Preoperative immunonutrition prior to radical cystectomy: a pilot study

Timothy D. Lyon, MD,[1] Robert M. Turner II, MD,[1] Dawn McBride, RN,[1] Li Wang, MS,[2] Jeffrey R. Gingrich, MD,[1] Ronald L. Hrebinko, MD,[1] Bruce L. Jacobs, MD,[1] Benjamin J. Davies, MD,[1] Tatum V. Tarin, MD[1]

[1]Department of Urology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[2]Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

LYON TD, TURNER II RM, MCBRIDE D, WANG L, GINGRICH JR, HREBINKO RL, JACOBS BL, DAVIES BJ, TARIN TV. Preoperative immunonutrition prior to radical cystectomy: a pilot study. *Can J Urol* 2017; 24(4):8895-8901.

Introduction: *To investigate the use of a high-arginine immunonutrient supplement prior to radical cystectomy for bladder cancer.*

Materials and methods: *We recruited 40 patients to consume a total of four high-arginine immunonutrient shakes per day for 5 days prior to radical cystectomy. The primary outcome measures were safety, tolerability and adherence to the supplementation regimen. Ninety-day postoperative outcomes were also compared between supplemented patients and a cohort of 104 prospectively identified non-supplemented radical cystectomy patients. Multivariable logistic regression models were used to compare overall complications, infectious complications, and readmission rates between groups.*

Results: *There were no serious adverse events during supplementation. Four patients (10%) stopped supplementation due to nausea (n = 2) and bloating (n = 2). Thirty-three patients (83%) consumed all prescribed shakes. Immunonutrient supplementation was not significantly associated with overall complications (adjusted odds ratio [OR] 1.08; 95% confidence interval [CI] 0.50-2.33), infectious complications (OR 1.23; 95% CI 0.49-3.07), or readmissions (OR 1.48; 95% CI 0.62-3.51) on multivariable analyses.*

Conclusions: *Preoperative supplementation with a high-arginine immunonutrient shake was safe and well tolerated prior to radical cystectomy. Contrary to prior reports, immunonutrient supplementation was not associated with lower postoperative infectious complications in this cohort, perhaps owing to the 5 day supplementation period. Further study is needed to identify the optimal immunonutrient supplement regimen for radical cystectomy patients.*

Key Words: bladder cancer, cystectomy, arginine, dietary supplement

Introduction

Radical cystectomy is the gold standard treatment for patients with muscle-invasive bladder cancer and is indicated in some patients with non-muscle-invasive disease. Unfortunately, radical cystectomy remains a highly morbid operation, with published complication rates as high as 66%.[1] Nutritional deficiency is considered a modifiable risk factor for postoperative complications.[1-3] Specifically, arginine, an amino acid essential for normal T cell function, is recognized as a potential supplementation target, as perioperative repletion of arginine has been shown to increase postoperative T lymphocyte function and may help prevent postoperative infection.[4,5] Several randomized controlled trials show high-arginine immunonutrient supplementation reduces overall and infectious complication rates and decreases hospital length of stay after gastrointestinal surgery.[6]

However, it remains unclear if immunonutrient supplementation improves outcomes following radical cystectomy. Two previous groups have demonstrated that preoperative high-arginine immunonutrient

Accepted for publication July 2017

Acknowledgements

The project described was supported by the Shadyside Hospital Foundation's Thomas H. Nimick, Jr. Competitive Research Fund Award. Statistical support through the Clinical and Translational Science Institute was supported by the National Institutes of Health through Grant Number UL1-TR-001857.

Address correspondence to Dr. Tatum V. Tarin, Department of Urology, University of Pittsburgh Medical Center, 3471 Fifth Avenue, Suite 700, Pittsburgh, PA 15213 USA

supplementation is associated with fewer postoperative infections following radical cystectomy, though these studies are limited by small sample size and higher than expected complication rates in the control populations. As the optimal dose and duration of immunonutrient supplementation remains elusive in this population, the use of high-arginine immunonutrient supplementation is not currently standard of care prior to radical cystectomy.[7,8]

For this reason, we conducted a pilot study to investigate preoperative high-arginine immunonutrient supplementation prior to radical cystectomy. We hypothesized that supplementation would be safe, well tolerated, and efficacious at reducing postoperative infections among a cohort of patients undergoing radical cystectomy.

