 Measurement of physical activity

The exposure of interest in the research studies that follow is physical activity in the immediate postoperative period. There are many different ways to measure physical activity, including subjective and objective methods. Subjective methods include self-reporting by keeping activity diaries, recording targets or milestones that have been achieved, or filling out questionnaires or specific instruments that have been designed to capture data on physical activity parameters[35]. Twenty years ago, the American College of Sports Medicine's journal documented over thirty different types of self-reported activity instruments[36]. Most of these instruments consist of questions regarding the walking frequency, intensity, speed or pace over a certain period of time. These parameters are not necessarily perceived the same way by everyone and may not be comparable between individuals. Another subjective method of measuring physical activity levels for postoperative patients involves nursing observations from the medical record. However, these data are likely to be recorded in a non-standardized fashion and are affected by many factors, for example differences between nurses' perceptions of their patients activity levels, number of patients per nurse, overall amount of work during any given shift, omitting or forgetting to document the patient's mobilization, etc. All of the subjective methods of physical activity recording are subject to recall bias and other influences and hence are not ideal for use in research contexts. For example, if a patient feels very pressured to walk by the healthcare team, he or she may overestimate the amount of walking done.

Several different types of objective methods exist for the measurement of physical activity levels, including direct observation, indirect calorimetry, and activity monitors. To add more complexity, there are also different units with which to quantify physical activity, for example measuring the number of steps taken when walking, intensity of physical activity, amount of energy expended during physical activity, time spent in different body positions or types of activities, etc. Direct observation allows for the measurement of time spent in specific body positions or in types of activities, for example walking on a treadmill, ascending or descending stairs, or cycling. While this method has been used as a gold standard against different types of activity monitoring devices[37], it falls short when the desired data pertains to intensity of physical activity or energy expenditure. In addition, this method is very impractical and resource intensive, as it requires the presence of someone to observe and record activity levels over extended periods of time. Indirect calorimetry is considered to be the gold standard for the measurement of energy expenditure during free-living activities[38, 39], however this measurement is usually carried out in a laboratory setting, and is therefore not practical for use in large-scale research studies or clinical settings[40]. Finally, there are many different activity-monitoring devices that are portable and practical, in both the research and clinical settings. There are several functions that an activity monitor can possess, the simplest of which is the pedometer function. A pedometer detects the number of steps by using a spring-loaded mass that measures and records the obvious impact produced when taking a step[41]. Another parameter that can be measured by activity monitors is accelerometry. The accelerometer function consists of a sensor that measures an object's linear acceleration along one or several reference axes[41]. Most activity monitors that have an accelerometer function can measure the speed along different axes, i.e. uniaxial, biaxial, or triaxial, and can thus determine the intensity of the activity being performed. Accelerometer data is measured in "counts" which are dimensionless units that are not easily recognizable and are specific to the brand of accelerometer being used. Counts however can differentiate between time spent in sedentary activities versus light, intermediate and heavy physical activities[42]. Lastly, some activity monitors have an inclinometer function, i.e. the device records the wearer's body position based on the monitor's angle of inclination[37]. This function requires that the monitor be worn in a specific location, usually on the hip, waist or thigh, in order to accurately capture the data.

In general, the measurement of physical activity in postoperative patients for research and clinical purposes should be performed in a reliable and reproducible way. As these patients are not usually carrying out high-intensity activities, the more meaningful functions are the pedometer and inclinometer functions as opposed to the characterization of intensity of physical activity by the accelerometer function. The activity monitor chosen for the observational study reported below includes all three functions, however the focus remains on number of steps and time spent in different body positions, as explained in further detail in Chapter 4.

1.4.2 Measurement of postoperative recovery

Postoperative recovery is a complex construct without a single accepted definition. There are many stakeholders involved, each of whom may place emphasis on different aspects of recovery after surgery[43]. For example, the surgeon may use variables such as length of stay (LOS) or postoperative complications to measure a patient's recovery after surgery, while the anesthesiologist may consider the patient to be sufficiently recovered after discharge from the recovery room. Patients, however, define recovery as returning back to their baseline preoperative level of functioning, which usually happens weeks to months after surgery[44].

Lee et al.[45] suggest a measurement framework that includes three distinct phases of recovery: the early phase, from the end of operation to discharge from the recovery room; the intermediate phase, from arrival to the surgical ward to discharge home; and the late phase, from hospital discharge to return to baseline functioning. We can measure various clinical, functional and patient-reported outcomes (PROs) at different time points in the trajectory of their recovery after surgery. For example, there are physiologic measures that can indicate whether the patient is safe to go to the surgical ward from the recovery room. When the patient is on the surgical ward, we consider symptoms (e.g. pain), normalization of organ functions (e.g. ileus), and ability to carry out activities of daily living as markers of recovery and criteria for safe discharge. Once the patient leaves the hospital, the late phase of recovery is assessed using measures of performance (e.g. the 6-minute walk test (6-MWT)), physical activities (e.g. CHAMPS questionnaire) and health-related quality of life, (e.g. Short form-36 (SF-36)).

In this thesis, we focus on the intermediate (in-hospital) phase of recovery using the following outcomes:

1. Return of gastrointestinal (GI) function:

   Almost all patients undergoing bowel resection will develop an interruption of gastrointestinal function in the postoperative period, which is referred to as postoperative ileus (POI), and is characterized by a "transient cessation in bowel function" leading to abdominal distension, nausea, vomiting and delayed passage of flatus and defecation[46]. Prolonged POI is considered a complication of bowel surgery as it delays discharge, mobilization and overall recovery after surgery, as well as decreases absorption of drugs and nutrients by the GI tract, increases the cost of hospitalization, and increases the risk of further complications such as pulmonary complications and/or nosocomial infections due to prolonged hospitalization[47].

   Return of GI function can be defined in different ways, such as the amount of time to passage of first flatus or bowel movement. By measuring gastric emptying and colonic transit using scintigraphy, van Bree and colleagues found that a composite measure of recovery of GI function, namely time to tolerance of solid oral intake and defecation, was the best indicator of recovery of GI transit after colonic surgery. Surgeons frequently instruct their patients to walk after surgery in order to accelerate return of GI function, a recommendation based largely on tradition or anecdotes.

2. Postoperative complications:

   Negative outcomes after surgery can be divided into three different categories: failure to cure (e.g. residual tumour after resection), sequelae (i.e. a known "after-effect" of the surgery, e.g. not being able to ambulate after amputation of the lower limb), and postoperative complications, which are defined as any deviation from the normal postoperative course[48]. The most common classification system for grouping complications by severity is the Clavien-Dindo system[48], which groups postoperative complications into seven categories (Table 1-2). These classification systems are useful in the research context in that they provide a clear definition for each group of postoperative complications and thus allow for standardized analysis of complications.

Table 1-3. Clavien-Dindo system for classifying postoperative complications.[48]

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including dialysis)
Grade IVa	Single organ dysfunction
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

3. Length of stay (LOS) and time to readiness for discharge (TRD):

   LOS is an easy-to-measure, objective variable that is often used as a proxy measure of intermediate recovery. It is easy to obtain from administrative data. While LOS is increased when patient recovery is prolonged due to complications, functional impairments or poorly controlled symptoms, it is also prolonged for non-medical issues. To address these limitations, time to readiness for discharge (TRD) can be determined. TRD is a measure of when the patient is sufficiently recovered so as to not need continued in-patient care, i.e. it indicates the number of days in which a patient has fulfilled specific criteria for discharge from hospital[49]. This value may differ from LOS if there are other circumstances leading to the patient remaining in-hospital, for example social issues, administrative delays, etc. TRD has been validated as a reliable measure of recovery after colorectal surgery[50] and can be used as an outcome variable in addition to LOS to determine if there are major differences between the two variables.

1.5 Thesis objectives

While best practice guidelines recommend early mobilization and increased physical activity after surgery, there is a disconnect between the strength of the recommendation ("strong") and the level of good quality evidence ("weak") used to support the recommendation[29]. This thesis aims to identify and evaluate the available evidence, in the form of observational as well as comparative studies, for early mobilization protocols after abdominal and thoracic surgery. The resulting information was used to design an observational study that aims to answer questions raised by the literature review, and to subsequently formulate new questions to be answered by future interventional studies on early mobilization within enhanced recovery programs.

CHAPTER 2:

MANUSCRIPT #1

The Effect of Early Mobilization Protocols on Postoperative Outcomes Following Abdominal and Thoracic Surgery: A Systematic Review

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2.1 STRUCTURED ABSTRACT

Background: Early mobilization is considered an important element of postoperative care, however how best to implement this intervention in clinical practice is unknown. This systematic review summarizes the evidence regarding the impact of specific early mobilization protocols on postoperative outcomes after abdominal and thoracic surgery.

Methods: The review was performed according to PRISMA guidelines. We searched 8 electronic databases to identify studies comparing patients receiving a specific protocol of early mobilization to a control group. Methodological quality was assessed using the Downs and Black tool.

Results: Four studies in abdominal surgery (3 randomized controlled trials (RCTs) and 1 observational prospective study) and 4 studies in thoracic surgery (3 RCTs and 1 observational retrospective study) were identified. None of the five studies evaluating postoperative complications reported differences between groups. One of 4 studies evaluating length of stay reported a significant reduction in the intervention group. One of 3 studies evaluating gastrointestinal function reported differences in favour of the intervention group. One of 4 studies evaluating performance-based outcomes reported differences in favour of the intervention group. One of 5 studies evaluating patient-reported outcomes reported differences in favour of the intervention group. Overall methodological quality was poor.

Conclusion: Few comparative studies evaluated the impact of early mobilization protocols on outcomes after abdominal and thoracic surgery. The quality of these studies was poor and results were conflicting. While bed rest is harmful, there is little available evidence to guide clinicians in effective early mobilization protocols that increase mobilization and improve outcomes.

2.2 INTRODUCTION

Early mobilization is regarded as an important component of postoperative care. One of the first surgeons to describe the concept of early mobilization after surgery was Dr. Emil Ries, a gynecologist in Chicago, in 1899[12]. Despite the report by Ries, the practice of early postoperative mobilization was slow to gain favour in North America and patients were still commonly kept on strict bed rest for several weeks after surgery in order to minimize pain and ensure adequate healing of wounds[51]. It was only by the 1940s that early mobilization became accepted among surgeons as a number of observational studies suggested that this practice was not harmful to patients[13, 52]. In addition, evidence about the negative effects of immobilization (i.e. risk of thromboembolism, pneumonia, muscle wasting and physical deconditioning) also became available, reinforcing the importance of avoiding prolonged bed rest after surgery[53].

Within the last twenty years, there has been significant progress in perioperative care with the development of standardized enhanced recovery pathways (ERPs). ERPs combine many different elements of care in the preoperative, intraoperative and postoperative periods, and aim to reduce morbidity, decrease hospital length of stay (LOS), and improve patients' recovery after surgery[19]. ERPs are comprised of up to 25 different interventions in the perioperative period, however the relative contribution of each of these elements to the overall recovery process remains unclear[54]. Early mobilization is considered to be a key component of ERPs, consistent with the goals of supporting the early reestablishment of normal function[29].

Guidelines for perioperative care from the Enhanced Recovery After Surgery (ERAS®) Society[29] give early mobilization a strong recommendation grade, despite a very low level of evidence supporting its use. Although it is suggested that early mobilization within an ERP is an independent predictor of early recovery after colon cancer surgery[34], adherence to this intervention remains quite low[55]. There is little evidence in the literature regarding strategies to promote compliance to early mobilization, and significant differences in targeted mobilization goals between programs. A potential approach to increase compliance is by employing a specific mobilization protocol supported by personnel dedicated to mobilizing patients, like a physiotherapist; however the additional benefit of this resource-intensive approach is unknown. In this systematic review, we summarize the evidence regarding the impact of early in-hospital mobilization protocols on postoperative outcomes after abdominal and thoracic surgery in comparison to standard care.

2.3 METHODS

This systematic review was registered at PROSPERO International prospective register of systematic reviews (CRD42015014684) and was conducted according to the PRISMA Statement guidelines[56].

