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STAPHLOCOCCUS AUREUS İLE OLUŞTURULAN DENEYSEL İNTRAABDOMİNAL KAYNAKLI BAKTERİYEMİ MODELİNDE BETA GLUKANIN İMMÜNOMODULATÖR ETKİSİNİN ARAŞTIRILMASI

INVESTIGATION OF THE IMMUNOMODULATOR EFFECT OF BETA GLUCAN IN THE EXPERIMENTAL INTRAABDOMINAL BACTERIEMIA MODEL WITH STAPHYLOCOCCUS AUREUS

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ÖZET

AMAÇ: Bu çalışmanın amacı S. aureus ile oluşturulan deneysel intraabdominal kaynaklı bakteriyemi modelinde beta glukanın immünomodulatör etkisini araştırmaktır.

GEREÇ VE YÖNTEM: Wistar albina sıçanlardan 30'u rastgele 4 gruba ayrıldı. Sırasıyla Staphylococcus aureus bakteriyemisi (SAB), sefazolin ile tedavi, beta glukan tedavi, beta glukan ve sefazolin tedavi grupları oluşturuldu. İntraabdominal yolla verilen 12x10 8 cfu/ml 1 cc S. aureus verildikten sonra intraabdominal 4 mg/kg beta glukan ve 100 mg/kg sefazolin verildi. 2 saat sonra 0,5 cc kan alınarak kan kültür şişesine ekim yapıldı. 4-6-8. saat sonra Tümör nekroz faktörü alfa (TNF-α), İnterlökin-1(IL-1), İnterlökin-6 (IL-6), İnterferon gama (IFN-γ) düzeyleri araştırıldı.

BULGULAR: Biyokimyasal analizlere göre; çalışma sonunda beta glukan 6. saatte IFN-γ'yı arttırdığı, ancak 4. ve 8. saatlerde arttırmadığı görüldü. Sefazolin ile birlikte verildiğinde 6. saatte bu artış daha belirgin olmaktadır. Ancak sefazolin verilen grupta IFN-γ değerleri beta glukandan daha yüksek düzeyde saptandı. Serum TNF-α düzeyleri değerlendirildiğinde, beta glukan verilen grupta 8. saatte TNF-α düzeyinde bir baskılanma saptansa da SAB grubundan daha yüksek olarak bulundu. Serum IL-1 düzeyleri değerlendirildiğinde, beta glukan verilen grupta 4-6 ve 8. saatlerde IL-1 düzeyleri SAB grubuna göre daha yüksekti. Beta glukana sefazolin eklenen grupta 8. saatte IL-1 düzeylerinde azalma tesbit edildiyse de, bu düzeyler SAB grubundan yüksek saptandı. Serum IL-6 seviyesi değerlendirildiğinde, beta glukan verilen grupta SAB grubuna göre ilk 8 saatte IL-6 salınımında artış saptandı. Beta glukan sefazolinle birlikte uygulandığında ise IL-6 artışının ilk 8. saatte en yüksek düzeye ulaştığı görüldü.

SONUÇ: Bu deneysel intraabdominal kaynaklı bakteriyemi modeli beta glukanın özellikle ilk saatlerde TNF-α, IL-1 üretimini baskılamadığını, IL-6, IFN-γ salınımını arttırdığını göstermiştir. Bu sonuçlara göre deneysel intraabdominal kaynaklı bakteriyemi tedavisinde beta glukan kullanımının yararı konusunda anlamlı bilgilere ulaşılamadı.

ANAHTAR KELİMELER: Bakteriyemi, Beta glucan, Sitokinler, Staphylococcusaureus

ABSTRACT

OBJECTIVE: The purpose of this study is to investigate the immunomodulatory effect of beta glucan in an experimental model of intraabdominal bacteremia induced by S. aureus.

MATERIAL AND METHODS: Thirty Wistar albino rats were randomly divided into four groups. Staphylococcus aureus bacteremia (SAB), treatment with cefazolin, treatment with beta glucan, treatment with both cefazolin and beta glucan groups were constituted respectively. 4 mg/kg beta glucan and 100 mg/kg cefazolin were given after 12x10 8 cfu/ml 1 cc S. aureus was given intraabdominally. After two hours, 0.5 cc blood was drawn and put into blood culture bottles. Levels of Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and Interferon gamma (IFN-γ) were evaluated after 4th, 6th and 8th hours.

