

MSc Nutrition and Dietetics

**Longterm effects of preoperative
carbohydrate loading for colorectal surgery**

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B17038 Dissertation

Assessment number E15854

Submitted February 2011

Word count 14028

Acknowledgements

I would like to express my sincere thanks to Mrs Kirstine Farrer and Professor Gordon Carlson for their continued support and guidance throughout this study, and in addition Ms Eva Almiron-Roig and Mr Daniel Commane for their supervision.

I would also like to thank Mr Andy Vail for his statistical assistance.

Lastly I would like to extend my gratitude to Vitaflo Ltd, who provided funding for the travel expenses incurred during this study.

Abstract

Recent changes in preoperative fasting guidelines have resulted in the development of preoperative carbohydrate drinks. Almost all research to date has examined the immediate/early postoperative metabolic and physiological effects, concluding beneficial clinical outcomes post surgery. The aim of this study was to test the hypothesis that preoperative carbohydrate loading results in longer term improvements in wellbeing, sustained return of postoperative physical function and better retention of muscle mass and nutritional status at a later (and potentially more clinically relevant) stage in the postoperative recovery period. This double-blinded placebo controlled randomised control trial took place at Salford Royal NHS Foundation Trust between 1st April 2008 and 31st January 2010. 10 males and 4 females, with a median age of 65.5 years, were included in the study and these were all listed for potentially curative colorectal cancer surgery. Each participant was assessed preoperatively, daily throughout their hospital admission and then at 30 days post surgery. Assessments included anthropometric measurements, analysis of dietary intake, physical activity and an evaluation of pain and well-being.

The results showed that carbohydrate loading had no significant effects on anthropometric, dietary, physical or well-being parameters. However it was seen that pain scores in those patients who received carbohydrate loading were significantly lower ($p=0.017$) 30 days post surgery than those who received the placebo drinks. The trial was a pilot study and has shown that further research is needed to determine whether carbohydrate loading may have long-term clinical benefits.

Declaration of original work

I hereby declare that all work contained herewith is original and is entirely my own work (unless otherwise indicated). It has not been previously submitted in support of any Degree, qualification or other course.

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List of abbreviations

ATP	Adenosine triphosphate
AAGBI	Association of Anaesthetists of Great Britain and Ireland
BMR	Basal metabolic rate
BMI	Body mass index
CI	Confidence Interval
ERAS	Enhanced Recovery After Surgery
HDU	High Dependency Unit
Interleukin 6	IL6
MAMC	Mid arm muscle circumference
MUAC	Mid upper arm circumference
NHS	National Health Service
POSSUM	Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity
REE	Resting energy expenditure
SE	Standard error
SD	Standard deviation
SRFT	Salford Royal NHS Foundation Trust
TEE	Total energy expenditure
TNF	Tumour necrosis factor
TSF	Tricep skinfold

1. Introduction

Surgery can have a significant impact on nutritional status, from preoperative restrictions on oral intake, the stress of the procedure to the postoperative period when nutritional intake may be sub-optimal. This clearly has an impact on surgical outcomes, particularly if energy demands are raised prior to the surgery due to the underlying condition (Hyltander, Drott, Korner, Sandstrom and Lundholm, 1991).

It is well-known that the systemic response to surgery brings about a change in metabolism, and this response to stress is divided into three phases:

1. The 'ebb' phase
 2. The 'flow' phase (also known as recovery phase)
 3. The anabolic phase.
- The *ebb phase* lasts between 12-24 hours after surgery and is characterized by a decrease in the basal metabolic rate, along with a reduced cardiac output and temperature. Energy is provided in the form of hepatic glycogen stores. (Van Cromphaut, 2009)
 - The *flow phase* represents the catabolic period, of which hypermetabolism and increased nitrogen losses are key indicators. Body temperature also increases at this time (Van Cromphaut, 2009). This phase can range in length, depending on the extent of the trauma; in uncomplicated colorectal surgery it would typically last between 2-4 weeks after surgery (Thorell, Efendic, Gutniak, Haggmark and Ljungqvist, 1994). It has been theorised that this stress response evolved to allow animals to survive injury by the provision of energy from the catabolism of their body stores (Desborough, 2000).

- It is during the *anabolic phase* that tissue breakdown can be reversed and nitrogen balance becomes positive, as the basal metabolic rate slows down and catabolic mediators reduce in circulation. This phase can last from weeks to months.

During the flow phase of the systemic stress response to surgery the metabolic rate increases and therefore energy demand is increased, if patients are fasted prior to undergoing surgery then glycogen stores are limited and therefore fat and protein are used in order to supply energy and this comes about through gluconeogenesis. Lipids, which consist of fatty acid molecules joined to molecules of glycerol, are hydrolysed to release glycerol and additionally proteins are catabolised into their component amino acids. These two substrates enter energy metabolism pathways as pyruvate or acetyl CoA intermediates, where they may be oxidised to produce adenosine triphosphate (ATP). This process is simplified in figure 1.

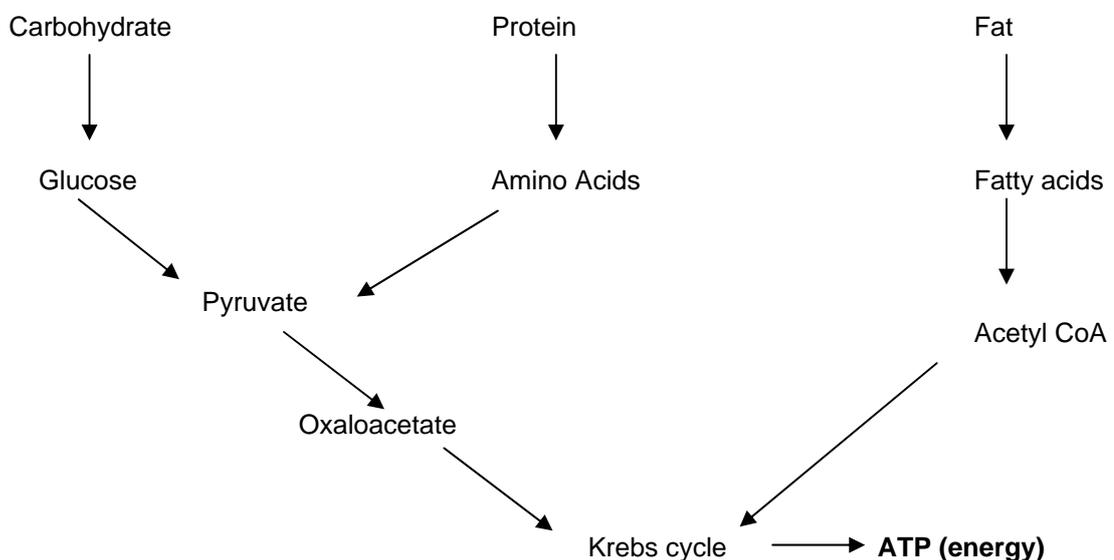


Figure 1. Energy production via the pathway of gluconeogenesis

The stress brought about by surgery involves an immune response whereby proteins are produced which bind to receptors on target cells with the role of signalling to other cells and marking the site of trauma (Giannoudis, Dinopoulos, Chalidis and Hall, 2006).

These proteins are named cytokines and include interleukin 6 (IL6) and tumour necrosis factor (TNF) which are believed to mediate insulin resistance (Witasp et al., 2009). Furthermore, the stress hormones catecholamines, cortisol and growth hormone are released (Witasp, Nordfors, Schalling, Nygren, Ljungqvist & Thorell, 2009). Catecholamines are also known to inhibit insulin release, and therefore the net result of the immune response is insulin resistance, resulting in reduced glucose uptake and thus increased blood glucose levels. To further exacerbate this condition, in response to the decreased insulin:glucagon ratio, gluconeogenesis is stimulated (Nygren, Thorell, Efendic, Nair and Ljungqvist, 1997), resulting in hyperglycaemia. In addition to this, hepatic protein synthesis increases to produce acute phase proteins therefore increasing protein requirements (Giannoudis et al, 2006).

Hyperglycaemia has been proven to have a negative effect on wound healing and to suppress immunity (Ljungqvist, Nygren, Soop and Thorell, 2005). Moreover studies which involve regulated glucose levels in metabolically stressed patients have been shown to reduce mortality and morbidity in both the early (Van den Berghe et al., 2001) and late postoperative periods (Hill, Douglas and Schroeder, 1993). There are a number of theories as to how hyperglycaemia induces this negative effect and increases complications. One theory is that those cells which do not require insulin for glucose uptake become overloaded with glucose due to the high extracellular levels, an effect that is further exacerbated by cytokines and results in glucose toxicity (Ljungqvist et al., 2005). It is proposed that this excess glucose overloads the mitochondria as it enters the Krebs cycle and results in an increased level of reactive oxidative species, thus altering mitochondria function and structure (Ljungqvist et al., 2005). This insulin resistance, and associated hyperglycaemia is most pronounced immediately post surgery, however it can last up to 20 days after the operation (Thorell et al., 1994).

Understanding this response enabled research into measures to limit insulin resistance and its associated detrimental effects. Perioperative intravenous infusions of glucose

and insulin were shown to greatly attenuate postoperative insulin resistance, (Ljungqvist, Thorell, Gutniak, Haggmark and, Efendic, 1994; Nygren et al., 1998a; Brandi et al., 1990) and thus reduce nitrogen losses, (Crowe, Dennison and Royle, 1984), as they increase hepatic glycogen content during surgery. However, such methods can be highly labour intensive and difficult to administer safely, as frequent monitoring of blood glucose levels and insulin infusions is required. Furthermore, as the glucose solution needed to be a moderately high osmolality then this caused vascular irritation to some patients. A previous study demonstrated a significant decrease in residual gastric volume at the time of anaesthesia, measured by suction, when water was given two hours prior to surgery (Agarwal, Chari and Singh 1989). This allowed for research into the use of oral provisions to potentially reduce postoperative insulin resistance. Nygren et al., (1995) used radioactively labelled carbohydrate-rich drinks and measured gastric emptying using a gamma camera, finding that after 90 minutes of consumption, the stomach was empty. Historically preparation for major surgery had involved a period of fasting for 12-16 hours in order to ensure complete gastric emptying; this was due to evidence that showed anaesthesia could lead to a loss of muscle tone in the upper airway and oesophagus (Hillman, Platt and Eastwood, 2003), thereby increasing the risk of passive regurgitation or vomiting. However this study demonstrated that gastric volumes and pH are within safe limits when clear fluids are given up to two hours prior to surgery, thus concluding that the traditional practice of complete prolonged fasting prior to surgery is neither necessary nor desirable.

In response to this The Association of Anaesthetists of Great Britain and Ireland (AAGBI) published amended guidelines in 2001 (AAGBI, 2001) on the preparation of patients for surgery, which recommend the following minimum fasting periods:

- Six hours for solid food, infant formula, or other milk
- Four hours for breast milk

- Two hours for clear non-particulate and non-carbonated fluids

This change in practice enabled further research to be carried out into the feasibility of carbohydrate drinks as an alternative to intravenous glucose infusion and indeed Nygren et al., (1998b) demonstrated that post-operative catabolism and thus insulin sensitivity were reduced by administration of a carbohydrate drink prior to surgery. There were of course limitations to this study as there were only seven participants in each group, which may have explained why significant results were not always found. Additionally the groups appeared not to be well matched, as pre-operative insulin sensitivity was higher in the fasted group than the intervention group, which could have affected the post-operative results. Furthermore, the groups were not matched for length of surgery, and this has been shown to independently affect insulin sensitivity (Thorell, Efendic, Gutniak, Haggmark and Ljungqvist, 1993). However further studies supported the findings of reduced postoperative insulin resistance when preoperative fasting was avoided (Soop, Nygren, Myrenfors, Thorell and Ljungqvist, 2001; Kaska et al., 2010). Additionally the timing of the carbohydrate drink was considered and it was shown that when provided in the morning, insulin action, and thus glucose disposal, increased by approximately 50% for three hours following the drink administration. However, when the carbohydrate drink was provided in the evening, insulin action was not affected (Svanfeldt et al., 2005). This suggests that the morning carbohydrate drink is of most significance as it changes the metabolic state to that of normal daytime and not the overnight fasted state. A disadvantage of Svanfeldt et al. (2005) however was its sample size, with a total of only six participants. It should also be considered that the study was unblinded and thus could have introduced bias from the participants and observers, but the authors argued that the study design did not enable it be blinded. It could be suggested that the provision of water, with sweetener to match the taste of the carbohydrate drink, could have been used in the controls.

So it becomes clear that whilst the evidence has some limitations, overall carbohydrate drinks were shown to reduce postoperative insulin resistance. This is because the glucose monomers provided preoperatively are bonded together during glycogenesis and stored in the form of glycogen within the liver. During and post surgery when energy demands are increased, these glycogen stores are broken down by glycogenolysis (figure 2). This therefore increases glucose supplies, which combined with a decrease in insulin resistance can potentially result in improved peripheral glucose uptake and oxidation (Nygren, 2006) and decreased glucose production (Ljungqvist, 2009). This effect could last for up to 3 days post-operatively (Soop, Carlson, Hopkinson, Clarke, Thorell, Nygren & Ljungqvist, 2004).