Search strategy

The database search was performed by one investigator (TL) using the following databases: MEDLINE (via OvidSP 1946 to 19/01/2015; via PubMed 1946 to 19/01/2015); Embase Classic

+ Embase (via OvidSP 1947 to 19/01/2015); BIOSIS Previews (via OvidSP 1969 to 2015 Week 7); CINAHL (via Ebsco 1937 to 19/01/2015); Web of Science (via ThomsonReuters 1996 to 19/01/2015); Scopus (via Elsevier 1996 to 19/01/2015); CENTRAL (via the Cochrane Library – issue 1 of 12, January 2015). The search was conducted in order to answer the research question: to what extent do early mobilization protocols impact upon postoperative outcomes in comparison to standard care? Relevant search and index terms were used to capture the following concepts: thoracic and abdominal surgery (e.g. thoracic, abdomen, abdominal, gastric, colorectal), early mobilization or exercise (e.g. early, accelerated, inpatient, postoperative, postsurgical, ambulation, walking, exercise therapy) and relevant outcomes (e.g. complications, length of stay, patient-reported outcomes, pain, quality of life). The MEDLINE search strategy is provided in Appendix 1. The reference lists of included studies were searched for relevant articles. The MEDLINE strategy was rerun prior to submission (06/02/2015) and no relevant studies were found.

Inclusion and exclusion criteria

Studies were included in the review if they met the following criteria: (1) involved adult patients undergoing abdominal or thoracic surgery, (2) a specific protocol for early in-hospital mobilization was used as an intervention (with out-of bed activities starting no later than postoperative day one), (3) a control group receiving either no structured mobilization protocol (i.e. patients were allowed to mobilize at-will) or a different mobilization protocol (i.e. if a standardized mobilization/physiotherapy protocol was already in place at the institution) was used as a comparator, (4) reported at least one of the outcome measures of interest and (5) were published in English or French. Studies were excluded if: (1) they involved patients undergoing cardiac or orthopedic procedures, (2) the early mobilization protocol was not described by the authors and (3) the early mobilization protocol was not tested in isolation (e.g. mobilization protocol within an enhanced recovery program vs. traditional care). We also excluded studies that employed additional outpatient mobilization strategies (without reporting any in-hospital outcomes) as we felt that we would not be able to separate the effects of early versus late mobilization on post-discharge outcomes. Studies where bed rest was prescribed for the control group were also excluded as this practice is no longer reflective of standard postoperative care.

Outcome measures

Outcome measures of interest in this review included postoperative complication rates, hospital length of stay (LOS), postoperative pulmonary function (spirometry), postoperative gastrointestinal (GI) function, performance-based functional tests (e.g. 6-minute walk test), patient-reported outcomes (PROs; measures of health status collected directly from patients through questionnaires) and adverse events. Data on the explanatory variable of amount of physical activity, as well as data on costs and adherence to the mobilization protocol were also extracted if available.

Study selection and data extraction

Two independent reviewers (TC and BA) screened through the titles and abstracts of the articles yielded by the search strategy. Articles that were clearly irrelevant were excluded. The remaining full-text articles were then screened independently against the selection criteria by two reviewers (TC and PN). Discrepancies were resolved by consensus within the research group.

Data were then independently extracted from the articles by two investigators (TC and PN) into a standardized data collection form. In addition to the outcome measures of interest, information about the study design, number of patients, age, gender, American Society of Anesthesiologists (ASA) score, preoperative diagnosis, type of surgery, and surgical approach were collected.

Quality assessment

The methodological quality of each study was independently evaluated by two investigators (TC and JF) using the Downs and Black tool[57]. This tool was chosen because it appraises the quality of both randomized controlled trials (RCTs) and non-randomized comparative studies and has been shown to have good internal consistency, test-retest reliability, inter-rater reliability and criterion-related validity[57]. A large-scale review assessing 194 tools to evaluate methodological quality deemed the Downs and Black tool as appropriate for use in systematic reviews[58]. The Downs and Black tool consists of twenty-seven items divided into five sub-scales: reporting (10 items), external validity (3 items), bias (7 items), confounding (6 items), and power (1 item). The original tool generates an overall score with a maximum of 32 points but, as recommended in previous literature[59, 60] we used a modified version with a maximum score of 28 (for simplicity, the last item was scored 0 or 1 instead of the original range of 0 to 5). Disagreements regarding the quality assessment were resolved by consensus within the research group.

Data analysis

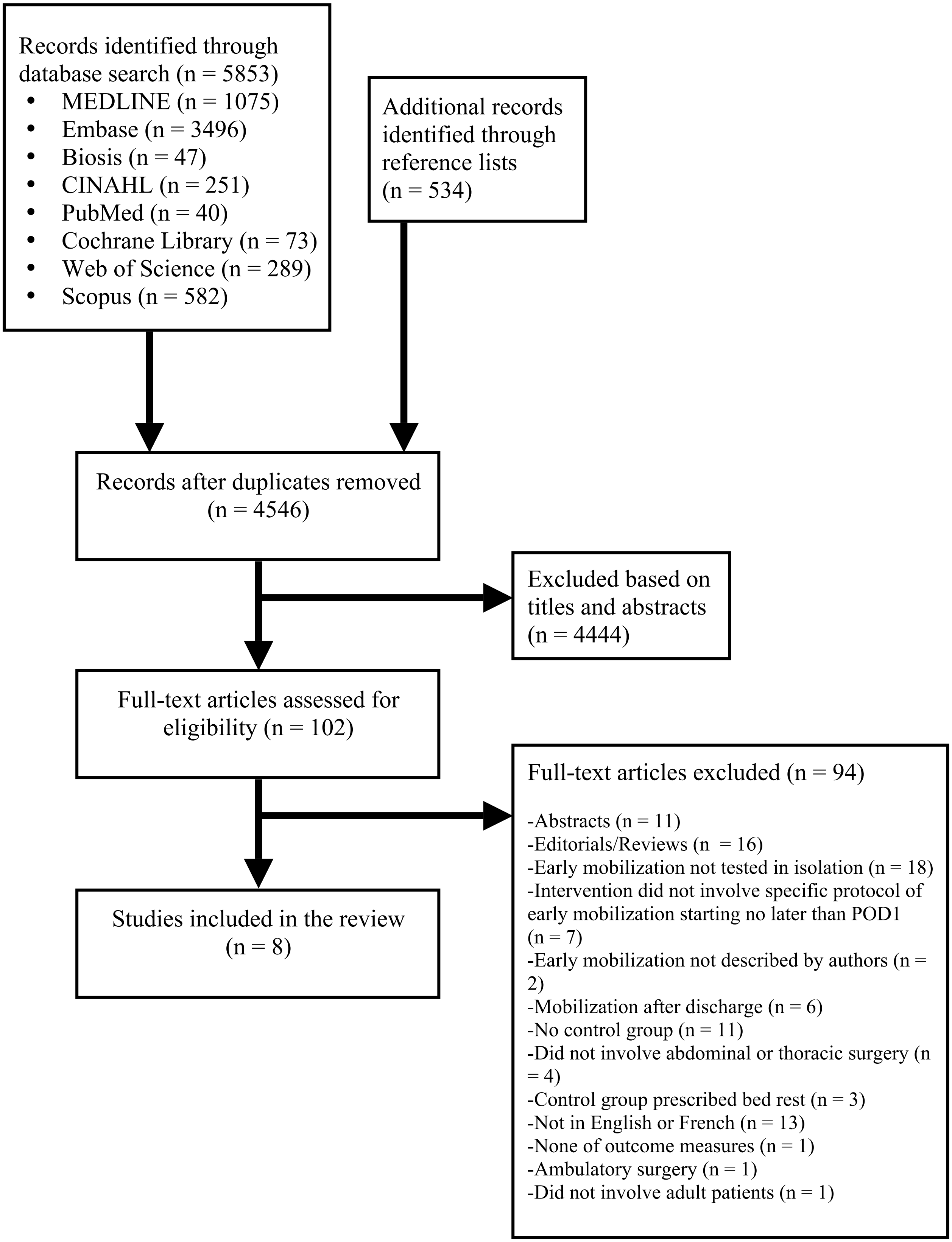
We intended to conduct a meta-analysis if studies were sufficiently homogeneous with respect to design, population, interventions and outcome measures; however, the studies identified by the search were considerably heterogeneous. As pooling of data from heterogeneous studies into a meta-analysis can produce misleading results[61], this systematic review is reported using a narrative synthesis approach.

2.4 RESULTS

Literature search

The literature search yielded a total of 4546 citations after the removal of duplicates. Of these citations, 102 full-text articles were screened and 94 were excluded (Figure 2-1).

Figure 2-1. PRISMA flowchart showing included and excluded articles



The excluded articles and reasons for exclusion are provided in Appendix 2. The main reasons for exclusion were: intervention was tested as part of an enhanced recovery program (n = 18), the article was an editorial or review (n = 16), the article was not in English or French (n = 13) and the study did not involve a control group (n = 11). Eight full text articles met our selection criteria and were included in the review[62-69].

Characteristics of the included studies

Four studies involved patients undergoing abdominal surgery (3 RCTs[63-65] and 1 prospective observational study[62]) and 4 studies involved patients undergoing thoracic surgery (3 RCTs[66-68] and 1 retrospective observational study[69]). The characteristics of these studies are summarized in Table 2-1 and their quality assessment scores are shown in Table 2-2.

Table 2-1. Summary of characteristics of included studies

Reference	Type of Surgery	Study Design	Total Number of Patients	Primary Outcome	Follow-Up*
Le, 2014	Abdominal	Prospective Observational	30	PRO	1 month
Ahn, 2013	Abdominal	RCT	31	LOS	30 days
Liebermann, 2013	Abdominal	RCT	129	# of steps 24 hours prior to discharge	In-hospital
Waldhausen, 1990	Abdominal	RCT	35	Myoelectric activity of bowel wall	1 month
Arbane, 2014	Thoracic	RCT	131	Physical activity	4 weeks
Granger, 2013	Thoracic	RCT	15	Safety, Feasibility	12 weeks
Arbane, 2011	Thoracic	RCT	51	PRO	12 weeks
Kaneda, 2007	Thoracic	Retrospective Observational	86	Safety	Not specified

*Length of maximum follow-up. RCT = randomized controlled trial, LOS = length of stay, PRO = patient-reported outcome.

The RCTs by Ahn et al.[63] and by Granger et al.[67] had the highest methodological quality (a score of 18/28 on the Downs and Black tool). The RCT by Waldhausen et al.[65] was the study with the lowest quality (score of 7/28). Common methodological issues observed in the included studies were poor reporting (i.e. no data on adverse events[62-66, 68] and losses to follow up[63-69]), lack of information on external validity (i.e. sampling strategy not described[62-69]), lack of blinding of outcome assessors[62-66, 69], lack of randomization[62, 65, 69], lack of concealment of allocation[62-69] and lack of information on statistical power[62, 65, 67, 69].

Table 2-2. Quality assessment scores of included studies, using modified Downs & Black Checklist

	Reporting (11)	External Validity (3)	Internal Validity – Bias (7)	Internal Validity – Confounding (6)	Power (1)	Total (28)
Abdominal						
Le, 2014	8	0	1	3	0	12
Ahn, 2013	9	0	4	4	1	18
Liebermann, 2013	7	1	4	3	1	16
Waldhausen, 1990	6	0	1	0	0	7
Thoracic						
Arbane, 2014	6	1	2	4	1	14
Granger, 2013	8	1	5	4	0	18
Arbane, 2011	6	0	2	1	1	10
Kaneda, 2007	6	1	1	2	0	10

There were a total of 508 participants included in the eight studies, 225 abdominal surgery patients and 283 thoracic surgery patients. There was inconsistent reporting of sample characteristics, with one study[65] completely omitting this information (Table 2-3). There were no statistically significant differences between mobilization and control groups in terms of age and gender, except in one RCT[66] where there were more females in the mobilization group (55% vs. 36% in the control group, p = 0.03). Studies in abdominal surgery included patients undergoing various GI procedures[62, 65], colon resection for cancer[63] or hysterectomy for benign and malignant diseases[64]. The majority of these studies included patients undergoing both open and laparoscopic surgery[62-64]. All studies in thoracic surgery included patients undergoing lung resection for cancer, with the majority including both open surgery and video-assisted thoracoscopic surgery (VATS)[66, 68].

Table 2-3. Sample characteristics

Reference	Sample Size (n)		Age (years)		Male (%)		BMI (kg/m^2)	
	Int	Control	Int	Control	Int	Control	Int	Control
Le, 2014	15	15	48.9±9.8	51.4±8.7	40%	53%	NR	NR
Ahn, 2013	17	14	55.6±7.1	57.4±6.1	71%	36%	24.27±3.39	22.59±2.01
Liebermann, 2013	61	68	56	53	0%	0%	30.5	30.6
Waldhausen, 1990	10	25	NR	NR	NR	NR	NR	NR
Arbane, 2014	64	67	67±11	68±11	45%	64%	26±4.6	26±4.7
Granger, 2013	7	8	57±16.2	72.4±12.4	42.9%	62.5%	26.9±4.7	28.7±5.9
Arbane, 2011	26	25	65.4	62.6	NR	NR	25.5±3.6	25.7±4.8
Kaneda, 2007	36	50	65±9	66±9	61%	54%	NR	NR

Table 2-3 cont'd.

