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Glossary

POF : Post Operative Fatigue

ICFS: Identity Consequence Fatigue Scale

ERAS: Enhanced Recovery After Surgery

FC: Fatigue Consequence Score

Chapter 1 : Overview of Post Operative Fatigue

Introduction

The presence of a feeling of debilitating tiredness, loss of energy or malaise is a well described medical complaint known as “fatigue”. Several medical and psychological conditions such as multiple sclerosis, chronic fatigue syndrome, sleep apnea, glucocorticoid withdrawal syndrome as well as depression have been associated with “fatigue”. Additionally, as well as being an indicator of disease, fatigue may also result from medical therapy such as treatment for cancer with radio- or chemotherapy.(1-4)

Fatigue is also a recognized condition following surgery and this “post-operative fatigue” can be present for up to a month in patients following abdominal operations (5) and continues to resolve for up to 3 months after uncomplicated gastrointestinal surgery.(6) However despite this, POF is often overlooked as a post-operative symptom by many clinicians. Furthermore the duration of POF and factors which delay convalescent after surgery are not well described. Lastly, there is no definition for the concept of POF.

The aim of this section is to introduce post-operative fatigue (POF), to review various clinical aspects of the concept of POF, discuss its significance, objective and subjective assessment tools, suggested aetiology and interventions which may influence POF. It is aimed to provide a clinically relevant definition for POF based on these discussions. This is not a systematic review on this topic but an up-to-date overview of POF.

Why is POF important?

Post-operative fatigue (POF) is an unpleasant and distressing symptom and frequently has a major impact on the patient's quality of life. (7) Not surprisingly, therefore, POF may be one of the main complaints after surgery and may last much longer than pain. It prevents return to normal function and activity, including housekeeping, family and child care. Fatigue contributes substantially to feelings of frustration, depression or hopelessness and to difficulty in concentrating or being attentive. Some patients describe fatigue as a "change in emotional state".(8)

POF may prevent otherwise fit patients from returning to work. Large numbers of patients report loss of wages as a result of this prolonged surgical recovery time. Patients miss an average of 6 weeks of work following uncomplicated abdominal operations. It also has a similar impact on caregivers.(8, 9)

A higher degree of POF is followed by worse emotional, physical and functional outcomes. (10) POF may also be a source of increased costs to the health service, with patients who suffer from fatigue placing significantly greater demands on their primary health care teams compared to those who feel less tired.(7-9)

Despite the severe impact of POF on overall recovery, POF has been largely ignored as an objective for prevention or treatment following surgery. It is obvious that POF has major consequences on patients' well being and thus there is considerable rationale for a proper understanding of the aetiology, pathophysiology, prevention and treatment of this condition.

Assessment of Fatigue

A significant factor which has hindered understanding of POF has been that there is no “gold standard” for fatigue assessment and clear objective correlates for fatigue have not been identified. There are several methods for obtaining subjective information relating to fatigue. Both interviews and questionnaires have been used for this purpose (Table 1).

Questionnaires, in particular, have been shown to be an effective tool for measuring subjective feelings of fatigue and there are a number of different instruments that have been developed for this purpose. These range from single-item scales of intensity such as visual analogue scales, to multidimensional measures. Variations between these scales are based on theoretical classifications of fatigue into different dimensions. Examples include assigning different mental and physical aspects to fatigue (11) or assessing fatigue on the basis of severity, circumstances, consequences and responsiveness to rest/sleep(12)

Because of the nature of fatigue as a condition different instruments may measure different aspects of fatigue. Any scale is most accurate when it is used to assess fatigue in the clinical condition for which it was designed. Thus its use for other conditions may not be appropriate. It is very important therefore that, for clinical trials, an instrument is utilised which measures appropriate aspects of fatigue. Secondly, the purpose of measurement should be clear. For example if the scale is being used to measure fatigue as an outcome measure, it should be able to detect changes in fatigue during the course of the illness or treatment (13) Lastly, an instrument should be used for the appropriate population for which it was designed and validated.

Table 1 : Characteristics and Properties of Some Commonly Used Fatigue Scales

One dimensional	
Krupp VAS (14)	
Global Vigor and Affect(15)	8-item visual analogue scale measuring severity
Pearson and Byars (16)	2 check lists of 13-item Fatigue Feeling Checklist
The brief Fatigue Inventory(17)	For screening and assessment of clinical outcomes in fatigued cancer patients, 9-item list
Fatigue Severity Scale (18)	Measures the impact of fatigue on different aspects of functioning rather than extent of symptoms of fatigue, 9-item list
Multi-dimensional	
EORTC-Quality of Life Questionnaire (19)	Nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale.
Profile of Mood States (POMS) (20)	The descriptive terms are related to four major states: Fatigue-Inertia, Tension-Anxiety, Depression-Dejection and Anger-Hostility
Wessely and Powell (11) physical fatigue and a mental fatigue scale	30 symptoms and is divided into three subscales: 1. General feelings of sleepiness 2. Mental feelings of fatigue 3. Specific bodily sensations
Piper Fatigue Self-report Scale (PFS) (21)	41 visual analogue scales representing the temporal, intensity, affective and sensory dimensions of fatigue
Tile Multidimensional Fatigue Inventory (MFI) (22)	20-item 5 dimensions: General Fatigue, Physical Fatigue, Mental Fatigue, Reduced Motivation Reduced Activity
Chalder fatigue scale (23)	Separates mental from physical fatigue, 11-items
Identity-Consequence Fatigue Scale (24)	31 items 5 Sub-Scales: feelings of fatigue, feelings of vigor, impact on concentration, impact on energy and IADL

IADL: Instrumental activities of Daily living

When investigating POF, the most commonly utilised scales are Christensen's visual analog scale (VAS) and the fatigue-inertia and vigor-activity subscales of the Profile Of Mood States (POMS).

Christensen's VAS was first described in 1982 and has since been used widely to measure POF. This has been a valuable instrument in POF research as it is simple and takes little time and effort to complete. However, it is not able to provide a comprehensive expression of patients' fatigue experience as it does not recognise that there are different physical, mental and behavioural components to POF.(12, 22) The original scale referred to both subjective feeling of fatigue and to the ability to carry out routine daily activities on the same scale. There is evidence that these two components are independent and although it is only a linear scale it attempts to measure more than one outcome. Additionally a linear scale is subject to impulsive answers (12) and individuals with the same overall fatigue may have different experiences of fatigue. One may feel physically tired and mentally fit whereas another may feel the opposite.

The Profile of Mood States, POMS (Educational and Industrial Testing Service, San Diego) consists of a checklist of 58 adjectives which describe different mood states. The patient assigns a number to each mood, from 0 to 4. The descriptive terms are related to four major states: Fatigue-Inertia, Tension-Anxiety, Depression-Dejection and Anger-Hostility. The scores for different aspect of each major state are added and averaged to give a single value for that state.

The fatigue scores measured by Christensen's analog scale strongly correlate to fatigue as defined by the POMS questionnaire.(25) However the POMS was designed specifically to

assess mood, not post-operative fatigue, and while, unlike Christensen's VAS, the fatigue and vigor subscales of the POMS contain more than single items, the range of these scales is still too narrow to be an effective tool in research relating to POF.(24) As a result there are studies where the fatigue and vigor subscales of POMS have failed to demonstrate any change in fatigue between pre-operative levels and early and late post-operative levels.(26)

Special scales have been devised to address the above issue. The Chalder fatigue scale uses a self-rating, 14-item fatigue questionnaire. It separates mental from physical fatigue.(23) This instrument is used widely for assessment of POF. However, although bi-dimensional, this scale focuses on the feelings of fatigue and hence is not designed to measure the impact of POF.

Recent progress and research in illness perception theory has provided different viewpoints from which conditions like fatigue can be conceptualized. Within this new framework, fatigue can be seen as Identity, Consequence, Cause, Timeline and Control. (Table 2) Using concepts of cognitive representation a new multidimensional fatigue scale has been developed and validated, consisting of 28 questions and 5 subscales, and is called the Identity-Consequence Fatigue Scale. This scale measures mental and physical feeling of fatigue as well as the impact of fatigue.(24)

Table 2: Characteristics of Identity-Consequence Fatigue Scale

Cognitive Aspect	*Explanation*
Identity	Relates to patients' ideas about the nature of their condition and focuses on reports of symptoms
Consequence	Relates to patients' ideas about the impacts their condition has on physical, social and psychological functioning.
Timeline	The perceived duration of their condition
Cause	Personal ideas about aetiology
Control	Component relates to patients' ideas about how one controls or recovers from the condition

OBJECTIVE CORRELATES WITH POF

Cardiovascular fitness

One of the first objective measures of fatigue was demonstration of a correlation between fatigue and an increase in pulse rate, secondary to orthostatic stress which was present for up to 30 days after surgery.(5) Also, postoperatively, exercise induced heart rate is higher than during the preoperative period and this increase is associated with POF.(27) Following surgery there is a reduction in bicycle ergometer work capacity (5, 27, 28) and an increase in the cardiorespiratory effort required to carry out a given task and the decline in these indicators of cardiorespiratory fitness are also associated with POF.(29) Therefore both light and heavy work capacities are reduced postoperatively with a demonstrable association with fatigue.

Fatigue and nutrition

It has been observed that patients who have more pronounced POF have experienced significantly greater postoperative weight loss as well as greater loss of triceps skin fold thickness.(30) Additionally, further correlations have been demonstrated between development of POF and preoperative weight, total body protein, decline in plasma transferrin levels and grip strength.(25, 30, 31)

Fatigue and Musculoskeletal changes

Development of post-operative fatigue has been shown to correlate with a reduction in the maximum force that a muscle can generate as well as a decline in muscle endurance (the ability of a muscle to maintain sustained contraction).(32) Electromyographic studies have objectively shown that throughout the early post operative period fewer muscle fibre units are

activated during voluntary movements whereas in the late postoperative course the decline in muscle performance is primarily due to weakness in individual muscle fibres.(32) In the immediate postoperative period(33) and for up to 10 days after surgery(34) objective measures of muscle function (as measured by electromyographic studies) remain unchanged(29) despite a measurable decline in voluntary muscle force and endurance in both small(35) and large (36) muscle groups. Therefore it has been argued that early fatigue is "central" in origin but late fatigue is "peripheral".(29)

Post-operatively there are a number of changes observed within muscle fibres. There is a reduction in muscle fibre diameter, (37) (similar to changes seen after prolonged detraining in healthy objects(38)) together with a reduction in muscle protein production,(39) oxidative phosphorylation capacities,(27) as well as changes in free amino acid composition in the muscle.(40) In addition, after surgery larger amounts of lactate are produced following exercise.(28) None of these post-operative changes have been shown to correlate with development of POF. However, a postoperative increase in muscle glycogen stores inversely correlates with POF.(27)

Based on these findings, grip strength is a commonly used objective measure in assessment of fatigue in clinical research.

Fatigue and biochemical markers

Development of POF correlates significantly to increased heart rate and a positive relationship is also observed to an exercise induced increase in plasma levels of noradrenaline, growth hormone and alanine.(28) Some correlation has also been demonstrated between fatigue and low serum transferrin at day 30 but not earlier.(30) A

larger noradrenaline response in the early postoperative course is associated with more fatigue and less vigor.(41) In one study, increases in POF were accompanied by decreased serum zinc and increased serum magnesium. (42)

The development of prolonged POF has not been shown to be related to pre-operative levels of serum transferrin, albumin, electrolytes, haemoglobin, lymphocyte count, other minerals, changes in total body protein or fat, involuntary muscle function, age, gender or duration of surgery or anaesthesia.(25, 30, 31)

Fatigue and type of operation

It has been demonstrated that the type of the operation can influence the extent of POF with significant differences in fatigue following middle-ear surgery and abdominal surgery of similar duration. (31) Generally, major abdominal and cardiac surgeries are associated with greater POF than minor surgery.(43) In addition, significant POF has not been observed following joint arthroplasty.(10) It has been observed that the diagnosis, particularly cancer, has some influence on the development of POF.(25)

Fatigue and Psychological factors

In the past, POF was thought to be a purely physical phenomenon. This was because some early data had suggested that POF may have no association with preoperative anxiety as measured by the State-Trait Anxiety Inventory.(44) Additionally, it was shown that neither pre- nor postoperative performance during concentration tests correlated to POF. Other studies also demonstrated that POF was not associated with preoperative anxiety, depression, hostility or preoperative stress. Later research showed a correlation between pre-operative

and post-operative fatigue, such that patients who presented for surgery already fatigued were those who were most likely to suffer from prolonged POF. (25)

However, as more appropriate instruments were developed and became available to measure POF, further studies demonstrated that throughout the postoperative period, there was a measurable and significant relationship between both physical and mental aspects of fatigue and low mood (10) and it was further established that anxiety and emotional distress have in fact a highly significant association with POF.(43)

It is now thought that psychological factors, such as pre-operative negative mood may be predictive of the development of POF. For example it has been shown that patients, who complain of negative mood pre-operatively, have a higher level of mental fatigue post-operatively, regardless of their pre-operative level of fatigue.(10, 45) Additionally, pre-operative fatigue has been shown to predict low postoperative physical and emotional states.(10) Greater preoperative expectations of fatigue also predict greater POF.(43) Positive pre-operative coping strategies and optimism predict decreased physical and mental POF (45)whereas negative coping strategies have the opposite effect. (26, 45)

Aetiology of POF

The aetiology of POF is most likely to be multifactorial with interactions between biological, psychological and possibly social factors.

The biological aspect of POF can be divided into a physiological response to surgical trauma (i.e. the surgical stress response), a decline in nutritional status and a reduction in physical fitness following surgery.

As mentioned above, fatigue increases significantly following major abdominal surgery. However no such increase in fatigue is observed after middle-ear surgery, despite the fact that the durations of anaesthesia and surgery are similar in the two groups.(31) General anaesthesia alone does not lead to any changes in whole body protein breakdown whereas these parameters are significantly affected after surgery.(46) Thus it has been postulated that it is the type of operation (i.e. magnitude of the trauma) rather than other factors such as the duration of anaesthesia which may be involved in the pathogenesis of POF.

However, although POF has been demonstrated following major abdominal and pelvic surgery in a number of studies, (8, 47-49) significant POF has not been observed following orthopaedic operations (joint arthroplasty), (10, 41) despite the fact that the latter procedure has been shown to be associated with a similar magnitude of systemic hormonal response following surgery.(50) In fact, after joint arthroplasty, 70% of the variability of long term POF has been accounted for by non surgical factors, such as preoperative fatigue, sex, cognition about activity, cardiovascular fitness and emotional distress.(43) Furthermore, if POF was solely related to the systemic plasma endocrine-metabolic response to surgery, it

would be expected that suppression of this physiological response would significantly influence POF. However, in a controlled study, epidural analgesia and systemic non-steroidal inflammatory drug treatment did not modify POF following major abdominal surgery, despite decreasing the endocrine response.(51) Additionally laparoscopic cholecystectomy has been shown to be associated with less POF compared to open surgery despite a similar metabolic response to surgery.(52) Therefore, the variation in fatigue measurements following different types of operations cannot be solely due to the extent of surgical trauma, as measured by plasma markers of inflammation or stress hormones and other factors must also be implicated.

Fatigue and nutrition

Following major surgery there is a decline in spontaneous food intake for several weeks(53-55) with a consequent significant reduction in total energy and protein intake.(56) Consequently, during the first 10 postoperative days, patients lose 4% to 6% of their bodyweight.(30, 57) which is not regained for up to 30 days after surgery. (30) As previously mentioned a number of indicators of decline in nutritional status have been linked to development of POF.(28, 30, 58) Based on these findings it is thought that nutritional factors may be involved in the pathogenesis of POF. Additionally, decline in quality of nutritional intake following abdominal surgery, secondary to loss of GI function, has been thought to be a factor which could partially explain the higher levels of POF in abdominal surgery compared to orthopaedic or middle-ear operations. However, fasting alone cannot explain the onset of fatigue following surgery as healthy fasting people do not demonstrate the reduction in working capacity, skeletal muscle function and fatigue which is seen following major surgery.(29) Furthermore, nutritional interventions alone have not been shown to be effective in reducing POF. (59) However, when the catabolic response to surgery is controlled by

treatment with anabolic agents, such as human growth hormone as well as nutritional support, improvements in total muscle strength and lean tissue mass are associated with a reduction in POF.(60) Hence nutritional deficits partially, but not completely, explain the aetiology of POF.

Fatigue and Physical Fitness

Reduction in physical fitness and mobility has been linked to development of POF. Surgery is followed by a prolonged period of reduced activity (43, 61) and this can lead to significant impairment in muscle functioning, particularly endurance, similar to changes seen in volunteers undergoing bed rest.(36) Additionally, cardiovascular fitness also deteriorates following surgery and objective measures of cardiovascular fitness and musculoskeletal deterioration both correlate with development of POF.(5, 25, 27-29) Therefore as muscular endurance and cardiac fitness both decline, patients may need to use more energy to perform a given physical task and this may lead to sensations of fatigue.(43) These factors are thought to lead to reduced mobility and contribute to fatigue.(29) It has been shown that patients who believe in the efficacy of post-operative physical activity in recovery, and hence may be more active after their operation, experience less POF and those with less physical fitness are more fatigued post-operatively.(43) Disappointingly, in a randomised controlled trial, combined postoperative strength and aerobic training in patients undergoing major colorectal surgery failed to improve the decline in physical function when compared to a placebo group. This intervention only moderately reduced early fatigue and did not influence late POF. (62)

Fatigue and Psychological Theory

In early studies it was demonstrated that POF was not associated with preoperative anxiety, (44) performance during concentration tests or preoperative levels of fatigue. Thus it was

concluded that psychological factors have little influence on POF. (63) Therefore, POF has been historically viewed as only a physical variable. However more recent research has shown that POF is in fact influenced by pre-operative levels of fatigue (25) and therefore, there are non-physical factors which contribute to the development of POF. Thus there appears to be an emotional component in development of POF. (64) A clear relationship has been demonstrated between POF and emotional states and patients' coping styles. (10)' (45)

The psychological aspect of POF has been explained by somatization and cognitive-behavioral theories. The somatization concept is related to the Response Expectancy Theory which states that response expectancies are sufficient to cause nonvolitional outcomes (i.e. physiological symptoms).(65) According to somatization theory, patients experience negative mood after surgery but misinterpret this as fatigue. This is due to environmental factors such as being hospitalized and also due to the presence of preoperative fatigue. Therefore patients continue to monitor and anticipate worsening of these feeling. (66) Cognitive-behavioral factors include patients' interpretation of their own symptoms and of the medical advice they receive as well as their coping strategies and the course of action which they take during their recovery course. These factors are thought to influence their subjective feelings of fatigue. (43)

Somatization can partially explain the difference in POF seen in orthopedic and abdominal operations.(43) In an orthopedic procedure such as an elective hip replacement, the operation precedes a waited event, such as improved mobility, whereas an abdominal procedure has little obvious immediate quality of life benefits for the patient. Hence patients may feel more fatigued following an abdominal operation. Cognitive-behavioral factors, such as having a firm belief in the efficacy and benefits of post-operative activity in late post-operative course,

are predictive of less POF. However it has been shown that it is the specific expectation of fatigue, not other factors such as the prospect of generalized disability or risks and benefits of the operation, which relates to development of POF. (43) Thus the idea that postoperatively, patients reinterpret any negative emotion such as anxiety or depression as fatigue (i.e. somatization) can not entirely explain the aetiology of POF. It is thought that early symptoms of fatigue may be due to somatization and late fatigue secondary to cognitive-behavioral factors. (43)

The level of social support available for patients may partly determine their postoperative activity levels. Greater social support has been linked to better emotional outcome after an operation although more support may delay mobilisation (61) and greater support has in fact been linked to higher levels of fatigue after viral infections. (43) Nevertheless, no links have been shown between social support and POF and social factors seem to have little influence on the onset of POF. (43, 67, 68)

Tryptophan is the precursor of the neurotransmitter 5-hydroxytryptamine (5-HT), known to be involved in sleep and fatigue. In the blood, tryptophan binds to albumin, but it is the free tryptophan which competes with branched chain amino acids (BCAA) for entry into the brain. Free tryptophan levels in blood are increased after surgery and this is associated with an increased amount of tryptophan entering the brain. (69) This may lead to a higher 5-HT concentrations in some parts of the brain, contribute to a need for increase in sleep and possibly an increase in central fatigue. (69) Subsequently significant correlations have been shown between fatigue scores measured by POMS and plasma free tryptophan and the plasma concentration ratio of free tryptophan/BCAA. (70) Post-operative sleep disturbance, on its own, does not seem to correlate with the development of POF. (71)

Fatigue and Inflammatorily Cytokines: A Hypothesis

More recently, associations between fatigue and inflammatory cytokines have been demonstrated. Many pro-inflammatory cytokines have been shown to induce fatigue following exogenous administration.(72) Many medical conditions such as chronic fatigue syndrome (2), sleep apnoea (73), glucocorticoid withdrawal syndrome (2), depression (4) and multiple sclerosis (MS) (1) are known to have altered levels of cytokines in the peripheral circulation with a tendency towards a T helper type 1 pro-inflammatory profile. It has been shown that patients with MS who experience fatigue have significantly higher levels of IFN gamma and TNF alpha than MS patients who do not experience fatigue with considerable correlation between these pro-inflammatory cytokines and fatigue scores. (1) Healthy volunteers administered with cytokine inducing lipopolyscaccharides (LPS) show a reduction in verbal and non-verbal declarative memory function tests as well as increased depression scores.(74-76) Even low levels of cytokines, which do not influence increased temperature or other physical symptoms, can cause a decline in mood in healthy volunteer subjects. In a study of healthy volunteers, injection of *Salmonella typhi* vaccine led to an increase of IL-6 levels in plasma and this was associated with a significant reduction in mood in absence of any other physical symptoms. Furthermore, this change significantly correlated with plasma IL-6 levels.(77) Further studies have demonstrated that cytokines (IL-1beta and IL-6) can induce human “sickness behaviour” such as fever, malaise, pain, fatigue, low mood and poor concentration.(75, 78)

POF may also be linked to production of pro-inflammatory cytokines. Following surgery there are two possible channels of communication between the periphery and the brain. One is a hormonal route by which the cytokines produced at the site of surgery enter the blood stream and proceed through a variety of mechanisms to act directly on the brain. The second

method is a neural route represented by paracrine actions of cytokines on primary afferent neurons which innervate the body site where the injury has taken place.(79) In the abdominal cavity, the vagus nerve plays an important role in the latter form of communication. (80) Therefore cytokines produced at the site of surgery may act via the vagus and play a key role in production of POF. Within the peritoneum, vagal sensory neurons, express receptors for a number of immune-derived mediators. Some vagal sensory neurons express IL-1 messenger RNA. In addition, many vagal nerve fibers express receptors for prostaglandins and other inflammatory mediators. (81, 82)

The unique role of the vagus nerve, with its termination at nucleus tractus solitarius (NTS),(80) may potentially, at least partly, explain the aetiology of POF in abdominal surgery. The NTS is intensely activated following peripheral immune challenges,(83) and also is by far the most sensitive area in the brain following immune stimulation.(84, 85) The NTS projects monosynaptically to many regions of the brain which mediate sickness responses.(80) Subdiaphragmatic vagotomy in animals has been shown to block or reduce a broad spectrum of sickness responses to intraperitoneal administration of cytokines as well as inhibiting the neural activation of the brainstem, hypothalamus and limbic structures in response to these stimuli.(79) It is important to note that the role of the vagus afferents are mainly to influence behavioural changes rather than affecting fever or activation of hypothalamic-pituitary-adrenal axis.(72) Thus a pro-inflammatory cytokine pathway with direct action on the vagus nerve is a feasible partial explanation for POF. Interestingly, in a study where high doses of preoperative steroids were administered to patients undergoing major abdominal surgery, plasma IL-6 levels as well as POF scores were significantly less in the steroid group. Although peritoneal cytokines were not measured and no direct correlation

was suggested in this study, this reinforces the idea that inflammatory factors may play a significant role in the aetiology of POF. (86)

Another relevant factor may be the concentration of various cytokines at the site of surgery. Although following joint arthroplasty there is an increase in the plasma level of cytokines similar to that observed following major abdominal surgery, the local concentration of these cytokines has been shown to be much smaller following joint arthroplasty as compared to abdominal procedures. Hence the concentration of cytokines at the site of the injury may also be an important determinant of the severity of injury following surgery, duration of recovery and POF (Figure 1). (87, 88)

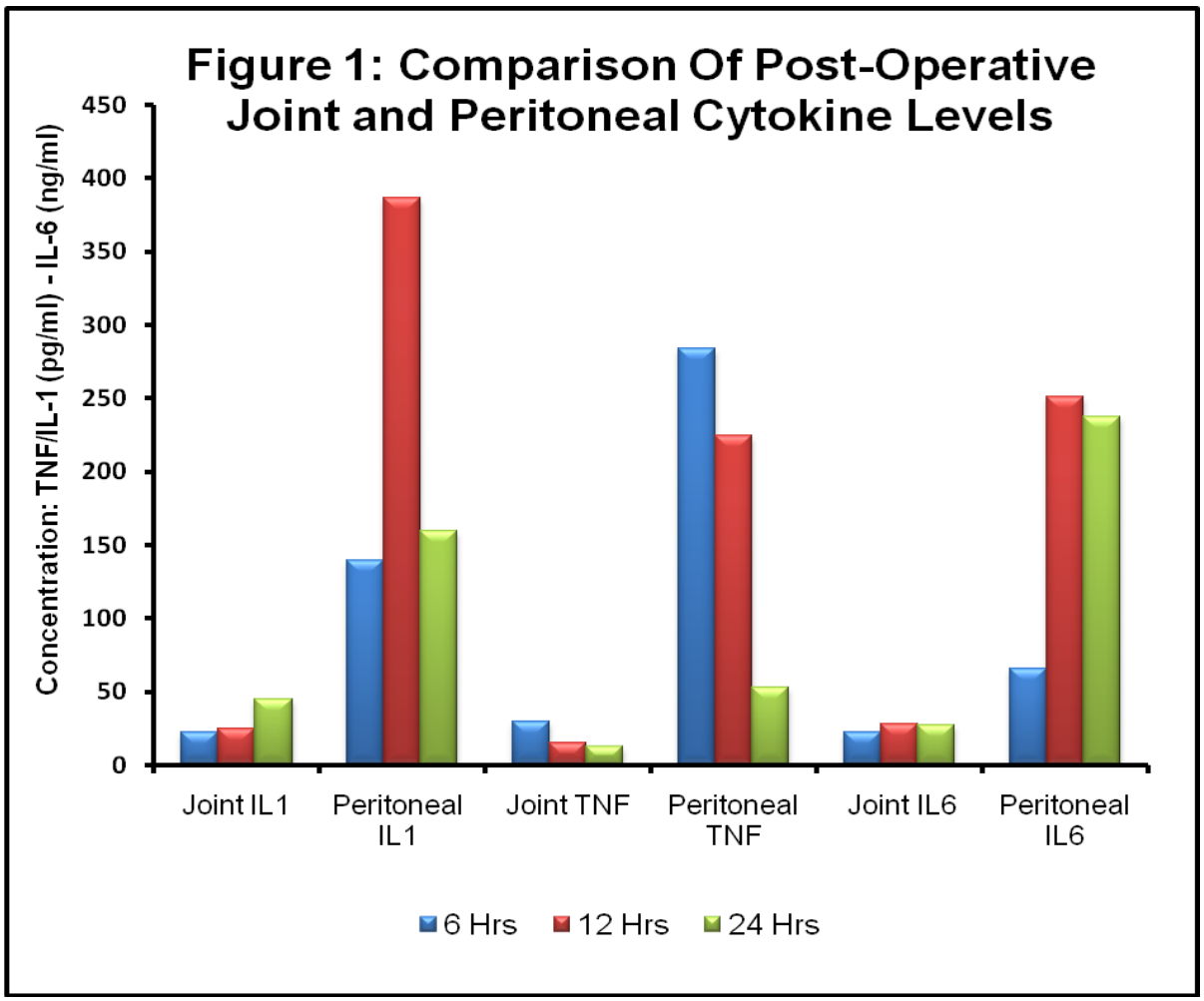


Figure 1: Comparison of Post-Operative Joint and Peritoneal Cytokine Levels

Prevention and Treatment of POF

As several different theories for aetiology of postoperative fatigue exist, different interventions have been undertaken in order to reduce POF and thereby improve recovery.

A meta-analysis has shown that increasing analgesia may improve symptoms of POF within the 1st postoperative day but not at any other stage (59). Neither epidural opioid analgesia nor epidural Bupivacaine and systemic indomethacin have been shown to be effective in reducing POF (51, 89).

Psychological interventions have also failed to produce significant improvements in POF. Methods such as emotional or psychiatric support, (20, 90) relaxation training (91-94), coping skills training (59) and provision of information (95-98) in various types of surgical procedures have not been very successful.

Nutritional intervention in the form of protein supplementation (99) or early enteral (100, 101) or parenteral (59) feeding have not been shown to make significant improvements either.

Laparoscopic surgery has been shown to be associated with some minor reductions in early POF in two studies(52, 102) but not other studies.(103-105) Overall there are no consistent data on the long term beneficial effect of laparoscopic surgery with respect to POF. (59)

As mentioned earlier, administration of a large preoperative dose of glucocorticoid has been shown to improve fatigue for up to 8 days postoperatively (86, 106) although these findings

are not consistent with results of other studies (106, 107). Human growth hormone is another intervention which has been shown to improve long-term POF (at day 30 and 90) following major bowel surgery in malnourished patients. However it has not been effective following aortic aneurysm repairs or minor operations. (60, 108, 109)

Post-operative physical training is another intervention which has been shown to improve fatigue scores within the first 7 days after the operation but not late POF. (62) Another study has also confirmed that early POF is significantly less in patients who undergo surgery under multimodal care pathways.(110)

Summary

Postoperative fatigue remains a significant problem for many patients. POF can delay recovery and return to normal activity and therefore is of clinical significance.

Post-operative fatigue should be defined as a collection of physical and psychological symptoms which delay return to normal activity following surgery. This definition recognizes the fact that POF has a multimodal etiology and it disrupts normal function following surgery and hence is clinically significant.

Different instruments for measurement of fatigue exist and correlation between values from these various instruments has been difficult. Improvement in our understanding of POF has led to design and validation of more accurate methods of assessment of POF.

Different etiologies for POF have been suggested. Surgical stress, nutrition, mobility and psychological factors are to name a few. There seems to be a complex interaction between these factors, therefore a single cause cannot be held responsible for the onset and persistence of this phenomenon. Furthermore, other factors such as local inflammatory mediators may also play an important role and require further investigation.

Based on these, a number of interventions have been undertaken, though a single modality approach seems to have little influence on progression of POF. However with implementation of multimodal enhanced care pathways, combining strategies such as psychological intervention, thoracic epidural, early nutrition, minimal access surgery and

early mobilization there is evidence that significant and clinically measurable improvements in POF can be achieved. (110, 111)

Although multimodal strategies are the most obvious way of reducing POF, there is still room for further research into the aetiology of POF with identification of strategies which may influence POF further.

In the subsequent chapters various aspects of a multimodally enhanced care pathway will be discussed and the evidence which exist for such perioperative programs and how they may differ from common surgical practices will be reviewed.

Chapter 2 : Overview of Enhanced Recovery After Surgery Pathways

Introduction

In the previous chapter we concluded that Post-Operative Fatigue (POF) has a multi- factorial aetiology. In this chapter aims to breakdown various aspects of perioperative care and review the evidence available to support enhanced recovery after surgery (ERAS) or Fast-Track (FT) care pathways.

Colonic resection is associated with 6-11 days of hospital stay and a complication rate of 15–20%.(112) Fatigue following these major abdominal operations may last up to three months.(6) This prolonged recovery has a multi-factorial aetiology with contributions from biological, psychological and social factors.(66) With increasing appreciation of the impact of surgical trauma and perioperative practices on recovery, efforts have been made to modify surgical care in such a way to minimise the physiological and psychological stresses associated with surgery. This involves a structured and evidence based approach to surgery rather than pursuing traditionally accepted surgical practices. The development of enhanced recovery after surgery (ERAS) or Fast-Track (FT) care pathways are based on such principles.

ERAS is a collection of strategies brought together in a structured care pathway. This approach aims to modify surgical pathophysiology and address psychological and environmental factors which contribute to post-operative morbidity. A recent systematic review has identified seventeen different component strategies, with variations in selection between different ERAS programs. (113-119)

With ERAS, the median duration of hospital stay in some centres following colonic surgery has been reduced to 2-3 days.(112) Strategies such as use of multimodal analgesia, early mobilization and early oral feeding decrease post-operative nausea, vomiting and ileus, which lead to an earlier return of gastrointestinal function and accelerated recovery. (115, 117, 120) ERAS programs may also be associated with reduced post-operative morbidity secondary to beneficial effects on cardiac and respiratory function.(114, 120)

This is a review of the practical aspects of an ERAS programme for colonic surgery with a focus on associated evidence and potential benefits of the various elements which are thought to contribute to the effectiveness of such programmes (Table 3).

Table 3: Pre-operative Strategy

Information
Pre-operative Plan
Daily Milestones
Discharge Plan
Medical Assessment
Alcohol
Smoking
Social Assessment
Factors which may delay discharge
Ward Visit
Perioperative Carbohydrate Drinks
Pre-habilitation

Pre-Operative Care

Information

Appropriate preoperative education is associated with diminished anxiety, fewer complications, shorter hospital stay, decreased use of analgesia and earlier return of gastrointestinal function after surgery. Well informed patients also comply better with rehabilitation programs.(121-123) RCTs have shown that the style and nature of the information provided, such as preoperative suggestions or structured preoperative instructions also influence outcomes. For an ERAS programme this should include defining expectations and setting daily milestones for individual patients.(123, 124) A pre-operative visit to the ward may enhance sense of security and independence after admission.(125) This in turn may eliminate a factor which could hinder mobilisation.

Although definitive evidence is currently lacking, many ERAS programmes advocate the use of a dedicated pre-operative session where, based on patients' preference, adequate information is provided, expectations and milestones are set in place, discharge planning is commenced and social issues which may delay discharge are addressed.

Pre-habilitation

Careful preoperative assessment of patients for detection of organ dysfunction and optimisation of medical status prior to surgery is routine practice. Poor preoperative fitness has been shown to increase 30 day operative mortality and result in a significantly longer hospital stay, with a greater possibility of surgical complications and pain.(126-128) A review article on this topic has concluded that in abdominal surgery pre-habilitation may lead to improved quality of life, reduction in postoperative pain, complication rates and overall mortality.(129) Although not described previously as part of ERAS programmes, a structured

pre-habilitation program consisting of aerobic and strength training combined with nutritional support may be considered for specific surgical patients in order to reduce the risk of complications and improve outcomes.(129) The exact contents, duration and nature of such a program particularly within an ERAS setting should be further investigated.