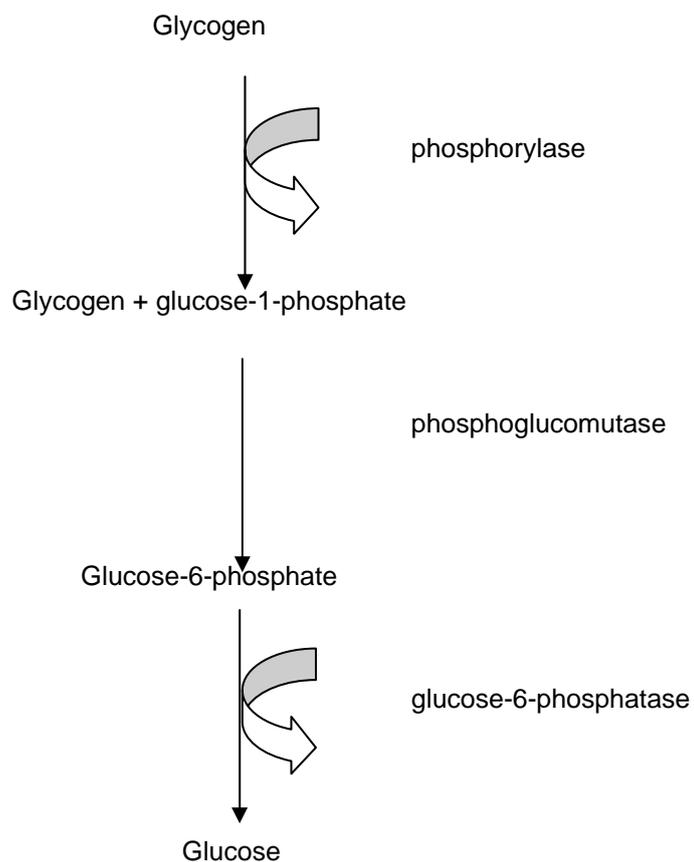


Figure 2. Energy production from glycogen via glycogenolysis

This research led to the development of commercial carbohydrate drinks, consisting of complex mixtures of oligosaccharides at a sufficient level to induce the shift into a metabolic fed state following fasting, whilst also ensuring rapid transit through the

stomach and thus meeting the requirements of the AAGBI. Research then extended to examine the effects of preoperative carbohydrate loading, and its associated decrease in insulin resistance, on various clinical outcomes.

1.1 Effects of preoperative carbohydrate loading

1.1.1 Length of stay

Insulin resistance has been shown to be an independent predictive factor for length of hospital stay post-surgery (Thorell, Nygren and Ljungqvist, 1999). Therefore it may be expected that through reducing insulin resistance preoperative carbohydrate loading could reduce length of stay, but there are currently few studies which have examined this.

One study showed a significant reduction of 5.5 days in the median time to fitness for surgical discharge for those patients given a carbohydrate drink preoperatively compared with those given water (Noblett et al., 2006). A limitation to the study was the impossibility to blind the subjects to the intervention. Additionally the report does not state who randomised the participants, prepared the drinks or took the measurements. Whilst it states that the medical staff were blinded, it does not declare whether the nursing staff and chief researchers were blinded and thus there is potential for bias.

The reduction in length of stay reported by Noblett et al., (2006) was also reflected by Ljungqvist, Nygren and Thorell (1998) who performed a meta-analysis of three prospective controlled trials and showed that the use of carbohydrate drinks can reduce hospital stay by an average of one day (20%) when compared to overnight fasting. One further report on a double-blind randomised, placebo-controlled study of 65 participants showed an overall trend towards a reduction in hospital stay in those participants who received a carbohydrate drink, but the results were not found to be

significant (Yuill, Richardson, Davidson, Garden and Parks, 2005). Whilst the study design appeared to be appropriate to the aims, it was noted that the report did not provide a sample size calculation.

Clearly the results appear promising but more research would be valuable due to the implications of a reduced stay on both patient wellbeing and healthcare costs.

1.1.2 Preservation of lean body mass

As discussed above the metabolic response to stress results in catabolism, however, with carbohydrate drinks improving glucose uptake post surgery and preventing the metabolic fasted state then this may have an effect on lean body mass. Yuill et al., (2005) found in a study of sixty-five surgical patients that even though there was no difference in body mass index (BMI) or fat mass between the control and intervention groups, a significant reduction in mid-arm muscle circumference was seen in the control group, suggesting that the carbohydrate drink was effective at preserving lean muscle mass.

Other studies investigated the effects on muscle function, with Noblett et al., (2006) demonstrating a significant decrease (11%) in the grip strength of those patients who underwent overnight fasting, whilst no significant decrease was shown in those patients given carbohydrate drinks. This suggests that preoperative fasting may be associated with a greater degree of protein loss.

Quadricep strength has also been investigated with comparable results to Noblett et al., (2006), showing a significantly greater decrease in muscle function when fasted compared with carbohydrate loading (Henriksen et al., 2003).

1.1.3 *Well-being*

Well-being can incorporate a number of parameters and was considered one of the principal reasons for amending the guidelines on the preparation of patients for surgery, in order to reduce discomfort due principally to thirst. It is therefore interesting to consider whether the provision of carbohydrate improves this wellbeing further.

Hausel et al., (2001) concluded from an extensive study of 252 patients that preoperative carbohydrate provision increases wellbeing prior to surgery. Their results showed a significant decrease in hunger and thirst in those given carbohydrate drinks, and furthermore, the carbohydrate-treated group also showed a significant decrease in anxiety, less malaise and less unfitness. Previous research had also shown a reduction in thirst following administration of a carbohydrate drink (Nygren et al., 1995), however they did not see any significant change in hunger, or anxiety. It could be argued however that comparison is made difficult by the fact the Nygren et al., (1995) included only 12 participants in their study. In contrast to these results, Bisgaard, Kristiansen, Hjortso, Jacobsen, Rosenberg & Kehlet (2004) examined general wellbeing, fatigue and appetite in a sample of 94 patients and found no differences between groups either pre- or post- operatively. These three studies all used visual analogue scores (VAS) to measure well-being parameters.

A further aspect of wellbeing that has been researched is the prevalence of nausea and vomiting. Bisgaard et al. (2004) also examined this parameter post-operatively and found no significant improvement in nausea and vomiting in those subjects who had received carbohydrate treatment. However, Hausel, Nygren, Thorell, Lagerkranser and Ljungqvist (2005) showed in a randomised control trial of 172 subjects that the incidence of postoperative nausea and vomiting was significantly reduced when participants were given a carbohydrate drink prior to their surgery, compared to those who had fasted or received a placebo. The authors considered that potential

confounding factors, including anaesthetic, opioid, antiemetic and intravenous fluid use were similar across the groups.

Comparable results have been found more recently, with an observed trend towards a reduction in postoperative vomiting in those given carbohydrate treatment, however, these results were not found to be significantly different (Faria et al., 2009). This could perhaps in part be due to the small sample size of 21 subjects; nevertheless this sample was based on a sample size calculation. Additionally, although the study was a randomised control trial it was not blinded and thus there is the potential for subject and observer bias. However, the design of this study made blinding impossible and it may have improved the validation of the results if a placebo was used in place of fasting for the control. A further drawback of the study design was that we cannot conclude whether the effect seen was due to the actual carbohydrate drink, or just the fact that the patient was not fasted, as we know that this independently improves wellbeing. It is possible that the same effect could have been achieved simply through normal clear fluids.

It is interesting that Bisgaard et al., (2004) in their double blinded randomized placebo-controlled trial reported no overall improvement in clinical outcome following preoperative carbohydrate loading despite including more subjects than was required from the power calculation. They considered that their findings may have been due to using subjects who had undergone laparoscopic cholecystectomy, which they felt may have been less likely to induce insulin sensitivity due to its minimal invasiveness compared to other surgeries. However, both Hausel et al., (2005) and Faria et al., (2009) also studied patients undergoing laparoscopic cholecystectomy and found significant improvements in clinical outcome measures in those patients treated with the preoperative carbohydrate drink. Bisgaard et al., (2004) report in their paper that participants were contacted by telephone the evening prior to their surgery, which could imply that they were not admitted to hospital until the following morning. The report

therefore relies on accurate reporting from the participants on the timings and volume of the drinks consumed, something which could affect the reliability of the results. Furthermore, the study considered sleep quality and again found no significant differences between groups, but it is possible this could be due to the way the data was collected. The authors requested the participants keep a record of the time taken to go to sleep and to wake up, and also the number of nocturnal episodes of waking. It could be suggested that it would be very difficult for participants to measure the time at which they got to sleep as they would likely be unable to view a clock during the process of going from wakefulness to sleep, and they may therefore estimate. Furthermore it is not clear whether there was a criteria for measuring these parameters, for example whether nocturnal waking constitutes solely waking to turn over or being awake for a specified length of time.

1.1.4 Nutritional intake

Only one study was found that measured postoperative nutritional intake (Henriksen et al., 2003) and this requested participants to keep their own records of diet and fluids consumed during their admission. It was found that preoperative carbohydrate loading did not affect postoperative nutritional intake. Whilst it could be argued that self-reporting of intake may reduce accuracy, it could be considered that a third party completing diet and fluid record charts would be unlikely to increase accuracy as it would rely on to constant monitoring of the patients, something that is not possible on general wards in most hospitals.

On a similar matter, Hausel et al., (2001), examined preoperative discomfort using a visual-analogue scale and found that preoperative hunger and thirst were significantly reduced when carbohydrate drinks were administered, compared with water alone, thus improving general patient wellbeing.

1.1.5 Postoperative complications

It has been proposed that the reduction in insulin resistance may have an effect on postoperative complications; however there is currently very little research in this area. Noblett et al., (2006) found the incidence of postoperative complications to be the same in the carbohydrate group as the fasting group. One other study has examined the effect of preoperative nutrition on immunity and found that when subjects were given pre-operative nutrition then exposed to a variety of different intradermal antigens postoperatively, the cellular immunity response increased (Rasmussen, Segel, Trier Aagaard and Hesso, 1985). This study however was carried out prior to the development of carbohydrate drinks and thus used parenteral nutrition for one week prior to surgery. Furthermore, the subjects all received the same treatment, and therefore the lack of a control group suggests that it may not be possible to extrapolate these findings to conclude about preoperative carbohydrate drinks, however they do provide optimism for further research in this area.

1.2 Cancer

The population being studied in this trial is those undergoing elective surgery for colorectal cancer. Cancer is a major concern in the United Kingdom, and is currently the leading cause of mortality for individuals under the age of 75 years (Department of Health, 2007). Currently health costs for cancer in England are approximately £4.35 billion each year (Department of Health, 2007). The most recent information released by the Office for National Statistics reports that colorectal cancer is the second most common cancer for women and third most common for men within the United Kingdom (Office for National Statistics, 2010) and therefore this type of cancer is clearly having a significant effect on the population and economy of this country. Disturbingly, a recent study predicted that the incidence of colorectal cancer is likely to rise in view of the increasing obesity epidemic (de Vries et al, 2010). Moreover, cancer incidence in

general is predicted to increase due to the effect of population growth and increasing lifespan (Department of Health, 2007).

Of the total expenditure on cancer programmes, approximately 27% is being spent on inpatient costs (Department of Health, 2007). Therefore, methods to improve recovery and reduce hospital stay are likely to reduce costs to the National Health Service (NHS) and also have a considerable impact on the patient. As well as the psychological impact of recovering more rapidly there are other factors, for example reduced loss of earnings, that will benefit the patient. This is also particularly relevant in the current climate where the NHS is required to save £15-20 billion by the end of 2013/14 (Department of Health, 2009).

Colo-rectal cancer is classified according to pathological staging and in turn this determines the treatment and likely prognosis of patients. The predominant factor in staging is the extent to which surrounding tissues has been invaded by the tumour. There are two staging systems used in the UK, these are outlined in figure 3.

Stage

Dukes stage

Figure 3. Staging of colorectal cancer (Taken from Treanor and Quirke, 2007)

1.3 Aims and objectives

From the literature review it can be seen that the recent change in preoperative fasting guidelines has resulted in a new area of dietetics being developed in the form of preoperative carbohydrate loading, with extensive research suggesting that there are significant benefits to be achieved. So much so that the recent ESPEN guidelines (Braga et al., 2009) recommend preoperative carbohydrate loading to be the primary treatment for most patients, based on grade A evidence. It could be argued however, that whilst the greater part of the evidence is based on randomised controlled trials, there have been many that are not blinded and also very few meta-analyses or systematic reviews in order to analyse combined findings and draw overall conclusions. It is also notable that most of the research to date is from other European countries, and thus it is possible that these populations are not representative of those being treated at Salford Royal NHS Foundation Trust. For example, socio-economic status and ethnic composition may vary, which both in turn affect dietary choices and underlying nutritional status prior to surgery.

Of primary importance, however, is that almost all research to date has examined only the immediate/early postoperative metabolic and physiological effects and there has been only one study investigating long-term outcomes. It should be considered whether by using carbohydrate loading we could be discharging patients quicker, but then delaying the identification of potential nutritional problems. Following discharge it may be harder to identify these problems and the appropriate support may be less accessible from the home. The aim of this study is to specifically test the hypothesis that preoperative carbohydrate loading results in longer term improvements in wellbeing, sustained return of postoperative physical function and better retention of muscle mass and nutritional status at a later (and potentially more clinically relevant and useful) stage in the postoperative recovery period. (See table 1).

	Outcomes	Objectives	Hypotheses
Main aim	To investigate the long-term effects of preoperative carbohydrate loading on colorectal patients		
Primary	Weight and anthropometry as a measure of nutritional status	To investigate whether carbohydrate loading affects changes in weight and anthropometry from pre-op to 30 days post surgery	Carbohydrate loading results in better retention of weight and muscle mass at 30 days post surgery.
Secondary	Nutritional intake as a measure of nutritional status.	To investigate whether carbohydrate loading affects the time taken to meet nutritional requirements.	Carbohydrate loading improves nutritional intake and status immediately post-surgery and at 30 days post surgery.
Other outcomes	Relationship between carbohydrate loading and wellbeing.	To investigate whether carbohydrate loading affects changes in wellbeing and pain scores from pre-op to 30 days post surgery.	Carbohydrate loading results in short and longer term improvements in wellbeing.
	Time spent on a high dependency unit (HDU) and overall length of stay in hospital.	To investigate whether carbohydrate loading affects the number of days spent on HDU and length of stay.	Carbohydrate loading reduces length of time spent on HDU and overall length of stay.
	Activity levels as a measure of physical function	To investigate whether carbohydrate loading affects physical activity levels.	Carbohydrate loading results in improved return of physical function post surgery.

Table 1. Study aims and objectives.