RESULTS: According to the biochemical analyses; At the end of the study it was seen that beta glucan increased the level of IFN-γ at 6th hour, but did not at 4th and 8th hours. This increase became more apparent at 6 th hour when it was given with cefazolin. However IFN-γ levels were found to be higher in the group which cefazolin was given than beta glucan was. As the level of serum TNF-α was evaluated, although there was a supression at 8th hour, it was found to be higher in the group which beta glucan was given than the SAB group. Serum IL-1 levels were higher at 4th, 6th and 8th hours in the group beta glucan was given than the SAB group. Although a decline in IL-1 level was detected in the group which cefazolin was added to beta glucan at 8th hour, this level was found to be higher than the SAB group. When the serum IL-6 level was evaluated, an increase in release of IL-6 was found in the group beta glucan was given in the first 8 hours when it was compared with SAB group. When beta glucan was given with cefazolin, it was observed that IL-6 increased to the highest level at 8th hour.

CONCLUSIONS: This experimental intra-abdominal bacteremia model, demonstrated that beta glucan did not supress the production of TNF-α and IL-1, and increased the release of IL- 6 and IFN-γ, especially in the first hours. According to these results, no significant knowledge could be obtained about the benefit of using beta glucan in the treatment of experimental model of intraabdominal bacteremia.

KEYWORDS: Bacteremia, Beta-Glucans, Cytokines, Staphylococcus aureus

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INTRODUCTION

Sepsis is a potentially fatal infectious disease, which involves several organ systems, leading to hemodynamic changes, shock, and organ function failure. *Staphylococcus aureus* bacteremia (SAB) is a clinical table with high mortality rates that can be of both community or hospital origin (1). Despite supportive treatments and strong antibiotics, the development of SAB-origin sepsis can result in death at the rate of 30%-70% (2).

For a sufficient immune response to infection, there has to be interaction between the natural immune system and the specific immune system, including monocyte, T-cell and neutrophil response. In recent years, research has intensified on the subject of immunopathophysiology in sepsis, especially on T-cells (3). When sepsis develops as a result of bacteremia, the hemodynamic, metabolic, and immune changes seen in the organism are mediated by cytokines and mediators that have a role in intracellular signal transmission. The effects of cytokines are not only through interference in systemic circulation, but may also be seen with a direct cell-cell relationship and at small concentrations (4).

Therefore, in the prevention of sepsis emerging as a result of bacteremia, the reduction or suppression of the effects of pro-inflammatory cytokines can be evaluated as an important step in the reduction of mortality rates.

Beta-glucan obtained from bread yeast (*Saccharomyces cerevisiae*) is a natural polysaccharide which strengthens the immune system. It increases the proliferation of macrophages, the adhesion capability, chemotactic activity and cytotoxic properties (5). Several studies have shown the tissue regeneration and anti-neoplastic effect of beta-glucan, and strong antioxidant effects against radiation. It has also been reported that it has shown synergistic effects with some antibiotics, antifungal and antiparasitic drugs (6). The aim of this study was to investigate the immunomodulator effect of beta-glucan in intra-abdominal-origin experimental SAB, taking into consideration the ability to increase the defence mechanisms of the body in various infectious and malignant diseases.

MATERIAL AND METHOD

The study inccluded a total of 30 male, Wistar albino rats, aged 6 months, and each weighing 150-250 gr. One week before the experiment, the rats were randomly separated into 4 groups of 6, and kept at room temperature with free access to food and drinking water. From the night before the experiment, the rats were fasted with continued access to drinking water, against complications which may develop.

Standard *S. aureus strain* (*ATCC 29213*) was used to create the SAB model in the rats. For confirmation purposes, the strain was seeded in sheep blood agar. The colonies produced following incubation at 37˚C for 18-24 hours were evaluated. There was β hemolysis and golden yellow colour pigment in the colonies. Gram staining was applied to these colonies, and gram (+) roots were seen. The catalase test was applied to the colonies and was seen to be positive. Thus, the colonies were confirmed as *staphylococcus*. The coagulase test was then applied to the staphylococcus colonies and those that were coagulase positive were identified as *S. aureus*.

Using sterile saline, these colonies were brought to suspension form with standard McFarland 4 (12 x 108 cfu/ml) ensured under densometer control. A total of 24 suspensions of 1 ml were prepared.

