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Pre-operative immunonutrition therapy in upper gastrointestinal cancer patients: Post-operative outcomes and patient acceptance

Ellen Paynter[1], Emma Whelan[2], Chanelle Curnuck[2], Satvinder Dhaliwal[1], and Jill Sherriff[1]

1. School of Public Health, Curtin University, Bentley, WA, Australia
2. Department of Nutrition and Diet Therapy, Sir Charles Gairdner Hospital, Nedlands, WA, Australia

RESEARCH

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Corresponding Author:
Jill Sherriff
School of Public Health
Curtin University, Bentley, WA, Australia
Email: J.Sherriff@curtin.edu.au

ABSTRACT

Background
Pre-operative immunonutrition for upper gastrointestinal cancer patients is provided in a number of Australian tertiary hospitals. However, previous studies yielded inconsistent results; limited information on patient acceptance of pre-operative supplementation is likely to be an as yet unexplored contributing factor.

Aims
To determine patient acceptance of a pre-operative immunonutrition supplement protocol and to compare post-operative outcomes pre- and post-implementation of the protocol.

Methods
A retrospective review of medical records was undertaken for upper gastrointestinal cancer surgery patients pre- and post-implementation of a pre-operative immunonutrition protocol. Endpoints noted were surgery type, timing of attendance at the pre-admission clinic, post-operative complications, intensive care unit admissions, diet progression and length of stay. Patient feedback on the immunonutrition protocol and supplement acceptability was obtained via interview.

Results
The audit identified 74 patients as having undergone upper gastrointestinal cancer surgery (36 patients pre- and 38 patients post-implementation). Less than half of the post-implementation patients attended the pre-admission clinic as per protocol. Infectious and non-infectious complication rates were similar between the two groups. Number of days until patients received full diets post-operatively were 0.80 days shorter post-implementation, but not statistically significant. Patients in the post-implementation group with infective complications spent significantly longer time nil by mouth than those who did not incur complications (26.15 vs 17.13 days, p=0.024). Length of stay was 1.5 days shorter in the post-implementation group but not statistically different.

Conclusion
We found no difference in post-operative outcomes; however, the pre- and post-implementation comparison was limited by poor adherence to the protocol as a consequence of late attendance at pre-admission clinic. Of those who did attend as planned, patient acceptance was high. Future studies incorporating prospective, quantitative pre-operative immunonutrition intake are needed.

Key Words
Immunonutrition, length of stay, upper gastrointestinal cancer

What this study adds:

1. What is known about this subject?
Previous research into pre-operative immunonutrition for upper gastrointestinal cancer patients yielded inconsistent results, potentially confounded by factors such as patient acceptance.

2. What new information is offered in this study?
This research provides information on patient acceptance of pre-operative supplementation.

3. What are the implications for research, policy, or practice?
The factors identified as affecting patient acceptance of pre-operative immunonutrition should be addressed in future prospective investigations into patient outcomes.

Background

In 2013 over 600 people were diagnosed with upper gastrointestinal (UGI) cancer (primary cancer of the oesophagus, stomach, pancreas, gall bladder and bile ducts) in Western Australia (WA).[1] UGI cancer accounts for approximately 16 per cent of all cancer mortality in WA and is the second most common cause of cancer-related mortality amongst males and third most common amongst females.[1] Treatment for UGI cancers involves surgery, radiation, chemotherapy or a combination of these.[2] As UGI cancers are predominantly discovered at an advanced stage, few patients are eligible for surgery, however surgical resection offers the only chance of a long-term cure.[2]

In patients undergoing surgery, reduced immunity can have negative outcomes including increased risk of infection, morbidity and extended length of stay (LOS), as well as mortality.[3] Cancer places an increased stress on the body, which can lead to suppression of the immune system.[4] Immunity is also compromised by malnutrition, which is common in UGI patients as they have a compromised intake, and altered digestion, metabolism and absorption of nutrients.[5]

Research has suggested that, regardless of patients' pre-operative nutrition status, elevated intake of immune modulating substrates, pre-operatively and/or post-operatively, can result in the attenuation of post-operative immune and inflammatory responses.[3,6-8] Furthermore, early post-operative feeding (as soon as 12-24 hours after gastrointestinal surgery), can assist with improving immune function.[9]

