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Effects of Immunonutrition for Cystectomy on Immune Response and Infection Rates: A Pilot Randomized Controlled Clinical Trial

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Abstract

After radical cystectomy (RC), patients are at risk for complications including infections. The expansion of myeloid-derived suppressor cells (MDSCs) after surgery may contribute to the lower resistance to infection. Immune response and postoperative complications were compared in men consuming either specialized immunonutrition (SIM; $n = 14$) or an oral nutrition supplement (ONS; $n = 15$) before and after RC. MDSC count (Lin[−] CD11b⁺ CD33⁺) was significantly

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different between the groups over time ($p = 0.005$) and significantly lower in SIM 2 d after RC ($p < 0.001$). MDSC count expansion from surgery to 2 d after RC showed a weak association with an increase in infection rate 90 d after surgery ($p = 0.061$).

Neutrophil:lymphocyte ratio was significantly lower in SIM compared with ONS 3 h after the first incision ($p = 0.039$). Participants receiving SIM had a 33% reduction in postoperative complication rate (95% confidence interval [CI], 1–64; $p = 0.060$) and a 39% reduction in infection rate (95% CI, 8–70; $p = 0.027$) during late-phase recovery. The small sample size limits the study findings.

Patient summary—Results show that the immune response to surgery and late infection rates differ between radical cystectomy patients receiving specialized immunonutrition versus oral nutrition supplement in the perioperative period.

Trial registration—[ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01868087) NCT01868087.

Keywords

Arginine; Bladder cancer; Radical cystectomy; Myeloid-derived suppressor cells; PG-SGA; Neutrophil:lymphocyte ratio; Fish oil

Radical cystectomy (RC) is associated with morbidity, and postoperative complications are reported in up to 65% of patients [1]. Infections account for 25% of complications at 30 and 90 d [2]. Improving immune function through a specialized immunonutrition (SIM) drink could be a low-risk, high-impact means of protecting against infections after RC. SIM provides supplemental L-arginine, fish oil, vitamin A, and dietary nucleotides derived from yeast RNA. In surgical oncology patients, perioperative enteral feeding with SIM reduced infections [3]. Bertrand and colleagues reported a 37% absolute reduction in complication and infection rates ($p = 0.008$) in RC patients consuming SIM orally before surgery versus a historical cohort [4]. Myeloid-derived suppressor cells (MDSCs) are immune cells that expand rapidly after physical injury but quickly differentiate into granulocytes, macrophages, or dendritic cells. MDSC accumulation suppresses T cells and lowers the resistance to infection. MDSCs express and release arginase-1, depleting plasma arginine concentrations [5]. Arginine deficiency imposed by surgery impairs lymphocyte proliferation and T-cell receptor integrity. We hypothesize that arginine-enriched SIM will modulate the immune response to surgery.

Twenty-nine men scheduled to undergo RC for primary bladder cancer were randomized using a sequence generated by the statistician to either SIM ($n = 14$; Impact Advanced Recovery; Nestlé HealthCare Nutrition, Florham Park, NJ, USA) or the oral nutrition supplement (ONS) control group ($n = 15$; Boost Plus; Nestlé HealthCare Nutrition). Blocked randomization using blocks of 10 were used to allocate participants according to a computer-generated randomization list with a predetermined ratio of 1:1. The statistician was not involved in the study implementation. The allocation list was only accessible to the study coordinator via a password-protected file. The cartons were wrapped with opaque tape and coded numerically. Health care providers and data collectors were blinded to the intervention. The study was restricted to men to reduce the variability in RC outcomes known to exist between genders [6]. Exclusion criteria were swallowing difficulties,

metastasis, 10% weight loss in past 6 mo, body mass index <18.5, viral infection or immune deficiency, gout, or relevant food allergies. Patients were instructed to consume three cartons per day for 5 d before and 5 d after RC (Supplementary Fig. 1 and Supplementary Table 1 and 2). Anesthetic, surgical, and postoperative management were provided according to the standard pathways of our academic institution and consistent with Enhanced Recovery After Surgery pathways. The pilot clinical trial was approved by the institutional review board at the University of Kansas Medical Center. The primary end point of the study was the immune response to surgery (change in total MDSC counts); secondary end points were postoperative complication and infection rates.