Study Groups

Group 1: SAB group (n=6). The bacteremia model described by Sherwood et al was formed (7). 1cc bacteria suspension containing 12 x 10 8 cfu/ml *S.aureus* was administered intraperitoneally (ip) to the rats. Anaesthesia of 3-5 mg/kg xylazine (Rompan, Bayer) and 40-90 mg/kg *ketamine* (ketamine Hcl 50 mg/l, Pfizer) was administered, and after 2 hours, 0.5cc blood was taken from the rats. Peds Plus/F (BD Bactec) culture seeding was made from the withdrawn blood to investigate whether or not SAB had developed. In the rats where SAB developed, 1 cc blood was taken 3 times at 4, 6, and 8 hours after the ip S. aureus injection, and Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), and Interferon gamma (IFN-γ) were examined in the serums.

Group 2: SAB+ *cefazolin* group (n=6). The procedures described above were applied then after the creation of SAB, 100mg/kg cefazolin (I. E. Ulagay Ilac, Turkey) was administered ip.

Group 3: *SAB+ beta-glucan* group (n=6). The procedures described above were applied then after the creation of SAB, 4 mg/kg beta-glucan (Mustafa Nevzat Ilac, Turkey) was administered ip.

Group 4: SAB+*beta-glucan+cefazolin* group (n=6). The procedures described above were applied then after the creation of SAB, 100mg/kg *cefazolin* (I. E. Ulagay Ilac, Turkey) and 4 mg/kg beta-glucan (Mustafa Nevzat Ilac, Turkey) were administered ip.

Microbiological Evaluation

In the evaluations made in the Medical Microbiological Laboratory of Afyon Kocatepe University Medical Faculty, samples for blood culture in Peds Plus/F (*BD BACTEC*) aerobic blood culture bottles were incubated in the Bactec 9050 (Becton Dickinson, USA) automated blood culture system. After placement of the blood culture bottles in the Bactec device, production was determined in mean 20 hours. In this system, the samples determined with positivity from the bottles were transferred to blood agar and eosin- methylene-blue (EMB agar) plates and incubated for 18-24 hours at 37˚C. At the end of this period, the colonies produced were identified with the conventional methods of catalase and coagulase tests. Blood cultures that did not give a positivity signal within 7 days were accepted as negative.

Biochemical Evaluation

For the serum samples, 1 ml blood withdrawn into tubes without anticoagulant was centrifuged at 3000 rpm for 10 mins. The plasma remaining uppermost after the centrifugation was stored at -80˚C until assay of TNF–α, IL-1, IL-6 and IFN-γ. Cytokine measurements were made using in vitro ELISA commercial kits for TNF-α (Invitrogen Corporation, Camarillo), serum IL-1 (Invitrogen Corporation Carlsbad, California, USA), serum IL-6 (Invitrogen Corporation, Camarillo) and serum IFN-γ (Bender MedSystems GmbH, Vienna, Austria). The reading of the absorbancy and calculation of the results of the ELISA kits was made on the Trinity Biotech Captia Reader (Trinity Biotech PLC, Bray Co. Wicklow, Rep. of Ireland). The measurement units for TNF–α, IL-1, IL-6 and IFN-γ were determined as pg/ml.

Ethical Committee

This study was conducted in the Experimental Animal Research and Application Centre Laboratory of Afyon Kocatepe University. Approval for the study was granted by the Experimental Animal Research Ethics Committee of Afyon Kocatepe University(AKUHEK-61-07) (BAP Project number 08.TIP.14).

Statistical Analysis

Data obtained in the study were analysed statistically using SPSS 13.0 for Windows and Winks SDA 6 software. Conformity of the data to normal distribution was assessed with the Shapiro-Wilk test. In the comparisons of the groups, One-Way Variance Analysis was used and for the comparisons of the repeated measurements of each parameter at the specified hours, variance analysis. To determine from which group the difference orginated, the Tukey HSD test, as a post-hoc multiple comparison test, was used. Descriptive statistics were stated as mean ± standard deviation (SD). A value of $p<0.05$ was accepted as statistically significant.

RESULTS

According to the serum IFN-γ measurement results, no difference was determined between the groups at 4 hours. At 6 hours, a statistically significant difference was observed between Group I, Group II, Group III and Group IV (p=0.006), **(Table 1)**.

