EXPERIMENTAL STUDY

Effect of β-glucan on serum levels of IL-12, hs-CRP, and clinical outcomes in multiple-trauma patients: a prospective randomized study

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ABSTRACT

BACKGROUND: Trauma is associated with a profound immunological dysfunction. This predisposes patients to infections and adverse outcomes. β-glucan has been implicated in the initiation of anti-microbial immune response. The present study aimed to evaluate the effects of an enteral diet containing β-glucan on serum levels of IL-12 and highly-sensitive C-reactive protein (hs-CRP), occurrence of infection, and clinical outcomes in critically ill multiple-trauma patients.

METHODS: Forty multiple-trauma patients requiring enteral nutrition for at least 10 days were randomly assigned to the intervention group (n=20) or the placebo group (n=20). The intervention group received a high-protein enteral diet providing 3 g β-glucan, and the control group received a similar diet, except for 3 g of maltodextrin as a placebo. Serum levels of IL-12 and hs-CRP were measured on days 0, 10, and 21.

RESULTS: The β-glucan group showed significantly higher serum levels of IL-12 on day 21 compared to the control group. Infection frequency and duration of mechanical ventilation were significantly lower in the β-glucan group. A significant difference was found in the Sequential Organ Failure Assessment (SOFA) score in favor of the β-glucan group. No difference was found in the serum levels of hs-CRP, length of ICU stay, occurrence of infection, and mortality rates between the two groups.

CONCLUSION: β-glucan may increase serum levels of IL-12, shorten the duration of mechanical ventilation, and reduce organ failure in critically ill multiple-trauma patients.

Keywords: Enteral nutrition; ICU; infection; prebiotic.

INTRODUCTION

Due to weakened immune systems and gut barriers, trauma patients admitted to intensive care unit (ICU) frequently exhibit elevated levels of infection and inflammation compared to other ICU patients. Additionally, critical illness, coupled with invasive devices and procedures, increases such patients' exposure to pathogens in the hospital environment or mixed with their microflora. A trauma patient's length of stay in ICU can be influenced by infection, pulmonary complications, sepsis, respiratory failure, and multiple-organ dysfunction (MODS), resulting in an overall proinflammatory response and immunosuppression.[1,2]

Studies have shown that that interleukin-12 (IL-12) is essential for the differentiation, proliferation, and maintenance of T-helper 1 responses, leading to the production of interferon gamma, and IL-2. Trauma causes a reduction in IL-12 production.[3,4] In turn, these cytokines promote T-cell responses and macrophage activation.[5,6] Furthermore, reduced IL-12 production promotes T-cell commitment toward a T-helper 2 pattern that correlates with adverse clinical outcomes in patients.[3,4]

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Some studies have shown that the prebiotic consumption can result in the production of colonic small chain fatty acids; have beneficial effects on endotoxemia, inflammatory cytokine production,[7] and probiotics including isomalto-oligosaccharides and fructooligosaccharide; and increased the IL-12 production in mice.[8,9] Prebiotics such as β-glucan are non-digestible food ingredients that stimulate probiotic bacterial growth or activity in the colon healthy ways.[10] β-glucan also enhances IL-12 production in human blood dendritic cells (DCs) and monocytes-derived DCs.[11] Animal studies have shown that oral or parenteral administration of oat β-glucan can prevent parasitic, bacterial, and viral infections.[12,13] Some in vitro studies have also supported the beneficial effects of β-glucan on the immune system.[14,15] Studies on humans have shown that the administration of soluble fiber or intravenous β-glucan in trauma patients and in patients with severely acute pancreatitis reduced the infection, length of ICU stay, and septic morbidity.[16–18]

Unfortunately, most studies have been done in vitro or on animals. Moreover, the few studies conducted on humans have been limited to intravenous administration of β-glucan. In the present study, we investigated the clinical outcomes of oral β-glucan supplementation with respect to serum levels of IL-12 and hs-CRP in trauma patients admitted to ICU.

