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The Effect of Preoperative Immunonutrition on Surgical Outcomes in Patients Undergoing Resection for Pancreatic Malignancy

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Abstract

Background: There are no published data on Immunonutrition (IMN) in an Australian pancreatic cancer population. The aim of this study was to investigate the effect of preoperative oral IMN on surgical outcomes in patients undergoing pancreatic cancer resection, compared to those who received Standard Care (SC).

Methods: A retrospective review of a prospectively maintained database was conducted, and 64 consecutive records of patients undergoing curative intent pancreatic cancer resection over a 12-year period (2005-2017) were included. The primary outcome was the incidence of Clavien-Dindo III-IV complications. Secondary endpoints were infectious complications and the length-of-stay.

Results: Twenty-nine patients received IMN and dietary counselling compared to 35 patients in the SC group. The overall rate of Clavien-Dindo III-IV complications was 28%. Baseline characteristics, length-of-stay and Clavien-Dindo III-IV complications between the groups was not different on univariate analysis. Analysis of infectious complications not accounting for nutritional status favoured SC likely due to younger age distribution of the cohort ($p=0.03$). A Cochran-Mantel-Haenszel test controlling for Clavien-Dindo ≥ 3 and IMN after adjustment for stratified data showed a summary odds ratio of 0.71 (95% confidence interval 0.47-1.08).

Conclusion: In this cohort of pancreatic cancer resections, the benefit of preoperative oral immunonutrition was not shown.

Keywords: MeSH, Nutritional support; Dietary supplements; Pancreaticoduodenectomy; Pancreatic neoplasm; Humans

Introduction

Pancreatic cancer is the seventh leading cause of global cancer-related mortality [1], and the fourth leading in Australia [2]. Despite early detection and treatment, the five-year survival rate for a diagnosis of pancreatic malignancy remains significantly low at 9% [1-3]. Currently, the single curative treatment option for pancreatic cancer is surgical resection, with addition of adjuvant chemotherapy showing improved survival rates [3]. Although advances in surgical techniques have reduced the incidence of complications, surgery for pancreatic cancer remains a highly morbid procedure [4].

Poor nutritional status is a risk factor for increased morbidity after major abdominal surgery [5], and in the setting of gastrointestinal malignancy malnutrition can affect between 40-80% of patients [6-10]. Malnutrition in pancreatic cancer can manifest as a result of cancer related weight loss, steatorrhea, malabsorption, pain and anorexia which can often be present for extended periods due to delayed diagnosis, with up to 80% of patients reporting >10% weight loss at diagnosis [9]. Patients often experience ongoing symptoms and weight loss during treatment [9-11]. Nutritional support should be provided for at least 7-14 days preoperatively for severely malnourished patients, and oral or enteral nutrition is preferred [4,5]. However, there is limited evidence regarding the optimal timing and formulation of nutritional support that should be provided [12]. A significant amount of research into peri-operative nutrition in major abdominal surgery has centred around pharmaconutrition, also known as Immunonutrition (IMN). Immunonutrition refers to nutritional

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Table 1: Baseline characteristics and univariate surgical outcomes.

	Immunonutrition n=29	Standard Care n=35	p value
Gender (Female: Male)	9:20	11:24	0.99 [‡]
Age [†] (years)	72 (63-78)	65 (58-73)	0.05 [§]
Extent of pancreatic resection:			
Whipple	22(76%)	32(91%)	0.33
Total pancreatectomy	3(10%)	2(6%)	
Partial/distal	2(7%)	1(3%)	
Completion pancreatectomy	2(7%)	0	
Diabetes (yes: no)	14:15	10:25	0.11 [‡]
Smoking (yes: no)	3:26	5:30	0.66 [‡]
Body Mass Index (kg/m ²) [†]	26.9 (24.23-30.85)	26.4 (23.13-29.47)	0.29 [§]
Malnourished at time of surgery as assessed by dietitian (yes: no)	14:15	16:19	0.87
Clavien-Dindo < 3: ≥ 3	22:7	24:11	0.61 [‡]
Presence of Infectious Complications (yes: no)	10:19	4:31	0.03 [‡]
White Cell Countx 10 ⁹ /L [†]	9.90 (7.95-12.85)	11.10 (8.75-14.68)	0.27 [§]
Lymphocytesx 10 ⁹ /L [†]	1.20 (0.90-1.85)	1.60 (1.00-9.13)	0.10 [§]
Length of Stay (days) [†]	12 (9.00-21.25)	13 (11.00-17.75)	0.37 [§]