Randomised controlled trials (RCTs) have yielded mixed results in post-operative outcomes and LOS when comparing pre-operative immunonutrition (IN) to standard diet or standard nutrition supplements. IN oral supplements contain protein and carbohydrate as well as additional immune-modulating substrates: arginine, omega-3 polyunsaturated fatty acids and nucleotides, and other micronutrients.[7] A recent systematic review and meta-analysis[10] examined the effects of pre-operative IN compared to either standard nutritional supplements or regular diet with no supplements in a range of GI surgeries. Only the comparison with non-supplemented regular diet yielded a significant reduction in infectious complications and LOS. However, larger patient numbers with a clearer delineation of nutritional status and reduced variation in the standard nutritional supplements are required to clarify the impact of pre-operative IN.[10-14]

Another factor that may contribute to mixed results is the dose of pre-operative IN consumed. While the optimal doses of immunonutrients have not been defined,[10] common usage is three tetrapacks of oral IN for 5–7 days pre-operatively.[15] Research into the barriers relating to the implementation of an immunonutrition protocol identified that the main one is patient compliance with 42 per cent of patients having intake of oral nutrition support below the recommended daily dose.[15] It was hypothesized that compliance with IN supplements may be related to patients' motivation and the level of education and support provided rather than to disease-related symptoms.[15]

There are no evidence-based guidelines for the nutrition management of UGI cancer patients undergoing surgery in Australia[2,16] and as a result a wide range of protocols has been identified in Australian hospitals.[14,17] European guidelines recommend that pre-operative nutrition support preferably with immune modulating substances (arginine, long chain omega-3 fatty acids and nucleotides) are provided for 5-7 days in cancer patients undergoing major upper abdominal surgery.[7,8] In an Australian study, 18 (50 per cent) dietitians reported recommending immune-enhancing oral supplements preoperatively.[16]

A pre-operative IN protocol for UGI surgery was implemented at a tertiary setting in Perth, WA. To improve patient compliance with IN supplementation, patient education and support were factored into the IN protocol. We aimed to compare post-operative outcomes before and after the introduction of the oral pre-operative IN protocol, as well as patient acceptance. We predicted that introduction of the protocol would result in earlier commencement of oral intake and progression onto a normal diet, fewer post-operative complications and shorter LOS.

Method

On 1st December 2014, a pre-operative IN supplementation protocol for patients undergoing surgery for UGI cancers was implemented in a tertiary hospital in Perth, WA.

Patients attending the pre-admission clinic (PAC) as per standard pre-operative care were provided with 15×237mL tetra packs of IN supplementation (Impact Advanced Recovery, Nestle Medical Nutrition, St Louis Park, MN, USA), and instructed via an information leaflet and by PAC nursing staff to consume three tetra packs per day for five days prior to surgery. Each tetra pack contained; 18g protein; 340 Cal; 4.2g added L-arginine; 1.1g alpha-linolenic acid; 672mg eicosapentaenoic acid; 423mg docosahexaenoic acid; 430mg nucleotides.[15] Patients were not eligible to receive IN if they met any of the following exclusion criteria: under 18 years of age, on a low energy diet for morbid obesity, febrile, or allergic to dairy, soy or fish.

Recruitment method part 1

The data for this single centre retrospective audit were collected from the hospital's surgical database for the interval 1st February 2014 to 30th September 2015. The pre-implementation group consisted of all patients admitted for UGI surgery between 1st February and 30th November 2014 and the post-implementation patients were all those admitted and eligible between 1st December 2014 and 30th September 2015.

Data collection part 1

Data on post-operative complications, intensive care unit (ICU) admissions, LOS and readmissions for both groups were collected from the electronic database iSoft Clinical Manager and medical records. Post-operative complications were classed into infectious and non-infectious complications as per verification from the surgeons and as used in previous publications.[11,14,18] Infectious complications were abdominal abscess, pneumonia, sepsis, urinary tract infection; venous catheter infection and wound infection. Non-infectious complications were anastomotic leaks, chyle leaks, deep vein thrombosis, fistula, ileus, pulmonary embolism, respiratory failure, surgical emphysema and wound dehiscence.