Reference	Diagnosis		Surgical Approach*		LOS	
	Int	Control	Int	Control	Int	Control
Le, 2014	NR	NR	"Similar"	"Similar"	5.2±5.5	5.1±6
Ahn, 2013	Colon cancer	Colon cancer	Lap 14 Open 2 Robotic 1	Lap 11 Open 2 Robotic 1	7.82±1.07	9.86±2.66
Liebermann, 2013	Gyne-onc 35 Uro-gyne 17 Benign 9	Gyne-onc 29 Uro-gyne 24 Benign 15	Lap 13 Open 14 Robotic 27 Vaginal 7	Lap 12 Open 20 Robotic 22 Vaginal 14	1.54	1.71
Waldhausen, 1990	NR	NR	Open	Open	NR	NR
Arbane, 2014	NSCLC	NSCLC	VATS 19 Open 45	VATS 12 Open 45	7.5 (5 to 8)	7.1 (6 to 8)
Granger, 2013	Suspected or confirmed cancer	Suspected or confirmed cancer	NR	NR	4 (3 to 9)	9 (4 to 17)
Arbane, 2011	NSCLC	NSCLC	VATS or open	VATS or open	8.9±3.3	11.0±8.9
Kaneda, 2007	NSCLC	NSCLC	Open	Open	NR	NR

Values are reported as mean±standard deviation, median (interquartile range), Int = intervention, NR = not reported, BMI = body-mass index, gyne-onc = gynecologic-oncology, uro-gyne = urologic-gynecology, NSCLC = non-small cell lung cancer, lap = laparoscopic, VATS = video-assisted thoracoscopic surgery. *Open refers to laparotomy for abdominal surgery and thoracotomy for thoracic surgery.

There was a considerable amount of variation in the protocols of early mobilization received by patients, the details of which are summarized in Table 2-4. Three studies in abdominal surgery involved early mobilization protocols supervised by a health professional[62, 63, 65] and in one study the protocol was unsupervised (involved clear goal setting with encouragement and education)[64]. In 3 studies, the protocol involved only sitting and walking[62, 64, 65] and 1 study included more complex exercises (stretching, straightening and balance)[63]. In all studies involving thoracic surgery, the intervention comprised a protocol of early mobilization supervised by a healthcare professional. In one study, the protocol involved only sitting and walking[69] and 3 studies included aerobic (walking or cycling) and strengthening exercises[66-68]. Mobilization protocols in abdominal surgery were compared to a control group where patients did not receive a specific early mobilization intervention, but were not restricted to bed rest; whereas all studies in thoracic surgery involved a control group receiving some form of less intensive early mobilization intervention supervised by a healthcare professional, which was already the standard of care at the institution.

Table 2-4. Specific mobilization protocols of each study

	Mobilization Group	Control Group
Le, 2014	• Walking with volunteers, a minimum of one lap around the floor	• Not walking with volunteers (i.e. walking independently, ad lib)
Ahn, 2013	**POD 1:** • Supervised exercise (twice/day) • Stretching (neck, shoulder, wrist, ankle, pelvis) • Core exercise (pelvic tilt) • Resistance exercise • Unsupervised sitting or walking in the ward **POD 1 – 3:** • Supervised exercise (twice/day) • Stretching (whole body, leg, shoulder) • Core exercise (pelvic tilt and thrust, one leg raise, crunch) • Resistance exercise (chest, shoulder, arm, thigh,	• Unsupervised sitting or walking in the ward • Unsupervised sitting or walking in the ward

	calf) • Unsupervised walking in the hallway **POD 2 – discharge:** • One supervised and one unsupervised exercise • Stretching (whole body, leg, shoulder) • Core exercise (pelvic tilt, bridge, one leg raise, crunch) • Resistance exercise (chest, shoulder, arm, thigh, calf) (12 repetition x3 sets) • Supervised balance exercise (once/day) • One leg standing, one leg calf raise, hip adduction/abduction, hip flexion with knee bent, hip extension • Unsupervised walking in the hallway	• Unsupervised sitting or walking in the ward
Liebermann, 2013	• Specific ambulation goal: at least 500 steps before discharge • Bedside signs, signs on the patient's hospital room door • Reminders at every encounter with health care team members	• No extra encouragement for ambulation • No ambulation goals
Waldhausen, 1990	• Ambulatory regimen starting 12 to 24 hours after operation • Walking at least 75 yards during each session • Any ad lib walking that patients desired	• Did not ambulate outside their hospital rooms until after POD 4
Arbane, 2014	• Standard care, as control group • Once-daily cycle (30 minutes/session) and strength training sessions from POD 1-5 • Additional daily mobilization encouraged • Upon discharge, home walking program	• Standard care, including routine physiotherapy, airway clearance techniques, and upper limb activities
Granger, 2013	• Standard care, as control group • Twice daily structured exercise program involving aerobic, resistance, and stretching exercises from POD 1 until discharge • Upon discharge, home exercise routine	• Standard care, including routine physiotherapy and mobilization, respiratory physiotherapy if developed pulmonary complications, and thoracic spine and shoulder stretches
Arbane, 2011	• Standard care, as control group • Twice daily strength and mobility training from POD 1-5 • Upon discharge, further 12-week home program of paced exercise	• Standard care, including routine physiotherapy, airway clearance techniques, mobilization as able, and upper limb activities
Kaneda, 2007	• Sitting position for 30 minutes, 3.5 hours after surgery • Walking approximately 30 metres total, 4 hours after surgery	• Same protocol as the mobilization group, except was performed on POD 1

Postoperative complications

Of the studies involving abdominal surgery, only two[62, 63] reported on postoperative complications. Ahn et al.[63] described one wound infection (5.9%) in the mobilization group and one case of postoperative ileus (7.1%) in the control group, and there were no reoperations or readmissions within thirty days of hospital discharge. Le et al.[62] reported the same rate of overall complications in both groups (26.7%), including pancreatic fistula, abscess, dehiscence, difficulty weaning from total parenteral nutrition, acute anemia secondary to blood loss, and wound infection. Neither study reported an inferential comparison between groups (i.e. p-values).

Of the thoracic studies, three[66, 68, 69] reported on postoperative complications, however these complications were not uniformly defined across all studies. The 2014 study by Arbane et al.[66] had complications predefined by the surgical team, and divided them into respiratory, cardiac and other, and also included mortality and transfer to critical care units >72 hours after surgery. They found 31% of participants in the mobilization group (16% respiratory, 8% cardiac, 8% other) and 33% of participants in the control group (24% respiratory, 0% cardiac, 9% other) suffered postoperative complications, with no inferential statistics reported (p-values). The 2011 study by Arbane et al.[68] defined postoperative complications as "X-ray changes reported by radiologist as pneumonia, respiratory complications requiring additional ventilatory support and/or necessitating a return to high dependency care." There were 2 patients in the mobilization group and 3 patients in the control group who had predefined complications, however there were no statistically significant differences between the groups. Kaneda et al.[69] reported only specific postoperative complications, including respiratory complications (bacterial pneumonia, acute exacerbation of interstitial pneumonia, acute respiratory distress syndrome), deep venous thrombosis, and skin ulcers, of which no participants suffered.

Hospital length of stay

Of the abdominal studies, three[62-64] reported on hospital LOS. Ahn et al.[63] reported the mean ± SD LOS in the mobilization group to be significantly shorter, at 7.82 ± 1.07 days versus 9.86 ± 2.66 days in the control group ($p = 0.005$). The other two studies did not find a significant difference. Liebermann et al.[64] found a mean LOS of 1.54 days in the mobilization group and 1.71 days in the control group ($p = 0.388$). Le et al.[62] showed a mean ± SD LOS of 5.2 ± 5.5 days in the mobilization group and 5.1 ± 6 days in the control group ($p = 0.98$).

Of the thoracic studies, three[66-68] reported information regarding hospital LOS and none found statistically significant differences between the groups. Arbane et al.[66] found a median LOS of 7.5 (IQR 5 to 8) days in the mobilization group and 7.1 (IQR 6 to 8) days in the control group. Arbane et al.[68] showed a mean ± SD LOS of 8.9 ± 3.3 days in the mobilization group and 11.0 ± 8.9 days in the control group. Granger et al.[67] found a median LOS of 4 (range 3 to 9) days in the mobilization group and 9 (4 to 17) days in the control group.

Pulmonary function tests

None of the abdominal studies reported pulmonary function test results.

Three[66-68] of the thoracic surgery studies report baseline pulmonary function test results (e.g. forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC)) and found no significant differences between mobilization and control groups, however none of these studies assess pulmonary function in the postoperative period as one of their outcome measures.

Return of gastrointestinal (GI) function

In abdominal surgery, two[63, 65] studies included GI function as an outcome of interest, with varying degrees of detail. Waldhausen et al.[65] reported return of GI function as the primary outcome of interest, and the authors report this in terms of myoelectric activity of the gut wall and do not describe this phenomenon in clinical terms. The authors carried out a complex study in which they placed seromuscular bipolar recording electrodes in the stomach, jejunum, colon, and Roux limb (if present) at the time of laparotomy. They subsequently measured "slow wave frequency, presence of migrating myoelectric complexes (MMCs), amount of spike activity in phases II and III and presence of colonic discrete and continuous electric-response activity patterns" at POD1-5 and 7, and at one month postoperatively, in both the early ambulation and control groups. These recordings were to determine if early ambulation affects the risk of postoperative ileus. They found no significant difference between the groups in terms of early recovery of gastrointestinal myoelectric activity. Ahn et al.[63] reported the mean ± SD time to first flatus, which was demonstrated to be statistically significant between groups (52.18 ± 21.55 hours after surgery in the intervention group vs. 71.86 ± 29.2 hours in the control group; $p = 0.036$). The authors also reported the mean time to liquid diet intake, however there was no significant difference between the groups (76.91 ± 24.36 hours in the intervention group vs. 86.04 ± 20.68 hours in the control group; p = 0.177).

In thoracic surgery, only one study[69] reported information regarding GI function. The Kaneda et al. study quantified the “amount of diet” consumed on POD1, with increased intake indicating a faster return of GI function, but found no significant difference between the groups (66.9 ± 35.6% in the intervention group vs. 55.8 ± 35.6% in the control group; p = 0.16).

Performance-based functional tests

One abdominal study[63] evaluated the effect of an early postoperative mobilization protocol on performance-based measures. The tests were performed before surgery and at hospital discharge. There were no significant differences detected postoperatively for the sit-stand test (15.00 ± 4.75 repetitions (reps) in the intervention group vs. 13.00 ± 5.54 reps in the control group; p = 0.208), balance ability (15.46 ± 15.27 seconds in the intervention group vs. 8.18 ± 6.49 seconds in the control group; p = 0.722), and functional capacity as measured by the Tecumseh step test (90.21 ± 11.50 beats per minute (bpm) in the intervention group vs. 100.50 ± 12.00 bpm in the control group; p = 0.877).

Three of the studies in thoracic surgery[66-68] included data on performance-based functional tests; however these studies involved a home exercise program component, so only in-hospital data was analyzed. The 2014 Arbane et al.[66] trial reported results from the incremental shuttle walk test and the quadriceps strength test at 5 days after surgery, which showed no significant differences between mobilization and control groups. The 2011 Arbane et al.[68] trial included results from the 6-minute walk test (6MWT) and the quadriceps strength test. The authors found no significant differences in 6MWT results between the groups at 5 days after surgery, however they did find a significant difference in quadriceps strength between the groups, with the mobilization group at 37.6 ± 27.1 kg vs. the control group at 21.5 ± 7.7 kg, p = 0.04. The study by Granger et al.[67] did not report any performance-based outcomes during hospital stay.

Patient-reported outcomes (PROs)

In abdominal surgery, two[62, 64] of the four studies included PROs. Le et al.[62] administered a modified version of the Patient Recovery Profile-17 (PRP-17)[70] at hospital discharge and the Short-Form 12v2 (SF-12v2)[71] at one month after discharge. The authors reported an increased PRP-17 composite score in the control group (12.5 vs. 9.9 in the walking group, p = 0.003), indicating that the control group had a better postoperative recovery. They also reported indicator sums in the context of the PRP-17, which are defined as the "total number of axes in which an individual reports no symptoms," where increasing scores correlate with better recovery. The indicator sums were higher in the walking group (9.8 vs. 8.4 in the control group, p = 0.04). Finally, the authors described a trend towards better scores of the physical composite score of the SF-12v2 in the walking group (44.4 ± 5.4 vs. 41.7 ± 4.3 in the control group, p = 0.07), but there was no difference in mental composite scores between the groups. The study by Liebermann et al.[64] used a visual analogue scale to rate difficulty with walking, and also developed a non-validated questionnaire that included ten questions regarding perception of barriers to ambulation. They found a significant difference amongst participants between preoperative difficulty ambulating (1.47 out of 10) and postoperative difficulty ambulating (4.79 out of 10), $p < 0.001$. They had an 80% response rate for their questionnaire, which showed that the most common obstacles to ambulation included urinary catheters (38.5%), intravenous poles (28%) and pain (12.5%). These findings were not significantly different between groups.