Materials and methods

Study design

This was a phase II pilot study comparing outcomes of supplemented patients to non-supplemented patients. Although using high-arginine immunonutrition prior to radical cystectomy is not standard of care, our institutional review board did not permit us to perform a randomized trial, citing concerns over withholding a supplement shown to be beneficial in the gastrointestinal surgery literature. At the time of protocol creation, there were no published studies on immunonutrition and radical cystectomy to our knowledge. The study was designed to generate preliminary efficacy and safety data to support a future randomized protocol. The University of Pittsburgh institutional review board approved the study protocol, which was also registered at ClinicalTrials.gov (NCT02655081).

Study population

Between October 2014 and August 2016, we prospectively enrolled 44 patients who underwent radical cystectomy at the University of Pittsburgh Medical Center. Four patients were excluded from final analysis due to death prior to radical cystectomy (n = 1), unresectable disease at time of surgery (n = 1), and robotic-assisted laparoscopic radical cystectomy (n = 2), leaving a final supplementation cohort of 40 patients. We excluded robotic cases since there were no robotic surgeries in the non-supplemented group. The low rate of enrollment was attributable to the loss of a departmental study coordinator for 1 year during the study period; during the time when a coordinator was not present, patients undergoing cystectomy were not actively enrolled.

The comparison population consisted of a series of 104 consecutive patients who underwent radical cystectomy at our institution between January 2015 and August 2016. One of these patients declined supplementation, and the remainder were not offered enrollment as they were cared for during a time without a study coordinator. Initially a historical control group was planned, but due to the number of patients who underwent cystectomy while the protocol was open who did not receive supplementation, this group was instead used as a contemporary comparison population.

A total of four surgeons contributed patients to both supplemented and non-supplemented groups, and a fifth surgeon contributed patients only to the non-supplemented group. Sensitivity analysis was performed due to potential for confounding from addition of this surgeon's patients; outcomes were not meaningfully altered and therefore these patients were included in the final analysis to maximize statistical power.

Study protocol

Patients in the supplementation cohort were asked to consume a total of four Impact: Advanced Recovery shakes (Nestlé HealthCare Nutrition, Florham Park, NJ, USA) per day for 5 days prior to radical cystectomy. Each shake volume is 237 mL, leading to total recommended consumption of 948 mL/day. This regimen was based upon literature suggesting that high-arginine supplementation with approximately 0.5-1 liter/day for a total of 5-7 days was efficacious at reducing postoperative complications, and which also showed that pre and postoperative supplementation offered no measurable benefit over pre-operative supplementation alone.[9,10] Patients with preoperative glomerular filtration rate < 30 mL/min were excluded. Use of neoadjuvant chemotherapy and type of urinary diversion were left to the discretion of the primary surgeon. All operations were performed in an open fashion by high-volume, fellowship trained urologic oncologists; intra and postoperative care was provided as per our standard postoperative pathways. These pathways were not altered during the study period; an enhanced recovery after surgery pathway was introduced after study enrollment had completed. Aside from perioperative antibiotic dosing, no prophylactic antibiotics were used while ureteral stents were in place.

Outcomes

The primary study outcome was safety, tolerability, and adherence to the supplementation regimen as measured through telephone conversations and patient-completed logs of supplement consumption.

Secondary outcomes included differences in 90 day postoperative complications, infectious complications, readmission rates, and length of initial postoperative hospital stay between supplemented and non-supplemented patients. Changes in weight or serum albumin were not measured as duration of supplementation was expected to be too short to alter these values. Infectious complications were defined as any use of non-prophylactic antibiotics and/or abscess drain placement. Pyelonephritis was defined as fever > 38.5 degrees Celsius plus one additional systemic inflammatory response syndrome criteria (heart rate > 90 beats per minute, respiratory rate > 20 breaths per minute, or white blood cell count > 12,000 cells/mm^3), positive urine culture, and absence of another clinically apparent source of infection.

Statistical analysis

Primary outcome measures are reported as frequencies and percentages. Baseline clinical and pathologic characteristics are reported as frequencies or medians with interquartile range (IQR), and compared between supplemented and non-supplemented patients using chi-square and Fisher's exact tests for categorical variables and Mann-Whitney U test for continuous variables. Analysis was carried out in an intent-to-treat fashion. Univariate and multivariable logistic regression models were performed to evaluate predictors of secondary outcomes. Any covariate with $p < 0.2$ on univariate analysis was included in the multivariable model as was immunonutrient supplementation. To detect a 25% absolute difference in infectious complications between groups, from a baseline rate of 35% to 10% in the supplemented group, a magnitude of difference previously seen in the gastrointestinal literature,[9] a sample size of 100 non-supplemented and 40 supplemented patients was needed to achieve 80% power (alpha 0.05, two-tail). Data were analyzed using SPSS, version 24 (IBM Corp., Armonk, NY, USA). Significance was defined at the $p < 0.05$ level using two-tailed tests.