2. Methods

2.1 Design

This double-blinded placebo controlled randomised control trial took place at Salford Royal NHS Foundation Trust (SRFT). All data was gathered by one trained research dietitian to prevent inter-observer bias.

A sample size calculation was used (appendix 1), concluding that in order to see differences at 0.05 level of significance 90 recruits were required in each group. It was decided that the scale of the study was much greater than was feasible with one researcher in the space of the time allocated, and thus the decision was made to carry out this study as a pilot trial, with a view to extending it in the future. The intention was to include 10 participants in each group however due to poor uptake and recruitment, this was reduced to seven participants in each group in order that the trial could be completed within the time allocation.

Ethical approval was granted by Salford and Trafford Local Research Ethics Committee, and the Research and Development department at Salford Royal NHS Foundation Trust (SRFT) (Appendix 2).

2.1.1 Population and subjects

All colorectal cancer participants over the age of 18 years of age listed for potentially curative colorectal cancer surgery at SRFT were invited to participate in this double-blinded placebo controlled randomised control trial. Initially the trial included only participants undergoing open abdominal surgery, however after only six patients were recruited in the first eight months, an amendment to the protocol was submitted to the ethics committee to extend eligibility to laparoscopic surgery. This was accepted and thus the inclusion criteria then comprised of both open abdominal surgery and laparoscopic abdominal surgery. In order to prevent the research dietitian influencing

invitees, the colorectal nurses or Enhanced Recovery After Surgery (ERAS) Specialist Nurse provided the invitation letter and participant information sheet to participants meeting the inclusion criteria, at the time of their consultant appointment. The participants then completed the tear-off slip and returned this to the research dietitian in order that they could be contacted for their consent and initial assessment. There were no instances of any participants who did not speak English as their first language; however interpretations would have been used if this was the case. Subjects received no reimbursement for their participation in the trial.

A criteria was devised for participants to be excluded from participation which consisted of those who were unable to give written informed consent and participants with the following conditions: neurological impairment or dementia, pre-existing conditions limiting mobility and independence at home (e.g. severe rheumatoid arthritis), advanced cancer undergoing palliative surgery (likely to have a progressive decline in physical status irrespective of treatment), Diabetes Mellitus, a history of gastric surgery or any other clinical conditions known to impair gastric emptying.

A dietitian who was not participating in the study randomised each patient at point of entry, following patient consent, to avoid selection bias. Patients were stratified into two groups: treatment group or control group using simple randomisation. An envelope was used containing the names of both groups and the dietitian stratifying the patients blindly removed one name to determine which group that patient went into. Neither the research dietitian, nor the surgical or nursing teams were aware of the allocation; this was kept in a locked filing cabinet in the dietetic department until the data analysis step. The patients were not aware of which group they were allocated to, and the drinks were matched to taste.

The carbohydrate drink used in this study was 'Preload'[®], a product of VitaFlo Ltd. Preload was created specifically for the purpose of carbohydrate-loading prior to

surgery and is available in 50g sachets, containing 190kcal and 40g carbohydrate. Each 50g sachet is mixed with 400ml cold water to produce an odourless and colourless low-osmolality (120mOsm/kg) drink, (see appendix 3 for nutritional analysis).

The placebo drink was derived using 400ml cold water and 7.5tsp granular sweetener, to produce an odourless and colourless drink providing a total of 14.2kcal in 400ml.

These measurements were deemed by the research dietitian, and two dietitians who were not participating in the study, to be a match to the taste of Preload.

2.2 Procedures: Pre-surgery

Once participants had consented to partake they were visited either at home, or in pre-op outpatient clinic for their initial assessment, a minimum of seven days prior to admission. The following demographical details were recorded: age, date of birth, sex, stage and site of cancer. The interview consisted of the following components:

- (i) Measurement of
 - a. weight, height and BMI
 - b. mid arm muscle circumference (MAMC).
 - c. grip strength
- (ii) Explaining and gaining participant's consent to wear the SenseWear[®] Armband for three consecutive days.
- (iii) Explaining and gaining participant's consent for them to complete a detailed three day food diary.
- (iv) Calculation of nutritional requirements
- (v) Well-being assessment

Details of the procedures for each of the components are listed below. These results were then used as baseline data for each participant and allowed comparison against outcome data at 30 days postoperatively. Therefore each participant acted as their

own control for nutritional intake, nutritional status, well-being, energy expenditure and activity levels.

2.2.1 Weight, height and BMI

Participants were weighed using calibrated stand-on Seca® scales, and all subjects were asked to remove their shoes and wear light clothing. Height was measured using a wall mounted tape measure or a Seca® portable stadiometer. It was necessary to use two different methods for height measurement as the assessments were carried out in either the home or hospital setting. The two devices were tested for comparability prior to commencing the study. The weight and height measurements enabled calculation of BMI, using the following equation (Garrow and Webster, 1985):

$$\frac{\text{Weight in kilograms (kg)}}{(\text{Height in metres})^2}$$

2.2.2 Mid arm muscle circumference

Lean body muscle mass was estimated by measuring mid-upper arm circumference (MUAC) (Bishop, Bowen and Ritchley, 1981). Subcutaneous fat stores were then estimated by measuring tricep skinfold (TSF) measurements, using Holtain skinfold calipers at the same midpoint of the triceps. In order to achieve reliable results each measurement was taken three times and an average value used. The validity of these measurements is optimised as the same research dietitian performed each measurement for every subject, using the same equipment (Gibson, 2005).

Mid Arm Muscle Circumference (MAMC), which is an index of muscle mass, was then calculated using the following equation (Bishop et al, 1981):

$$\text{MAMC(cm)} = \text{MAC(cm)} - (\text{TSF(mm)} \times 0.314).$$

2.2.3 Grip strength

Grip strength was measured using a Takei single spring handgrip dynamometer. The device was held by the participant in the non-dominant hand and squeezed three times, with the highest reading being recorded. This result provides an indication of muscle strength and thus gives a functional indicator of nutritional status. Results were compared to reference values for age and gender (Goode, Howard and Woods, 1985; Klidjian, 1982).

2.2.4 Nutritional assessment

Energy requirements were estimated using the equations of Schofield (1985) to calculate basal metabolic rate (BMR), which were then adjusted for physical activity level (Department of Health, 1991) based on reported activity level. Stress factors were not added preoperatively. If patients had a BMI of greater than 30 then the energy requirement was taken as BMR only, in line with ASPEN recommendations (A.S.P.E.N Board of Directors and the Clinical Guidelines Task Force, 2002). The results for energy requirements were then able to be compared with the resting energy expenditure measurement obtained from the SenseWear[®] armband (see section 2.2.6).

Nitrogen requirements were calculated using the normal value of 0.17g/kg/day (Elia, 1990) and then converted to protein by multiplying by 6.25.

Participants were requested to complete a detailed diary of every food and drink consumed for three consecutive days to establish their baseline nutritional intake. This was then analysed by the research dietitian using Microdiet (Downlee Systems Ltd, Chapel-en-le-Frith), based on the data set of food and nutrients published in McCance and Widdowson (2002).

2.2.5 Wellbeing and pain assessment

Visual analogue scales were used, based on the validated tool used by Hausel et al., (2001) to examine subject's anxiety, depression, hunger, inability to concentrate, malaise, nausea, pain, thirst, tiredness, unfitness and weakness (appendix 4).

Subjects were asked to mark on the 100mm scale where they perceived themselves to be at the moment in time for each parameter.

2.2.6 SenseWear[®] armband

The SenseWear[®] Armband is a simple, non-invasive device, which allowed simultaneous collection of heat loss, body movement and position data to compute metabolic data in participants. The armband has four sensors to measure skin temperature, galvanic skin response, heat flux sensors and a two axis accelerometer (to measure motion). These sensors enabled the calculation of the following data daily:

- total energy expenditure (TEE),
- physical activity duration,
- duration lying down,
- duration sleeping
- number of steps taken

The SenseWear[®] armband was worn on the right upper arm and participants were advised to avoid getting the device wet. A new battery was provided in each device.

The armband has been validated successfully against the doubly labelled water (DLW) technique (Mignault, St. Onge, Karelis, Allison and Rabasa-Lhoret, 2005).

2.2.7 Admission

The afternoon prior to their surgery, participants were admitted to Salford Royal NHS Foundation Trust and seen by the research dietitian. The drink was prepared in a clear jug by the dietitian who had randomised the patient, and information regarding the trial, contact details for the research dietitian and instructions for administering the drink

were given to the nursing team. Furthermore a copy of the signed consent form was placed in the written medical notes and an entry made on the patient's electronic notes to inform all staff of this patient's involvement in the clinical trial. The participant was provided with a well-being and pain assessment to complete the following morning prior to their surgery. Also at this time, the SenseWear[®] armband and completed food diary were collected from the patient.

Patients were requested to consume their drink at the following times:

400ml evening prior to surgery

400ml before 4am morning prior to surgery

400ml 2 hours prior to surgery.

The total volume of drink consumed, out of the 1200ml provided, was recorded by the nursing staff on the ward.

2.3 Procedures: Post surgery

Participants were monitored daily from day one post surgery by the research dietitian. They were asked to wear the SenseWear[®] Armband continually for 14 days or until fit for surgical discharge as defined by the surgical team (whichever came first).

2.3.1 Nutritional assessment

Daily food record charts were kept by nursing staff in order that energy and protein intake could be assessed and these were later analysed by the research dietitian using Microdiet to establish participant's daily energy and protein intake for days one to three post surgery, and their overall energy intake during admission.

2.3.2 Wellbeing and pain scores

The wellbeing questionnaire was completed by patients every other day during their admission. A pain questionnaire was used, based also on the validated visual analogue

score used by Hausel et al (2001) to determine pain experienced when carrying out various functions (appendix 5).

During admission the following data were also collected:

- Length of time the patient spent on HDU area, as defined by surgical team, before transfer to the ward.
- Postoperative complications, as defined by surgical team
- Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM score) (Copeland, Jones and Walters, 1991)
- Presence of Stoma
- Length of time taken for stoma to function or for the patient to open their bowels
- Total length of hospital stay

2.3.3 POSSUM score

POSSUM is the abbreviation for Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity. This is used by the colorectal surgeons at SRFT and is calculated using 12 physiological and six operative parameters (appendix 6). This enables a prediction of mortality and morbidity. These scores were calculated by each participant's respective consultant surgeon.

2.3.4 Discharge

When patients were considered fit for discharge by the surgical team then the SenseWear[®] armband was removed and the following parameters measured, comparable to the pre-op assessment:

- (i) Weight, height and BMI.
- (ii) MAMC
- (iii) Grip strength.
- (iv) Calculation of nutritional requirements

- (v) Well-being assessment

Energy requirements were re-calculated using most recent weights and adding a stress factor of 10% in view of recent uncomplicated surgery (Long, Schaffel, Geiger, Schiller and Blakemore, 1979). As with the preoperative assessment, those participants with a BMI greater than thirty had energy requirements calculated as BMR (A.S.P.E.N Board of Directors and the Clinical Guidelines Task Force, 2002).

Nitrogen requirements were calculated using the hypermetabolic value of 0.2g/kg/day (Elia, 1990) and then converted to protein by multiplying by 6.25.

2.4 Procedures: Post-discharge

Each participant was contacted to arrange a home visit by the research dietitian on day 30 following their date of surgery, or the closest possible date to this.

Three days prior to this the research dietitian delivered the SenseWear[®] armband to the participant in order that it could be worn for three consecutive days and then removed at their final assessment, and a three day food diary was provided for completion by the participant.

At the final assessment the following parameters were again measured using the methods documented above:

- (i) Weight, height and BMI.
- (ii) MAMC
- (iii) Grip strength.
- (iv) Calculation of nutritional requirements
- (v) Well-being assessment

Energy requirements were re-calculated using most recent weights and no stress factor was used as it was deemed that patients would be likely to be out of the flow phase of the surgical stress response. As with the preoperative assessment, those participants with a BMI greater than 30 had energy requirements calculated as BMR (A.S.P.E.N Board of Directors and the Clinical Guidelines Task Force, 2002).

Nitrogen requirements were calculated using the normal value of 0.17g/kg/day (Elia, 1990) and then converted to protein by multiplying by 6.25.

A summary timeline of the trial's design is shown overleaf.