Blood was collected at baseline, during surgery (3 h after first incision), and on postoperative days 2, 14, and 30. The ratio of the absolute neutrophil-to-lymphocyte count was abstracted from the complete blood count with differential. MDSC (Lin[−] CD11b⁺ CD33⁺) counts were determined by flow cytometry and sorted into phenotypes using published methods [7]. Differences in the immune response were assessed longitudinally using the generalized linear model, SAS procedure GLIMMIX with spatial power covariance structure (SP[POW]). Postoperative complications were defined as early (<30 d) versus late (31–90 d). Complications were graded according to the Clavien-Dindo scheme; a postoperative ileus was defined as a delay in institution of a regular diet >5 d postoperatively. Infectious complications were defined by the need for intervention or prescription of nonprophylactic antibiotics. Complication and infection rates between groups were compared by a chi-square test using the intention-to-treat principle. Logistic regression was used to evaluate the association between MDSC expansion and infection rates. A $p < 0.05$ was considered statistically significant.

All adverse events related to the study intervention were gastrointestinal (Supplementary Table 3). Participants receiving SIM were more likely to self-report postoperative diarrhea ($p = 0.008$). No one stopped treatment because of adverse events, and none of the reported adverse events were graded as serious.

MDSC counts were significantly different between the SIM and ONS groups over time ($p = 0.005$; Fig. 1a). Monocytic MDSC (M-MDSC) phenotype counts were significantly different between the SIM and ONS groups over time ($p = 0.008$) (Fig. 1b). Granulocytic and immature phenotypes did not differ significantly between groups. Neutrophil:lymphocyte ratio (NLR) was significantly lower in the SIM group compared with the ONS group 3 h after incision ($p = 0.039$) (Supplementary Fig. 2), but NLR did not differ significantly between the SIM and ONS groups over time.

Table 1 shows postoperative complication and infection rates. No differences were detected in the early period. Participants receiving SIM had a 33% reduction in postoperative complication rate (95% confidence interval [CI], 1–64; $p = 0.060$) and a 39% reduction in infection rate (95% CI, 8–70; $p = 0.027$) during late-phase recovery.

MDSC expansion restrains the activation of T cells and lowers resistance to infection; with every unit increase in MDSC count from surgery to 2 d postoperatively, the odds of infection rate 90 d after surgery increased by 2.5% ($p = 0.061$).

This study shows that immune response to surgery and late infection rates differ between RC patients receiving SIM versus ONS in the perioperative period, but our study was limited by a small sample size. Diarrhea was reported more frequently in participants receiving SIM, similar to other interventions supplementing fish oil [8] or L-arginine [9]. We report the M-MDSC subtype appears to be the most responsive phenotype to RC and may be restrained by SIM intake. M-MDSC counts in cancer patients positively correlate with regulatory T-cell counts, and in vitro, M-MDSC mediates T-cell suppression [10]. We report fewer postoperative complications and infections in RC patients receiving SIM, which is similar to the findings reported by Bertrand et al [4] and Braga et al [3]. Given that NLR has been suggested as a biomarker for predicting clinical course in surgical populations [11], the lower NLR response 3 h after first incision in the SIM group compared with the ONS group suggests SIM consumption may modulate the acute immune response to surgical stress. We infer that the differences in the short-term immune response between SIM and ONS alter the trajectory of a patient's resistance to infection as time progresses. The sample size was powered for detecting a difference in MDSC counts over time between SIM and ONS control, not overall complication or infection rates. The novel findings from this small pilot study need to be confirmed in an adequate size clinical trial of RC patients to confirm definitively whether SIM can significantly reduce complications.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Take Home Message

Radical cystectomy patients are at risk of infections. Expansion of myeloid-derived suppressor cells (MDSCs) after surgery suppresses the immune system. Specialized immunonutrition (SIM) may reduce infections by restraining MDSC expansion. Immune response to surgery and late infection rates differ between SIM and oral nutrition supplements.

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Fig. 1.

Mean counts (plus standard deviation) of total myeloid-derived suppressor cells (MDSCs; Lin⁻ CD11b⁺ CD33⁺) and monocytic (Lin⁻ CD11b⁺ CD33⁺ CD14⁺ CD15⁻) MDSCs at five time points before and after radical cystectomy in two patient groups: oral nutrition supplement (ONS) control ($n = 15$) and specialized immunonutrition (SIM; $n = 14$). Change in total MDSC counts was the primary end point. A sample size of 30 participants (15 in each arm) and 80% power at a two-sided level of significance of 0.05 would detect a change in total MDSC counts of 7. Generalized linear models with longitudinal measures were used