All four studies in thoracic surgery evaluated the impact of the intervention on PROs. Three of these studies[66-68] included a home exercise program and reported only post-discharge data, so their results were not analyzed. The fourth study in thoracic surgery, by Kaneda et al.[69] used the modified Borg scale to quantify postoperative pain, and found no significant difference between the intervention and control group (2.1 ± 1.3 vs. 2.0 ±1.2, respectively, $p = 0.68$).

Physical activity

There were 2 studies in abdominal surgery[63, 64] and 1 study in thoracic surgery[66] that documented the amount of physical activity. The study by Ahn et al.[63] stated that the "amount of walking was monitored daily" but the authors did not describe how this monitoring was accomplished, e.g. direct observation vs. self-reported by patients vs. activity monitors. The mean ± SD walking distance during hospital stay was 1481 ± 651 meters for the exercise group and 2187 ± 1469 meters for the control group, however these values were not statistically significant ($p = 0.12$). The primary outcome of the study by Liebermann et al.[64] was the number of steps taken in the 24 hours immediately prior to discharge. Patients wore pedometers to capture this data, and the median number of steps taken was 80 steps (range 0 – 2353) for the ambulation group and 87 steps (range 0 – 3576) for the control group, and these values were also not significant ($p = 0.70$).

The only study in thoracic surgery that attempted to document amount of physical activity was the 2014 Arbane study[66]. The primary outcome of this study was physical activity, and patients wore activity monitors preoperatively, during the first 5 postoperative days or until hospital discharge, and for one week at 4 weeks postoperatively in order to capture this data. The authors state that there were changes in hospital admission policy that prevented the use of this data and that they only obtained data for 16% of patients; however, there were no significant differences between the groups for preoperative and four-week postoperative data, using imputed data. The authors do not mention differences for postoperative in-hospital activity, i.e. POD 0-5.

Other outcomes

The study by Ahn et al.[63] reported that 84.5% of the patients were adherent to the mobilization protocol, but no other studies reported on adherence. Two studies in thoracic surgery reported on adverse events during mobilization. In the study by Granger et al.[67], no patients had abnormal vital signs, new onset arrhythmias, chest pain, diaphoresis or falls during the exercise sessions. Kaneda et al. [69] also did not report any adverse events during the intervention (i.e. falls or chest tube issues).

None of the studies included in this review reported a cost analysis.

2.5 DISCUSSION

While convincing evidence suggests that patients should not be kept in bed after surgery[53], there is little guidance on how best to achieve early mobilization, particularly whether adhering to a specific structured mobilization protocol has additional benefits compared to allowing patients to mobilize at will (i.e. as tolerated). This systematic review demonstrates a gap in the body of evidence regarding the impact of specific early mobilization protocols on postoperative outcomes after abdominal and thoracic surgery, compared with allowing patients to ambulate but without a specific protocol. Only eight relevant articles were identified based on the inclusion and exclusion criteria, and of these studies, only two are of relatively good quality. As results were generally inconsistent we were not able to draw strong conclusions regarding the benefits of early postoperative mobilization protocols.

One challenge in performing trials of complex interventions is the selection of the primary outcome. As the negative effects of bed rest are well-known (e.g. thromboembolism, pneumonia, muscle wasting and physical deconditioning), mobilization could be hypothesized to decrease the risk of complications associated with immobilization. Five out of eight studies reported on postoperative complications, two in abdominal surgery and three in thoracic surgery, without major differences reported between intervention and control groups. However, the definition of complications was variable, and none of these studies used a classification system of postsurgical complications, such as the Clavien-Dindo classification[48] or the Comprehensive Complication Index[72]. Most of the studies selectively compared complication rates between mobilization groups and control groups using descriptive statistics; however there was no mention of the statistical significance of these results, except for one study[68]. In addition, only one study[63] reported the duration of follow-up in which postoperative complications were considered. In future research, complications should be defined using standardized classification systems, follow-up periods should be specified and inferential statistics (i.e. p-values and/or 95% confidence intervals) reported.

LOS was a very heterogeneous outcome variable between the studies, which suggests that there were very different patient populations being studied. However within each study, whether involving thoracic or abdominal surgery, the diagnoses and types of operations performed were similar. LOS was reported in the majority of studies, and only one[63] found a significant difference between the intervention group and the control group. Although it is a relatively good quality study, it had a small sample size that was even smaller than anticipated because of early termination of recruitment due to implementation of a mandatory ERP (and the resulting violation of the study's exclusion criteria). These results may be suggestive of a decreased LOS in patients who ambulate early after surgery. While some other studies demonstrated a trend towards a shorter LOS in the intervention groups, none of these results were statistically significant. This discrepancy of results can be attributed to differences in statistical power or to the presence of non-clinical factors delaying discharge. LOS is not an ideal outcome for studies on interventions aimed to improve postoperative recovery as this measure is influenced by several confounders (e.g. health care system, surgeon preferences, patient expectations)[45, 73] and patients are not necessarily discharged when they are clinically ready or "recovered".

Functional status is an important outcome of recovery for patients[74] and performance-based functional testing is an objective way of measuring postoperative recovery. The results of performance-based functional testing for three studies were considered in this review. In thoracic surgery, only one study[68] found a significant difference for one of the tests of functional capacity between the groups, however there was some missing data, therefore these results should be interpreted with caution. The abdominal surgery study[63] did not find any significant differences in functional capacity between the groups. Perhaps these studies did not find significant differences in performance testing simply because it was too early in the process of recovery to find a detectable difference. Alternatively, one could argue that performing these functional tests early in recovery may increase the likelihood of detecting significant differences between the groups, and that in fact, early mobilization may not increase functional capacity in the immediate postoperative period. As these studies were RCTs with relatively high methodological quality, the somewhat consistent finding that early mobilization protocols have little impact on performance-based outcomes may be more meaningful than other results reported in this review.

The description of PROs was widely variable amongst the studies included in this review and the quality of reporting is questionable. Only one study[69] in thoracic surgery used a validated scale, the Borg scale for pain, and provided a correct interpretation of these results. The other study[62] in abdominal surgery using questionnaires for postoperative recovery (PRP-17) and health-related quality of life (SF-12v2) provided conflicting results. The PRP-17 composite scores and indicator sums did not correlate as they should, but this finding was not explained. Although the authors concluded that these results were both indicative of better recovery in the ambulation group, in fact they found conflicting results. The last study[64] in abdominal surgery that included

PROs used a questionnaire that was created by the authors and not validated by previous research. The authors presented information regarding barriers specific to ambulation, and did not find a significant difference between groups. This analysis may be helpful in order to identify potential strategies to improve patients' ability to walk postoperatively and increase adherence to the mobilization protocol, however the results are not necessarily generalizable to other centres.

Information regarding physical activity levels and comparisons between intervention and control groups should be documented. Studies considering physical activity levels that were included in this review do not comment on their findings, i.e. the lack of significant differences between the groups, and how this impacts their ability to draw conclusions regarding the effect of early mobilization protocols on outcomes. In order to demonstrate differences in outcome variables such as postoperative complications, LOS, performance-based functional testing, etc., it is first necessary to show that the patients actually participated in the mobilization protocol and that there was a difference in physical activity levels between the intervention and control groups. The measurement of physical activity can be performed in different ways, for example number of steps, time spent out of bed, or intensity of activity (light vs. moderate vs. high), and it is not known which of these is the best parameter to measure physical activity. Future studies should be done in order to elucidate the best way to quantify physical activity levels in postoperative patients.

Information on cost analysis and adherence was not provided by the studies in this review. There is little known about the costs associated with implementation of specific mobilization strategies that may require additional resources. The types of mobilization protocols included in the studies in this review were very variable. Some of them included interventions from physiotherapists while others simply involved encouragement from healthcare workers with specific goals of ambulation, or walking with volunteers. The costs associated with each of these different programs are likely to be variable, and adherence may differ. One may argue that protocols that are unsupervised and self-motivated may result in lower adherence in comparison to supervised protocols and thus, patients would not experience the theoretical benefits of early mobilization. The results from this review, however, do not provide evidence about the superiority of supervised protocols compared to other strategies. Further research in this area would be helpful to elucidate the best ways to achieve maximum adherence in a cost-effective way.

This review was limited by the small number of studies identified and by the methodological limitations of these studies. There was substantial heterogeneity in study design, specific mobilization protocols and outcome reporting, which supports our decision not to conduct a meta-analysis. Also, language bias cannot be excluded as we targeted only articles in English and French. A large number of articles (94) were excluded after full-text review, with the majority excluded because they did not evaluate mobilization in isolation, did not involve an early mobilization protocol, or did not involve a control group. This finding is not a limitation of the review, but rather demonstrates the paucity of comparative studies in this field. This may reflect the challenges of conducting RCTs with "behavioural" interventions such as mobilization; however multiple trials involving perioperative exercise (e.g. "prehabilitation"[75, 76]) have been successfully conducted, suggesting that RCTs in this field are feasible. Both abdominal surgery and thoracic surgery were included in this review, as we aimed to evaluate the effects of early mobilization protocols on a broad group of postoperative patients. We understand that these two patient groups may have different barriers associated with postoperative mobilization; for example, the challenge of having one or more chest tubes may make mobilization more cumbersome in thoracic surgery. As such, we have chosen to present our results and analysis for abdominal and thoracic surgery separately.

Although it is well recognized that prolonged bed rest is harmful and should not be advocated in postoperative care[11], the best way to manage postoperative mobilization is still unknown. It is intuitive that using specific protocols to facilitate (or "enforce") early mobilization would be beneficial; however several questions regarding the clinical effects of this intervention remain unanswered. At what frequency and intensity should patients mobilize after surgery? What mobilization targets should be used? Do we need personnel dedicated to facilitate early mobilization? Do patients treated with an early mobilization protocol have better postoperative outcomes compared to those mobilizing at will (i.e. being counseled not to stay in bed, but mobilizing as much as they feel comfortable)? This review highlights the need for further studies in this field. As randomized controlled trials provide the optimal design for studies on health interventions, we believe that this should be the design of choice. In these trials, specific mobilization protocols should be compared to currents standards of care at different institutions (e.g. preoperative education regarding early mobilization, daily encouragement by surgeons and other healthcare professionals). Studies should also be performed in order to determine what type of physical activity should be advocated in postoperative patients, as well as intensity and duration, and whether or not certain thresholds can be targeted in the early postoperative period. Conducting such studies in institutions using ERPs may help understanding the relative contribution of early mobilization protocols in this context of care. Adherence to early mobilization within ERPs is low[55], but the need to implement interventions to enhance adherence is uncertain. Trials should follow the CONSORT Statement[77] to optimize study design and reporting. Methods of randomization and concealment of allocation, blinding of outcome assessors and management of missing data should be carefully set. Sample size calculations should be conducted to prevent type II error. Outcome measures should be standardized and lengths of follow-up specified. Examples of well-validated measures for use in future research include postoperative complications as classified by Clavien-Dindo[48] and the Comprehensive Complication Index[72] and recovery of functional walking capacity as measured by the 6MWT[78]. The use of measures of functional in-hospital recovery (e.g. time to functional recovery[73], time to readiness for discharge[50]) can overcome the limitations associated with measuring LOS. However, outcomes like complications and hospital stay have many other influences in addition to patient mobilization. It is important to report time out of bed and time spent mobilizing as explanatory variables that can be measured using Actigraphy or pedometers. When non-randomized trials are conducted, authors should follow specific criteria for reporting their results, for example using the STROBE Statement[79]. Data on the relationship between adherence to mobilization protocols and postoperative outcomes would also provide important information.

In summary, there are still many unanswered questions regarding the impact of using a specific early mobilization protocol on postoperative outcomes after abdominal and thoracic surgery, and whether additional resources should be committed to achieving specific mobilization goals. No firm conclusions can be drawn from this review as studies were generally of poor methodological quality and had conflicting results. Some studies suggest that the use of early mobilization protocols has the potential to accelerate return of bowel function and reduce hospital LOS, which is encouraging for future research. Although there is a strong body of literature suggesting that prolonged bed rest is harmful[11], whether a specific protocol ensures early mobilization above and beyond what is accomplished by patient education is unknown. Early mobilization protocols, especially when driven by additional dedicated health professionals, may require additional resources and should be justified by evidence.