Alcohol, Smoking and Surgery

Alcohol abusers have a two to three fold increase in postoperative morbidity, the most frequent complications being bleeding, wound and cardio-pulmonary complications. One month of preoperative abstinence reduces postoperative morbidity in alcohol abusers by improving organ function.(130, 131)

Smoking is another patient factor which has a negative influence on recovery. Current smokers have increased risk of postoperative pulmonary and wound complications.(132) At least 4 weeks of abstinence from smoking is required in order to reduce the incidence of pulmonary and wound complications.(132, 133)

Nutritional Support

A number of RCTs have demonstrated that malnourished cancer patients benefit from pre-operative enteral supplementation. In addition to cancer patients, other severely malnourished surgical patients, with more than 15% weight loss, will also benefit from this intervention. Furthermore, patients with Crohn's disease, alcoholics and the elderly, have been found to have significant micronutrient deficiencies or ingest levels of vitamins and minerals below recommended allowances. Therefore nutritional evaluation and preoperative micronutrient supplementation has also been recommended in these groups of patients. (134-139) A recent review has shown that nutritional supplementation has the greatest impact when started in

pre-operative course and this is associated with a reduction in infectious complications and anastomotic leaks. (140)

According to the latest guidelines preoperative nutritional support should be commenced in patients with severe nutritional impairment 10-14 days prior to surgery by means of dietary advice and oral dietary supplementation (Table 4). (141) The parenteral route should be considered if the oral route is thought to be inadequate. Selected patients should receive nutritional support prior to surgery and the observed benefits are more pronounced if this treatment continues throughout the perioperative period.(138-142)

Table 4: ESPEN Definition of Severe Nutritional risk (141)

ESPEN Definition
Weight loss > 10-15% within 6 months
BMI < 18.5 kg/m^2
Subjective Global Assessment Grade C
Albumin < 30 g/l

Pre-Operative Fasting

A time-honored tradition in surgery is overnight fasting prior to elective surgery in order to avoid pulmonary aspiration of gastric contents. However this induced starvation leads to activation of fasting metabolic pathways and eventual depletion of liver glycogen reserves with resulting net catabolism of fat and protein stores, increased gluconeogenesis and an overall amplification of the surgical stress response. In short, preoperative fasting generates unnecessary physiological stress. Management of perioperative metabolism has been shown to be an important technique in improving outcomes following surgery. [143, 144]

It is now accepted that the free intake of clear fluids, such as water, tea and coffee can be allowed up until 2 hours prior to induction of anaesthesia without increasing the risk to the patient.(145) The aim of preoperative carbohydrate administration is to switch the patient from the fasted to the fed state before the onset of surgery, therefore avoiding the metabolic consequences associated with a fasting state post-operatively.(146)

Pre-operative carbohydrate ingestion reduces postoperative insulin resistance following major abdominal surgery. (147) It may attenuate postoperative depletion of muscle mass, lead to shorter hospital stay and reduced preoperative discomfort.(148-150) A small randomised trial in patients undergoing colorectal surgery has suggested that pre-operative carbohydrate loading is superior to fasting or supplementary water and is associated with a significantly shorter hospital stay and a trend towards earlier return of bowel function. (151) Although the extent of the true clinical impact is still debated, this practice is safe and its use should be advocated in the majority of lower GI procedures.

Mechanical bowel preparation

Mechanical bowel preparation (MBP) was first described in 1959.(152) The morbidity of colorectal surgery significantly diminished over the next few decades and efficient MBP was considered to be a critical factor in preventing infectious complications after colorectal surgery. A recent survey has shown that 94% of surgeons across Europe and the United States employ some form of preoperative MBP.(153)

MBP aims to clean the colon of solid stool. It is postulated that the "clean" bowel has a lower bacterial content. It is also easier to handle and there is a smaller chance of spillage of faecal material and contamination of the wound and peritoneal cavity during surgery.(154) However, MBP is associated with patient discomfort, dehydration and electrolyte disturbances and hence safe use of MBP requires hospital admission and intravenous fluid administration. (155, 156)

With improvements in surgical techniques and better perioperative care, including routine use of effective prophylactic antibiotics, morbidity rates in colorectal surgery have fallen.(157-159) According to the most recent reviews (Table 5) on this topic, MBP is considered not to be beneficial and can safely be avoided in elective colonic surgery.(160-164) In situations where a transanal stapling device is likely to be utilised intraoperatively, one can clean out the rectum prior to surgery with an enema.

Table 5: Mechanical Bowel Preparation in Colorectal Surgery

Author	Type of Study	No of cases	Main outcome	Results
Guenaga (2009) (164)	Cochrane Review	4777 patients (13 RCTs)	Anastomotic leakage	No Difference in leak rate(OR 1.26 NS), possible trend towards increased rate of anastomotic leakage and wound complications with MBP
Fa-Si-Oen (2005) (163)	Multicentre RCT	250 Patients (5 centres)	Wound infection and anastomotic leak	No difference in any of the outcome parameters
Slim (2009) (160)	Meta-analysis	4859 patients (14 RCTs)	Anastomotic leakage	No difference in anastomotic leakage rate, all surgical site infections more in MBP group (OR = 1.40, *P* = 0.02)

MBP: Mechanical Bowel Preparation, RCT : Randomised Controlled Trial, OR: Odds Ratio

Environmental factors

Environment influences behaviours, actions and interactions. Elements of space and the environment may influence recovery. For example duration of hospital stay and community and hospital mortality rates have been linked to sunlight.(165, 166) In the post-operative period sunlight decreases stress, pain and analgesia use.(125) There are studies suggesting that the built environment can influence patient outcomes by reducing anxiety, increasing social interactions and modifying patients' behaviour.(166-168)

However there has been little or no mention of the environmental settings suitable for an ERAS ward. There are no data investigating the influence of the ward design on recovery in this setting and the ward environment has not been thought of as an independent ERAS strategy. Our data show that patients recover more quickly in an elective-only unit.(169) Thus we propose that this should be considered as a key ERAS element. The ward should be regarded as a small rehabilitation unit, characterised by exclusion of acutely admitted patients from elective patients, a ward design which facilitates the feeling of security, encourages independence and allows free access to food preparation and self-care facilities.(170) Variations in the ward environment may be a factor in widely different outcomes seen in ERAS programmes utilising the same protocols.(171) In light of deficiencies in data related to this topic, further research on the influence of ward environment on recovery should be conducted.

Nursing Care

The nursing aspect of care plays a key role in delivering many of the strategies within an ERAS programme. Nursing care should be driven by structured care pathways and such pathways should be recognized as an important aspect of ERAS. However published literature has not placed sufficient emphasis on this topic. These pathways should provide guidance to ensure that important daily milestones are met by structuring and organizing elements of care such as mobilisation, oral intake and ongoing discharge planning.

Additionally, specialized ERAS nurse practitioners may be able to play an important role in implementation of ERAS programs. They can be involved in preoperative assessment and education, post-operative care and community follow up of patients. In clinical practice the latter two points may improve the low post-operative compliance rates seen with some ERAS programmes.(171) A motivated, well educated nursing team can ease the transition from a conventional care model to an ERAS model.

Intra-Operative

Prophylactic Antibiotics

A systematic review has shown that for patients undergoing colorectal surgery, routine use of antimicrobial prophylaxis leads to reduced rates of wound infection. Although many different agents are effective in achieving this, certain regimens appear to be inadequate. Antibiotics should be administrated prior to incision and should be active against both aerobic and anaerobic bacteria. Administration of a single dose immediately prior to the operation is as effective as continuous postoperative prophylaxis.(157) A recent Cochrane review has demonstrated that combined oral and intravenous antibiotic prophylaxis when compared to intravenous alone or oral alone, may further improve surgical site wound infection rates.(172)

Perioperative Oxygen Therapy

Recent studies have attributed various benefits to high peri-operative oxygen therapy. There are large RCTs suggesting that patients who receive 80% inspired oxygen both intraoperatively and in the immediate post-operative period, have a significantly reduced risk of wound infection.(173, 174) There is further evidence showing that the latter regimen may also be associated with an improvement in relative anastomotic hypoperfusion following colorectal surgery. However further data in this field is still required and the role of supplemental oxygen therapy in the healing of colorectal anastomoses is still very much at an early experimental stage.(175)

Oxygen therapy also reduces the incidence of postoperative nausea and vomiting and in this respect oxygen is as effective as antiemetics such as Ondansetron.(176, 177) Perioperative Supplemental oxygen administration is a simple, inexpensive and well-tolerated option to

improve patient outcome.(178) The optimal oxygen concentration and duration of this treatment as well as its role as an ERAS strategy still need to be further evaluated.

Epidural anaesthesia

Analgesia

According to a meta-analysis, epidural analgesia, regardless of the location of catheter placement or the analgesic agent used, provides superior postoperative analgesia compared with parenteral opioids.(179) This is also associated with reduced rates of deep venous thrombosis, pulmonary embolism, myocardial infarction and stroke, as well as reduced mortality rates.(179, 180)

Analgesic agent

An opioid epidural provides a degree of analgesia which is comparable to a local anaesthetic (LA) epidural. However a Cochrane review has concluded that a LA epidural reduces gastrointestinal ileus in patients undergoing laparotomy an effect which is not seen with opioid epidural analgesia.(181) The addition of epidural opioid to epidural LA improves the quality of pain relief and may not significantly inhibit its ileus-reducing effect. According to a meta-analysis, LA epidural also improves pulmonary function.(182) Hence a LA epidural with or without low dose opioid is superior to an opioid only epidural.(179)

Catheter Location

Lumbar or thoracic epidural anaesthesia (TEA) are often alternative choices for abdominal surgery. Evidence suggests that TEA is superior to lumbar epidural analgesia. Compared to a lumbar epidural, TEA may be easier to place. (183, 184) Controlled studies have

demonstrated that TEA is associated with smaller reductions in systolic and diastolic pressure and leads to compensatory reduction of myocardial work and oxygen demand .(185, 186) Under stressful conditions, patients with coronary artery disease benefit from TEA rather than a lumbar epidural.

Duration of blockade

The timing and duration of the blockade is of importance. An RCT has concluded that there are no beneficial postoperative effects on plasma or urinary hormonal responses or on nitrogen balance with short or only intraoperative epidural use.(187) Thus ERAS guidelines generally recommend a prolonged blockade, preferably at least 24-48 hours, in order to reduce overall surgical stress.(188, 189)

Epidural and Gastrointestinal function

One other major benefit of TEA is its impact on recovery of gastro-intestinal function. Patients with local anaesthetic TEA (blocking the splanchnic fibers T5–T10) show improvements in gastrointestinal motility and which is not observed with a lumbar epidural.(190) A systematic review has concluded that epidural anaesthesia reduces postoperative ileus in patients undergoing laparotomy.(181) According to a meta analysis, this earlier recovery of GI function combined with subsequent early enteral feeding results in improved outcomes.(191) Experimental studies have shown that the local anaesthetic in a TEA blocks the activity of sympathetic fibers innervating the blood vessels in the mesentery and hence it improves the mucosal blood flow, even in the presence of reduced perfusion pressures. (192-194) In this way, use of TEA may theoretically lead to a lower rate of anastomotic complications after abdominal surgery although evidence is deficient in this area.(195)

A continuous TEA with at least 10 mg of bupivacaine per hour, continued for 24-48 hr postoperatively should be used within an ERAS programme.(181, 187-189) Although it is not proven that an epidural alone improves outcomes for colorectal surgery, there is evidence that it leads to improvements in GI function and hence can reduce ileus related nausea and vomiting and increase food intake. The superior quality of pain relief provided by TEA can lead to increased mobilisation, with long-lasting effects on exercise capacity and health-related quality of life.(196) While a single RCT has shown that within an ERAS programme, an opioid PCA (Patient Controlled Analgesia) provides results comparable to TEA, this evidence is not sufficient to suggest that an opioid PCA is as effective as TEA within an ERAS setting and the bulk of evidence demonstrates the superiority of epidural analgesia. (197, 198)

Epidural and Hypotension

A common problem with epidural analgesia is bradycardia and a decrease in both systolic and diastolic blood pressure. This is largely due to blockade of the sympathetic nervous system. This also causes arterial and venous vasodilation, leading to functional hypovolaemia. Epidural related hypotension is usually treated with fluid boluses especially while the patients are on the ward. However, a small RCT has shown that TEA does not lead to changes in blood volume and administration of hydroxyethyl starch and ephedrine have similar haemodynamic effects;(199) therefore pressors may be preferred in the treatment of epidural related hypotension rather than repeated fluid boluses.

The Choice of Incision

Currently there is no consensus on the use of a transverse or a vertical incision for elective laparotomy and in clinical practice this is usually based on the surgeons' preference. From a surgical perspective concerns regarding adequacy of exposure, duration of the procedure and

postoperative complications, particularly wound dehiscence and infection as well as long-term risk of incisional hernia, are the determining factors.

The type of abdominal incision can influence post-operative morbidity. Two meta-analyses have suggested that following elective laparotomy with a transverse incision, there may be a lower incidence of complications such as pain, burst abdomen and pulmonary morbidity and in addition a transverse incision may result in fewer incisional herniae.(200, 201) However sufficient data are not available to reach definitive conclusions in particular with respect to elective colonic surgery.

There is limited data for both right and left sided colectomies suggesting that a transverse incision may be superior to a midline vertical incision.(202-204) A large retrospective analysis and a smaller randomized prospective study have suggested that in colonic surgery a transverse incision may result in less pain, faster improvement of respiratory function and shorter hospital stay without restricting access to the operative field or increasing the operating time.(202, 204)

Further trials are necessary in order to examine the role of transverse incisions for colorectal surgery particularly in presence of epidural analgesia. This is because an epidural may provide better analgesia with a transverse incision, which covers a smaller number of dermatomes as compared to a vertical incision. At the present time there is evidence that a transverse incision is at least as good as a vertical incision for right sided colonic resections and may in fact have some advantages.(202, 205)

Laparoscopic Surgery

Laparoscopic surgery is one of the more controversial topics in enhancements of perioperative care. It is accepted that some positive physiological affects, such as moderate inhibition of various inflammatory responses are attributable to laparoscopic surgery. However it has been argued that it only slightly modifies the overall surgical stress response and has no important effects on the classic endocrine metabolic response to surgery.(206) Clinically, in a setting of conventional care, a Cochrane review has concluded that single-modality intervention with laparoscopic surgery has some advantages over open colonic resection, including slightly shorter hospital stay, shorter duration of ileus, less pain, bleeding and improved pulmonary function and oxygenation.(207) However, uncontrolled studies have suggested that patients may recover faster with open surgery within an ERAS programme, than laparoscopic surgery under conventional care.(112) Hence the combination of laparoscopic surgery and ERAS may improve care further.(118, 208) Nonetheless, this is still debated and various studies have reached contradicting conclusions. Large multi-centre studies are underway in order to assess the role of laparoscopic approach in an ERAS setting.(209)

Prophylactic Use of Drains

Historically surgeons have also used drains for prophylactic purposes and currently many surgeons around the world continue to use them on a routine basis.(210) In colonic surgery drains fail to accomplish the purpose for which they were inserted as, in cases of anastomotic dehiscence, neither faeces nor pus emerges via the drain.(211, 212) Systematic reviews have confirmed that routine drainage after colonic surgery does not prevent anastomotic dehiscence, wound infections or other extra-abdominal complications.(213, 214) Based on the evidence currently available this practice should be abandoned.

Prophylactic Use of Nasogastric Tubes

For the past 300 years tubes have been inserted into the stomach via the nose or mouth for the purpose of evacuating gas and liquid. The prophylactic use of nasogastric tubes (NGT) after abdominal operations has become so prevalent that it has even been described as "the standard of care".(215) Currently approximately 60% of surgeons in the United States and Europe routinely use prophylactic NGT for up to 3 days post-operatively following elective surgery.(153)

Prophylactic use of NGT has been thought to speed up the return of bowel function following surgery. Other arguments for its routine prophylactic use have been that it empties the stomach, eases respiration and reduces the risk of aspiration of gastric contents, and therefore decreases the risk of pulmonary complications; it increases patient comfort by lessening abdominal distension; protection of intestinal anastomoses; and shortening hospital stay.(215)

Meta-analyses have show that the use of NGT is ineffective in achieving any of the goals described above. Conversely, significant benefits such as earlier return of bowel function and improvements in pulmonary and wound complication rates may result from avoidance of routine use of NGT. Selective tube insertion is only beneficial to relieve gastric symptoms.(215, 216) Routine use of prophylactic NGT following abdominal surgery should be avoided.

Intra-Operative Fluid therapy

Fluid therapy is a controversial topic in perioperative care. Current perioperative fluid therapy is largely based on concepts developed in the late 1950s and early 1960s. Moore argued that the net physiological response to trauma is conservation of water and sodium; therefore he recommended restriction in fluid therapy.(217) In contrast, Shires postulated that

following major surgery, fluids are redistributed to a hypothetical space (i.e., the “third space”), leading to a decreased in extracellular fluid volume and therefore proposed replacement of the third space losses with crystalloid administration to maintain adequate plasma volume. (218)

The latter still dictates modern perioperative fluid management. Current fluid therapy regimens in major surgery may cause a weight increase of 3–6 kg.(219) Several factors, including concern about preoperative dehydration, attempts to support the circulation and cardiac function after general and regional anaesthesia, administration of crystalloid or colloid to avoid blood transfusion, maintenance of urine output and preservation of a high CVP (Central Venous Pressure) lead to excess perioperative fluid administration.(220)

However administration of excess fluid may contribute to postoperative morbidity. It increases demand on the heart, due to an excessive shift to the right on the Starling myocardial performance curve and this may adversely affect postoperative cardiac function.(220) Excessive fluid administration may also lead to increased pulmonary complications.(221) Fluid overload may lead to oedema of the GI tract and hence contribute to oral intake intolerance, prolonged ileus, bacterial translocation and sepsis.(222) Excess fluid has shown to decrease tissue oxygen tension with potential deleterious effects on anastomotic and incisional wound healing as collagen deposition is directly and significantly proportional to wound oxygen tension.(220, 223, 224) Finally, coagulation may be enhanced with crystalloids which may predispose patients to postoperative thrombosis. (225) On the other hand intraoperative hypovolaemia is common and may be a potential cause of organ dysfunction, increased postoperative morbidity, and death.(226) Based on these findings it is obvious that a balanced perioperative intravenous fluid regimen will be effective in reducing

complications and enhancing recovery after major elective gastrointestinal surgery and various methods have been recommended.

One approach is to restrict perioperative intravenous fluid therapy. RCTs in patients undergoing abdominal surgery have shown that this approach can lead to reduced morbidity and hospital stay.(227, 228) In a randomised blinded, multi-centre trial under the setting of continuous epidural anaesthesia and early oral feeding in patients undergoing elective colorectal surgery, limited perioperative fluid therapy, aiming to maintain total body weight, proved to be successful in significantly reducing postoperative complications.(227) However more accurate methods for monitoring of intra-operative fluids administration are available.

Shoemaker et al. suggested that tissue-perfusion variables should themselves become the goals of therapy. This has become known as “goal-directed therapy”. Conventional intraoperative circulatory monitoring in its simplest form includes heart rate, blood pressure, urine output, and central venous pressure with periodic measurements of haematocrit and arterial blood gases. (229)

By using the Oesophageal Doppler Monitor (ODM) as a mean to estimate intra-operative cardiac output, significant improvements in outcome have been observed in patients undergoing major orthopaedic and cardiac procedures.(230, 231) A number of randomised trials in patients undergoing major abdominal surgery have demonstrated that goal-directed intraoperative fluid administration using ODM may result in improved outcomes such as reduced number of critical care admissions, earlier return of bowel function, lower incidence of postoperative nausea and vomiting as well as reduced hospital stay and overall morbidity. (232-235). These findings are further highlighted in a recent meta-analysis.(236)

Interestingly patients in the ODM study groups, with goal directed fluid therapy regiments, received larger volumes of intraoperative intravenous fluids than the non-ODM groups with improved outcomes (Table 6). Three of the mentioned studies that have shown benefits of intra-operative ODM in abdominal surgery had “conventional” perioperative care methods hence further data under settings of continuous intra-operative thoracic epidural and early oral feeding is required in order to further clarify the role of ODM. However as demonstrated in a recent study, it is clear that an adequate and balanced intra-operative fluid management strategy with sufficient end organ perfusion and accurate post-operative assessment of fluid status may contribute to accelerated recovery rather than strict protocols to restrict fluid therapy. (237)

Table 6: Goal Directed Fluid Therapy

Author	Type of Fluid	Doppler	Control	Main Out-Come*
Wakeling (2005)(234)	Col	2000* ml	1500 ml	1.5 days reduced length of stay
	Cry	3000 ml	3000 ml	
Gan (2002) (233)	Col	847* ml	282 ml	1 day reduced length of stay
	Cry	4405 ml	4375 ml	
Conway (2002) (232)	Col	28* ml/kg	19.4 ml/kg	Reduced No. of ICU admissions
	Tot	64.9ml/kg	55.2 ml/kg	
Noblett (2006) (235)	Col	1340 ml	1209 ml	2 days reduced length of stay
	Cry	2298 ml	2625 ml	

Col: colloid, Cry: Crystalloid, Tot: Total fluid * Statistically significant

Post-Operative

Post Operative Nausea and Vomiting

Postoperative nausea and vomiting (PONV) are among the most common adverse events related to surgery and anaesthesia. This leads to patient discomfort, dehydration and electrolyte disturbances as well as delayed oral feeding.

A systematic, multimodal approach may be the most effective method of controlling PONV. This should consist of decreasing the baseline risk factors for all patients, identifying patients with high risk of PONV for administration of appropriate prophylactic therapy and suitable rescue antiemetics if these measures fail. Use of regional anaesthesia, minimization of perioperative opioid use, propofol for induction and maintenance of anaesthesia, adequate hydration and avoidance of volatile anaesthetics, nitrous oxide and large dose neostigmine as well as administration of supplemental oxygen may all reduce the baseline risk for PONV. Prophylactic therapy usually has been reserved for those who are deemed high risk. However within an ERAS programme all patients should benefit from prophylactic therapy. Overall, treatment with agents from different therapeutic classes is superior to single drug therapy for PONV prophylaxis. If a patient has received no prophylaxis, therapy with a small dose of a 5-HT3 (5-Hydroxytryptamine3) receptor antagonist should begin at the first signs of PONV. For those who have failed prophylactic therapy the rescue treatment should contain drugs from different classes than the prophylactic agent. Interestingly it has recently been shown that that most commonly used drugs reduce PONV to the same degree with no convincing differences between their efficacies. This structured and multimodal approach may be the most appropriate method in controlling PONV in patients within an ERAS programme.(238, 239)

Early Oral Feeding and post-operative dietary supplementation

Traditional restrictions on oral intake following surgery are not based on scientific evidence. A number of historical issues such as postoperative nausea, vomiting and ileus plus fears of anastomotic dehiscence have led to the practice of restrictive postoperative oral nutrition (nil per mouth).(240) Within 24 hrs after surgery, muscle protein catabolism begins with the intestine followed by the skeletal muscle being the main sites for protein catabolism**.** However controlled studies have shown that this catabolic response to surgery can be counteracted by nutritional support.(241)

A recent Cochrane review has concluded that there is no need to delay oral feeding following gastrointestinal surgery with a positive trend towards reduced complications with early feeding. Individual studies have shown that early feeding may decrease postoperative infections, length of hospital stay, muscle loss and fatigue. It decreases intestinal mucosal permeability and leads to a positive nitrogen balance. Experimental and clinical studies have demonstrated increased wound healing and anastomotic strength in the intestines and somatic tissues with early feeding. These reduced rates of postoperative complications are independent of preoperative nutritional status.(101, 191, 242-246)

In addition to early oral feeding, dietary supplementation can provide added benefits in terms of reduction in fatigue, weight loss and overall morbidity in normal as well as malnourished patients. The combination of specific nutrients such as arginine, nucleotides, ω-3 fatty acids and glutamine (i.e. immunonutrition) has been shown to improve nutritional, immunologic, and inflammatory parameters. A recent systematic review has shown that in elective surgical patients, immunonutrition can lead to a significantly lower incidence of infectious complication and reduced length of hospital stay. (140)

Once established, the rate of feeding can be adjusted according to the intestine's reduced capability and employing techniques that reduce ileus such as thoracic epidural analgesia, restricted intravenous fluid therapy and avoidance of opioids may facilitate this further. Early oral feeding with or without supplementation, is safe and it may be associated with major benefits and should be routinely practiced although conclusive data with regards to exact beneficial effects are still awaited.

Balanced analgesia

Opioids are commonly thought to be a very effective form of analgesia in surgical patients, however they are most effective during rest, rather than activity (e.g., cough, mobilization) (247, 248) and thus opioids alone cannot provide functional pain relief. Additionally, they are associated with a number of known adverse effects on various organ systems (Table 7). Opioids also act on the vomiting centre in CNS and cause nausea and vomiting, especially during movement. Even a single dose of opioid may lead to prolonged vomiting. Opioids have well known adverse affects on gastrointestinal motility. Both systemic and epidural opioids have negative effects on urinary bladder function, which may result in urinary retention. Although none of these side effects are potentially life-threatening or represent a risk for serious morbidity in healthy patients, they may significantly limit early postoperative recovery.(249)

Peri-operatively, an effective way of avoiding opioids is administration of nonsteroidal anti-inflammatory drugs (NSAID) which have well documented opioid-sparing effects.(249) Secondary to this opioid sparing role they lead to reduction in sedation, improvements of sleep and respiratory function, reduction in nausea and antiemetic use and improvements in gastric emptying.(249)

It is recommended that post-operative analgesia be managed with a balanced or dynamic analgesia regimen, with avoidance or small doses of opioids combined with NSAIDs and more effective analgesic techniques such as peripheral and central neural blockades.(250)

Table 7: Summary of some known adverse affects of Opioids

System	Adverse effects
Cardio-Respiratory	Hypotension, depression of the cough reflex Hypercapnia Reduced chest wall compliance, Tidal volume and expiratory force.(249)
CNS	Sedation Reduced respiratory rate Reduced sensitivity to hypoxemia Nausea and vomiting (via vomiting centre) (249)
Sleep	Significant sleep disturbance (251) Reduce respiratory function during sleep (252)
Immune Function	Immunosuppression Enhancement of tumour growth.(253)
Bladder	Urinary retention (254, 255)

Postoperative Urinary Drainage

Postoperative voiding dysfunction is a clinically important issue. It can occur with an incidence of 10-60 % after major operations with the highest frequency after pelvic surgery.(256, 257)

A number of different factors contribute to postoperative urinary retention. These include older age, a history of voiding problems, inability to stand or sit after surgery, drugs that inhibit urinary detrusor function, intraoperative damage to the autonomic pelvic nerves, excess intraoperative fluids or stress-induced activation of inhibitory sympathetic reflexes.(258, 259) Consequently, in many surgical procedures routine postoperative bladder catheterization is used to avoid urinary retention and the resulting negative effects on bladder function.

However, the routine use of indwelling urinary catheter (IDC) may increase the risk of urinary tract infection and this is related to the duration of bladder catheterization.(257, 260) IDCs may also restrict patient mobility and cause patient discomfort.

Following abdominal surgery, even in the presence of TEA, it has been shown that the incidence of urinary retention after removal of IDC on day 1 is only 9% and the risk of subsequent urinary infection is reduced to 4%. It has been suggested that routine urinary bladder catheterization is not required despite ongoing continuous TEA.(258) Early removal of the IDC will lead to subsequent ease of mobilisation and reduced infectious complications. Postoperatively, prolonged use of IDCs is therefore not necessary and should be avoided.

Conclusion

It has been our experience that altering traditionally accepted practices and implementing new ideas is extremely challenging and involves a considerable amount of communication, planning, effort and commitment. Organization of an enhanced care pathway requires a multidisciplinary approach with close collaboration between different medical teams. Furthermore protocols alone are inadequate for successful implementation of ERAS programmes as hospitals employing identical protocols have major differences in outcomes and also within the same hospital different clinicians have different results.(116, 171) Experience and confidence with the use of protocols as well as variations in compliance rates and organisation of care are elements which may be related to these observed dissimilarity in results. Identification of clear criteria for discharge should also be an important element of ERAS care pathways. There are also a number of other strategies such as anticoagulation therapy and prevention of intraoperative hypothermia which are common in practice and have not been mentioned here. In this review we have identified a number of additional factors which should be incorporated with the ERAS framework for further discussion and examination. It is essential to note that single-modality interventions in isolation may not lead to significant reduction in organ dysfunction and improved outcomes seen with ERAS, but it is the combined influence of individual strategies which may lead to enhanced recovery.

In the subsequent chapters will review the clinical outcomes from an ERAS programme which was established as part of this research project.

Chapter 3 : Materials and Methods

Post Operative Fatigue Review

A database search was conducted of Medline, Embase, PsychInfo, Pubmed and the Cochrane Collaboration library from inception to December 2008 for English language papers containing surgery related MeSH or free text terms and combined with fatigue related MeSH or free text. Papers were reviewed with respect to relevance to this article, in particular focusing on subjective and objective assessment as well as aetiology. The reference sections of all reviewed papers were also checked for further relevant studies. This was not a systematic review but an overview of the available literature on this topic.

Enhanced Recovery After Surgery Review

Topics in this clinical review article were chosen based on previously published reviews on Randomised Controlled Trials (RCT) on ERAS, recommended guidelines and also our own experience.(113, 119) For each topic MEDLINE and Cochrane databases were searched for the most recent and relevant reviews and RCTs as well as other publications, where appropriate. This is not a systematic review on the topic but an updated review with focus on the evidence relevant to ERAS programmes.

Enhanced Recovery Programme After Surgery (ERAS)

An Enhanced Recovery Programme After Surgery (ERAS) or Fast-Track Programme, forms an important frame work within which the research discussed in this thesis is conducted. This section describes the details of the ERAS program used.

The Operations:

The following operative procedures were considered for the ERAS programme.

- Right Hemicolectomy
- Left Hemicolectomy
- High Anterior resection

Both open and laparoscopic surgeries were included in the ERAS programme.

The Patients:

All patients were selected from those undergoing colonic resection at Middlemore Hospital under the care of three colorectal surgeons.

Inclusion:

- Elective Colectomy
- Operation at Manukau Surgical Centre
- Patient willingness to participate

Exclusion:

- Patients requiring a stoma
- Major medical co-morbidities with American Society of Anaesthesiology Score (ASA) of more than IV
- Significant cognitive impairment

The Ward:

Manukau Surgical Centre (MSC) is a stand-alone surgical facility which caters for elective surgeries only. There are no acute medical or surgical admissions to the wards. All nursing staff are trained to look after patients within the ERAS programme according to the set protocols.

Patient Recruitment:

Eligible patients were identified through the surgical out-patients clinics. Following this, they were approached for participation within the ERAS programme. After recruitment, they were seen in a dedicated pre-operative session. This is the first step of the ERAS programme.

Pre-Operative Session:

On this occasion routine pre-operative medical assessments were conducted. This included a routine physical examination, electrocardiograms (ECG) and routine blood tests (Full Blood Count, Urea and Electrolytes and Coagulation Screen). Following the medical assessment, patients were introduced to the ERAS programme. This incorporated a step by step introduction to various facets of the programme from the day prior to admission to the day of anticipated discharge as well as expected follow up arrangements.

Information about the operation and possible complications were provided as part of the consent process. Expected milestones were discussed and explained to the patients these included:

- Sitting up in a chair on the afternoon of the surgery
- Drinking at least 800 ml of liquids at the day of surgery
- Eating a full breakfast on the morning of post-operative day 1
- Having a shower on day 1
- Staying out of bed for at least 8 hrs on day 1 with mobilisation on at least two occasions
- Drinking protein drinks (Resource Plus®, at least 4 x 237ml boxes per day, Table9)
- Continuation of mobilisation on day 2
- Consideration for discharge on day 3

Discharge criteria would be explained to the patients. At this time the living situation and other social factors which could delay discharge were assessed, possible issues would be identified and steps would be taken to address these prior to admission and surgery.

Patients would be taken to the surgical ward and be introduced to the nursing staff. They were shown around the ward by the staff. The layout of the ward and the rooms as well as location of various facilities within the ward would be shown to the patients. On the conclusion of this session, patients would be provided with a information sheet, highlighting important aspect of the pathway (Appendix 8: Fast Track Patient Information**).**

Pre-Operative Carbohydrate Drinks:

All patients undergoing surgery within our ERAS programme were provided with six boxes of 200 ml carbohydrate drink (PreOP®, Nutricia; Numico, Zoetermeer, The Netherlands). Nutricia preOp is a 0.5kcal/ml, clear, non-carbonated, lemon flavoured, iso-osmolar carbohydrate drink. Patients were asked to drink four on the night prior to surgery and two on the morning of their operation, 2 hours prior to the expected time of surgery (Table 8).

Table 8: PreOP Contents

AVERAGE CONTENTS		per 100ml	per 400ml
Energy	kcal	50	200
	kj	215	860
Protein	**(g)**	-	-
Carbohydrate	**(g)**	12.6	50.4
polysaccharides	(g)	10	40
sugars	(g)	2.1	8.4
lactose	(g)	-	-
% of total energy	%	100	100
Fat	(g)	-	-
Dietary Fibre	(g)	-	-
Minerals			
Sodium	mg (mmol)	50 (2.2)	200 (8.6)
Potassium	mg (mmol)	122 (3.1)	488 (12.2)
Chloride	mg (mmol)	6 (0.2)	24 (0.7)
Calcium	mg (mmol)	6 (0.1)	24 (0.6)
Phosphorus	mg (mmol)	1 (0.0)	4 (0.1)
Magnesium	mg (mmol)	1 (0.0)	4 (0.2)
Water	(g)	92	368
Osmolarity	(mOsm)	240	240
Osmolality	(mOsm/ H2O)	260	260
Potential Renal Solute Load	(mOsmol)	55	55
pH		4.9	4.9

Mechanical Bowel Preparation (MBP):

MBP was avoided in most patients undergoing open colonic surgery within the ERAS programme. However, on occasions and based on surgeons' preference, selected patients received MBP prior to surgery. All laparoscopic cases where admitted to the hospital one day prior to surgery for MBP.

All other left sided cases had an enema (Fleet Phosphate, 120 ml, 19 g of monobasic sodium phosphate and 7 g of dibasic sodium phosphate) on the morning of the operation.

Admission:

All patients were admitted on the morning of their operation. On arrival, they would undergo a routine pre-operative nursing assessment, which may have included an enema and stoma marking, depending of the planned type of the operation. Patients undergoing laparoscopic surgery would be admitted at least one day prior to surgery for MBP.

Anaesthesia:

Premedication:

- Paracetamol 1g p.o.

Epidural:

Epidural catheters were inserted pre-operatively. The site was at level of T6 to T12 depending on the type and length of the anticipated surgical incision and the type of the operation. These were loaded intraoperatively with appropriate volumes of Bupivacaine of at least 0.25% concentration and 100 to 200mcg of fentanyl. Lower concentrations of local anaesthetic were used based on haemodynamic parameters and based on the anaesthetist's assessment.

Epidural related hypotension (defined as systolic blood pressure less that 100 mmHg or as seen appropriate by the anaesthetist in charge) was treated with vasopressor agents such as adrenaline or Metaraminol (Aramine® Metaraminol Bitartrate, Merck Sharp & Dohme, Auckland, New Zealand) as bolus or continuous infusion. Repeated fluid boluses were avoided as much as practical. High Dependency Unit (HDU) or Intensive Care Unit (ICU) admission was considered for management of hypotension if ongoing support was required.

General anaesthesia:

Protocols were designed for anaesthesia as part of the ERAS protocols.

Co-induction and induction agents of choice: Propofol (Propofol Injection 20mg/ml, InterMed Medical Ltd, Auckland, New Zealand).