Table 1: Fourth, sixth and eighth hours serum IFN-γ, TNF-α, IL-1, IL-6 levels (mean± SE)

Cytokines	Hour	Grup 1 (n=6)	Grup 2 (n=6)	Grup 3 (n=6)	Grup 4 (n=6)	P value
IFN-γ pg/ml	4th	6.45	6.99	6.87	13.56	0.056
	6th	8.97a	9.97a	8.55a	27.17b	0.006
	8th	9.83	16.01	7.54	9.15	0.083
TNF-α pg/ml	4th	9.53	11.81	9.47	10.99	0.574
	6th	10.45	11.50	14.21	12.07	0.500
	8th	11.64	13.07	12.35	10.52	0.707
IL-1 pg/ml	4th	4.92	2.63	8.10	9.84	0.073
	6th	4.87a	3.33a	14.33b	12.90b	0.01
	8th	3.83a	2.538a	15.02b	4.71a	0.000
IL-6 pg/ml	4th	29.92	36.40	54.45	376.94	0.249
	6th	77.672a	65.08a	961.96b	920.07b	0.029
	8th	795.07a	486.89a	2872.21b	591.12a	0.009

Note: The different letters in terms of each column group indicate that there are differences between the groups. (P<0.05).

At 8 hours, no significant difference was determined between these groups (p=0.083). When the IFN-γ levels were evaluated within the groups according to the different times, no difference was determined in Group I and Group III (p=0.083). In Group II, the increase at 8 hours was determined to be statistically significant compared to that at 4 hours and 6 hours (Table 1). In Group IV, a statistically significant increase was determined from 4 hours to 6 hours, and the level at 8 hours was determined to be below the level at 4 hours. The increase in this group between 4 and 6 hours was determined to be statistically significant (p=0.005) (Table 1).

In the evaluation of the serum TNF-α levels, no statistically significant difference was determined between the four groups at 4, 6, and 8 hours. When the groups were examined within themselves, only the changes in Group III were seen to be statistically significant (Table 1).

In the evaluation of the serum IL-1 levels, no statistically significant difference was determined between the four groups at 4 hours (Table 1). At 6 and 8 hours, a statistically significant difference was observed (p=0.01, p=0.000) (Table 1). When the groups were examined within themselves, no statistically significant difference was determined in the four groups at 4, 6, and 8 hours.

In the evaluation of the serum IL-6 levels, no statistically significant difference was determined between the four groups at 4 hours. At 6 and 8 hours, a statistically significant difference was observed (p=0.029, p=0.009) (Table 1).

When the groups were examined within themselves, the increase at 8 hours was found to be statistically significant compared to that at 4 and 6 hours in Group I, Group II, and Group III (p=0.003, p=0.002, p=0.017).

DISCUSSION

SAB is an important agent of sepsis. Despite a general decrease in the incidence of SAB, mortality rates remain high. There is no endotoxin in gram-positive bacteria, but peptidoglycan and lipoteichoic acid are found in the cell wall. These 2 molecules have the ability to bind to receptors of the cell surface and express pro-inflammatory cytokines. The expression of TNF-α, IL-1, IL-6 and IL-8, which are pro-inflammatory cytokines (IL-2, IL-4 and GMCSF are expressed as a result of IL-1 and IL-6 activation), and the expression of IL-10, which is an anti-inflammatory cytokine is seen (8).

IL-6, IL-8, IL-12, IFN-γ, granulocyte colony stimulating factor (G-CSF) and IL-10 which have anti-inflammatory and inflammatory properties, play a role in the development of the host response in sepsis. IL-10 is produced from monocytes, macrophages, T and B lymphocytes and neutrophils. In experimental animal models, it has been shown that when IL-10 is administered intraperitonally and intravenously, there is a protective effect against the effects of lipopolysaccharide (LPS). As a consequence of the protective role of IL-10, the production of pro-inflammatory mediators such as TNF-α, IL-1β, IL-8, IFN-γ, nitric oxide, IL-6 and prostaglandin metabolites is prevented. TNF-α plays a role in immune diseases, in the inflammatory response to fever, shock, and tissue damage, in the expression of additional inflammatory mediators and in the expression of nitric oxide, free oxygen radicals and adhesion molecules (9). In sepsis, TNF-α and IL-1 have the ability to form inflammatory mediators. During infection, TNF-α is the first cytokine expressed by macrophages. IL-6 directly induces IL-1 and TNF-α, which is the primary cytokine of sepsis. In sepsis, the IL-6 level elevates more rapidly and reaches peak level at the end of the 2nd hour. The elevated serum level is seen for a longer period than for TNF-α and IL-1 (10). The pro-inflammatory cytokines, IL-1 and IL-6 trigger coagulation. IL-10 regulates coagulation by inhibiting tissue factor expression from monocytes. High levels of IL-10 and IL-6 are precursors of high mortality in septic patients (11). IL-10 levels have been reported to be correlated to the APACHE score in severe inflammatory response with multi-organ failure or death (12).