CHAPTER 3:

ACTIVITY LEVELS WITHIN ERPs:

MORE QUESTIONS TO ANSWER

The previous chapter discusses eight comparative studies that involve an intervention to increase physical activity in the postoperative period, however none of these studies actually quantifies the differences in patients' activity levels. In order to demonstrate whether one protocol is superior to another, one must first demonstrate that the mobilization protocol actually increases early mobilization in postoperative patients. In addition, none of the included studies in the previous chapter evaluates early mobilization protocols within ERPs. The combination of many elements of ERPs has been shown to improve overall recovery as demonstrated by shortened LOS, decreased morbidity, reduced time to recovery of GI function, etc. However, whether early mobilization has a significant impact on outcomes within an ERP has not been well studied.

We performed an observational study in order to begin to address the above issues, and the manuscript is presented in the next chapter. First we wanted to quantify postoperative physical activity levels. We chose a specific activity monitor (ActiGraph GT3X26) that records step counts and time spent in different body positions, i.e. supine, sitting and standing, in order to determine which of these parameters, if any, is associated with changes in clinical outcomes. In doing so, we aimed to provide evidence for a benchmark for ERPs to use as a target for the type of early mobilization (i.e. staying out-of-bed vs. number of steps), as well as potentially provide threshold levels that patients should aim to attain during their hospital stay in order to see an improvement in overall recovery. The patients included in this observational study were treated within a well-established ERP, as described in Chapter 1. This patient population was studied in order to tease out the effects of early mobilization on clinical outcomes while using other components of the ERP.

CHAPTER 4:

MANUSCRIPT #2

Association of postoperative physical activity and in-hospital recovery after colorectal surgery in an enhanced recovery program

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4.1 STRUCTURED ABSTRACT

Purpose: Surgeons encourage patients to mobilize as much as possible after surgery to accelerate recovery and reduce complications, however adherence with the recommendation is variable. Our aim was to estimate the extent to which physical activity is associated with length of hospital stay (LOS), return of GI function and complications after colorectal surgery in an Enhanced Recovery Program (ERP).

Methods: This was a secondary analysis of data from a randomized controlled trial. Step counts and body position (i.e. standing, sitting or supine) on the day of surgery until postoperative day 3 (POD 0 – 3) were recorded using an activity monitor (ActiGraph GT3X26). Patients were enrolled in a multidisciplinary ERP. Outcomes included LOS, time to passage of first flatus, time to return of GI function (defined as time to tolerance of solid food and first defecation), and serious in-hospital complications (Clavien $\geq$ 2). Statistical analysis was conducted using linear and logistic regression models. Data expressed as median (IQR).

Results: 60 patients were included (58% male, mean age 61(SD 14), 78% laparoscopic, 34% new stoma, 45% thoracic epidural use, 58% malignancy, 38% rectal surgery). Median step counts and time spent in each body position were significantly lower on POD 0 compared to later days, but there were no significant differences between POD 1, 2 and 3. Median LOS was 3 days (3-5), median time to first flatus was 25 hours (19-40) and median time to return of GI function was 46 hours (28-68). Longer standing time, sitting time, non-supine time and step counts were each associated with decreased LOS. Longer standing time was associated with faster return of GI function. Neither step counts nor time spent in any particular position were associated with time to passage of first flatus or in-hospital complications.

Conclusion: In an ERP, increased standing and walking in the first day after surgery was associated with faster return of GI function and earlier discharge after colorectal surgery. Future research should investigate whether the use of specific interventions to facilitate postoperative mobilization within ERPs can further improve clinical outcomes.

4.2 INTRODUCTION

Early mobilization has long been valued as a cornerstone of postoperative care in order to prevent the deleterious effects of bed rest, which include physical deconditioning, venous thromboembolism, muscle loss, and a decline in postoperative functioning[11]. However, despite encouragement from the healthcare team, adherence to early mobilization in the immediate postoperative period is low. After colon resection, a multicentre European study reported that only half of patients were walking by postoperative day (POD) 3[17]. Adherence may be even lower after upper abdominal surgery, with one prospective study reporting median "uptimes" of only 3 minutes on POD 1 and only 35 minutes by POD 4[18].

Enhanced recovery programs (ERPs) combine numerous pre-, peri- and postoperative interventions, including patient education, laparoscopic surgery, early postoperative feeding, multimodal analgesia, fluid management and others, in a standardized pathway in order to reduce surgical stress and "fast track" the patient's recovery[19]. Early postoperative mobilization is considered an important component of ERPs[29], however adherence has been reported to be as low as 25-30%[20] and the evidence base supporting specific protocols or benchmarks is weak[80].

To justify the need to direct additional healthcare resources to increase adherence with specific early mobilization benchmarks, further research is needed to contribute evidence about the association between early mobilization and postoperative outcomes.

In this study, we aim to estimate the extent to which early mobilization is associated with improved clinical outcomes including length of hospital stay (LOS), return of gastrointestinal function and in-hospital complications after colorectal surgery in an ERP.

4.3 METHODS

Patients

The data used in this study were collected from a randomized controlled trial investigating the impact of postoperative walking on recovery after hospital discharge (NCT02131844). The study population consisted of adult patients undergoing elective colon and/or rectal resection from July 2014 to March 2015. Patients were excluded if they had known metastatic disease, medical comorbidities that precluded postoperative mobilization, and an inability to understand English or French. Perioperative care was standardized with an Enhanced Recovery Program established in 2009[30].

Measurements

Demographic data (age, gender, body-mass index (BMI), American Society of Anesthesiologists (ASA) score, diagnosis), operative characteristics and in-hospital postoperative outcomes were collected from the patients' medical charts by an assessor masked to patient activity levels. Self-reported outcomes, i.e. time to first flatus, defecation and tolerance of solid food, were collected by assessors masked to patient activity levels.

All patients wore an activity monitor (ActiGraph GT3X26, Pensacola, FL, USA) after arrival to the surgical ward on POD 0 until POD 3 or hospital discharge. The ActiGraph GT3X26 is a small, portable, non-invasive, lightweight device that records body movement, step counts and body position. We chose to use the ActiGraph GT3X26, which is a triaxial monitor (i.e. it measures the linear acceleration of the wearer along three axes) because in addition to its accelerometer and pedometer functions, it also has a unique inclinometer function. The inclinometer function allows the device to measure the time spent in different body positions, i.e. standing, sitting and supine. In order to ensure the accuracy of this measurement, the monitor was worn on the patient's left or right hip. Measurements were recorded for each POD for a twenty-four hour period beginning from 6:00 AM, except on POD 0 when the recordings began upon placement of the monitor after arrival on the surgical ward. Data collected from the activity monitors included step counts, standing time and sitting time. We defined "non-supine time" as sitting time plus standing time to represent the time spent out-of-bed.

Outcomes of interest included length of hospital stay (LOS), time to readiness for discharge[50] (TRD) (i.e. a checklist to determine if the patient is clinically ready to be discharged which does not take into account other reasons for delayed discharge such as social, administrative, or other reasons; this checklist is provided in Appendix 3), time to first passage of flatus (measured from the time at the end of the surgery), time to return of GI function (time to tolerance of solid oral intake and defecation[81]), and in-hospital complications. Complications occurring within the index hospital stay up to 30 days postoperatively were recorded from the medical record and classified using the Clavien-Dindo scale[48]. For the analysis, the grade of the most severe complication for each patient was used as the outcome, and complications were defined as major if they required pharmacologic or additional interventions (Clavien II – V).

Enhanced Recovery Program

Patients all received standardized perioperative care within the Enhanced Recovery Program at the Montreal General Hospital. This care pathway was implemented in 2009 and includes 22 unique elements. Patients receive standardized preoperative education by dedicated nurses at the preoperative clinic, as well as written materials prepared by the Patient Education Office at the McGill University Health Centre. Postoperatively there are daily benchmarks, including specific early mobilization targets (two hours out-of-bed on POD 0 and six hours out-of-bed each day thereafter, as per the Enhanced Recovery After Surgery (ERAS®) Society guidelines), access to full oral diet as of POD 1, removal of urinary catheter on the morning of POD 1 and daily laxatives and gum chewing three times per day to accelerate return of GI function. Thoracic epidural analgesia is used for open surgery and rectal resection[82] for 48 hours, followed by transition to oral multimodal analgesia if tolerated.

The subjects in this study were enrolled in a randomized controlled trial (NCT02131844). The main objective of the trial was to determine the effects of facilitated early mobilization on outcomes after colorectal surgery. Patients randomized to the intervention group were mobilized by members of the research team from POD 0 to POD 3. On the day of surgery, patients were helped out-of-bed and stayed in the chair for two hours if tolerated. Each subsequent day until POD 3 or hospital discharge, patients were mobilized, i.e. taken for a walk in the corridor by members of the research team, three times per day for approximately twenty minutes each session, if tolerated. The control group did not have scheduled times with the research team for mobilization, but the participants were given a booklet including daily mobilization goals, with postoperative reinforcement of these goals by the healthcare team and posters on the ward, as per standard care in the ERP. The sixty patients included in this observational study were the first sixty patients enrolled in the randomized trial, therefore our population consists of patients who were part of the intervention group as well as the control group. These sixty patients were analyzed as one group in this observational study. It should also be noted that there is no pre-hoc stated clinical significance in activity parameters in the current literature and that our research group did not conduct a pilot study in order to determine minimal clinically important differences (MCID).

Statistical Methods

The exposure and outcome variables were non-normally distributed therefore non-parametric statistical tests were performed. Differences in step counts, standing time and sitting time for each POD were evaluated using the Kruskal-Wallis test and post-hoc testing was performed using the Mann-Whitney-U test. Linear regression models were used to test the relationships between exposures and the outcome variables LOS, time to first passage of flatus and time to return of GI function. A natural log transformation of these variables was conducted to meet the assumptions of normality required by this analysis. Logistic regression was used to test the relationships between each of the exposures and in-hospital complications. The models were adjusted for age, gender, new stoma and operative approach. Physical activity variables from

POD 0 – 1 were used in the univariate and multivariate analyses as these days had the largest and most representative sample of patients. Statistical significance was defined as $p < 0.05$. All statistical analyses were performed using Stata 13.1 (StataCorp 2013, College Station, TX: StataCorp LP).

4.4 RESULTS

Sixty consecutive adults patients undergoing elective colon and/or rectal resection were analyzed. Patient characteristics are displayed in Table 4-1. The most common indication for surgery was neoplasm (73.3%). The majority of patients (78%) had laparoscopic resection and 80% were ASA class I-II.

Table 4-1. Patient characteristics (n = 60).

Age, years (mean ± SD)	61.5 ± 14.0
Gender (n, % male)	35 (58.3%)
BMI, kg/m^2 (mean ± SD)	26.5 ± 4.7
ASA (n, %)	
I	4 (6.7%)
II	43 (71.7%)
III	12 (20.0%)
IV	1 (1.7%)
Diagnosis (n, %)	
Neoplasm	44 (73.3%)
Malignancy	35 (58.3%)
Polyps	9 (15.0%)
Diverticular disease	5 (8.3%)
Inflammatory bowel disease	11 (18%)
Crohn's disease	6 (10%)
Ulcerative colitis	5 (8%)
Site of operation (n, %)	
Colon	37 (61.7%)
Rectum	23 (38.3%)
Surgical Approach (n, %)	
Laparoscopic	47 (78.3%)
Converted	5 (8.3%)
Open	8 (13.3%)
Use of thoracic epidural (n, %)	27 (45.0%)
New stoma (n, %)	20 (33.3%)

Median step counts and time spent in the standing and sitting positions for each postoperative day are presented in Table 4-2. Values for POD 0 were significantly lower compared to subsequent days ($p < 0.0001$), with no significant differences between POD 1 and 2, 1 and 3, or 2 and 3. There were missing data for two patients on POD 0 – 1 (one patient was brought back to the operating room on POD 0 and the monitor was removed, and one patient removed the monitor herself and it was replaced incorrectly therefore did not capture accurate data). Missing data on POD 2 and 3 were due to patient discharge.

Table 4-2. Step counts and body position on each postoperative day.

	POD 0 (n = 58)*	POD 1 (n = 58)*	POD 2 (n = 54)*	POD 3 (n = 31)*
Step counts	20 (5 – 48)	361 (77 – 1908)	447 (142 – 2828)	465 (104 – 1442)
Standing time, mins	2 (0 – 16)	96 (36 – 210)	145 (62 – 264)	112 (56 – 172)
Sitting time, mins	44 (2 – 126)	318 (206 – 522)	353 (214 – 448)	388 (226 – 472)
"Non-supine" time, mins	66 (2 – 156)	451 (286 – 738)	470 (336 – 682)	514 (288 – 640)

Values are reported as median (interquartile range). * $p < 0.0001$ for differences between POD 0 and POD 1, 2 and 3. Non-supine time defined as sitting time plus standing time.