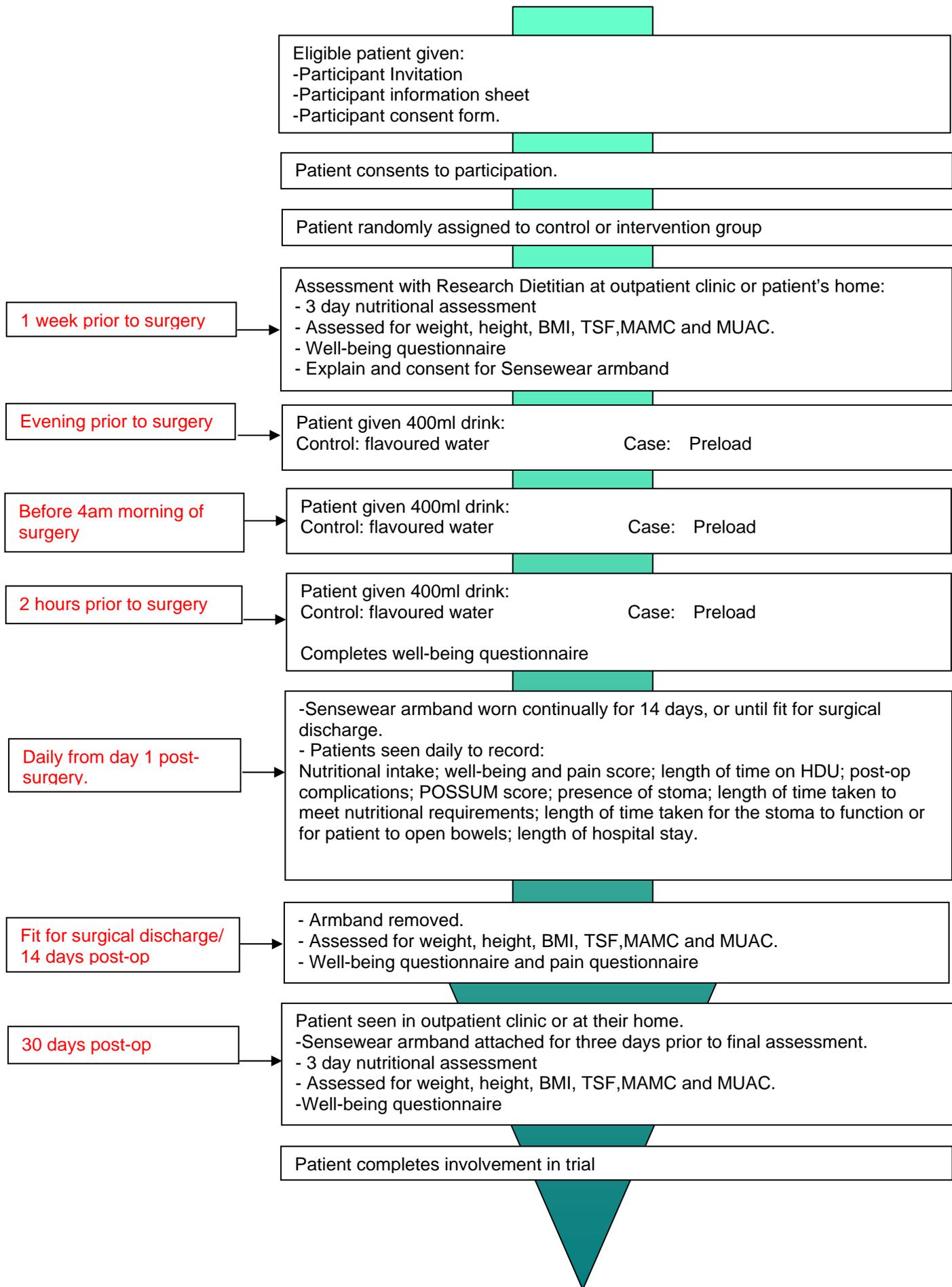


Figure 4. Summary timeline of trial

2.5 Data analysis

Data were entered into a Microsoft Excel spreadsheet and subsequently the research dietitian was informed of the randomisation code prior to analysis to allow comparison between the two groups. The statistical software package IBM® SPSS® version 17 was used for all analysis. Mean values and standard deviation (SD) or standard error of the mean (SEM) were calculated and median values were also used for several data. When measuring changes in values between different time intervals, mean values and 95% confidence intervals of the difference were calculated.

All data was checked for errors prior to carrying out analyses using the IBM® SPSS® function of analysing variables. The Kolmogorov-Smirnov test for normality was used in order to determine normality. It was concluded that parametric tests should be used for all data.

Statistical analysis was not carried out for baseline or surgical data due to the small amount of data. Due to observed differences between the control and intervention groups at baseline then all anthropometric data were analysed by comparing changes within groups between the time intervals of: preoperative assessment to discharge from hospital; discharge from hospital to 30 days post-surgery; and preoperative assessment to 30 days post-surgery. Independent sample T-tests were used for these analyses.

Data for nutritional intakes were compared between the two groups, by analysing mean intakes of energy and protein intakes using independent sample T-tests for different time periods throughout the study. Wellbeing, pain, physical function and resting data were assessed in the same way by analysing mean data between groups for each time period using independent sample T-tests.

Length of time on HDU and length of admission were analysed also using independent sample T-tests, however for the statistical analysis of the complications related to surgery, Fisher's exact test was used due to the small number of data. The level of significance was set at 0.05 for all analyses.

3. Results

3.1 Baseline and surgical data

Between 1st April 2008 and 31st January 2010, 18 patients consented to partake in the clinical trial. During this time a total of 101 patients underwent surgery for colorectal cancer, however not all of these may have been eligible for participation according to the trial exclusion criteria.

Of those who consented, one subject who was due for open surgery had this converted to laparoscopic surgery; this was prior to the change in inclusion criteria and thus she was excluded from the study at that time. A further two patients were excluded due to the Sensewear[®] armband failing to record any pre-operative results, thereby leaving a large gap in the data collected. Following the amendment of inclusion criteria to include laparoscopic patients, only one laparoscopic patient consented and completed the trial therefore it was considered that due to insufficient numbers in this group it was necessary to also exclude this patient. This is due to differing stress responses between laparoscopic and open surgery (COLOR, 2005) making it likely that this patient was not matched to the rest of the population within the group. It is known that laparoscopic surgery is less invasive and traumatic, resulting in a reduced catabolic effect and immunological response (COLOR, 2005). Furthermore, a previous study has shown insulin resistance to be reduced in laparoscopic compared with open surgery (Thorell et al., 1996). The remaining 14 subjects completed their participation in the trial.

The participants consisted of 10 males and 4 females, of median age 65.5yrs (range 44-83yrs), see table 2 for all baseline data. There was no negative feedback from any recruits on the palatability of either drink, and the nursing notes showed that all subjects consumed the total amount of drink required.

	Intervention (n=7)	Control (n=7)
Age (yrs) Median (range)	69 (55-77)	62 (44-83)
Gender Male Female	6 (86%) 1 (14%)	4 (57%) 3 (43%)
Mean weight (kg)	85.5 (SD 15.3)	73.3 (SD 15.4)
Mean BMI (kg/m ²)	29.8 (SD 4.7)	25 (SD 4.87)
Mean MAMC (cm)	27.5 (SD 3.7)	26 (SD 3.4)
Mean grip strength (mm)	34.1 (SD 9.4)	30.6 (SD 9.7)
Mean daily energy requirement (kcal)	2549 (SD 444)	2212 (SD 625.7)
Mean daily energy intake (kcal)	1861 (SD 439.7)	1942 (SD 636.8)
Mean no. pts meeting >90% of energy requirement (%)	2 (29%)	2 (29%)
Mean daily protein requirement (g)	81 (SD 6.7)	75 (SD 15.3)
Mean daily protein intake (g)	79 (SD 14.5)	79 (SD 26.2)
Mean no. pts meeting >90% of protein requirement (%)	5 (71%)	4 (57%)
Mean physical activity duration (hr:min)	1:13 (SD 0:46)	1:32 (SD 1:13)
Mean number of steps	5658 (SD 3875)	7698 (SD 4606)
Mean hours of sleep (hr:min)	5:45 (SD 1:58)	5:51 (SD 2:56)

Table 2. Descriptive data of all participants at baseline.

All participants underwent open surgery for potential curative resection of colorectal cancer, data was collected on the site and stage of the cancers, note one patient in the control group had two carcinoma, of Dukes B and C (table 3).

Cancer	Intervention	Control
Site		
Rectum	5	6
Mid-ascending colon	2	
Sigmoid loop		1
Caecum		1
Stage		
Dukes A	4	
Dukes B	2	5
Dukes C	1	3

Table 3. Data for all participants on the cancer site and stage.

Only three participants did not have a stoma formed during their surgery and all three of these patients were in the intervention group. The length of time for either the stoma to work, or bowels to open was recorded however data was missing for one participant in the intervention group, see table 4.

Number of days post surgery	Intervention	Control
0		1
1	3	2
2		1
3	1	1
4	2	
5		
6		
7		1
8		
9		
10		1
Total	6	7
Mean number of days	1.5	2

Table 4. Time taken for stoma to work or bowel to open (data in red for those without a stoma).

3.2 Outcome data

3.2.1 Anthropometry

To analyse the anthropometric data, comparisons were made within the two groups, intervention and control, at each of the three time intervals: from preoperative assessment to discharge from hospital; from discharge from hospital to 30 days post-surgery; and from preoperative assessment to 30 days post-surgery. Values for the mean difference within groups at each interval showed no significance for any anthropometric parameter. Indeed in all instances the confidence intervals of the difference include zero which indicates no effect of the intervention, as shown in tables 5 to 8, and figures 5 to 8.

	Pre-op to discharge		Discharge to 30d post-surgery		Pre-op to 30d post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean weight difference (kg)	-4.79 (SE 8.22)	-5.49 (SE 7.59)	0.29 (SE 8.1)	-0.314 (SE 7.17)	-4.5 (SE 8)	-5.8 (SE 7.85)
95% CI of the difference	-13 to 22.7	-11 to 22	-17 to 17	-15 to 15	-13 to 22	-11 to 22
P value	0.571	0.484	0.972	0.966	0.587	0.474

Table 5. Mean weight change (kg) within each group at each of the three time intervals explored.

	Pre-op to discharge		Discharge to 30d post-surgery		Pre-op to 30d post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean BMI difference (kg/m ²)	-2.01 (SE 2.42)	-1.84 (SE 2.21)	0.07 (SE 2.20)	-0.24 (SE 2.01)	-1.94 (SE 2.30)	-2.06 (SE 2.43)
95% CI of the difference	-3.28 to 7.31	-3.67 to 5.99	-4.87 to 4.72	-3.47 to 5.27	-3.07 to 6.96	-3.24 to 7.35
P value	0.423	0.611	0.975	0.662	0.415	0.414

Table 6. Mean BMI change (kg/m²) within each group at each of the three time intervals explored.

	Pre-op to discharge		Discharge to 30d post-surgery		Pre-op to 30d post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean MAMC difference (cm)	-0.91 (SE 2)	-1.45 (SE 1.68)	0.21 (SE 1.95)	-0.16 (SE 1.65)	-0.71 (SE 1.93)	-1.61 (SE 1.79)
95% CI of the difference	-3.44 to 5.28	-2.19 to 5.11	-4.47 to 4.05	-3.45 to 3.77	-3.49 to 4.91	-2.3 to 5.52
P value	0.914	0.401	0.917	0.925	0.720	0.386

Table 7. Mean change in MAMC (cm) within each group at each of the three time intervals explored.

	Pre-op to discharge		Discharge to 30d post-surgery		Pre-op to 30d post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean grip strength difference (mm)	-3.43 (SE 5.21)	-2.96 (SE 4.91)	0.86 (SE 5.30)	-0.96 (SE 4.51)	-2.57 (SE 5.11)	-3.93 (SE 4.81)
95% CI of the difference	-7.93 to 14.79	-7.73 to 13.65	-12.41 to 10.7	-8.9 to 10.8	-8.6 to 13.71	-6.55 to 14.4
P value	0.523	0.557	0.874	0.834	0.624	0.430

Table 8. Mean change in grip strength (mm) within each group at each of the three time intervals explored.

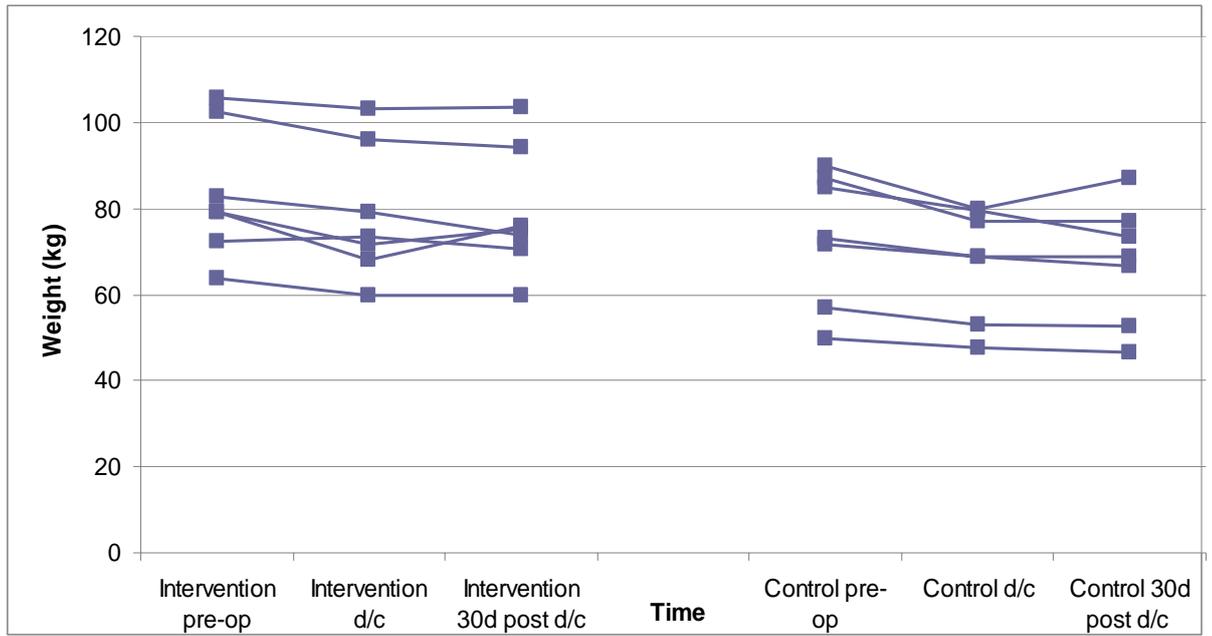


Figure 5. Changes in weight (kg) for each subject at the three time points.