MATERIALS AND METHODS

This randomized, double-blind, controlled, clinical trial was conducted in a tertiary care university hospital between June 2013 and November 2015. Informed consent for the participation of patients in the study was obtained from first-degree relatives. Patients were enrolled if they were older than 18 years of age, had two or more organ-system traumas, had life expectancy of more than 21 days after randomization, had normal weight (body mass index = 18.5–29.9), were not immunosuppressed or did not have previous infection, and were in need of mechanical ventilation. All patients were to receive more than 75% of total energy within 48 hours. After inclusion, a computer-generated random number with a ratio of 1:1 assigned the patients to the β-glucan group or control group. Acute Physiology and Chronic Health Evaluation III (APACHE III) Score, and Injury Severity Score (ISS) were recorded for all patients. All patients were fed a hospital-prepared, high-protein, standard kitchen formula. Daily energy consumption was calculated by 25-30 kcal/kg for each patient based on weight and metabolic condition. The distribution of macronutrients was as follows: 20% protein, 30% lipid, and 50% carbohydrate. The β-glucan group received 3 g of oat β-glucan (Arian Salamat Sina Company, Tehran, Iran) daily, and the control group received 3 g of maltodextrin as placebo daily. The patients did not consume any other product or food containing prebiotics during the trial. The energy intake from tube feeding during the study period was recorded for each patient daily. The patients, investigators, and all clinical personnel were blinded to the randomization throughout the study.

Data Collection

We collected the following data from each patient: occurrence of infection, ventilator-associated pneumonia (VAP), MODS, number of mechanical ventilation days, length of ICU stay, and mortality.

Infection

Sepsis and bacteremia were defined according to a consensus panel convened by the American College of Chest Physicians and the Society of Critical Care Medicine (SCCM).[19]

Central nervous system (CNS) infection was diagnosed according to the Centers for Disease Control's definitions for nosocomial infections.[20]

Urinary tract infection was diagnosed by examining urine culture.[21]

Wound infection was defined as a positive result of bacterial growth of more than 1×10^5 colony-forming units per gram of tissue.[22]

VAP was defined as a new infiltrate on chest X-rays occurring more than 48 hours after endotracheal intubation plus two or more of the following: fever (body temperate >38.3°C), leukocytosis (white blood cell count $>12\times10^9$/ml), leucopenia (white blood cell count $<4\times10^9$/ml), and purulent tracheobronchial secretions.[23]

Organ Failure

Occurrence of MODS was monitored during the hospitalization. The Sequential Organ Failure Assessment (SOFA) score was used to determine the extent of organ function in patient. Each patient was evaluated for cardiovascular failure (systolic blood pressure ≤ 90 mmHg or requiring vasopressor support), CNS failure (Glasgow coma score ≤12), coagulation failure, hepatic failure (bilirubin ≥2 mg/dL), and renal failure (serum creatinine ≥2 mg/ dL or 25% increase from the baseline).[24]

Laboratory Data

To measure hs-CRP and IL-12 levels, blood samples were taken on study days 0 (before starting enteral nutrition), 10, and 21 (unless the patient was discharged or expired before day 21).Sera were frozen at −80°C. They were subsequently analyzed in duplicate using enzyme-linked immunoassay (ELISA) in dilutions that allowed interpolation from simultaneously run standard curves. IL-12 was measured using human high sensitivity IL-12 ELISA kit (Diaclone, France). The minimum detectable dose of IL-12 was <0.75 pg/ml, with an inter-assay precision of 7.9% and an intra-assay precision of 16.1%. hs-CRP was measured using commercially available ELISA (Diagnostics Biochem Canada Inc). The minimum detectable concentration for hs-CRP is 0.001 mg/dL serum

levels of IL-12; hs-CRP were determined according to manufacturer's instructions.

Statistical Analysis

The minimum sample size estimated for each group was 15 at a power (1–β) of 80% and α=0.05 for a parallel interventional study with two-tailed testing to detect the reduction of ICU length of stay with a pooled standard deviation of 7.3 days, according to the study by Min Tan et al.[25] Demographic data, baseline values, and outcome measures were compared using Student's t-test or Mann–Whitney test for all continuous variables. Categorical data between the groups were compared using Fisher's exact test. Paired t-tests or Wilcoxon test were applied for comparisons of variables before and after intervention. Results were reported as mean±standard deviation for parametric tests and as median (Q_1–Q_3) for nonparametric tests. P-values of <0.05 were considered significant; all statistical analyses were performed using SPSS version 18.

RESULTS

Study Population Characteristics

Overall, 68 patients were included in the study; 13 patients from the control group and 15 patients from the β-glucan group were excluded because of refusal to continue the study, discharge, or death before 10 days of intervention and refusal to initiate supplemental parenteral nutrition during intervention. Therefore, finally, 20 patients in the β-glucan group and 20 patients in the control group completed the study. The patients' mean age was 38.8±13.9 years. The patients' baseline characteristics are shown in Table 1. No significant differences in baseline characteristics were observed between the two groups.