Postoperative outcomes of the study cohort are summarized in Table 4-3. As time to readiness for discharge and LOS were similar, LOS was used for the remaining analyses evaluating the relationship between early mobilization parameters and postoperative outcomes (Tables 4-4 – 4-7).

Table 4-3. Postoperative outcomes.

Time to first passage of flatus, hours	24.7 (18.6 – 40.1)
Time to return of GI function, hours	45.7 (28.3 – 67.6)
TRD, days	3 (3 – 4)
LOS, days	3 (3 – 5)
Complications (Clavien-Dindo grade)	
None	37 (61.7%)
Grade I	9 (15%)
Grade II	11 (18.3%)
Grade IIIa	1 (1.7%)
Grade IVa	1 (1.7%)
Grade IVb	1 (1.7%)

Values are reported as median (interquartile range), or n (%).
TRD: time to readiness for discharge

Step counts

In univariate models, higher step counts were significantly associated with shorter LOS, reduced time to return of GI function and reduced risk of in-hospital complications (Table 4-4). However, after adjustment for potential confounders, the only significant association was between step counts and LOS. There was no association between step counts and time to passage of first flatus. Each step taken on POD 0-1 reduced the LOS by 0.01%, and therefore each lap of the corridor, which consists of approximately 300 steps, was associated with a 3% reduction in LOS.

Standing time

Increased standing time was significantly associated with shorter LOS and faster time to return of GI function in both unadjusted and adjusted models (Table 4-5). There was no association between standing time and time to passage of first flatus or in-hospital complications. Each minute spent standing was associated with a 0.13% reduction in LOS, and thus each hour spent standing is potentially associated with a 7.8% decrease in LOS. Each minute spent in the standing position was associated with a 0.17% reduction in time to return of GI function, therefore each hour spent standing may potentially reduce time to recover GI function by 10%.

Sitting time

Increased sitting time was associated with reduced LOS in both univariate and multivariate models, however there was no association between sitting time and any of the other outcomes

(Table 4-6). Each minute spent sitting was associated with a 0.05% reduction in LOS, therefore each hour spent sitting may potentially reduce LOS by 3%.

Non-supine time

Increased non-supine time, defined as the time spent sitting plus the time spent standing, was significantly associated with shorter LOS and faster return of GI function in the unadjusted model, however only shorter LOS maintained statistical significance in the adjusted model (Table 4-7). There was no association between non-supine time and time to passage of first flatus or in-hospital complications. Each minute spent in the non-supine position, i.e. either sitting up in bed or in the chair and/or standing, was associated with a 0.06% reduction in LOS, and thus each hour spent in the non-supine position is potentially associated with a 3.6% decrease in LOS.

Table 4-4. Results of regression models estimating the effect of total step counts from POD 0-1 on time to first passage of flatus, return of GI function and LOS (linear regression), and on in-hospital complications (logistic regression)

	Unadjusted model			Adjusted model		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
LOS, days	β -0.00014	-0.00022 to -0.000047	0.003	β -0.00011	-0.00020 to -0.000012	0.03
Time to first flatus, hours	β 0.00011	-6.06e-6 to 0.00023	0.06	β 0.000075	-0.000055 to 0.00020	0.25
Time to return of GI function, hours	β -0.00012	-0.00025 to 2.02e-6	0.05	β -0.000084	-0.00022 to 0.000054	0.23
In-hospital complications, none/grade I vs. grade II/III/IV	OR 0.9981	0.9964 to 0.9998	0.03	OR 0.9983	0.9966 to 1.0001	0.06

Multivariate model adjusted for age, gender, surgical approach and new stoma formation.

Table 4-5. Results of regression models estimating the effect of total standing time from POD 0-1 on time to first passage of flatus, return of GI function and LOS (linear regression), and on in-hospital complications (logistic regression)

	Unadjusted model			Adjusted model		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
LOS, days	β -0.0017	-0.0027 to -0.00067	0.002	β -0.0013	-0.0025 to -0.00023	0.02
Time to first flatus, hours	β 0.00068	-0.0007 to 0.0021	0.33	β 0.000098	-0.0015 to 0.0017	0.90
Time to return of GI function, hours	β -0.0020	-0.0034 to -0.00062	0.006	β -0.0017	-0.0033 to -0.00010	0.04
In-hospital complications, none/grade I vs. grade II/III/IV	OR 0.9892	0.9803 to 0.9983	0.02	OR 0.9908	0.9811 to 1.0007	0.07

Multivariate model adjusted for age, gender, surgical approach and new stoma formation.

Table 4-6. Results of regression models estimating the effect of total sitting time from POD 0-1 on time to first passage of flatus, return of GI function and LOS (linear regression), and on in-hospital complications (logistic regression)

	Unadjusted model			Adjusted model		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
LOS, days	β -0.00062	-0.0011 to -0.00014	0.01	β -0.00051	-0.0010 to -4.33e-06	0.05
Time to first flatus, hours	β 0.00047	-0.00015 to 0.0011	0.13	β 0.00032	-0.00038 to 0.0010	0.37
Time to return of GI function, hours	β -0.00058	-0.0012 to 0.000094	0.09	β -0.00043	-0.0012 to 0.00032	0.26
In-hospital complications, none/grade I vs. grade II/III/IV	OR 0.9986	0.9963 to 1.0010	0.25	OR 0.9995	0.9970 to 1.002	0.70

Multivariate model adjusted for age, gender, surgical approach and new stoma formation.

Table 4-7. Results of regression models estimating the effect of total non-supine time from POD 0-1 on time to first passage of flatus, return of GI function and LOS (linear regression), and on in-hospital complications (logistic regression)

	Unadjusted model			Adjusted model		
	Estimate	**95% CI**	**p-value**	**Estimate**	**95% CI**	**p-value**
LOS, days	β -0.00067	-0.0011 to -0.00029	0.001	β -0.00058	-0.0010 to -0.00015	0.008
Time to first flatus, hours	β 0.00043	-0.000088 to 0.00094	0.10	β 0.00025	-0.00035 to 0.00085	0.41
Time to return of GI function, hours	β -0.00069	-0.0012 to -0.00015	0.01	β -0.00057	-0.0012 to 0.000060	0.08
In-hospital complications, none/grade I vs. grade II/III/IV	OR 0.9980	0.9960 to 1.0001	0.06	OR 0.9988	0.9966 to 1.0010	0.29

Multivariate model adjusted for age, gender, surgical approach and new stoma formation.

4.5 DISCUSSION

The results of this observational study suggest that higher step counts, standing time, sitting time and non-supine time on POD 0-1 are associated with shorter LOS after colorectal surgery within an ERP. Increased standing time was also associated with faster return of GI function (time to tolerance of solid oral intake and defecation[81]) in this sample of patients. There was no significant association between early mobilization variables and time to passage of first flatus or in-hospital complications.

The Enhanced Recovery After Surgery (ERAS®) society recommends that patients spend two hours out-of-bed on the day of surgery and six hours per day thereafter[83]. On the day of surgery, the patients in our sample spent a median non-supine time of 66 minutes, a median standing time of 2 minutes and a median sitting time of 44 minutes, indicating that the majority of patients do not meet the targets set by the ERAS® society. However, measurement on POD 0 is complicated by the fact that some patients are transferred to the ward from the recovery room late in the day or evening, and that they are less likely to get out of bed or walk due to lack of assistance, as there are fewer nurses and allied health professionals working during the evening and night shifts. On POD 1 – 3, median non-supine times (i.e. time sitting plus standing) were 7.5, 7.8 and 8.6 hours respectively, which surpassed the ERAS® recommendation of 6 hours out-of-bed per postoperative day. However this should be interpreted with caution as our measure overestimates time spent out-of-bed since it would also capture time sitting up in bed; i.e. when patients were in their beds with the head of the bed raised above approximately 45 degrees, the activity monitor reading changed from supine to sitting, and likely overestimates the time spent out-of-bed. The median step counts and time spent standing decreased on POD 3, but this represents the fact that almost half of the patients were discharged on POD 3 and that the patients remaining in-hospital were likely those experiencing some complications, which may result in less mobilization time. For this reason, we decided to use activity data from POD 0-1 instead of from the entire hospital stay to minimize the potential bias caused by missing activity data from patients discharged at POD 2 and 3.

We found an association between increased step counts, standing time, sitting time and non-supine time and shorter LOS. This finding is in line with results from Vlug et al.[34], who showed in a multivariate secondary analysis of data obtained in the LAFA trial that early mobilization with diet were independent predictors of shorter length of total hospital stay, even in patients without complications. We postulate that increasing mobilization after surgery may give patients more confidence that they will be able to cope with their activities of daily living at home, and may make them more likely to agree with early discharge.

The main goal of early mobilization after surgery is to prevent the harmful effects of bed rest. Surgeons also often encourage mobilization in order to accelerate first flatus, but we found no such association. The lack of significant association may be surprising to clinicians, but is in fact consistent with previous research on this topic. There has only been one published study[84] that showed a significant reduction in time to passage of first flatus with increased early mobilization. This was shown in a sample of patients post-colectomy for colon cancer, the majority of whom underwent laparoscopic surgery. This patient population was similar to ours, however their median time to passage of first flatus was 51 hours in the exercise group and 74 hours in the control group, compared to a median time of 25 hours in our study. This finding can be attributed to the fact that our patients were all treated within an ERP, which has been shown to significantly reduce time to recover bowel function[85]. It is possible that the additional ERP elements render the independent effects of early mobilization on bowel function non-significant, which is a potential reason to explain our lack of association between early mobilization and time to passage of first flatus. We did however find an association between increased standing time and faster return of GI function, a composite of tolerance of diet and defecation. In addition, we did not find any association between sitting time or non-supine time and time to recovery of GI function. This suggests that the most important mobilization benchmarks to improve overall recovery are standing and step counts (i.e. walking), rather than "time out-of-bed", which includes sitting, even as early as the first postoperative day. However, we were not able to differentiate time spent sitting up in bed from time sitting in a chair.

We did not find an association between increased mobilization and in-hospital complications. It is unclear how early mobilization and complications are temporally associated with each other, as in a "chicken and egg" scenario. Do patients have more complications because they mobilize less, or do they mobilize less because they have complications? Some complications may be directly associated with bed rest (or decreased mobilization), such as venous thromboembolism, atelectasis and subsequent pneumonia, and will occur several days or weeks after surgery. On the other hand, other complications may occur have an earlier onset, such as intraabdominal abscess, which may result in a catabolic state that decreases the patient's ability and willingness to mobilize postoperatively. The timing of postoperative complications is complex and depends on the type of and reason for the complication, and this affects our ability to determine a clear directionality of the causal relationship between early mobilization and postoperative complications.

The combination of different perioperative interventions within ERPs has a synergistic effect on recovery after surgery and leads to an overall reduction in surgical stress. A major strength of this study is that it is the first to evaluate the association between early postoperative mobilization in isolation and clinical outcomes within the context of a well-established ERP. It is important to clarify these relationships in order to better delineate the effects of early mobilization on outcomes and whether or not specific protocols and resources should be dedicated to this postoperative intervention, in addition to what is already done in an established ERP. Another strength of this study is that different types of physical activity were studied, i.e. number of steps, and time spent out-of-bed, whether standing, sitting or non-supine. This distinction was made in order to provide a clearer benchmark for future recommendations within ERPs. However, our study was limited by some inaccuracies in the collection of physical activity data. Step counts were accurate for normal stride length, however for decreased stride length, for example patients who shuffled their feet, and for slower paces, the step counts were not always accurate and in fact, may have underestimated the actual values. Another limitation was encountered in attempting to quantify the amount of time spent out-of-bed, which was not possible since the “sitting” position could have been attained while sitting up in bed. As explained above, when the head of the bed was raised above 45 degrees, the activity monitor reading changed from supine to sitting, therefore the term “time spent out-of-bed” was changed to “non-supine time”, and likely overestimates the time spent out-of-bed. In addition, there may be measurable differences in the beneficial effects of sitting out-of-bed versus standing, and we wanted to elucidate whether one is better than the other versus overall time spent out of bed. We created the “non-supine time” outcome as a way of comparing supine time versus time out-of-bed, however as described above, our measures were imprecise. We do not yet have the data to yield an accurate weighted calculation of the benefits of sitting versus standing. Future research with more accurate means of measuring body position and actual time out-of-bed may help to create a formula that will better capture the separate and combined effects of sitting and standing on overall recovery after surgery. We considered using a receiver-operating characteristic curve-type analysis to determine if there is indeed an activity threshold effect for step counts and non-supine time. However, there was too much noise in the data, such that this type of analysis would not yield accurate results. Our activity measures were not precise enough to carry out this analysis, which would be acceptable for the group level (i.e. for comparison between groups in comparative studies), but not useful for the individual level (i.e. to predict outcomes in individual patients).