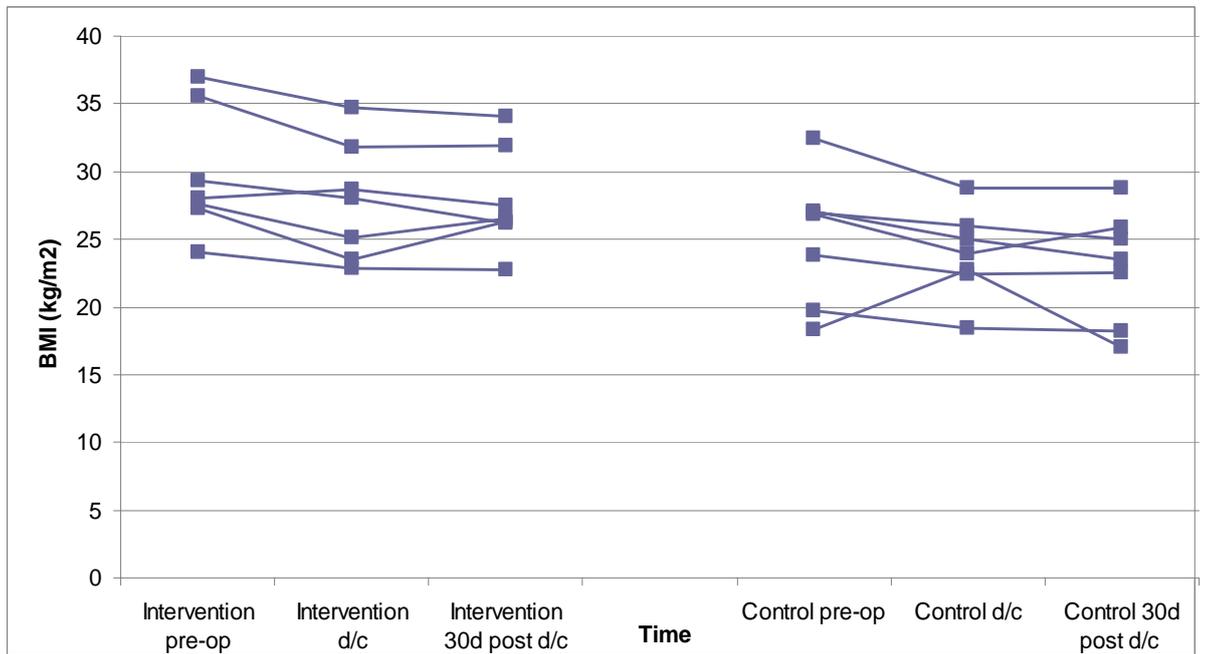


Figure 6. Changes in BMI (kg/m²) for each subject at the three time points.

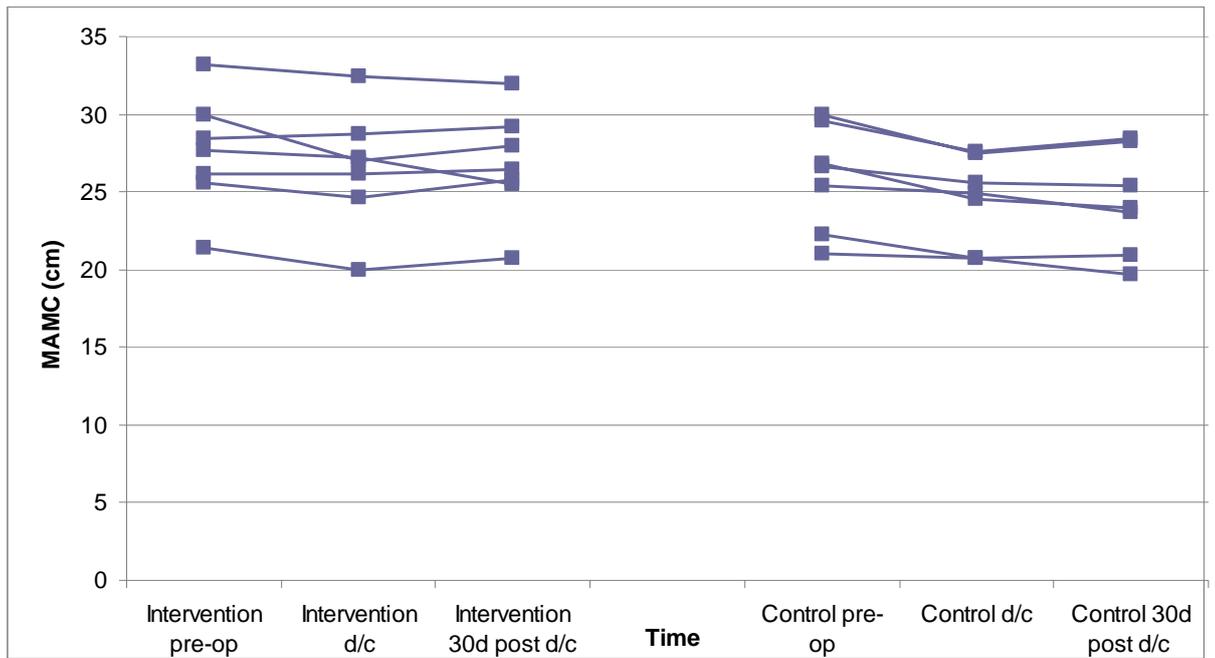


Figure 7. Changes in mid arm muscle circumference (MAMC) for each subject at the three time points.

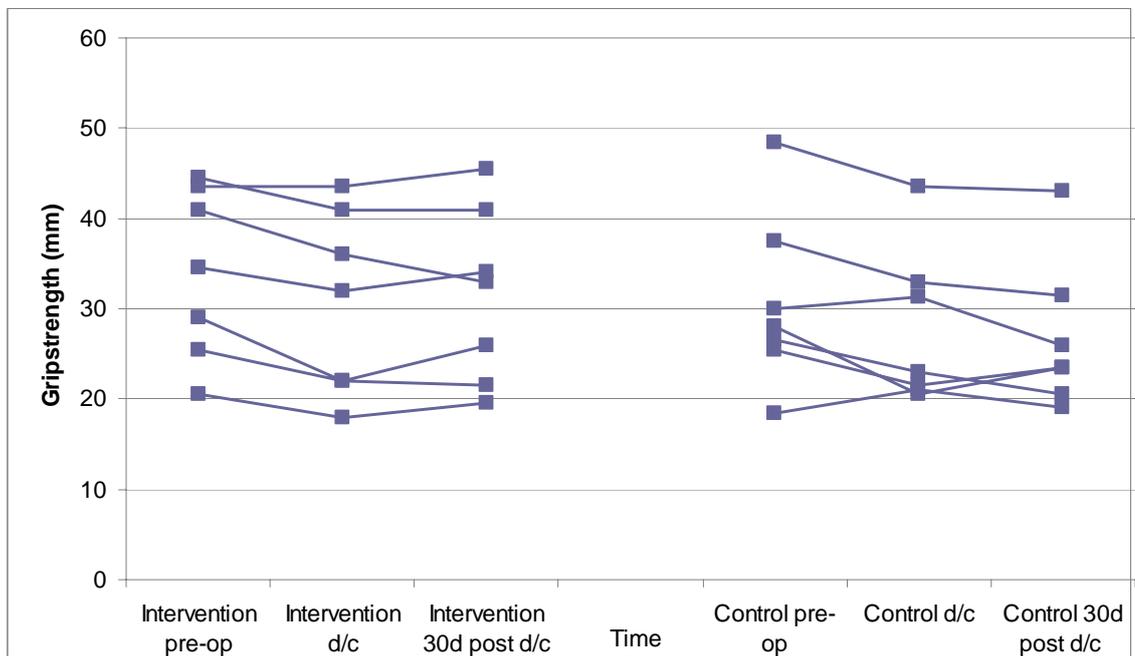


Figure 8. Changes in grip strength (mm) for each subject at the three time points.

3.2.2 *Nutritional intake*

Mean energy and protein intakes were compared between the intervention and control groups for days one to three post surgery. It was seen that energy and protein intakes were higher in the intervention groups than controls (tables 9 and 10). Despite this, comparison of mean intakes for the overall duration of admission showed the energy and protein levels to be higher in the control group (tables 11 and 12), although differences did not reach significance. Furthermore, there was no significant difference in the percentage of patients who met more than 90% of their requirements at any time point (tables 13 and 14, figure 9), and indeed very few patients were able to achieve this intake. In all instances the confidence intervals of the difference include zero which indicates no effect of the intervention.

	Day 1 post surgery		Day 2 post surgery		Day 3 post surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean energy intake (kcal)	551 (SD 683.1)	422 (SD 490.6)	769 (SD 465.4)	484 (SD 461)	911 (SD 507.7)	652 (SD 553.3)
95% CI of the difference between groups	-563.4 to 821.8		-282.1 to 852.7		-388.8 to 906.4	
P value	0.692		0.292		0.398	

Table 9. Mean energy intake (kcal) for each of the control and intervention groups at days one, two and three post surgery.

	Day 1 post surgery		Day 2 post surgery		Day 3 post surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean protein intake (g)	26 (SD 33.2)	16.8 (SD 19.4)	29 (SD 16.8)	23 (SD 22.2)	38 (SD 24.2)	23 (SD 18.9)
95% CI of the difference between groups	-22.5 to 40.8		-18 to 29.6		-11.6 to 42.2	
P value	0.541		0.602		0.237	

Table 10. Mean protein intake (g) for each of the control and intervention groups at days one, two and three post surgery.

	During admission in hospital		30 days post-surgery	
	Intervention	Control	Intervention	Control
Mean energy intake (kcal)	712 (SD 268.2)	867 (SD 282.4)	1880 (SD 482.9)	1845 (SD 839.8)
95% CI of the difference between groups	-475.8 to 165.7		-783.8 to 854.9	
P value	0.313		0.926	

Table 11. Mean energy intake (kcal) for each of the control and intervention groups.

	During admission in hospital		30 days post-surgery	
	Intervention	Control	Intervention	Control
Mean protein intake (g)	31 (SD 10.6)	45 (SD 16)	79 (SD 16.4)	81 (SD 35.5)
95% CI of the difference between groups	-30.5 to 3.28		-35.1 to 30.6	
P value	0.104		0.883	

Table 12. Mean protein intake (g) for each of the control and intervention groups.

	Day 1 post surgery		Day 2 post surgery		Day 3 post surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Number meeting >90% of energy requirements	2 (28.6%)	2 (28.6%)	0 (0%)	0 (0%)	2 (28.6%)	2 (28.6%)
P value (comparison between groups)	1.0		1.0		1.0	

Table 13. Number of subjects meeting more than 90% of their energy requirements.

	Day 1 post surgery		Day 2 post surgery		Day 3 post surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Number meeting >90% of protein requirements	6 (85.7%)	5 (83.3%)	0 (0%)	1 (14.3%)	5 (71.4%)	5 (71.4%)
P value (comparison between groups)	1.0		1.0		1.0	

Table 14. Number of subjects meeting more than 90% of their protein requirements.

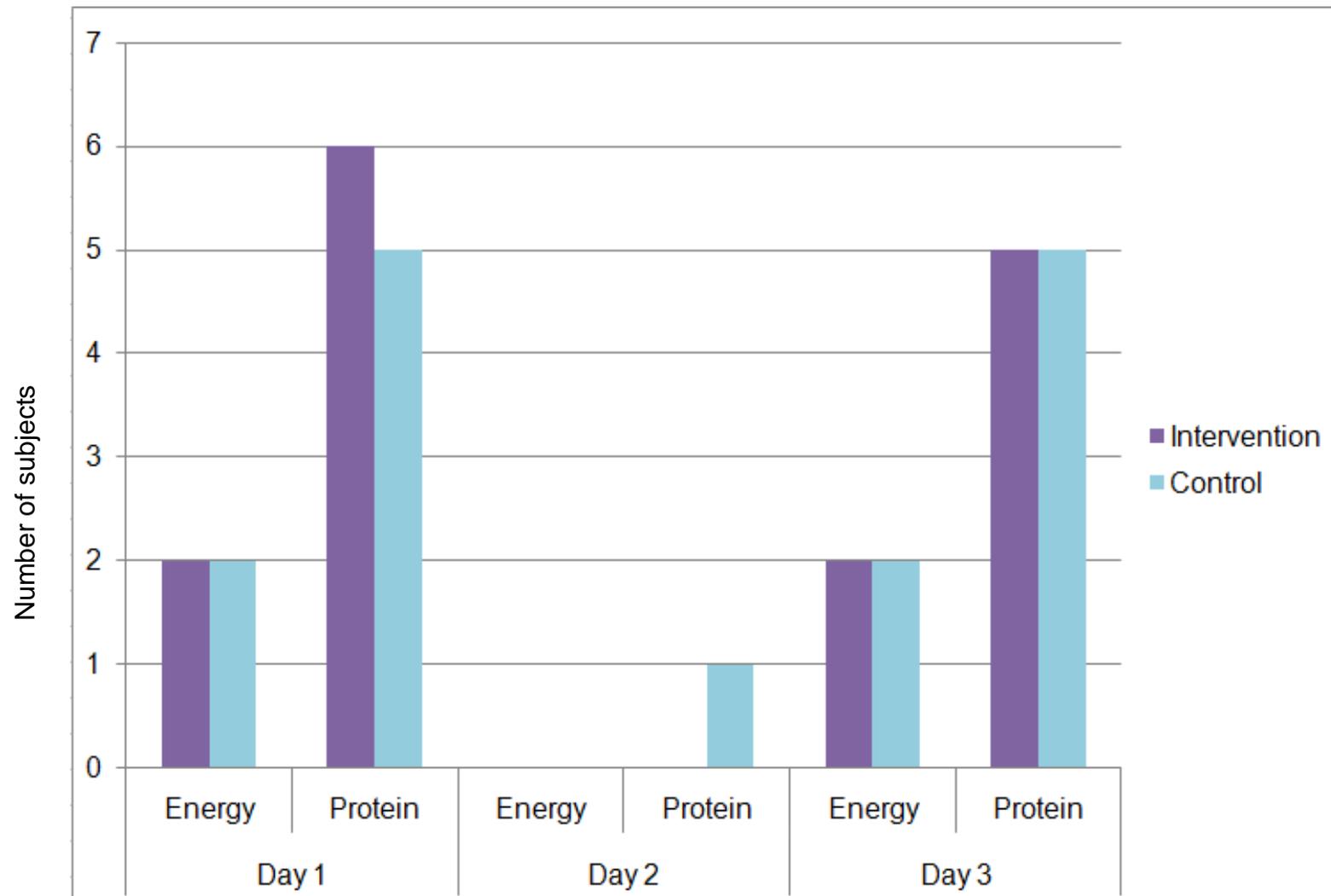


Figure 9. Number of subjects meeting more than 90% of their energy and protein requirements.