Neuromuscular blockade: Rocuronium (Esmeron®, Rocuronium bromide, Pharmaco Ltd, Auckland, New Zealand) Vecuronium (Norcuron®, Vecuronium bromide, Pharmaco Ltd, Auckland, New Zealand) or Atracurium (Tracrium®, Atracurium besylate, GlaxoSmithKline Ltd, Auckland , New Zealand). Reversal was at discretion of the anaesthetist.

Maintenance was with oxygen, air and Desflurane (Suprane®, Desflurane USP, Baxter Healthcare Limited, Auckland, New Zealand) avoiding Nitrous Oxide.

Intraoperatively long-acting opioids were avoided when possible with use of short acting agents such as Remifentanil (Ultiva®, Remifentanil hydrochloride for injection, GlaxoSmithKline Ltd, Auckland, New Zealand), Fentanyl (Fentanyl, fentanyl citrate

Injection, AstraZeneca Limited, Auckland, New Zealand) or Alfentanil (Rapifen®, alfentanil 0.5 mg/mL injection, Janssen-Cilag Pty Ltd, Auckland, New Zealand).

Intraoperative intravenous fluid (IVF) use was limited to a maximum of 500 ml of colloid and 1500 ml of crystalloid soulutions. Hemodynamic parameters such as urine output, directed the use of IVF.

Ondansetron (Zofran®, Ondansetron hydrochloride dehydrate, GlaxoSmithKline Ltd, Auckland, New Zealand) 4mg, was used intraoperatively preferably prior to conclusion of anaesthesia.

Post Operative Care Unit

Epidural block level and analgesic adequacy were confirmed as soon as possible. Epidural infusion was started with 0.125% Bupivacaine and fentanyl 2mcg/ml solution (AstraZeneca Limited, Auckland, New Zealand) at appropriate rates. Epidural analgesia was optimised prior to transfer to the ward. Post-operatively, epidural related hypotension was treated with vasopressor agents, such as continuous infusion of Metaraminol.

Surgery:

Antibiotic prophylaxis consisted of a Cephalosporin (Cefuroxime sodium or Cefoxitin Sodium, Mefoxin®, Merck Sharp & Dohme Ltd. Auckland, New Zealand) with Metronidazole (Pharmacia, Auckland, New Zealand). The type of incision was left to the discretion of the operating surgeon. However transverse incisions were used for right sided operations when possible. All the other operations were performed through a midline,

longitudinal incision. Bowel anastomosis was achieved with stapling devices or hand sewn, depending on surgeons' preference.

Nasogastric Tubes (NGT):

Routine use of NGT was avoided in all patients. Use of NGT was reserved only for symptomatic relief in cases such as vomiting secondary to gastrointestinal ileus.

Urinary Drainage (IDC):

An IDC was inserted in the operating theatre. IDCs were routinely removed on the morning of the 1st post-operative day if urine output was adequate overnight (an average of at least 20ml/hr was expected). These were reinserted if clinically indicated.

Oral Intake:

Patients were encouraged to start oral intake as soon as possible. They were expected to drink at least 800 ml of fluids, including at least 2 boxes of Resource Plus® (237ml, Novartis, Auckland, New Zealand) protein drinks, following the surgery, on the day of the operation. Dinner on the day of operation was based on patients' preference however they were expected to start full oral intake from the morning of the 1st day.

Dietary supplementation was provided throughout the hospital stay and for 7 days after discharge. These consisted of at least 4 boxes of Resource Plus® per day. Each day, patients were expected to drink at least 2000 ml of oral fluids (Table9).

Table9: Resource Plus Contents

Contents		**Per 237 mL**	**Per 1000 mL**
Energy	Kcal	**360**	**1520**
	kJ	**1510**	**6375**
Protein	g	**13**	**55**
Carbohydrate	g	**52**	**220**
Fat	g	**11**	**46**
Linolenic Acid	g	3.9	16
Sodium	mg (mEq)	310 (13.5)	1310 (57)
Potassium	mg (mEq)	460* (11.8)	1940 (50)
Vitamin A	IU	1250	5280
Vitamin C	mg	36	150
Thiamine	mg	0.6	2.5
Riboflavin	mg	0.68	2.9
Niacin	mg	8	34
Calcium	mg	300	1270
Iron	mg	4.5	19
Vitamin D	IU	100	420
Vitamin E	IU	7.5	32
Vitamin B_6	mg	0.8	3.4
Folic Acid	mg	0.1	0.42
Vitamin B_{12}	mg	0.0024	0.01
Phosphorus	mg	250	1060
Iodine	mg	0.038	0.16
Magnesium	mg	100	420
Zinc	mg	6	25
Copper	mg	0.5	2.1
Biotin	mg	0.075	0.32
Pantothenic Acid	mg	2.5	11
Vitamin K	mg	0.02	0.085
Choline	mg	100	420
Chloride	mg (mEq)	340 (9.6)	1440 (41)
Manganese	mg	0.5	2.1
Selenium	mg	0.018	0.074
Chromium	mg	0.03	0.13
Molybdenum	mg	0.019	0.079

Antiemetic:

All patients were provided with regular pre-emptive antiemetic medications with the following being the agents of choice:

- Ondansetron, 4-8 mg, Q8hr, IV/Oral, Maximum of 24 mg per day
- Cyclizine, 25-50 mg, Q6hr, IV/Oral, Maximum of 200 mg per day
- Metoclopramide, 10-20 mg, Q4-6 hr, IV/Oral

Analgesia:

- A Thoracic Epidural was inserted pre-operatively and continued until the morning of the 2nd post-operative day (Bupivacaine hydrochloride 0.125% with fentanyl citrate 2 mcg/mL infusion solution).
- Paracetamol 1g, Qid was provided regularly for all patients
- From day 1, Nonsteroidal Anti-Inflammatory Drugs (NSAID) were started. The NSAID of choice was oral Tenoxicam 20 mg, twice a day (Tilcotil®, Roche Limited, Auckland, New Zealand). This continued for 7 days postoperatively. NSAIDs were avoided in patients with chronic renal failure and history of peptic ulcers.
- Systemic opioids were avoided in ERAS patients. Breakthrough pain was treated with oral opioid medications. The agents of choice being:
    - Tramadol Hydrochloride capsules, 50-100 mg, Oral, Q4-6 hr, maximum of 400 mg per day. (AFT Pharmaceuticals Ltd, Auckland, New Zealand)
    - Morphine sulphate tablet 10-20 mg, Oral, Q4 hr (Sevredol®, Douglas Pharmaceuticals Ltd, Auckland, New Zealand)

Deep Vein Thrombosis (DVT) Prophylaxis:

- Preoperatively all patients had Thrombo-Embolic Deterrent stockings (TED).
- Intraoperatively intermittent pneumatic calf compression was used.
- Post-operatively low molecular weight heparin (Enoxaparin sodium, Clexane®, Sanofi-Aventis, Auckland, New Zealand) 20 mg or 40 mg subcutaneously was used. The TED stockings and the Clexane continued in the postoperative period until discharge.
- The mobilisation plan facilitated the DVT prophylaxis regimen.

Intravenous Fluids (IVF):

Intraoperative IVFs were limited to a maximum of 500 ml of colloid and 1500 ml of crystalloid. Hemodynamic parameters such as urine output, dictated the use of IVF. Post-operatively routine use of IVF was avoided unless indicated by hemodynamic parameters. Fluid boluses for control of epidural related hypotension were limited to 2 boluses of 500 ml of a colloid (Gelofusine®). Patients were encouraged to drink at least 2000 ml of fluids per day.

Mobilisation Plan:

Patients were to stay at least 2 hrs out of bed on the day of their operation. On day 1, they were expected to mobilise to the shower and bathroom and on at least two occasions walk the length of the ward, staying a total of 8 hrs out of bed. On day 2, they were expected to continue with the same plan.

Nursing Care Pathways:

Nursing care pathways were designed specifically for the ERAS programme. These consisted of daily check lists for various aspects of the programme. The aim was to ensure that all of the components of the programme were adhered to. The nurses were educated about the various features of the programme as well as the pathways by the senior nursing staff (Page 168).

Discharge Criteria:

For the purpose of our ERAS programme as well as the clinical studies planned, we specified clear discharge criteria which consisted of:

- Ability to eat and drink without discomfort (e.g. nausea or vomiting)
- Ability to pass regular flatus and/or bowel motion
- Pain being controlled with oral medications only
- Having adequate support at home

Patients were only discharged once they met all of these specified criteria.

Discharge Information:

Patients were provided with clear information at discharge. This included an action plan in case of complication. Patients were told to return to the emergency department if:

- They develop severe pain lasting more than 1 hr
- They develop persistent vomiting, leading to inability to drink

They were provided with the ward phone number to contact one of the nursing staff if they had any queries about wound care or other similar problems. Patients were discharged with at least one week supply of oral analgesia and Resource Plus® drinks.

Follow Up:

On days 3 or 4 after discharge one of the nursing staff would contact the patients at home to monitor on their overall progress. This would involve a short telephone interview which was used as an audit tool for the programme.

On days 7 to 10, depending on the day of surgery, patients would be seen in the surgical outpatients' clinic. Their wound would be checked, surgical clips or sutures would be removed and the results of their histological findings and other aspects of care would be discussed.

Comparison of Outcomes of an Enhanced Recovery After Surgery (ERAS) programme versus Conventional Care

The major aim of this chapter was to compare the clinical endpoints between a group of patients undergoing colonic surgery within an ERAS programme with those who had similar operation under conventional care.

Intervention Group:

The intervention group was made up of consecutive patients who entered our ERAS programme for elective colonic surgery. These were treated according to the protocols discussed earlier.

Control Group:

The Control arm was selected from a comparable group of patients who underwent similar operations by the same surgeons in the same hospital prior to establishment of the ERAS programme in December 2005. An electronic search was conducted on Middlemore hospital's operation note database (Plato®). This aimed to identify all patients who underwent elective colonic surgery at Middlemore hospital prior to December 2005. We aimed to select a comparable control group, therefore patients who would not meet the inclusion criteria for entry into our ERAS programme were excluded from the control group. The exclusions were patients who:

- Had ASA scores greater than IV
- Required a de-functioning stoma

- Had medical comorbidities which influenced the duration of hospital stay e.g. documented cognitive impairment, requiring anticoagulation
- Had a prolonged hospital stay secondary to social factors

Once the patients were identified, their medical records for the relevant admissions were reviewed. These included admission notes, operation notes, radiology and laboratory results as well as any relevant follow up.

All endpoints were clearly defined. In order to ensure comparable data, all complications were also defined and recorded based on our predefined criteria (Table 10: Definition for Peri-operative Complications).

Table 10: Definition for Peri-operative Complications

Complication	Criteria
Ileus	No flatus, abdominal distension, nausea or vomiting which prevented oral intake or required therapeutic use of naso-gastric tube.
UTI	Symptomatic infection and positive microbiology requiring treatment
Wound	Documented erythema, discharge requiring antibiotic treatment or wound dehiscence requiring closure
Chest infection	Documented clinical (pyrexia, hypoxia and sputum with positive bacteriological culture) or radiological diagnosis requiring antibiotic treatment
Fluid Overload	Documented clinical (hypoxia, examination findings) or radiological diagnosis requiring diuretic therapy
Cardiac	New onset ischaemia (electrocardiograms and plasma cardiac markers) or arrhythmia requiring intervention
Urinary retention	Failure to pass urine requiring insertion of urinary catheter
Anastomotic Leak	Clinical or radiological which required intervention

Perioperative Care in The Control Group

Patients in the control group received traditional, non-structured perioperative care. Patients received mechanical bowel preparation for left sided cases and they were admitted to the ward prior to their surgery. They received anaesthesia as per anaesthetists' discretion. There were no protocols in place for fluid therapy, mobilisation or analgesia. Patients were seen by the surgical team on daily basis. Decision for discharge was by the senior members of the team, with no specified discharge criteria in place. There were no nursing care pathways in place.

Power Calculation:

Based on previous data from our institution's post-operative hospital stay for patients undergoing major colonic surgery, in order to detect a 50% reduction in post-operative hospital stay, with a type I error of 0.05 and a type II error of 0.2, 49 patients would be required in each group. We aimed to include 50 in each arm.

Statistical Analysis:

Results were analysed using SPSS® for Windows® version 14.0 (SPSS, Chicago, Illinois, USA). Results were expressed as median and range. Relationships between groups were assessed using the $\chi 2$ test (Pearson chi-square and Fisher's exact test when appropriate) for binary outcomes and continuous variables were compared with the Mann–Whitney *U* test. Correlations were expressed using Spearman's rho (correlation coefficient, significance). Statistical significance was accepted at the 5 per cent level.

A Prospective Study on The Influence of a Fast-Track Programme on Post Operative Fatigue and Functional Recovery After Major Colonic Surgery

Due to the practical issues associated with conducting a randomised controlled trial in this field, we designed a prospective, controlled non-randomised study of 52 patients undergoing elective open colonic resection.

Patients requiring stomas or undergoing laparoscopic surgery were not included in the study. From June 2004, 26 consecutive patients undergoing open colonic resection under a conventional care (CON group) pathway were recruited in the study and monitored for 2 months.

Following this, we established an Enhanced Recovery After Surgery (ERAS) programme for patients undergoing colonic resection within our institution.

The CON group patients were admitted to hospital one day prior to their operation and there were no standardized protocols for anaesthesia, operation or post-operative care. They were discharged after assessment by senior members of the surgical team.

The ERAS group was treated utilizing previously described standardized anesthetic and peri-operative protocols (Page 53). The ERAS patients were matched to the CON group with respect to the operation type. Complications were recorded according to criteria defined in Table 10 .

Post Operative Fatigue (POF) was assessed at time intervals relevant to the expected duration of hospital stay in order to measure the impact of early discharge on patients' return to normal activity. These intervals were pre-operative (baseline), pre-discharge, within the first week after discharge, 30 days and 60 days post-operatively. Hence POF was measured pre-operatively and at days 5, 14, 30 and 60 in the CON group and pre-operatively and at days 3, 7, 30 and 60 in the ERAS group.

POF was measured using the previously validated, multi-dimensional, Identity-Consequence Fatigue Scale (ICFS)(24) which is specifically designed to measure POF with a 20-item assessment of feelings (scored from 1-6) and 11 items assessing Instrumental Activities of Daily Living (IADL) (scored from 1-5). Details of this instrument are provided in the next section. Both POF and Fatigue Consequent (FC) are expressed as a percentage of the maximum possible scores.

Based on the previous data,(24) in order to reduce day 30 POF scores by one third with a type I error of 0.05 and a type II error of 0.2, 25 patients would be required in each arm of the study.

Results were analysed using SPSS® for Windows® version 14.0 (SPSS, Chicago, Illinois, USA). Relationships between groups were assessed using the $\chi 2$ test for binary outcomes and continuous variables were compared using the Mann–Whitney U test. Correlations were expressed using Spearman's rho (correlation coefficient). The Area Under the Curve (AUC) was calculated using trapezoidal integration of POF or FC against time curves for each data point. Statistical significance was accepted at the .05 level.

Identity-Consequence Fatigue Scale (ICFS)

Identity-Consequence Fatigue Scale (ICFS) has been used as the main instrument to measure Post-Operative Fatigue (POF) in the studies discussed in this thesis. This chapter focuses on various aspects of this instrument.

ICFS conceptualises POF as a multi-aetiology phenomenon, hence it aims to measure various dimensions of POF. It is based on Leventhal's cognitive representation model. This model assumes that in order to make sense of and respond to health challenges, patients generate their own representations or models of the health threats which they encounter. The cognitive components of these "representations" have been considered to be organized into five different dimensions. These have been labelled as identity, consequences, cause, timeline and control. Identity relates to patients' believes about the nature of their condition and is relevant to patients' symptoms. Consequence relates to patients' beliefs with regards to the impacts that the illness has on their physical, social and psychological functioning. Cause is personal beliefs about the aetiology of one's illness. Timeline is the perceived duration of their condition and lastly, the control component relates to patients' beliefs about how they can control or recover from their particular condition or illness. (24)

ICFS applies this cognitive representation model to the concept of POF. ICFS focuses on the Identify and Consequence aspect of this condition. The remaining aspects (timeline, cause and control) have been applied elsewhere (The revised illness perception questionnaire) and do not apply to measurements of POF. ICFS has been validate as a tool for measurement of POF.(24)

ICFS questionnaire consists of 31 items (Page 161). The first 20 items assess of “feelings” (scored from 1-6) and the remaining 11 items are for assessment of Instrumental Activities of Daily Living (IADL) (scored from 1-5). The ICFS questionnaire measures five different subscales of POF:

1. Feelings of Fatigue (5 questions)
2. Feelings of Vigor (4 questions)
3. Impact on Concentration (5 questions)
4. Impact of Energy (6 questions)
5. IADL (11 questions

The scoring for the first 20 items is as follows:

1. Not at All
2. Almost Never
3. Some of the time
4. Fairly Often
5. Very Often
6. All of the time

The last 11 items are scored as:

1. Not at all
2. Only occasionally
3. Sometimes, but less than usual
4. Nearly as often as usual
5. As often as usual

For some of the items, the scoring should be reversed because of the nature of the question (1 changed to 6 and 2 to 5 and so on). If an item is not applicable (N/A) or is not answered by the patient, then that question is ignored from the subscale. Hence subscale scores are the percentage of the maximum possible score in each subscale, based on the number of the questions which are answered in that subscale.

Feelings of Fatigue Subscale

This subscale is measured based on 5 items, questions number 1, 5,7, 15 and 17. Maximum score of 30.

Feelings Of Vigor Subscale:

This subscale is measured based on 4 items, questions number 3, 6, 8 and 20. All reversed. Maximum score of 24.

Impact On Concentration Subscale

This subscale is measured based on 5 items, questions number 4, 9, 12, 13 and 18. Item number 12 is reversed scored. Maximum score of 30.

Impact Of Energy Subscale

This subscale is measured based on 6 items, questions number 2, 10, 11, 14, 16 and 19. Item number 16 is reversed scored. Maximum score of 36.

Instrumental Activities Of Daily Living Subscale

This subscale corresponds to items 21-31. All items are reversed scored. Maximum score of 55.

Overall there are 2 scores calculated.

1. Post-Operative Fatigue Score: this is the mean of the 3 subscales: Feelings of Fatigue, Feelings of Vigor and Impact on Concentration.
2. Fatigue-Consequence score which is the mean of the remaining 2 subscales: Impact of Energy and of Instrumental Activities of Daily Living

Area Under the Curve (AUC) can be calculated using trapezoidal integration model for POF and FC against time curves for each data point. For POF this area represents the total fatigue score between any two time points and for FC this area represents total impact at any chosen interval.

Double blind randomised controlled trial of the effect of Glucocorticoids on peritoneal inflammation and post-operative recovery following colectomy.

The aim of this study was to assess the influence of steroids on post-operative recovery.

Patients:

Consecutive patients undergoing open elective colonic surgery at Manukau Surgical centre under our Enhanced Recovery After Surgery (ERAS) programme.

Exclusion:

- ASA greater than IV
- Patients Requiring a Stoma
- Patients receiving steroids or other immunosuppressant medications
- Inability to speak English
- Cognitive Impairment

Operations:

- Right Hemicolectomy
- Left Hemicolectomy
- High Anterior Resection

Intervention:

Patients eligible for the study would receive either 10 ml of solution containing 8 mg of Intravenous Dexamethasone (Dexamethasone Sodium Phosphate Injection, 4mg/ml, Hospira NZ Limited, Wellington, New Zealand) or 10 ml of normal saline (placebo) at least 90

minutes prior to incision. Glucocorticoids bind to the intracellular glucocorticoid receptor, and effects are predominantly mediated through an altered protein synthesis via gene transcription.(261) Therefore, onset of biologic action is generally 1–2 hours, depending on the route of administration.(262) Since activation of the early mediators of the metabolic response to surgery occurs immediately after the surgical incision, administration of glucocorticoids 1–2 hours preoperatively may be of importance to achieve full postoperative benefit of the treatment.(263)

Randomisation and Blinding:

One hundred opaque coded enveloped were prepared. The codes (from 01 to 100) were unknown to the investigators. There were one of two different type of instructions within each envelop. One provided instructions to prepare a 10 ml syringe with 10 ml of normal saline (Appendix 5: Placebo Test Dose) and the other instructed to prepare a 10 ml syringe with 8 mg of Dexamethasone (4mg/ml, 2 ml total volume) and top it off with 8 ml of normal saline to make up 10 ml of solution (Appendix 6: Dexamethasone Test Dose). An individual who was not involved in the care of the patients prepared the solutions and handed it to the investigator. The saline and Dexamethasone solutions appeared transparent and completely identical at the time syringes were given to the investigator. Thus, the patient, the anaesthesiologist, the surgeon, and the study observer were all blinded with respect to the study group. Randomisation was carried out using computer generated random numbers. The last 2 digits of the generated number were used (00 for 100).

Perioperative Care:

All patients were treated within our ERAS programme as described earlier. For the purpose of this study one modification was made. A surgical drain (15 F Blake drain, Johnson & Johnson, Somerville, NJ) was left in the peritoneal cavity.

Outcome Measures:

Baseline Characteristics

Age

Gender

Height

Weight

Smoking Status

ASA Score

Type of Operation

Type of Incision

Haemoglobin level prior to surgery

Urea level prior to surgery

Cr-POSSUM Cardiac Status

Preoperative Systolic Blood Pressure

Preoperative Pulse rate

Operative Soiling (Cr-POSSUM)

Cancer Staging

Subjective Outcome Measures:

(Appendix 4: Patient Questionnaire – Physiological Parameters)

Pain

Pain was measured using 100mm Visual Analog Scale (1 to 10) with three points defined as "No Pain", "Moderate Pain" and "Severe Pain". There were two pain related questions. One assessing pain at rest the other assessing pain while coughing. Pain was measured preoperatively and in the morning of day 1, 2 and 3 post-operatively.

Nausea

Nausea was measured by subjective questionnaires, preoperatively and in the morning of day 1, 2 and 3 post-operatively.

- 100 mm VAS, marked from 1 to 10 with 4 defining points of "Nil", "Mild", "Moderate" and "Severe"
- Verbal Rating Scale with 0 being no nausea at all and 3 being severe nausea.

Vomiting

- 100 mm VAS, marked from 1 to 10 with 4 defining points of "Nil", "Mild", "Moderate" and "Severe"
- Verbal Rating Scale with 0 being no vomiting at all and 3 being 3 or more episodes of vomiting

Hunger

Hunger was measured using 100mm Visual Analog Scale (1 to 10) with three points defined as “Not Hungry at All”, “Moderately Hungry” and “Very Hungry”. Hunger scores were measured preoperatively and in the morning of day 1, 2 and 3 post-operatively.

Thirst

Thirst was also assessed using 100mm Visual Analog Scale (1 to 10) with three points defined as “Not Thirsty at All”, “Moderately Thirsty” and “Very Thirsty”. Thirst scores were measured preoperatively and in the morning of day 1, 2 and 3 post-operatively.

Anxiety

Anxiety was scored by asking “How would you describe your anxiety level at present time?”. It was measured using a 100mm Visual Analog Scale (1 to 10) with three points defined as “Very Relaxed”, “Moderately Anxious” and “Very Anxious”. Anxiety scores were measured preoperatively and in the morning of day 1, 2 and 3 post-operatively.

Sleep

Sleep was measured using 100mm Visual Analog Scale (1 to 10) with three points defined as “No Sleep”, “Moderate Sleep” and “Excellent Sleep”. Sleep scores were measured preoperatively and in the morning of day 1, 2 and 3 post-operatively.

Fatigue

Fatigue was measured using two different instruments.

- 100mm Visual Analog Scale (1 to 10) with four points defined as “Fit”, “Slightly Tired”, “Tired” and “Fatigued”.
- Identity Consequence Fatigue Scale (ICFS)

VAS was used preoperatively, and on days 1, 2, 3, 7, 30 and 60 postoperatively.

ICFS was used preoperatively and on days 3, 7, 30 and 60 postoperatively.

Objective Outcome Measures

Biochemical

C-Reactive Protein (CRP), Complete Blood Count, Urea and Electrolyte Count as well as Glucose levels were measured preoperatively and on the morning of Day 1 postoperatively.

Return of Gastrointestinal Function

Time to first flatus was recorded for all patients

Vomiting Episodes

Number of vomiting episodes was recorded daily for all patients for the first 3 day post-operatively.

Antiemetic Use

Our ERAS programme has protocols for use of antiemetic. The daily use of antiemetic was recorded for the patients for the first 3 days.

Analgesia Use

Use of oral analgesia was recorded for all patients for the first 3 days post-operatively.

Time Meeting Discharge Criteria

The day in which patients met all discharge criteria was recorded. This was a surrogate endpoint for discharge as occasionally there were non-clinical factors which delayed discharge.

Time of Actual Discharge

Duration of post-operative stay was recorded as one of the main outcome measures.

Complications

All complications were recorded according to Table 10 within 30 days of surgery

Drainage Fluid

A surgical drain was left in the peritoneal cavity after surgery. In the morning of the first post-operative day, a sample of the fluid was collected. The volume of the fluid in drain was recorded. The fluid was collected in Buffered Sodium Citrate tubes. A simultaneous plasma sample was also collected in a plain tube. Both samples were transferred immediately, on crushed ice, to Middlemore Hospital's laboratory for centrifuge and freezing in -80 ºC freezer until time of analysis.

HUMAN CYTOKINE LINCO*plex* KIT 96 Well Plate Assay (Cat. #HCYTO-60K)

I. INTENDED USE

Single plex assay kit manufactured by Linco Research was used for the quantitative determination of human cytokines. This kit was used for the analysis of cytokines IL 10, IL 13, IL 1b, IL 6,IL 8 and TNF- α in plasma and peritoneal fluids.

II. REAGENTS USED

A. Antibody-Immobilized Beads:

- #01-Human IL-1b
- #12-Human IL-6
- #20-Human IL-8
- #23-Human IL-10
- #26-Human IL-13
- #40-Human TNF-a

B. Human Cytokine/Chemokine Standard Cocktail 1 vial containing human cytokine standard cocktail, lyophilized Quantity: 1 vial

C. Human Cytokine/Chemokine Quality Controls Control I – 1 vial containing mixed cytokine cocktail, lyophilized Control II – 1 vial containing mixed cytokine cocktail, lyophilized Quantity: 1 vial/Control

D. Serum Matrix, lyophilized (optional – for serum/plasma samples) Serum containing 0.08% Sodium Azide Quantity: 1 ml/vial

E. Bead Diluent 1 vial containing diluent for bead preparation Quantity: 3.5 ml/bottle

F. Mixing Bottle Quantity: 1 Bottle

G. Human Cytokine/Chemokine Detection Antibodies 1 bottle containing a cocktail of biotinylated detection antibodies in Assay Buffer Quantity: 3.2 ml/bottle

H. Streptavidin-Phycoerythrin 1 bottle containing Streptavidin-Phycoerythrin prepared in Assay Buffer Quantity: 3.2 ml/bottle

I. Assay Buffer 50 mM PBS with 25 mM EDTA, 0.08% Sodium Azide, 0.05% Tween-20, and 1% BSA, pH 7.4. Quantity: 30 ml/bottle

J. 10X Wash Buffer 1:10 dilution required with deionized water to give 10 mM PBS with 0.05% Proclin, and 0.05% Tween-20, pH 7.4. Quantity: 30 ml/bottle

K. Microtiter Filter Plate Quantity: 1- 96 Well Filtration Plate

L. Plate Sealers Quantity: 2 Plate Sealers

III. STORAGE CONDITIONS

Recommended storage for kit components were 2 -8°C. Once the standards and controls were reconstituted, there were immediately transferred into polypropylene vials. For long-term storage, reconstituted standards and controls were frozen at ≤ -20°C. Multiple (>2) freeze-thaw cycles were avoided.

IV. OTHER MATERIALS USED

A. Reagents

- Luminex Sheath Fluid (Luminex Catalogue #40-50000)

B. Instrumentation/Materials

- Adjustable Pipettes with Tips capable of delivering 25 µl to 1000 µl
- Multichannel Pipettes capable of delivering 5 µl to 50 µl or 25 µl to 200 µl
- Reagent Reservoirs
- Polypropylene Microfuge Tubes
- Aluminum Foil
- Absorbent Pads
- Laboratory Vortex
- Sonicator (Branson Ultrasonic Cleaner, Model #B200)
- Titer Plate Shaker (Lab-Line Instruments, Model #4625)

- Vacuum Filtration Unit (Millipore Vacuum Manifold Catalogue #MAVM0960R)
- Luminex Instrument

V. SPECIMEN COLLECTION AND STORAGE

A. A maximum of 25 µl per well of serum or plasma was used.

B. Preparation of Plasma Samples:

Plasma was collected using EDTA as an anticoagulant. Samples were transferred to Middlemore hospital lab on crushed ice immediately following collection. Samples were centrifuged for 10 minutes at 1000 Xg within 60 minutes of blood collection. Plasma was removed and assayed immediately and stored at ≤ -80ºC. Samples were centrifuged again prior to assay setup. Serum Matrix was used as the diluent for samples which required dilution prior to assay.

C. All samples were stored in polypropylene tubes.

D. Samples with gross haemolysis were avoided

VI. TECHNICAL GUIDELINES

The following precautions were taken prior to the assay set-up.

A. The Antibody-Immobilized Beads were light sensitive and were covered with aluminium foil at all times. The assay plate containing beads were covered with aluminium foil during all incubation steps.

B. All reagents were allowed to warm to room temperature (20-25°C) before use in the assay.

C. The bottom of the Microtiter Filter Plate was not in direct contact with any absorbent material during assay set-up or during incubation.

D. After the wash steps, the bottom of the Microtiter Filter Plate was always dried and cleaned to prevent any leakage due to capillary action.

E. The vacuum suction on the plate was kept as low as possible. It was recommended to use a vacuum setting that would remove 200 µl of buffer in ≥ 5 seconds (equivalent to < 100 mmHg).

F. After hydration, all standards and controls were transferred to polypropylene tubes. Glass tubes were avoided.

G. The standards prepared by serial dilution were always used within 1 hour of preparation. All unused standards were discarded.

H. The plates were read immediately after the assay was finished.

I. The titre plate shaker was set at a speed which provided maximum agitation without splashing of liquid outside the wells. This was a setting of 5-7 which is approximately 500-800 rpm.

J. The needle probe was cleaned using Alcohol Flushes. Probe height was adjusted to the Lincoplex filter plate prior to reading an assay.

VII. PREPARATION OF REAGENTS FOR IMMUNOASSAY

A. Preparation of Antibody-Immobilized Beads

The antibody-bead bottle was sonicated for 30 seconds; vortexed for 1 minute. 0.15 ml from the antibody bead bottle was added to the Mixing Bottle and brought to final volume of 3.0 ml with Bead Diluent.

B. Preparation of Human Cytokine Standard Cocktail

1.) Before use, the Human Cytokine Standard Cocktails were reconstituted with 250 µl of Deionized Water to give a 10,000 pg/ml concentration of standard. The vials were inverted several time and vortexed for 10 seconds to ensure mixing. The vials were allowed to set for 5-10 minutes and then transferred the standard to appropriately labelled polypropylene microfuge tube. This was used as the 10,000 pg/ml standard; the unused portions were stored at ≤ -20°.

2). Preparation of Working Standards

Five polypropylene microfuge tubes were labelled 2000, 400, 80, 16, and 3.2 pg/ml. 200 µl of Assay Buffer was added to each of the five tubes. Serial dilutions were prepared (when required) according to the following instructions: adding 50 µl of the 10,000 pg/ml reconstituted standard to the 2000 pg/ml tube, mix well and transfer 50 µl of the 2000 standard to the 400 pg/ml tube, mix well and transfer 50 µl of the 400 standard to the 80 pg/ml tube, mix well and transfer 50 µl of the 80 standard to 16 pg/ml tube, mix well and transfer 50 µl of the 16 pg/ml standard to the 3.2 pg/ml tube and mix well. The 0 pg/ml standard (Background) will be Assay Buffer.

Standard Concentration (pg/ml)	Volume of Deionized Water to Add	Volume of Standard to Add
10,000	250 µl	0

Standard Concentration*	**Volume of Assay Buffer to Add**	**Volume of Standard to Add**
2000	200 µl	50 µl of 10,000 pg/ml
400	200 µl	50 µl of 2000 pg/ml
80	200 µl	50 µl of 400 pg/ml
16	200 µl	50 µl of 80 pg/ml
3.2	200 µl	50 µl of 16 pg/ml

*(pg/ml)

C. Preparation of Controls

Before use, Human Cytokine Control 1 and Human Cytokine Control 2 were reconstituted with 250 µl of Deionized Water. Inverted several times to mix and then vortexed. Samples were allowed to set for 5-10 minutes. The controls were transferred to appropriately labelled polypropylene microfuge tubes.

D. Preparation of Wash Buffer

The 10X Wash Buffer was brought to room temperature and mixed to bring all salts into solution. 30 ml of 10X Wash Buffer was diluted with 270 ml of deionised water. Unused portions were stored at 2-8°C .

E. Preparation of Serum Matrix

1.0 mL of deionized water was added to the bottle containing lyophilized Serum Matrix. Mixed well and allowed at least 10 minutes for complete reconstitution. Left-over reconstituted Serum Matrix was stored at ≤ -20° when required.

VIII. IMMUNOASSAY PROCEDURE

The following precautions were taken during the immunoassay procedure in addition to what was described in Technical Guidelines outlined in Section VI.

1. All reagents were allowed to warm to room temperature (20-25°C) before use in the assay.
2. Placement of Standards, 0 (Background) 3.2, 16, 80, 400, 2000, and 10,000 pg/ml, Controls 1 and 2, and samples were diagrammed on Well Map Worksheet (Figure 2: Well Map Worksheet) in a vertical configuration. All assays were run in duplicate.

3. The filter plate was blocked by pipetting 200 µL of Assay Buffer into each well of the microtiter plate. Sealed and mixed on a plate shaker for 10 minutes at room temperature (20-25°C).
4. Assay Buffer was removed by vacuum. Inverting of plates was avoided. Any excess Assay Buffer was removed from the bottom of the plate by blotting on paper towels.
5. 25 µL of Assay Buffer was added to the 0 Standard (Background).
6. 25 µL of Assay Buffer was added to the Sample wells.
7. 25 µL of each Standard or Control was added into the appropriate wells.
8. 25 µL of appropriate matrix diluent was added to the Background, Standards, and Control wells. When assaying plasma, Serum Matrix was used.
9. 25 µL of Sample was added into the appropriate wells.
10. Bead Bottle was vortexed and 25 µL of Mixed Beads was added to each well.
11. Sampled was sealed and covered with aluminium foil, and incubated with agitation on a plate shaker for 1 hour at room temperature (20-25°C).
12. The fluid was gently remove by vacuum, while avoiding inversion of plates.
13. Plates were washed 2 times with 200 µL/well of Wash Buffer, removing Wash Buffer by vacuum filtration between each wash. Any excess Wash Buffer was removed from the bottom of the plate by blotting on paper towels.
14. Detection Antibody was allowed to warm to room temperature. 25 µL of Detection Antibody Cocktail was added into each well.
15. Samples were sealed and covered with aluminium foil, and incubated with agitation on a plate shaker for 30 minutes at room temperature (20-25°C). Vacuum was avoided after incubation.
16. 25 µL of Streptavidin-Phycoerythrin was added to each well containing the 25 µL of Detection Antibody Cocktail.