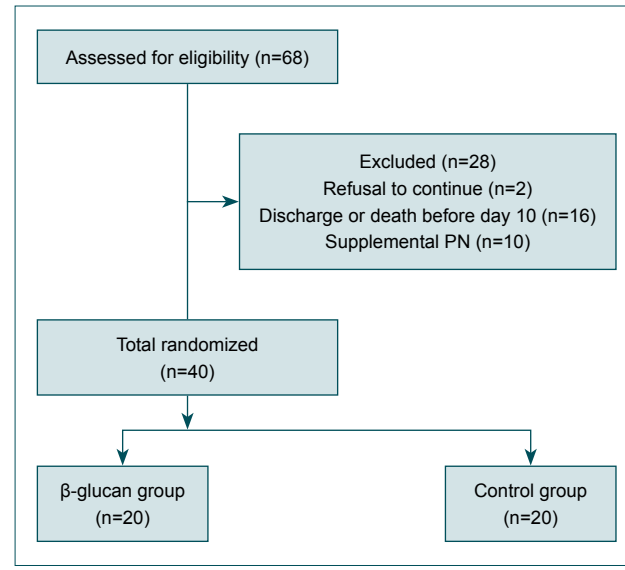

Figure 1. CONSORT flow diagram of the trial.

Nutritional Variables

No significant difference was observed in the amount of feeding tolerance between the β-glucan group and control group during the study period (1710.5±117.03 kcal vs. 1718.2±182.4 kcal, p=0.6). For all patients, enteral feeding was initiated within 24–48 hours of admission. In addition, No significant difference in the serum albumin levels were observed between the β-glucan group and control group on

Table 1. Baseline characteristic of the patients

	β-glucan (n=20)	Placebo (n=20)	p
Age, median (Q_1–Q_3)*	43 (29–53)	32 (25.5–43)	0.1
Gender, n (%)**			1
Male	18 (90)	18 (90)	
Female	2 (10)	2 (10)	
GCS, median (Q_1–Q_3)*	7 (5–7)	6 (5–7)	0.7
Serum albumin (Mean±SD)***	3±0.3	3.1±0.4	0.9
APACHE III, median (Q_1–Q_3)*	62 (56.25–67)	62 (53.25–64.75)	0.7
ISS (Mean±SD)***	38.75±13.7	36.75±14.7	0.6
Energy intake (Mean±SD)***	1710.5±117 kcal	1718.2±182.4 kcal	0.64
Type of surgery, n (%)**			1
Abdominal surgery	5 (25)	4 (20)	
Neurosurgery	14 (70)	14 (70)	
Orthopedic surgery	6 (30)	7 (35)	
No surgery	5 (25)	4 (20)	

*Mann-Whitney U test; **Fisher exact test; ***Student's t-test. GCS: Glasgow Coma Scale; SD: Standard deviation.

Table 2. Changes in serum levels of IL-12 and hs-CRP in study period

	β-glucan (n=20)	Placebo (n=20)	p*
IL-12 (pg/dL), median (Q_1–Q_3)			
Day 0	86.6 (61.5–104.8)	70.25 (59.3–98.2)	0.47
Day 10	67.4 (41.3–77.5)	50.6 (35.05–59.6)	0.14
Day 21	129.65 (73.7–181.0)	73.85 (40.7–107.9)	0.03
hs-CRP (mg/dL), (Mean±SD)			
Day 0	14.08±0.5	14.02±0.31	0.7
Day 10	14.04±0.47	13.88±0.38	0.2
Day 21	9.96±0.44	10.15±0.37	0.1

*P with Mann-Whitney for IL-12 and Student's t-test for hs-CRP. hs-CRP: Nighly-sensitive C-reactive protein.

Table 3. Comparison of clinical outcomes in the two groups

	β-glucan (n=20)	Placebo (n=20)	p*
Length of ICU stay (Mean±SD)*	27.55±7.8	31.2±15.8	0.07
SOFA score, median (Q_1–Q_3)**	5 (4.25–6)	9 (6–10)	<0.001
Ventilator days, median (Q_1–Q_3)**	15 (10–22.5)	28 (11–39.75)	0.01
Mortality, n (%)***	1 (5%)	4 (20%)	0.1

*Student's t-test; **Mann-Whitney U Test; ***Fisher exact test. SD: Standard deviation. SOFA: Sequential Organ Failure Assessment; ICU: Intensive care unit.

Table 4. Type and number of infection

	β-glucan (n=20)	Placebo (n=20)	p
Type of infection, n (%)*			
Ventilator Associated Pneumonia	4 (20)	4 (20)	1
Urinary tract	0	4 (20)	0.1
Wound	2 (10)	4 (20)	0.6
Sepsis	0	2 (10)	0.4
Central nervous system	0	3 (15)	0.2
Infection rate, n (%)*	5 (25)	11 (55)	0.1
Infection frequency**	5 times	26 times	0.03

*Fisher exact test; **Mann-Whitney U Test.

day 0 (3±0.3 mg/dL vs. 3.1±0.4 mg/dL, p=0.9), day 10 (2±0.5 mg/dL vs. 1.8±0.4 mg/dL, p=0.7), or day 21 (2.1±0.2 mg/dL vs. 2±0.2 mg/dL, p=0.9).