In conclusion, this study suggests that the perioperative team should encourage patient standing and walking on the first day after surgery in order to improve GI recovery and accelerate recovery. This is likely to be facilitated by other aspects of the ERP, including patient education, laparoscopic surgery, multimodal analgesia, allowing patients solid food on POD 1 and avoiding drains and catheters. Our findings are encouraging for future research on the topic of early mobilization after surgery within ERPs. This study was an observational study that demonstrated a positive association between mobilization in the first day after surgery with time to return of GI function and LOS. Future comparative studies should evaluate the success of specific strategies to increase standing and walking, and evaluate their impact on postoperative outcomes. This may include studies evaluating the impact of wearable sensor technologies (e.g. Fitbit) to increase adherence with perioperative physical activity benchmarks.

CHAPTER 5:

CONCLUSION AND FUTURE DIRECTION

Early mobilization after surgery is a widely advocated aspect of postoperative care. While it is clear that bed rest is not beneficial and prolonged bed rest is harmful, much remains to be learned about the relationship between in-hospital physical activity and outcomes. There has been very little research evaluating the isolated impact of specific early mobilization protocols on different types of outcomes after surgery, especially when other elements of perioperative care are standardized and early hospital discharge is achieved. Several important questions remain unanswered. How much should patients mobilize after surgery, i.e. what should the daily targets be? What types of activities are the most beneficial for patients to perform after surgery, i.e. should we encourage time spent out-of-bed or a specific activity? From the results of our observational study, it seems that patients should be encouraged to spend more time standing and walking in order to improve overall in-hospital recovery. Should we focus on activities other than walking, for example strength training? Future studies should be performed in order to tease out these details. Certain types of mobilization protocols may be more resource intensive than others, therefore cost analyses would be a key factor to consider in future research.

The results of our study suggest that increased early mobilization may be associated with improved overall recovery, as reflected by faster return of GI function and shorter LOS. These associations should be further studied in a larger, randomized trial in order to explore the relationship between early mobilization and postoperative outcomes in an unbiased way. A larger RCT within the context of a full ERP would be helpful in order to tease out the specific effects of mobilization on postoperative outcomes. Given the inaccurate measurements of the activity parameters used in the observational study, it would be useful to better define each parameter and capture the data in a more precise way. This would enable us to potentially perform an ROC-type analysis, to obtain threshold values and to provide clearer mobilization targets to patients and healthcare providers. This type of study also has the potential to guide health professionals and hospital administrators as to whether or not to devote more resources to facilitating mobilization after surgery. The data from our study were a subset of data collected from a randomized controlled trial (NCT02131844) on facilitated early mobilization in postoperative colorectal patients, the analysis of which is ongoing and may help to answer some of the questions posed in this thesis.

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Appendix 1. MEDLINE search strategy*

1 general surgery/
2 thoracic surgery/
3 exp Digestive System Surgical Procedures/
4 exp Urologic Surgical Procedures/
5 exp Urogenital Surgical Procedures/
6 Splenectomy/
7 exp Laparoscopy/
8 exp Thoracic Surgical Procedures/
9 ((abdominal or abdomen or stomach or colorectal or colo-rectal or thoracic*) adj3 (surger* or surgical or operati* or resect* or laparoscop* or laparotom* or procedure*)).tw,kf.
10 or/1-9
11 Early Ambulation/
12 exp Exercise/
13 exp Exercise Therapy/
14 12 or 13
15 Time/
16 Time Factors/
17 Inpatients/
18 Postoperative Care/
19 Postoperative Period/
20 or/15-19
21 14 and 20
22 ((early or accelerat* or soon* or postoperat* or post-operativ* or postsurg* or post-surg* or inpatient*) adj3 (mobilis* or mobiliz* or walk or walking or ambulat* or exercis*)).tw,kf.
23 11 or 21 or 22
24 10 and 23
25 Treatment Outcome/
26 "Length of Stay"/
27 exp Postoperative Complications/
28 Pain/
29 "Quality of Life"/
30 exp Patient Satisfaction/
31 exp Hospitalization/
32 "Recovery of Function"/
33 Convalescence/
34 (length adj3 (hospital* or stay*)).tw,kf.
35 LOS.tw,kf.

36 ((outcome* or recover* or pain* or complicat*) adj5 (surger* or surgical or operati* or resect* or laparoscop* or laparotom* or procedure* or postoperativ* or post-operativ* or post-discharg*)).tw,kf.
37 (patient reported outcome* or PRO or PROs).tw,kf.
38 ("quality of life" or QOL).tw,kf.
39 or/25-38
40 24 and 39
41 Animals/ not (Animals/ and Humans/)
42 40 not 41
43 (exp child/ or exp infant/ or adolescent/) not exp adult/
44 (newborn* or new-born* or neonat* or neo-nat* or infan* or child* or adolesc* or paediatr* or pediatr* or bab* or toddler* or kid or kids or boy* or girl* or juvenile* or teen* or youth* or pubescen*).ti.
45 43 or 44
46 42 not 45
47 remove duplicates from 46

*The full MEDLINE search strategy was applied to all databases used in the literature review, with modifications to search terms as necessary.

Appendix 2. Excluded Articles with Reasons for Exclusion.

Abstracts:

1. Agostini, P., et al. (2011). "Exploration of patient activity levels following thoracotomy and lung resection." Thorax **66**: A125.
2. Arbane, G., et al. (2009). "An early exercise intervention prevents quadriceps weakness after thoracotomy for non-small cell lung cancer: Randomised controlled trial." Thorax **64**: A20-A21.
3. Ayabe, H., et al. (2011). "The effects of perioperative physiotherapy after open abdominal surgery." American Journal of Respiratory and Critical Care Medicine **183**.
4. Carli, F. (1998). "An intensive versus graded perioperative management program for recovery after colorectal surgery: Preliminary results on quality of life." Regional Anesthesia and Pain Medicine **23**(3 SUPPL.): 11.
5. Dierich, M. G., et al. (2010). "Effect of a 3 week in-patient rehabilitation program following lung transplantation on body composition and exercise performance." American Journal of Respiratory and Critical Care Medicine **181**
6. Edmondson, D. M., et al. (2009). "Use of a specialized walker for aggressive ambulation after thoracic surgery in patients with non-small cell lung cancer (NSCLC): Propensity score analysis of postoperative outcomes." Chest **136 (4)**.
7. Khandhar, S. J., et al. (2013). "Early post-operative ambulation is feasible and safe." Journal of Thoracic Oncology **8**: S158-S159.
8. Ota, H., et al. (2013). "Evaluation of perioperative physiotherapist (PT)-led rehabilitation (PPR) within ERAS (Enhanced Recovery after Surgery) protocol in colorectal surgery." Colorectal Disease **15**: 61.
9. Rivard, C., et al. (2012). "Post-operative walking enhancements for recovery (POWER): A randomized controlled trial." Journal of the American College of Surgeons **1)**: S64.
10. Sureshbalaji, et al. (2011). "Effect of thoracic mobilization exercises with chest physiotherapy in postoperative patients." Indian Journal of Physiology and Pharmacology **1)**: 331.
11. Wong, C. H. E., et al. (2011). "Effectiveness of physiotherapy management after bariatric operation." Hong Kong Physiotherapy Journal **29**(2): 95-95.

Editorials/Reviews:

12. Aceto, P., et al. (2005). "Postoperative management of elective esophagectomy for cancer." Rays - International Journal of Radiological Sciences **30**(4): 289-294.
13. Agostini, P., et al. (2011). "Prophylactic physiotherapy after thoracotomy and lung resection: Is there really no benefit?" European Journal of Cardio-Thoracic Surgery **39**(4): 612.
14. Ambrosino, N. and L. Gabbrielli (2010). "Physiotherapy in the perioperative period." Best Practice & Research. Clinical Anaesthesiology **24**(2): 283-289.
15. Bartels, M. N. (2006). "The role of pulmonary rehabilitation for patients undergoing lung volume reduction surgery." Minerva Pneumologica **45**(3): 177-196.

16. Bloomgarden, Z. T. (2010). "Bariatric surgery, exercise, and inpatient glycemia treatment: The American Diabetes Association's 57th Annual Advanced Postgraduate Course." Diabetes Care **33**(12): e168-e172.
17. Covalt, N. K. (1948). "Bed exercises in early convalescence and ambulation." Physical Therapy Reviews **28**(2): 51-59.
18. Czyzewski, P., et al. (2009). "Role of physiotherapy in "fast track colorectal surgery" strategy." Proktologia **10**(2): 117-123.
19. Elgamil, E. R. and C. E. Lortz (2002). "Remobilization following obesity related surgery." Acute Care Perspectives **11**(1): 15-17.
20. Fiore, J. F. (2012). "Use of breathing exercises and enforced mobilization after colorectal surgery." Surgery **151**(4): 632-633.
21. Gordon, E. J., et al. (2005). "Needed: Tailored exercise regimens for kidney transplant recipients." American Journal of Kidney Diseases **45**(4): 769-774.
22. Havey, R., et al. (2013). "Guarding the gut: early mobility after abdominal surgery." Critical Care Nursing Quarterly **36**(1): 63-72.
23. Makhabah, D. N., et al. (2013). "Peri-operative physiotherapy." Multidisciplinary Respiratory Medicine **8**(1).
24. Mraz, M. (2006). "Perioperative physiotherapy for the thoracic patients. [Polish, English]." Fizjoterapia **14**(2): 71-73.
25. Pashikanti, L. and D. Von Ah (2012). "Impact of early mobilization protocol on the medical-surgical inpatient population: an integrated review of literature." Clinical Nurse Specialist: The Journal for Advanced Nursing Practice **26**(2): 87-94.
26. Patel, B. K. and J. B. Hall (2013). "Perioperative physiotherapy." Current Opinion in Anaesthesiology **26**(2): 152-156.
27. Reis, S. (2000). "Review: early mobilization may be better than bed rest for medical conditions and after surgery... commentary on Allen C, Glasziou P, Del Mar C. Bed rest: a potentially harmful treatment needing more careful evaluation. LANCET 1999 Oct 9;354:1229-33." ACP Journal Club **132**(3): 91-91.

Early mobilization not tested in isolation:

28. Anderson, A. D., et al. (2003). "Randomized clinical trial of multimodal optimization and standard perioperative surgical care." British Journal of Surgery **90**(12): 1497-1504.
29. Bardram, L., et al. (1996). "[Two days' hospital stay after laparoscopic colon resection]." Ugeskrift for Laeger **158**(42): 5920-5924.
30. Basse, L., et al. (2002). "Accelerated postoperative recovery programme after colonic resection improves physical performance, pulmonary function and body composition." British Journal of Surgery **89**(4): 446-453.
31. Boyden, A. M. (1946). "Transverse abdominal incisions and early postoperative ambulation." Northwest Medicine **45**: 491-494.
32. Brodner, G., et al. (2001). "Multimodal perioperative management--combining thoracic epidural analgesia, forced mobilization, and oral nutrition--reduces hormonal and metabolic stress and improves convalescence after major urologic surgery." Anesthesia & Analgesia **92**(6): 1594-1600.
33. Burch, J. C. and C. F. Bradley (1947). "Wound disruption and early ambulation." Annals of Surgery **125**(6): 768-777.