Results

There were no serious adverse events reported during the study period. A total of four of forty supplemented patients (10%) reported side effects, namely nausea (n = 2) and bloating (n = 2). Thirty-three patients (83%) consumed all twenty prescribed shakes. The remaining seven patients cited the following reasons for not consuming all shakes: volume too filling (n = 2), nausea (n = 1), forgot (n = 1), failure to return consumption log (n = 2) and unspecified (n = 1). Three of these patients failed to provide an estimate of shake consumption; of the remaining four, all drank at least 10 of the prescribed 20 shakes.

Baseline clinical and pathologic characteristics of the study population are reported in Table 1. Fifteen patients (10%) were treated with neoadjuvant chemotherapy, including dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (n = 10), gemcitabine and cisplatin (n = 4), or etoposide and cisplatin (n = 1). The experimental group was more likely to have an ileal conduit diversion than non-supplemented patients ($p = 0.004$). Groups were similar on all other measured characteristics.

Ninety-day postoperative outcomes are summarized in Table 2. There were no differences between the supplemented and non-supplemented populations with regards to complication rate, infectious complication rate, pyelonephritis, postoperative length of stay, or readmission rate (all $p > 0.4$).

Immunonutrient supplementation was not significantly associated with overall complications (adjusted odds ratio [aOR] 1.08; 95% confidence interval [CI] 0.50-2.33, Table 3), infectious complications (aOR 1.23; 95% CI 0.49-3.07, Table 4), or hospital readmission (aOR 1.48; 95% CI 0.62-3.51, Table 5) on multivariable analyses.

Sensitivity analysis was performed after excluding patients of a surgeon only represented in the non-supplemented group. Results of the multivariable models were not meaningfully changed. Specifically, immunonutrient supplementation did not show a significant relationship with infectious complications (aOR 1.05; 95% CI 0.38-2.93).

Discussion

Preoperative high-arginine immunonutrient supplementation was found to be safe and well tolerated among patients undergoing radical cystectomy with a large majority of patients (83%) consuming all prescribed shakes. In contrast to previous reports, immunonutrition was not associated with a decreased risk of postoperative complications, infectious complications, or hospital readmission. The present study is the largest to our knowledge to investigate immunonutrient supplementation among radical cystectomy patients and contributes to a better understanding of the optimal immunonutrition regimen.

Arginine, an amino acid necessary for normal T lymphocyte function and proliferation, is an important component of immunonutrition.[5,11,12] Surgical injury induces myeloid-derived suppressor cells to release the enzyme arginase 1, which metabolizes arginine, leading to a reduction in circulating arginine levels

TABLE 1. **Baseline characteristics of study population**

	Experimental n = 40	Control n = 104	p value*
Age, years, median (IQR)	70 (63-78)	69 (61-76)	0.28
Gender (%)			0.79
Male	29 (73)	73 (70)	
Female	11 (27)	31 (30)	
Race (%)			0.40
White	37 (93)	100 (96)	
Nonwhite	3 (7)	4 (4)	
Active smoker (%)	19 (48)	33 (32)	0.08
BMI, kg/m^2, median (IQR)	28.1 (24.2-30)	27.8 (24.9-32)	0.50
Preoperative albumin, g/dL, median (IQR)	3.9 (3.6-4.2)	4.0 (3.8-4.3)	0.09
Charlson Comorbidity Index (%)			0.08
0	22 (55)	40 (38)	
1	13 (32.5)	34 (33)	
2+	5 (12.5)	30 (29)	
Neoadjuvant chemotherapy (%)	6 (15)	9 (9)	0.36
Diversion type (%)			0.004
Conduit	36 (90)	65 (63)	
Neobladder	4 (10)	34 (33)	
Continent cutaneous	0	5 (5)	
Operative time, min, median (IQR)	298 (260-341)	272 (238-321)	0.06
EBL, mL, median (IQR)	600 (425-875)	600 (425-950)	0.88
Pathologic stage (%)			0.51
Organ confined (Tis, T1-2)	24 (60)	56 (54)	
Nonorgan confined (T3-4)	16 (40)	48 (46)	
Node positive (%)	9 (23)	23 (22)	0.96
Positive margin (%)	1 (3)	5 (5)	0.99