Information on post-operative non-oral nutrition and diet progression was obtained from medical notes for both the pre- and post-implementation groups. Non-oral nutrition was defined as either enteral feeding or parenteral nutrition. The diet stages were nil by mouth (NBM), clear fluids, nourishing fluids and normal diet (any solid or texture modified solid food). The number of post-operative days on each diet stage was defined as the number of days following surgery before the consultant specified a diet upgrade for the patient.

Recruitment and data collection part 2

Patients who had UGI cancer surgery between 1st July and 31st December 2015 (n=25) were invited to participate in a face-to-face or telephone interview to discuss their experience with taking IN. This group of patients was chosen as they had undergone surgery within three months of being invited for an interview, therefore would be expected to have good recollection of their IN experience. Those who gave informed consent and who had received the IN supplements at PAC were asked a series of open and closed questions about their experience with taking the IN (outlined in Table 1) by a researcher who had no involvement with their medical treatment. "Yes" or "No" answers were quantified and answers to open questions and further information volunteered were collated to identify common themes between participants.

Ethics approval for all research was obtained from the Human Research Ethics Committee at the hospital and Curtin Human Research Ethics Committee. Access to patient medical notes was granted, including a waiver of consent to view medical notes and de-identify the obtained information. Patient consent was obtained prior to conducting the patient interviews.

Statistical analysis

As data were not normally distributed, non-parametric Mann-Whitney U tests were used. Fisher's exact tests were used for comparisons of categorical outcomes. Statistical analyses were carried out using SPSS (IBM, version 21).

Results

Audit data were collected and compared for a total of 74 patients, 36 patients in the pre-implementation group and 38 patients in the post-implementation group. No significant differences were found between patient demographics in the pre- and post-implementation groups for either sex or age (p=0.814 and p=0.545, respectively) (Table 2). Patients in both groups were categorised by type of surgery; gastrectomy, oesophagectomy, pancreatectomy or Whipples (Table 2).

Of the 38 patients in the audit post-implementation group, 15 attended PAC $\geq$5 days prior to surgery, eight attended 3-4 days, and 11 attended 1-2 days before surgery. Four patients attended PAC the same day or did not attend PAC. There was a decrease in the mean LOS of 1.5 days between pre- and post-implementation groups (n=15.42±2.10 and n=13.92±1.08), but this was not statistically significant (p=0.451, Table 3). Across all four surgical categories the mean hospital LOS was shorter in the post-implementation

group, although not statistically significant. Infectious complication rates were not significantly different between the two groups (19 per cent *vs.* 26 per cent, p=0.584, Table 3). Non-infectious complication rates were the same: 33 per cent and 26 per cent in the pre- and post-implementation groups (p=0.613, Table 3). There was one unplanned ICU admission due to post-operative complications in the pre-implementation group, which was not statistically different from the post-implementation group which had no unplanned ICU admissions (p=0.486, Table 3).

There was no significant difference between the pre- and post-implementation groups in the number of patients who received non-oral nutrition support following UGI cancer surgery (9 *vs.* 13, respectively, p=0.251, Table 3). The number of post-operative days that patients were NBM, were designated to clear or nourishing fluids or did not receive a normal diet was not statistically different between the two groups (p=0.866, p=0.659 and p=0.334, respectively), but all were lower after implementation by 0.60, 0.18 and 0.03 days, respectively (Table 3). However, within the post-implementation group, patients who had infective complications post-operatively spent significantly longer time NBM than those who did not incur complications (26.15 and 17.13 days, p=0.024).

Of the 27 patients identified as having undergone UGI surgery for cancer between 1st July and 31st December 2015 and who had met the criteria for pre-operative IN, one was deceased and another was unable to be contacted. Sixty-eight per cent of interviewed patients received the IN product (n=17), one patient received the incorrect supplement, and 28 per cent (n=7) did not receive IN (as documented in the medical records and/or as specified by the patient). The average number of days between PAC and surgery date for the interviewed patients was 7 days (range 1-19 days) for the patients who received IN compared to 1.7 days (range 0–3 days) for the 28 per cent of patients who did not receive IN (Table 4).