to test differences between the immune response outcomes measured over the five longitudinal time points using the GLIMMIX procedure (SAS v.9.4, TS level T1M0; SAS Institute, Cary, NC, USA) with spatial power covariance structure (SP[POW]). A $p < 0.05$ was considered statistically significant. (a) MDSC counts were significantly different between the SIM and ONS groups over time ($p = 0.005$). MDSC count was significantly lower in the SIM group compared with the ONS group at postoperative day 2 ($p < 0.001$). The difference between MDSC counts obtained at baseline and postoperative day 2 was significantly lower in the SIM group than the ONS group ($p = 0.002$). Also, the change in MDSC counts obtained during surgery (3 h after first incision) and postoperative day 2 was significantly lower in the SIM group than the ONS group ($p = 0.0005$). (b) Monocytic MDSC phenotype counts were significantly different between the SIM and ONS groups over time ($p = 0.008$). Monocytic MDSC phenotype count was significantly lower in the SIM group compared with the ONS group at postoperative day 2 ($p < 0.001$). The difference between monocytic MDSC phenotype counts obtained at baseline and postoperative day 2 was significantly lower in the SIM group than the ONS group ($p = 0.001$). In addition, the change in monocytic MDSC counts obtained during surgery (3 h after the first incision) and postoperative day 2 was significantly lower in the SIM group than the ONS group ($p = 0.001$).

MDSC = myeloid-derived suppressor cells; POD = postoperative day.

Table 1Postoperative complications of men after bladder cancer surgery¹

	Specialized immunonutrition, <i>n</i> = 14 men	Oral nutrition supplement, <i>n</i> = 15 men	Differences between groups, % (95% CI)
Complications, <i>n</i> (%)			
30 d	10 (71)	11 (73)	−2 (−36 to 33)
90 d*	2 (14)	7 (47)	−33 (−70 to −5.7)
High-grade complications, <i>n</i> (%)			
30 d	2 (14)	2 (13)	1 (−25 to 27)
90 d	0 (0)	2 (13)	−13 (−37 to 11)
Antibiotic use, <i>n</i> (%) ²			
30 d	5 (36)	9 (60)	−24 (−66 to 18)
90 d**	2 (14)	8 (53)	−39 (−77 to −0.94)
Intra-abdominal infection, <i>n</i> (%)			
30 d	1 (7)	4 (27)	−20 (−53 to 14)
90 d	0 (0)	1 (7)	−7 (−26 to 13)
Ileus >5 d, <i>n</i> (%)	4 (27)	2 (13)	14 (−21 to 51)
Length of stay	6.3 (3.1)	6.1 (1.9)	0.2 (−1.79 to 2.23)
SIRS, <i>n</i> (%) ³	1 (7)	2 (13)	−6 (−34 to 22)
Readmission, <i>n</i> (%)			
Yes	4 (29)	6 (40)	−11 (−53 to 30)
No	10 (71)	9 (60)	11 (−29 to 53)
Clavien-Dindo grade 30 d, <i>n</i> (%) ⁴			
Grade 0	0 (0)	0 (0)	
Grade 1	2 (14)	1 (7)	7 (−22 to 37)
Grade 2	8 (57)	8 (53)	4 (−36 to 44)
Grade 3a	0 (0)	1 (7)	−7 (−26 to 13)
Grade 3b	0 (0)	1 (7)	−7 (−26 to 13)
Grade 4–5	0 (0)	0 (0)	
Clavien-Dindo grade 90 d, <i>n</i> (%)			
Grade 0	0 (0)	0 (0)	
Grade 1	0 (0)	0 (0)	
Grade 2	2 (14)	5 (33)	−19 (−56 to 18)
Grade 3a	0 (0)	2 (13)	−13 (−37 to 11)
Grade 3b	0 (0)	0 (0)	
Grade 4–5	0 (0)	0 (0)	

CI = confidence interval; SIRS = systemic inflammatory response syndrome.

¹ Recruitment and follow-up occurred from September 2013 to April 2015. Clinical outcomes data abstracted at 30 and 90 d were analyzed from all participants who signed the informed consent and who received any allocated supplements. Rates were compared using a chi-square test using intention to treat for categorical variables. A *p* < 0.05 was considered statistically significant.

² Infectious complications were defined by the need for intervention or prescription of nonprophylactic antibiotics. All patients followed the same antibiotic protocol according to the standard pathways of the University of Kansas Medical Center. All patients receive 24 h of Mefoxin followed by 1 mo of Macrodonin 100 mg every day.

³ SIRS, based on temperature ($<36^{\circ}\text{C}$ or $>38^{\circ}\text{C}$), heart rate (>90 beats/min), respirations (>20 breaths/min or $\text{PaCO}_2 <4.3$ kPa), white blood cell count (<4000 cells/mm³ or $>12\,000$ cells/mm³ or $>10\%$ bands present).

⁴ Clavien-Dindo classification of surgical complications; a higher grade indicates a greater severity of complication.