Biochemistry

Changes in serum levels of IL-12 and hs-CRP in the study period are shown in Table 2. Baseline serum levels of IL-12 and hs-CRP were not significantly different between the β-glucan group and the control group. Serum levels of IL-12 on days 21 were significantly higher in the β-glucan group than in the control group. Serum levels of hs-CRP decreased in both groups on day 21 with no significant difference between the β-glucan group and the control group.

Clinical Outcomes

The patients' clinical outcomes are shown in Table 3. The SOFA score for developing organ failure was significantly lower in the β-glucan group than in the control group. There

was no difference in the mean length of ICU stay between the two groups (p=0.07). Duration of mechanical ventilation was significantly lower in the β-glucan group (p=0.01). The overall in-ICU mortality rate was 12.5%. There was no difference in mortality rate between the two groups (p=0.1). Forty percent of all patients developed infection, of which 25% were in the β-glucan group and 55% in the control group, without showing any significant difference. It was noted that infection frequency was significantly higher in the control group (Table 4).

DISCUSSION

Results of the present study indicated that patients who were fed an enteral diet with β-glucan, showed a significantly lower duration of mechanical ventilation, higher IL-12 production, lower rates of organ failure, and lower rates of infection. We did not find any difference in the ICU length of stay and mortality rate between the two groups. Several in vitro and in vivo studies have shown that β-glucan increases IL-12 production. It has been shown that β-glucan can induce human peripheral blood mononuclear cell proliferation and phenotypic and functional maturation of DCs, with significant IL-12 and IL-10 production.[11] In addition, β-(1, 4) glucan can induce significant IL-12 production by in vitro macrophage cell lines.[26] In Qi et al.[27] study, particulate β-glucan induced DCs to produce high levels of IL-12 but low amounts of IL-6 and IL-10. In a clinical trial comprising women with breast cancer, 21 days of administration of oral β-glucan significantly increased the serum levels of IL-12.[28]

CRP is a positive, acute-phase protein produced by hepatocytes in response to inflammatory conditions. CRP levels quickly increase in response to trauma, inflammation, and infection and decrease just as quickly as the body condition improves. Therefore, CRP levels are widely used to monitor various inflammatory conditions.[29,30] In our study, although the decrease in serum levels of CRP was not significant between the two groups, serum levels of IL-12 in the β-glucan group increased significantly on day 21 compared to that in the control group, which may have contributed to the improvement in clinical outcomes. These results indicate that even in situations involving inflammation, β-glucan may play an important role in immune system modulation.

Literature review suggests that β-glucan administration could reduce infection. Animal studies have shown that β-glucan reduces parasitic and bacterial infection in infected mice.[12] In an experimental model of sepsis, administration of β-glucan indicated reduced serum levels of TNF-α, IL-6, and IL-1β and decreased mortality rate.[31] In mice infected with Staphylococcus aureus and Candida albicans, oral administration of β-glucan increased the expression of dectin-I and Toll-like receptors (β-glucan receptors) in immune cells, with the elevation of serum levels of IL-12, thereby resulting in higher resistance to infection.[32]

A review study concluded that the oral and parenteral administrations of β-glucan have the same efficacy on enhancing resistance to pathogen infections.[33]

Three clinical trials showed that the pretreatment of high-risk surgical patients with intravenous PGG-glucan can shorten the length of ICU stay, reduce rates of infection, decrease need for antibiotic therapy, and reduce mortality rate.[34–36] A review study evaluating the role of immune-enhancing enteral diet in perioperative patients showed significance reduction inmortality and complications compared to standard formulas.[37] In a study of patients with severe acute pancreatitis, enteral nutrition containing soluble and insoluble prebiotic fiber was compared with the standard enteral solution. The intervention group exhibited a decreased mean duration of APACHE II normalization, decreased mean duration of CRP normalization, decreased length of ICU stay, and decreased overall complications compared to the control group.[16] One clinical trial explored the prevention of nosocomial pneumonia and sepsis by treating patients with intravenous administration of β-glucan. The results showed a significant decrease in the occurrence of pneumonia and sepsis in the β-glucan group compared to the control group. Moreover, the mortality rate related to infection was significantly higher in the control group.[17] A separate randomized controlled clinical trial in trauma patients showed that after the intravenous administration of β-glucan for 7 days, total mortality and septic morbidity rates were significantly lower in the β-glucan group.[18]