Of the patients who received IN supplements, 100 per cent said that they were informed (via verbal and/or written information) of the reasons to take IN supplements pre-operatively and were aware that the product was important for their post-operative recovery. Forty-one per cent of these patients (n=7) claimed the IN to have been beneficial to their health, such as leading to a good recovery after surgery or increasing their energy levels. Eighty-two per cent (n=14) of patients enjoyed the supplement, and the remaining three patients stated the supplement was too thick, too sweet or that they disliked milk. Two-thirds of patients claimed that the IN did not affect their appetite (n=11). Of the patients who reported the IN did affect their appetite (n=6), two said they consumed smaller or lighter meals in order to be able to consume the supplements.

Discussion

The primary aim of pre-operative IN is to optimise immune responses after surgery and thus reduce morbidity. The first part of this study involved a retrospective audit to determine if a recently introduced IN protocol had reduced post-operative complications and resulted in faster diet progression and reduced LOS in a cohort of UGI cancer patients.

No differences in infective or non-infective complication rates were detected between the pre- and post-implementation groups. Using a control group who consumed normal diet, the RCT by Aida et al. (2014) did demonstrate statistically significant reductions of pre-operative IN on IGU post-operative infective complications but only patients undergoing pancreatoduodenectomy were included.[9]

While the decrease in LOS of 1.5 days observed in the present study was not statistically significant, it does represent savings in health care costs making it clinically significant. Barker et al.[14] reported a non-significant trend (p=0.11) with the same reduction in LOS in their RCT of pre-operative IN in upper and lower GI surgical patients (n=46 in the intervention group and 46 in the control). One explanation for the lack of statistical significance in both these studies may be that patients don't consume sufficient of the allocated level of IN supplements to achieve critical blood levels of the immunonutrients. In their recent systematic analysis, Hegazi et al.[10] noted that many studies failed to include data on patient compliance. Grass et al.[15] found that only 58 per cent (n=82) of their patients were compliant (consumed at least 11 of 15 doses) but no analysis of post-operative outcomes and compliance was reported. The audit component of the present study revealed that less than half of the patients had attended PAC in time to consume the planned number of doses, therefore adherence to the protocol was low and has compromised assessment of the impact of IN in the post-implementation group. We weren't able to determine actual consumption but the patient interviews revealed that, among those who consumed the supplement, acceptability was high. However, as with all oral nutritional supplements,[19] the product wasn't universally liked or tolerated therefore some patients may not have been able to consume the recommended volumes. Interestingly, all

patients interviewed in this study reported they had been well educated on the importance of IN, so this is unlikely to have been a barrier to IN consumption in this patient group. It is possible that patients' preference of meals over supplements, the difficulty of increasing intake pre-operatively and IN tolerance may have been barriers to compliance. Future research should aim to quantitatively assess patient compliance to the IN protocols.

A strength of this study was the inclusion of time to full oral diet as a post-operative outcome. To our knowledge, no other study has used the diet progression time-frame as an endpoint to monitor post-operative outcomes of pre-operative IN. Generally, UGI surgical patients at our hospital are discharged when they can tolerate a full diet. Although not statistically different, the shorter time for progression from NBM to full diet observed in the post-implementation group may have contributed to the shorter LOS as early post-operative feeding has been shown to enhance recovery and in turn reduce LOS.[4,16,20-22] The reverse effect may explain the lack of statistical difference of LOS in the present study as the patients in the post-implementation group with post-operative complications spent a significantly *longer* time NBM. The latter was an unexpected result as the percentage of infectious complications pre- and post-implementation was not significantly different. However, the fact that complications were not graded for severity may account for this result.

There were several limitations to this study. We selected a narrow audit time of 10 months for the pre- and post-implementation groups to ensure that temporal factors (for example, surgical practice and antibiotic use) that might affect post-operative outcomes had not changed between the groups, and thus this limited the total patient numbers. Fewer than half the patients in the post-implementation group attended PAC sufficiently early to allow for the consumption of the prescribed intake before surgery. In addition, we were not able to measure consumption of the product. These factors combined to limit our ability to assess the potential of IN supplementation to influence post-operative outcomes.

