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Original Research Article

Even preoperative carbohydrate loading is too hard? Why RCT's should not be considered the gold standard for nutrition research in acute hip fracture: results of a feasibility study

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ABSTRACT

Background: Malnutrition is a high-risk co-morbidity in acute hip fracture patients. Pre-operative carbohydrate loading may improve nutritional status and therefore patient outcomes. The feasibility of nutrition focused randomised control trial designs in hip fracture is at best questionable. This study was designed to undertake efficacy testing of pre-operative carbohydrate loading and explore the broader feasibility of conducting randomised controlled trials in acute hip fracture.
Methods: This two arm randomised controlled feasibility study recruited patients previously living in the community who had fractured their hip undergoing surgery at our institution. Patients in the intervention arm received a 400 mL (50g) carbohydrate load 2 hours prior to surgery. Information was collected regarding the fidelity of pre-operative carbohydrate provision and consumption as well as patient demographic and admission details.
Results: Thirty-two patients consented to participate, 60% of the eligible patient cohort. Results demonstrated evenly matched intervention and control groups in terms of demographic details and pre-surgical morbidity and mortality risk. However, of the 17 patients allocated to the intervention arm less than half (41%) completed the carbohydrate loading intervention and even fewer 23.5% (n=4) completed all follow up due to a number of patient and system related factors.
Conclusions: Evaluating the clinical effectiveness of providing pre-operative carbohydrate loading in hip fracture and the associated outcomes is not feasible using a randomised control trial methodology. It is recommended that researchers consider a 'silver standard' of research and practice such as pragmatic, registry-based cluster randomised trials to ensure feasibility, relevancy and applicability when evaluating nutritional interventions in this cohort.

Keywords: Clinical trial, Hip fracture, Malnutrition, Research design, Carbohydrate loading, NOF

INTRODUCTION

Older people who break their hip are recognized as exceptionally vulnerable. Malnutrition is not only an independent predictor of twelve month mortality in acute hip fracture populations but is the most costly co-morbidity likely to prolong hospital length of stay, increase the risk of post-operative complications and increase morbidity.[1,2] One in two hip fracture patients are malnourished on admission, complicated by the reduced oral intake and increased metabolic demands of injury and surgery contributing to ongoing post-operative nutritional decline.[3] Currently, many hip fracture units employ nutritional supplementation, fortified diet prescription and multidisciplinary education procedures.[4] These strategies alone post-surgery may be insufficient as patients are already in a catabolic state following trauma and the subsequent surgical stress response.[5]

Carbohydrate loading is an additional pre-operative nutritional intervention that may be beneficial in acute hip fracture cohorts. In theory, carbohydrate loading shifts cellular metabolism to a more anabolic state to prevent muscle wasting, preserve function and optimize the use of nutritional supplementation post-operatively.[6-8] Literature consistently demonstrates that carbohydrate supplementation does not increase the risk of aspiration and improves preoperative patient comfort.[9-12] However the impact on clinical outcomes remains vague.[12]

The 2016, Cochrane review of nutritional supplementation in hip fracture patients called for adequately sized randomised trials with robust methodology to improve the quality of evidence, reporting trials completed to date were often methodologically flawed.[5] However, nutrition intervention studies in hip fracture patients require a highly constrained research environment in order to both recruit patients and demonstrate the clinical effect of interventions. The need for informed consent in this acutely unwell, multi-morbid patient demographic during an unplanned hospital admission results in many hip fracture studies excluding more than half of the initial potential patient population.[13-20] For example, many hip fracture RCTs exclude patients with cognitive impairment or dementia although the number of patients excluded is not always acknowledged.[13,16,19,21-23] Considering up to 50% of hip fracture patients have cognitive impairment it could be assumed a large proportion of patients are routinely excluded.[24] This is selection bias against patients' who would benefit most, and masks the effect of nutritional interventions on outcomes. For this reason, it is not surprising that RCTs, and the resultant reviews of these studies, have failed to clearly define consistent and adequate evidence to guide nutritional care in hip fracture.

Recruitment issues and selection bias are significant barriers to an effective study involving hip fracture patients. However, surmounting these difficult issues aside, pre-operative carbohydrate loading appears to be poorly adhered to in unplanned surgical settings.[25,26] There is general nutrition consensus that a preoperative dose of carbohydrate supplementation 2-3 hours prior to surgery is as effective as adding a dose the night prior. Svanfeldt et al reported the morning carbohydrate dose enhances insulin metabolism with the evening dose alone does not have the same effect.8 Our study aims to determine the feasibility of providing a 400 mL (50g) carbohydrate load (similar to that of eating a meal) via oral sip supplement prior to surgery and collection of associated outcomes in acute hip fracture inpatients.27 However, the overarching objective of this study is an assessment of the broader feasibility of conducting nutrition focused RCTs in the acute hip fracture population using a simple, inexpensive and low risk intervention.