IQR = interquartile range; BMI = body mass index; EBL = estimated blood loss
*p values generated from Fisher's exact or Pearson Chi-Square test for categorical variables and Mann-Whitney U test for continuous variables

within several hours of a surgical stress.[5,13] This process results in downregulation of Th1 helper T cells, which play a role in killing intracellular pathogens, potentially leading to increased susceptibility to infection.[14,15] Immunonutrient supplements were developed containing high doses of arginine in addition to other anti-inflammatory nutrients including omega-3 fatty acids, nucleotides, and vitamin A in an attempt to modulate the body's immunologic response to a surgical stress or physical injury.[16]

Robust clinical evidence suggests that immunonutrient supplementation can decrease infectious complication rates after gastrointestinal surgery. A landmark randomized controlled trial of patients undergoing colorectal cancer resection enrolled 200 patients into one of four groups.[9] Group 1 consumed 1 liter of Impact: Advanced Recovery for 5 days preoperatively; group 2 took in 1 liter of Impact for 5 days preoperatively and the infusion continued through a nasojejunal tube postoperatively; group 3 was supplemented preoperatively for 5 days with a non-immunonutrition supplement; group 4 was asked to take in a standard peri-operative diet. Results revealed that both immunonutrition groups had significantly lower postoperative infection rates than the non-immunonutrition groups (12% and 10% versus 32% and 30%, respectively, $p < 0.04$). There was no statistical difference between the immunonutrition groups, suggesting that postoperative supplementation did not add benefit over preoperative supplementation

TABLE 2. **90 day postoperative outcomes**

	Experimental n = 40	**Control n = 104**	**p value***
Complication (%)			0.84
None	18 (45)	42 (40)	
Minor (Clavien 1-2)	16 (40)	43 (41)	
Major (Clavien 3-5)	6 (15)	19 (18)	
Infectious complication (%)	14 (35)	32 (31)	0.63
Pyelonephritis (%)	6 (15)	14 (13)	0.81
LOS, days, median (IQR)	6 (5-7)	6 (5-7)	0.84
Readmission (%)	16 (40)	34 (33)	0.41

LOS = length of stay; IQR = interquartile range
*p values generated from Fisher's exact or Pearson Chi-Square test for categorical variables and Mann-Whitney U test for continuous variables

TABLE 3. **Multivariable predictors of a 90 day complication**

Predictors	**Univariate OR [95% CI]**	**p value**	**Adjusted OR [95% CI]**	**p value**
Charlson Comorbidity Index		0.12		0.13
0		Ref.		Ref.
1	1.48 [0.69-3.17]	0.32	1.50 [0.69-3.23]	0.31
2+	2.50 [1.03-6.07]	0.04	2.51 [1.01-6.30]	0.05
Duration (min)	1.00 [1.00-1.01]	0.54	1.01 [0.99-1.01]	0.65
IN supplement	0.95 [0.46-2.00]	0.90	1.08 [0.50-2.33]	0.84

OR = odds ratio; CI = confidence interval; IN = immunonutrition

TABLE 4. **Multivariable predictors of an infectious complication**

Predictors	**Univariate OR [95% CI]**	**p value**	**Adjusted OR [95% CI]**	**p value**
Charlson Comorbidity Index		0.06		0.09
0		Ref.		Ref.
1	1.77 [0.76-4.13]	0.19	1.64 [0.65-4.15]	0.30
2+	2.89 [1.18-7.05]	0.02	3.13 [1.13-8.61]	0.03
Serum albumin	0.43 [0.18-1.04]	0.06	0.46 [0.19-1.15]	0.10
Duration (min)	1.01 [0.99-1.01]	0.10	1.01 [0.99-1.01]	0.14
IN supplement	1.21 [0.56-2.62]	0.63	1.23 [0.49-3.07]	0.66

OR = odds ratio; CI = confidence interval; IN = immunonutrition

alone. A systematic review composed of 2331 patients from 19 randomized trials found that immunonutrient supplementation prior to surgery for gastrointestinal cancers was associated with a significantly decreased risk of infectious complications (relative risk [RR] 0.44; 95% CI 0.32-0.60) and non-infectious complications (RR 0.72; 95% CI 0.54-0.97) when compared to a standard diet.[6]

