Editorial

Post-discharge oral nutritional supplementation after surgery for gastrointestinal cancer: Real or marginal gains?

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Nutritional interventions that target the postoperative and post-discharge periods have been under investigation for several decades. One of the first randomized controlled trials (RCT) that used postoperative oral nutritional supplements in patients undergoing major gastrointestinal surgery saw only 40 of the 54 participants enrolled complete the study [1]. Participants were randomized to receive a normal ward diet postoperatively or the same diet supplemented *ad libitum* by an oral nutritional sip feed commencing from the day they were adjudged to be capable of ingesting free fluids to the day of discharge. The authors reported that the mean daily energy and protein intakes were 700 kcal/day (2.9 MJ/day) and 13 g/day greater respectively in the intervention group than in the control group ($P<0.0001$). While weight remained stable in the intervention group, those in the control group lost approximately 5 kg by the time of discharge. Muscle function declined to a greater extent ($P<0.03$) and infectious complications were higher ($P<0.02$) in the control group.

The same group of investigators [2], demonstrated within the setting of a two phase RCT that initial postoperative oral nutritional supplementation improved nutritional status during the inpatient period. However, in the post-discharge phase of the trial, continuation of supplementation for 4 months in the intervention group led to no appreciable differences in outcomes, including nutritional status, postoperative complications and quality of life. Nevertheless, at the turn of the 21st century, enteral nutritional supplementation in malnourished surgical patients during the post-discharge period was shown to lead to statistically significant improvements in nutritional status, quality of life, and morbidity [3]. Despite this study [3], and other similar ones subsequently [4], meta-analyses have shown little or no benefit [5, 6] and doubts still surround the nutritional gain, improvement in quality of life and the economic benefit of post-discharge oral nutritional supplementation.

It is, therefore, not surprising that although recommended, post-discharge nutritional supplementation is not standard care even in the era of enhanced recovery after surgery [7].

It is now accepted that up to 40% of patients presenting with gastrointestinal cancer will have a degree of malnutrition and weight-loss, and a smaller proportion will have cancer cachexia [8]. The preoperative and postoperative periods, therefore, are an obvious target for nutritional intervention and support. Several RCTs, and recent systematic reviews and meta-analyses [8, 9] derived from these have pointed to the benefits of specific nutritional support or interventions during these periods. However, in patients with gastrointestinal cancer, it is noteworthy that the tumor burden, systemic inflammation, increased basal metabolic activity and the lack of appetite that ensues potentiate loss of weight and malnutrition to an extent that is unlikely to be counteracted completely by perioperative nutritional support alone. Additionally, although these patients often have neoadjuvant and adjuvant treatments such as chemotherapy, radiotherapy or both, those who are nutritionally depleted are less likely to tolerate these therapies [10]. Therefore, continuation of nutritional support and supplementation, beyond the initial preoperative and immediate postoperative periods, into the post-discharge phase seems an attractive and potentially important frontier in the nutritional care of patients with gastrointestinal cancer.

The concept of post-discharge nutritional care itself is not novel [2-6]. However, contemporary studies that have focused on patients with gastrointestinal cancers in particular are sparse. A recent RCT on 104 participants who underwent surgery for gastric or colorectal cancer showed that participants receiving post-discharge oral nutritional supplements had a significant increase in body weight at 60 and 90 days when compared with controls who received dietary advice alone. However, no differences between groups

were noted in anthropometric measurements, nutrition-related laboratory tests, or quality of life indicators [11]. It is for this reason that the two RCTs from the same center and using similar methodology published in this issue of *Clinical Nutrition* [12, 13], addressing two distinct gastrointestinal cancers evoke interest.

Gastric cancer and post-discharge nutrition

In this single center, non-blinded RCT, 353 patients were randomized but 337 who completed the study per protocol were included in the analysis [12]. The intervention group consisted of 171 participants who received 370 ml of oral nutritional supplements daily with dietary advice and the control group comprised 166 who received dietary advice alone. Following 3 months of oral nutritional supplementation, weight loss was significantly less, and body mass index and skeletal muscle index were significantly higher in the oral nutritional supplementation group than in the control group ($P<0.05$). Additionally, although the prevalence of sarcopenia at baseline was similar in both groups, significantly more participants in the control group were sarcopenic at three months than those in the intervention group. However, there were no differences in readmission rates or in the overall quality of life as defined by the global health status. Nevertheless, specific symptoms scales, fatigue ($P=0.035$) and appetite loss ($P=0.013$) were significantly lower in the intervention group.