Although monocyte and macrophage cells are a source of IFN-γ, it is a protein produced by natural killer (NK) cells and T lymphocytes. IFN-γ has multiple functions in bacterial infection and sepsis. It increases CD4 cells and shows differentiation of Th1 cells, associated with anti-

gen stimulation. The immune response occurs mediated by cytokines and antibodies such as IL-1β, IL-2, TNF-α, and IFN-γ with Th1 response. As the most effective cells against intracellular bacteria, INF-γ and TNF-α cause the apotosis of cells.

According to many previous clinical studies of beta-glucan, there are positive results in the prevention of infections following tumour immunotherapy and surgery. Breivik et al showed that soluble *1.3/1.6 glucan* prevented periodontal disease created experimentally in Wistar rats (13). In *in-vitro* studies, it has been shown that beta-glucans of large molecular weight or particles increased reactive oxygen and nitrogen-mediated antimicrobial activities by increasing the phagocytic and cytoxic activities of leukocytes, thereby directly rendering leukocytes active, in addition to stimulating cytokines such as IL-8, IL-1β, IL-6 and TNF-α (14, 15).

In several studies conducted with glucans of different structures obtained from *S. cerevisiae* (1 - 3), the immunomodulator efficacy of glucan in (1 - 6) *β-D* structure has been proven (16, 17).

As a result of in-vitro LPS application, Soltys et al reported that there was signficantly increased IFN-γ production in lymphocytes and monocytes isolated from rats treated with beta-glucan (18). In a study by Sherwood et al, which evaluated the direct stimulating property of IFN-γ production of glucan phosphate, it was shown that at 3 hours after LPS induction there was a 2-fold increase in IFN-γ serum levels in rats treated with glucan compared with a control group given saline, while at 6 hours, the increase was more than double. It was reported that glucan phosphate caused IFN-γ production in the immune system as a response to an inflammatory stimulus and there was an association between increased antimicrobial immunity and increased IFN-γ secretion of glucan (7).

In the current study, beta-glucan was determined to have increased IFN-γ expression in the 4th hour, but at the 6th and 8th hours, there was no increase compared to the SAB group. Thus it can be concluded that beta-glucan increases IFN-γ in the first hours (first 4 hours) of SAB.

The highest level of IFN-γ was reached with the administration of beta-glucan together with cefazolin, especially in the 6th hour. The IFN-γ values reached in the group administered cefazolin were found to be higher than those of the group administered beta-glucan. These results suggest that beta glucan induced IFN-γ more in the first hours, but this effect was not as great as that of an antibiotic (cefazolin), and together with antibiotic, this effect was more evident in the first 6 hours. These findings were seen to be compatible with those of Soltys et al and Sherwood et al. (7, 18).

In an experimental animal sepsis model, Şener et al determined low TNF-α levels following beta glucan adminstration (19, 20). At 8 hours after in vitro LPS application, Soltys et al compared TNF-α production in lymphocytes obtained from rats given and not given beta-glucan and found a lower level in those administered beta-glucan. It was stated that beta glucan suppressed pro-inflammatory cytokine production and especially TNF-α production in rats, and the administration of beta-glucan could control cytokine induction in SAB, and could reduce mortality (18). In a sepsis model created following cecal ligation in rats, Bedirli et al showed that plasma TNF-α, IL-1 and IL-6 concentrations increased, and when beta-glucan was administered, the expression of TNF-α, IL-1β and Il-6 was blocked (21). In the current study, a suppression in the TNF-α level was determined at the 8th hour. However, despite this suppression, the TNF-α value measured at the 8th hour was found to be higher than that of the SAB group.