Two previous studies have examined the effect of immunonutrition on patients undergoing radical cystectomy. Bertrand et al supplemented 30 patients with Impact: Advanced Recovery for 7 days before radical cystectomy and compared postoperative outcomes to a matched cohort of non-supplemented patients. They found patients who

TABLE 5. **Multivariable predictors of readmission**

Predictors	Univariate OR [95% CI]	p value	Adjusted OR [95% CI]	p value
Charlson Comorbidity Index		0.12		0.14
0		Ref.		Ref.
1	1.37 [0.60-3.11]	0.46	1.37 [0.56-3.35]	0.49
2+	2.50 [1.05-5.95]	0.4	2.67 [1.01-7.03]	0.047
Serum albumin	0.38 [0.16-0.92]	0.03	0.42 [0.17-1.03]	0.06
IN supplement	1.37 [0.65-2.92]	0.41	1.48 [0.62-3.51]	0.38

OR = odds ratio; CI = confidence interval; IN = immunonutrition

received immunonutrition had fewer postoperative complications (40% versus 76%, p = 0.008) and postoperative infections (23% versus 60%, p = 0.008). In 2016, Hamilton-Reeves et al randomized patients to supplementation with 3 shakes/day of Impact: Advanced Recovery (n = 14) or a standard protein shake (n = 15) for 5 days before and 5 days after cystectomy. No differences were found in 30 day complications, however there was a 33% reduction in overall complications (47% versus 14%, p = 0.06) and a 39% reduction in postoperative infections (53% versus 14%, p = 0.03) for immunonutrition patients in the late phase of recovery (31-90 days).

Several factors may explain why our findings do not support a reduction in overall or infectious complications. The present analysis is underpowered to find a small difference in infectious complications, as this was not the primary outcome of this phase II study. It is worth noting that infection rates among controls in two prior series investigating immunonutrition in cystectomy (60% and 53%)[7,8] are higher than observed in the present study (32%) and also higher than the 25% rate observed in a series of over 1,100 cystectomies.[1] Higher than expected baseline rates of infectious complications in these prior analyses raises concerns that their findings may be due to type 1 error. As mentioned previously, our study was powered to detect a 25% absolute difference in infectious complication rates. Therefore, had the infection rate been 57% in the non-supplemented group and decreased to the observed rate of 32% in the supplemented group, a magnitude of difference seen in both prior cystectomy series,[7,8] a significant difference could have been demonstrated in the present study.

Duration of supplementation in prior studies was longer than 5 days – namely 7 days prior to[7] and 5 days both before and after radical cystectomy,[8] respectively – which may also account for differences in observed outcome. A 5 day period was chosen on the basis of data in the general surgery literature suggesting efficacy,[6,9,10] however this may not be directly generalizable to radical cystectomy patients due to the presence of ureteroenteric anastomoses, which may alter postoperative propensity to infection.

In the current protocol, no postoperative supplementation was given, based upon data from gastrointestinal cancers[9] in addition to concerns that postoperative supplementation would be difficult in patients with ileus. The Hamilton-Reeves group used post-operative supplementation but the Bertrand series did not, which could have led to efficacy in the former study.[7,8] All patients in the Bertrand series were treated with neoadjuvant chemotherapy, which was used in a minority of patients in this analysis (10%). Due to low sample size, a subset analysis of those who received neoadjuvant chemotherapy was not possible.

These findings should be considered in the context of several limitations. As with any non-randomized protocol, a risk of selection bias from unmeasured confounders or unbalanced groups exists. We attempted to account for this by performing multivariable analyses, rather than matched analyses, due to the relatively small non-supplemented population (n = 104) from which to match patients. Seven of the 40 supplemented patients did not consume all shakes, and future trials examining this question should account for an expected drop out rate when determining sample size. Although serum albumin was compared, other nutritional parameters, such as prealbumin levels or frailty indices, were not tracked, as the duration of supplementation was felt to be too short to meaningfully influence these values, although these are potential sources of unmeasured confounding. Neoadjuvant chemotherapy and robotic cystectomy are uncommonly used at our institution, making these findings poorly generalizable to populations where these therapies are more commonly employed. Additionally, one of the five participating surgeons contributed patients only to the non-supplemented group. The likely explains the

higher continent diversion rate as well as the shorter operative times in the non-supplemented group, which could alter risk of postoperative infection. We chose to keep these patients in the final analysis in order to increase statistical power only after sensitivity analysis demonstrated no change in the outcomes of interest from their inclusion. Operative time was included in the multivariable models and was not found to be independently associated with infection.