METHODS

Study protocol and participants

This two arm randomised controlled feasibility study of 32 hip fracture patients was designed to undertake efficacy testing and explore the broader acceptability, feasibility and fidelity of conducting an RCT in the acute hip fracture population.[28] The study has been approved by our institutions Human Research Ethics Committee on the 4th of April 2017.

All patients admitted to our institutions Hip Fracture Unit were screened for eligibility by the admitting orthopaedic team. This unit facilitates admission of approximately 350 acute hip fracture patients annually. All patients with confirmed neck of femur fracture on imagining who were community dwelling prior to admission were eligible for inclusion. Patients were excluded if less than 18years of age, admitted from supported living accommodation including residential aged care facilities, were for non-operative management, as well as patients with diabetes requiring insulin, had oral feeding aversion or required thickened fluids or significant baseline intellectual impairment or mental health conditions (other than delirium) were excluded.

Patients meeting the eligibility criteria or their carer were approached for consent. Consenting participants were randomised into one of two study groups by computer generated blocked randomisation using block sizes of four. Block randomisation was undertaken to achieve equal samples sizes within each group in the study timeframe. The investigator (SB) provided a sealed opaque envelope from the relevant block allocation containing randomisation instructions to the medical team but remained blinded to the intervention allocation.

Standard care in both groups remained unchanged and aligned with the Australian and New Zealand Guideline for Hip Fracture care – only the administration of the carbohydrate supplement differed between groups.[4]

Routine practice continued to place patients awaiting surgery nil by mouth until operating theatre times are identified or nil by mouth from midnight if surgery was the following day. Patients in the intervention group were prescribed a 400 ml carbohydrate drink (Nutricia PreOp) to be administered by nursing staff three hours prior to the scheduled surgery time allowing the patient one hour to consume the beverage and a minimum of two hours fasting pre-operatively to align with the Australian and New Zealand College of Anesthetists pre-Anaesthesia preparation guidelines.[29] Analgesia was provided in accordance with standard care principles of the Hip Fracture Unit. Anaesthesia choice was at the discretion of the attending anaesthetist. Other post-operative therapies including physiotherapy and nutrition support were provided according to routine practice.

Outcome measures

Demographic data was collected as part of eligibility screening for all patients including age, gender and American Society of Anesthetists (ASA) score. Increased ASA score is associated with mortality and morbidity risk in this patient group.[30,31] Additional administration data including presenting comorbidities, length of stay, surgical notes, hospital-acquired complications, functional measures and quality of life metrics were collected for all consenting patients.

Statistical analysis

The size of the study was chosen to evaluate the feasibility of implementing pre-operative carbohydrate supplementation and therefore not adequately powered to determine significance of secondary measures. Data was analysed based on intention to treat as part of determining feasibility. Univariate associations between groups were performed using the Mann-Whitney U test and Fishers exact test (IBM SPSS Statistics 23). A P value of <0.05 was considered statistically significant.

RESULTS

One hundred and thirty-one patients were admitted to the acute hip fracture unit at our institution between August 2017 and February 2018. The details of the enrollment process are shown on a CONSORT 2010 flow diagram in Figure 1.[32]