In the group administered beta-glucan together with cefazolin, a lower TNF-α value was determined compared to the SAB group. Furthermore, the same result was not reached in the group administered beta glucan alone. Thus, according to these results, beta-glucan alone is not sufficient to suppress TNF-α.

IL-1 causes pro-inflammatory events by activating various cell types. IL-1 and TNF-α mobilise together in the inflammatory sepsis cascade, causing an increase in the release of other pro-inflammatory cytokines (IL-12, IL-18) (22).

Sandvik et al reported that there was a mild increase in IL-1α basal plasma level in rats with endotoxemia formed with LPS *E.coli* intravenous infusion, and treated with subcutaneous β-1.3/1.6-glucan treatment, but there was no significant change in the levels of other cytokines. It was determined that the increase in plasma IL-1α, IFN-γ, IL-6 and IL-12 levels induced by LPS formed later with prophylactic β-1.3/1.6-glucan treatment, and in the rats treated with β-1.3/1.6-glucan treatment, these mediators, as an early mediator of sepsis, returned more rapidly to basal plasma levels (23).

In a study by Wakshull et al, no increase was reported in the expression of inflammatory cytokines following the administration of beta-glucan (24). Lyuksutova et al stated that there was a reduction in the expression of inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (25). In contrast to that study, the results of the current study showed that the IL-1 levels of the group administered beta-glucan were higher than those of the conttrol group at 4, 6 and 8 hours.

When cefazolin was added to beta-glucan, although a reduction was determined in the IL-1 levels at 8 hours, the level was higher than that of the SAB group. Thus, the use of betaglucan was not determined to have the effect of suppressing IL-1 levels. It was concluded that the use of beta-glucan does not seem to be significant for the suppression of IL-1 cytokine.

Soltys et al reported a great increase in IL-6 production at 24 and 48 hours in lymphocytes isolated from rats treated with beta-glucan following in vitro LPs application (18). Iraz et al created gr(-) sepsis and found that the IL-6 levels at 12 hours in the LPS and the LPS+ beta glucan groups were significantly lower than those of the control and beta-glucan groups and the basal values. It was reported that the IL-6 level in the control group was significantly high and this was decreased by administering beta-glucan (26). In another study by Engstad et al, the effects on TNF-α, IL-6, IL-8 and IL-10 secretion and monocyte tissue factor production were examined when soluble beta 1. 3 glucan and LPS were used alone or combined. It was reported that the IL-6 level increased progressively throughout 8 hours and then returned to the same level (27).

In a model of intra-abdominal sepsis created with the cecal ligation method, the effect of beta-glucan on the lungs was investigated by Babayiğit et al, and a significant increase in IL-6 was determined in the sepsis group treated with glucan. The more significant increase in the group treated with glucan compared to the untreated sepsis group was thought to be associated with the stimulation of macrophages.

It was reported that beta-glucan had reduced neutrophil accummulation in the lungs and the blood in sepsis and increased IL-6 production, and could therefore be used in the clinic to prevent and reduce pulmonary complications of sepsis (28). It is important that IL-6 has both pro-inflammatory and anti-inflammatory properties. Consistent with the findings of previous studies, a progressive increase was determined in the IL-6 levels in the first 8 hours in the current study group that was administered beta-glucan. When applied together with cefazolin, this effect was more evident in the first 4 hours. These findings show that beta-glucan was effective in increasing IL-6, and could provide useful results when applied as adjuvant therapy in the treatment of sepsis. In this study it was determined that beta glucan did not suppress the production of pro-inflammatory cytokines, TNF-α and IL-1. The production of IFN-γ increased in the first hours. However, as this increase was greater in the group given cefazolin, this suggests that the increase in IFN-γ expression in the first hours by beta-glucan was not clinically significant. Beta-glucan led to a significant increase in IL-6 expression in the first 8 hours, suggesting that it could be a useful addition to the treatment of SAB-related sepsis. In conclusion, beta-glucan has been used for many years as an immunomodulator agent in the treatment of many diseases. The results obtained in the current study showed that in this experimental model of SAB, TNF-α and IL-1 production were not suppressed in the beta-glucan group, and an increase was determined in IL-6 and IFN-γ values, especially in the first hours. Therefore, in SAB and in the treatment of SAB-related sepsis, the administration of beta-glucan in addition to antibiotics could be beneficial. Nevertheless, there is a need for further studies to be able to comment on the levels of effectiveness.

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