Strengths of the current manuscript include that this is the largest cohort to our knowledge in which a high-arginine supplement prior to radical cystectomy has been studied and that the supplement was not provided by industry. These results deepen the current understanding of the optimal immunonutrient regimen prior to radical cystectomy, suggesting that longer than 5 days may be necessary. In contrast to prior series, this analysis did not observe a reduction in overall or infectious complication rate after supplementation. While several shortcomings in this analysis may explain why these differences were not seen, it is also possible that significance in prior series are due to type 1 error and higher than expected complication rates in a small sample of unexposed patients. An appropriately powered, randomized protocol with varied supplement duration is needed to definitively answer these questions. Such a protocol is currently under development.

Conclusion

A high-arginine immunonutrient supplement was safe and well tolerated in patients undergoing radical cystectomy. When compared to non-supplemented patients, 5 days of preoperative supplementation did not decrease overall complications, infectious complications, or readmission rate following radical cystectomy.

Disclosures

Dr. Bruce Jacobs is a consultant for ViaOncology. All remaining authors have no relevant financial conflicts of interest. □

References

1. Shabsigh A, Korets R, Vora KC et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur Urol* 2009;55(1):164-174.
2. Gibbs J, Cull W, Henderson W, Daley J, Hur K, Khuri SF. Preoperative serum albumin level as a predictor of operative mortality and morbidity: results from the National VA Surgical Risk Study. *Arch Surg* 1999;134(1):36-42.
3. Gregg JR, Cookson MS, Phillips S et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. *J Urol* 2011;185(1):90-96.
4. Zhu HL, Liu YL, Xie XL, Huang JJ, Hou YQ. Effect of L-arginine on intestinal mucosal immune barrier function in weaned pigs after Escherichia coli LPS challenge. *Innate Immun* 2013;19(3):242-252.
5. Zhu X, Herrera G, Ochoa JB. Immunosupression and infection after major surgery: a nutritional deficiency. *Crit Care Clin* 2010; 26(3):491-500.
6. Zhang Y, Gu Y, Guo T, Li Y, Cai H. Perioperative immunonutrition for gastrointestinal cancer: a systematic review of randomized controlled trials. *Surg Oncol* 2012;21(2):e87-e95.
7. Bertrand J, Siegler N, Murez T et al. Impact of preoperative immunonutrition on morbidity following cystectomy for bladder cancer: a case-control pilot study. *World J Urol* 2014; 32(1):233-237.
8. Hamilton-Reeves JM, Bechtel MD, Hand LK et al. Effects of immunonutrition for cystectomy on immune response and infection rates: a pilot randomized controlled clinical trial. *Eur Urol* 2016;69(3):389-392.
9. Braga M, Gianotti L, Vignali A, Carlo VD. Preoperative oral arginine and n-3 fatty acid supplementation improves the immunometabolic host response and outcome after colorectal resection for cancer. *Surgery* 2002;132(5):805-814.
10. Waitzberg DL, Saito H, Plank LD et al. Postsurgical infections are reduced with specialized nutrition support. *World J Surg* 2006; 30(8):1592-1604.
11. Zhu X, Pribis JP, Rodriguez PC et al. The central role of arginine catabolism in T-cell dysfunction and increased susceptibility to infection after physical injury. *Ann Surg* 2014;259(1):171-178.
12. Bronte V, Serafini P, Mazzoni A, Segal DM, Zanovello P. L-arginine metabolism in myeloid cells controls T-lymphocyte functions. *Trends Immunol* 2003;24(6):302-306.
13. Makarenkova VP, Bansal V, Matta BM, Perez LA, Ochoa JB. CD11b+/Gr-1+ myeloid suppressor cells cause T cell dysfunction after traumatic stress. *J Immunol* 2006;176(4):2085-2094.
14. Mannick JA, Rodrick ML, Lederer JA. The immunologic response to injury. *J Am Coll Surg* 2001;193(3):237-244.
15. Marik PE, Flemmer M. The immune response to surgery and trauma: Implications for treatment. *J Trauma Acute Care Surg* 2012; 73(4):801-808.
16. Daly JM, Lieberman MD, Goldfine J et al. Enteral nutrition with supplemental arginine, RNA, and omega-3 fatty acids in patients after operation: immunologic, metabolic, and clinical outcome. *Surgery* 1992;112(1):56-67.