17. Samples were sealed and covered with aluminium foil, and incubated with agitation on a plate shaker for 30 minutes at room temperature (20-25°C).
18. All contents were gently removed by vacuum, avoiding inversion.
19. The plate was washed 2 times with 200 µL/well Wash Buffer, removing Wash Buffer by vacuum filtration between each wash. Any excess buffer on the bottom of the plate was wiped with a tissue.
20. 100 µL of Sheath Fluid was added to all wells. Covered with aluminium foil and resuspended the beads on a plate shaker for 5 minutes.
21. The plates were then run on Luminex Instrument.
22. The median data using a 5-parameter or spline fit data reduction was saved and evaluated.

IX. EQUIPMENT SETTINGS

The following equipment settings were selected:

- Events: 50 per bead
- Sample Size: 50 ml
- Bead Set:
    - 01 for IL-1b
    - 12 for IL-6
    - 20 for IL-8
    - 23 for IL-10
    - 26 for IL-13
    - 40 for TNF-a
- **Gate (for 1.7 System): 8,060 to 13,000

These specifications were for the Luminex100 with software v.1.7

X. ASSAY CHARACTERISTICS

A. Standard Comparison

The following LINCO*plex* standards with known values of mass and standards received from the National Institute of Biological Standards and Controls with assigned Bioassay units and approximate mass determinations were assayed together to provide the following conversion factor:

Cytokine	NCI Lot #	1 Linco*plex* pg/ml =
IL-1b	86/680	303 mIU/ml
IL-6	88/514	3.9 mIU/ml
IL-8	89/520	10.4 mIU/ml
IL-10	92/516	3.8 mIU/ml
TNFa	87/650	154 mIU/ml

B. Assay Sensitivities (minimum detectable concentrations, pg/ml)

Table 11: Assay Sensitivities

Cytokine	Two-hour Assay Sensitivity	Overnight Assay Sensitivity
IL-1b	0.86	0.19
IL-6	1.29	0.79
IL-8	1.12	0.32
IL-10	2.17	0.41
IL-13	3.31	4.06
TNF-a	0.66	0.22

C: Precision

Intra-assay precision is generated from the mean of the %CV's from 8 reportable results across two different concentration of cytokines in a single assay. Interassay precision is generated from the mean of the %CV's from two reportable results across two different concentrations of cytokine across 8 different assays.

Table 12: Assay Precision

Cytokine	Intra-assay (%CV)	Inter-assay (%CV)
IL-1b	13.5	13.3
IL-6	13.6	12.7
IL-8	10.3	11.0
IL-10	11.8	13.5
IL-13	10.4	9.4
TNFa	9.0	10.9

D: Accuracy

Accuracy, defined as percentage of cytokines recovered from samples spiked with known quantity, is generated from calculating the %Recovery of three different levels of cytokine spiked into 6 different human serum samples with known low or no measurable cytokine levels.

Table 13: Assay Accuracy

Cytokine	%Recovery in Matrix	%Recovery in Serum
IL-1b	118.9	105.2
IL-6	103.3	84.6
IL-8	108.3	100.5
IL-10	110.4	99..0
IL-13	112.9	76.8
TNF-a	114.7	98.9

WELL MAP

	1	2	3	4	5	6	7	8	9	10	11	12
A	0 pg/ml Standard (Background)	400 pg/ml Standard	QC-II Control									
B	0 pg/ml Standard (Background)	400 pg/ml Standard	QC-II Control									
C	3.2 pg/ml Standard	2000 pg/ml Standard										
D	3.2 pg/ml Standard	2000 pg/ml Standard										
E	16 pg/ml Standard	10,000 pg/ml Standard										
F	16 pg/ml Standard	10,000 pg/ml Standard										
G	80 pg/ml Standard	QC-I Control										
H	80 pg/ml Standard	QC-I Control										

Figure 2: Well Map Worksheet

Assay Method for Human Cytokine Linco*plex* HCYTO-60K Kit

Well #	Well Identification	Assay Buffer		Assay Buffer	Standard/ Control/Sample	Serum Matrix/ Test Media	Mixed Beads		Detection Antibody		SA-PE		Sheath Fluid
1A, 1B	0 pg/ml Standard (Background)	200 µl	**Seal, Agitate, Incubate 10 minutes at Room Temperature. Remove Assay Buffer by Vacuum**	25 µl	-	25 µl	25 µl	**Seal, Agitate, Incubate 1 hour at Room Temperature or overnight at 4°C . Wash 2X with 200 µl Wash Buffer**	25 µl	**Seal, Agitate, Incubate 30 or 60 minutes at Room Temperature.**	25 µl	**Seal, Agitate, Incubate 30 minutes at Room Temperature. Wash 2X with 200 µl Wash Buffer**	100 µl
1C, 1D	3.2 pg/ml Standard	↓		-	25 µl	25 µl	↓		↓		↓		↓
1E, 1F	16 pg/ml Standard			-	25 µl	25 µl							
1G, 1H	80 pg/ml Standard			-	25 µl	25 µl							
2A, 2B	400 pg/ml Standard			-	25 µl	25 µl							
2C, 2D	2000 pg/ml Standard			-	25 µl	25 µl							
2E, 2F	10,000 pg/ml Standard			-	25 µl	25 µl							
2G, 2H	Control I			-	25 µl	25 µl							
3A, 3B	Control II			-	25 µl	25 µl							
3C, 3D	Sample			25 µl	25 µl	-							
3E, 3F	Sample			25 µl	25 µl	-							
3G, 3H	Sample			25 µl	25 µl	-							
4A, 4B ↓	Sample			25 µl	25 µl	-							
Final Sample	Sample	↓		25 µl	25 µl	-	↓		↓		↓		↓

Chapter 4 : A Prospective Study on Clinical Benefits of ERAS

Introduction

In this chapter we will review the results of an Enhanced recovery after surgery (ERAS) care pathway which was established as an important part of this research project.

ERAS care pathways for colonic surgery have been developed over the past decade. As discussed previously, these consist of a number of evidenced based interventions which individually have been associated with improved outcomes following major surgery. A multimodal utilization of these strategies aims to reduce surgical stress and hasten return of organ function and hence accelerate recovery following major surgery. (264)

Even in centers where there are long-established ERAS programmes, compliance rates with these pathways are problematic. Furthermore, units which have employed identical ERAS protocols have had inconsistent outcomes. This reiterates the many challenges involved in implementing and sustaining such programmes.(116, 265)

The majority of the published literature on this topic, has focused on reduction of hospital stay as the most significant outcome measure for ERAS programmes. (110, 114-117, 266-268) Only one prospective study and a systematic review have shown significant reductions in morbidity rates with these pathways.(113, 114)

In December 2005 we commenced an ERAS programme for elective colonic resection within Manukau Surgical Centre in Auckland. Our approach emphasizes structured nursing care pathways within an environment where there is a focus on early recovery, with incorporation of a number of other peri-operative strategies within an ERAS framework. The aim of this

chapter is to evaluate the impact of this ERAS programme on major patient outcomes with a focus on complications as well as assessing the extent of protocol compliance within our programme. The details of our program are discussed in detail in the method section of this thesis.

Patients and Method:

From December 2005 to March 2007, consecutive patients who were entered into our ERAS programme for elective colonic surgery at Manukau Surgical Centre (MSC) were prospectively studied. Patients with significant cardio-pulmonary comorbidities (American Society of Anesthesiologists score, ASA≥ IV), significant cognitive impairment and those who declined to take part were not enrolled within this programme. Those who required a stoma were not considered for our EARS programme during the duration of this study as management of a stoma required strategies which were not part of our ERAS protocols.

The control group consisted of a comparable, consecutive series of patients who underwent elective colonic surgery by the same surgeons, at the same institution prior to start of the ERAS programme. Patients in the control group received traditional, non-structured perioperative care and discharge was left at the discretion of the senior members of the team, with no specified discharge criteria in place.

An electronic data base (Plato®) search was performed to identify consecutive patients who had undergone elective colonic surgery prior to December 2005, by the surgeons involved in the ERAS programme. Subsequently the medical records of these patients were examined. Patients who had comorbidities which would exclude them from our current ERAS

programme were excluded from the control group. We aimed to obtain a control group was matched with the ERAS group with respect to ASA score, CR-POSSUM and operation type. CR-POSSUM (Colorectal Physiological and Operative Severity Score for the enUmeration of Mortality) is a 6 factor physiological score and 4 factor operative severity score which has been validated as practical tool for prediction of post-operative mortality.(269)

Data was collected from patients' clinical records which included all their clinical, radiological and laboratory results from the pre-operative period to 30 days after surgery. In order to ensure that recorded complications were comparable in both groups, specific complications were defined according to the criteria shown in Table 10. Furthermore in order to prevent over estimation of complications in the retrospective control arm we ensured that we only included well documented events which required specific interventions.

Based on previous data from our institution's post-operative hospital stay for patients undergoing major colonic surgery, in order to detect a 50% reduction in post-operative hospital stay, with alpha and beta of 0.05 and 0.2 respectively, 49 patients would be required in each group. We aimed to include 50 in each arm.

Results were analysed using SPSS® for Windows® version 14.0 (SPSS, Chicago, Illinois, USA). Results were expressed as median and range. Relationships between groups were assessed using the $\chi 2$ test (Pearson chi-square and Fisher's exact test when appropriate) for binary outcomes and continuous variables were compared with the Mann–Whitney *U* test. Correlations were expressed using Spearman's rho (correlation coefficient, significance). Statistical significance was accepted at the 5 per cent level.

Results:

From December 2005 to March 2007, 50 consecutive patients who entered our ERAS programme were prospectively studied. During this period, 10 patients were excluded from this programme due to significant renal impairment (2), significant cardiac comorbidity (2), cognitive impairment (2), inability to speak English (2) as well as those who wished not to participate in this programme (2).

From Sep 2004 to Sep 2005, a retrospective group of 50 consecutive patients, who would currently be candidates for our ERAS programme, were included in the Control group (CON). During this period 8 patients were excluded from the control group because of renal impairment (2), Dementia (2), Addison's disease (1) and Hematological disorders (3).

At baseline, the groups were comparable with respect to sex, body mass index, ASA scores and physiological Cr-POSSUM scores. The ERAS group was slightly younger (Table 14 and Table 15).

Table 14: Baseline Characteristics

Baseline		**ERAS (n=50)**	**Conventional (n=50)**	**P**
Age*		65.6 (39-92)	70.7 (40-85)	.021†
Sex	Male	26	28	.688‡
	Female	24	22	.688‡
ASA Score	I	8	8	1.00‡
	II	29	31	.683‡
	III	13	11	.640‡
BMI		28.6	27.4	.588†
CR-POSSUM*	Physiological	10.3	9.7	.524†
	Operative	9.2	8.3	.061†
OPERATION	Right Hemi	26**	29	.546‡
	Left Hemi	19	14	.288‡
	Lap Left Hemi	4	7	.525‡
	Total Col	1	0	1.00‡
DIAGNOSIS	Diverticulosis	2	4	.674‡
	IBD	1	1	1.000‡
	Adenoma	4	2	.674‡
	Dukes' A	6	5	.749‡
	Dukes' B	15	8	.096‡
	Dukes' C	19	21	.683‡
	Dukes' D	3	9	.124‡

* Mean Scores, †Mann–Whitney *U* test; ‡$\chi 2$ test; CR-POSSUM: Colorectal Physiological and Operative Severity Score for the enUmeration of Mortality,**: 14 Transverse and 12 Midline

Table 15: CR-POSSUM Baseline Scores

CR-POSSUM Scores		ERAS	Conventional	P*
Age Group	Less Than 60	8	14	.148
	61-70	15	13	.656
	71-80	21	15	.211
Cardiac Failure	More Than 81	6	8	.564
	None or Mild	38	30	.086
	Moderate	12	18	.190
	Severe	0	2	.495
Systolic BP	100-170	41	30	.015
	>170 or 90-99	9	20	.015
	<90	0	0	1.000
Pulse	40-100	47	43	.182
	101-120	3	7	.318
	>120 or <40	0	0	1.000
Urea (mmol/l)	<10	48	45	.240
	10-15	1	5	.204
	>15	1	0	1.000
Haemoglobin (g/dl)	13-16	27	22	.317
	10-13 or 16-18	22	24	.688
	<10 or >18	1	4	.359
Median Total Physiological Score		10	9.5	.524†
Operative Severity	Minor	0	0	1.000
	Intermediate	0	0	1.000
	Major	41	32	.043
	Complex Major	9	18	.043
Peritoneal Soiling	None or Serous fluid	46	47	.695
	Local Pus	3	2	1.000
	Free Pus or Faeces	1	1	1.000
Operative Urgency	Elective	50	50	1.000
	Urgent	0	0	1.000
Cancer Staging	No cancer or Dukes' A-B	28	20	.109
	Dukes' C	19	21	.683
	Dukes' D	3	9	.124
Median Total Operative Score		8	8	.061†

* All comparisons $\chi 2$ test, †Mann–Whitney *U* test.

As can be seen in Table 16, twelve (24%) patients in the ERAS group were admitted at least one day prior to surgery compared to twenty nine (58%) in the CON group (p<0.001).

There was no significant difference between the rate of epidural use between the two groups (p 0.223).The ERAS group received less intraoperative fluids compared to the CON group (p<0.001). Furthermore, during the first three post-operative days, the ERAS group received significantly smaller volumes of intravenous fluids administered (p<0.001).

The CON group had longer duration of epidural and urinary catheterization compared to the ERAS group. The ERAS group was successfully mobilized on median day 1 compared to day 3 in the CON group (p<0.001). The ERAS patients had their 1st meal earlier and passed flatus earlier compared to the CON group.

Median post-operative stay and total hospital stay (including readmissions) for the ERAS group were both 4 days, compared to 6.5 and 8 days, respectively, for the control group (p <0.001). Mean (Standard Deviation) post-operative stay was 5.78 (4.26) days for the ERAS group and 8.32 (5.29) days for the CON group. Total hospital stay was 5.90 (4.36) in ERAS and 10.0 (6.27) days in the CON group.

Four patients in the ERAS group underwent laparoscopic colectomy, compared to 7 in the CON group, with a median post-operative stay of 3 days in the ERAS group (3-3) compared to 4 days (3-7) in the CON group (P=0.039). Those selected patients who had a right hemicolectomy through a transverse incision had a median stay of 3 days (3-6) compared to 6 days (3-9) for right hemicolectomies with a mid-line incision (P= 0.002).

There were significant correlations between duration of total hospital stay and volume of intraoperative (0.278, *P*= 0.007) and post-operative (0.641, p<0.001) fluids, duration of IDC use (0.685, p<0.001), time of first mobilisation (0.665, p<0.001), first meal (0.533, p<0.001) and first flatus (0.494, p<0.001). There was a positive and strong correlation between duration of IDC use and time of first mobilisation (0.660, p<0.001).

Table 16: Summary of Results

Outcome	ERAS (N=50)	Conventional (N=50)	P*
Admission Prior to Surgery	24%	58%	P<0.0001 †
Epidural Analgesia	89%	76%	P 0.223 †
Intraoperative IVF	2 L (1-8)	3 L (1-7.5)	P<0.0001
IVF in 1st 3 days	2 L (1-10)	6.5 L (1-12)	P<0.0001
Duration of Epidural	2 Days (0-3)	3 Days (0-4)	P<0.0001
IDC time	1 (1-14)	3 (1-14)	P<0.0001
Mobilisation	1 (1-3)	3 (1-7)	P<0.0001
1st meal	1 (1-3)	2 (1-15)	P<0.0001
Flatus	2 (0-8)	3 (0-18)	P<0.0001
Post-Operative Stay	4 (3-34)	6.5 (3-18)	P<0.0001
Total Hospital Stay	4 (3-34)	8 (4-29)	P<0.0001

Results expressed as Median (Range); IVF: Intravenous Fluids, IDC: Indwelling Urinary Catheter; * All comparisons Mann–Whitney *U* test; †χ2 test;

Complications and Readmissions

Complications were defined as seen in Table 17.

Table 17: Definition for Peri-operative Complications

Complication	Criteria
Ileus	No flatus, abdominal distension, nausea or vomiting which prevented oral intake or required therapeutic use of naso-gastric tube.
UTI	Symptomatic infection and positive microbiology requiring treatment
Wound	Documented erythema, discharge requiring antibiotic treatment or wound dehiscence requiring closure
Chest infection	Documented clinical (pyrexia, hypoxia and sputum with positive bacteriological culture) or radiological diagnosis requiring antibiotic treatment
Fluid Overload	Documented clinical (hypoxia, examination findings) or radiological diagnosis requiring diuretic therapy
Cardiac	New onset ischaemia (electrocardiograms and plasma cardiac markers) or arrhythmia requiring intervention
Urinary Retention	Failure to pass urine requiring insertion of urinary catheter
Anastomotic Leak	Clinical or radiological which required intervention

UTI: Urinary Tract Infections

Patients in the ERAS group had significantly fewer episodes of urinary tract infections (P=0.004) and ileus (P=0.005). The overall rate of cardio-pulmonary complications was also significantly lower in the ERAS group (P=0.032). There were 4 patients in each arm who required unplanned return to the operating room. Anastomotic leak resulted to 3 emergency laparotomies in ERAS group and 2 in the CON group and wound dehiscence required 1 reoperation in the ERAS group and 2 in the CON group. (Table 18)

There was no difference in the rate of readmissions (P=0.766) or total duration of readmissions (P=0.772) between the two groups. One patient in the conventional group died of an acute myocardial infarction after being readmitted. Table 19 summarizes the reasons for and the duration of readmissions.

Table 18: Summary of Complications

Complications	ERAS (n=50)	Conventional (n=50)	*P**
Urinary Infection	2	12	.008
Ileus	5	18	.005
Cardio-Pulmonary	11	21	.032
Wound	6	10	.275
Intra-abdominal collection	1	1	1.000
Urinary Retention	5	3	.715
Anastomotic Leak	4	3	1.000
Reoperation	4	4	1.000
Readmissions	6	7	.766
Death	0	1	1.000
Uncomplicated Recovery	23	17	.221

* All comparisons $\chi 2$ test;

Table 19: Reason for and Duration of Readmissions

ERAS Group	Conventional Group
Anastomotic Leak 5 days	Wound Infection 5 days
Anastomotic Leak 25 days	Post-operative Ileus 3 days
Colo-cutaneous Fistula 30 days	Intra-abdominal Abscess 20 days
Post-operative Vomiting 1 day	Post-operative Vomiting 4 days
Intra-abdominal Abscess 10 days	Pulmonary Embolism 7 day
Urinary Infection 2 days	Myocardial Infarction (Death)
	Post-operative Ileus 5 days

Protocol Compliance

Table 20 shows the extent of protocol compliance with the ERAS protocols. As can be seen, there is overall good protocol compliance, however, the protocol was not adhered to in all cases, with a non-compliance rate of up to 33% in some areas, with a subsequent daystay compliance of 40%.

Table 20: Protocol Compliance

Intervention	Target	Compliance
Admission Prior to Surgery	0 Days	80%
Epidural Analgesia	100%	92%
Intraoperative IVF	2 L	67%
Duration of Epidural	2 Days	85%
Duration of IDC	1 Day	80%
1st Meal	1 Day	78%
Mobilisation	1 Day	80%
Post-Operative Stay	3 Days	40%

Discussion

In this study it was shown that multimodal preoperative care strategies combined with a well structured care pathway, within an environment where there is an emphasis on early recovery, can not only reduce the duration of hospital stay, but also is a practical approach for reducing the rate of complications following major colonic surgery.

The principle flaw of this study is the retrospective nature of data collection for the control group. Currently very few randomised controlled trials have been conducted in this field because of the practical difficulties associated with these.(113, 115, 117) For this study it was attempted to select a very comparable control group and it was endeavoured to use endpoints which were accessible and reliable. Furthermore endpoints and complications were clearly defined to ensure comparable data for both ERAS and CON groups. Secondary to the relatively slow recruitment to the ERAS arm, it was decided to only include elective patients who did not require a stoma, were ASA < IV and were operated on by the 3 senior surgeons.

In this study, patients in the ERAS group had a slightly decreased median overall age. However, there was no significant difference between the groups in terms of age categories as defined by the CR-POSSUM scoring system. The CON group had more complex major procedures and also more cases with Dukes' D diagnosis. However the total operating score was not significantly different. Overall matching attempted to ensured that at baseline, the groups were comparable with respect to clinically relevant characteristics. Furthermore, there was no significant correlation between age and any of the monitored outcomes, including the duration of hospital stay.

ERAS programmes have traditionally been associated with a shortened duration of hospital stay, however there is significant variation in outcomes between different programmes. (110, 114-117, 266-268) The median duration of hospital stay in this study for the ERAS group was 4 days. The 6.5 days seen in the matched control group is shorter than the research unit's overall median for colonic surgery (8 days) which reflects the fact that those patients with significant co-morbidities were excluded from this matched comparison group.

There were a relatively small number of patients undergoing laparoscopic surgery within both groups (ERAS 4, CON 7). However the duration of hospital stay was significantly shorter in the ERAS patients for this type of procedure. One can attribute this difference to the care pathways as the patients had similar baseline characteristics, had the same type of surgery and were operated on by the same surgeon. Although a number of studies have shown no significant difference between conventional laparoscopic and open Fast-track surgery,(112, 266) improvements in outcomes have previously been described with laparoscopic surgery within an ERAS programme compared to a conventional approach, (118) suggesting that the benefits of an ERAS programme are not limited to patients undergoing open colectomy. Although laparoscopy can be considered as an additional strategy to preexisting ERAS protocols and has been show to be associated with additional benefits.(208)

In this study, ERAS was associated with a reduced rate of complications as well as hospital stay. The reduced rate of urinary infections may relate to a shortened duration of catheterization.(257) Lower observed rates of post-operative ileus may be due to a number of different factors, including effective afferent neural blockade with local anaesthetic thoracic epidural, avoidance of opioids, limited intravenous fluids, early feeding and early mobilisation.(219, 228, 270, 271) Lower rates of cardiopulmonary complications could also be related to the use of epidurals, limited fluids and early mobilisation. (114, 220, 227, 228)

A similar reduction in medical complications has been observed in earlier publications.(113, 114) It is has previously been documented that single modality interventions may have a smaller individual impact on the observed improvements and that the influence of each intervention is difficult to assess.(114, 117) For example although there is a Cochrane review confirming the ileus reducing effects of local anaesthetic thoracic epidurals, accelerated recovery and discharge has been achieved in programmes where epidurals are not utilized (272-275) and according to a recent meta-analysis, in colorectal surgery epidurals do not reduce hospital stay. Although it should be noted that the studies included in this meta-analysis did not utilize ERAS perioperative care pathways (276)

This study demonstrated an acceptable readmission rate of 12% for the ERAS patients, which is consistent with a number of other similar programmes (114-116, 267, 268). This may be due to the median hospital stay of 4 days, compared to 2-3 days in some other units.(112, 114) It has been shown that within an ERAS setting, the planned duration of stay has a significant impact on readmission rates as well as levels of patient satisfaction.(277) In this study, patients received close community contact following discharge, enabling patients to call the ward for questions as well as phone follow-ups and early clinic visits after discharge, which all may contribute to the current readmission rates.

Although it has been suggested previously that protocols (116) may contribute to improved outcomes following surgery, this study, as well as results from a recent multicentre trial, (265) suggest that a number of other factors are essential in order to ensure effective implementation of such protocols. These include organization of care, unit experience and dedication to the program as well as the level of patient education and patients' commitment to the pathways.

When analyzing protocol compliance within this programme, it can be observed that the median date for each component of the programme met the pre-defined target date of the protocol, with only a relatively small proportion of non-compliance rates for each category. This can be attributed to close involvement of nurses with this programme, nursing education and structured ERAS nursing care pathways as well as close collaboration between anaesthetist and surgeons. Protocol compliance is the key to success of ERAS. As noted, those patients who had less perioperative fluids and mobilized earlier, passed flatus earlier and were subsequently discharged home earlier. However the median discharge date is 4 days which is longer than the planned 3 days in this study's protocol. Only 40% of the patients were discharged on day 3. This possibly reflects that in order to achieve overall shorter duration of stay, each individual patient should reach all the predefined target days and therefore, the observed compliance rates may not be adequate to achieve this.

There are further strategies, which may need to be incorporated within the discussed protocols such as use of high flow oxygen, routine laxatives and use of esophageal Doppler for accurate and cardiac output directed management of intraoperative fluids. There is evidence that these strategies may reduce the rate of wound infections, accelerate the return of bowel function and reduce overall morbidity. (232-235) A number of studies have suggested various benefits of peri-operative oxygen therapy. There is evidence indicating that patients who receive high perioperative inspired oxygen, have significantly reduced risk of wound infection (173, 174, 278) as well as a reduced incidence of postoperative nausea and vomiting. (176, 177) Laxatives have been used in a number of ERAS programs (114, 118) as a method to hasten return of bowel function. There is a recent study which has shown that laxatives improve recovery of bowel function after fast-track hysterectomy. (279)

The ERAS program discussed here is run within an elective only surgical facility. Currently there is little emphasis on the suitable environmental settings for an ERAS ward. There are some preliminary data which suggest that patients may recover more quickly in an elective-only unit.(280) Thus it can be proposed that environment should be considered as a key ERAS element and the surgical ward should be considered as a post-operative rehabilitation unit, characterised by exclusion of acutely admitted patients from elective patients, a ward design which facilitates the feeling of security, encourages independence and allows free access to food preparation and self-care facilities.(170)

In conclusion, the ERAS program discussed here, is associated with a reduced duration of hospital stay and decreased rate of complications; In the next section we will discussed the influence that ERAS program may have on post operative fatigue.

Chapter 5 : Can ERAS Influence Post Operative Fatigue? – A prospective Study

Introduction

As it was discussed in earlier chapters, Post-Operative Fatigue (POF) is a significant issue following major colonic surgery. It is often present for up to a month in patients following abdominal operations (5) and can persist for up to 3 months after major uncomplicated gastrointestinal surgery. (6) POF is unpleasant and distressing and may adversely affect patient quality of life (7) and also that of patients' caregivers.(8, 9) It lasts much longer than pain and prevents otherwise fit patients from returning to work. (8, 9) Patients miss up to an average of 6 weeks of work following uncomplicated abdominal operations. A higher degree of POF is followed by worse emotional, physical and functional outcomes. (10) POF may also be a source of increased health service costs, with patients who suffer from fatigue placing significantly greater demands on their primary health care teams compared with those who feel less tired. (7-9)

As discussed previously, POF has a complex and multi-factorial etiology. It was demonstrated in earlier chapters that both biological and psychological factors contribute to development and progression of POF. Hormonal and inflammatory changes related to the surgical stress response (magnitude of surgery), post-operative changes in nutritional status and cardiovascular fitness as well as low mood, anxiety, emotional distress and pre-operative fatigue are all known to have significant correlations with the development of POF. There is new evidence suggesting that locally occurring inflammatory responses may influence development of POF. (7, 10, 43, 63, 66, 281)

Numerous single modality interventions such as epidural anaesthesia, nutritional supplementation and pre-operative counseling have been shown to be ineffective in influencing POF,(59, 89) however, there is some evidence that peri-operative multimodal interventions may be effective in reducing POF. (110) Therefore this chapter attempts to assess the impact of a multimodal perioperative intervention program on POF and functional recovery following major colonic surgery.

Method

Due to the practical issues associated with conducting a randomised controlled trial in this field, it was decided to design a prospective, controlled non-randomised study of 52 patients undergoing elective open colonic resection. Patients requiring stomas or undergoing laparoscopic surgery were not included in the study. From June 2004, 26 consecutive patients undergoing open colonic resection under a conventional care (CON group) pathway were recruited in the study and monitored for 2 months. Following this, an Enhanced Recovery After Surgery (ERAS) programme was established for patients undergoing colonic resection within the same institution. The CON group patients were admitted to hospital one day prior to their operation and there were no standardized protocols for anaesthesia, operation or post-operative care. They were discharged after assessment by senior members of the surgical team. The ERAS group was treated utilizing previously discussed standardized evidence-based anesthetic and peri-operative protocols (Page 53). Complications were recorded according to criteria defined in Table 17: Definition for Peri-operative Complications.

POF was assessed at time intervals relevant to the expected duration of hospital stay in order to measure the impact of early discharge on patients' return to normal activity. These intervals were pre-operative (baseline), pre-discharge, within the first week after discharge, 30 days

and 60 days post-operatively. Hence POF was measured pre-operatively and at days 5, 14, 30 and 60 in the CON group and pre-operatively and at days 3, 7, 30 and 60 in the ERAS group.

POF was measured using the previously validated, multi-dimensional, Identity-Consequence Fatigue Scale (ICFS)(24) which is specifically designed to measure POF with a 20-item assessment of feelings (scored from 1-6) and 11 items assessing Instrumental Activities of Daily Living (IADL) (scored from 1-5) (Page 161). The ICFS questionnaire measures five different subscales of POF: feelings of fatigue (5 questions), feelings of vigor (4 questions), impact on concentration (5 questions), impact on energy (6 questions) and IADL (11 questions). The overall POF score is the mean of the first three subscales and the Fatigue-Consequence (FC) score is the mean of the latter two subscales. Both POF and FC are expressed as a percentage of the maximum possible scores.

Based on the previous data,(24) in order to reduce day 30 POF scores by one third with a type I error of 0.05 and a type II error of 0.2, 25 patients would be required in each arm of the study.

Results were analysed using SPSS® for Windows® version 14.0 (SPSS, Chicago, Illinois, USA). Relationships between groups were assessed using the $\chi 2$ test for binary outcomes and continuous variables were compared using the Mann–Whitney U test. Correlations were expressed using Spearman's rho (correlation coefficient). The Area Under the Curve (AUC) was calculated using trapezoidal integration of POF or FC against time curves for each data point. Statistical significance was accepted at the .05 level.

Results

From June 2004 to August 2005, 26 patients undergoing open colonic resection were enrolled into this study. From June 2006 to March 2007, 26 consecutive eligible patients entering our ERAS programme were also included in the study. The ERAS patients were matched to the CON group with respect to the operation type.

At baseline there were no statistically significant differences with respect to age, gender, ASA scores, use of epidural analgesia or CR-POSSUM scores between the CON and ERAS groups (Table 21 and Table 22).

Table 21: Baseline Characteristics

Baseline		**CON**	**ERAS**	**P**
Age*		74 (45-88)	66 (37-92)	0.082†
Gender	Male	5	10	0.126‡
	Female	21	16	0.126‡
ASA Score	I	5	6	0.734‡
	II	15	15	1.000‡
	III	6	5	0.734‡
CR-POSSUM*	Physiological	10 (6-16)	9 (6-17)	0.193†
	Operative	7 (7-12)	8 (7-13)	0.193†
Epidural		20	23	0.271‡
Operation	Right Hemi	15	15	1.000‡
	Left Hemi	7	7	1.000‡
	Anterior Resection	3	3	1.000‡
	Total Colectomy	1	1	1.000‡

* Median Scores, †Mann–Whitney *U* test; ‡χ^2 test;

Table 22: Breakdown of CR-POSSUM Scores

CR-POSSUM		CON	ERAS	P*
Age Group	Less Than 60	5	9	.211
	61-70	6	7	.749
	71-80	10	7	.375
	More Than 81	5	3	.701
Cardiac Failure	None or Mild	23	23	1.000
	Moderate	3	3	1.000
	Severe	0	0	1.000
Systolic BP	100-170	23	23	1.000
	>170 or 90-99	3	3	1.000
	<90	0	0	1.000
Pulse	40-100	25	25	1.000
	101-120	1	1	1.000
	>120 or <40	0	0	1.000
Urea (mmol/l)	<10	24	23	1.000
	10-15	2	3	1.000
	>15	0	0	1.000
Haemoglobin (g/dl)	13-16	10	12	.575
	10-13 or 16-18	14	12	.579
	<10 or >18	2	2	1.000
Total Physiological Score		10 (6-16)	9 (6-17)	0.193†
Operative Severity	Minor	0	0	1.000
	Intermediate	0	0	1.000
	Major	15	15	1.000
	Complex Major	11	11	1.000
Peritoneal Soiling	None or Serous fluid	26	24	1.000
	Local Pus	0	1	1.000
	Free Pus or Faeces	0	1	1.000
Operative Urgency	Elective	26	26	1.000
	Urgent	0	0	1.000
Cancer Staging	No cancer or Dukes' A-B	17	16	.773
	Dukes' C	9	10	.773
	Dukes' D	0	0	1.000
Total Operative Score		7 (7-12)	8 (7-13)	0.193†

* All comparisons $\chi 2$ test, †Mann–Whitney *U* test.

The median duration of total hospital stay was significantly shorter for the ERAS group (4 v 7 days p<0.001). There were fewer episodes of urinary tract infections (*P*=0.028) and ileus (*P*=0.042) in the ERAS group. There were no major differences in the rate of other complications including readmissions (Table 23 and Table 24).

Table 23: Results

Outcome	CON (n=26)	ERAS (n=26)	P
Epidural Analgesia	20	23	.271†
Readmissions	3	3	1.000†
Post-Operative Stay	6	4	.002‡
Total Hospital Stay	7	4	.000‡

†$\chi 2$ test, ‡Mann–Whitney *U* test.