3.2.3 *Wellbeing and pain score*

The scores for each wellbeing parameter (anxiety, depression, hunger, inability to concentrate, malaise, nausea, pain, thirst, tiredness, unfit and weakness) were totalled and an average calculated for each patient at each time interval (preoperative assessment, during admission from hospital and 30 days post-surgery). Due to the format of the visual analogue scale used to gather these data, a higher score indicates reduced wellbeing. Results showed that mean wellbeing scores were higher in the control groups at each time interval (table 15) and therefore patients were more anxious, depressed, hungry and so on, although these results were not statistically significant.

The pain scores were assessed in the same way, and for these data a higher score indicated increased pain. Pain was not assessed pre-operatively, as outlined in the methods as the surgical intervention had not taken place. Mean pain scores were higher in the control group, with a significant difference seen at 30 days post surgery ($p=0.017$) (table 16).

	Preoperative assessment		During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean wellbeing score (SD)	18.68 (SD 14.39)	28.77 (SD 21.34)	30.89 (SD 11.68)	47.44 (SD 6.30)	16.14 (SD 7.39)	39.11 (SD 20.34)
95% CI of the difference between groups	-31.29 to 11.11		-33.32 to 0.21		-40.5 to -4.88	
P value	0.320		0.53		0.17	

Table 15. Mean values for wellbeing score of each of the control and intervention groups.

	During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control
Mean pain score (SD)	28.16 (SD 17.12)	33.17 (SD 18.6)	16.41 (SD 7.39)	39.11 (SD 20.34)
95% CI of the difference between groups	-25.85 to 15.82		-40.52 to -4.88	
P value	0.610		0.017	

Table 16. Mean values for pain score of each of the control and intervention groups.

3.2.4 Physical function

Three parameters were used to investigate physical function: physical activity duration, number of steps taken and total energy expenditure (TEE). Each of these parameters were measured at the same three time points as the anthropometry and nutritional assessment. Comparisons were made between the intervention and control groups, as shown in tables 17-19.

Although the figures varied between the control and intervention groups, there were no significant differences between groups over the course of the study.

	Preoperative assessment		During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean physical activity duration (hr:min)	1:13 (SD 0:46)	1:32 (SD 1:13)	0:06 (SD 0:05)	0:10 (SD 0:11)	0:46 (SD 0:30)	0:35 (SD 0:33)
95% CI of the difference between groups	-1:30 to 0:51		-0:13 to 0:06		-0:30 to 0:52	
P value	0.561		0.421		0.56	

Table 17. Mean values for physical activity (hr:min).

	Preoperative assessment		During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean number of steps	5658 (SD 3875)	7698 (SD 4607)	575 (SD 402)	390 (SD 188)	4079 (SD 4295)	3059 (SD 2131)
95% CI of the difference between groups	-6998 to 2917		-181 to 551		-3341 to 5381	
P value	0.387		0.292		0.614	

Table 18. Mean values for the number of steps taken.

	Preoperative assessment		During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean TEE (kcal)	2286.9 (SD 591.7)	2303.6 (SD 692.4)	1763.1 (SD 213.1)	1613.1 (SD 276.9)	2026.4 (SD 472.9)	1851.7 (SD 506.7)
95% CI of the difference between groups	-766.8 to 733.3		-137.8 to 437.8		-455.7 to 805.2	
P value	0.962		0.278		0.551	

Table 19. Mean values for the total energy expenditure (TEE) (kcal).

3.2.5 *Resting data*

Comparisons were made between groups for sleep duration and hours spent lying down using independent sample T-tests, as shown in tables 20 and 21. These analyses showed no significant differences however the direction of the data goes towards longer sleep duration in the control group at each time period.

	Preoperative assessment		During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean hours of sleep (hrs:mins)	5:45 (SD 1:58)	5:51 (SD 2:56)	3:31 (SD 1:21)	4:08 (SD 2:05)	6:42 (SD 1:23)	7:27 (SD 0:45)
95% CI of the difference	-3:00 to 2:49		-2:40 to 1:25		-2:20 to 0:49	
P value	0.944		0.519		0.302	

Table 20. Mean values for the hours of sleep taken.

	Preoperative assessment		During admission		30 days post-surgery	
	Intervention	Control	Intervention	Control	Intervention	Control
Mean hours spent lying down (hrs:mins)	7:31 (SD 2:01)	7:10 (SD 3:50)	5:55 (SD 3:18)	5:26 (SD 3:07)	8:28 (SD 1:24)	9:42 (SD 1:00)
95% CI of the difference	-3:13 to 3:54		-3:15 to 4:14		-2:55 to 0:27	
P value	0.837		0.781		0.133	

Table 21. Mean values for the number of hours spent lying down.

3.3 Process outcomes

3.3.1 Length of time on HDU and length of admission

All participants were admitted to the Intensive Care Unit or Surgical High Dependency Unit (HDU) following their surgery. No significant differences were seen between groups for length of time on HDU or total length of admission (table 22).

	Intervention	Control	95% CI of the difference	P value
Length of time on HDU (days)	4 (SD 3.2)	5 (SD 1.7)	-4.1 to 1.8	0.419
Length of admission (days)	9 (SD 4.74)	13 (SD 7.5)	-11.8 to 2.9	0.212

Table 22. Mean values for length of time spent on HDU, and length of admission.

3.3.2 Complications

Complications related to the surgery were experienced by three intervention participants and four control participants, as shown in table 23. The most common complication overall was postoperative nausea and vomiting however there was no significant difference in complications experienced between groups.

Complication	Intervention	Control	P value (comparison between groups)
Nausea and vomiting	2 (29%)	3 (42.9%)	1.0
Ileus	1 (14.3%)	2 (29%)	
Thrombus	0	1 (14.3%)	
Infection	0	1 (14.3%)	
Any of the above	3 (42.9%)	4 (57.1%)	

Table 23. Complications experienced by participants.

3.3.3 POSSUM scores

POSSUM scores for morbidity and mortality were calculated for each patient by their respective consultant surgeon, as shown in table 24. It can be seen that the scores were higher in the control group than the intervention group. No statistical analysis was carried out as this was additional data collected for surgical purposes.

Group	Patient no	POSSUM morbidity	POSSUM mortality
Intervention	1	26.115	1.086
	2	13.5	0.6
	3	35.4	1.3
	4	43	1.9
	5	38.7	2.3
	6	40.854	2.085
	7	42.311	2.028
	Median	38.7	1.9
Control	1	36.355	1.791
	2	45.5	2.4
	3	39.2	1.5
	4	23.148	0.918
	5	76	6
	6	62.5	3.2
	7	54.983	3.279
	Median	45.5	2.4

Table 24. POSSUM scores for morbidity and mortality for each participant.

4. Discussion

This pilot study has investigated the role of preoperative carbohydrate loading in improving recovery after colorectal surgery, focusing particularly on the long-term effects, an area for which there is currently limited evidence.

The trial showed that the direction of the data was towards a reduction in length of hospital stay, although this did not reach significance possibly due to a small sample size. Further results in this study suggest that carbohydrate loading may have long-term benefits including better retention of weight and muscle mass, improved nutritional intake, improved wellbeing and improved return of physical function at 30 days post surgery. Furthermore the results may back up research on the benefits immediately post surgery, including preservation of lean body mass, improved well-being and reduced postoperative complications. Whilst none of these results showed significant differences, this pilot study could be used as the basis for a larger randomised control trial.

4.1 Baseline data

Participants were allocated randomly to either the control or intervention groups but due to the small number of recruits, the two groups were not matched exactly for gender. Indeed the study overall included more than double the number of males than females and whilst it is known that colorectal cancer affects more men than women, this is not exactly representative of national incidence. In 2007 diagnosis rates were reported as 17,100 male cases and 14,400 female cases (Office for National Statistics, 2010). The age range for both groups also varied, with a range of almost 40 years in the control group, and only approximately 20 years in the intervention. Despite this though, the median age was similar for each group, and again representative of national statistics, which show that of those people diagnosed with colorectal cancer, greater than four out of five will be over the age of 60 years (Office for National Statistics, 2010).

The mean weight at baseline differed by 12.2kg between the groups with the mean BMI for the control group within normal weight range, however subjects within the intervention group were on average overweight. It could be argued that as the data analysis considered mean weight change within each group and not between groups then this may not have affected the results. The mean anthropometry data for each group showed that these participants were on average not depleted. Whilst these data were taken as their baseline, it may not be representative of the recruits' 'normal' status and the following factors may have influenced this:

4.1.1 Altered metabolism.

When participants were recruited to the study they may have been suffering with cancer for a period of time, and therefore the baseline weight which was recorded may not have been reflective of their 'normal' weight. The study did not examine whether participants had already lost weight at their baseline assessment and this would have been valuable to know as recent unplanned weight loss has been shown to be an independent risk factor for malnutrition (Parekh and Steiger, 2004). All patients who were entering the study at baseline were likely to have had increased energy demands due to their cancer, as tumour presence increases resting energy expenditure (Hyltander et al., 1991) and this alone could have resulted in weight loss.

4.1.2 Reduced oral intake

The baseline results showed that 1/7 of participants in both the control and intervention groups were meeting greater than 90 per cent of their energy requirements whilst the number of patients meeting this target for protein was higher in the intervention group, though still not optimal. This compromised intake could have been due to symptoms experienced secondary to their cancer, for example abdominal pain (Nygren, 2006) or altered bowel habits. It is also possible that anxiety may have affected dietary intake as this is a common emotion associated with a cancer diagnosis; furthermore recruits were

assessed at a maximum of one week prior to their surgery and therefore may have been apprehensive about their forthcoming treatment and the risks involved. Anxiety was considered as part of the wellbeing assessment at baseline and the results showed that patients in the intervention group had a greater feeling of wellbeing than those in the control at baseline though this was not significantly different ($p=0.320$). Previous research by Hausel et al (2001) has only examined the effect of carbohydrate loading on the state of wellbeing, and not studied the potential effects that this may have, for example whether this may independently affect pain scores or length of hospital stay.

The data for physical activity and number of steps showed the patients to be quite sedentary, and again no significant differences were seen between groups. This again could be related to symptoms secondary to their tumour, but also it was noted that a number of patients reported at their baseline assessment that they were 'resting' prior to their surgery and therefore these data may not be representative of their normal status. Each group took a similar number of hours sleep per day.

4.2 Preoperative assessment to discharge from hospital

Between baseline preoperative assessment and discharge from hospital the control group had a greater decrease in weight and mid-arm muscle circumference than the intervention group, which may suggest that the carbohydrate drink helped to preserve lean body mass, although there was no significant difference between the two groups. It is interesting however that the results for grip strength showed the control group lost less strength than the intervention group, and whilst this was not statistically significant either it did not reflect previous studies which had shown less reduction in hand grip strength when subjects were given preoperative carbohydrate loading (Noblett et al., 2006 and Henriksen et al., 1999). However, these studies examined dominant hand grip strength, whereas this study looked at the non-dominant hand as this is normal practice within the UK.

The results for physical activity showed that during admission the control group were slightly more active. Interestingly, however the results for the mean number of steps taken and the TEE do not reflect this as the mean values for each of these parameters were higher in the intervention group. Comparison of results for physical function between the two groups were not significantly different and it is also possible that there are some inaccuracies in the recordings. Therefore further research is required to consider the study hypothesis that carbohydrate loading results in improved return of physical function post surgery.

Previous research by Yuill et al (2005) suggested that preoperative carbohydrate loading preserves lean body mass by increasing glucose supplies. In combination with a decrease in insulin resistance, then the net result is increased glucose uptake and a reduced need for other substrates, thereby preserving protein and fat stores.

A further explanation for the preservation of lean body mass could be the direction of data towards a higher energy and protein intake in days 1-3 post surgery in the intervention group, however this was not statistically significant. It could be suggested that if more energy was being supplied extrinsically then less would be required from intrinsic stores. Indeed previous studies have shown that when post-operative nutrition is optimised in combination with preoperative carbohydrate loading then nitrogen losses are reduced (Soop et al., 2004; Svanfeldt, Thorell, Nygren and Ljungqvist, 2006), However, in the present study there were still few subjects in either group meeting more than 90% of their energy and protein requirements. The increased oral intake in the intervention group may also be a reflection of the greater feeling of wellbeing seen in this group during their admission. In particular this score included the feeling of nausea, and whilst this wasn't considered independently, it was recorded as a complication and shown to be lower in the intervention group, though not statistically significant. Other studies have shown conflicting responses, with Hausel et al (2005) finding a significant reduction in nausea

and vomiting in patients given preoperative carbohydrate loading, however Bisgaard et al (2004) saw no association.

A further factor that may have promoted nutritional intake is the finding that pain scores were significantly lower in the intervention group. The validity of dietary data should be considered as daily intake during admission was recorded by nursing or support staff, however the records were checked daily with the patient by the researching dietitian. It is possible that participants could have completed the food diaries themselves however this could have been considered an added burden for them or also affected validity. It is well known that dietary assessment is open to inaccuracies (Beaton, Burema and Ritenbaugh, 1997) and these could be either accidental or intentional for example portion sizes may have been recorded inaccurately by staff or participants, or foods may have been forgotten or purposely omitted. It is also possible that participants may have been unwilling to disclose information on their dietary habits, especially as they knew it was being analysed by a dietitian. Previous research has suggested that subjects may see analysis of dietary routines as invasion of their privacy (Blundell, 2000), however these participants all consented to the study knowing that dietary data would be collected and therefore may be less likely to withhold information. Furthermore there is a chance that inaccuracies could have come about from imprecise interpretation of data when entering the data into the analysis software, for example error in portion sizes. This however is likely to be consistent for all participants as it was only the one researcher who carried out all the analyses.