Conclusion

There are no evidence-based guidelines for pre-operative nutrition support in patients undergoing UGI surgery in Australia leading to a large variability in practice in Australian hospitals.[16,17] The present study sought to determine if a recently introduced IN protocol had resulted in any changes in patient outcomes and to assess patient acceptance of the protocol. We found no differences in outcomes; however, adherence was limited by late attendance at PAC which limited the pre- and post-comparison. However, of those patients who did attend, acceptance of the protocol was high. Larger studies that prospectively monitor patients' referral and attendance to PAC and IN consumption are required so that post-operative outcomes of patients fully compliant with the protocol can be used to assess the impact of pre-operative IN in UGI cancer patients.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

Ethics approval was obtained from the Sir Charles Gairdner Osbourne Park Health Care Group Human Research Ethics Committee (reference 2015-092) and Curtin Human Research Ethics Committee (reference HR186/2015).

Table 1: Questions asked during patient interviews

1	Did you receive immunonutrition supplements before your surgery?
2	Did you understand the reasons for taking the immunonutrition supplements?
3	Did you like the taste of the immunonutrition supplements?
4	Did you find that the immunonutrition supplements affected your appetite?
5	Did you receive the information leaflet on immunonutrition supplements? If so, was it helpful?
6	Were you worried about taking immunonutrition supplements with your health condition?
7	Is there anything else you would like to mention about the immunonutrition supplements?

Table 2: Audit patient demographics and clinical data

	Pre-implementation	**Post-implementation**	**p-value**
Patients	36	38	0.959
Sex (F/M)	16/20	15/23	0.814
Age (years, mean±SE)	63.61±1.69	63.76±2.03	0.545
Surgical category			
Gastrectomy	5	3	0.474
Oesophagectomy	6	10	0.401
Pancreatectomy	7	7	1
Whipples	18	18	1

Table 3: Post-operative outcomes from audit

	Pre-implementation	**Post-implementation**	**p-value**
Patients	36	38	0.959
Length of stay in hospital (days, mean±SE)	15.42±2.10	13.92±1.08	0.451
Received non-oral nutrition support	9	13	0.251
NBM[(a)] without non-oral nutrition support (days, mean±SE)	4.28±0.33	3.68±0.33	0.866
Clear fluids (days, mean±SE)	1.44±0.21	1.26±0.13	0.659
Nourishing fluids (days, mean±SE)	1.14±0.15	1.11±0.18	0.334
Time to full diet (days, mean±SE)	6.83±0.41	6.03±0.49	0.317
Infectious complications			
Gastrectomy	2 (40%)	1 (33%)	1
Oesophagectomy	4 (67%)	2 (20%)	0.118
Pancreatectomy	0	1 (14%)	1
Whipples	1 (6%)	6 (33%)	0.088
All surgeries	7 (19%)	10 (26%)	0.584
Non-infectious complications			
Gastrectomy	1 (20%)	0	1
Oesophagectomy	4 (67%)	5 (50%)	0.633
Pancreatectomy	2 (29%)	0	0.462
Whipples	5 (28%)	5 (28%)	1
All surgeries	12 (33%)	10 (26%)	0.613
Unplanned ICU admissions	**1**	**0**	**0.486**

[(a)] NBM, nil by mouth

Table 4: Patient feedback on immunonutrition acceptability

		Received immunonutrition	Did not receive immunonutrition
Patients		17	8
Time between PAC[(a)] and surgery (days, mean±SE)		6.68±1.18	2.00±0.46
PAC information			
Received information about IN		17	8
Immunonutrition palatability			
Flavour	Liked the taste	2	-
	Taste was acceptable	6	-
	Very or too sweet	3	-
	Did not like the taste	2	-
Commented on the thickness of the immunonutrition supplement		4	-
Disliked milk products		3	-
Side effects of immunonutrition consumption			
Experienced nausea and vomiting		2	-
Suppressed appetite		4	-

[(a)] PAC, pre-admission clinic