We noted significantly shorter duration of mechanical ventilation dependency in the β-glucan group than in the control group. In general, for patients needing mechanical ventilation, respiratory and diaphragmatic muscles were weakened and mucociliary motility is diminished.[38,39] β-glucan can reportedly improve pulmonary function[40,41] and increase the production of lysozyme in respiratory mucosal secretion.[42] In addition, there is growing evidence that β-glucan improves brain function, as demonstrated in terms of neuroprotection and improvements in cognition and mood.[43]

In the present study, organ failure involvement was significantly lower in the β-glucan group than in the control group. Multiple hypotheses have been proposed to explain this outcome. Bacterial translocation due to the disruption in the gut-barrier function may contribute to the development of organ failure. Therefore, consumption of foods that improve the gut-barrier function may prevent bacterial translocation. Prebiotics enhance immune system functions by enhancing the gut-barrier function, reducing the intestinal colonization of pathogenic bacteria to decrease proinflammatory cytokines, improving the balance of the peripheral immune system, and improving the production of bacteriocins and immunoglobulin A (IgA) levels in the small intestine and caecum.[44,45] This may explain the lower incidence of organ failure in the β-glucan group.

Most studies on critically ill patients have investigated the effect of probiotic or symbiotic formulas. Because probiotics are living organisms, their administration may cause infection in the host. Bloodstream infections resulting from probiotics can be attributed to the bacterial translocation across gut mucosa.[46,47] ASPEN guidelines do not make a recommendation at this time for the routine use of probiotics across the general population of ICU patients.[48] In contrast, β-glucan, a prebiotic, does not introduce the risk of bloodstream infections. Therefore, given their beneficial contribution to enhance immune system and gut-barrier functions, which in turn contribute to reduce mortality and morbidity rates, β-glucan could be included as a source of carbohydrates in the enteral formula for critically ill multiple-trauma patients.

The present study has some limitations and therefore should be considered as a pilot study. It was a single center study wirh small sample size. Therefore, larger, multicenter studies are further required to test the effect of β-glucan on serum levels of IL-12 and clinical outcomes.

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DENEYSEL ÇALIŞMA - *ÖZET*

Çoklu travma hastalarda β –glukanın serum IL-12, hs-CRP değerleri ve klinik sonuçları üzerine etkisi: İleriye yönelik randomize çalışma

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AMAÇ: Travma yoğun immünolojik işlev bozukluğuyla ilişkilidir. Bu durum hastaları enfeksiyonlara ve olumsuz sonuçlara yatkınlaştırır. Beta-glukan antimikrobiyal immün yanıtın başlamasıyla ilişkilendirilmiştir. Bu çalışma kritik çoklu travma hastalarında β-glukan içeren enteral diyetin serum IL-12 ve yüksek derecede duyarlı C-reaktif protein (hs-CRP) düzeyleri, enfeksiyon oluşumu ve klinik sonuçlar üzerine etkilerini değerlendirme amaçlanmıştır.

GEREÇ VE YÖNTEM: En az 10 gün enteral beslenmesi gereken 40 çoklu travma hastası girişim grubu (n=20) veya plasebo grubuna (n=20) randomize edildi. Girişim grubuna 3 g β-glukan içeren yüksek proteinli enteral diyet, kontrol grubuna ise benzer bir diyet ve plasebo olarak 3 g maltodekstrin verildi. Başlangıçta (0. gün), 10. ve 21. günde serum IL-12 ve hs-CRP düzeyleri ölçüldü.

BULGULAR: Kontrol grubuna göre beta-glukan grubu 21. günde anlamlı derecede daha yüksek serum IL-12 düzeyleri sergiledi. Beta-glukan grubunda enfeksiyon sıklığı ve mekanik ventilasyon süresi anlamlı derecede daha düşüktü. SOFA (Sequential Organ Failure Assessment, Ardışık Organ Yetersizliği Değerlendirme) skorunda β-glukan grubu lehine anlamlı derecede olumlu bir farklılık mevcuttu. İki grup arasında serum hs-CRP düzeyleri, yoğun bakım ünitesinde kalış süresi, enfeksiyon oluşumu ve mortalite oranları arasında herhangi bir farklılık saptanmadı.

TARTIŞMA: Beta-glukan kritik çoklu travma hastalarda serum IL-12 düzeylerini yükseltebilir, mekanik ventilasyon süresini kısaltabilir ve organ yetersizliğini hafifletebilir.

Anahtar sözcükler: Enfeksiyon; enteral beslenme; prebiyotik; yoğun bakım ünitesi.

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