Resting data showed variation between groups during admission as the intervention group were seen to spend more time lying down however less time asleep. There are many factors that may have affected these parameters, and pain and wellbeing could be considered to have a negative impact on sleep, however whilst these scores were lower in the intervention group they were not statistically significant. It is possible that other

factors, for example general noise on the ward and interruptions from nursing and medical staff may have affected sleep. Another factor may have been physiotherapy input as this may have affected hours spent lying down, and physical activity levels. Physiotherapy from the day of surgery is part of the Enhanced Recovery After Surgery (ERAS) programme AT SRFT and therefore all patients should have received this, though the intensity would depend on each individual and their ability to mobilise. Whilst these data weren't collected, this could be considered in future research as a possible factor affecting physical function and resting data.

4.3 Discharge from hospital to 30 days post surgery

During this time period perhaps of the most interesting and clinically relevant results were seen which would warrant future research. Weight and therefore BMI were shown to increase in the intervention group, and yet decrease further in the control group, though due to the small sample size these were not statistically different. Similarly MAMC and grip strength followed the same pattern, however significance levels were not achieved again. The data for grip strength is particularly interesting as the results of the intervention group were shown to increase following discharge, whereas in the control group they decreased. Whilst none of the grip strength results were statistically significant the direction of the data could suggest that the period following discharge is clinically important and that the benefits of carbohydrate loading do extend for longer than the days immediately post-surgery. It is known that the catabolic period can extend for up to two to four weeks in this patient population (Thorell et al., 1994) however if this catabolic response is reduced in those patients receiving preoperative carbohydrate, as previously explained, then this may explain why they are not losing intrinsic energy stores.

Whilst it may be expected that dietary intake would also affect weight and lean body mass, the results at 30 days post surgery showed similar intakes between the two groups, with the intervention group taking on average slightly more energy, yet less protein.

Despite this, the number of participants who were meeting more than 90% of their energy and protein requirements were exactly the same in both groups. It is interesting that these data showed that only 28.6% of patients in the intervention group were meeting more than 90% of their energy requirements and yet on average these patients were gaining weight. This could reflect inaccuracies in both reported intake using a food diary and also the accuracy of the estimated calculated requirements. The equation used to calculate energy requirements was the Schofield equation (Schofield WN 1985) however these calculations are based on studies conducted between 1914-1980, of which almost half of the subjects were Italian military adults. It could be argued that this population is not likely to be comparable the population being studied in this trial due to the likely differences in lifestyle, physical activity levels, diet and the effect these would have on BMR. As an alternative the more recent Oxford equations (Henry 2005) could have been used as these include data from a greater number of individuals, from studies up to 2005, and exclude outliers and extreme circumstances (for example high altitude data).

Another method to collect data on dietary intake could have been used, for example a seven day weighed food record. However this would have been more labour-intensive and therefore compliance may have been affected; also this may have affected recruitment to the study due to the additional effort required. It is recommended to use independent measures of validity for all methods of dietary assessment (Black et al., 1993) and in this study it was possible to assess the validity of reported energy intake by comparing with energy expenditure. This was measured using the Sensewear armband, a method which itself has been validated against doubly labelled water (Mignault et al., 2005). Indeed the mean results for total energy expenditure and energy intake per day at 30 days post surgery showed a difference of 146.3kcal in the intervention group and 7.1kcal in the control group, showing that these may actually be accurate representations of energy intake. Protein intake was unable to be validated as the usual method would be

to use 24-hour nitrogen excretion (Black, Bingham, Johansson and Coward, 1997) however there was not the adequate equipment available to use this method in this study.

Wellbeing continued to be greater in the intervention group at 30 days surgery however this was not significantly different. Whilst this seemingly had no effect on energy and protein intake, it could be related to physical function and thus their improved anthropometry results. All measures of physical function, (physical activity duration, number of steps and TEE) were higher in the intervention group than the control. It could be suggested that if wellbeing parameters were lower, for example weakness, nausea, tiredness and malaise then subjects may have felt more able to mobilise; therefore if participants are being more active they are more likely to retain muscle mass. Pain scores were significantly lower ($p=0.017$) at 30 days post surgery and this too may have contributed to the difference in physical activity levels. The confidence interval of this difference confirmed that the score in the control group was higher than the intervention group and demonstrated that this study was powered enough for the detection of differences in VAS scores for pain between groups. It is significant that participants were still in pain at this time following surgery, and this further supports the theory that recovery may be improved in those given a preoperative carbohydrate loading. This may also relate to the resting data, according to which the control group spent a longer duration lying down each day, and also slept for longer.

4.4 Preoperative assessment to 30 days post surgery

Having already examined the effects of preoperative carbohydrate loading at different time intervals throughout the study, these results enable us to establish the overall effects seen from commencing the study through to the final assessment at 30 days post-surgery. An overall direction in data of reducing weight, MAMC and grip strength was seen, and whilst these appeared to be reduced more in the control group, no significant differences were seen. The trend would warrant further research to investigate the hypothesis, as already

discussed, that carbohydrate loading results in better retention of weight and muscle mass at 30 days post surgery.

Upon comparing energy and protein intakes within groups at 30 days post surgery with those at baseline it could be seen that the intervention group consumed very slightly more energy at 30 days post surgery, whereas the control group consumed less at this time, however a level of significance was not achieved. Whilst this could be interpreted that when patients are given preoperative carbohydrate loading their energy intake returns to their 'normal' baseline level quicker, the same cannot be said for protein intakes and more interestingly when comparing the percentage of subjects meeting more than 90% of their energy and protein requirements at the two time intervals there was no difference seen at all. Therefore it is likely that at 30 days post surgery, preoperative carbohydrate loading is no longer having an effect on dietary intake and therefore may disprove the secondary aim of the study, although it should always be kept in mind that this may be due to chance and if a larger group were studied then more significant results may have been seen.

Wellbeing cannot be compared between the two intervals since the assessment at baseline was shortly prior to surgery and therefore not representing a 'normal' psychological state for subjects (Sutherland, 1952). Furthermore, subjects at 30 days post surgery may still have anxieties regarding their surgery and their recovery, especially as at this time point they may not have received the histology results from their surgery and therefore may be anxious about whether future treatments are required.

Physical activity data showed that neither group had returned to their baseline activity level. The intervention group were closer to their baseline than the control for each parameter suggesting that they may be recovering more quickly however a level of statistical significance was not achieved. Similarly the resting data showed that neither group was near to their baseline data, with both taking on average more rest and sleep 30 days post surgery. However, again the intervention group was closer to baseline than the

control. It should be considered however that both groups may have been resting more following their surgery as patients perceive rest as part of their recovery from surgery..

4.5 Process outcomes

4.5.1 Complications

It was seen that complications were experienced less in the intervention group than the control group however this result was not statistically significant, reflecting the results of Yuill et al., (2005) and Noblett et al., (2006) where no reductions in complications were seen when preoperative carbohydrate loading was given. This conflicts with Ljungqvist et al., 2005 where the results suggested that preoperative carbohydrate loading reduces insulin resistance and thus hyperglycaemia, which has previously been shown to independently reduce the risk of complications.

Furthermore the rate of infection was lower in the intervention group than the control group, though this was not statistically significant either. Previous research by Rasmussen et al., (1985) showed that preoperative carbohydrate loading may improve immunity. This could also be attributed to the reduction in insulin resistance which would reduce the cytokine response and thus catabolic effect. However, this current study does not support the work by Rasmussen et al., (1985).

4.5.2 POSSUM scores

POSSUM scores also varied between groups, and it was seen the intervention group had lower scores for both morbidity and mortality. Seemingly other studies have not investigated whether this treatment directly affects POSSUM scores, however of the parameters which are considered when calculating the score, there are only 5 of the 10 which may be attributed to the stress response. The remaining parameters, including cancer stage, severity of operation, age and mode of surgery, will not be affected by

carbohydrate loading. As the groups were not matched for these parameters then it could be argued that comparisons cannot be made between groups for POSSUM scores.

4.5.3 Gastrointestinal function

Gastrointestinal function was measured by examining the time taken for stoma to function or bowels to open. There was no difference between the mean length of time for either group, however it should be remembered that data was missing for one subject of the intervention group. Previous studies have shown trends towards a quicker return of gastrointestinal function when preoperative carbohydrate loading was given (Noblett et al., 2006 and Henriksen et al., 2003) however these observations were not significant and therefore may be due to chance.

4.5.4 Length of stay and time on HDU

There was a direction in the data towards a reduction in length of stay in the intervention group, which although not statistically significant, may back up previous research (Yuill et al., 2005; Ljungqvist, Nygren and Thorell 1998; Noblett et al., 2006). As insulin resistance is linked to length of stay (Thorell et al., 1999) then these findings suggest that preoperative carbohydrate loading may reduce the length of hospital stay by reducing insulin resistance. This could potentially have major cost implications for the NHS. Currently the average cost of an inpatient bed on a standard surgical ward at SRFT stands at £227. Based on this study whereby 101 patients were eligible within 22 months, this means an average of 55 patients per year undergo potentially curative surgery for colorectal cancer. Should these 55 patients see the average reduction in stay of approximately four days that was demonstrated in this study then this would save the Trust £49940 per year. Accounting for the cost of the drink, which is currently bought in at £5.68 for the three doses per person there is the potential to save an estimated total of £49628 annually for this Trust.

The time on HDU should also be considered as this was shown to be approximately one day less in the intervention group. This too will have cost implications as within SRFT the cost of an HDU bed currently stands at £354, which is £127 more than a bed on a standard surgical ward. Therefore by reducing the stay on HDU this is further reducing NHS costs. In addition to the cost effects, a reduced HDU stay may also have beneficial psychological effects for patients. It is likely that patients see the move from a high dependency to a general ward as a large step forward in their recovery and this may improve their mental wellbeing. It is therefore possible that the reduction in HDU care may contribute towards a greater wellbeing postoperatively. Another factor which patients report is lack of sleep on the HDU due to noise of machines alarming and the increased activity of nursing and medical staff on the ward. This finding does not correlate with the data for hours of sleep, whereby the intervention group had less sleep than the control, but these results were an average of the total admission and not just the period of time whilst on HDU.

At the time of the final assessment, if there were concerns identified regarding dietary intake or weight loss then subjects were given the option to be referred to the dietitian for further support. In total five subjects were considered to be suitable for further dietetic monitoring and all accepted the referral. Of these three were in the control group, compared with only one in the intervention group, and whilst it was not possible to analyse these due to the small numbers it is possible that this supports the theory of improved recovery in those who received preoperative carbohydrate loading.

4.6 Recruitment

Poor recruitment to the trial was the primary weakness to this study. Whilst it was originally agreed that 90 participants in each arm, as suggested by the power calculation, was in excess of that which one researcher could achieve in the time scale required, it

was still not possible to recruit the desired 10 recruits in each arm. There are several factors which may have influenced this:

4.6.1 Sensitivity of the area

All patients who were invited to partake in the clinical trial had just received a diagnosis of cancer. It was appreciated that this would be likely to have an extreme psychological impact on many patients and as such it is possible that involvement in the study may have been perceived as an added stress or burden. Additionally it could be proposed that patients may have felt that by receiving an alternative preoperative treatment that their outcome could have been adversely affected. This was addressed in the participant information provided at the time of invitation, and it was explained there that would be no risk of any detrimental outcome. However it was also explained that there was a chance that their recovery *could* be improved should they receive the carbohydrate drink. Seeing as preoperative carbohydrate loading is standard practice for all colorectal patients at the hospital, potential recruits may have felt that they had a better chance of an improved outcome by receiving the standard practice, a guarantee if they were not part of the study.

4.6.2 Invitation

In order to avoid bias the principal researcher was unable to invite participants to partake in the clinical trial. It was therefore initially agreed with the colorectal nurses that as they see all patients in outpatient clinic with the consultant at the time of diagnosis and upon consenting to surgery, then they would provide the invitation during this appointment. This however relied upon them providing the invitation to every patient who met the eligibility criteria. The principal researcher also attended the weekly multi-disciplinary meeting in which all patients being investigated for colorectal cancer were discussed. It became apparent after two to three months however that occasionally nurses were either forgetting to provide the invitation to patients during particularly busy clinics, or selectively

choosing not to when patients were particularly upset or deemed by the nurses to be inappropriate. At this time, a specialist ERAS nurse had been recruited within the hospital that would be seeing every colorectal patient due for surgery. It was agreed that the ERAS nurse would therefore provide the invitations to patients. Furthermore it was proposed that this arrangement would improve liaisons between the nurse and the researcher and also reduce subjective opinion on eligibility.

4.6.3 Response times

A further complication was that of the limited time available between diagnosis and surgery. National government targets require all patients to be seen by a specialist within two weeks of being referred for suspected cancer, and to wait no more than 31 days to receive treatment once diagnosis is confirmed (Department of Health, 2009). Therefore in many cases once the decision to undergo surgery had been made, there was then only a short time period before their admission which may have been less than a week. Often this was not an adequate timeframe to allow patients to think about the trial and make a decision regarding participation. If they did decide to partake then it took time to send back their tear-off slip from the invitation and consent form through the post. Furthermore, the patient then needed to undergo the pre-op assessment a minimum of 3 days prior to admission in order to collect baseline data from the Sensewear[®] armband and food diaries at home.

A change in inclusion criteria was approved by the local ethical committee in February 2009 following an initial slow uptake as it was felt that the number of patients undergoing laparoscopic surgery was increasing, and therefore they should be included in order to capture a greater number of recruits. Also this would enable a better reflection of the population undergoing potentially curative colorectal surgery for cancer. However, following the change in criteria, only one patient who was recruited underwent laparoscopic surgery and therefore this patient was not included in the data analysis due

to differing stress responses between laparoscopic and open surgeries as previously explained.

4.7 Potential confounding factors

4.7.1 Gender

Research has shown that the cytokine response may vary according to gender, indeed in small study (n=25), Ono, Tsujimoto, Hiraki, Takahata, Kinoshita & Mochizuki (2005) showed that cytokine response and surface antigen expression in monocytes were significantly higher in females (n=9) than males (n=16) prior to and after surgery for gastric carcinoma. A further study by Schneider, Schwacha and Chaudry (2006) found similar results relating to gender in mice models. This has seemingly not been considered in relation to carbohydrate loading, however it could be suggested that if women undergo this increased cytokine response then this could therefore further reduce their insulin sensitivity. This is of relevance as gender was not previously considered to be a variable in this study and therefore groups were mixed for male and females. With the small number of recruits it was not possible to match the groups for gender and therefore it is possible that differences seen may be affected by differing immune responses and thus levels of insulin resistance.