Table 24: Complications

Complications	CON (n=26)	ERAS (n=26)	P†
Urinary Infection	8	1	.028
Ileus	9	2	.042
Cardio-Pulmonary	7	4	*.308*
Wound	7	3	*.159*
Urinary Retention	1	4	*.347*
Anastomotic Leak	1	1	*1.000*
Readmissions	3	3	*1.000*
Other	1	2	*1.000*
Death	0	0	*1.000*

†$\chi 2$ test,

At baseline there were no differences between the groups in the levels of POF as measured by ICFS. After surgery, POF significantly increased in both CON and ERAS groups, reaching a maximum just prior to discharge in both arms. However this peak level was significantly smaller in the ERAS group. At this time, the median POF in the CON group had risen by 35% from the pre-operative levels compared with 23% in the ERAS group (P=0.001). Subsequently, POF continued to resolve, reaching pre-operative levels at day 30 in both groups, and remained unchanged thereafter to day 60. At day 30, 80% of patients in each group had reached baseline fatigue levels and there was no difference in median POF levels between the two groups (P=0.217). (Figure 3)

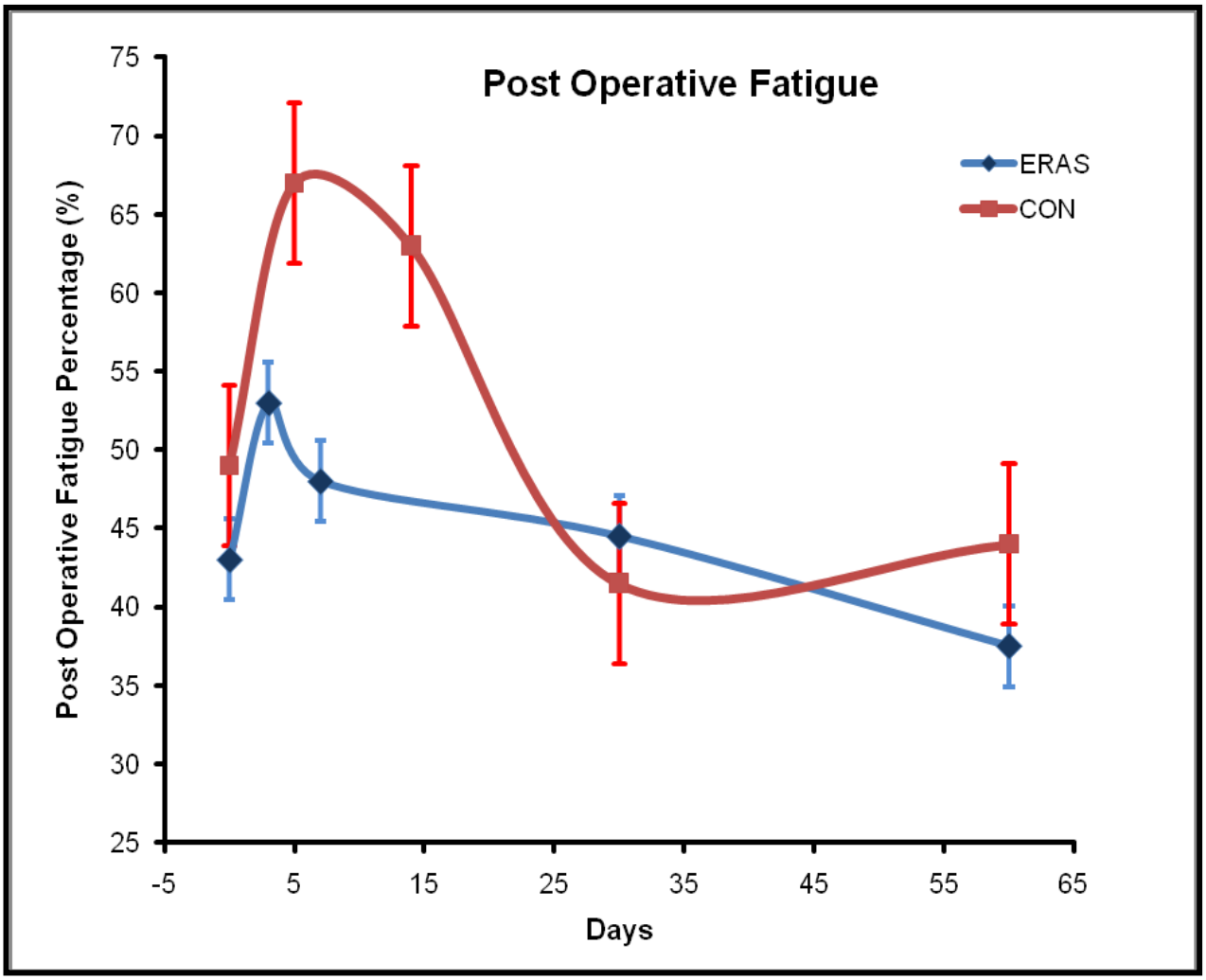


Figure 3: Changes in POF, Median and Standard Error

The Fatigue-Consequence (FC) scores as measured by ICFS were similar in the two groups at baseline (*P*=0.487). FC scores also reached a peak just prior to discharge and continued to resolve up to day 60. However, the median peak in Fatigue-Consequence score was significantly lower in the ERAS group (*P*=0.001) and this difference remained statistically significant between the two groups at each measured interval up to and including day 30 (*P*=0.003). At day 30, the Fatigue-Consequence scores were still 15% greater than the baseline values in the CON group, but had returned to baseline levels in the ERAS group. At day 60, there were no differences between the Fatigue-Consequence scores between the 2 groups (*P*=0.090) (Figure 4). Table 25 summarizes the fatigue results.

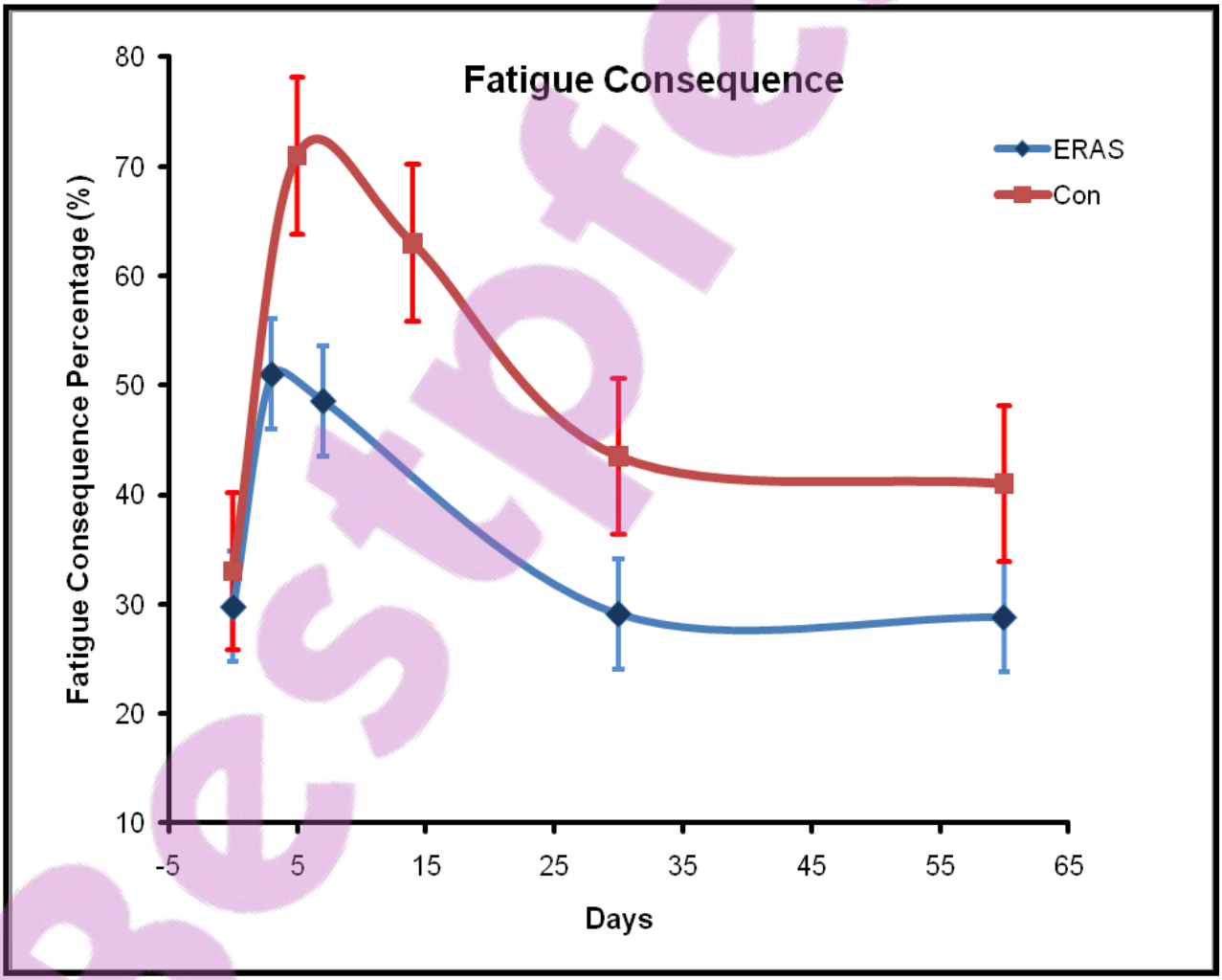


Figure 4: Changes in FC, Median and Standard Error

Table 25: Median POF Sub-Scale Scores

Time	Subscale	CON	ERAS	P†
Baseline	FF	34.00	28.00	.045
	FV	72.50	65.00	.078
	IC	28.00	32.00	.797
	IE	50.00	40.00	.107
	IDA	24.00	15.40	.241
	POF	49.50	43.00	.070
	FC	38.00	29.77	.487
Days 3-5	FF	74.00	56.00	.015
	FV	97.50	67.50	.000
	IC	44.00	32.00	.046
	IE	78.50	58.34	.007
	IDA	68.50	40.00	.017
	POF	67.00	53.00	.001
	FC	71.00	51.00	.002
Days 7-14	FF	56.00	48.00	.364
	FV	90.00	65.00	.001
	IC	40.00	26.00	.080
	IE	73.00	60.00	.049
	IDA	57.00	32.74	.004
	POF	63.00	48.00	.015
	FC	63.00	48.57	.003
Day 30	FF	33.50	36.00	.586
	FV	67.50	60.00	.008
	IC	24.00	30.00	.587
	IE	49.00	41.67	.007
	IDA	35.00	18.18	.003
	POF	41.50	44.50	.217
	FC	43.50	29.13	.003
Day 60	FF	36.00	28.00	.190
	FV	65.00	55.00	.106
	IC	32.00	28.00	.563
	IE	47.00	36.67	.012
	IDA	31.00	20.45	.248
	POF	44.00	37.50	.147
	FC	41.00	28.83	.090

FF: Feelings of Fatigue; FV: Feelings of Vigor; IC: Impact on Concentration; IE: Impact on Energy; IDA: Instruments of Daily Activity; POF: Overall Post-Operative Fatigue; FC: Fatigue-Consequence; † Mann–Whitney *U* test.

When plotting time against POF and FC scores for each group, the Area Under the Curve (AUC) is a representation of the total fatigue experience and the total fatigue impact for each group. From baseline to day 30, the median AUC for POF was 1577 units in the CON group and 1393 units in the ERAS group (P=0.035). AUC for FC from day 0 to 30, was 1628 units for the CON group and 1266 units for the ERAS group (P=0.005). These results represent a significant overall difference in POF and FC scores between the two groups.

There were no correlations between age or ASA scores and duration of hospital stay and POF scores at any time point. Complications influenced some of the outcomes as there were strong correlations between post-operative stay and overall complication rate in both groups, with this relationship being stronger in the ERAS (0.609 P=0.001) compared with the CON group (0.438 P=0.025). Within each group however, overall complications did not correlate with POF or FC at any time point.

Discussion

POF is often overlooked as an index of recovery despite POF being a major problem following colorectal surgery. Furthermore, when POF has been measured, it usually has been with simple instruments such as visual analog scales, which are not ideal for this purpose.(12) In addition, little or no attention has been paid to measurement of the impact of POF on daily living and resumption of normal function. The Identity-Consequence Fatigue Scale is a validated instrument specifically designed for measurement of POF as well as the impact of POF on daily function.(282) In this study, it has been further demonstrated that the ICFS is also an effective tool for measuring the change in POF between different groups of patients undergoing similar operations.

One significant limitation of this study is the fact that this is a nonrandomized and unblinded study. This has been the challenge for several other studies which have assessed various fast-track programs. Currently very few randomised controlled trials have been conducted in this field because of the practical difficulties associated with these.(113, 115, 117) In this study, data was collected prospectively and complications and discharge criteria were recorded according to set of pre-defined criteria which aimed to reduce observer bias. From a patients' perspective, clinicians attempts to provide sufficient information to the patients, to motivate them and to set them expected milestones may have influenced their subjective reporting of their fatigue, however this pre-operative "psychological intervention" is an important part of this fast-track package. Nevertheless there were objective differences between the two groups which indicate that the overall intervention has been effective.

In this study, there were no significant differences between the distribution of ages of patients in the two groups and there were similar numbers of cases in each age category as defined by the CR-POSSUM scoring system. Moreover, age was not found to correlate with hospital stay, POF or FC scores at any measured time point. Patients in each group were matched based on the type of surgery, as the magnitude of the surgical trauma is likely to contribute to POF.(31, 43) Furthermore patients undergoing laparoscopic surgery and patients with stomas were not included in the study. Analgesia has also been shown to reduce immediate POF (59), hence in this study attempts were made to account for this factor by use of continuous thoracic epidurals in both groups.

At baseline POF fatigue scores approached statistical significance ($P=0.07$), although as mentioned previously, no significant baseline differences were detected in any of the clinical characteristics which we assessed. One explanation for this may be the timing of the

intervention. The ERAS patients completed their baseline pre-operative ICFS questionnaire after they had concluded the preoperative ERAS session and in absence of other baseline differences this may be partially responsible for this observation of lesser baseline POF.

When measuring fatigue in surgical patients, consideration should be given to further post-operative interventions such as chemotherapy which can also influence fatigue levels and hence may affect the results. While attempts were not made to specifically control for this, in this study the patients in each group had similar pathological findings and had not started chemotherapy while in this study. (3, 283)

It is generally accepted that POF has a complex and multimodal etiology. As mentioned previously changes in nutritional status, cardiovascular fitness, magnitude of surgery and various psychological factors have been linked to the development of POF. However, not all potential contributing factors may have been identified and it has also been shown that the majority of single modality interventions are ineffective in reducing POF.(59)

Jakobsen et al (110) have shown that patient undergoing major colonic surgery within an ERAS programme have less POF up to day 30, with POF levels returning to pre-operative levels by this time. They also demonstrated that the consequences of fatigue had also decreased more substantially in non-ERAS patients. This study confirms most of these results demonstrating that Fatigue-Consequence scores in the ERAS group reached a lower peak following surgery and remained lower across the 60 days of the study relative to the CON group. Furthermore, overall both POF and FC during the first 30 days after surgery were significantly decreased by the ERAS programme.

It should be noted that in this study the POF and FC scores were not measured at identical time points between the two groups. This was because the expected duration of hospital stay was different between the CON and ERAS groups. The ICFS questionnaire assesses POF and FC based on a number of questions which relate to normal daily activities such as energy to exercise, wash, shop, do errands etc. Hence it would significantly influence the results if one compared scores from the CON group at days which they were still in hospital with those from the ERAS group when they were discharged. Because of this, POF and FC were compared on days which were clinically comparable. Overall focus was on functional recovery and the impact that an ERAS programme had on return to normal activity, regardless of time of discharge.

This study has shown that ERAS does not eliminate POF but is effective in reducing early POF by reducing the magnitude of the peak fatigue levels and by systematically reducing the consequences of fatigue and promoting earlier return to normal functioning following surgery. Total Fatigue and Total Fatigue Impact over 30 days, as shown by AUC, was notably smaller in the ERAS group reflecting that these patients experienced less overall fatigue and were less affected by it. In conclusion it has been demonstrated that the ICFS is a valid tool not only for measurement of POF, but it is also effective in detecting changes in POF between different groups. Secondly, by utilizing a multimodal approach which aims to control various factors which influence recovery, it is possible to minimize the magnitude of POF and hence reduce the overall impact of POF and lead to an earlier return to normal function.

There is new evidence suggesting that locally produced inflammatory mediators within the peritoneum may play a role in the development of POF and therefore incorporating strategies

which can suppress this post operative inflammatory response as part of ERAS programmers may be the next step in managing POF.

Chapter 6 : Double Blinded Randomised Trial on the Influence of Dexamethasone on Post Operative Fatigue

Introduction

In previous chapters we have shown that Post Operative Fatigue (POF) has a multifactorial aetiology. Furthermore we demonstrated that through utilization of Enhanced Recovery After Surgery Pathways (ERAS) we are able to suppress the magnitude of POF.

Research studies suggest a complex bio-psycho-social aetiology,(284) but there is recent evidence that locally occurring peritoneal inflammatory responses may influence development of fatigue via the neuro-immuno-humoral axis.(281) Paddison et al measured peritoneal fluid cytokine concentrations in patients 24 hours following open colorectal surgery, and found a significant positive correlation between peritoneal IL-6, IL-10 and TNF-α and fatigue scores after controlling for age, gender, co-morbidity, and pre-surgery fatigue.(281)

It is thought that these local cytokines may mediate POF via stimulation of the vagus nerve which has direct connections to the nucleus tractus solitarius (NTS).(80) The NTS is intensely activated following peripheral (peritoneal) immune stimulation(84, 85) and projects monosynaptically to regions of the brain which mediate sickness responses.(80) Subdiaphragmatic vagotomy in animals has been shown to block or reduce a broad spectrum of sickness responses to intraperitoneal administration of cytokines as well as inhibiting the neural activation of the brainstem, hypothalamus and limbic structures in response to these stimuli.(79)

Glucocorticoids blunt inflammatory pathways, decreasing cytokine production. We hypothesised that administration of pre-operative intravenous glucocorticoids to patients undergoing colonic resection may decrease fatigue by reducing local peritoneal production of cytokines.

Methods

Inclusion and exclusion criteria:

Consecutive patients undergoing open elective colonic surgery at Manukau Surgical Centre were invited to participate in this study. These patients were managed within an Enhanced Recovery After Surgery (ERAS) program, where other factors which may influence POF are controlled.(285-287) Discharge criteria were the ability to pass flatus, eat and drink without discomfort and maintain adequate analgesia with oral medications alone. Previously established exclusion criteria for our ERAS program included American Society of Anaesthesiologists score (ASA) greater than or equal to IV, a requirement for a stoma, inability to speak English and cognitive impairment.(285-287) For this study in particular, patients receiving steroids or other immunosuppressant medications were also excluded. Ethical approval from regional and local ethics committees was obtained. All patients were consented and verbal and written information was provided to all participants. This study was registered on the Australian New Zealand Clinical Trials Registry (ANZCTR) prior to the commencement of patient recruitment.

Intervention

Patients eligible for the study received an intravenous injection of either 10 ml of clear solution containing 8 mg of Dexamethasone (Dexamethasone Sodium Phosphate Injection, 4mg/ml, Hospira NZ Limited, Wellington, New Zealand) or 10 ml of normal saline (Placebo)

at least 90 minutes prior to incision. Randomisation was carried out using coded opaque envelopes and computer generated random numbers. Envelopes provided instructions to prepare a 10 ml syringe with 10 ml of normal saline or a 10 ml syringe with 8 mg of Dexamethasone (4mg/ml, 2 ml total volume) and top it off with 8 ml of normal saline to make up 10 ml of clear solution. An individual who was not involved in the care of the patients prepared the solution and handed it to the investigator. The saline and Dexamethasone solutions were transparent and appeared completely identical. Thus, the investigators, the patient, the anaesthetist, and the surgeon, were all blinded with respect to the study group.

Outcome measures

Fatigue was measured preoperatively, and at days 3, 7, 30 and 60 using the Identity-Consequence Fatigue Scale (ICFS). The ICFS is a validated, multi-dimensional measure which has been specifically designed to measure fatigue and return to normal activity in surgical patients.(24, 281, 288)

A surgical drain (15 F Blake drain, Johnson & Johnson, Somerville, NJ) was left in the peritoneal cavity at the conclusion of the operation. Plasma samples were taken preoperatively and on the morning of day 1 simultaneously with a sample of drain fluid. This time was chosen, because peritoneal IL-6 levels peak at this time.(87) The samples were collected in buffered Sodium Citrate tubes. Both samples were transferred immediately, on ice, to the laboratory for centrifuge and freezing in a -80 ºC freezer until the time of analysis. Cytokine assays were carried out by multiplexed cytometric bead immunoassays using the LINCOplex system (LINCO Research, St Charles, MO, USA). The samples were assayed in duplicate for pro-inflammatory cytokines IL-1β, TNF-α, IL-6, IL-8, IL-10 and IL-13 concentrations (with a minimum detection limit of 0.19, 0.22, 0.79, 0.32, 0.41, 4.06 pg/ml

respectively). Data were acquired using a Luminex cytofluorimeter and analysed using Luminex 100 IS software version 2.3 running a 4-parameter curve fit. Concentrations are expressed as picograms per milliliter (pg/mL).

Preoperatively, and at days 1, 2 and 3, questionnaires were completed by all the patients. These included the Visual Analog Scales (VAS) of pain (at rest and while coughing), nausea, vomiting, anxiety, sleep and appetite. Time to first passage of flatus, time to meeting discharge criteria and time of actual discharge were also recorded. Preoperative blood and blood taken on day 1 were analysed for leukocyte count and plasma C-Reactive Protein levels. Complications were prospectively recorded according to our previously published criteria.(285)

Power calculation and statistical analysis

Based on previous data,(24, 281, 288) we calculated that in order to reduce day 30 ICFS scores by 50% with a type I error of 0.05 and a type II error of 0.2, 30 patients would be required in each arm of the study. We aimed to include 70 to allow for possible drop outs.

Results were analysed using SPSS® for Windows® version 14.0 (SPSS, Chicago, Illinois, USA). Relationships between groups were assessed using the $\chi 2$ test for binary outcomes and continuous variables were compared using the Mann–Whitney U test. Correlations were expressed using Spearman's rho (correlation coefficient). Statistical significance was accepted at the 0.05 level.

Results

From June 2006 to March 2008, 70 consecutive patients undergoing elective open colonic resection within our ERAS programme were included in this study. Ten patients were excluded after randomisation, 9 requiring a defunctioning stoma intraoperatively and 1 declining further participation after surgery. Six of the excluded cases were in the Dexamethasone group and 4 in the placebo group. Excluded cases were similar in baseline characteristics to the study population. Overall 60 patients were included in the final analysis, 29 in the Dexamethasone group and 31 in the placebo group.

Table 26 shows that at baseline there were no differences in age, gender, ASA score, pathology, Body mass Index (BMI), physiological and operative Cr-POSSUM scores (Colorectal Physiological and Operative Severity Score for the enumeration of Mortality (269)), the type of operation, or the rate or duration of epidural use.

Table 26: Baseline Characteristics

Baseline		Placebo	Dexamethasone	P
Age		69 (34-87)	71 (37-92)	0.941†
Sex	Male	16	9	0.106‡
	Female	15	20	0.106‡
ASA	I	5	4	1.000‡
	II	15	16	0.599‡
	III	11	9	0.715‡
Body Mass Index		25.7 (17.7-37.6)	26.6 (19.7-33.9)	0.478†
CR-POSSUM	Physiological	9 (6-17)	9 (6-17)	0.692†
	Operative	8 (7-12)	8 (7-13)	0.823†
Epidural Duration		2 (1-5)	2 (0-3)	0.148†
OPERATION	Right Hemi	20	21	0.511‡
	Left Hemi	5	4	1.000‡
	Ant Res	5	4	1.000‡
	Total Col	1	0	1.000‡
Pathology	Dukes A	3	1	0.654‡
	Dukes B	10	12	0.464‡
	Dukes C	13	10	0.553‡
	Benign	4	5	0.914‡
	Other	1	1	1.000‡

† Mann–Whitney *U* test; ‡ $\chi 2$ test ;

Post-Operative Fatigue

Figure 5 and Figure 6 show that there were no differences in the baseline scores for Post Operative Fatigue (POF) or Fatigue Consequence (FC) as measured by ICFS. POF increased in both groups reaching a maximum at day 3 and declined gradually thereafter. POF and FC were significantly less for the Dexamethasone group on days 3 and 7. These differences were not maintained at days 30 or 60. Total fatigue Score and Total fatigue Consequence as measured by Area Under The Curve were significantly smaller for the Dex group. (Table 27)

Table 27: Fatigue Scores

ICFS		Placebo		Dexamethasone		*P* †
		Median	Range	Median	Range	
Baseline	POF	49.7	25.3-87.8	50.4	28.6-72.2	.408
	FC	42.2	19.7-70.4	41.7	19.3-75.4	.964
Day 3	POF	66.5	37.5-95.6	61.8	37.8-78.6	.046
	FC	66.0	42.5-97.4	61.5	38.1-96.7	.042
Day 7	POF	60.0	33.3-95.6	53.2	42.2-76.7	.006
	FC	67.7	30.4-87.6	58.7	46.5-81.2	.005
Day 30	POF	54.4	18.1-82.2	48.6	27.8-68.9	.498
	FC	45.0	18.3-75.3	46.2	19.7-65.6	.803
Day 60	POF	47.3	22.2-70.0	37.2	19.4-69.7	.145
	FC	37.6	21.1-63.4	33.6	21.1-57.3	.418
POF (VAS)	Base	3.0	1.0-10.0	3.0	1.0-9.0	.540
	1	6.0	2.0-10.0	4.0	1.0-8.0	.015
	2	6.0	3.0-10.0	5.0	1.0-7.0	.030
	3	7.0	1.0-9.0	5.0	1.0-8.0	.001
	7	5.0	3.0-10.0	4.0	3.0- 10.0	.021
AUC 0-30	POF	1874.4	1126.9-2787.6	1772.2	1065.0-2545.3	.047
	FC	1900.7	305.0-2738.3	1806.3	1193.1-2575.0	.006
AUC 0-60	POF	3840.6	1753.8-5531.4	3535.7	2310.8-5145.3	.012
	FC	3816.1	305.0-4950.8	3428.8	2584.7-4629.1	.003

ICFS: Identity-Consequence fatigue Scale; AUC : Area Under the Curve; POF : Post Operative Fatigue score; FC : Fatigue Consequence score; VAS: Visual Analog Scale, † Mann–Whitney *U* test;

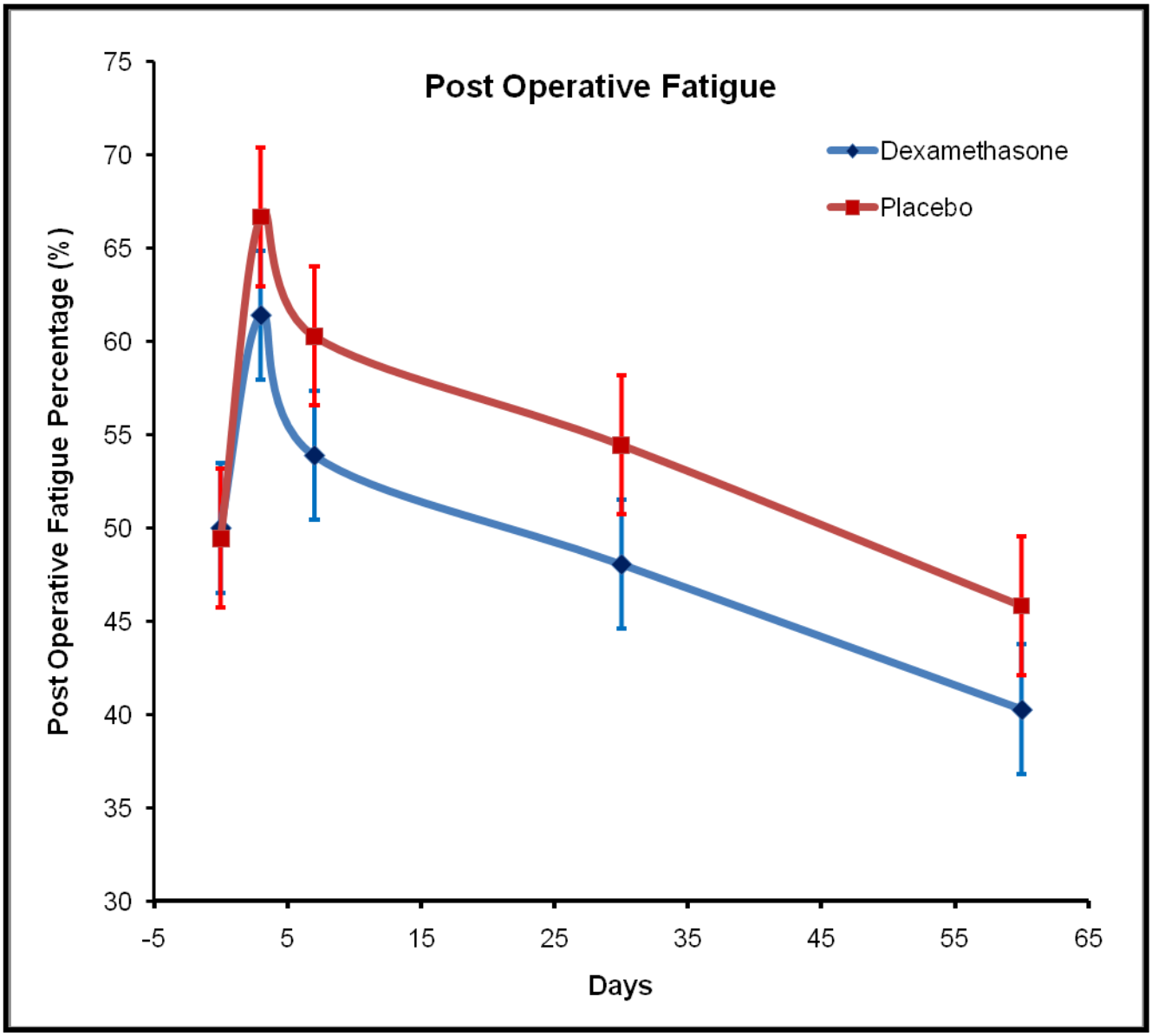


Figure 5: Post Operative Fatigue and Standard Error

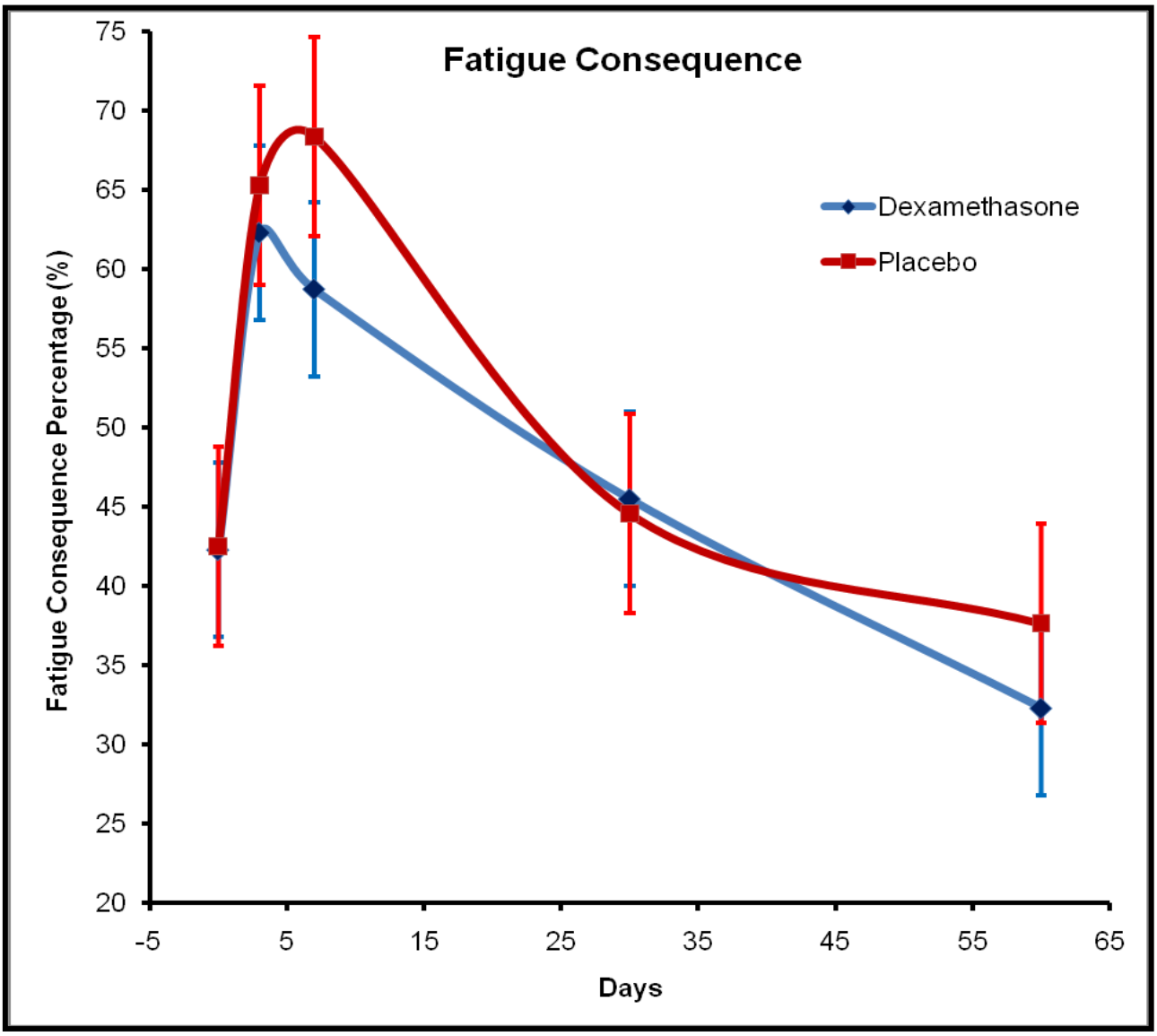


Figure 6: Fatigue Consequence and Standard Error

Cytokine levels

At the time of sample collection on the morning of day 1, there was no difference in the volume of drain fluid between the Dexamethasone (160 mls, 40-450) and the Placebo (150 mls, 20-400) groups (P=0.455).

Table 28 shows that there was a strong trend towards reduced concentration of plasma and peritoneal cytokines in the Dexamethasone group. The data were not normally distributed and non-parametric statistics were used. The difference between the groups reached statistical significance for peritoneal IL-6 and IL-13 and plasma levels of IL-6 and IL-8.

There were significant correlations between plasma IL-6 concentrations and POF and FC from day 3 to day 60 in both placebo and Dexamethasone groups (Table 29).There was also a significant correlation between drain fluid IL-6 levels and FC on day 3.

Table 28: Biochemical Markers

Cytokines (pg/ml)		**Placebo**			**Dexamethasone**			**% Reduction**	**P†**
		Median	Range		Median	Range			
Peritoneal	IL 10	4046	1257	10000	5104	70	10000	-26	0.215
	IL 13	60	0	383	7	0	461	89	0.002
	IL 1b	10	0	303	4	0	112	60	0.298
	IL 6	40069	11066	101591	37349	1325	96767	7	0.047
	IL 8	3247	596	10000	2126	16	10141	35	0.526
	TNF-α	122	38	1050	141	0	553	-16	0.956
Plasma	IL 10	64	18	3588	45	17	998	31	0.107
	IL 13	7	0	371	6	0	305	16	0.986
	IL 1b	0	0	6	0	0	4	0	0.625
	IL 6	128	26	5297	53	11	525	59	0.005
	IL 8	33	9	269	19	7	70	42	0.025
	TNF-α	15	0	72	14	7	31	6	0.817
WBC (x 10^9/L)	Pre	6.8	3.8	17.1	8.5	4.3	13.9	-25	0.052
	D1	11.2	6.2	20.4	14.3	9.6	28.8	-28	0.004
Neut (x 10^9/L)	Pre	4.4	2.2	15.7	5.2	2.0	11.3	-18	0.105
	D1	8.8	4.6	17.1	11.1	6.9	23.3	-26	0.014
CRP (mg/L)	Pre	<4	4<	25	4<	4<	65	N/A	0.735
	D1	83.5	34	130	71.5	33	194	14	0.197

IL: Interleukin; TNF-α : Tissue Necrosis Factor Alpha; WBC: White Blood Cell Count; Neut: Neutrophil Count; CRP: C-Reactive Protein Concentration; Pre: Preoperative Value; D1 value on Day 1; † Mann–Whitney *U* test;

Table 29: Spearman's Correlation Between Fatigue Scores and Plasma And Peritoneal Cytokines

		Base				Day 3				Day 7				Day 30				Day 60			
		POF		FC		POF		FC		POF		FC		POF		FC		POF		FC	
		CC	P	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P	CC	P
Drain	IL 10	.011	.939	.137	.337	.087	.537	.012	.934	.100	.483	.032	.822	-.261	.067	-.178	.215	-.012	.934	.069	.633
	IL 13	.010	.947	.084	.560	.201	.153	.308*	**.026***	.116	.417	.132	.355	-.034	.814	.017	.905	.104	.470	.197	.169
	IL 1b	.129	.369	.070	.624	.178	.206	.183	.193	.104	.470	.148	.300	-.097	.501	.014	.924	.173	.229	.249	.082
	IL 6	-.042	.768	.045	.753	.156	.268	.305*	**.028***	.203	.153	.148	.300	.067	.643	.259	.069	.259	.070	.197	.170
	IL 8	.003	.982	-.081	.573	.152	.282	.108	.448	.052	.715	.156	.275	-.136	.345	-.056	.700	.044	.762	.092	.524
	TNF	.044	.759	.087	.544	.156	.268	.120	.396	.172	.227	.089	.535	-.105	.467	.013	.929	.128	.375	.230	.108
Plasma	IL 10	-.079	.576	-.066	.642	.122	.383	.212	.128	.000	.998	.178	.206	.160	.261	.114	.424	-.018	.898	.022	.879
	IL 13	.046	.748	.005	.970	-.067	.632	-.059	.673	.066	.641	.015	.916	.177	.214	.107	.453	-.059	.682	.037	.796
	IL 1b	.018	.899	.014	.921	.124	.375	.123	.382	.019	.892	.200	.155	.105	.463	.096	.501	-.040	.779	-.027	.849
	IL 6	.158	.263	.214	.127	.291*	**.035***	.407**	**.002***	.403**	**.003***	.484**	**.000***	.286*	**.042***	.211	.137	.245	.083	.295*	**.035***
	IL 8	.111	.432	.189	.181	.299*	**.030***	.292*	**.034***	.213	.129	.271	.052	.155	.276	.100	.484	.097	.498	.133	.351
	TNF	.101	.474	.096	.501	.011	.939	.158	.260	-.026	.855	.050	.724	.157	.270	.200	.159	.042	.770	.106	.461

POF : Post Operative Fatigue; FC: Fatigue Consequence; CC : Correlation Coefficient (Spearman's rho); P: level of Significance

Other clinical outcomes:

Patients in the Dexamethasone group had significantly lower VAS nausea scores at days 1, 2 and 3 (Table 31). Subjective VAS vomiting scores and the number of daily vomiting episodes were significantly lower for the Dexamethasone group on day 1. There was no difference in antiemetic use between the two groups (Table 30), but patients in the Dexamethasone group passed flatus 1 day earlier (2 *vs.* 3 days, P=0.013).