† median (Inter-Quartile Range IQR); ‡ difference in proportions; § Mann-Whitney test; || χ² test

formulas supplemented with high quantities of omega-three fatty acids, arginine and nucleotides, with or without glutamine [13]. It is hypothesised that these immune-modulating ingredients can assist the immune and inflammatory response to surgical stress, thus resulting in improved surgical outcomes [13].

Despite a high volume of research conducted, the efficacy of IMN remains controversial. The results of meta-analyses have been mixed [14-20]. It has been suggested that malnourished patients undergoing hepatobiliary resection may benefit the most from IMN, resulting in decreased infectious complications [12,14]. There have been limited studies reporting on the use of pre-operative oral IMN in pancreatic resection specifically [16]. There have been no published data regarding the use of IMN therapy in an Australian pancreatic cancer population. The aim of our retrospective cohort study was to investigate the effect of preoperative oral IMN on the surgical outcomes of patients undergoing pancreatic cancer resection, compared to those who received Standard Care (SC).

Methods

Data collection

A retrospective review of a prospectively maintained database was conducted. Ethical approval was obtained from the Western Health Human Research Ethics Committee (Review Reference 2013.36). We reviewed 106 consecutive records of patients undergoing major pancreatic resection in our institution, over a 12-year period (2005-2017). Only those who received elective curative intent resection for pancreatic malignancy were included. The demographic characteristics and presence of relevant co-morbidities were recorded by a single researcher. Postoperative Length Of Stay (LOS) and inpatient surgical complications were recorded and graded according to the Clavien-Dindo classification system by the same researcher [21]. Biochemical markers of inflammation, White Cell Count (WCC) and lymphocytes collected during routine care at day three post-surgery were also recorded. Patients were categorised as having received IMN or SC by a second, independent researcher who was blinded to the LOS and surgical complications data. Body Mass Index (BMI) and nutritional status were recorded, as per the documented assessment by a surgical dietitian either immediately before or after surgery. Malnutrition

was diagnosed using The International Classification of Diseases, 10th Revision Australian modification (ICD-10-AM) classification for malnutrition [22]. The ICD-10-AM defines malnutrition as BMI < 18.5 kg/m² or unintentional loss of weight (>5%), with evidence of suboptimal intake resulting in moderate loss of subcutaneous fat and/or moderate muscle wasting [22].

Nutritional intervention

The IMN group received five days of preoperative oral IMPACTR Advanced Recovery (Nestlé Health Science), three cartons per day totalling 750 ml, regardless of nutritional status. Malnourished patients were also counselled by a surgical dietitian on the importance of maintaining adequate energy and protein intakes prior to surgery according to their individual needs. The SC group were not provided with any supplementation of IMN or any dietary advice before surgery.

Study endpoints

Incidence of major Clavien complications, defined as grade III-V, was the primary endpoint. The incidence of infectious complications as defined using the Centers for Disease Control (CDC) guidelines [23], differences in postoperative inflammatory markers (WCC and lymphocytes), and LOS were the secondary endpoints. Both primary and secondary endpoints were analysed for malnourished and well-nourished participants, who received either IMN or SC. Potential confounders including sex, age, BMI, smoking, diabetes and surgery type were also accounted for in the analysis.

Statistical analysis

Descriptive data were presented as median and Inter-Quartile Range (IQR). For univariate analysis, difference in binomial proportions between groups were assessed using exact test. Continuous data were analysed using the Mann-Whitney-U statistics. After stratification of data by potential confounders, the Cochran-Mantel-Haenszel test was used to generate Odds Ratios (OR) graphically presented as a Forest plot. P-value (2-sided) of <0.05 was deemed statistically significant. All analyses were undertaken with StatXact v9 (Cytel Inc. Cambridge MA, USA) and Stata v14 (StataCorp, College Station, TX, USA).