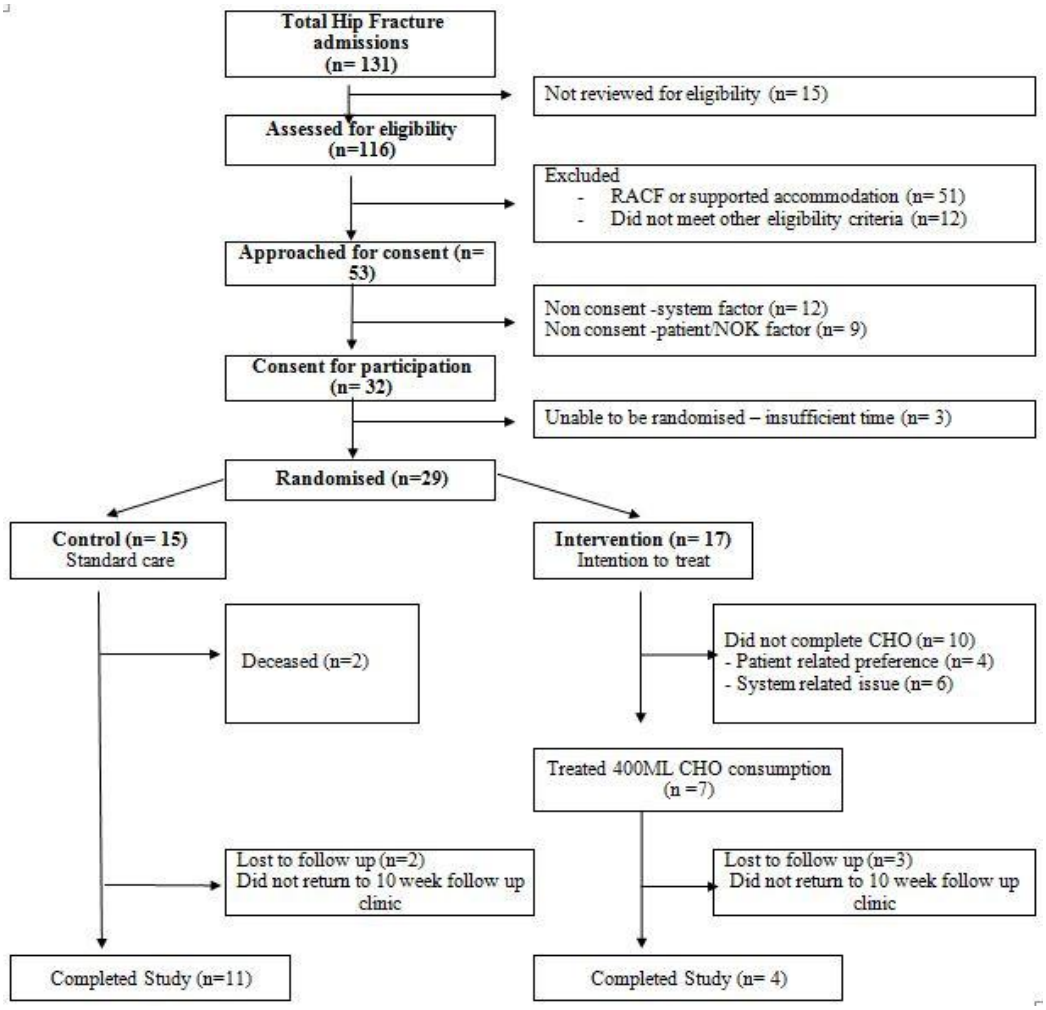

Figure 1: The details of the enrollment process shown on the consort 2010 flow diagram.

RACF = Residential Aged Care Facility, NOK = Next of Kin, CHO = carbohydrate loading supplement.

Thirty-two patients – 60% of eligible patients - consented to participate in the study. Data collected regarding patient reason for non-consent was divided into system and patient factors as shown on the CONSORT 2010 flow chart. After hours admissions accounted for the majority (n=7) of the non-consent system factors. Nine patients declined to participate citing reasons as too many things happening/research involvement is not a priority (n=3), feeling too unwell (n=2), unable to understand materials (n=1), unable to contact decision maker (n=2), medical team deemed too unwell (n=1). Of the patients that declined to participate, 90% were female with an average age of 80 years (55-94) and median ASA score of 3 (2.5-4). Consenting and non-consenting patient groups were similarly matched.

Table 1: Characteristics of consenting patients.

		Intervention (n=15)	Control (n=17)	P value
Gender N (%)	Male	7 (46.7)	8 (53.3)	0.266
	Female	4 (23.5)	13 (76.5)	
Age (years)	Mean (range)	82.5 (69-92)	83.9 (68-96)	0.719
ASA*	Median (range)	3 (2-4)	3 (2-4)	0.323

*ASA unavailable for one patient that passed away.

The demographic characteristics (Table 1) did not differ significantly between intervention and control groups.

Less than half of the treatment arm (Figure 1) consumed 100% of the carbohydrate intervention. Reasons for non-completion were divided into system factors and patient factors. System factors related to surgery schedule changes: carbohydrate supplement intake completed and then surgery postponed (n=3); surgery moved forward (n=2) with carbohydrate supplement orders cancelled or not re-scripted; and one instance of carbohydrate supplement not provided despite appropriate pre-surgical script. Three patients consented to participate, however were unable to be randomised due to inadequate time (<3hours) for supplement scripting and consumption between gaining consent and scheduled surgery time. Patient factors included one patient who consumed the carbohydrate supplement yet had their operation cancelled, and then refused to drink a dose again the following day when surgery was rescheduled due to nausea following initial consumption. Two patients only partially consumed the carbohydrate supplement due to a dislike, and one patient was deemed at risk of aspiration and had the carbohydrate supplements removed.

DISCUSSION

This RCT feasibility study aimed to evaluate pre-operative carbohydrate loading in acute hip fracture. Although a relatively simple, inexpensive and low risk intervention, our study - as encountered in other studies previously - demonstrated a lack of feasibility within an established multidisciplinary model of care.[33] Many nutrition related hip fracture studies cite a major limitation of RCTs in this population is the inevitable selection bias that clouds the true effect of nutritional interventions.[13,16,19,21-23] Our findings however, indicate limited selection bias between eligible and non-eligible groups and between the consenters and non-consenting patient groups. Demographic data and mean ASA scores of consenters and non-consenters are reflective of the general hip fracture population as reported in the 2017 Bi-National Annual Report for Hip Fracture Care.[34] We had expected that patients enrolled in hip fracture RCT's to be partially representative of patients in clinical practice however, our study disputes this.