Median pain scores at rest and while coughing were significantly lower for the Dexamethasone group at day 3 only (Table 32). There were no differences the use of epidurals or oral analgesia use between the two groups at any time point (Table 30). At days 1 and 2 there was a small but statistically significant difference in the subjective VAS sleep scores between the 2 groups, favouring the Dexamethasone group (Table 32).

Median time to reaching discharge criteria was 3 days for the Dexamethasone group and 4 days for the placebo group (P= 0.058). Median duration of total hospital stay was 4 days for the Dexamethasone group and 5 days for the placebo group (P=0.628). Seventeen patients (57%) in the Dex group reached the discharge criteria on day 3 or earlier compared to 10 patients (33%) in the placebo group (P=0.040).

Table 30: Antiemetics and Analgesia Use

Medication		Placebo		Dexamethasone		P †
		Median	Range	Median	Range	
Ondansetron	Day 0	8	0-12	4	0-16	.104
	Day 1	4	0-20	4	0-20	1.000
	Day 2	4	0-16	4	0-16	.885
	Day 3	0	0-16	4	0-12	.393
Cyclizine	Day 0	0	0-100	0	0-50	.069
	Day 1	0	0-75	0	0-100	.309
	Day 2	0	0-100	0	0-150	.588
	Day 3	0	0-50	0	0-100	.897
Metoclopramide	Day 0	0	0-10	0	0-20	.766
	Day 1	0	0-50	0	0-20	.180
	Day 2	0	0-20	0	0-30	.375
	Day 3	0	0-20	0	0-20	.261
Tramadol	Day 0	0	0-300	.00	0-150	.286
	Day 1	50	0-300	50	0-350	.967
	Day 2	150	0-350	50	0-350	.486
	Day 3	0	0-250	0	0-500	.619
Sevradol	Day 0	0	0-0	0	0-0	1.000
	Day 1	0	0-100	0	0-40	.685
	Day 2	20	0-120	20	0-120	.592
	Day 3	0	0-120	0	0-100	.734

† Mann–Whitney *U* test;

Table 31: VAS Nausea and Vomiting Scores

Outcome		Placebo		Dexamethasone		P†
		Median	Range	Median	Range	
Nausea	Pre-op	1	1-3	1	1-3	.321
	Day 1	3	1-6	1	1-6	.001
	Day 2	2	1-9	1	1-7	.009
	Day 3	1	1-7	1	1-4	.008
Vomiting	Pre-op	1	1-1	1	1-1	1.00
	Day 1	1	1-8	1	1-4	.019
	Day 2	1	1-4	1	1-2	.056
	Day 3	1	1-8	1	1-4	.834
No. Of Vomiting Episodes	Day 1	1	0-3	0	0-2	.048
	Day 2	0	0-1	0	0-1	.131
	Day 3	0	0-2	0	0-1	.677

VAS :Visual Analog Scale; No: Number; † Mann–Whitney *U* test;

Table 32: Subjective Visual Analogue Scores for Pain, Hunger, Thirst, Anxiety and Sleep for the first three days after surgery

Outcome		Placebo		Dexamethasone		*P*†
		Median	Range	Median	Range	
Pain At Rest	**Pre-op**	1.0	1.0-5.0	1.0	1.0-5.0	.753
	Day 1	3.0	1.0-8.0	2.0	1.0-7.0	.171
	Day 2	4.5	1.0-7.0	3.0	1.0-6.0	.164
	Day 3	4.0	1.0-9.0	3.0	1.0-6.0	.037
Pain While Coughing	**Pre-op**	1.0	1.0-3.0	1.0	1.0-5.0	.266
	Day 1	5.0	1.0-10.0	4.0	1.0-8.0	.131
	Day 2	5.5	1.0-8.0	5.0	1.0-7.0	.127
	Day 3	5.0	1.0-10.0	3.0	1.0-7.0	.003
Hunger	**Pre-op**	1.0	1.0-8.0	1.0	1.0-10.0	.588
	Day 1	3.5	1.0-9.0	4.0	1.0-8.0	.108
	Day 2	2.0	1.0-6.0	3.0	1.0-7.0	.195
	Day 3	2.0	1.0-7.0	3.0	1.0-10.0	.526
Thirst	**Pre-op**	4.0	1.0-7.0	4.5	1.0-10.0	.091
	Day 1	4.0	1.0-7.0	5.0	1.0-8.0	.121
	Day 2	4.0	1.0-7.0	5.0	1.0-10.0	.105
	Day 3	5.0	1.0-8.0	5.0	1.0-8.0	.427
Anxiety	**Pre-op**	5.0	1.0-8.0	4.5	1.0-8.0	.261
	Day 1	3.5	1.0-7.0	4.0	1.0-6.0	.623
	Day 2	4.0	1.0-8.0	5.0	1.0-6.0	.805
	Day 3	4.0	1.0-8.0	5.0	1.0-7.0	.343
Sleep	**Pre-op**	7.0	2.0-10.0	6.5	2.0-10.0	1.00
	Day 1	5.0	2.0-9.0	6.0	2.0-10.0	.027
	Day 2	6.0	2.0-8.0	6.0	2.0-9.0	.019
	Day 3	6.0	2.0-10.0	6.0	3.0-10.0	.524

† Mann–Whitney *U* test;

Complications

There were no differences in the total number of complications between the groups (Table 33). Of interest, the rate of wound infections was significantly lower for the Dexamethasone group. There were 2 anastomotic leaks requiring surgical intervention in the Dexamethasone group (a further patient presented several weeks after discharge with a fistula that settled with conservative management) and 1 in the Placebo group (P=0.56). There were two other major surgical complications in the Dexamethasone group with one patient developing an intra-abdominal abscess from an intra-operative iatrogenic bowel injury and another patient developing an intra-abdominal haematoma. Both cases were managed conservatively without further complications.

Non surgical complications included a patient who required readmission with recurrent falls in the placebo group and three in the Dexamethasone group with haemorrhoidal bleeding, hyponatraemia and an acute duodenal ulcer. There were 4 readmissions in the Placebo group and 5 in the Dexamethasone group (P=0.64).

Table 33: Complications

Complication	Placebo	Dexamethasone	P †
Wound Infection	6	0	0.04
Chest Infection	3	3	0.93
Urinary Infection	1	3	0.56
Ileus	3	1	0.65
Anastomotic Leak	1	3	0.56
Cardiac Complications	2	3	0.94
Urinary Retention	5	2	0.48
Other Surgical complications	0	2	0.44
Other Non-Surgical complications	1	3	0.56
Total	22	20	0.87

† $\chi 2$ test;

Discussion

In this double blinded randomized controlled trial it has been demonstrated that patients undergoing colonic surgery who are administered a single preoperative dose of Dexamethasone experience a moderate reduction in postoperative fatigue as measured by a multidimensional fatigue instrument. Within the first 7 post-operative days, this study detected a moderate but significant reduction in POF scores for the patients who received dexamethasone and subsequently 57% of these patients had reached discharge criteria by day 3 compared with 33% in the placebo group. It should be noted that this decrease in POF and improvement in functional recovery has been confirmed in addition to decreases in POF that have previously been shown in an enhanced recovery environment. Thus these changes may be more significant in the context of a conventional care programme.

Furthermore, this study has demonstrated an association between fatigue and the post-operative pro-inflammatory reaction as assessed by peritoneal and plasma cytokine levels on the first post operative day. The administration of Dexamethasone resulted in significantly lower levels of peritoneal IL-6 and IL-13 and plasma IL-6 and IL-8. The concentration of peritoneal cytokines, particularly IL-6, was much larger than the plasma levels of these mediators. This is consistent with findings from previous studies.(87, 289) As described in the Chapter I, it is postulated that these peritoneal derived inflammatory mediators act via cytokine receptors on vagus nerve endings in the peritoneal cavity and in turn lead to activation of areas of the brain involved in production in a variety of sickness responses.(290) Thus these data support the hypothesis that peritoneal inflammation is important in the pathogenesis of POF and postoperative recovery.(281)

Dexamethasone is an effective agent for control of post-operative nausea and vomiting,(291, 292) but it has not previously been tested for this purpose in the setting of major colonic surgery. In this study it significantly reduced nausea within the first 3 post operative days and vomiting episodes within the first day after surgery. It should be noted that these improvement were observed in a setting of an ERAS programme, where thoracic epidural, avoidance of systemic opioids and pre-emptive analgesia were used.(286, 287) Patients in the Dexamethasone group passed also flatus earlier. It has been previously described that the inflammatory mediators, released as a part of stress response, contribute to the development of postoperative ileus.(293, 294) Furthermore, in some animal studies a relationship has been demonstrated between the migration of leukocytes into the intestinal muscularis externa and ileus.(295) This may provide an explanation for the observed earlier return of bowel function in our study.

This study has shown that patients in the Dexamethasone group had less pain at rest and while coughing on day 3, with no differences at days 1 and 2. This may be as a result of the ERAS protocol where epidurals were removed on day 2. It has been demonstrated that systemic administration of glucocorticoids reduces tissue levels of bradykinin, prostaglandins and other nociception promoting neuropeptides. However, an analgesic effect of glucocorticoids in abdominal surgery has not been a consistent finding from previous studies. (262, 291, 296, 297)

In this study Dexamethasone was not associated with any adverse effects on wound healing. There were fewer episodes of wound infection in the Dexamethasone group and no wound dehiscences. This may be related to reduced tissue swelling and oedema which in turn results in higher wound oxygen tension which is an important predictor of the development of wound infection.(223, 224, 298) Overall, there is no convincing evidence that glucocorticoids such as

dexamethasone adversely affect wound healing.(106, 291, 299) There were 3 episodes of anastomotic leaks (two requiring laparotomy) in the Dex group compared to a single episode in the placebo group. Although this difference did not reach statistical significance this study was not designed nor powered to measure the impact of dexamethasone on the individual endpoint of anastomotic integrity.

The exclusion of patients receiving a stoma in this study may also have influenced this endpoint (although none of these patients developed a clinical anastomotic leak). However, previous studies have utilised large doses of methylprednisolone preoperatively in colonic surgery and have not found a negative impact on leak rates or wound healing.(107) These results need to be interpreted with caution and larger studies, or a meta-analysis of existing studies, with this endpoint in mind need to be conducted before preoperative glucocorticoids can be confidently recommended in colonic surgery.

Eight milligrams of Dexamethasone was the agent of choice for this study. This dose has been used in prior studies and has been shown to be safe.(291) This dose was effective in producing a significant biochemical impact in terms of plasma and peritoneal cytokines as well as plasma leukocyte counts. Glucocorticoids, such as Dexamethasone, bind to intracellular glucocorticoid receptors, and effects are predominantly mediated through altered protein synthesis via gene transcription.(261) Therefore, onset of biologic action is 1–2 hours, depending on the route of administration.(262) Since activation of the early mediators of the metabolic response to surgery occurs immediately after the surgical incision, administration of glucocorticoids 1–2 hours preoperatively may be of importance to achieve the full postoperative benefit of the treatment.(263)

Two other studies have measured the effect on fatigue after a single preoperative dose of glucocorticoids in abdominal surgery. Nagelschmidt et al used a high dose of methylprednisolone in a double-blinded RCT in abdominal surgery. (106) Despite small numbers, a 47% reduction in fatigue was demonstrated on day 1, as well as a significant reduction in plasma CRP on day 3. Because half the patients had incisional hernia repairs, and there were only 10 patients in each arm, inferences to major abdominal surgery were limited. Schulze et al also evaluated the use of methylprednisone in open colonic surgery in a randomised non-blinded study.(86) However, there was significant co-intervention bias as the intervention group also received neural blockade and non-steroidal analgesia post-operatively, and the control group did not. This made it impossible to tell whether the significant reduction in fatigue and plasma cytokines were due to the glucocorticoids per se.

The generalisability of this data data is limited by the exclusion criteria. The ERAS programme discussed here, excludes patients with stomas as these may influence postoperative recovery and quality of life, which are important endpoints in this study. Patients with ASA≥ IV were excluded as these patients were not operated on at Manukau Surgical Centre due to limited facilities for ventilation at this facility. Conclusions from the cytokine data are also limited by the fact that these were only measured at a single time point. Preoperative plasma levels of peritoneal or plasma cytokines were not assayed and it is thus possible that these were different between the groups preoperatively. This seems unlikely however as other patient variables potentially associated with altered cytokine levels were similar between the two groups.

In conclusion, in this double blinded randomized controlled trial, it has been shown that 8 mg of preoperative dexamethasone may result in a significant reduction in early post-operative fatigue

and an improvement in return to normal activity. This is associated with a diminished peritoneal pro-inflammatory cytokine reaction on day 1, supporting the hypothesis that peritoneal inflammation is an important contributor to fatigue after major abdominal surgery. In addition, this intervention may be an effective method of improving outcomes for patients undergoing colonic surgery within a multimodal enhanced perioperative care pathway. Although the overall complication rate was not increased, the wholesale application of these data to major colorectal surgery should be preceded by trials large enough to exclude a clinical impact of systemic glucocorticoids on anastomotic healing.

Chapter 7 : Conclusion

In the first section of this thesis, we reviewed the concept of Post Operative Fatigue. It was shown that POF is a major factor which delays return to normal activity following surgery, and is therefore of clinical significance. As discussed, POF has a multifactorial aetiology with interactions between psychological and biological variable.

The psychological aspect of POF has been explained by somatization and cognitive-behavioral theory. According to somatization theory, patients experience negative mood after surgery but misinterpret this as fatigue. Cognitive-behavioral factors include patients' interpretation of their own symptoms and of the medical advice they receive as well as their coping strategies and the course of action which they take during their recovery course.

The biological aspect of POF includes the surgical stress response, diminished nutritional status and a decline in physical fitness following surgery. Furthermore, it was shown that there is evidence suggesting that inflammatory mediators may also contribute to development of POF. It was hypothesized that inflammatory mediators produced at the site of surgery act via the Vagus nerve and stimulate areas of the brain which are involved in sickness behavior.

It was concluded that as POF has a multifactorial aetiology, in order to control the development of POF, multimodal interventions are required to address various factors which contribute to POF.

A definition was proposed of POF as a collection of physical and psychological symptoms which delay return to normal activity following surgery. This definition recognizes the fact

that POF has a multimodal etiology and it disrupts normal function following surgery and prolongs convalescence and for this reason is clinically significant.

Furthermore we discussed that measurement of POF has been a limiting factor for research into POF. We described various methods used and concluded that Identity Consequence Fatigue Scale (ICFS, Page 72) is an effective tool for measurement of POF as it measures fatigue levels as well as impact of fatigue.

In Chapter 2, we reviewed various pre-operative, intraoperative and post-operative interventions that have been investigated and we further analyzed the evidence supporting each individual intervention. We have shown that certain interventions are aimed at minimizing the magnitude of surgical stress response, while others aim to prevent the decline in the nutritional status following surgery. A number of other interventions were focused on providing the patients with adequate information and setting their expectations and milestones, hence addressing psychological issues which may be related to development of POF.

Subsequently we established an Enhanced Recovery After Surgery (ERAS) program which encompassed a number of the described perioperative interventions. In Chapter 3 it was confirmed that such programs are practical to install and associated with significant clinical benefits. It was shown that ERAS patients passed flatus earlier and had shorter duration of hospital stay. Additionally ERAS was associated with fewer episodes of post operative ileus, urinary tract infections and cardiopulmonary complications. It was demonstrated that there was good protocol compliance within the program further highlighting that such program are practical and sustainable.

Having established an ERAS program the next step involved analyzing the influence of such intervention on POF. In Chapter 4 it was shown that our ERAS program was associated with reduction in POF. After surgery, POF significantly increased in both conventionally treated patients as well as ERAS patients, reaching a maximum just prior to discharge in both arms. However this peak level was significantly smaller for the ERAS patients. At this time, the median POF for the conventional group had risen by 35% from the pre-operative levels compared with 23% in the ERAS group (P=0.001). The impact of Fatigue was also less severe for the ERAS patients. Fatigue-Consequence scores were significantly lower in the ERAS group and this difference remained statistically significant between the two groups at each measured interval up to and including day 30 (P=0.003). At day 30, the Fatigue-Consequence scores were still 15% greater than the baseline values in the conventional patients, but had returned to baseline levels in the ERAS group. It was further shown that Total Fatigue Score and Total Fatigue Consequence for the first 30 post operative days were significantly less for the ERAS patients. It was concluded that although ERAS does not eliminate POF but is effective in reducing early POF by reducing the magnitude of the peak fatigue levels and by systematically reducing the consequences of fatigue and promoting earlier return to normal functioning following surgery. ERAS is effective in modifying POF as it aims to modify factors which are known to contribute to development of POF.

Chapter 5 focused on the link between POF and perioperative inflammatory response. In a double blinded randomised controlled trial patients undergoing colonic surgery were administered 8 mg of pre-operative intravenous dexamethasone or placebo. All patients were managed within our established ERAS program ensuring that perioperative care was standardized and thus minimizing the influence of confounders and bias.

It was shown that administration of dexamethasone was associated with statistically significant reduction in peritoneal IL-6 and IL-13 and plasma levels of IL-6 and IL-8. Furthermore there was a significant correlation between plasma IL-6 concentrations and POF and FC from day 3 to day 60 in both placebo and Dexamethasone groups. Finally we demonstrated that patients in the dexamethasone group have less Post Operative Fatigue and Fatigue-Consequence for the first 7 days after surgery. Therefore we demonstrated that in a setting were all other factors are controlled for, change in post operative inflammatory response was associated with clinically detectable change in POF and therefore supporting the hypothesis that a link between POF and peritoneal inflammatory mediators is plausible.

We propose that the next logical step in this pathway is to block the transmission of neural messages from the peritoneal cavity to the central nervous system by blocking the transmission through the Vagus nerve. Blocking Vagus transmission by means such as peritoneal local anaesthetic agents may potentially lead to changes in post operative fatigue levels.

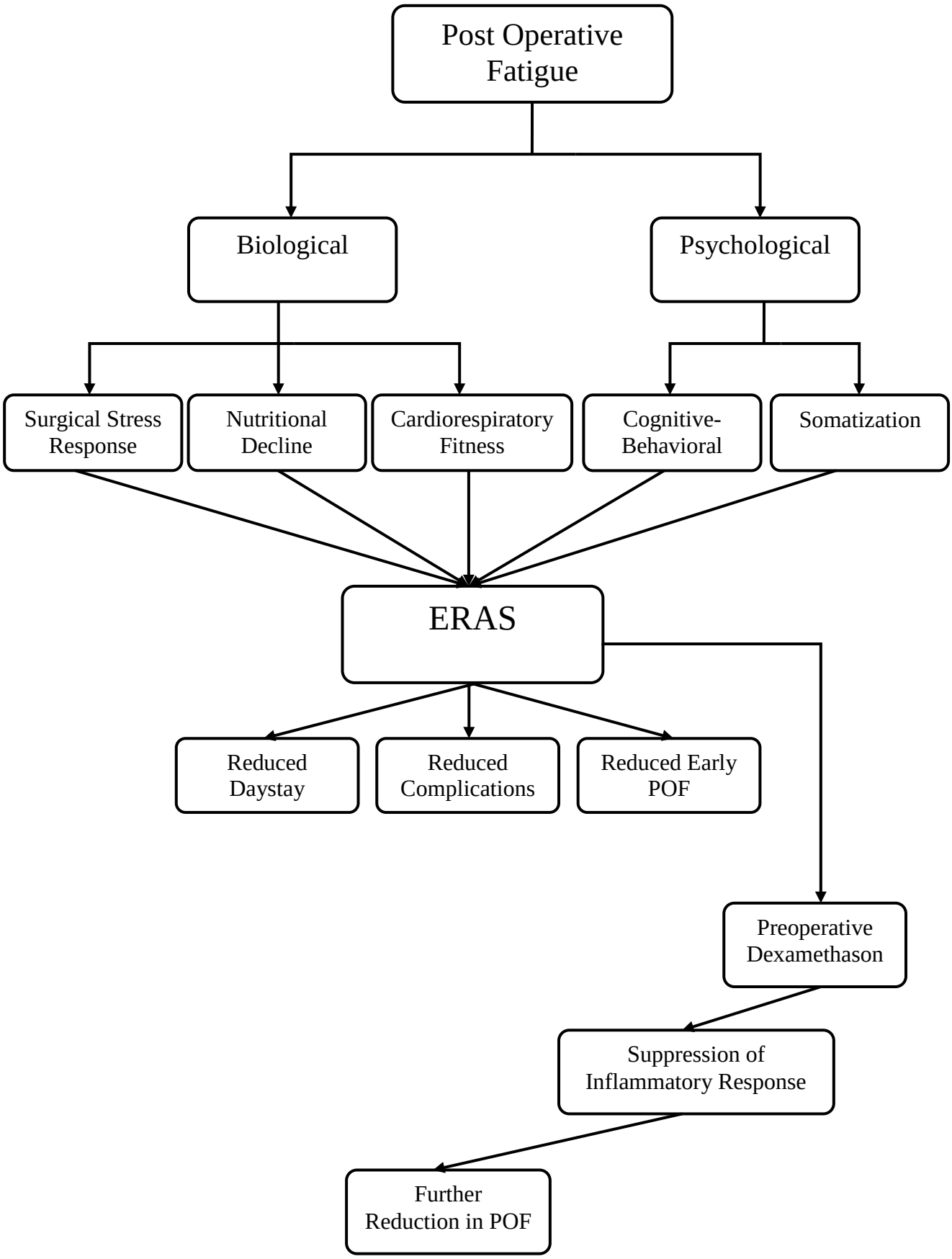


Figure 7: Project Over View

Chapter 8 : Appendix

Appendix 1: Consent form

Consent Form

Title: **Preoperative Steroids and their effect on postoperative recovery in major colonic surgery**

Principal Investigator: Assoc. Prof Andrew G Hill, General Surgeon, Department of Surgery, Middlemore Hospital, Phone 276 0000 ext 8424

Patient Name: **Date of Birth:**

Request for Interpreter

English	I wish to have an interpreter	Yes	No
Maori	E hiahia ana ahau I tetahi hei korero Maori ki ahau	Ae	Kao
Samoan	Oute mana'o e iai se fa'amatala upu	Ioe	Leai
Tongan	'Oku fiema'u ha fakatonulea	Io	Ikai
Cook Island	Ka inangaro au i tetai tangata uri reo	Ae	Kare
Niuean	Fia manako au ke fakaaoga e tagata fakahokohoko vagahau	E	Nakai

I have read and I understand the information sheet dated Dec 2005 for volunteers taking part in this study. I have had the opportunity to discuss the study. I am satisfied with the answers I have been given. I have had this project explained to me by _____.

I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time and that this will in no way affect my continuing health care.

I understand that my participation in this study is confidential and that no material that could identify me will be used in any reports on this study.

I understand that to participate in the study I am required to disclose my medical history.

I agree to details of my admission to hospital being entered onto a data sheet that will be confidential.

I understand the compensation provisions for this study.

I have had time to consider whether to take part.

I know whom to contact if I have concerns or questions about the study.

I consent to the researchers using a specimen of my blood and surgical drain fluid for analysis of inflammatory chemicals / I have had an opportunity to discuss this with my family / iwi

I would like to receive a copy of the results when available. Yes / No
I consent to my GP (Family Doctor) being informed of my condition if necessary. Yes / No

I am clinically responsible for this patient's care at Middlemore Hospital and I have no objection to his/her participation in this project.

Signed:_____
Date_____ (attending physician)

I_____(full name) hereby consent to take part.
Signed (subject)_____
Date_____
In my opinion consent was given freely and with understanding
Signed (witness)_____
Date_____
Consent obtained by_____
Date_____

If you have any concerns about the study, you may contact:
Health Advocates Trust Tel 0800 555 050 (Auckland to Franklin)
Assoc Prof Andrew Hill, Department of Surgery: Tel 276 0000 ext 8424

Appendix 2: Patient Information Sheet

The effects of dexamethasone on post operative fatigue

Principal Investigator: Assoc Prof. Andrew G Hill, General Surgeon, Department of Surgery, Middlemore Hospital-Phone 276 0000 ext 8424 or pager 93 8974

Introduction

You are invited to take part in a clinical research study. Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part this will not affect any future care or treatment.

The information sheet and consent form gives you detailed information about the research study which your doctor will discuss with you. Once you are happy that you understand the study you will be asked to sign the form if you wish to participate.

About the Study

Recovery from surgery is dependent on many factors that are controlled by our bodily processes. There are many ways that we, as doctors, can control or manipulate these processes; examples include the use of antibiotics or pain relief. But as our knowledge about the human body improves we have realised that there are many other processes in the body which affect the way that we feel or recover after surgery.

The usual complete recovery period following large bowel surgery is between two and three months. We are aiming to investigate the effect of new treatments in reducing the length of this recovery period by reducing fatigue, pain, nausea and vomiting.

We are inviting you to participate in a new study which is aiming to investigate improvements in the energy levels and speed of recovery after operation, following administration of a *single dose* of a medication called Dexamethasone.

We are hoping to invite 70 patients who are going to have a major bowel operation to take part in this study. If you agree to participate, you will randomly be assigned to receive either a single intravenous dose of Dexamethasone or saline just prior to the operation. You will not know which one you have received. This is a one off administration and you will not be given any further doses of this drug. Following that, you will have the same routine, standardised care plan as all the other patients and your participation in this trial will not affect your standard of care in any way.

At the end of the operation your surgeon will insert a surgical drain to monitor for bleeding after the operation. This is common for bowel surgery. This drain will be removed the day after the operation.

During the post operative period we will ask you to complete a number of questionnaires with the assistance of the researchers. These will ask you about your pain and energy levels.

We will also collect a small sample of your surgical drainage fluid for testing of levels of some chemicals that cause swelling and pain. We will ask for your permission prior to doing so. This is painless and does not involve any genetic testing. The samples will be discarded after the testing.

Participants must note that some Iwi disagree with storage of tissue or blood samples citing whakapapa, and advice their people to consult prior to participation in research where this occurs. However, it is acknowledged that individuals have the right to choose to participate.

You will not be subjected to any extra tests or procedures for the study and any test, such as blood tests or x-rays, will be done as is seen fit by your treating surgeon.

About Dexamethasone

Dexamethasone is a commonly used drug classified as a "steroid". It is usually used for control of nausea and vomiting or reducing swelling and inflammation in some conditions.

A single dose of Dexamethasone has not been shown to have any adverse affects or complications. A relatively small dose of this drug will be used in our study.

Risks and Benefits

Participation in the study may not directly benefit you but the information we obtain from the study may help to benefit future patients. There are no known risks associated with participating in the study. Dexamethasone is a commonly used and safe medication. There will be no costs or payments to you.

Alternatives

You may choose not to participate in this study. This will not affect your treatment in any way.

Participation

Your participation is entirely voluntary (your choice). You do not have to take part in this study, and if you choose not to take part this will not affect any future care or treatment.

If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason and this will in no way affect your continuing health care.

No material which could personally identify you will be used in any reports on this study.

General

Further information can be obtained from Dr Andrew Hill, Department of Surgery (Tel 021 679488 or 276 0000 pager 938974).

An interpreter will be provided if you would like one.

If you have any queries or concerns, regarding your rights as a participant in this research, you may contact the Health Advocates Trust, telephone 0800 555 050 (Northland to Franklin) or 0800 423 638 (the rest of North Island).

Confidentiality

Your hospital records are confidential. Your name or any other personally identifying information will not be used in reports or publications resulting from this study. The information about your medical history and medications required to interpret the research results will be identified using a code to ensure your confidentiality.

Compensation

In the unlikely event that you suffer a physical injury as a result of your participation in this study, you will be covered by the accident compensation legislation with its limitations. If you have any questions about ACC please feel free to ask the researcher for more information before you agree to take part in this study.

Results

The final results of the research will not be known until December 2007. If you wish to find about the results of the study contact Prof Andrew Hill, General Surgeon, Middlemore Hospital (ph 2760000 pager 938974)

Statement of Approval: This study has received ethical approval from the Northern Y Regional Ethics Committee.

Appendix 3: Identity Consequence Fatigue Scale (ICFS) Questionnaire

Investigating feelings of tiredness

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

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

Thank you for taking the time to fill out this questionnaire

Part 1

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

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

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

Part 2

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

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

Examples of why you might tick the "N/A" box include:
You are still in hospital and are not required to do things like run errands.
You are not the person who usually cooks in your household.
Or, you have a wound that is vacuum-sealed and you are not able to do household chores because of this.

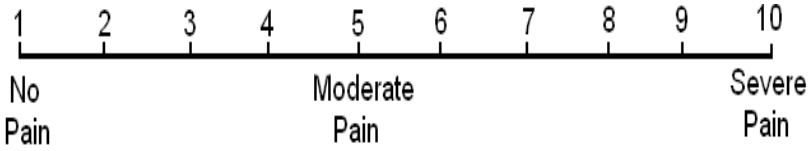
During the last two days, I have had enough energy to…	Not at all ▼	Only occasion ally ▼	Sometimes, but less than usual ▼	Nearly as often as usual ▼	As often as usual ▼	N/A ▼
21. Read a newspaper/book or watch TV	☐	☐	☐	☐	☐	☐
22. Bath/wash	☐	☐	☐	☐	☐	☐
23. Dress	☐	☐	☐	☐	☐	☐
24. Do household chores	☐	☐	☐	☐	☐	☐
25. Cook	☐	☐	☐	☐	☐	☐
26. Work	☐	☐	☐	☐	☐	☐
27. Visit or socialize with family and friends	☐	☐	☐	☐	☐	☐
28. Engage in leisure or recreational activities	☐	☐	☐	☐	☐	☐
29. Shop or do errands	☐	☐	☐	☐	☐	☐
30. Walk	☐	☐	☐	☐	☐	☐
31. Exercise other than walk	☐	☐	☐	☐	☐	☐

Appendix 4: Patient Questionnaire – Physiological Parameters

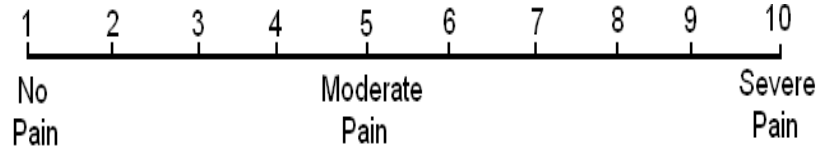
Patient Questionnaire – Physiological Parameters

Please take your time in answering the following question with assistance of your Doctor: Circle the appropriate answer or write in the space provided.

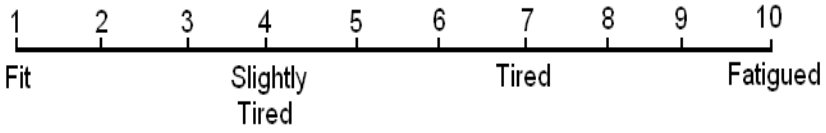
1. How would you describe your pain level at the present time, *while resting in bed:*



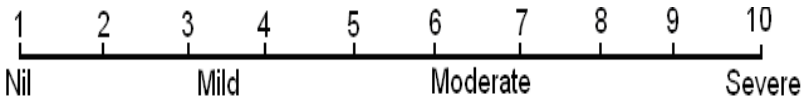
2. How would you describe your pain level at the present time, *while coughing*:



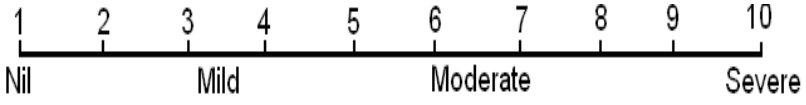
3. How would you described your energy levels at present time:



4. How would you describe your level of *nausea* at *present time*?
   0. No nausea at all
   1. Mild, tolerable nausea
   2. Moderate nausea, requiring medication
   3. Severe nausea



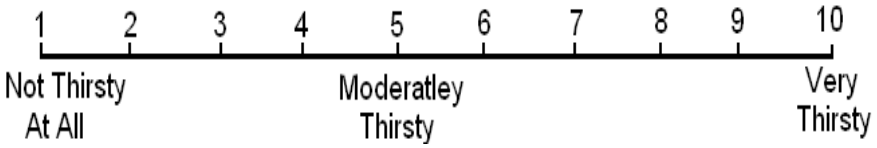
5. Have you vomited in the past 6 hrs?
   0. No
   1. Yes, only once
   2. Yes 2-3 times
   3. Yes more than 3 times



6. At the present time, do you feel

Hungry?

Thirsty?



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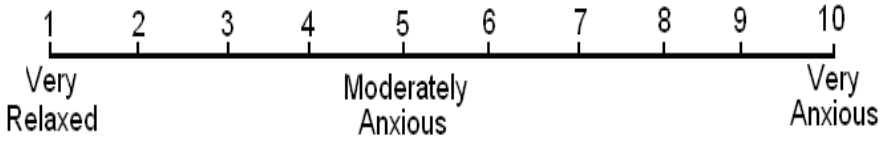
7. How would you describe your anxiety level at present time?



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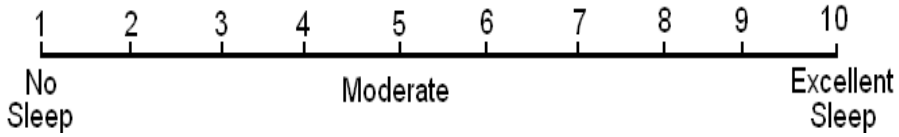
8. How would you rate your Sleep quality over the past 24 Hrs?