Table 2: Surgical outcomes-accounting for nutritional status.

	Immunonutrition n =29	Standard Care n = 35	P value
Clavien-Dindo <3:≥3	malnourished 9:3 well-nourished 13:4	malnourished 11:5 well-nourished 13:6	0.77 [‡] 0.67 [‡]
Presence of infectious complications (yes:no)	malnourished 4:8 well-nourished 6:11	malnourished 2:14 well-nourished 2:17	0.22 [‡] 0.08 [‡]
Length of Stay (days) <12:≥12	malnourished 3:9 well-nourished 9:8	malnourished 4:12 well-nourished 6:13	0.99 [‡] 0.31 [‡]

‡ Difference in proportions

Results

Of the 106 records reviewed, eight patients had benign pathology, 21 patients had non-pancreatic malignant pathology, one patient received inpatient total parenteral nutrition preoperatively. These records were excluded. Twelve patients had incomplete data with regards to receiving IMN and were also excluded. A total of 64 records were included in the final analysis, all with malignant pancreatic pathology. Twenty-nine patients received IMN, and 35 patients received SC. Univariate analysis showed no differences between the groups for any demographic, biochemical or surgical outcome variables, except that infectious complication rates were lower in the SC group (10 vs 4, $p=0.03$), which had a younger age distribution with a median age of 65 (58-73) compared to 72 (63-78) in the IMN group (Table 1). There was no occurrence of postoperative mortality in either group. The prevalence of malnutrition in both groups was approximately 45% (Table 1). When adjusted for nutritional status, no differences in primary or secondary outcomes were found (Table 2). Cochran-Mantel-Haenszel analysis, adjusted for potential confounders demonstrated no difference for primary outcome of Clavien complications ≥ 3 , with a summary OR for stratified data of 0.71 (0.47-1.08) as seen in the Forest plot presentation (Figure 1).

Discussion

In this study, we found no differences in severe surgical complications nor LOS for pancreatic cancer patients provided with oral IMN five days pre-surgery, compared with those who received SC. Results were consistent across both malnourished and well-nourished patients. The overall complication and mortality rates of our cohort were acceptable compared to the international literature [3]. The lower rate of overall infectious complications in the SC was likely due to the younger age of the cohort and was not demonstrated after stratified analysis. This is in keeping with the findings of Gade and colleagues who conducted a small Randomised Control Trial (RCT) of seven days of oral IMN prior to pancreatic cancer resection [24]. In a recent RCT of patients undergoing major liver resection, Russell and colleagues also found that patients who received preoperative oral IMPACTR had a higher incidence of infectious complications than the controls, and plasma markers of inflammation (interleukin-6) remained elevated at seven days' post-surgery [25]. However, other studies investigating preoperative IMN in pancreatic cancer have demonstrated positive findings. Aida et al., conducted a prospective RCT on 50 patients undergoing pancreaticoduodenectomy comparing preoperative IMN versus standard diet and demonstrated reduced severe and infectious complications [26]. Shirakawa et al., retrospectively evaluated a group of 25 patients undergoing pancreaticoduodenectomy and found that consumption of preoperative oral IMPACTR resulted in lower incisional wound infection rates [27]. To the author's knowledge, there are no published studies investigating the use of IMN in an Australian pancreatic cancer cohort.