4.7.2 Analgesia use

Epidural analgesia is the infusion of localised anaesthesia via a catheter into the epidural space (outer part of spinal canal) as a method for pain relief post surgery. However, it has been shown to also reduce insulin resistance as it impedes the release of stress hormones, which in turn reduces the hypermetabolic effects seen post surgery (Ljungqvist et al., 2005; Uchida, Asoh, Shirasaka & Tsuji, 1988). Within the present study, groups were not matched for epidural use and therefore this may have affected insulin resistance and thus their post-operative recovery.

Furthermore, opioid use was not monitored and this may have affected dietary intake due to its effect on gastric and gut motility (Ljungqvist et al., 2005).

4.7.3 Cancer stage

Cancer stage may be a confounding factor for this study as groups were not matched for this. It is evident that those patients with tumour invasion and metastasis are likely to be more stressed as tumour growth results in increased REE (Hyltander et al 1991). It would therefore be expected that those patients with larger tumours and metastasis (stages II to IV) would have a higher metabolic rate than those of stage I. Indeed Cao et al (2010) demonstrated those patients with stage IV cancer had a higher REE than those with stages I-III.

4.7.4 Length of surgery

Within this study the groups were not matched for length of surgery, and this has been shown to independently affect insulin sensitivity (Thorell et al., 1993). It is therefore possible that the trends seen and believed to be due the preoperative carbohydrate loading may have also been affected by varying insulin sensitivities as a result of different surgery durations. On reflection it would have been advantageous to gather data from the surgery notes on duration of surgery in order to conclude whether this may have been a confounding factor.

5. Conclusions

This study set out to test the hypothesis that preoperative carbohydrate loading results in longer term improvements in wellbeing, sustained return of postoperative physical function and better retention of muscle mass and nutritional status.

Overall the data suggested that there was no effect of preoperative carbohydrate loading seen in any parameter with the exception of pain (table 25). All values from statistical analysis, with the exception of pain at 30 days post surgery were >0.1 and therefore no trends were seen. It is likely that this was due to the small sample size, which was considerably lower than that required by the power calculation.

	Outcomes	Objectives	Hypotheses	Hypothesis supported (✓) or not supported (x)
Main aim	To investigate the long-term effects of preoperative carbohydrate loading on colorectal patients			
Primary	Weight and anthropometry as a measure of nutritional status	To investigate whether carbohydrate loading affects changes in weight and anthropometry from pre-op to 30 days post surgery	Carbohydrate loading results in better retention of weight and muscle mass at 30 days post surgery.	x
Secondary	Nutritional intake as a measure of nutritional status.	To investigate whether carbohydrate loading affects nutritional intake post-operatively.	Carbohydrate loading improves nutritional intake and status immediately post-surgery and at 30 days post surgery.	Immediately post surgery: x 30 days post surgery: x
Other outcomes	Relationship between carbohydrate loading and wellbeing.	To investigate whether carbohydrate loading affects wellbeing and pain scores pre-operatively up to 30 days post surgery.	Carbohydrate loading results in short and longer term improvements in wellbeing.	x Pain at 30 days post surgery: ✓

	Time spent on a high dependency unit (HDU) and overall length of stay in hospital.	To investigate whether carbohydrate loading affects the number of days spent on HDU and length of stay.	Carbohydrate loading reduces length of time spent on HDU and overall length of stay.	x
	Activity levels as a measure of physical function	To investigate whether carbohydrate loading affects physical activity levels.	Carbohydrate loading results in improved return of physical function post surgery.	x

Table 25. Summary of study outcomes related to proposed hypotheses.

6. Future research

This pilot study certainly warrants further research and clearly this would need to include a larger sample size. Although only one significant result was found, there were differences seen between groups and it is possible that with a larger sample some significant findings could be seen, with potential consequences for clinical practice. It would also be interesting to examine the effects for longer than 30 days, as the significant increased pain in the control group was seen at 30 days post surgery and therefore the effects of preoperative carbohydrate loading may last further past this time point. A further suggestion would be to reduce the number of aims studied in future research in order to reduce the chance of results being due to other variables.

9. Implications for practice

The results of this study could have been beneficial to the NHS if positive, for example cost savings could be made, and the patient journey improved. This could also impact on dietetic referrals as it is possible that carbohydrate loading may improve nutritional intake post surgery. Furthermore, it is possible that these findings could also be extrapolated, or suggest future research opportunities for other surgical areas, for example elective orthopaedics or gynaecology. A further possibility is to consider the option of increasing the dose of carbohydrate given, considering that this may enhance the effects of improved

recovery. However a larger dose may affect osmolality and therefore gastric emptying, making it unsafe to use.

Aside from the clinical findings of this study, what is also relevant is that through carrying out this comprehensive research study an appreciation has been attained of the difficulty of undertaking research. The poor recruitment rates and other difficulties were not expected and demonstrated why larger scale studies take place over such a long time scale and require so many investigators. Indeed, it also highlights the importance of interpreting other studies with caution and thoroughly examining research methods and confounding factors before accepting the findings of the study.

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Appendix 1

Sample Size Calculation Information

1. Variables of interest (type of data):

- Weight (Continuous)
- Body mass index (Continuous)
- Mid Arm Muscle Circumference (Continuous)
- Well-being (Measured using Visual Analogue Scale) (Continuous)
 - i. Hunger
 - ii. Thirst
 - iii. Tiredness
 - iv. Nausea
 - v. Anxiety

2. The desired power

80%

3. The desired significance level

P<0.05

4. The effect size of clinical importance

- Weight: -10%
- Arm Muscle Circumference (AMC) : loss of muscle mass, indicated by change in AMC from baseline to discharge, was significantly greater in the control group (control -1.1 ± 0.15 cm; carbohydrate drink -0.5 ± 0.16 cm, P<0.05, t-test) (Yuill et al., 2005, p 35)
- VAS: Unable to use in calculation as rank not ratio data

5. Mean and Standard deviation of continuous outcome variables (based on prior studies)

Arm Muscle Circumference (Bishop et al., 1981)

	AMC 50 th centile	SD AMC*
Males 45-54 y	28.1 cm	2.2
Males 55-64 y	27.9 cm	1.75
Females 45-54 y	22.2 cm	2.2
Females 55-64 y	22.6 cm	2.53

- The approximate SD had to be estimated from Mid arm circumference and triceps skinfold data (Frisancho AR, 1990) as Bishop et al. (1981) did not publish SDs.

Weight (kg) Frisancho (1990)

	Mean Weight	SD
Males 45-49.9 y	80.8 kg	14
Males 50-54.9 y	79.5 kg	13.9
Males 55-59.9 y	79.4 kg	13.9
Males 60-64.9 y	77.3 kg	13.1
Females 45-49.9 y	68.2 kg	16.3
Females 50-54.9 y	68.3 kg	14.8
Females 55-59.9 y	69.2 kg	16.3
Females 60-64.9 y	68.0 kg	14.2

6. One- or two-sided tests

Two sided test

7. Design of the study:

- randomised controlled trial
- includes repeated measures
- groups of approximately equal size

SAMPLE SIZE CALCULATIONS

Weight Based Calculations

Group	N per group (independent measures)	N per group (repeated measures)
Males 45-49.9 y	48	26
Males 50-54.9 y	48	26
Males 55-59.9 y	49	26
Males 60-64.9 y	46	25
Females 45-49.9 y	90	?
Females 50-54.9 y	74	?
Females 55-59.9 y	88	?
Females 60-64.9 y	69	?

Arm muscle circumference based calculations

Group	Number required per group (repeated measures)*
Males 45-54 y	34
Males 55-64 y	34
Females 45-54 y	49
Females 55-64 y	49

*Unable to calculate estimates of number required to detect a difference between independent groups as required data not available.

Summary

To detect a 10% difference in weight between groups of males with 80% power at 0.05 level of significance we will need approximately 50 per group. Due to greater variation in weight in women we would need approximately 90 per group. For arm muscle circumference, to detect a change of 1.1 cm within a group we would need approximately 34 per groups for males (45-54 y) or (55-64 y). For women we would need 49 (for 45-54 y) or (55-64 Y).

Appendix 2: Ethics approval

National Research Ethics Service

Salford & Trafford Local Research Ethics Committee

Room 181
Gateway House
Piccadilly South
Manchester
M607LP

Telephone: 0161 2372438
Facsimile: 0161 2372383

19 November 2007

Miss Claire Beadman
Dietitian

Dear Miss Beadman

Full title of study:
**Randomised control trial investigating the long term
effects of preoperative carbohydrate-loading for
colorectal surgical patients.**

REC reference number:
07/H1004/147

Thank you for your letter of 14 November 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by Ms Beverly Harrison, qualitative expert member of the Committee in place of Mrs Janet Marsden, Vice-Chair, who is currently out of the country ..

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The Committee has designated this study as exempt from site-specific assessment (SSA). There is no requirement for [other] Local Research Ethics Committees to be informed or for site-specific assessment to be carried out at each site.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

<i>Document</i>	<i>Version</i>	<i>Date</i>
Application	5.4	03 September 2007
Investigator CV		
Protocol	1	03 September 2007
Covering Letter		15 August 2007
Summary/Synopsis	1	03 September 2007
Questionnaire: Assessment of well being	2	22 October 2007
Letter of invitation to participant	2	22 October 2007
Participant Information Sheet	2	22 October 2007
Participant Consent Form	2	22 October 2007
Response to Request for Further Information		14 November 2007
Sponsor Signature		25 September 2007
CV - Kirstine Farrar - Educational Supervisor		21 September 2007

R&D approval

All researchers and research collaborators who will be participating in the research at NHS sites should apply for R&D approval from the relevant care organisation, if they have not yet done so. R&D approval is required, whether or not the study is exempt from SSA. You should advise researchers and local collaborators accordingly.

Guidance on applying for R&D approval is available from <http://www.rdforum.nhs.uk/rdform.htm>.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Website > After Review

Here you will find links to the following

- a) Providing feedback. You are invited to give your view of the service that you have received from the National Research Ethics Service on the application procedure. If you wish to make your views known please use the feedback form available on the website.
- b) Progress Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
- c) Safety Reports. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
- d) Amendments. Please refer to the attached Standard conditions of approval by Research Ethics Committees.
- e) End of Study/Project. Please refer to the attached Standard conditions of approval by Research Ethics Committees.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nationalres.org.uk

With the Committee's best wishes for the success of this project

Yours sincerely

Mrs Janet Marsden
Vice-Chair, Salford and Trafford REC

Email: maggie.twiney@northwest_nhs.uk

Appendix 3

Nutritional Composition of PreLoad[®]

Composition of 50g sachet of dry Powder

Energy	kcal	190
	kJ	805
Protein	g	nil
Carbohydrate	g	48
Fat	g	nil
Sodium	mg	<15
	mmol	<1
Potassium	mg	<2
	mmol	<0.1
Chloride	mg	<20
	mmol	<0.6
Osmolality		120mOsm/kgH ₂ O/litre
Osmolarity		285mOsm

Appendix 4

(Based on tool used by Hausel et al, 2001)

Assessment of well-being.

Please mark on each scale how you are currently feeling for each factor.

How anxious are you feeling at present?

Not at all anxious Extremely anxious

How would you rate your depression at the moment?

Not at all depressed Extremely depressed

How would you describe your hunger at present?

Not at all hungry Extremely hungry

How would you rate your ability to concentrate?

Fully able to concentrate Unable to concentrate

How would you rate your general feeling of bodily discomfort at present?

Feeling generally well Feeling generally very unwell

Are you suffering any feeling of sickness at the moment?

No feeling of sickness at all Feel extremely sick

Are you in any pain at the moment?

No pain at all Very severe pain

Please rate your thirst at the present time

Not at all thirsty Extremely thirsty

How tired are you feeling at present?

Not at all tired Extremely tired

Please rate your feeling of fitness at the moment

No feeling of unfitness at all Extremely unfit

Are you feeling weak at the moment?

No feeling of weakness at all Extremely weak

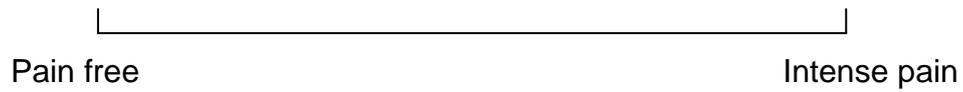
Appendix 5

(Based on tool used by Hausel et al, 2001)

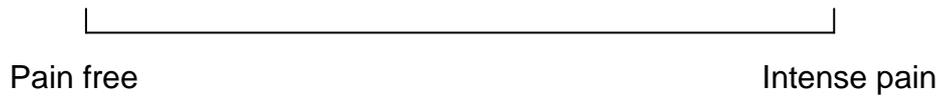
Assessment of Pain

Please mark on each scale the pain that you currently experience for each of the following activities.

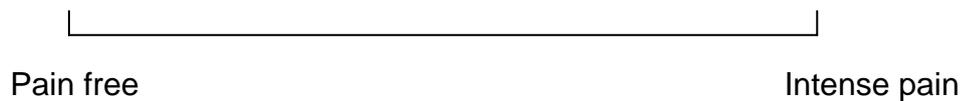
At rest



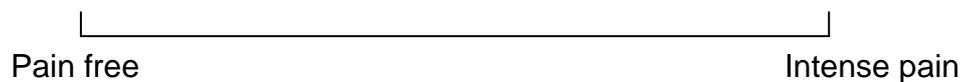
Standing up beside the bed



Coughing



When moving around



Appendix 6. POSSUM score calculation
Taken from Pratt, Joseph, Callery and Vollmer (2008)