Colorectal cancer and post-discharge nutrition

In the second RCT, 232 participants who underwent surgery for colorectal cancer surgery were randomized and 212 participants were analyzed per protocol. There were 105 who received oral nutritional supplements and 107 in the control group [13]. The mean oral

supplement intake was 410 ml/day. At three months, the skeletal muscle index was significantly greater in the oral nutritional supplementation group and significantly fewer participants were sarcopenic than in the control group. However, no significant differences were found between the two groups in terms of weight, weight loss, body mass index, serum albumin and hemoglobin concentrations. There was no difference in readmission rate or quality of life indices. From an economic standpoint, the lack of impact on overall quality of life and readmission rates renders the intervention difficult to recommend when taken on its own value.

Critique of the two studies

Although both studies have a relatively large sample size when compared with other similar studies [1-4, 11], some limitations must be highlighted. The two studies presented were unblinded trials undertaken by the same research group from the same institution and reported on a population with predominantly the same ethnicity, thereby limiting their generalizability. The sample size calculation for the gastric cancer study was based on a change in weight [12] while that for the colorectal cancer study [13] was based on the change in skeletal muscle index. It is not clear why the authors chose different end points for the calculation of sample size in the two studies rather than a single patient-centered clinically relevant primary end point. Data analysis was on a per protocol rather than an intention to treat basis. Although the target was 500 ml/day, participants in the intervention group took a modest 370 ml/day (370 kcal/1.55 MJ and 15.2 g protein) of oral nutritional supplements in the gastric cancer study [12] and 410 ml/day (410 kcal/1.72 MJ and 16.8 g protein) in the colorectal cancer study [13]. However, the authors do not provide any information on the total energy and protein intake in the two groups in each study, which is

a major limitation for an accurate interpretation of results. In both studies, the major findings were that postoperative nutritional supplementation diminished the decline in skeletal muscle index and reduced the proportion of participants with sarcopenia when compared with the control group. Nevertheless, the actual mean differences at 3 months in skeletal muscle index between the two groups were quite small (1.6 cm^2/m^2 in the gastric cancer study and 1.7 cm^2/m^2 in the colorectal cancer study). Participants who received oral nutritional supplements tolerated postoperative chemotherapy better in both studies and this is an important finding. Although weight loss and consequent decrease in body mass index were less in the intervention group in the gastric cancer study, there were no differences between groups in the colorectal cancer study. In addition, there were no differences between the groups when readmission rates or overall quality of life in both studies. Nonetheless, these findings could represent some of the marginal gains of post-discharge nutritional supplementation.

Marginal gains theory applied to nutritional supplementation

The marginal gains theory, popularized in the sport of cycling has been advocated in other competitive sports, aviation, business, and even healthcare [14]. When applied to perioperative nutrition, it would theoretically be plausible to envisage a scenario where the known benefits in preoperative nutritional supplementation [8] and enhanced recovery after surgery principles [7] are augmented by post-discharge nutritional supplementation. The cumulative effect of the marginal gains on benefit from preoperative, postoperative and post-discharge nutritional support could result in substantial gains for the individual patient undergoing surgery for gastrointestinal cancer. This undoubtedly provokes the question – whether or not, nutritional intervention studies should be undertaken in isolation or in

144 combination – to exploit the potential benefits and marginal gains of preoperative,
145 postoperative and post-discharge nutritional care. Moreover, patient partnership and
146 education is important for cooperation and compliance and this is easier done in the time
147 waiting for an operation than in the postoperative period.

148 **Future directions**

149 The European Society for Clinical Nutrition (ESPEN) recommends the use of appropriate
150 post-discharge nutritional support therapy for surgical patients including those with cancer
151 at risk of malnutrition [15-18], but there is a dearth of high-quality evidence underpinning
152 these consensus recommendations. Although these two new studies [12, 13] add to the
153 body of evidence, there is a need for larger multicenter studies, with appropriate sample size
154 calculations based on patient-centered clinically relevant primary outcome measures, from
155 mixed population groups, with staggered duration of post-discharge supplementation and
156 variations in the oral supplements themselves, to allow us to fully assess, appreciate,
157 generate and disseminate the evidence base on post-discharge nutritional supplementation.
158 Importantly, these studies should be conducted to take advantage of and incorporate
159 enhanced recovery after surgery protocols so that patients are provided the best possible
160 care package.

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