The heterogeneity of the current body of IMN research makes it

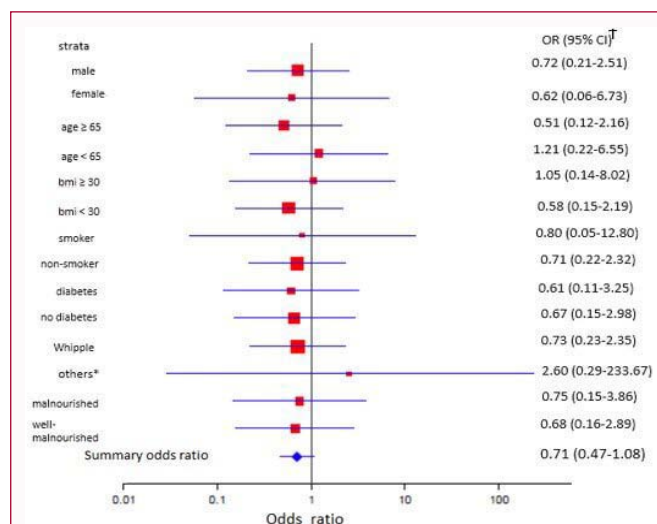


Figure 1: Forest plot of Cochran-Mantel-Haenszel analysis controlling for Immunonutrition and Clavien-Dindo score ≥ 3 after adjustment for stratified data [7]. [†] Odds ratio (95% confidence interval); *Total, Partial, Completion pancreatectomy; BMI= Body Mass Index.

difficult to determine how much, when and to whom IMN may be of the most benefit [14-20]. Routes of administration are enteral, oral and parenteral, whilst timing and dosage of interventions IMN are not comparable. A large meta-analysis of 83 RCTs ($n=7116$) in major abdominal surgery found a reduction in complications and LOS for IMN, however the surgical populations and IMN interventions were heterogeneous, and results demonstrated high risk of sponsorship bias [14]. A recent meta-analysis of 16 studies ($n=1387$) conducted by Adiamah and colleagues demonstrated that compared with isocaloric supplementation, the use of the preoperative oral IMN formula IMPACTR reduced the rate of infectious complications and LOS after major gastrointestinal cancer surgery [16]. However, the review included studies in colorectal, gastric, liver and pancreatic cancer cohorts. In pancreaticoduodenectomy specifically, provision of enteral IMN in the post-operative period reduces incidence of infectious complications and decreases LOS, however there is limited research to support preoperative oral supplementation [20]. The European Society for Enteral and Parenteral Nutrition surgical nutrition guidelines do not recommend routine provision of preoperative IMN over standard oral nutrition formula for those having major abdominal surgery, due to insufficient evidence of benefit [5].

Strengths of this study include the homogeneity of the population and the timing of the intervention; all patients had pancreatic cancer and the IMN was provided only preoperatively. The type and dosage of IMN, five days of 750 ml IMPACTR, has previously been utilised in the majority of oral IMN research [19]. This was also an unsponsored clinical study, and two independent researchers recorded the surgical complications and IMN data, ensuring they were blinded from the

dependent variable of interest for unbiased results. We adjusted for potential confounders in the analysis and accounted for nutritional status, given that malnourished patients may benefit more from IMN than those who are well-nourished [5].

Although we captured data on pancreatic cancer resections spanning 12 years at a major tertiary institution, the sample size in this study was relatively low, and it may have been under powered to detect statistically significant differences between the groups. Due to the retrospective nature of our study, we were unable to determine the compliance with IMN or measure immune specific biochemical markers, and we could not calculate the overall dietary intakes of patients. Lower compliance with IMN and insufficient dietary protein intake may influence results [24]. The timing and delivery route of nutritional supplementation post pancreatic surgery can also impact surgical outcomes [28]. In our study, all patients in both the IMN and SC groups received post-operative assessment and intervention from a surgical dietician; however the exact nutritional management of these patients varied depending on the postoperative course. Finally, the effect of dietitian delivered dietary counselling provided to malnourished patients in the IMN group may have also influenced results, as the SC group received no nutritional intervention. In other upper gastrointestinal cancer populations, individualised dietary counselling can improve surgical complication rates [29]. Future research should ensure that intervention and control groups receive standardised pre-and post-operative dietary counselling and intervention, to enable true distinction of the benefits of IMN over standard oral supplements.

Conclusion

This study is the first to report on the provision of IMN in an Australian pancreatic cancer population undergoing surgery. There were no additional benefits of provision of preoperative oral immunonutrition demonstrated compared to standard diet on surgical complications and LOS in malnourished and well-nourished patients undergoing curative intent pancreatic cancer surgery. Future research *via* randomised control trials should be undertaken.

Disclosure Statement

Irene Deftereos has received an unrestricted project grant from Nestlé Health Science in 2019, for an unrelated observational study, not investigating immunonutrition. The remaining authors have no conflict of interest to declare.

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