34. Carli, F., et al. (2009). "An integrated multidisciplinary approach to implementation of a fast-track program for laparoscopic colorectal surgery." Canadian Journal of Anesthesia **56**(11): 837-842.
35. Cassidy, M. R., et al. (2014). "Reducing Postoperative Venous Thromboembolism Complications with a Standardized Risk-Stratified Prophylaxis Protocol and Mobilization Program." Journal of the American College of Surgeons **218**(6): 1095-1104.
36. Fagevik Olsen, M., et al. (1997). "Randomized controlled trial of prophylactic chest physiotherapy in major abdominal surgery." British Journal of Surgery **84**(11): 1535-1538.
37. Henriksen, M. G., et al. (2002). "Enforced mobilization, early oral feeding, and balanced analgesia improve convalescence after colorectal surgery." Nutrition **18**(2): 147-152.
38. Lee, S. M., et al. (2012). "Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic low anterior resection: A prospective randomized controlled trial." Surgical Endoscopy and Other Interventional Techniques **26**: S190.
39. Lee, T. G., et al. (2011). "Comparison of early mobilization and diet rehabilitation program with conventional care after laparoscopic colon surgery: a prospective randomized controlled trial." Diseases of the Colon & Rectum **54**(1): 21-28.
40. Mackay, M. R., et al. (2005). "Randomised clinical trial of physiotherapy after open abdominal surgery in high risk patients." Australian Journal of Physiotherapy **51**(3): 151-159.
41. Silva, Y. R., et al. (2013). "Does the addition of deep breathing exercises to physiotherapy-directed early mobilisation alter patient outcomes following high-risk open upper abdominal surgery? Cluster randomised controlled trial." Physiotherapy **99**(3): 187-193.
42. Singhal, V., et al. (2014). "Is heparin prophylaxis with aggressive ambulation enough to prevent thrombo-embolic complications even in higher risk patients undergoing baratric surgery?" Surgical Endoscopy and Other Interventional Techniques **28**: 390.
43. Souza Possa, S., et al. (2013). "Implementation of a guideline for physical therapy in the postoperative period of upper abdominal surgery reduces the incidence of atelectasis and length of hospital stay." Revista Portuguesa de Pneumologia.
44. Thompson, J. B., et al. (1949). "Role of the transverse abdominal incision and early ambulation in the reduction of postoperative complications." Archives of Surgery **59**(6): 1267-1277.
45. Zutshi, M., et al. (2004). "Shorter hospital stay associated with fastrack postoperative care pathways and laparoscopic intestinal resection are not associated with increased physical activity." Colorectal Disease **6**(6): 477-480.

Intervention did not involve a specific protocol of early mobilization (with out-of-bed activities starting no later than postoperative day one):

46. Carli, F., et al. (2010). "Randomized clinical trial of prehabilitation in colorectal surgery." British Journal of Surgery **97**(8): 1187-1197.
47. Chen, L. C., et al. (2013). "Two ports thoracoscopic lobectomy without routine intensive care unit stay." Surgical Endoscopy and Other Interventional Techniques **27**: S156.

48. Li, C., et al. (2012). "Trimodal prehabilitation program improves functional recovery in colorectal cancer surgery: A pilot study." Surgical Endoscopy and Other Interventional Techniques **26**: S243.
49. Massey, R. L. (2010). "A randomized trial of rocking-chair motion on the effect of postoperative ileus duration in patients with cancer recovering from abdominal surgery." Applied Nursing Research **23**(2): 59-64.
50. Nomori, H., et al. (2003). "Difference in the impairment of vital capacity and 6-minute walking after a lobectomy performed by thoracoscopic surgery, an anterior limited thoracotomy, an anteroaxillary thoracotomy, and a posterolateral thoracotomy." Surgery Today **33**(1): 7-12.
51. Reeve, J., et al. (2010). "A postoperative shoulder exercise program improves function and decreases pain following open thoracotomy: a randomised trial." Journal of Physiotherapy **56**(4): 245-252.
52. van Ginneken, B. T. J., et al. (2007). "Physical fitness, fatigue, and quality of life after liver transplantation." European Journal of Applied Physiology **100**(3): 345-353.

Early mobilization program not described by the authors:

53. Kibler, V. A., et al. (2012). "Early Postoperative Ambulation: Back to Basics." American Journal of Nursing **112**(4): 63-69.
54. Kim, K., et al. (2013). "Association of nursing-documented ambulation with length of stay following total laparoscopic hysterectomy for benign gynecologic disease." Obstetrics & Gynecology Science **56**(4): 256-260.

Mobilization program continued after hospital discharge (with no in-hospital outcomes reported) or only started after discharge:

55. Ahmed, M. T., et al. (2009). "Effect of exercise on functional independence after abdominal surgery in the elderly." Indian Journal of Physiotherapy & Occupational Therapy **3**(3): 49-54.
56. Chang, N. W., et al. (2014). "Effects of an early postoperative walking exercise programme on health status in lung cancer patients recovering from lung lobectomy." Journal of Clinical Nursing.
57. Dimeo, F. C., et al. (2004). "Effect of aerobic exercise and relaxation training on fatigue and physical performance of cancer patients after surgery. A randomised controlled trial." Supportive Care in Cancer **12**(11): 774-779.
58. Houborg, K. B., et al. (2006). "Postoperative physical training following colorectal surgery: A randomised, placebo-controlled study." Scandinavian Journal of Surgery **95**(1): 17-22.
59. Langera, D., et al. (2012). "Exercise training after lung transplantation improves participation in daily activity: A randomized controlled trial." Journal of Cardiopulmonary Rehabilitation and Prevention **32**(3): 171-172.
60. Tomas, M. T., et al. (2013). "The impact of exercise training on liver transplanted familial amyloidotic polyneuropathy (FAP) patients." Transplantation **95**(2): 372-377.

Did not include a control group:

61. Agard Pocock, W. and W. Kark (1947). "Early rising after operation." South African medical journal **21**(13): 473-479.
62. Agostini, P. J., et al. (2014). "Potentially modifiable factors contribute to limitation in physical activity following thoracotomy and lung resection: a prospective observational study." Journal Of Cardiothoracic Surgery **9**: 128.
63. Bergman, S., et al. (2005). "Measuring surgical recovery: the study of laparoscopic live donor nephrectomy." American Journal of Transplantation **5**(10): 2489-2495.
64. Beyer, N., et al. (1999). "Improved physical performance after orthotopic liver transplantation." Liver Transplantation and Surgery **5**(4): 301-309.
65. Browning, L., et al. (2007). "The quantity of early upright mobilisation performed following upper abdominal surgery is low: an observational study." Australian Journal of Physiotherapy **53**(1): 47-52.
66. Carey, E. J., et al. (2010). "Six-minute walk distance predicts mortality in liver transplant candidates." Liver Transplantation **16**(12): 1373-1378.
67. Hoffman, A. J., et al. (2014). "A rehabilitation program for lung cancer patients during postthoracotomy chemotherapy." OncoTargets and Therapy **7**: 415-423.
68. Hsieh, C. B., et al. (2010). "Correlation between SF-36 and six-minute walk distance in liver donors." Transplantation Proceedings **42**(9): 3597-3599.
69. Nesbitt, J. C., et al. (2012). "Postoperative ambulation in thoracic surgery patients: standard versus modern ambulation methods." Nursing in Critical Care **17**(3): 130.
70. Sterrenberg, S., et al. (2014). "Pre-transplant 6-minute walk test predicts early post-operative ambulation and outcomes after lung transplantation." Journal of Investigative Medicine **62 (1)**: 187.
71. Zafiropoulos, B., et al. (2004). "Physiological responses to the early mobilisation of the intubated, ventilated abdominal surgery patient." Australian Journal of Physiotherapy **50**(2): 95-100.

Did not involve abdominal or thoracic surgery:

72. Bindoff, C., et al. (2009). "Mobilization and physiotherapy of patients with a levitronix centrimag short-term mechanical circulatory support device." Journal of Heart and Lung Transplantation **1)**: S280-S281.
73. Busch, J. C., et al. (2010). "Effects of daily functional training vs. standard rehabilitation on six minute walk distance and quality of life in very old patients after coronary artery bypass graft surgery." European Heart Journal **31**: 382-383.
74. Sturgess, T., et al. (2014). "A pilot thoracic exercise programme reduces early (0-6 weeks) sternal pain following open heart surgery." International Journal of Therapy & Rehabilitation **21**(3): 110-117.
75. Wright, D. J., et al. (2002). "Is early, low level, short term exercise cardiac rehabilitation following coronary bypass surgery beneficial? A randomised controlled trial." Heart **88**(1): 83-84.

Control group prescribed bedrest:

76. Palumbo, L. T. and R. E. Paul (1952). "Effects of early ambulation in primary inguinal hernioplasty." American Surgeon **18**(11): 1128-1133.
77. Powers, J. H. (1958). "Early ambulation: Its influence on postoperative complications and return to work following; hernioplasty in a rural population." Ann **N. Acad. Sci. 73**(2): 219-241.
78. Preston, O. J. (1950). "Inguinal hernia: Delayed versus early ambulation." Industrial Medicine and Surgery **19**(1): 7-12.

Not in English or French:

79. (2007). ""Fast track" in visceral surgery--3: Postoperative care": the emphasis is on restoring patient activity. [German]." Pflege Zeitschrift **60**(2): 74-76.
80. (2012). "The effect of early ambulation on the prevalence of postoperative headache in patients undergoing cesarean section under spinal anesthesia [Farsi]." Journal of the Faculty of Medicine (1735-5311) **36**(2): 1p.
81. Abe, T., et al. (1973). "Rehabilitation of patients after abdominal surgical operation through positive and graded physical excercise (Japanese). [Japanese]." Journal of Tokyo Women's Medical College **43**(5): 348-353.
82. Chen, J., et al. (2004). "Effect of pulmonary function exercise on the pulmonary postoperative complication and courses in elder patients with pulmonary insufficiency. [Chinese]." Chinese Journal of Clinical Rehabilitation **8**(5): 842-843.
83. Czyzewski, P., et al. (2013). "The influence of physical activity on physiotherapy effects after abdominal surgery in elderly people. [Polish]." Postepy Rehabilitacji **27**(3): 5-12.
84. Dmitriev, A. E., et al. (1978). "Therapeutic gymnastics following surgery on the abdominal organs of late middle aged and elderly patients." Voprosy kurortologii, fizioterapii, i lechebnoi fizicheskoi kultury(5): 32-34.
85. Gregor, J. I., et al. (2008). ""Fast-track" rehabilitation in thoracic surgery. First experiences with a multimodal, interdisciplinary, and proven perioperative treatment course. [German]." Chirurg **79**(7): 657-664.
86. Inah, K. and L. Haejung (2014). "Effects of a Progressive Walking Program on Physical Activity, Exercise Tolerance, Recovery, and Post-Operative Complications in Patients with a Lung Resection [Korean]." Journal of Korean Academy of Nursing **44**(4): 381-390.
87. Lapshin, V. P., et al. (2002). "[Physiotherapeutic methods and elements of exercise treatment in rehabilitation of patients after liver transplantation in early postoperative period (preliminary results)]." Voprosy Kurortologii, Fizioterapii i Lechebnoi Fizicheskoi Kultury(6): 40.
88. Lindvall, S. (1949). "Early ambuiation. [Italian]." Tidskr **1 Mil. Halsovard. 2**: 27-32.
89. Xie, G., et al. (2010). "Research on influence of early bed exercise on intestinal function of patients after undergoing laparoscopic operation in gynecology department [Chinese]." Chinese Nursing Research **24**(5B): 1234-1235.

90. Wang, Y., et al. (2005). "Effect of rehabilitation exercises on the recovery outcomes of lung function in postoperative patients with lung cancer. [Chinese]." Chinese Journal of Clinical Rehabilitation **9**(24): 66-68.
91. Zhang, P., et al. (2000). "Clinical study on functional rehabilitation exercise carried out by abdominal post-operation patients [Chinese]." Shanxi Nursing Journal **14**(2): 54-56.

Did not include any of the outcomes defined by the review:

92. Sunil, P. D. (2012). "Early ambulation: an ugly phrase for a beautiful idea." Nursing Journal of India **103**(2): 57-58.

Ambulatory surgery:

93. Wasowicz-Kemps, D. K., et al. (2009). "Resumption of daily physical activity after day-case laparoscopic cholecystectomy." Surgical Endoscopy **23**(9): 2034-2040.

Did not involve adult patients:

94. Yimlamai, D., et al. (2013). "Pretransplant six-minute walk test predicts peri- and post-operative outcomes after pediatric lung transplantation." Pediatric Transplantation **17**(1): 34-40.

Appendix 3. Time-to-readiness for discharge (TRD) criteria.

DISCHARGE CRITERIA	Endpoints to determine when criteria should be considered to have been achieved
Tolerance of oral intake	Patient is able to tolerate at least one solid meal without nausea, vomiting, bloating or worsening abdominal pain. Patient drinks liquids actively (ideally > 800-1000 ml/day) and do not require intravenous fluids infusion to maintain hydration.
Recovery of lower GI function	Patient has passed flatus.
Adequate pain control with oral analgesia	Patient is able to rest and mobilize (sit up and walk, unless unable preoperatively) without significant pain (i.e. patient reports pain is controlled or pain score ≤ 4 on a scale from 0 to 10) while taking oral analgesics.
Ability to mobilize and self-care	Patient is able to sit up, walk and perform activities of daily living (e.g. go to the toilet, dress, shower and climb stairs if needed at home) unless unable preoperatively.
Clinical examination and laboratory tests show no evidence of complications or untreated medical problems	Oral temperature is normal. Pulse, blood pressure and respiratory rate are stable and consistent with preoperative levels. Serum hemoglobin concentration is stable, within acceptable levels. Patient is able to empty the bladder without difficulty or match preoperative level of bladder function.