Appendix 5: Placebo Test Dose

Double-Blind Randomised-Control study on the effects of dexamethasone on recovery in colonic surgery

Requirements:

1. 10 ml of normal saline
2. 10 ml syringe

Please Fill a 10 ml syringe with 10 ml of normal saline and give it back to the doctor.

Please ensure that you do not mark the syringe.

The doctor and the patient should remain unaware of the contents of the syringe.

The doctor will record the administration of the “test” solution and the in the medication chart.

Thank you for assisting us with this project.

Appendix 6: Dexamethasone Test Dose

Double-Blind Randomised-Control study on the effects of dexamethasone on recovery in colonic surgery

Requirements:

1. 10 ml syringe
2. 10 ml of normal saline
3. Dexamethasone (8 mg) i.e. 2 ml of dexamethasone (4 mg / ml)

Withdraw 2 ml of dexamethasone (4 mg / ml) into a 10 ml syringe and top up with normal saline to make a 10 ml of solution.

Please ensure that you do not mark the syringe.

The doctor and the patient should remain unaware of the contents of the syringe.

The doctor will record the administration of the “test” solution and the in the medication chart.

Thank you for assisting us with this project.

Appendix 7: ERAS Care Pathway

COUNTIES MANUKAU DISTRICT HEALTH BOARD
A Community Partnership

Affix patient's identification label here

FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Date:

Admission Date: _____ Surgery Date: _____

Planned Procedures: _____

Bowel Prep: _____

- ☐ Not required
- ☐ Prescribed
- ☐ IV Fluids Prescribed

Preoperative Stoma Intervention: _____

- ☐ Explanation given re: stoma requirement
- ☐ Shown stoma picture
- ☐ Shown stoma appliances
- ☐ Access to stoma supplies discussed
- ☐ Sites selected for stoma placement

Social Assessment: _____

Discharge Plan: _____

Planned Discharge Date: _____

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

FAST-TRACK RECOVERY

Developed by: Lisa Thompson, Charge Nurse, Manukau Surgery Centre; Lorraine Andrews, Colorectal Nurse Specialist

Re-Order No. SURG009 Revised May 2007

COUNTIES MANUKAU DISTRICT HEALTH BOARD
A Community Partnership

Affix patient's identification label here

FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Operation: **Date:** **Side A:**

Prescriptions:
Standard analgesia ☐ ☐
Clexane 1800 hrs ☐

Stoma Care
(see separate Care Map as required)

1) Cerebral Function ☐ ☐ ☐

2) Sleep and Rest ☐ ☐ ☐

3) Pain Assessment ☐ ☐ ☐
Score ☐ ☐ ☐

4) TED Stockings ☐ ☐ ☐

5) Epidural Site Check ☐ ☐ ☐

6) Intravenous Line Checked ☐ ☐ ☐

7) Respiration/Circulation
Respiration ☐ ☐ ☐ Pulse ☐ ☐ ☐
O_2 sat ☐ ☐ ☐ BP ☐ ☐ ☐
Temp ☐ ☐ ☐

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

FAST-TRACK RECOVERY

COUNTIES MANUKAU DISTRICT HEALTH BOARD
A Community Partnership

Affix patient's identification label here

FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Operation: **Date:** **Side B:**

8) Nutrition >1500mls
Protein Drinks
Normal Food

9) Nausea & Vomiting

10) Wound Check

11) Urination

12) Intestinal Function
Flatus +/-
Defaecation +/-

13) Mobilisation

Mobilise x 2hrs

Walk x 1

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

FAST-TRACK RECOVERY

COUNTIES MANUKAU DISTRICT HEALTH BOARD
A Community Partnership

Affix patient's identification label here

FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 1: **Date:** **Side A:**

Prescriptions:
Standard analgesia
Clexane 1800 hrs

Dressing Removed
IDC Removed
Stoma Care
(see separate Care Map as required)

Information:
Operation Explained
Plan/goals for day
Preparation for discharge

1) Cerebral Function

2) Sleep and Rest

3) Pain Assessment
Score

4) TED Stockings

5) Epidural Site Check

6) Intravenous Line Checked

7) Respiration/Circulation
Respiration
O_2 sat
Temp
Pulse
BP

8) Nutrition
Fluids > 2000mls
Normal Diet
Protein Drinks

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 1: **Date:** **Side B:**

9) Nausea & Vomiting ☐ ☐ ☐

10) Wound Check ☐ ☐ ☐

11) Urination ☐ ☐ ☐

Time Volume

12) Intestinal Function
Flatus +/- ☐ ☐ ☐
Defaecation +/- ☐ ☐ ☐

13) Mobilisation
Mobilised for meals ☐ ☐ ☐
Mobilised 2 x 2hrs Day Shift ☐ ☐
Mobilised 2 x 2hrs Afternoon ☐ ☐
Walked x 3 ☐ ☐ ☐
Personal Hygiene ☐

14) Discharge & Planning
Information Family ☐
Transport ☐
Homehelp organised ☐
Medications discussed (referrals if needed) ☐

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 2: **Date:** **Side A:**

Prescriptions:	Fluid Balance	Information:
Standard analgesia ☐ ☐ ☐ ☐	Remove IV ☐	Plan/goals for day explained ☐
Clexane 1800 hrs ☐	Stop Epidural 0900hrs ☐	
Stoma Care (see separate Care Map as required)	Remove Epidural ☐	

1) Cerebral Function ☐ ☐ ☐

2) Sleep and Rest ☐ ☐ ☐

3) Pain Assessment ☐ ☐ ☐
Score ☐ ☐ ☐

4) TED Stockings ☐ ☐ ☐

5) Epidural Site Check ☐ ☐ ☐

6) Intravenous Line Checked ☐ ☐ ☐

7) Respiration/Circulation
Respiration ☐ ☐ ☐ Pulse ☐ ☐ ☐
O_2 sat ☐ ☐ ☐ BP ☐ ☐ ☐
Temp ☐ ☐ ☐

8) Nutrition
Fluids > 2000mls ☐ ☐ ☐
Normal Diet ☐ ☐ ☐
Protein Drinks ☐ ☐ ☐ ☐

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 2: **Date:** **Side B:**

9) Nausea & Vomiting ☐ ☐ ☐

10) Wound Check ☐ ☐ ☐

11) Urination ☐ ☐ ☐

Time Volume

12) Intestinal Function
Flatus +/- ☐ ☐ ☐
Defaecation +/- ☐ ☐ ☐

13) Mobilisation
Mobilised for meals ☐ ☐ ☐
Mobilised 2 x 2hrs Day Shift ☐ ☐
Mobilised 2 x 2hrs Afternoon ☐ ☐
Walked x 3 ☐ ☐ ☐
Personal Hygiene ☐

14) Discharge & Planning
Post discharge SOPC appl 7/7 & 30/7 ☐
Protein drinks supplied for discharge ☐
Commence Community Home Care (referrals if needed) ☐

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 3: **Date:** **Side A:**

Prescriptions:
Standard analgesia ☐ ☐ ☐ ☐
Stoma care
(see separate Care Map as required)

Information:
Plan/goals for day explained ☐

1) Cerebral Function ☐ ☐ ☐

2) Sleep and Rest ☐ ☐ ☐

3) Pain Assessment ☐ ☐ ☐
Score ☐ ☐ ☐

4) TED Stockings ☐ ☐ ☐

5) Respiration/Circulation
Respiration ☐ ☐ ☐ Pulse ☐ ☐ ☐
O_2 sat ☐ ☐ ☐ BP ☐ ☐ ☐
Temp ☐ ☐ ☐

6) Nutrition
Fluids > 2000mls ☐ ☐ ☐
Normal Diet ☐ ☐ ☐
Protein Drinks ☐

7) Nausea & Vomiting ☐ ☐ ☐

8) Wound Check ☐ ☐ ☐

9) Urination ☐ ☐ ☐
Time Volume

Care map completed by:
Initial Night

Initial AM

Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 3: **Date:** **Side B:**

12) Intestinal Function
Flatus +/-
Defaecation +/-

13) Mobilisation
Mobilised for meals
Mobilised 2 x 2hrs Day Shift
Mobilised 2 x 2hrs Afternoon
Walk x 3

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 4: **Date:** **Side A:**

Prescriptions:
Standard analgesia ☐ ☐ ☐ ☐
Stoma care
(see separate Care Map as required)

Information:
Plan/goals for day explained ☐

1) Cerebral Function ☐ ☐ ☐

2) Sleep and Rest ☐ ☐ ☐

3) Pain Assessment ☐ ☐ ☐
Score

4) TED Stockings ☐ ☐ ☐

5) Respiration/Circulation
Respiration ☐ ☐ ☐ Pulse ☐ ☐ ☐
O_2 sat ☐ ☐ ☐ BP ☐ ☐ ☐
Temp ☐ ☐ ☐

6) Nutrition
Fluids > 2000mls
Normal Diet
Protein Drinks ☐ ☐ ☐ ☐ ☐ ☐ ☐

7) Nausea & Vomiting ☐ ☐ ☐

8) Wound Check ☐ ☐ ☐

9) Urination ☐ ☐ ☐
Time Volume

Care map completed by:
Initial Night

Initial AM

Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 4: **Date:** **Side B:**

12) Intestinal Function
Flatus +/-
Defaecation +/-

13) Mobilisation
Mobilised for meals ☐ ☐ ☐
Mobilised 2 x 2hrs Day Shift ☐ ☐ ☐
Mobilised 2 x 2hrs Afternoon ☐ ☐ ☐
Walk x 3 ☐ ☐ ☐ ☐

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 5: **Date:** **Side A:**

Prescriptions:
Standard analgesia ☐ ☐ ☐ ☐
Stoma care
(see separate Care Map as required)

Information:
Plan/goals for day explained ☐

1) Cerebral Function ☐ ☐ ☐

2) Sleep and Rest ☐ ☐ ☐

3) Pain Assessment ☐ ☐ ☐
Score ☐ ☐ ☐

4) TED Stockings ☐ ☐ ☐

5) Respiration/Circulation
Respiration ☐ ☐ ☐ Pulse ☐ ☐ ☐
O_2 sat ☐ ☐ ☐ BP ☐ ☐ ☐
Temp ☐ ☐ ☐

6) Nutrition
Fluids > 2000mls ☐ ☐ ☐
Normal Diet ☐ ☐ ☐ ☐
Protein Drinks

7) Nausea & Vomiting ☐ ☐ ☐

8) Wound Check ☐ ☐ ☐

9) Urination ☐ ☐ ☐
Time Volume

Care map completed by:
Initial Night

Initial AM

Initial *PM*

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

Post-operative Day 5: **Date:** **Side B:**

12) Intestinal Function
Flatus +/-
Defaecation +/-

13) Mobilisation
Mobilised for meals
Mobilised 2 x 2hrs Day Shift
Mobilised 2 x 2hrs Afternoon
Walk x 3

Nursing Observations and Interventions:

Care map completed by: *Initial Night*	*Initial AM*	Initial *PM*

FAST-TRACK RECOVERY

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FAST-TRACK RECOVERY – STANDARD CARE MAP COLONIC RESECTION

FAST-TRACK RECOVERY

Before your surgery, you will be seen by our colorectal nurse specialist who will be able to answer many of your questions. She will also show you the ward that you will be staying in after your operation.

The day of operation:

The night before your operation you will be asked to drink 4 small boxes of a special carbohydrate drink and another 2 on the morning of the operation.

In the operating room

Firstly you will be seen by the anaesthetic doctor. Then You will be taken to the operating room and an epidural will be inserted into your back. This will provide excellent pain relief after the operation.

Subsequently you will be given a general anaesthetic and we will proceed with the operation. The operation usually takes around 2 -3 hrs.

When you wake up from anaesthesia you will be in the post operative recovery room. You will have an abdominal wound with a dressing, IV lines with fluids running through, a urinary catheter and also your epidural catheter in your back. We expect you to be relatively pain free at this stage. You will be given medications to prevent nausea and vomiting.

After a short time you will be taken to the ward. The IV fluids will be stopped, you will sit up in a chair and you will be allowed to drink fluids. We will provide you with a few boxes of high energy drinks. This is conducive to a faster and more efficient recovery.

In the ward

Day 1

In the morning after the operation we will remove your urinary catheter. You will have a blood test. You will be encouraged to continue drinking. You will start walking around the ward with assistance of your nurse and the physiotherapist. Your epidural will provide sufficient pain relief. You will also receive a small injection into your abdomen for prevention of clots.

Day 2

In the morning we will remove your epidural catheter. We will give you *regular* oral analgesia for pain relief. It is important for you to take this even if you are feeling pain free as this will stop further pain from developing.

You will be allowed to start eating a light diet. You might be feeling low in appetite but we will strongly encourage you to have 3 light meals on the second day. You will continue to mobilise on day 2. You will have another anti-clot injection.

Day 3

If by day 3 you have been able to tolerate light diet, have passed wind or had a bowel motion and your pain is under control you will be discharged home. If there are any concerns by you or the medical team we will not discharge you at this stage. You will only be discharged once all the above criteria are met.

It is very important that you to arrange for someone to be with you after discharge, *prior* to you coming to hospital for your operation.

We will provide you with further instructions at the time of your discharge.

Summary

- *This is a enhanced surgical care plan which leads to faster recovery and subsequent early discharge*
- *Safety is the most important aspect of our management*
- *Your co-operation and enthusiasm is the most essential part of this plan*
- *We will provide more information at the time of discharge.*

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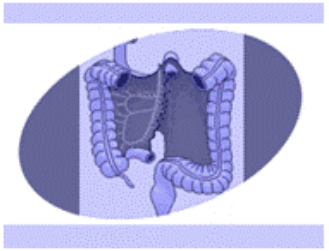
Fast-track surgery



Patients usually stay in hospital for 7-9 days after a bowel operation similar to that which you are going to have. With research and experience gained at Manukau Surgical Centre, we have learnt that if we, modify our management practices, we can reduce this period of hospital stay to 3 days, by optimising peri-operative care. This is the basis of Fast-track surgery.

We have designed a patient care plan which will enhance your recovery in a way which will help *you to feel well enough* to go home on the 3rd day after your operation.

Fast-track Surgery

This is an enhanced surgical care plan which leads to faster recovery and subsequent early discharge
Safety is the most important aspect of our management
Your co-operation and enthusiasm is the most essential part of this plan
We will provide more in formation at the time of discharge.

Summary

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This pamphlet will provide some information about what this plan involves

Chapter 9 : References

1. Heesen C, Nawrath L, Reich C, Bauer N, Schulz KH, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? J Neurol Neurosurg Psychiatry. 2006 Jan;77(1):34-9.

2. Papanicolaou DA, Amsterdam JD, Levine S, McCann SM, Moore RC, Newbrand CH, et al. Neuroendocrine aspects of chronic fatigue syndrome. Neuroimmunomodulation. 2004;11(2):65-74.

3. Smets EM, Garssen B, Schuster-Uitterhoeve AL, de Haes JC. Fatigue in cancer patients. Br J Cancer. 1993 Aug;68(2):220-4.

4. Lee BN, Dantzer R, Langley KE, Bennett GJ, Dougherty PM, Dunn AJ, et al. A cytokine-based neuroimmunologic mechanism of cancer-related symptoms. Neuroimmunomodulation. 2004;11(5):279-92.

5. Christensen T, Bendix T, Kehlet H. Fatigue and cardiorespiratory function following abdominal surgery. Br J Surg. 1982 Jul;69(7):417-9.

6. Schroeder D, Hill GL. Postoperative fatigue: a prospective physiological study of patients undergoing major abdominal surgery. Aust N Z J Surg. 1991 Oct;61(10):774-9.

7. Rubin GJ, Hardy R, Hotopf M. A systematic review and meta-analysis of the incidence and severity of postoperative fatigue. J Psychosom Res. 2004 Sep;57(3):317-26.

8. DeCherney AH, Bachmann G, Isaacson K, Gall S. Postoperative fatigue negatively impacts the daily lives of patients recovering from hysterectomy. Obstet Gynecol. 2002 Jan;99(1):51-7.

9. Bisgaard T, Klarskov B, Rosenberg J, Kehlet H. Factors determining convalescence after uncomplicated laparoscopic cholecystectomy. Arch Surg. 2001 Aug;136(8):917-21.

10. Aarons H, Forester A, Hall G, Salmon P. Fatigue after major joint arthroplasty: relationship to preoperative fatigue and postoperative emotional state. J Psychosom Res. 1996 Sep;41(3):225-33.

11. Wessely S, Powell R. Fatigue syndromes: a comparison of chronic "postviral" fatigue with neuromuscular and affective disorders. J Neurol Neurosurg Psychiatry. 1989 Aug;52(8):940-8.

12. Schwartz JE, Jandorf L, Krupp LB. The measurement of fatigue: a new instrument. J Psychosom Res. 1993 Oct;37(7):753-62.

13. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. J Psychosom Res. 2004 Feb;56(2):157-70.

14. Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol. 1988 Apr;45(4):435-7.

15. Monk TH. A Visual Analogue Scale technique to measure global vigor and affect. Psychiatry Res. 1989 Jan;27(1):89-99.

16. Pearson PG, byars G. The developement and validation of a checklist measuring subjective fatigue (report No. 56-115). Texas: school of aviation USAF, Randolf AFB1956.

17. Mendoza TR, Wang XS, Cleeland CS, Morrissey M, Johnson BA, Wendt JK, et al. The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory. Cancer. 1999 Mar 1;85(5):1186-96.

18. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol. 1989 Oct;46(10):1121-3.

19. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993 Mar 3;85(5):365-76.

20. Fawzy FI, Cousins N, Fawzy NW, Kemeny ME, Elashoff R, Morton D. A structured psychiatric intervention for cancer patients. I. Changes over time in methods of coping and affective disturbance. Arch Gen Psychiatry. 1990 Aug;47(8):720-5.

21. Piper BF LA, Dodd M J, Ferketich S, Paul SM, Weller S. . The development of an instrument to measure the subjective dimension of fatigue. Funk SG TE, Campagene MT, Archer Gopp Lm, Wiese RA, editor. New York: Springer Publishing Company; 1989.

22. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995 Apr;39(3):315-25.

23. Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res. 1993;37(2):147-53.

24. Paddison JS, Booth RJ, Hill AG, Cameron LD. Comprehensive assessment of peri-operative fatigue: development of the Identity-Consequence Fatigue Scale. J Psychosom Res. 2006 Jun;60(6):615-22.

25. Schroeder D, Hill GL. Predicting postoperative fatigue: importance of preoperative factors. World J Surg. 1993 Mar-Apr;17(2):226-31.

26. Matsushita T, Murata H, Matsushima E, Sakata Y, Miyasaka N, Aso T. Emotional state and coping style among gynecologic patients undergoing surgery. Psychiatry and clinical neurosciences. 2007 Feb;61(1):84-93.

27. Christensen T, Nygaard E, Stage JG, Kehlet H. Skeletal muscle enzyme activities and metabolic substrates during exercise in patients with postoperative fatigue. Br J Surg. 1990 Mar;77(3):312-5.

28. Christensen T, Stage JG, Galbo H, Christensen NJ, Kehlet H. Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. Surgery. 1989 Jan;105(1):46-50.

29. Zeiderman MR, Welchew EA, Clark RG. Changes in cardiorespiratory and muscle function associated with the development of postoperative fatigue. Br J Surg. 1990 May;77(5):576-80.

30. Christensen T, Kehlet H. Postoperative fatigue and changes in nutritional status. Br J Surg. 1984 Jun;71(6):473-6.

31. Christensen T, Hougard F, Kehlet H. Influence of pre- and intra- operative factors on the occurrence of postoperative fatigue. Br J Surg. 1985 Jan;72(1):63-5.

32. Christensen T, Wulff C, Fuglsang-Frederiksen A, Kehlet H. Electrical activity and arm muscle force in postoperative fatigue. Acta Chir Scand. 1985;151(1):1-5.

33. Brough W, Horne G, Blount A, Irving MH, Jeejeebhoy KN. Effects of nutrient intake, surgery, sepsis, and long term administration of steroids on muscle function. Br Med J (Clin Res Ed). 1986 Oct 18;293(6553):983-8.

34. Newham DJ, Harrison RA, Clark CG. Skeletal muscle function after major abdominal surgery. Hum Nutr Clin Nutr. 1987 Sep;41(5):363-71.

35. Maxwell A. Muscle power after surgery. Lancet. 1980 Feb 23;1(8165):420-1.

36. Edwards H, Rose EA, King TC. Postoperative deterioration in muscular function. Arch Surg. 1982 Jul;117(7):899-901.

37. Christensen T, Nygaard E, Kehlet H. Skeletal muscle fiber composition, nutritional status and subjective fatigue during surgical convalescence. Acta Chir Scand. 1988 May-Jun;154(5-6):335-8.

38. Klausen K, Andersen LB, Pelle I. Adaptive changes in work capacity, skeletal muscle capillarization and enzyme levels during training and detraining. Acta Physiol Scand. 1981 Sep;113(1):9-16.

39. Petersson B, Wernerman J, Waller SO, von der Decken A, Vinnars E. Elective abdominal surgery depresses muscle protein synthesis and increases subjective fatigue: effects lasting more than 30 days. Br J Surg. 1990 Jul;77(7):796-800.

40. Essen P, Wernerman J, Sonnenfeld T, Thunell S, Vinnars E. Free amino acids in plasma and muscle during 24 hours post-operatively--a descriptive study. Clin Physiol. 1992 Mar;12(2):163-77.

41. Hall GM, Salmon P. Physiological and psychological influences on postoperative fatigue. Anesth Analg. 2002 Nov;95(5):1446-50, table of contents.

42. Cordova A. Variations of serum magnesium and zinc after surgery, and postoperative fatigue. Magnes Res. 1995 Dec;8(4):367-72.

43. Rubin GJ, Cleare A, Hotopf M. Psychological factors in postoperative fatigue. Psychosom Med. 2004 Nov-Dec;66(6):959-64.

44. Christensen T, Hjortso NC, Mortensen E, Riis-Hansen M, Kehlet H. Fatigue and anxiety in surgical patients. Acta Psychiatr Scand. 1986 Jan;73(1):76-9.

45. Ai AL, Peterson C, Tice TN, Rodgers W, Seymour EM, Bolling SF. Differential effects of faith-based coping on physical and mental fatigue in middle-aged and older cardiac patients. International journal of psychiatry in medicine. 2006;36(3):351-65.

46. Carli F, Ramachandra V, Gandy J, Merritt H, Ford GC, Read M, et al. Effect of general anaesthesia on whole body protein turnover in patients undergoing elective surgery. Br J Anaesth. 1990 Sep;65(3):373-9.

47. Carlson KJ, Miller BA, Fowler FJ, Jr. The Maine Women's Health Study: I. Outcomes of hysterectomy. Obstet Gynecol. 1994 Apr;83(4):556-65.

48. Gould D, Wilson-Barnett J. A comparison of recovery following hysterectomy and major cardiac surgery. J Adv Nurs. 1985 Jul;10(4):315-23.

49. Richards DH. A post-hysterectomy syndrome. Lancet. 1974 Oct 26;2(7887):983-5.

50. Hall GM, Peerbhoy D, Shenkin A, Parker CJ, Salmon P. Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. Br J Anaesth. 2001 Oct;87(4):537-42.

51. Schulze S, Roikjaer O, Hasselstrom L, Jensen NH, Kehlet H. Epidural bupivacaine and morphine plus systemic indomethacin eliminates pain but not systemic response and convalescence after cholecystectomy. Surgery. 1988 Mar;103(3):321-7.

52. Hill AG, Finn P, Schroeder D. Postoperative fatigue after laparoscopic surgery. Aust N Z J Surg. 1993 Dec;63(12):946-51.

53. Hoover HC, Jr., Ryan JA, Anderson EJ, Fischer JE. Nutritional benefits of immediate postoperative jejunal feeding of an elemental diet. Am J Surg. 1980 Jan;139(1):153-9.

54. Hessov I, Wara P. [Energy and protein consumption in patients with intestinal resections during hospitalization]. Ugeskr Laeger. 1978 Jun 19;140(25):1469-73.

55. Hackett AF, Yeung CK, Hill GL. Eating patterns in patients recovering from major surgery--a study of voluntary food intake and energy balance. Br J Surg. 1979 Jun;66(6):415-8.

56. Hessov I. Oral feeding after uncomplicated abdominal surgery. Br J Clin Pract Suppl. 1988 Dec;63:75-9.

57. Guess CW, Werth R, Pollard M, Wood CD. An assessment of nutritional depletion following major colonic surgery. Dis Colon Rectum. 1984 Oct;27(10):669-71.

58. Christensen T, Kehlet H, Vesterberg K, Vinnars E. Fatigue and muscle amino acids during surgical convalescence. Acta Chir Scand. 1987 Oct;153(10):567-70.

59. Rubin GJ, Hotopf M. Systematic review and meta-analysis of interventions for postoperative fatigue. Br J Surg. 2002 Aug;89(8):971-84.

60. Kissmeyer-Nielsen P, Jensen MB, Laurberg S. Perioperative growth hormone treatment and functional outcome after major abdominal surgery: a randomized, double-blind, controlled study. Ann Surg. 1999 Feb;229(2):298-302.

61. Baker CA. Recovery: a phenomenon extending beyond discharge. Sch Inq Nurs Pract. 1989 Fall;3(3):181-94; discussion 95-7.

62. Houborg KB, Jensen MB, Rasmussen P, Gandrup P, Schroll M, Laurberg S. Postoperative physical training following colorectal surgery: a randomised, placebo-controlled study. Scand J Surg. 2006;95(1):17-22.

63. Christensen T, Kehlet H. Postoperative fatigue. World J Surg. 1993 Mar-Apr;17(2):220-5.

64. Salmon P. Nutrition, cognitive performance, and mental fatigue. Nutrition. 1994 Sep-Oct;10(5):427-8.

65. Kirsch I. Changing expectations: A key to effective psychotherapy. . Brooks/Cole, editor: Pacific Grove; 1990.

66. Salmon P, Hall GM. A theory of postoperative fatigue: an interaction of biological, psychological, and social processes. Pharmacol Biochem Behav. 1997 Apr;56(4):623-8.

67. Webb C. Professional and lay social support for hysterectomy patients. J Adv Nurs. 1986 Mar;11(2):167-77.

68. Borstlap M, Zant JL, van Soesbergen RM, van der Korst JK. Quality of life assessment: a comparison of four questionnaires: for measuring improvements after total hip replacement. Clin Rheumatol. 1995 Jan;14(1):15-20.

69. Yamamoto T, Castell LM, Botella J, Powell H, Hall GM, Young A, et al. Changes in the albumin binding of tryptophan during postoperative recovery: a possible link with central fatigue? Brain Res Bull. 1997;43(1):43-6.

70. McGuire J, Ross GL, Price H, Mortensen N, Evans J, Castell LM. Biochemical markers for post-operative fatigue after major surgery. Brain Res Bull. 2003 Apr 15;60(1-2):125-30.

71. Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbances: mechanisms and clinical implications. Br J Anaesth. 1996 Apr;76(4):552-9.

72. Konsman JP, Parnet P, Dantzer R. Cytokine-induced sickness behaviour: mechanisms and implications. Trends Neurosci. 2002 Mar;25(3):154-9.

73. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. J Clin Endocrinol Metab. 2000 Mar;85(3):1151-8.

74. Cohen O, Reichenberg A, Perry C, Ginzberg D, Pollmacher T, Soreq H, et al. Endotoxin-induced changes in human working and declarative memory associate with cleavage of plasma "readthrough" acetylcholinesterase. J Mol Neurosci. 2003;21(3):199-212.

75. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry. 2001 May;58(5):445-52.

76. Krabbe KS, Reichenberg A, Yirmiya R, Smed A, Pedersen BK, Bruunsgaard H. Low-dose endotoxemia and human neuropsychological functions. Brain Behav Immun. 2005 Sep;19(5):453-60.

77. Wright CE, Strike PC, Brydon L, Steptoe A. Acute inflammation and negative mood: mediation by cytokine activation. Brain Behav Immun. 2005 Jul;19(4):345-50.

78. Vollmer-Conna U, Fazou C, Cameron B, Li H, Brennan C, Luck L, et al. Production of pro-inflammatory cytokines correlates with the symptoms of acute sickness behaviour in humans. Psychological medicine. 2004 Oct;34(7):1289-97.

79. Dantzer R, Konsman JP, Bluthe RM, Kelley KW. Neural and humoral pathways of communication from the immune system to the brain: parallel or convergent? Auton Neurosci. 2000 Dec 20;85(1-3):60-5.

80. Maier SF, Goehler LE, Fleshner M, Watkins LR. The role of the vagus nerve in cytokine-to-brain communication. Ann N Y Acad Sci. 1998 May 1;840:289-300.

81. Ek M, Kurosawa M, Lundeberg T, Ericsson A. Activation of vagal afferents after intravenous injection of interleukin-1beta: role of endogenous prostaglandins. J Neurosci. 1998 Nov 15;18(22):9471-9.

82. Goehler LE, Gaykema RP, Hansen MK, Anderson K, Maier SF, Watkins LR. Vagal immune-to-brain communication: a visceral chemosensory pathway. Auton Neurosci. 2000 Dec 20;85(1-3):49-59.

83. Wan W, Wetmore L, Sorensen CM, Greenberg AH, Nance DM. Neural and biochemical mediators of endotoxin and stress-induced c-fos expression in the rat brain. Brain Res Bull. 1994;34(1):7-14.

84. Ericsson A, Kovacs KJ, Sawchenko PE. A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. J Neurosci. 1994 Feb;14(2):897-913.

85. Butler PD, Edwards E, Barkai AI. Imipramine and tetrabenazine: effects on monoamine receptor binding sites and phosphoinositide hydrolysis. Eur J Pharmacol. 1989 Jan 24;160(1):93-100.

86. Schulze S, Sommer P, Bigler D, Honnens M, Shenkin A, Cruickshank AM, et al. Effect of combined prednisolone, epidural analgesia, and indomethacin on the systemic response after colonic surgery. Arch Surg. 1992 Mar;127(3):325-31.

87. Badia JM, Whawell SA, Scott-Coombes DM, Abel PD, Williamson RC, Thompson JN. Peritoneal and systemic cytokine response to laparotomy. Br J Surg. 1996 Mar;83(3):347-8.

88. Kristiansson M, Soop M, Sundqvist KG, Soop A, Suontaka AM, Blomback M. Local vs. systemic immune and haemostatic response to hip arthroplasty. Eur J Anaesthesiol. 1998 May;15(3):260-70.

89. Zeiderman MR, Welchew EA, Clark RG. Influence of epidural analgesia upon postoperative fatigue. Br J Surg. 1991 Dec;78(12):1457-60.

90. Pick B, Molloy A, Hinds C, Pearce S, Salmon P. Post-operative fatigue following coronary artery bypass surgery: relationship to emotional state and to the catecholamine response to surgery. J Psychosom Res. 1994 Aug;38(6):599-607.

91. Deisch P, Soukup SM, Adams P, Wild MC. Guided imagery: replication study using coronary artery bypass graft patients. Nurs Clin North Am. 2000 Jun;35(2):417-25.

92. Ashton RC, Jr., Whitworth GC, Seldomridge JA, Shapiro PA, Michler RE, Smith CR, et al. The effects of self-hypnosis on quality of life following coronary artery bypass surgery: preliminary results of a prospective, randomized trial. J Altern Complement Med. 1995 Fall;1(3):285-90.

93. Leserman J, Stuart EM, Mamish ME, Benson H. The efficacy of the relaxation response in preparing for cardiac surgery. Behav Med. 1989 Fall;15(3):111-7.

94. Peerbhoy D, Keane P, Maciver K, Shenkin A, Hall GM, Salmon P. The systematic assessment of short-term functional recovery after major joint arthroplasty. J Qual Clin Pract. 1999 Sep;19(3):165-71.

95. Ridgeway V, Mathews A. Psychological preparation for surgery: a comparison of methods. Br J Clin Psychol. 1982 Nov;21 (Pt 4):271-80.

96. Wallace LM. Pre-operative state anxiety as a mediator of psychological adjustment to and recovery from surgery. Br J Med Psychol. 1986 Sep;59 (Pt 3):253-61.

97. Cupples SA. Effects of timing and reinforcement of preoperative education on knowledge and recovery of patients having coronary artery bypass graft surgery. Heart Lung. 1991 Nov;20(6):654-60.

98. Moore SM, Dolansky MA. Randomized trial of a home recovery intervention following coronary artery bypass surgery. Res Nurs Health. 2001 Apr;24(2):93-104.

99. Jensen MB, Hessov I. Randomization to nutritional intervention at home did not improve postoperative function, fatigue or well-being. Br J Surg. 1997 Jan;84(1):113-8.

100. Watters JM, Kirkpatrick SM, Norris SB, Shamji FM, Wells GA. Immediate postoperative enteral feeding results in impaired respiratory mechanics and decreased mobility. Ann Surg. 1997 Sep;226(3):369-77; discussion 77-80.

101. Schroeder D, Gillanders L, Mahr K, Hill GL. Effects of immediate postoperative enteral nutrition on body composition, muscle function, and wound healing. JPEN J Parenter Enteral Nutr. 1991 Jul-Aug;15(4):376-83.

102. Heikkinen TJ, Haukipuro K, Koivukangas P, Sorasto A, Autio R, Sodervik H, et al. Comparison of costs between laparoscopic and open Nissen fundoplication: a prospective randomized study with a 3-month followup. J Am Coll Surg. 1999 Apr;188(4):368-76.

103. Schwenk W, Bohm B, Muller JM. Postoperative pain and fatigue after laparoscopic or conventional colorectal resections. A prospective randomized trial. Surg Endosc. 1998 Sep;12(9):1131-6.

104. Heikkinen TJ, Haukipuro K, Hulkko A. A cost and outcome comparison between laparoscopic and Lichtenstein hernia operations in a day-case unit. A randomized prospective study. Surg Endosc. 1998 Oct;12(10):1199-203.

105. Stage JG, Schulze S, Moller P, Overgaard H, Andersen M, Rebsdorf-Pedersen VB, et al. Prospective randomized study of laparoscopic versus open colonic resection for adenocarcinoma. Br J Surg. 1997 Mar;84(3):391-6.

106. Nagelschmidt M, Fu ZX, Saad S, Dimmeler S, Neugebauer E. Preoperative high dose methylprednisolone improves patients outcome after abdominal surgery. Eur J Surg. 1999 Oct;165(10):971-8.

107. Schulze S, Andersen J, Overgaard H, Norgard P, Nielsen HJ, Aasen A, et al. Effect of prednisolone on the systemic response and wound healing after colonic surgery. Arch Surg. 1997 Feb;132(2):129-35.

108. Vara-Thorbeck R, Guerrero JA, Ruiz-Requena E, Garcia-Carriazo M. Can the use of growth hormone reduce the postoperative fatigue syndrome? World J Surg. 1996 Jan;20(1):81-6; discussion 6-7.

109. Barry MC, Mealy K, O'Neill S, Hughes A, McGee H, Sheehan SJ, et al. Nutritional, respiratory, and psychological effects of recombinant human growth hormone in patients undergoing abdominal aortic aneurysm repair. JPEN J Parenter Enteral Nutr. 1999 May-Jun;23(3):128-35.

110. Jakobsen DH, Sonne E, Andreasen J, Kehlet H. Convalescence after colonic surgery with fast-track vs conventional care. Colorectal Dis. 2006 Oct;8(8):683-7.

111. Hjort Jakobsen D, Sonne E, Basse L, Bisgaard T, Kehlet H. Convalescence after colonic resection with fast-track versus conventional care. Scand J Surg. 2004;93(1):24-8.