Delirium or cognitive impairment was not an exclusion criterion for this study and was not cited as a reason for non-consent for any patients. This may be unnecessary exclusion criteria in many hip fracture studies. Moppett et al published a protocol with similar intervention for hip fracture patients, however the study terminated mid 2017 due to a lack of recruitment and changes to clinical practice.[35] Other hip fracture nutrition studies report recruitment rates ranging from 14 to 22% highlighting high probability for selection bias.[16,17,21] We had a reasonable consent rate for eligible patients (60%) due to the high caliber and well-established nutrition care focused multidisciplinary team described by Bell et al. Unfortunately, afterhours admissions and competing time pressures of the admitting team resulted in 11% of patients not being screened for eligibility, a limitation of this study.

The aim of this study was to determine if a larger, pre-operative carbohydrate trial should progress to efficacy testing – however, due to small study completion numbers (less than a quarter of the study patients had completed data sets for analysis), no conclusion can be drawn regarding clinical effectiveness. We can however, explore the factors that limited intervention fidelity. Many studies do not provide detail regarding inclusion or adherence to the carbohydrate loading component as part of larger Enhanced Recovery After Surgery (ERAS) protocols and those that do, tend to report limited adherence rates.[25,36,37] Liu et al implemented a multifaceted ERAS program collecting pre and post implementation data for two cohorts: elective colorectal (n=3768) and emergency hip fracture repair (n=5002) patient groups. They found significant decreases in hospital length of stay and postoperative complication rates overall; however, when reviewing the decreased fasting times and pre-operative carbohydrate loading component, it appears that <5% of the hip fracture cohort adhered to this component. Similarly, although a much smaller sample size, Roulin et al reviewed ERAS component adherence in urgent colorectal patients with only 25% of these patients receiving the carbohydrate loading component.[25] ERAS protocols result in improved length of stay and patient outcomes. However, the utility

and evidence of carbohydrate supplementation in practice appears at best over emphasized.

Our study highlights a range of patient and systematic difficulties associated with providing 400mL carbohydrate load prior to surgery, resulting in less than half (41%) of study patients completing the intervention in its entirety. Surgery schedule changes were the largest influencing system factor to supplement consumption contrary to other studies that report the barrier to pre-operative carbohydrate supplementation is fear of having to postpone surgery.[38] In our study, theatre times were not altered as a result of supplement consumption. However, some patients were unable to be randomised and have enough time to consume the carbohydrate supplement prior to surgical intervention. Early surgery is a key in this patient cohort, and delaying surgery for supplement consumption in a research context may be unethical - highlighting another factor limiting the acceptability of carbohydrate loading in this patient group.[4]

Randomised controlled trials (RCTs) continue to hold a mesmerizing grip on the definition and descriptors of what stands for high quality, 'gold standard' research and practice.[39] Carbohydrate supplements are a relatively simple, inexpensive and low risk intervention. This study, like many more nutritional RCT's before it, has been unable to apply an RCT trial design to efficacy testing in this emergent surgical population. These results clearly articulate the difficulties associated with the trial design including system and patient factors in a well-established nutrition focused multidisciplinary team. Furthermore, this study raises the question that if simple carbohydrate nutrition supplement RCT is not feasible in acute hip fracture - should researchers consider focusing efforts on other trial designs. Newer and novel study designs, such as pragmatic and registry-based randomised trials/cluster-randomised trials or step wedge trial designs are receiving increasing attention.[40] Bell and colleagues have described a successful pragmatic nutrition based study using CONSORT guidelines for a pragmatic trial reporting in hip fracture.[33,41] The Australian and New Zealand Hip Fracture Registry provides a unique opportunity to combine the advantage of randomisation with the advantages of registry data potentially eliminating many system factors experienced in this study.[40] Ideally an opt-out consent process would improve the quality of nutritional related evidence in the hip fracture population. These alternate studies design although considered a 'silver' standard of evidence perhaps are more feasible, acceptable and generalizable then the current gold standard of the RCT in the acute hip fracture cohort.

In conclusion, although RCTs are widely encouraged as the ideal methodology for causal inference, when it comes to hip fracture and nutrition care, feasibility of these trials is unattainable. Evaluating the clinical effectives of providing pre-operative carbohydrate loading in hip fracture and the associated outcomes is not feasible using a RCT methodology. It is recommended that researchers consider a 'silver standard' of research and practice such as pragmatic, registry-based randomised trials to ensure feasibility, relevancy and applicability when evaluating nutritional interventions in the acute hip fracture cohort.

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