112. Basse L, Jakobsen DH, Bardram L, Billesbolle P, Lund C, Mogensen T, et al. Functional recovery after open versus laparoscopic colonic resection: a randomized, blinded study. Ann Surg. 2005 Mar;241(3):416-23.

113. Wind J, Polle SW, Fung Kon Jin PH, Dejong CH, von Meyenfeldt MF, Ubbink DT, et al. Systematic review of enhanced recovery programmes in colonic surgery. Br J Surg. 2006 Jul;93(7):800-9.

114. Basse L, Thorbol JE, Lossl K, Kehlet H. Colonic surgery with accelerated rehabilitation or conventional care. Dis Colon Rectum. 2004 Mar;47(3):271-7; discussion 7-8.

115. Anderson AD, McNaught CE, MacFie J, Tring I, Barker P, Mitchell CJ. Randomized clinical trial of multimodal optimization and standard perioperative surgical care. Br J Surg. 2003 Dec;90(12):1497-504.

116. Delaney CP, Zutshi M, Senagore AJ, Remzi FH, Hammel J, Fazio VW. Prospective, randomized, controlled trial between a pathway of controlled rehabilitation with early ambulation and diet and traditional postoperative care after laparotomy and intestinal resection. Dis Colon Rectum. 2003 Jul;46(7):851-9.

117. Gatt M, Anderson AD, Reddy BS, Hayward-Sampson P, Tring IC, MacFie J. Randomized clinical trial of multimodal optimization of surgical care in patients undergoing major colonic resection. Br J Surg. 2005 Nov;92(11):1354-62.

118. Raue W, Haase O, Junghans T, Scharfenberg M, Muller JM, Schwenk W. 'Fast-track' multimodal rehabilitation program improves outcome after laparoscopic sigmoidectomy: a controlled prospective evaluation. Surg Endosc. 2004 Oct;18(10):1463-8.

119. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005 Jun;24(3):466-77.

120. Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. Br J Anaesth. 1997 May;78(5):606-17.

121. Hathaway D. Effect of preoperative instruction on postoperative outcomes: a meta-analysis. Nurs Res. 1986 Sep-Oct;35(5):269-75.

122. Egbert LD, Battit GE, Welch CE, Bartlett MK. Reduction of Postoperative Pain by Encouragement and Instruction of Patients. a Study of Doctor-Patient Rapport. N Engl J Med. 1964 Apr 16;270:825-7.

123. Disbrow EA, Bennett HL, Owings JT. Effect of preoperative suggestion on postoperative gastrointestinal motility. West J Med. 1993 May;158(5):488-92.

124. Pager CK. Randomised controlled trial of preoperative information to improve satisfaction with cataract surgery. Br J Ophthalmol. 2005 Jan;89(1):10-3.

125. Walch JM, Rabin BS, Day R, Williams JN, Choi K, Kang JD. The effect of sunlight on postoperative analgesic medication use: a prospective study of patients undergoing spinal surgery. Psychosom Med. 2005 Jan-Feb;67(1):156-63.

126. Playforth MJ, Smith GM, Evans M, Pollock AV. Pre-operative assessment of fitness score. Br J Surg. 1987 Oct;74(10):890-2.

127. Cook JW, Pierson LM, Herbert WG, Norton HJ, Fedor JM, Kiebzak GM, et al. The influence of patient strength, aerobic capacity and body composition upon outcomes after coronary artery bypass grafting. Thorac Cardiovasc Surg. 2001 Apr;49(2):89-93.

128. Fortin PR, Clarke AE, Joseph L, Liang MH, Tanzer M, Ferland D, et al. Outcomes of total hip and knee replacement: preoperative functional status predicts outcomes at six months after surgery. Arthritis Rheum. 1999 Aug;42(8):1722-8.

129. Carli F, Zavorsky GS. Optimizing functional exercise capacity in the elderly surgical population. Curr Opin Clin Nutr Metab Care. 2005 Jan;8(1):23-32.

130. Tonnesen H, Rosenberg J, Nielsen HJ, Rasmussen V, Hauge C, Pedersen IK, et al. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. BMJ. 1999 May 15;318(7194):1311-6.

131. Tonnesen H, Kehlet H. Preoperative alcoholism and postoperative morbidity. Br J Surg. 1999 Jul;86(7):869-74.

132. Sorensen LT, Karlsmark T, Gottrup F. Abstinence from smoking reduces incisional wound infection: a randomized controlled trial. Ann Surg. 2003 Jul;238(1):1-5.

133. Bluman LG, Mosca L, Newman N, Simon DG. Preoperative smoking habits and postoperative pulmonary complications. Chest. 1998 Apr;113(4):883-9.

134. Geerling BJ, Badart-Smook A, Stockbrugger RW, Brummer RJ. Comprehensive nutritional status in patients with long-standing Crohn disease currently in remission. Am J Clin Nutr. 1998 May;67(5):919-26.

135. Payette H, Gray-Donald K. Dietary intake and biochemical indices of nutritional status in an elderly population, with estimates of the precision of the 7-d food record. Am J Clin Nutr. 1991 Sep;54(3):478-88.

136. Kehlet H, Wilmore DW. Multimodal strategies to improve surgical outcome. Am J Surg. 2002 Jun;183(6):630-41.

137. Perioperative total parenteral nutrition in surgical patients. The Veterans Affairs Total Parenteral Nutrition Cooperative Study Group. N Engl J Med. 1991 Aug 22;325(8):525-32.

138. Gianotti L, Braga M, Nespoli L, Radaelli G, Beneduce A, Di Carlo V. A randomized controlled trial of preoperative oral supplementation with a specialized diet in patients with gastrointestinal cancer. Gastroenterology. 2002 Jun;122(7):1763-70.

139. Braga M, Gianotti L, Nespoli L, Radaelli G, Di Carlo V. Nutritional approach in malnourished surgical patients: a prospective randomized study. Arch Surg. 2002 Feb;137(2):174-80.

140. Waitzberg DL, Saito H, Plank LD, Jamieson GG, Jagannath P, Hwang TL, et al. Postsurgical infections are reduced with specialized nutrition support. World J Surg. 2006 Aug;30(8):1592-604.

141. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr. 2006 Apr;25(2):224-44.

142. Meijerink WJ, von Meyenfeldt MF, Rouflart MM, Soeters PB. Efficacy of perioperative nutritional support. Lancet. 1992 Jul 18;340(8812):187-8.

143. Thorell A, Alston-Smith J, Ljungqvist O. The effect of preoperative carbohydrate loading on hormonal changes, hepatic glycogen, and glucoregulatory enzymes during abdominal surgery. Nutrition. 1996 Oct;12(10):690-5.

144. Ljungqvist O, Nygren J, Soop M, Thorell A. Metabolic perioperative management: novel concepts. Curr Opin Crit Care. 2005 Aug;11(4):295-9.

145. Soreide E, Eriksson LI, Hirlekar G, Eriksson H, Henneberg SW, Sandin R, et al. Pre-operative fasting guidelines: an update. Acta Anaesthesiol Scand. 2005 Sep;49(8):1041-7.

146. Nygren J, Thorell A, Jacobsson H, Larsson S, Schnell PO, Hylen L, et al. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. Ann Surg. 1995 Dec;222(6):728-34.

147. Ljungqvist O, Soreide E. Preoperative fasting. Br J Surg. 2003 Apr;90(4):400-6.

148. Nygren J, Thorell A, Ljungqvist O. Preoperative oral carbohydrate nutrition: an update. Curr Opin Clin Nutr Metab Care. 2001 Jul;4(4):255-9.

149. Yuill KA, Richardson RA, Davidson HI, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively--a randomised clinical trial. Clin Nutr. 2005 Feb;24(1):32-7.

150. Hausel J, Nygren J, Lagerkranser M, Hellstrom PM, Hammarqvist F, Almstrom C, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001 Nov;93(5):1344-50.

151. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorectal Dis. 2006 Sep;8(7):563-9.

152. Goligher JT. Treatment of carcinoma of the colon. 5th ed ed. London: Bailliere Tindal; 1984.

153. Kehlet H, Buchler MW, Beart RW, Jr., Billingham RP, Williamson R. Care after colonic operation--is it evidence-based? Results from a multinational survey in Europe and the United States. J Am Coll Surg. 2006 Jan;202(1):45-54.

154. Zmora O, Pikarsky AJ, Wexner SD. Bowel preparation for colorectal surgery. Dis Colon Rectum. 2001 Oct;44(10):1537-49.

155. Beloosesky Y, Grinblat J, Weiss A, Grosman B, Gafter U, Chagnac A. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. Archives of internal medicine. 2003 Apr 14;163(7):803-8.

156. Platell C, Barwood N, Makin G. Randomized clinical trial of bowel preparation with a single phosphate enema or polyethylene glycol before elective colorectal surgery. Br J Surg. 2006 Apr;93(4):427-33.

157. Song F, Glenny AM. Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomized controlled trials. Br J Surg. 1998 Sep;85(9):1232-41.

158. Bucher P, Mermillod B, Gervaz P, Morel P. Mechanical bowel preparation for elective colorectal surgery: a meta-analysis. Arch Surg. 2004 Dec;139(12):1359-64; discussion 65.

159. Wille-Jorgensen P, Guenaga KF, Castro AA, Matos D. Clinical value of preoperative mechanical bowel cleansing in elective colorectal surgery: a systematic review. Dis Colon Rectum. 2003 Aug;46(8):1013-20.

160. Slim K, Vicaut E, Launay-Savary MV, Contant C, Chipponi J. Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg. 2009 Feb;249(2):203-9.

161. Guenaga KF, Matos D, Castro AA, Atallah AN, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2005(1):CD001544.

162. Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg. 2004 Sep;91(9):1125-30.

163. Fa-Si-Oen P, Roumen R, Buitenweg J, van de Velde C, van Geldere D, Putter H, et al. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. Dis Colon Rectum. 2005 Aug;48(8):1509-16.

164. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2009(1):CD001544.

165. Freedman DM, Dosemeci M, McGlynn K. Sunlight and mortality from breast, ovarian, colon, prostate, and non-melanoma skin cancer: a composite death certificate based case-control study. Occup Environ Med. 2002 Apr;59(4):257-62.

166. Beauchemin KM, Hays P. Dying in the dark: sunshine, gender and outcomes in myocardial infarction. J R Soc Med. 1998 Jul;91(7):352-4.

167. Pattison HM, Robertson CE. The effect of ward design on the well-being of post-operative patients. J Adv Nurs. 1996 Apr;23(4):820-6.

168. Douglas CH, Douglas MR. Patient-friendly hospital environments: exploring the patients' perspective. Health Expect. 2004 Mar;7(1):61-73.

169. Vather R, Zargar-Shoshtari K, Metcalf P, Hill AG. The influence of hospital environment on postoperative length of stay following major colorectal surgery. N Z Med J. 2007;120(1266):U2828.

170. Williams AM, Irurita VF. Enhancing the therapeutic potential of hospital environments by increasing the personal control and emotional comfort of hospitalized patients. Appl Nurs Res. 2005 Feb;18(1):22-8.

171. Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, et al. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. Br J Surg. 2007 Jan 4;94(2):224-31.

172. Nelson RL, Glenny AM, Song F. Antimicrobial prophylaxis for colorectal surgery. Cochrane Database Syst Rev. 2009(1):CD001181.

173. Greif R, Akca O, Horn EP, Kurz A, Sessler DI. Supplemental perioperative oxygen to reduce the incidence of surgical-wound infection. Outcomes Research Group. N Engl J Med. 2000 Jan 20;342(3):161-7.

174. Belda FJ, Aguilera L, Garcia de la Asuncion J, Alberti J, Vicente R, Ferrandiz L, et al. Supplemental perioperative oxygen and the risk of surgical wound infection: a randomized controlled trial. JAMA. 2005 Oct 26;294(16):2035-42.

175. Garcia-Botello SA, Garcia-Granero E, Lillo R, Lopez-Mozos F, Millan M, Lledo S. Randomized clinical trial to evaluate the effects of perioperative supplemental oxygen administration on the colorectal anastomosis. Br J Surg. 2006 Jun;93(6):698-706.

176. Goll V, Akca O, Greif R, Freitag H, Arkilic CF, Scheck T, et al. Ondansetron is no more effective than supplemental intraoperative oxygen for prevention of postoperative nausea and vomiting. Anesth Analg. 2001 Jan;92(1):112-7.

177. Greif R, Laciny S, Rapf B, Hickle RS, Sessler DI. Supplemental oxygen reduces the incidence of postoperative nausea and vomiting. Anesthesiology. 1999 Nov;91(5):1246-52.

178. Kabon B, Kurz A. Optimal perioperative oxygen administration. Curr Opin Anaesthesiol. 2006 Feb;19(1):11-8.

179. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA, Jr., Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003 Nov 12;290(18):2455-63.

180. Rodgers A, Walker N, Schug S, McKee A, Kehlet H, van Zundert A, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ. 2000 Dec 16;321(7275):1493-505.

181. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database Syst Rev. 2000(4):CD001893.

182. Ballantyne JC, Carr DB, deFerranti S, Suarez T, Lau J, Chalmers TC, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg. 1998 Mar;86(3):598-612.

183. Sprung J, Bourke DL, Grass J, Hammel J, Mascha E, Thomas P, et al. Predicting the difficult neuraxial block: a prospective study. Anesth Analg. 1999 Aug;89(2):384-9.

184. Tanaka K, Watanabe R, Harada T, Dan K. Extensive application of epidural anesthesia and analgesia in a university hospital: incidence of complications related to technique. Reg Anesth. 1993 Jan-Feb;18(1):34-8.

185. Saada M, Catoire P, Bonnet F, Delaunay L, Gormezano G, Macquin-Mavier I, et al. Effect of thoracic epidural anesthesia combined with general anesthesia on segmental wall motion assessed by transesophageal echocardiography. Anesth Analg. 1992 Sep;75(3):329-35.

186. Saada M, Duval AM, Bonnet F, Rey B, Castillon G, Macquin-Mavier I, et al. Abnormalities in myocardial segmental wall motion during lumbar epidural anesthesia. Anesthesiology. 1989 Jul;71(1):26-32.

187. Brodner G, Van Aken H, Hertle L, Fobker M, Von Eckardstein A, Goeters C, et al. Multimodal perioperative management--combining thoracic epidural analgesia, forced mobilization, and oral nutrition--reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. Anesth Analg. 2001 Jun;92(6):1594-600.

188. Kehlet H. Modification of responses to surgery by neural blockade: clinical implications. Cousins M, Bridenbough P, editors. Philadelphia: Lippincott-Raven; 1998.

189. Kehlet H. Manipulation of the metabolic response in clinical practice. World J Surg. 2000 Jun;24(6):690-5.

190. Steinbrook RA. Epidural anesthesia and gastrointestinal motility. Anesth Analg. 1998 Apr;86(4):837-44.

191. Lewis SJ, Egger M, Sylvester PA, Thomas S. Early enteral feeding versus "nil by mouth" after gastrointestinal surgery: systematic review and meta-analysis of controlled trials. BMJ. 2001 Oct 6;323(7316):773-6.

192. Hogan QH, Stekiel TA, Stadnicka A, Bosnjak ZJ, Kampine JP. Region of epidural blockade determines sympathetic and mesenteric capacitance effects in rabbits. Anesthesiology. 1995 Sep;83(3):604-10.

193. Sielenkamper AW, Eicker K, Van Aken H. Thoracic epidural anesthesia increases mucosal perfusion in ileum of rats. Anesthesiology. 2000 Sep;93(3):844-51.

194. Adolphs J, Schmidt DK, Mousa SA, Kamin B, Korsukewitz I, Habazettl H, et al. Thoracic epidural anesthesia attenuates hemorrhage-induced impairment of intestinal perfusion in rats. Anesthesiology. 2003 Sep;99(3):685-92.

195. Zugel N, Bruer C, Breitschaft K, Angster R. [Effect of thoracic epidural analgesia on the early postoperative phase after interventions on the gastrointestinal tract]. Chirurg. 2002 Mar;73(3):262-8.

196. Carli F, Mayo N, Klubien K, Schricker T, Trudel J, Belliveau P. Epidural analgesia enhances functional exercise capacity and health-related quality of life after colonic surgery: results of a randomized trial. Anesthesiology. 2002 Sep;97(3):540-9.

197. Zutshi M, Delaney CP, Senagore AJ, Mekhail N, Lewis B, Connor JT, et al. Randomized controlled trial comparing the controlled rehabilitation with early ambulation and diet pathway versus the controlled rehabilitation with early ambulation and diet with preemptive epidural anesthesia/analgesia after laparotomy and intestinal resection. Am J Surg. 2005 Mar;189(3):268-72.

198. Werawatganon T, Charuluxanun S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. Cochrane Database of Systematic Reviews. 2006.

199. Holte K, Foss NB, Svensen C, Lund C, Madsen JL, Kehlet H. Epidural anesthesia, hypotension, and changes in intravascular volume. Anesthesiology. 2004 Feb;100(2):281-6.

200. Grantcharov TP, Rosenberg J. Vertical compared with transverse incisions in abdominal surgery. Eur J Surg. 2001 Apr;167(4):260-7.

201. Brown SR, Goodfellow PB. Transverse verses midline incisions for abdominal surgery. Cochrane Database Syst Rev. 2005(4):CD005199.

202. Lindgren PG, Nordgren SR, Oresland T, Hulten L. Midline or transverse abdominal incision for right-sided colon cancer-a randomized trial. Colorectal Dis. 2001 Jan;3(1):46-50.

203. Donati D, Brown SR, Eu KW, Ho YH, Seow-Choen F. Comparison between midline incision and limited right skin crease incision for right-sided colonic cancers. Tech Coloproctol. 2002 Apr;6(1):1-4.

204. Kam MH, Seow-Choen F, Peng XH, Eu KW, Tang CL, Heah SM, et al. Minilaparotomy left iliac fossa skin crease incision vs. midline incision for left-sided colorectal cancer. Tech Coloproctol. 2004 Aug;8(2):85-8.

205. Brown SR, Goodfellow PJ, Adam IJ, Shorthouse AJ. A randomised controlled trial of transverse skin crease vs. vertical midline incision for right hemicolectomy. Tech Coloproctol. 2004 Mar;8(1):15-8.

206. Kehlet H. Surgical stress response: does endoscopic surgery confer an advantage? World J Surg. 1999 Aug;23(8):801-7.

207. Schwenk W, Haase O, Neudecker J, Muller JM. Short term benefits for laparoscopic colorectal resection. Cochrane Database Syst Rev. 2005(3):CD003145.

208. King PM, Blazeby JM, Ewings P, Franks PJ, Longman RJ, Kendrick AH, et al. Randomized clinical trial comparing laparoscopic and open surgery for colorectal cancer within an enhanced recovery programme. Br J Surg. 2006 Mar;93(3):300-8.

209. Wind J, Hofland J, Preckel B, Hollmann MW, Bossuyt PM, Gouma DJ, et al. Perioperative strategy in colonic surgery; LAparoscopy and/or FAst track multimodal management versus standard care (LAFA trial). BMC Surg. 2006;6:16.

210. Petrowsky H, Demartines N, Rousson V, Clavien PA. Evidence-based value of prophylactic drainage in gastrointestinal surgery: a systematic review and meta-analyses. Ann Surg. 2004 Dec;240(6):1074-84; discussion 84-5.

211. Sagar PM, Hartley MN, Macfie J, Mancey-Jones B, Sedman P, May J. Randomized trial of pelvic drainage after rectal resection. Dis Colon Rectum. 1995 Mar;38(3):254-8.

212. Sagar PM, Couse N, Kerin M, May J, MacFie J. Randomized trial of drainage of colorectal anastomosis. Br J Surg. 1993 Jun;80(6):769-71.

213. Karliczek A, Jesus EC, Matos D, Castro AA, Atallah AN, Wiggers T. Drainage or nondrainage in elective colorectal anastomosis: a systematic review and meta-analysis. Colorectal Dis. 2006 May;8(4):259-65.

214. Jesus EC, Karliczek A, Matos D, Castro AA, Atallah AN. Prophylactic anastomotic drainage for colorectal surgery. Cochrane Database Syst Rev. 2004(4):CD002100.

215. Nelson R, Tse B, Edwards S. Systematic review of prophylactic nasogastric decompression after abdominal operations. Br J Surg. 2005 Jun;92(6):673-80.

216. Nelson R, Edwards S, Tse B. Prophylactic nasogastric decompression after abdominal surgery. Cochrane Database Syst Rev. 2005(1):CD004929.

217. Moore F. Metabolic care of the surgical patient. Philadelphia: WB Saunders; 1959.

218. Shires T, Williams J, Brown F. Acute change in extracellular fluids associated with major surgical procedures. Ann Surg. 1961 Nov;154:803-10.

219. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. Lancet. 2002 May 25;359(9320):1812-8.

220. Holte K, Sharrock NE, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. Br J Anaesth. 2002 Oct;89(4):622-32.

221. Arieff AI. Fatal postoperative pulmonary edema: pathogenesis and literature review. Chest. 1999 May;115(5):1371-7.

222. Ratner LE, Smith GW. Intraoperative fluid management. Surg Clin North Am. 1993 Apr;73(2):229-41.

223. Jonsson K, Jensen JA, Goodson WH, 3rd, Scheuenstuhl H, West J, Hopf HW, et al. Tissue oxygenation, anemia, and perfusion in relation to wound healing in surgical patients. Ann Surg. 1991 Nov;214(5):605-13.

224. Lang K, Boldt J, Suttner S, Haisch G. Colloids versus crystalloids and tissue oxygen tension in patients undergoing major abdominal surgery. Anesth Analg. 2001 Aug;93(2):405-9 , 3rd contents page.

225. Ruttmann TG, James MF, Aronson I. In vivo investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation. Br J Anaesth. 1998 May;80(5):612-6.

226. Boyd O, Bennett ED. Achieving the goal. Crit Care Med. 1999 Oct;27(10):2298-9.

227. Brandstrup B, Tonnesen H, Beier-Holgersen R, Hjortso E, Ording H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. Ann Surg. 2003 Nov;238(5):641-8.

228. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after intraabdominal surgery. Anesthesiology. 2005 Jul;103(1):25-32.

229. Bland R, Shoemaker WC, Shabot MM. Physiologic monitoring goals for the critically ill patient. Surg Gynecol Obstet. 1978 Dec;147(6):833-41.

230. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. BMJ. 1997 Oct 11;315(7113):909-12.

231. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. Arch Surg. 1995 Apr;130(4):423-9.

232. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. Anaesthesia. 2002 Sep;57(9):845-9.

233. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology. 2002 Oct;97(4):820-6.

234. Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR, et al. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. Br J Anaesth. 2005 Nov;95(5):634-42.

235. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg. 2006 Aug 3.

236. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. Br J Surg. 2009 Apr;96(4):331-41.

237. MacKay G, Fearon K, McConnachie A, Serpell MG, Molloy RG, O'Dwyer PJ. Randomized clinical trial of the effect of postoperative intravenous fluid restriction on recovery after elective colorectal surgery. Br J Surg. 2006 Dec;93(12):1469-74.

238. Carlisle JB, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. Cochrane Database Syst Rev. 2006;3:CD004125.

239. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, et al. Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg. 2003 Jul;97(1):62-71, table of contents.

240. Bisgaard T, Kehlet H. Early oral feeding after elective abdominal surgery--what are the issues? Nutrition. 2002 Nov-Dec;18(11-12):944-8.

241. Lopez-Hellin J, Baena-Fustegueras JA, Vidal M, Riera SS, Garcia-Arumi E. Perioperative nutrition prevents the early protein losses in patients submitted to gastrointestinal surgery. Clin Nutr. 2004 Oct;23(5):1001-8.

242. Moss G, Greenstein A, Levy S, Bierenbaum A. Maintenance of GI function after bowel surgery and immediate enteral full nutrition. I. Doubling of canine colorectal anastomotic bursting pressure and intestinal wound mature collagen content. JPEN J Parenter Enteral Nutr. 1980 Nov-Dec;4(6):535-8.

243. Beier-Holgersen R, Boesby S. Influence of postoperative enteral nutrition on postsurgical infections. Gut. 1996 Dec;39(96):833-5.

244. Keele AM, Bray MJ, Emery PW, Duncan HD, Silk DB. Two phase randomised controlled clinical trial of postoperative oral dietary supplements in surgical patients. Gut. 1997 Mar;40(3):393-9.

245. Carr CS, Ling KD, Boulos P, Singer M. Randomised trial of safety and efficacy of immediate postoperative enteral feeding in patients undergoing gastrointestinal resection. BMJ. 1996 Apr 6;312(7035):869-71.

246. Andersen HK, Lewis SJ, Thomas S. Early enteral nutrition within 24h of colorectal surgery versus later commencement of feeding for postoperative complications. Cochrane Database Syst Rev. 2006(4):CD004080.

247. Richmond CE, Bromley LM, Woolf CJ. Preoperative morphine pre-empts postoperative pain. Lancet. 1993 Jul 10;342(8863):73-5.

248. Collis R, Brandner B, Bromley LM, Woolf CJ. Is there any clinical advantage of increasing the pre-emptive dose of morphine or combining pre-incisional with postoperative morphine administration? Br J Anaesth. 1995 Apr;74(4):396-9.

249. Kehlet H, Rung GW, Callesen T. Postoperative opioid analgesia: time for a reconsideration? J Clin Anesth. 1996 Sep;8(6):441-5.

250. Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg. 1993 Nov;77(5):1048-56.

251. Rosenberg J, Wildschiodtz G, Pedersen MH, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxaemia and associated sleep pattern. Br J Anaesth. 1994 Feb;72(2):145-50.

252. Forrest WH, Jr., Bellville JW. The Effect of Sleep Plus Morphine on the Respiratory Response to Carbon Dioxide. Anesthesiology. 1964 Mar-Apr;25:137-41.

253. Colacchio TA, Yeager MP, Hildebrandt LW. Perioperative immunomodulation in cancer surgery. Am J Surg. 1994 Jan;167(1):174-9.

254. Dray A. Epidural opiates and urinary retention: new models provide new insights. Anesthesiology. 1988 Mar;68(3):323-4.

255. Petros JG, Alameddine F, Testa E, Rimm EB, Robillard RJ. Patient-controlled analgesia and postoperative urinary retention after hysterectomy for benign disease. J Am Coll Surg. 1994 Dec;179(6):663-7.

256. Tammela T, Kontturi M, Lukkarinen O. Postoperative urinary retention. II. Micturition problems after the first catheterization. Scand J Urol Nephrol. 1986;20(4):257-60.

257. Benoist S, Panis Y, Denet C, Mauvais F, Mariani P, Valleur P. Optimal duration of urinary drainage after rectal resection: a randomized controlled trial. Surgery. 1999 Feb;125(2):135-41.

258. Basse L, Werner M, Kehlet H. Is urinary drainage necessary during continuous epidural analgesia after colonic resection? Reg Anesth Pain Med. 2000 Sep-Oct;25(5):498-501.

259. Tammela T, Kontturi M, Lukkarinen O. Postoperative urinary retention. I. Incidence and predisposing factors. Scand J Urol Nephrol. 1986;20(3):197-201.

260. Givens CD, Wenzel RP. Catheter-associated urinary tract infections in surgical patients: a controlled study on the excess morbidity and costs. J Urol. 1980 Nov;124(5):646-8.

261. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. Clin Sci (Lond). 1998 Jun;94(6):557-72.

262. Sapolsky RM, Romero LM, Munck AU. How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocr Rev. 2000 Feb;21(1):55-89.

263. Wang JJ, Ho ST, Tzeng JI, Tang CS. The effect of timing of dexamethasone administration on its efficacy as a prophylactic antiemetic for postoperative nausea and vomiting. Anesth Analg. 2000 Jul;91(1):136-9.

264. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in postoperative recovery. Lancet. 2003 Dec 6;362(9399):1921-8.

265. Maessen J, Dejong CH, Hausel J, Nygren J, Lassen K, Andersen J, et al. A protocol is not enough to implement an enhanced recovery programme for colorectal resection. Br J Surg. 2007 Feb;94(2):224-31.

266. MacKay G, Ihedioha U, McConnachie A, Serpell M, Molloy RG, O'Dwyer PJ. Laparoscopic colonic resection in fast-track patients does not enhance short-term recovery after elective surgery. Colorectal Dis. 2007 May;9(4):368-72.

267. Senagore AJ, Delaney CP. A critical analysis of laparoscopic colectomy at a single institution: lessons learned after 1000 cases. Am J Surg. 2006 Mar;191(3):377-80.

268. Nygren J, Hausel J, Kehlet H, Revhaug A, Lassen K, Dejong C, et al. A comparison in five European Centres of case mix, clinical management and outcomes following either

conventional or fast-track perioperative care in colorectal surgery. Clin Nutr. 2005 Jun;24(3):455-61.

269. Tekkis PP, Prytherch DR, Kocher HM, Senapati A, Poloniecki JD, Stamatakis JD, et al. Development of a dedicated risk-adjustment scoring system for colorectal surgery (colorectal POSSUM). Br J Surg. 2004 Sep;91(9):1174-82.

270. Cali RL, Meade PG, Swanson MS, Freeman C. Effect of Morphine and incision length on bowel function after colectomy. Dis Colon Rectum. 2000 Feb;43(2):163-8.

271. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. Cochrane Database of Systematic Reviews. 2007;2.

272. Di Fronzo LA, Cymerman J, O'Connell TX. Factors affecting early postoperative feeding following elective open colon resection. Arch Surg. 1999 Sep;134(9):941-5; discussion 5-6.

273. Senagore AJ, Duepree HJ, Delaney CP, Dissanaike S, Brady KM, Fazio VW. Cost structure of laparoscopic and open sigmoid colectomy for diverticular disease: similarities and differences. Dis Colon Rectum. 2002 Apr;45(4):485-90.

274. Stephen AE, Berger DL. Shortened length of stay and hospital cost reduction with implementation of an accelerated clinical care pathway after elective colon resection. Surgery. 2003 Mar;133(3):277-82.

275. Delaney CP, Fazio VW, Senagore AJ, Robinson B, Halverson AL, Remzi FH. 'Fast track' postoperative management protocol for patients with high co-morbidity undergoing complex abdominal and pelvic colorectal surgery. Br J Surg. 2001 Nov;88(11):1533-8.

276. Marret E, Remy C, Bonnet F. Meta-analysis of epidural analgesia versus parenteral opioid analgesia after colorectal surgery. Br J Surg. 2007 Jun;94(6):665-73.

277. Andersen J, Hjort-Jakobsen D, Christiansen PS, Kehlet H. Readmission rates after a planned hospital stay of 2 versus 3 days in fast-track colonic surgery. Br J Surg. 2007 Jul;94(7):890-3.

278. Brasel K, McRitchie D, Dellinger P. Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 21: the risk of surgical site infection is reduced with perioperative oxygen. Can J Surg. 2007 Jun;50(3):214-6.

279. Hansen CT, Sorensen M, Moller C, Ottesen B, Kehlet H. Effect of laxatives on gastrointestinal functional recovery in fast-track hysterectomy: a double-blind, placebo-controlled randomized study. Am J Obstet Gynecol. 2007 Apr;196(4):311 e1-7.

280. Vather R, Zargar Shoshtari K, Hill AG. The influence of environment on recovery following elective colonic surgery. N Z Med J. 2007;120 (1266).

281. Paddison JS, Booth RJ, Fuchs D, Hill AG. Peritoneal inflammation and fatigue experiences following colorectal surgery: A pilot study. Psychoneuroendocrinology. 2008 May;33(4):446-54.

282. Paddison JS, Booth RJ, Hill AG, Cameron LD. Comprehensive assessment of post-surgical fatigue: development of the identity-consequence fatigue scale. Journal of Psychosomatic Research. 2005.

283. Iop A, Manfredi AM, Bonura S. Fatigue in cancer patients receiving chemotherapy: an analysis of published studies. Ann Oncol. 2004 May;15(5):712-20.

284. Salmon P, Hall G. A theory of postoperative fatigue: An interaction of biological, psychological, and social processes. Pharmacol Biochem Behav. 1997;56:623.

285. Zargar-Shoshtari K, Connolly AB, Israel LH, Hill AG. Fast-Track Surgery May Reduce Complications Following Major Colonic Surgery. Dis Colon Rectum. 2008 Jun 7.

286. Zargar-Shoshtari K, Hill AG. Optimization of perioperative care for colonic surgery: a review of the evidence. ANZ J Surg. 2008 Jan;78(1-2):13-23.

287. Zargar-Shoshtari K, Hill AG. Fast-track open colectomy is possible in a New Zealand public hospital. N Z Med J. 2008;121(1275):33-6.

288. Zargar-Shoshtari K, Paddison J, Booth R, Hill A. A prospective study on the influence of a fast-track programme on post operative fatigue and functional recovery after major colonic surgery The Journal of surgical research. 2008.

289. Wu FP, Sietses C, von Blomberg BM, van Leeuwen PA, Meijer S, Cuesta MA. Systemic and peritoneal inflammatory response after laparoscopic or conventional colon resection in cancer patients: a prospective, randomized trial. Dis Colon Rectum. 2003 Feb;46(2):147-55.

290. Zargar-Shoshtari K, Hill A. Post operative Fatigue - A Review. World J Surg. 2008 Accepted for publication.

291. Holte K, Kehlet H. Perioperative single-dose glucocorticoid administration: pathophysiologic effects and clinical implications. J Am Coll Surg. 2002 Nov;195(5):694-712.

292. Karanicolas PJ, Smith SE, Kanbur B, Davies E, Guyatt GH. The impact of prophylactic dexamethasone on nausea and vomiting after laparoscopic cholecystectomy: a systematic review and meta-analysis. Ann Surg. 2008 Nov;248(5):751-62.

293. Huge A, Kreis ME, Jehle EC, Ehrlein HJ, Starlinger M, Becker HD, et al. A model to investigate postoperative ileus with strain gauge transducers in awake rats. J Surg Res. 1998 Feb 1;74(2):112-8.

294. Neudecker J, Schwenk W, Junghans T, Pietsch S, Bohm B, Muller JM. Randomized controlled trial to examine the influence of thoracic epidural analgesia on postoperative ileus after laparoscopic sigmoid resection. Br J Surg. 1999 Oct;86(10):1292-5.

295. Kalff JC, Schraut WH, Simmons RL, Bauer AJ. Surgical manipulation of the gut elicits an intestinal muscularis inflammatory response resulting in postsurgical ileus. Ann Surg. 1998 Nov;228(5):652-63.

296. Hargreaves KM, Costello A. Glucocorticoids suppress levels of immunoreactive bradykinin in inflamed tissue as evaluated by microdialysis probes. Clinical pharmacology and therapeutics. 1990 Aug;48(2):168-78.

297. Hong D, Byers MR, Oswald RJ. Dexamethasone treatment reduces sensory neuropeptides and nerve sprouting reactions in injured teeth. Pain. 1993 Nov;55(2):171-81.

298. Hopf HW, Hunt TK, West JM, Blomquist P, Goodson WH, 3rd, Jensen JA, et al. Wound tissue oxygen tension predicts the risk of wound infection in surgical patients. Arch Surg. 1997 Sep;132(9):997-1004; discussion 5.

299. Henzi I, Walder B, Tramer MR. Dexamethasone for the prevention of postoperative nausea and vomiting: a quantitative systematic review. Anesth Analg. 2000 Jan;90(1):186-94.